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Ministry of Health
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NACO
National AIDS Control Organisation
India's voice against AIDS
Ministry of Health & Family Welfare, Government of India
www.naco.gov.in

National Guidelines for HIV Care and Treatment

2021



Section 1

General

1.1 Introduction

The first ever known case of HIV infection was diagnosed in June 1981 in Los Angeles, USA. Since then, there have been tremendous advances in the fields of prevention, diagnosis, care and treatment of HIV/AIDS globally. This global progress in identification of newer drug molecules that are more robust and less toxic, a significant reduction in the cost of therapy and innovative approaches to service delivery and increasing access to treatment have literally transformed the disease from a virtual death sentence in the early 1980s to a chronic manageable disease now. As per UNAIDS 2023 global report, an estimate of 39.0 million (33.1 million–45.7 million) people are living with HIV (PLHIV) with considerable variation in the numbers of PLHIV between countries. Approximately 1.3 million (1.0 million–1.7 million) acquired HIV worldwide in 2022, and an estimated 630 000 (480 000–880 000) lives were lost due to AIDS-related illnesses worldwide in 2022. An estimated 29.8 million of the 39 million (33.1 million–45.7 million) PLHIV were accessing antiretroviral therapy (ART) in 2022 globally.[1] Despite this great achievement, the challenge remains to put the rest on ART to reduce mortality and comorbidities, and to prevent further transmission of HIV.

As per India HIV estimation report 2023,[2] national adult (15–49 years) HIV prevalence was estimated at 0.20% (0.17%-0.25%) in 2023; 0.22 (0.18–0.27) among males and 0.19 (0.16–0.23) among females. Overall, the estimated adult HIV prevalence (15–49 years) has been declining in India since the epidemic's peak in 2000 when it was estimated at 0.56%, decreasing to 0.32% in 2010, and further reducing to an estimated 0.20% in 2023. Similar consistent declines were noted among both males and females at the national level.[2]

The country's epidemic is concentrated among groups with high-risk behaviours and is heterogeneously distributed with wide geographic variations in the vulnerabilities that drive the epidemic. Even with this low prevalence, in terms of absolute numbers, India has the third highest burden of HIV in the world with an estimated 25.44 lakh (21.68 lakh –30.38 lakh) in 2023. Children (<15 years of age) accounted for 2.5% (0.63 lakh) and 44.1% (11.22 lakh (9.56-13.32) of total infections were females.[2]

The first case of HIV in the country was detected among female sex workers screened for HIV in Chennai, Tamil Nadu, in 1986, followed by reports from other parts of the country. By 1987, approximately 135 more cases came to light, of which 14 had already progressed to AIDS. By 2006, an estimated 5.6 million cases of HIV existed in the country, concentrated mainly in six states, namely Maharashtra, Andhra Pradesh, Karnataka, Tamil Nadu, Manipur and Nagaland. However, by 2009, better estimation methods established the HIV burden to be around 2.3 million cases.

To respond to the challenge, the Government of India established the National AIDS Committee in 1986, which led to the establishment of National AIDS Control Organization (NACO) in 1992 to oversee the policies for prevention and control of the HIV infection. The first phase of the National AIDS Control Programme (NACP) started in 1992 and lasted until 1999. The first phase contained initial interventions focused on understanding modes of transmission and on prevention, blood safety and information,

education and communication (IEC) strategy to increase awareness. This was followed by NACP-II (2000–2005), NACP-III (2006–2011), NACP-IV (2012–2017), which was extended for a further four years till March 2021). In the meanwhile, a seven-year National Strategic Plan on HIV/AIDS and STIs (2017–2024) was initiated overlapping phases IV and V.

Table 1.1.1: National summary of the HIV/AIDS epidemic in 2023[2]

Indicators	Desaggregation	Value
Adult (15-49 years) Prevalence (in %)	**Total**	**0.20 (0.17 - 0.25)**
	Male	0.22 (0.18 - 0.27)
	Female	0.19 (0.16-0.23)
Number of People Living with HIV (in Lakh)	**Total**	**25.44 (21.68 - 30.38)**
	Adults (15+ years)	24.81 (21.15 - 29.61)
	Women (15+ years)	11.22 (9.56 - 13.32)
	Children (<15 years)	0.63 (0.51 - 0.79)
	Young people (15-24)	1.63 (1.27 - 2.17)
HIV Incidence per 1000 Uninfected Population	**Total**	**0.05 (0.03 - 0.08)**
	Male	0.06 (0.04 - 0.09)
	Female	0.04 (0.03 - 0.07)
Number of People Living with HIV (in Lakh)	**Total**	**68.45 (45.85 - 107.08)**
	Adults (15+ years)	66.11 (44.41 - 102.86)
	Women (15+ years)	27.04 (18.10 - 42.16)
	Children (<15 years)	2.35 (1.37 - 4.34)
	Young people (15-24)	16.19 (10.76 - 25.28)
Decline in New HIV Infections since 20.10 (%)	**Total**	**44.23**
	Adults (15+ years)	39.94
	Women (15+ years)	41.01
	Children (<15 years)	81.45
	Young people (15-24)	46.99
HIV Incidence per 1000 Uninfected Population	**Total**	**2.61 (1.77 - 3.95)**
	Male	3.39 (2.37 - 4.94)
	Female	1.78 (1.01 - 3.00)
AIDS-related Deaths (in Thousand)	**Total**	**35.87 (24.32 - 54.40)**
	Adults (15+ years)	34.68 (23.56 - 52.26)
	Women (15+ years)	11.32 (6.44 - 19.09)
	Children (<15 years)	1.19 (0.60 - 2.45)
	Young people (15-24)	0.90 (0.56 - 1.47)
Decline in AIDS-related deaths since 2010 (%)	**Total**	**79.26**
	Adults (15+ years)	78.57
	Women (15+ years)	81.64
	Children (<15 years)	89.29
	Young people (15-24)	76.3
Need of Services for EVTH (in Thousand)	**Total**	**19.96 (16.40 - 24.74)**
Final MTCT Rate of HIV(%)	**Total**	**11.75 (7.93 - 17.66)**

During NACP-II, the programme was decentralized to the states with the establishment of State AIDS Control Societies (SACS) with focus on blood safety, targeted intervention and low-cost care including management of opportunistic infections (OIs). The antiretroviral therapy (ART) was introduced in 2004 in the latter half of NACP-II. However, the coverage of services was limited to tertiary care centres. NACP-III aimed at reversing the epidemic over the next five years and focused on targeted interventions, district-level interventions and a massive scale-up of services with stringent quality assurance mechanisms in place. Reduction in new infections by 50% was a major achievement of NACP-III.

In the NACP-IV, the focus was on consolidating the gains achieved in the previous phases, dealing with emerging vulnerabilities and balancing between prevention and growing need for treatment. NACP-IV aimed at improving integration and mainstreaming HIV care in the general health system. In the current phase of NACP- V (2021–2026), the focus is on ensuring PLHIV survive longer and lead productive lives. This will be achieved through improving retention in HIV care and adherence to ART. The programme is transitioning towards a client-centric approach to providing care, support and treatment services through differentiated care service delivery models, community system strengthening and community-based service delivery. The current strategic plan aims to achieve zero new infections, zero AIDS-related deaths and zero discrimination for paving the way for an end of AIDS as a public health threat by 2030.[3]

The Government of India launched the free ART initiative on 1 April 2004 in eight tertiary-level hospitals across six high-prevalence states and the National Capital Territory of Delhi. Since then, there has been a massive scale-up and decentralization of ART services with the aim to have universal access to life-saving ART for all PLHIV in need. In addition to the evidence- based scale-up of ‘when to start ART’ and ‘what ART to start’, keeping pace with new evidence, global developments and recommendations, the Government of India is committed to providing universal access to comprehensive, equitable, stigma-free, quality care, support and treatment services to all PLHIV through an integrated approach. Currently, HIV care services are being delivered through a network of 620 ART centres and 1264 link ART centres (CST MPR March 2021) along with partner-supported 310 care and support centres to approximately 1.4 million PLHIV across the country. Many of the private institutions and providers refer to the national technical guidelines for ART services, besides being used by the government facilities.

India’s ART programme is the second largest globally and has been acclaimed as one of the best public health programmes providing HIV care services. PLHIV have direct access to free diagnostic facilities, free first-line therapy, second and third-line ART, prevention of parent to child transmission of HIV (PPTCT) services, prevention, diagnosis and management of OIs including management of TB with daily anti-TB treatment through a single-window approach. The national programme provides psychosocial support and follow-up services, individualized thematic counselling, positive living and positive prevention services with appropriate referral linkages to various social welfare schemes.

The impact of the NACP is evident. Adult (15–49 years) HIV prevalence in India has declined considerably since 2000, falling from 0.56% in 2000 to 0.32% in 2010 and further declining to 0.20% in 2023. Life-saving ART has improved more than a million lives. AIDS-related deaths have gone down by almost AIDS-related deaths have gone down by almost 86% since their peak in 2005 from an estimate of 278.72 thousand to 35.87 thousand in 2023. India’s programmatic gains contribute significantly to the global

success in the fight against HIV/AIDS.

The success is encouraging, and gains are to be consolidated. Yet, it is not the time to be complacent. Significantly, reaching the so far unreached, early diagnosis, need to improve linkages and retention across the continuum of HIV care and maintaining a high level of adherence are some of the key priorities. The principle of 'hit hard hit early" is becoming more and more pertinent as the programme is maturing.

As a signatory to the United Nations declaration on Sustainable Development Goals (SDGs), India is committed to achieving the "End of AIDS as a public health threat" by 2030. Specific 2020 Fast-Track Targets, including 75% decline in new HIV infections from the 2010 baseline value, attainment of 90-90-90 treatment goals, elimination of MTCT of HIV and elimination of HIV/AIDS-related stigma and discrimination have been identified to anchor the global AIDS response towards attaining the 'ENDGAME' by 2030.[4]

The Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome (Prevention and Control) Act, 2017 is a landmark move to provide a conducive environment to people infected with and affected by HIV and culmination of consistent efforts of community members, civil society and legal experts for more than one and half decades. The Act aims to address stigma and discrimination so that people infected with and affected by HIV cannot be discriminated at homes, for employment and in healthcare settings. Their right to insurance, movement, holding public and private office, residence etc. should be maintained as per the prevailing laws and policies. The Act also reinstates constitutional, statutory and human rights of these people. It also provides for a robust grievance redressal mechanism in the form of a Complaints Officer at establishments and an Ombudsman at state level.

'HIV Estimations 2023' provides critical epidemiological updates using the latest tool and data not only by informing the policymakers, programme managers and all other related stakeholders on the latest status of the epidemic but also as the present benchmark to inform the progress on 2025 Fast-Track Targets and 2030 'End of AIDS as a public health threat' goal.

To achieve this aim, standardized and uniform National Guidelines for HIV Care and Treatment remain the mainstay to standardize treatment practices and thereby improve the quality of HIV care across all sectors of healthcare in the context of our country, especially when many other guidelines with a wide spectrum of recommendations already exist.

The National Guidelines for HIV Care and Treatment are written based on the national recommendations that have been finalized based on national and global experiences and recommendations and taking into consideration the availability of diagnostic and treatment options in the country context. The current

guidelines are being finalized based on the recommendations of the Technical Resource Group for ART comprising of experienced clinicians and medical practitioners from the public and private sectors, technical experts, Government of India, WHO and other UN agencies, bilateral donors, pharmaceutical industries, network of positive people and non-governmental organizations (NGOs) involved in the care and treatment of PLHIV.

These guidelines aim to do the following:

- Harmonize treatment practices across the public and the private sectors since there are patients who seek care from both the sectors at the same time or at different points in time;
- Consolidate various existing guidelines and incorporate recommendations for all age groups, genders and populations;
- Provide standardized guidelines for prevention, screening, diagnosis and management of common OIs among PLHIV.

These guidelines will continue to evolve and will be revised and updated on a regular basis as per emerging national and global evidence and recommendations.

1.2 Diagnosis of HIV Infection in Adults and Children

Diagnosis of HIV

HIV is now considered as a chronic manageable disease and majority of the PLHIV remain healthy if correct and timely treatment is started. Late diagnosis is an important factor associated with HIV related morbidity and mortality. Voluntary HIV testing with informed consent should be offered and encouraged in a wide variety of settings. HIV infection in any individual beyond 18 months of age can be detected by laboratory test/s that demonstrate(s) either the virus or viral products or antibodies to the virus in the blood/serum/plasma. In children below 18 months of age, due to the persistence of maternal antibodies, diagnosis of HIV is made by Polymerase Chain Reaction (PCR) tests that detect HIV nucleic acid. The national programme recommends that HIV testing should be done using highly sensitive and specific rapid tests in HIV Counselling and Testing Services (HCTS) facilities, which provide reliable, timely and accurate test results, as per the prescribed quality standards.

Under the NACP, the most commonly used rapid tests are based on the principle of enzyme immunoassay, immuno-chromatography (lateral flow), immuno-concentration / dot-blot assays (vertical flow) and particle agglutination. All these different rapid tests should have a sensitivity of ≥99.5% and specificity of ≥98%.

Window period represents the period between infection with HIV and the time when HIV antibodies can be detected in the blood (6-12 weeks). A blood test performed during the window period may yield a negative test result for HIV antibodies. These cases may require further testing after 12 weeks.

Diagnosis of HIV infection in adults and children above the age of 18 months

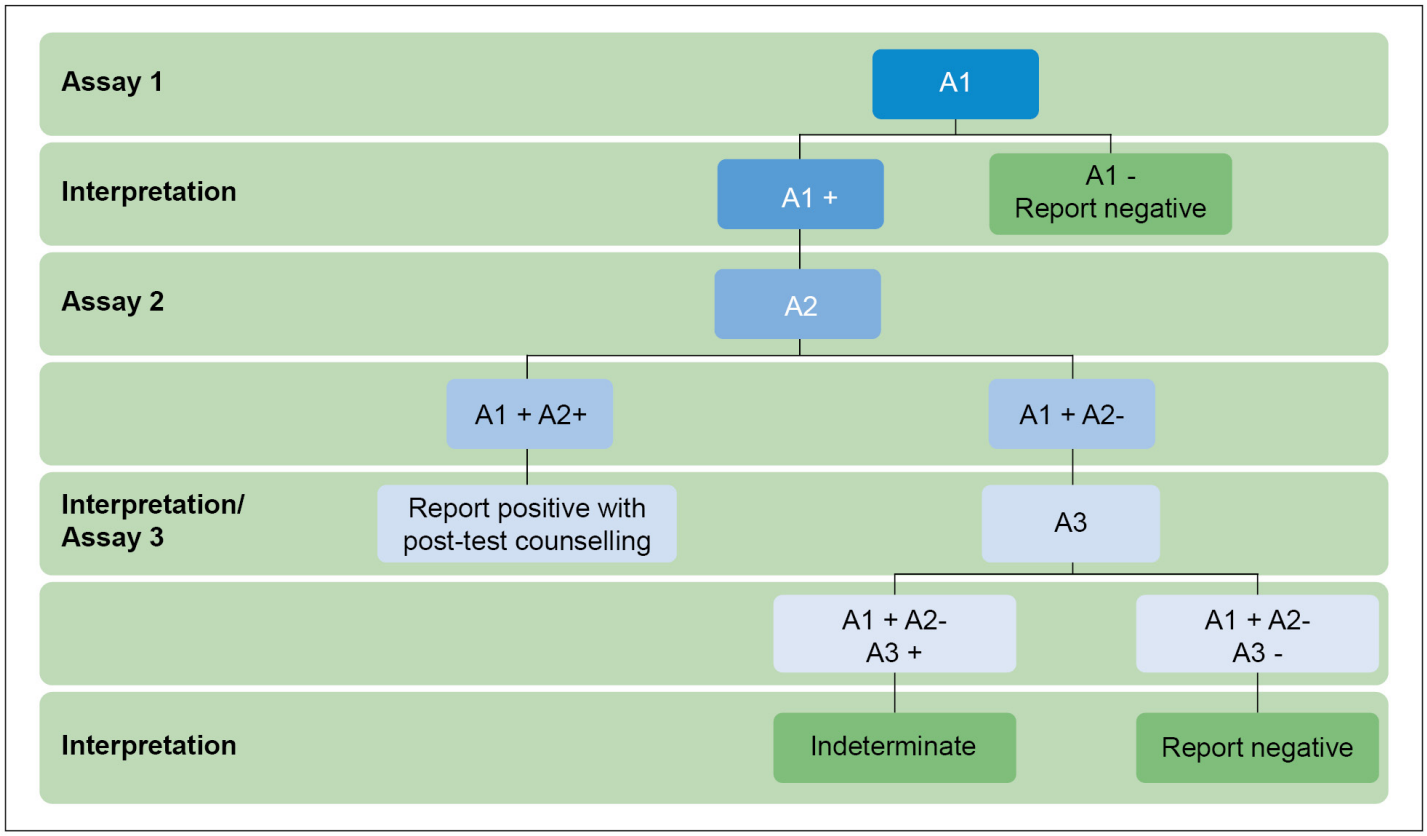
Confirmatory diagnosis of HIV infection is essential for ensuring access to care and treatment services. National HIV testing strategies enable the programme to screen for HIV or confirm the diagnosis of HIV at the nearest Integrated Counselling and Testing Centre (ICTC). In view of the low prevalence of HIV in India, it is necessary to use three different principles or antigen-based rapid tests to confirm the diagnosis. **All samples reactive in the first test should further undergo confirmatory second/third tests based on different principles/antigens using the same serum/ plasma sample as that of the first test.** The same blood sample is utilized for performing all the tests for identifying HIV antibodies. For indeterminate results, testing should be repeated on a second sample taken after 14–28 days.

A testing strategy for diagnosis describes a testing sequence for the specific testing objective of diagnosis (as opposed to screening only), taking into consideration the presumed HIV prevalence in the population. *The national programme follows strategy I for screening and strategy II (A) for surveillance purposes, whereas it uses strategy II (B) and strategy III for diagnosis in symptomatic and asymptomatic persons, respectively.* The following strategies are to be used for HIV testing and diagnosis in adults and children above the age of 18 months:

- **For clinically symptomatic individuals**: the sample should be reactive with two different kits (Strategy II (B);
- **For clinically asymptomatic individuals**: the sample should be reactive with three different kits (Strategy III).

For clinically symptomatic individuals: A patient who is clinically symptomatic and suspected to have HIV infection/disease is referred to the ICTC for confirmation of the diagnosis. In this case, the same blood sample is tested twice using kits with either different antigens or principles. The patient is declared HIV negative if the first test is non-reactive and HIV positive when both tests show reactive results. When there is discordance between the first two tests (first reactive and the second non-reactive), a third test is done. If the third test is also negative, it is reported as negative. If the third test is reactive, it is reported as indeterminate and the individual is retested after 14–28 days, as shown in Strategy II (B).

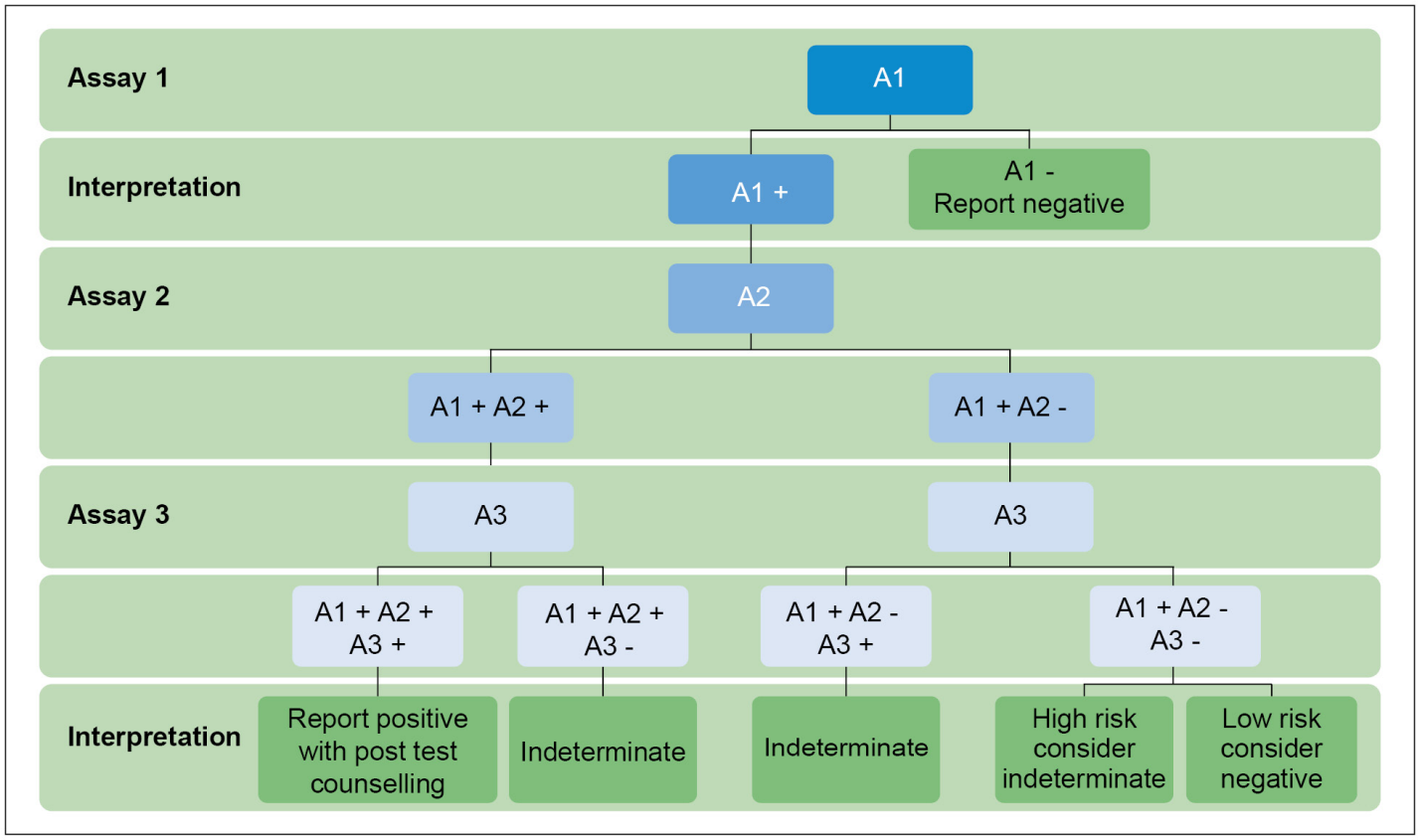
Figure 1.2.1: Strategy II (B): For diagnosis of clinically symptomatic individuals



For clinically asymptomatic individuals: Confirmation of HIV diagnosis in asymptomatic individuals is done at an ICTC using three rapid tests of three different antigens or principles. The individual is considered HIV negative if the first test is non-reactive and HIV positive when all three tests show reactive results. For indeterminate results, testing should be repeated on a second sample taken after 14–28 days, as shown in Strategy III.

All HIV testing should be provided following five essential Cs: Consent, Confidentiality, Counselling, Correct test results and immediate Connection/linkages to services for HIV prevention, treatment and care. All persons should undergo pre-test and post-test counselling and confidentiality should be maintained while disclosing the results. Post-test counselling is important both for those with reactive results and those with negative results.

Figure 1.2.2: Strategy III: For diagnosis of clinically asymptomatic individuals



In addition to the walk-in clients and community-based HIV testing, Provider-Initiated Testing and Counselling (PITC) is recommended in all healthcare settings for adults, adolescents or children, who present in clinical settings with signs and symptoms or medical conditions that could indicate possible HIV infection.

The spouses/partners of those with HIV-positive results and children of HIV-infected mothers should also be counselled and offered HIV testing. All persons found positive for HIV should be immediately linked to appropriate HIV care, support and treatment services.

For more details, please refer to the national HIV Counselling and Testing Services (HCTS) Guidelines, NACO, December 2016.

Diagnosis of HIV infection in infants and children less than 18 months of age

Maternal antibodies to HIV, transferred passively to the infant during pregnancy, usually persist for nearly 9–12 months in the infant. In some children, they may persist for as long as 18 months. Thus, during this period, children born to HIV-infected mothers will test positive for HIV antibodies regardless of their own infection status. A positive ELISA/Rapid test that detects antibodies to HIV, therefore, does not necessarily indicate the presence of HIV infection in the infant/child. Rather, a positive ELISA/Rapid test indicates exposure to HIV. More reliable indicators of the HIV infection status of the infant are tests that detect HIV viral RNA or antigens.

NACO recommends the use of Total Nucleic Acid (TNA) PCR test on a Dried Blood Spot (DBS) sample of the infant to detect viral nucleic acids for diagnosis of HIV-1 infection during infancy. This test is performed at 6 weeks of age or at the earliest opportunity when the infant and the mother come in contact with healthcare system/workers. At and after 6 months of age, TNA PCR must be performed after screening for HIV antibodies. It is also important to take breastfeeding into consideration in the HIV

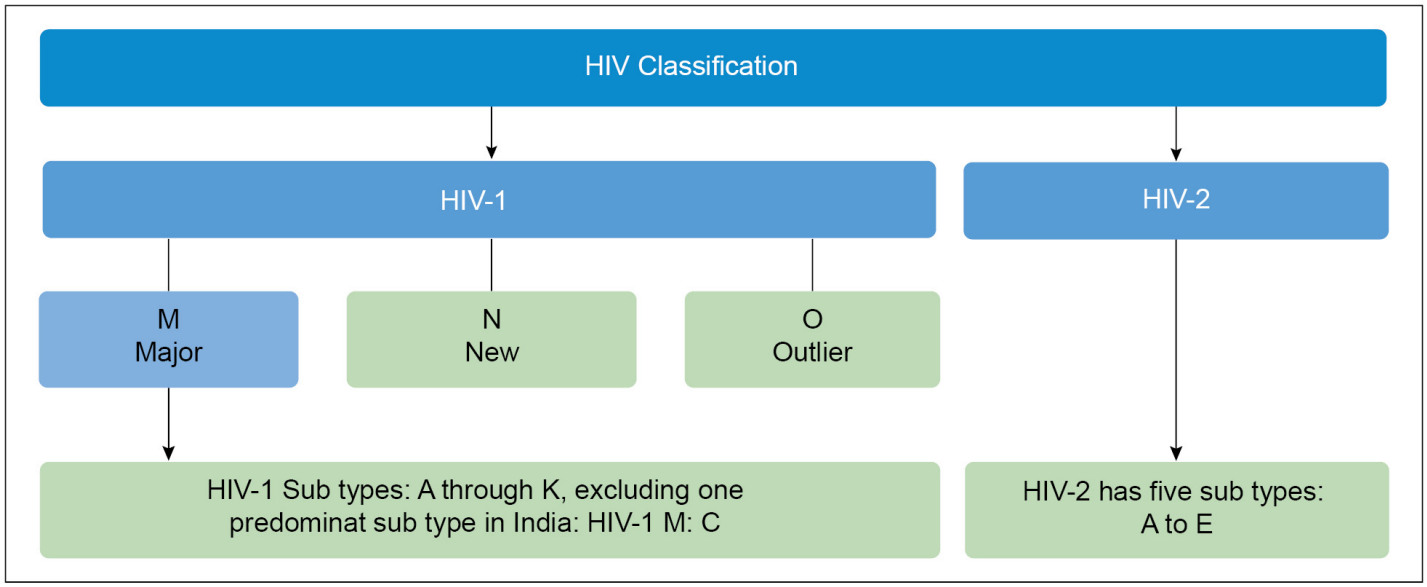
testing algorithm. Since breastfed children have an ongoing risk of HIV acquisition, they are tested (TNA PCR) 3 months after complete cessation of breastfeeding or 18 months of age, whichever is later, to reliably exclude HIV-1 infection. For more detailed information, refer to Chapter 2.1 on (Assessment of Adults and Adolescents with HIV Infection) and annexure 1 and 1x.

Diagnosis of HIV-2

There are two types of HIV: HIV type I (HIV-1) and HIV type 2 (HIV-2). The most common cause of HIV infection throughout the world is HIV-1 that comprises of several subtypes with different geographic distributions.

Information on the epidemiology of HIV-2 and dual infection in India is limited. However, cases of HIV-2 infection have been reported.

Figure 1.2.3: Classification of HIV-1 and HIV-2



Natural history studies indicate that HIV-2 is less pathogenic than HIV-1. Those infected with HIV-2 have slower disease progression, a much longer asymptomatic stage, slower decline in CD4 count, lower rates of vertical transmission, lower viral loads while asymptomatic and smaller gains in CD4 count in response to ART.

It is observed and well documented that infection with HIV-2 does not protect against HIV-1 or dual infection. Patients with dual infection (HIV-1 and HIV-2) tend to present at a more advanced stage of the disease than those infected with HIV-2 only. Infection with both HIV-1 and HIV-2 generally carries the same prognosis as that of HIV-1 single infection.

Although HIV-1 and HIV-2 are related, there are important structural differences between them. Accurate diagnosis and differentiation of HIV-1 and HIV-2 is crucial for treatment initiation and in the assessment of treatment failure. Since Dolutegravir (DTG) is now recommended as the preferred drug for all lines of treatment of HIV infection, it is expected that patients with HIV- 2 infection will benefit. However, in patients with HIV-2 infection, either alone or with HIV-1, treatment failure assessment entirely depends on the falling CD4 counts and not on virological failure, as HIV-2 viral load assessment in them is not possible in programme conditions. Hence, the knowledge/information of those PLHIV with HIV-2 infection is crucial for the treatment of infected individuals as well as for understanding the extent of HIV-2 infections in India. Rapid kits that differentiate between HIV-1 and HIV-2 are being used at ICTCs. Test results that show HIV-2 reactivity by two different testing kits/principles are reported as reactive for

HIV-2 and no further testing is required.

Samples that test reactive for HIV-1 and HIV-2 or test reactive for HIV-2 with only one kit need confirmation; NACO has established a network of laboratories for this designated as HIV-2 referral laboratories. The designated laboratories are responsible for confirming the presence of HIV-2 infection. Patients requiring confirmation of the HIV-2 reactive report will be referred, by the ICTC, to the nearest ART centre with the ICTC report and a referral slip. The guidance for HIV-2 diagnosis confirmation is as follows:

Figure 1.2.4: Guidance for HIV-2 diagnosis confirmation

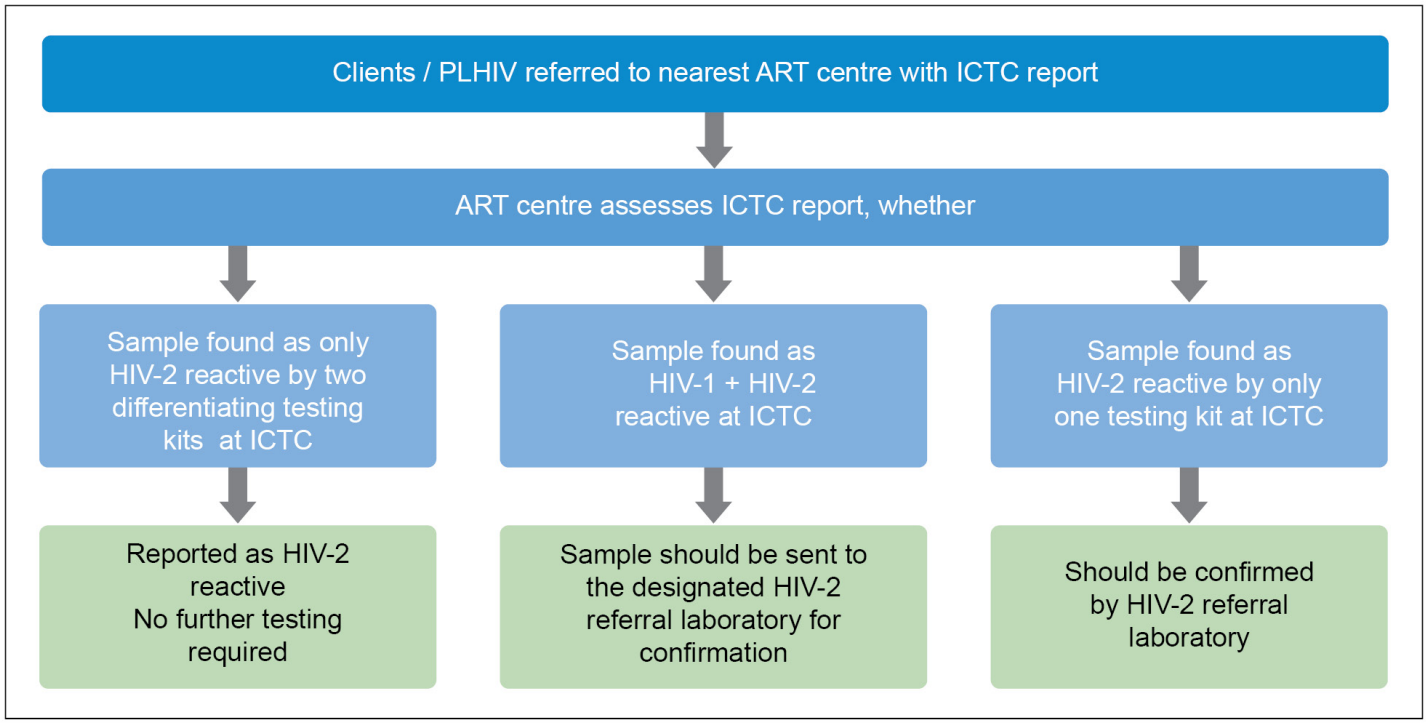
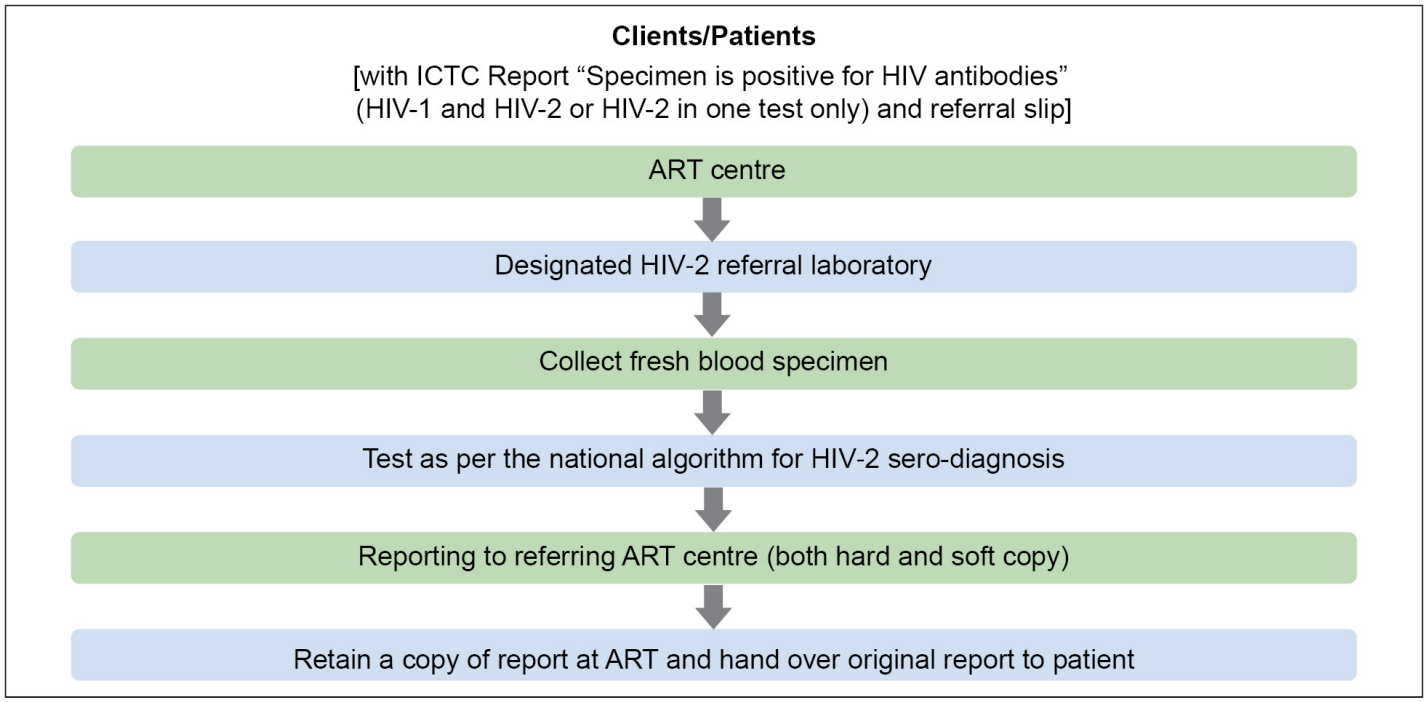


Figure 1.2.5: Flow chart for referring patient for HIV-2 testing from ART centre to reference laboratory



Section 2

Adults and Adolescents

2.1 Assessment of Adults and Adolescents with HIV Infection

Introduction

All persons diagnosed with HIV at the ICTC should be enrolled in the ART centres for HIV care and treatment services. 'Adolescents' are defined as persons aged between 10 and 19 years. Thorough clinical assessment, clinical history, physical examination and access to basic laboratory diagnostics are essential for rapid ART initiation.

This section deals with the assessment of adults and adolescents with HIV infection. The steps to be followed during initial evaluation of PLHIV are as below:

- Step 1: Clinical assessment and medical history
- Step 2: Physical examination
- Step 3: Baseline laboratory evaluation

Clinical Assessment

Once the PLHIV are enrolled in an ART centre, a comprehensive clinical assessment should be done to obtain baseline clinical status and to rule out OIs. This helps to:

- Determine the clinical stage of the HIV infection;
- Identify the current HIV-related illnesses that may require treatment;
- Identify any prior exposure to ARVs in the past;
- Determine the need for OI prophylaxis;
- Identify coexisting medical conditions such as Diabetes, Hypertension, Hepatitis or any other treatment that may influence the choice of ARV drugs;
- Determine nutritional status and needs;
- Elicit the history of past illnesses (especially TB, Sexually Transmitted Infections [STIs]);
- Elicit HIV status of family members/partners; offer index testing services for spouse, sexual and injecting partners and biological children;
- Assess the need for psychosocial support.

The recognition of HIV-related clinical events will help determine the WHO clinical stage of a patient and to decide initiation of OI prophylaxis and rapid ART (Please refer Table 2.1.3 for WHO clinical staging).

Medical History

Assessment and history taking should include the following:

- HIV testing
- 4 symptom screening for TB (Adults: fever, cough, weight loss, night sweats; Children: fever, cough,

poor weight gain/reported weight loss, h/o contact with a TB case);

- Any persistent symptoms – headache, poor concentration, seizures;
- General medical history for comorbid conditions like Diabetes, Hypertension and others;
- History of tuberculosis in past/family;
- Prior exposure to ARVs in the past;
- History of STI;
- HIV risk behaviour – multiple partners, key populations, injecting drug use;
- Substance abuse – alcohol, tobacco, oral or injecting drugs;
- Pregnancy and contraception;
- Allergies/medication/vaccines;
- Nutritional status;
- Psychosocial assessment.

Medical officers of the ART centres must obtain detailed medical history as per the checklist provided in Table 2.1.1.

Table 2.1.1: Medical History Checklist

HIV Testing	HIV Risks (can be multiple)
• Ever tested for HIV in the past • Date and place of the first HIV test • Reason for HIV testing • Documentation of the test result • Date of the last negative HIV test result • Previous CD4 cell counts (if applicable) • Previous viral load (if applicable)	• Unprotected sexual contact • Injecting drug use • Commercial sex work • Men having sex with men • Occupational exposure (Healthcare Worker [HCW]) • Perinatal transmission • Recipient of blood products • Sero-discordant couple • Unknown
Review of Clinical symptoms	**Past History of HIV-related Illness**
• Unexplained weight loss • Swollen lymph nodes • Night sweats and fever • Unusual headaches, poor concentration or confusion • Fever with chills/rigor • Change in appetite • Skin rash • Sores/Ulcers or white spots in mouth • Painful swallowing • Chest pain, cough, or shortness of breath	• Oral oesophageal candidiasis • Persistent diarrhoea • Tuberculosis • Varicella zoster (Shingles) • Oral hairy leucoplakia (OHL) • Pneumocystis jiroveci pneumonia (PCP) • Recurrent bacterial pneumonia • Cryptococcal meningitis • Toxoplasmosis • Kaposi's sarcoma
• Abdominal pain, vomiting or diarrhoea • Numbness or tingling in hand or feet • Muscular weakness / abnormal movements • Partial loss of vision or visual field defects	• Disseminated Mycobacterium avium complex • Cytomegalovirus (CMV) infection • Invasive cervical cancer
Tuberculosis History	**ART History**
• History of past TB infection and type of TB • Old chest X-ray (if available) • Treatment given (drugs and duration) • History of TB in family/close contacts • Ask the four TB screening questions '4S screening' (current cough, fever, weight loss and night sweats)	• Current and past exposure to ARVs • ARV use during pregnancy for prevention of mother to child transmission (PMTCT) • Use of Post Exposure Prophylaxis (PEP) in the past • Current/past use of Pre-Exposure Prophylaxis (PrEP) • Drugs taken and for how long • An understanding of the treatment and readiness to commence ART • Partner's ART history (if HIV positive)
Sexually Transmitted Infections	**Substance Use**
• Genital ulcer or other lesions • Genital discharge (abnormal vaginal discharge in women) • Scrotal swelling, urethral discharge, anal ulcers • Lower abdominal pain	• Alcohol, stimulant, opiate and use of other drugs • Smoking history
General Medical History	**Allergies**
• Any other past medical condition such as diabetes, hypertension, coronary artery disease, Hepatitis B, Hepatitis C, hyperlipidaemia, mental health issues, e.g., depression	• Known allergies to drugs or other substances or materials
Medication	**Vaccination History**
• Past use of drugs and reasons for taking those drugs • Current use of drugs and reasons • Current use of traditional/herbal remedies • Opioid Substitution Therapy (OST)	• BCG • Hepatitis A vaccine • Hepatitis B vaccine • Vaccination against Covid
Gynaecological History	**Pregnancy and Contraception History**
• Last PAP smear • Menstrual irregularities • Pelvic pain or discharge	• Previous pregnancies and medical termination of pregnancy (MTP) • Children and HIV status of the children (living and dead) • Exposure to ARVs during pregnancy • Drugs and duration of ART • Contraception used • Last menstrual period
Psychosocial History	**Functional Status**
• Family history, e.g., other immediate family members with known HIV infection • Social history e.g., marital status, education, occupation, source of income • Financial and family support status • Disclosure status, readiness to disclose • Availability of care and treatment supporter	• Able to work, go to school, do housework • Ambulatory but not able to work • Bedridden • Amount of day-to-day care needed

Physical Examination

It is essential to conduct a thorough physical examination to determine the clinical stage and screen for OIs.Table 2.1.2 details the specific physical signs related to HIV/AIDS that should be screened.

Table 2.1.2: Checklist for physical examination

General	• Record vital signs, body weight, height, body mass index (BMI), temperature, blood pressure, pulse rate, respiratory rate, pallor and icterus
Appearance	• Unexplained moderate or severe weight loss, HIV wasting • Rapid weight loss is suggestive of active opportunistic infections, especially if associated with fever • Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection • 'Track marks' and soft tissue infections common among injecting drug users • Disorientation or confusion
Consider conditions other than HIV	• Malaria, tuberculosis, syphilis, GI infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis
Skin	• Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of Pruritic Papular Eruption (predominant on the legs), seborrhoeic dermatitis on the face and scalp • Look for herpes simplex and herpes zoster or scarring of previous herpes zoster (especially multi-dermatome)
Lymph nodes	• Start with posterior cervical nodes • Persistent Glandular Lymphadenopathy (PGL) typically presents as multiple bilateral, soft, non-tender, mobile cervical nodes, other than axillary or inguinal nodes • Tuberculous lymph nodes typically present with constitutional symptoms such as fever, night sweats and weight loss
Mouth	• Look for signs suggestive of HIV infection including white plaques on tongue, cheeks and roof of mouth (oral candida), white striped lesions on the side of the tongue (OHL) and cracks at the corners of the mouth (angular cheilitis) • Difficulty in swallowing is commonly caused by oesophageal candida infection
Chest	• The most common problems are TB, Community Acquired Pneumonia (CAP) and PCP • Signs and symptoms are cough, shortness of breath, haemoptysis, weight loss/poor weight gain in children, fever, night sweats, congestion or consolidation • Perform a chest X-ray PA view and monitor saturation
Abdomen	• Hepatosplenomegaly, masses and local tenderness
Neurological	• Perform comprehensive neurological examination. • Fundus examination if CD4 less than 100 cells/mm^3
Anogenital	• Herpes simplex and other genital sores/lesions, vaginal or urethral discharge; perform PAP smear
Note: During each consultation, the patient must be clinically screened for TB (history, 4-symptom screening and physical examination)	

All PLHIV must be assessed for WHO clinical staging on the first and all the subsequent visits by the medical officer. (Please refer Table 2.1.3.)

Signs of serious illness

On examination, if the PLHIV present with any of the following signs of serious illness, then immediate referral for expert evaluation is a must:

- Temperature ≥ 39°C with headache
- Respiratory rate ≥ 30/min
- Heart rate ≥ 120/min
- SpO_2 (pulse oximeter) < 90%
- Altered mental status (e.g., confusion, strange behaviour, reduced consciousness)
- Other neurological problem (persistent severe headache, seizure, paralysis, difficulty in talking, rapid deterioration of vision)
- Unable to walk unaided
- Any other condition that requires emergency management.

Advanced HIV Disease

PLHIV with advanced HIV disease are defined as presenting with CD4 count <200 cells/mm^3 or WHO clinical stage 3 or 4 or children aged less than 5 years. PLHIV presenting with advanced HIV disease must be managed by the components of advanced disease package of services. Details of ADM package of services are provided in **Chapters 2.3 (Advanced Disease Management in PLHIV) and 3.3 (Advanced Disease Management in CLHIV less than 5 years of age).**

Table 2.1.3: WHO Clinical Staging in Adults, Adolescents and Children[1]

Adults and adolescents	Children
Clinical stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy (PGL)	• Asymptomatic • Persistent generalized lymphadenopathy (PGL)
Clinical stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (Sinusitis, Tonsillitis, Otitis Media, Pharyngitis) • Herpes Zoster • Angular Cheilitis • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Seborrhoeic Dermatitis	• Unexplained persistent hepatosplenomegaly • Recurrent or chronic upper respiratory tract infections (Otitis Media, Otorrhoea, Sinusitis, Tonsillitis) • Herpes Zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Extensive wart virus infection • Extensive Molluscum Contagiosum • Unexplained persistent parotid enlargement
Clinical stage 3	
• Unexplained severe weight loss (>10% of the presumed or measured body weight) • Unexplained chronic diarrhoea for more than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month) • Persistent Oral Candidiasis • Oral Hairy Leucoplakia • Pulmonary Tuberculosis • Severe bacterial infections (such as Pneumonia, Empyema, Pyomyositis, bone or joint infection, Meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, Gingivitis or Periodontitis • Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9/L) and/or chronic thrombocytopaenia (<50 x 10^9/L)	• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than 1 month) • Persistent Oral Candidiasis (after the first 6 weeks of life) • Oral Hairy Leucoplakia • Lymph node Tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial Pneumonia • Acute necrotizing ulcerative gingivitis or Periodontitis • Unexplained anaemia (<8 g/dl), neutropenia (<0.5 x 10^9/L) or chronic thrombocytopaenia (<50 x 10^9/L) • Symptomatic Lymphoid Interstitial Pneumonitis • Chronic HIV-associated lung disease, including Bronchiectasis
Clinical stage 4	
• HIV wasting syndrome • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial Pneumonia • Chronic Herpes Simplex infection (orolabial, genital or anorectal of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system Toxoplasmosis • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated non-tuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis • Chronic Isosporiasis • Disseminated mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis) • Lymphoma (cerebral or B-cell non-Hodgkin's) • Symptomatic HIV-associated nephropathy or cardiomyopathy	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial infections (such as Empyema, Pyomyositis, bone or joint infection, Meningitis, but excluding Pneumonia) • Chronic Herpes Simplex infection (orolabial or cutaneous of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi, or lungs) • Extra pulmonary Tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) • Central nervous system Toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated nontuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML)
• Recurrent septicaemia (including non-typhoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Chronic Cryptosporidiosis (with diarrhoea) • Chronic Isosporiasis • Disseminated endemic mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis, Penicilliosis) • Cerebral or B-cell non-Hodgkin's Lymphoma • HIV-associated nephropathy or cardiomyopathy

a. In the development of this table, adolescents were defined as 15 years or older. For those aged less than 15 years, the clinical staging for children should be used.

b. For children younger than 5 years, moderate malnutrition is defined as weight-for-height <–2 z-score or mid-upper-arm circumference ≥ 115 mm to <125 mm.

c. Some additional specific conditions can be included in regional classifications, such as Penicilliosis in Asia, HIV-associated rectovaginal fistula in southern Africa and reactivation of trypanosomiasis in Latin America.

d. For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 z-score; and severe acute malnutrition is either weight for height <–3 z-score or mid-upper-arm circumference <115 mm or the presence of oedema.

Nutritional Assessment

Good nutrition is a key factor for maintenance of good health and quality of life for all people whereas poor nutrition reduces a person's ability to work and be active. In PLHIV, poor nutrition worsens the effects of HIV by further weakening the immune system. This leads to frequent illnesses and an inability to replace and repair body cells and tissues, resulting in severe weight loss. It may lead to a more rapid progression of the disease.

Food and nutritional intake can influence the adherence to ARVs as well as the effectiveness of ARVs. HIV and associated infections increase the need for energy, proteins and micronutrients like iron, zinc, vitamin C, etc. OIs like TB, Pneumonia and Diarrhoea further increase the nutritional demands of the body, accelerating the decline in nutritional status. Thus, a vicious cycle exists between HIV infection and malnutrition.

Appropriate nutritional support from the early stages of HIV infection can prevent the onset of malnutrition and other nutritional deficiencies. It will also help maintain the performance of the immune system. Nutritional care and support, which includes counselling, education, information sharing and linkage to social welfare schemes, is an important component of the comprehensive package of care and support services for all PLHIV, including adults, adolescents and CLHIV.

Nutritional assessment

A BMI less than 18.5 kg/m^2 is a recognized independent risk factor for morbidity and mortality in HIV-positive adolescents and adults.

An initial nutritional status assessment and targeted further care are therefore essential components of comprehensive care of the HIV-positive patient. This attention to the nutritional care of patients can also improve adherence to ART and retention in care as well as supporting their continuation or return to a productive life.

There are many factors responsible for change in nutritional status of PLHIV. The details can be found in the **Chapter 3.6 (Nutritional Care of HIV-infected Children).**

Nutritional assessment should include the following:

- Anthropometric measurements: There are no specific measurements; however, BMI may be considered for clinical evaluations (Table 2.1.4).

Table 2.1.4: Nutritional classification and BMI value for adults (kg/m^2)

Nutritional Classification	BMI (kg/m^2)
Obese	30 and more
Overweight	25 to <30
Normal	18.5 to <25
Risk of acute malnutrition	17 to <18.5
Moderate acute malnutrition	16 to <17
Severe acute malnutrition	<16

- Assessment of oedema: Bilateral oedema is a sign of severe malnutrition. However, oedema in adults can be caused by other pathologies (renal, cardiac, hepatic, etc.); so these must be checked for before deciding that the oedema is being caused by malnutrition.
- Dietary/food history: This is important to modify the dietary requirements if PLHIV are deficient as per the recommended needs.

Comprehensive Laboratory Evaluation in HIV/AIDS

The purpose of the baseline laboratory evaluation is as follows:

- To rule out other concomitant infections, OIs;
- To determine baseline safety parameters.

The following investigations (Table 2.1.5) are recommended for monitoring of PLHIV at the ART centres:

Table 2.1.5: Laboratory monitoring for patients at ART centre

Baseline Investigations: Essential tests for all patients registering in HIV care at ART centre
• Haemogram/CBC • Urine for routine and microscopic examination • Fasting blood sugar • Blood urea, Serum creatinine • Serum bilirubin, ALT (SGPT) • VDRL • CD4 count • X-ray chest PA view
Additional tests at baseline as per the physician's decision
• Symptoms and signs directed investigations for ruling out OIs, including MTB by sputum/ appropriate specimen using Nucleic Acid Amplification Test (CBNAAT/Truenat) and/or other required investigations • Complete Liver function test (LFT) for those being initiated on Anti-tubercular treatment (ATT) and for patients with Hepatitis B or C co-infection • Lipid profile (if available) • Ultrasonography (USG) whole abdomen • rK-39 strip test to confirm or rule out leishmaniasis (especially in patients with HIV infection who live in or travel to endemic areas i.e., Bihar, Eastern Uttar Pradesh, Jharkhand and West Bengal) • Pregnancy test (if applicable) • For women, cervical PAP smear or other method of cervical cancer screening (if available) • For men having sex with men (MSM), anal PAP smear (if available)
NON-AVAILABILITY/NON-FEASIBILITY OF ANY OF THESE TESTS SHOULD NOT DELAY THE INITIATION OF ART Note: All the above investigations other than CD4 estimation shall be done from the health facility where the centre is located, with support from the State Health Department.

Assessment and Management of the Patient at First and at Follow-up Visits

Table 2.1.6: Assessment and management of the patient during the first and follow-up visits at the ART centre

Visit	Activities
Visit 1 (Day 1)	• Registration in HIV care • Medical history • Follow symptom screening checklist • 4-symptom TB screening • Physical examination • Behavioural/psychosocial assessment • Educational level, employment history, financial resources • Social support, family/household structure • Disclosure status, readiness to disclose • Understanding of HIV/AIDS, transmission, risk reduction, treatment options • Nutritional assessment • Family/household assessment to determine if there are other HIV-infected family members who may need care • Recommend condom use during every visit • Readiness assessment/Preparedness counselling • Baseline investigation: Essential tests including CD4 count and additional tests as per requirement • Initiate Cotrimoxazole Preventive Therapy (CPT), if eligible • Commence ART if the patient is adequately prepared: ART to be dispensed for one month and concurrently send samples for CD4 count and other baseline investigations as per NACO guidelines (Refer to Rapid ART initiation in **Chapter 2.2 [ART in Adults and Adolescents])**
Before follow-up visits (within 3–15 days after initiating ART)	• Review test results: If test reports are not normal, PLHIV to be called back to ART centre (as soon as possible, within 2 weeks of ART initiation) • ART counsellor to call all patients to learn about general well-being of patients within 2 weeks of ART initiation
Subsequent follow-up visits (after initiating ART)	• History (new problems) • Symptom checklist • Clinical examination • 4-symptom TB screening • Note any side effects (Insomnia, anaemia, rash, fever, signs of hepatotoxicity/nephrotoxicity) • Investigations as per monitoring and follow-up related to ARV • Counselling • Adherence assessment/support

2.2 ART in Adults and Adolescents

Introduction

There has been a rapid decline in HIV-related mortality and morbidity due to the wider availability of affordable, more efficacious and less toxic ARVs over the last two decades. ART consists of the use of a combination of at least three ARV drugs from different classes to inhibit the replication of HIV and reduce viraemia to undetectable levels.Continued suppression of viral replication leads to the restoration of immune response, reflected by an increase in the CD4 count. Increase in CD4 count leads to slowing of the disease progression, reduced frequency of OIs, improvement in the quality of life and increased longevity. Successes achieved by ART have now transformed the perception about HIV infection from being a 'virtual death sentence' to a 'chronic manageable illness'. ART was earlier known as Highly Active ART (HAART) and as combination ART (cART).

Goals of Antiretroviral Therapy

ART cannot cure HIV infection, as the currently available ARV drugs cannot eradicate the virus from the human body. This is because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection. HIV persists within the organs/cells and fluids (e.g., brain, liver and lymphoid tissue) despite prolonged suppression of plasma viraemia to undetectable level by ART. The primary goals of ART are maximal and sustained reduction of plasma viral load and restoration of immunological functions. The reduction in the viral load also leads to reduced transmissibility and reduction in new HIV infections. The defined goals of ART are depicted in Table 2.2.1.

Table 2.2.1: Goals of ART

Goals of ART	
Clinical goals	Increased survival and improvement in quality of life
Virological goals	Greatest possible sustained reduction in viral load
Immunological goals	Immune reconstitution, that is, both quantitative and qualitative
Therapeutic goals	Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence
Preventive goals	Reduction of HIV transmission by suppression of viral load

Due to continued viral suppression, the destruction of CD4 lymphocyte cells is reduced and, over time, there is an increase in the CD4 count, which is accompanied by partial restoration of pathogen-specific immune function. This leads to a reduction in incidence of OIs, reduced morbidity and mortality.

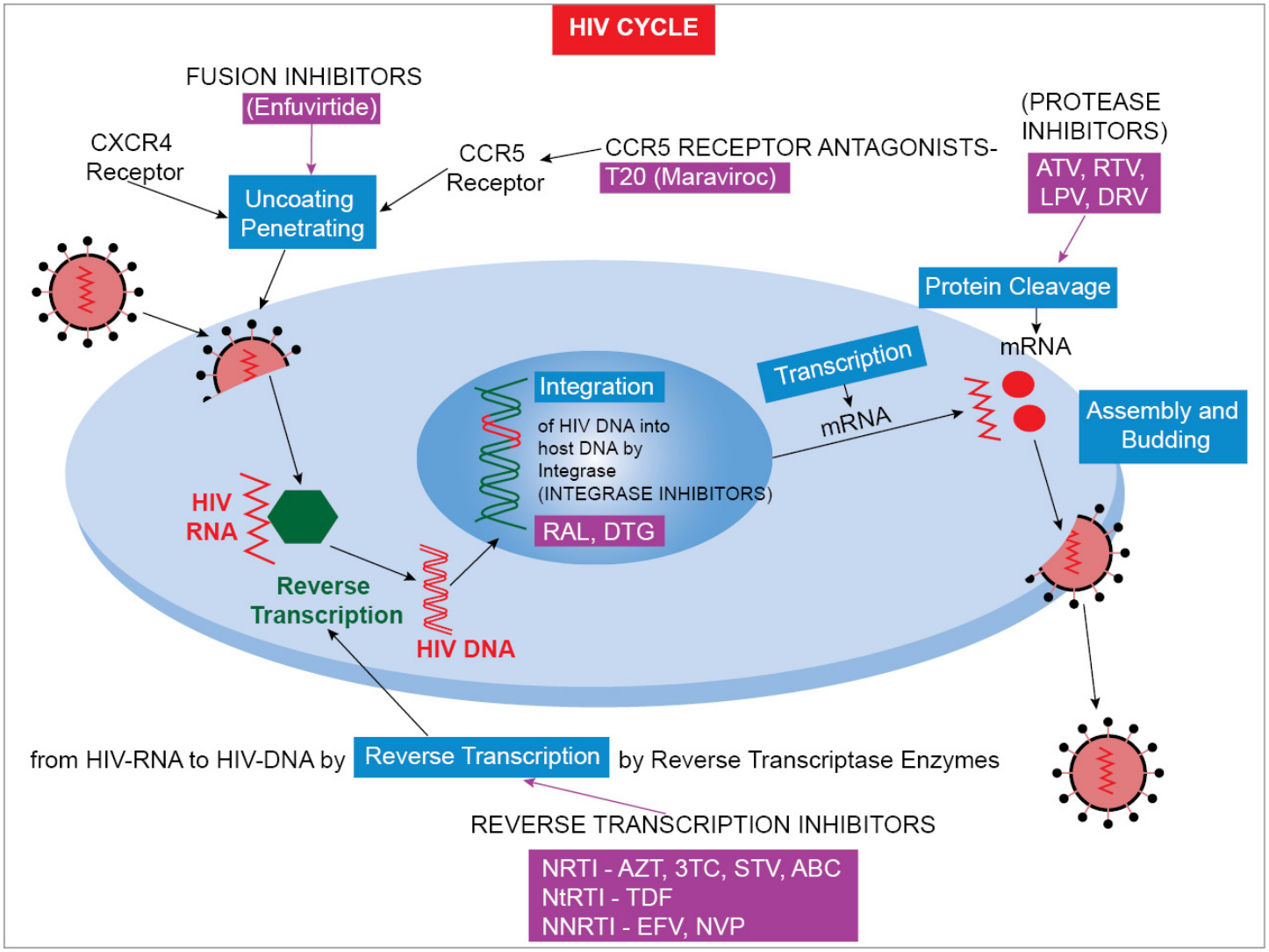
Principles of Antiretroviral Therapy

A continuous high level of HIV replication takes place in the body right from the early stages of the infection. At least one billion viral particles are produced during the active stage of replication. The ARVs

act on various stages of the HIV viral replication and interrupt the process of viral replication in the body. Figure 2.2.1 depicts the various enzymes involved in viral replication and the points where ARVs target the virus. The ARV drugs act on the viral replication in the following steps and their classes are labelled according to the site of their action:

1. Block binding of HIV to the target cell **(Fusion Inhibitors and CCR-5 co-receptor blockers)**
2. Block the viral RNA cleavage and one that inhibits reverse transcriptase **(Reverse Transcriptase Inhibitors)**
3. Block the enzyme integrase, which helps in the pro-viral DNA being incorporated into the host cell chromosome **(Integrase Inhibitors)**
4. Block the RNA to prevent viral protein production
5. Block enzyme protease (Protease Inhibitors)
6. Inhibit the budding of virus from host cells

Figure 2.2.1: Targets of antiretroviral drugs



The most used drugs target the virus mainly by inhibiting the enzymes reverse transcriptase (RT), integrase and protease. Various ARV classes are depicted in Table 2.2.2.

Table 2.2.2: Classes of ARV Drugs

Nucleoside reverse transcriptase inhibitors (NsRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)
Zidovudine (AZT)*	**Nevirapine (NVP)***	Saquinavir (SQV)
Stavudine (d4T)	**Efavirenz (EFV)***	**Ritonavir (RTV)***
Lamivudine (3TC)*	Delavirdine (DLV)	Nelfinavir (NFV)
Abacavir (ABC)*	Rilpivirine (RPV)	Amprenavir (APV)
Didanosine (ddI)	Etravirine (ETV)	Indinavir (INV)
Zalcitabine (ddC)	Doravirine (DOR)	**Lopinavir (LPV)***
Emtricitabine (FTC)	**Integrase Inhibitors**	Fosamprenavir (FPV)
Nucleotide reverse transcriptase inhibitors (NtRTI)	**Dolutegravir (DTG)***	**Atazanavir (ATV)***
	Raltegravir (RGV)*	Tipranavir (TPV)
	Elvitegravir (EVG)	**Darunavir (DRV)***
Tenofovir Disoproxil Fumarate (TDF)*	Bictegravir (BIC)	
Tenofovir Alafenamide (TAF)	Cabotegravir (CAB)	
Fusion inhibitors (FI)	**CCR5 entry inhibitor**	**Post attachment maturation inhibitor**
Enfuvirtide (T-20)	Maraviroc (MVC)	Ibalizumab (IBA)
***Available in the national programme**		

Clinical Pharmacology of Commonly Used ARV Drugs

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

The first effective class of ARV drugs discovered was the Nucleoside analogues, which act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new viruses. Nucleotide analogues work in the same way as nucleosides, but they have a non-peptidic chemical structure. The details of individual ARV drugs of this class are listed in Table 2.2.3.

Table 2.2.3: Commonly used NRTIs

Generic Name	Dose	Adverse effects
Tenofovir Disoproxil Fumarate (TDF)	300 mg once daily	Renal toxicity, bone demineralization
Zidovudine (AZT)	300 mg twice daily	Anaemia, neutropenia, bone marrow suppression, GI intolerance, headache, insomnia, myopathy, lactic acidosis, skin and nail hyperpigmentation
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily	Minimal toxicity, rash (though very rare)
Abacavir (ABC)	300 mg twice daily or 600 mg once daily	Hypersensitivity reaction in 3% to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath); rechallenging after reaction can be fatal

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) stop HIV production by binding onto the reverse transcriptase and preventing the conversion of RNA to DNA. These drugs are called 'non-nucleoside' inhibitors because, even though they work at the same stage as nucleoside analogues, as chain terminators, they inhibit the HIV reverse transcriptase enzyme by directly binding to it. The details of individual ARV of this class are shown in Table 2.2.4.

Table 2.2.4: Commonly used NNRTIs

Generic Name	Dose	Food-related advice	Adverse Effects
Efavirenz (EFV)	600 mg once daily (bedtime administration is suggested to decrease central nervous system side effects	Avoid taking after high-fat meals	Central nervous system symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than with NVP
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily	None	Hepatitis (usually within 12 weeks); sometimes, life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson's syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes should not be rechallenged.

Integrase Inhibitors (Integrase Strand-Transfer Inhibitor [INSTI])

Integrase inhibitors are a class of ART drugs designed to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell.

Since integration is a vital step in retroviral replication, blocking it can halt further replication of the virus.

Raltegravir (RAL): Raltegravir was the Integrase inhibitor approved for use in 2007. It is metabolized primarily through uridine diphosphate glucuronosyltransferase 1A1 and has a single inactive glucuronide metabolite.

It is not a substrate, inhibitor or inducer of cytochrome P450 enzymes and it exhibits low potential for drug–drug interactions. It is well tolerated; most reported adverse effects include nausea, headache, diarrhoea, fever, CPK elevation, muscle weakness and insomnia. The major toxicities are given in Table 2.2.5. Raltegravir was approved for use in both treatment-naive and treatment- experienced patients, and it had been primarily used for second- or third-line ART in the national ART programme.

Dolutegravir (DTG)

It was first approved for its usage by US FDA in 2013. Later, it was recommended by WHO in 2019 and NACO Technical Resource Group approved its usage since July 2020. NACO recommends Dolutegravir as the preferred drug for treatment of HIV-positive adults, adolescents and children (aged more than 6 years with bodyweight more than 20 kg) under the NACP. DTG is an orally bioavailable INSTI with activity against HIV type 1 and 2 (HIV-1/2 and both) infections. Upon oral administration, dolutegravir binds to the active site of integrase, an HIV enzyme that catalyses the transfer of viral genetic material into human chromosomes. This prevents integrase from binding to retroviral DNA, and blocks the strand transfer step, which is essential for the HIV replication cycle. This prevents HIV replication. Dolutegravir is currently the preferred drug in the first-line and also in second-line treatment regimens.

Table 2.2.5: Integrase Inhibitors used in National Programme

Generic Name	Dose	Adverse Effects
Dolutegravir (DTG) (Preferred INSTI in programme)	50 mg once daily 10 mg also available	• Insomnia: Patients with complaints of sleep disturbances need to be reviewed and to be managed accordingly. Sedatives should be added with appropriate consultation if that is affecting the daily routine of the patient. • Headache: If headache is persistent and affecting daily routine of activities, the PLHIV should be referred for expert opinion. • Dizziness • Tiredness • Allergic reactions • Weight gain: Weight gain is a known side effect and strict monitoring is required and information should be given to the PLHIV about the same.
Raltegravir (RAL)	400 mg twice daily	• Rhabdomyolysis, Myopathy, Myalgia, diarrhoea, fever, rash, Stevens-Johnson's syndrome, Toxic Epidermal Necrolysis, Hepatitis and Hepatic failure • Insomnia

Dolutegravir has drug interactions with the drugs listed in Table 2.2.6.

Table 2.2.6: Drug Interactions with Dolutegravir

Key Drug Interaction	Suggested Management
Amodiaquine	Use an alternative antimalarial agent
Carbamazepine	Use DTG twice daily or substitute with an alternative anticonvulsant agent
Phenytoin and phenobarbital	Use an alternative anticonvulsant agent
Dofetilide	Use an alternative antiarrhythmic agent
Metformin	Limit daily dose of metformin to 1000 mg when used with DTG and monitor glycaemic control
Polyvalent cation products containing Al, Ca, Fe, Mg and Zn (e.g., antacids, multivitamins and supplements)	Use DTG at least two hours before or at least six hours after supplements containing polyvalent cations
Rifampicin	Use DTG 50 mg twice daily or substitute with rifabutin

Protease Inhibitors

Protease inhibitors (PIs) work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. All PIs can produce GI intolerance, altered taste, abnormal liver function test and bone disorder and all have been associated with metabolic abnormalities, such as hyperglycaemia, insulin resistance and increase in triglycerides, cholesterol and body fat distribution (lipodystrophy). The details of individual ARVs of this class are shown in Table 2.2.7.

Table 2.2.7: Commonly used PIs

Generic Name	Dose	Adverse Effects
Atazanavir/ ritonavir (ATV/r)	300 mg Atazanavir + 100 mg Ritonavir once daily	Unconjugated hyperbilirubinemia, lipid abnormality, hyperglycaemia, fat maldistribution, nephrolithiasis, cholelithiasis, PR prolongation
Lopinavir/ ritonavir (LPV/r) Heat-stable tablets	200 mg Lopinavir/ 50 mg Ritonavir Fixed dose tablet 2 tablets twice daily	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance
Darunavir (DRV)	600 mg twice a day (when used with Ritonavir 100 mg twice daily)	Hepatotoxicity, skin rash (10%), diarrhoea, nausea, headache, hyperlipidaemia, serum transaminase elevation, hyperglycaemia
Ritonavir (RTV)	100 mg once or twice daily according to the PI to be boosted	Common: GI (diarrhoea, nausea, vomiting, abdominal pain (upper and lower); Rarely, neurological disturbances (including paraesthesia)

Co-administration of antitubercular and ARV agents: Available clinical data suggest that, for most individuals, Rifampicin-based regimens can be successfully combined with the NNRTI, Efavirenz. However, PIs are associated with important drug–drug interactions. Combinations are limited by the alterations in the activity of the hepatic cytochrome P450 (CYP) enzyme system, which may produce sub-

therapeutic plasma concentrations of ARV drugs. For example, PIs must often be avoided if the potent CYP inducer Rifampicin is co-administered. Alternatively, Rifabutin, which has efficacy similar to Rifampicin, can be used with appropriate dose reduction instead of Rifampicin. Rifampicin-based regimens also suppress the bioavailability of DTG. However, Rifampicin in FDC can be used with a DTG-based ART regimen with an extra dose of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) for the entire duration of ATT. For further details on ATT and ART drug interactions, refer to **Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis).**

Considerations Before Initiation of ART

All people with confirmed HIV infection should be referred to the ART centre for registration into HIV care, comprehensive clinical and laboratory evaluation to assess baseline status, treatment of pre-existing opportunistic infections, treatment preparedness, counselling and rapid ART initiation, preferably the same day unless contraindicated otherwise.

The following principles need to be kept in mind:

- The patient should be adequately prepared, and informed consent should be obtained from the patient or from the caregiver in case the patient is a minor, before initiating HIV care and ART. (For modified consent form, refer to National Operational Guidelines for ART Services, 2021.)
- Treatment should be started based on the person's informed decision and preparedness to initiate ART with information and understanding of the benefits of treatment, lifelong course of medication, issues related to adherence and positive prevention.
- A caregiver should be identified for each person to provide adequate support. Caregivers must be counselled and trained to support treatment adherence, follow-up visits and shared decision-making.
- All patients with clinical stages 3 and 4 and those with CD4 less than 350 cells/mm^3 need to be put on CPT. All patients to be screened for TB using the 4-symptom tool (current cough, fever, night sweats and weight loss) and those who do not have TB need to be started on Tuberculosis Preventive Therapy (TPT) / (Isoniazid Preventive Therapy) in addition to ART.
- **ART should not be started in the presence of an active OI.** In general, OIs should be treated or stabilized before commencing ART. Mycobacterium Avium Complex (MAC) and Progressive Multifocal Leukoencephalopathy (PML) are exceptions in which commencing ART may be the preferred treatment, especially when specific MAC therapy is not available. For details on starting ART in patients with HIV–TB co-infection, please refer to the management of HIV–TB in **Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis)**. Some clinical conditions, which may regress following the commencement of ART, include candidiasis and cryptosporidiosis. The following OIs and HIV-related illnesses (Table 2.2.8) need treatment or stabilization before commencing ART.

Table 2.2.8: Opportunistic infections and HIV-related conditions and ART initiation

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable
Tuberculosis	• ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count (except when signs and symptoms of meningitis are present). • Among PLHIV with TB meningitis, ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered for adjuvant treatment of TB meningitis.
PCP	Treat PCP first; start ART when PCP treatment is completed.
Invasive fungal diseases: **Oesophageal Candidiasis, Penicilliosis, Histoplasmosis**	• Start treatment for Oesophageal Candidiasis first; start ART as soon as the patient can swallow comfortably; • Treat Penicilliosis and Histoplasmosis first; start ART when patient is stabilized or OI treatment is completed.
Cryptococcal Meningitis	• For people with signs and symptoms of meningitis, ART should be delayed till the results of lumbar puncture are available or patient is stabilized with presumptive treatment. • Due to risk of life-threatening immune reconstitution inflammatory syndrome (IRIS), immediate ART initiation is contraindicated in cryptococcal meningitis. • Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment. Thus, ART should be initiated between 4–6 weeks after undergoing antifungal treatment.
Bacterial Pneumonia	Treat Pneumonia first; start ART when treatment is completed.
Malaria	Treat Malaria first; start ART when treatment is completed.
Acute diarrhoea which may reduce absorption of ART	Diagnose the cause and treat diarrhoea first; start ART when diarrhoea is stabilized or controlled.
Non-severe anaemia (Hb <9 g/dl)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia).
Skin conditions such as Pruritic Papular Eruption and Seborrhoeic Dermatitis, Psoriasis, HIV-related Exfoliative Dermatitis	Start ART (ART may resolve these problems).
Suspected MAC, Cryptosporidiosis and Microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus Retinitis	Start treatment for CMV urgently and start ART after 2 weeks of CMV treatment
Toxoplasmosis	Treat Toxoplasmosis first; start ART after 6 weeks of treatment and when patient is stabilized

Once the evaluation is completed, the following are the key questions pertaining to ART:

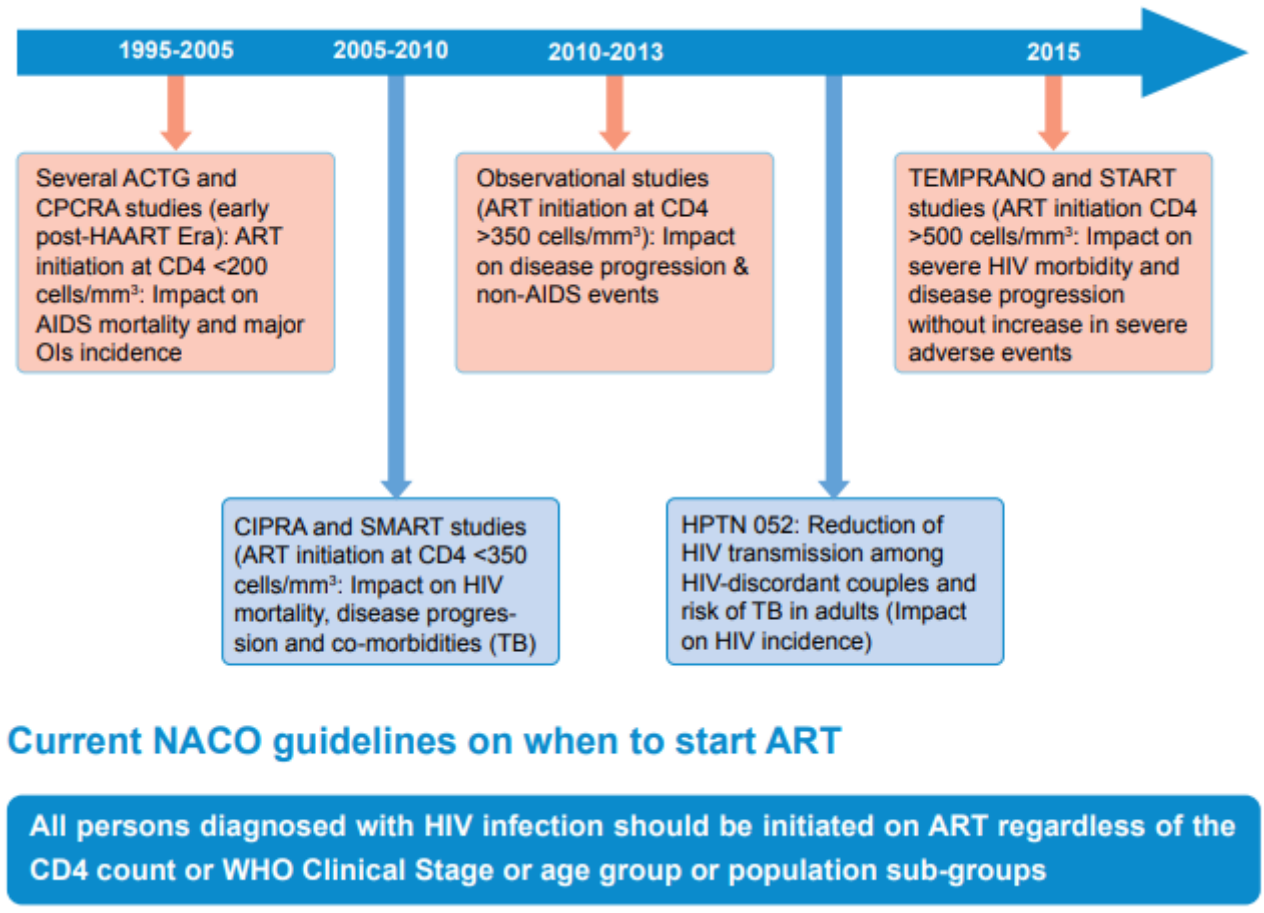
- When to start treatment?
- Which and how many agents to use? Choice of optimal regimen.
- How to monitor the therapy?
- How long to give therapy?
- When to change therapy and to what?
- Drug interactions involving ART

When to Start ART in Adults and Adolescents

In general, the clinical management of an HIV-infected patient revolves around optimizing the treatment regimen, reducing drug toxicity, reducing the pill burden and increasing adherence to the treatment.

The guidelines on when to start ART have evolved over the years towards early and rapid initiation of ART; CD4 count cut-off point for ART initiation moving from less than 200 cells/mm^3 in 2004 to less than 350 cells/mm^3 in 2011 and then to less than 500 cells/mm^3 in 2016. The current recommendation to **TREAT ALL**, regardless of the clinical stage or CD4 count is in the National Programme since 2017. These changes have been based on the evidence from various randomized clinical trials (RCT) and large observational cohorts, which have revealed that with early ART initiation, there is a significant delay in progression to AIDS and reduction in the incidence of TB. These studies are summarized in Figure 2.2.2.

Figure 2.2.2: Evolution of CD4 cut-offs for ART initiation over time



Ensuring good adherence to treatment is imperative for the success of the treatment as well as for the

prevention of drug resistance. To achieve this, counselling must start from the first contact of the patient with the clinical team. Counselling should include preparing the patient for treatment and providing psychosocial support through an identified caregiver/guardian/treatment support and support networks. All patients should undergo two to three counselling sessions (preparedness counselling) before the initiation of ART. The period of waiting for investigations and their results should be utilized for counselling, Cotrimoxazole prophylaxis, TPT in eligible patients, and treatment preparation. All efforts should be made to trace the patients who have missed their visits or are lost to follow-up to initiate ART in all PLHIV registered at the ART centres. NGOs and positive network linkages should be established by each ART centre for its respective locality.

What to Start: Antiretroviral Therapy Regimens

Fixed-dose combinations (FDCs) of ARVs are preferred because they are easy to prescribe and easy for patients to take, thereby facilitating improved and desirable treatment adherence. This is essential for PLHIV as the treatment is life-long and we need to minimize the chance of developing drug-resistant mutants in their body and the resultant treatment failure. Further, FDCs have distinct advantages in drug procurement and distribution, essentially the drug stock management itself. National experience has shown that regimens with FDCs are more acceptable, well tolerated and adequately complied with.

Recommended Choice of First-Line Regimen

In consideration of the WHO guidelines and based on recommendations of NACO Technical Resource Group, it has been decided to include DTG-containing regimens as the preferred first- line treatment for HIV-positive adults, adolescents and children (weighing more than 20 kg/age more than 6 years) under the NACP since July 2020.

Dolutegravir is known to have the following features:

- High genetic barrier: It is highly potent and has high genetic barrier. That is why it is an ideal drug.
- Rapid viral suppression: It helps in achieving rapid viral suppression. It has been found to reduce the viral copies to <50 copies/ml within 4 weeks and this helps reduce the chances of transmission.
- Fewer toxicities and side effects: DTG-based regimens are expected to have fewer side effects as compared to NNRTI-based regimens. These have lesser allergic reactions and chances of neuropsychiatric events compared to NNRTI-based regimens.
- Minimal drug interactions: DTG has minimal drug interactions with concomitant medications PLHIV might be on. Common drug interactions are listed in Table 2.2.6.
- Effective against HIV-2: DTG-based regimens can be prescribed for PLHIV infected with HIV-2 or combined HIV-1 and HIV-2. Prior to the availability of DTG in the programme, those infected with HIV-2 were being initiated with two NRTIs plus boosted PI regimen. With DTG in the programme, this will further bring harmonization across patient populations.
- No need for substitution of DTG-based ART regimen in PLHIV if co-infected with TB or HBV or HCV.

The regimens described in this chapter are for HIV-1, HIV-2 and HIV-1 & 2 infected individuals unless specified otherwise.

The basic principle for **first-line ART** for treatment-naive adult and adolescent patients is to use a triple drug combination from two different classes of ARVs.

The first-line ART essentially comprises of a NRTI backbone, preferably Non-Thymidine (Tenofovir plus Lamivudine) and one INSTI, preferably DTG. Based on the evidence supporting better efficacy and fewer

side effects, the **preferred first-line ART regimen for all PLHIV with age >10 years and weight >30kg is as follows:**

Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Dolutegravir (DTG 50 mg) regimen (TLD) as FDC in a single pill once a day (at a fixed time every day as per patient's convenience)

This regimen has the advantage of harmonization in the treatment of all adults, adolescents, pregnant women including those with HIV-1, HIV-2, HIV-1 & 2, women exposed to single dose nevirapine in the past and those co-infected with TB or Hepatitis.

It is a simple, potent and well-tolerated regimen that offers the advantage of a decentralized service delivery and monitoring. It also simplifies the supply chain and minimizes monitoring requirements.

In cases where the preferred first-line ARV regimen of TDF+3TC+DTG cannot be used, the alternative regimens are mentioned in Table 2.2.9.

Table 2.2.9: Alternate first-line ART in adults and adolescents

Condition	Alternate First-line Regimen
PLHIV with body weight <30 kg	ABC 600 mg + Lamivudine 300mg, one tablet + DTG (50 mg) once daily in the morning or any fixed time every day as per patient's convenience
All patients with high (above ULN for laboratory) serum creatinine values (Calculate Creatinine clearance*)	ABC 600 mg OD, Lamivudine (as per creatinine clearance**) and DTG 50 mg once daily in the morning or any fixed time every day as per patient's convenience
PLHIV on Rifampicin-containing ATT regimen	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) – FDC one tablet once daily (in the morning or any fixed time every day as per patient's convenience) **+** Additional dose of DTG 50 mg to be provided (12 hours after taking their regular dose) until 2 weeks after completion of ATT
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling* **	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600mg) If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]

*For all patients with high serum creatinine values (above ULN for laboratory), calculate creatinine clearance.

**Lamivudine, along with Abacavir, may be used in full dose if creatinine clearance is more than 30 ml per minute, with patient being closely monitored.

***Women of childbearing potential receive full information and medical guidance that is appropriate to their situation and are supported in making an informed decision.

General Guidance

- A single pill of TLD should be taken preferably at bedtime, and instances where additional dose of DTG is indicated should be taken preferably in the morning.
- Patients with severe Diabetes and Hypertension should be monitored more closely for TDF toxicity.

- Patients starting on DTG should be monitored for blood glucose (six monthly) and weight gain (on monthly visits). Appropriate physical activity should be advised to prevent weight gain.
- Guidance on laboratory investigations is mentioned in the laboratory investigations (Table 2.2.11).

Considerations for ART in Adolescents

According to WHO, adolescence is the period between 10 and 19 years of age. During this period, healthy HIV-infected adolescents pass through well-described stages of physical, psychological and sexual maturation for which appropriate support and care are required.

An estimated 1.74 million adolescents (10–19 years old) were living with HIV globally in 2019. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second leading cause of death among adolescents worldwide with 34,000 (23,000–50,000) estimated number of adolescents dying of AIDS-related causes in 2019 (UNAIDS, 2019).

Adolescence is marked by rapid physical, neuro-developmental, emotional and social changes. Adolescents have significantly lesser access to ART and coverage of ART than adults, high risk of loss to follow-up, suboptimal adherence and special requirements for comprehensive care, including psychosocial support and sexual and reproductive healthcare. Adolescents also face significant barriers to the access of essential health and support services, especially because of policy and legal barriers related to the age of consent.

Perinatally infected adolescents are more likely to experience chronic diseases and neurodevelopmental growth and pubertal delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

Physicians giving care and treatment to such adolescents should consider the following issues:

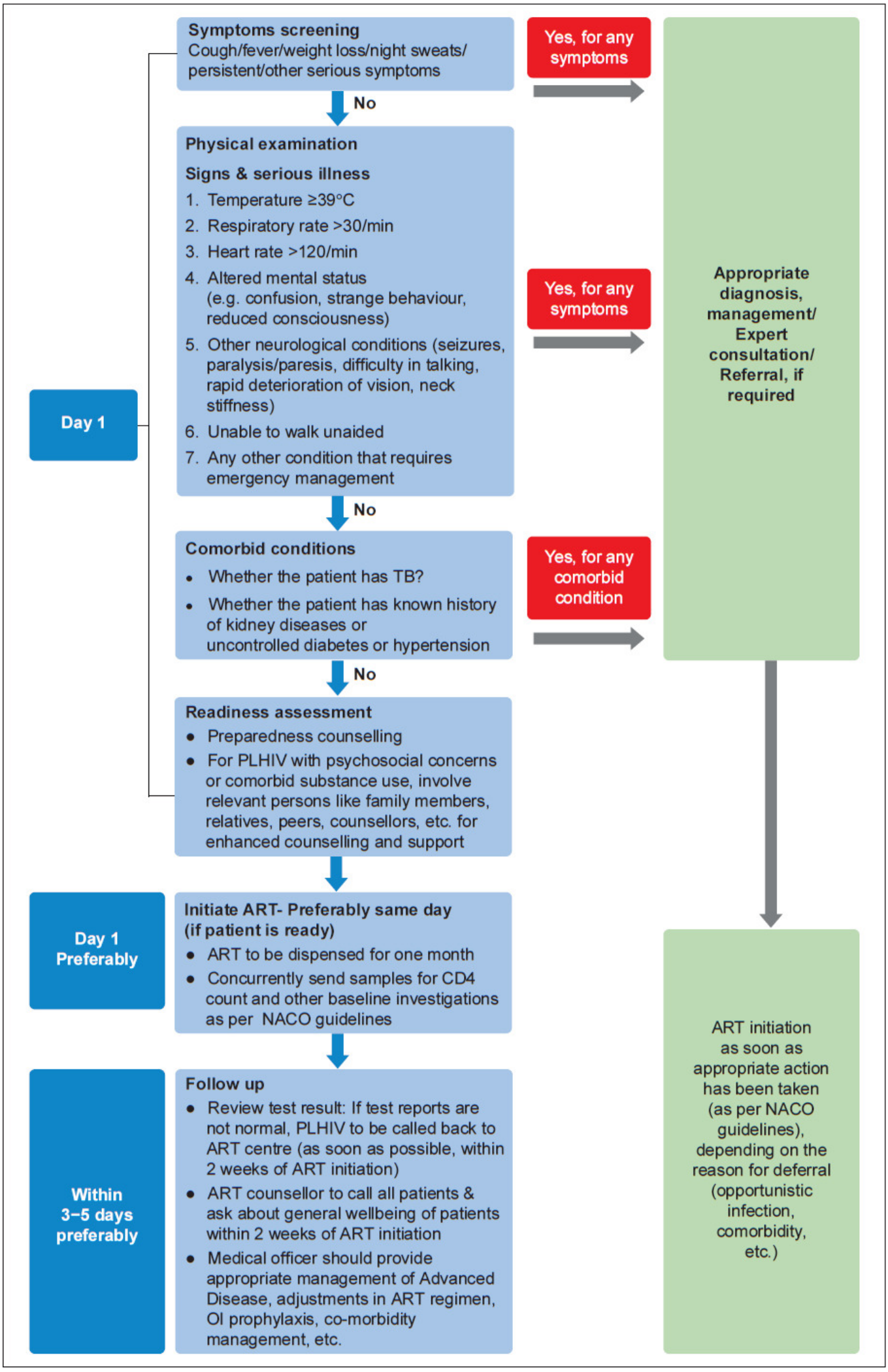
- Disclosure
- Developmental delays
- Transition difficulties from childhood to adulthood that may influence choice of appropriate ART regimens
- Adherence issues
- Psychosocial support needs
- Physical and sexual issues

Rapid ART Initiation for Newly Diagnosed PLHIV at ART Centre

The introduction of the ‘Treat All’ recommendation supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. Rapid ART initiation is defined as **“ART initiation within seven days from the day of HIV diagnosis”**. Following a confirmed HIV diagnosis and clinical assessment, same-day /rapid ART initiation should be offered to all PLHIV adequately prepared and ready for initiation. However, if an active OI is present, ART initiation may be deferred as required.

PLHIV should be assessed for readiness for ART initiation using the algorithm provided in Figure 2.2.3 (with concurrent sample collection for CD4 testing and baseline investigation). This algorithm focusses on clinical screening of PLHIV for potential presence of common OIs/advanced HIV disease/comorbid conditions:

Figure 2.2.3: Rapid ART initiation algorithm in PLHIV


Symptoms screening
Cough/fever/weight loss/night sweats/ persistent/other serious symptoms
Yes, for any symptoms
No
Physical examination
Signs & serious illness
1. Temperature ≥39°C
2. Respiratory rate >30/min
3. Heart rate >120/min
4. Altered mental status (e.g. confusion, strange behaviour, reduced consciousness)
5. Other neurological conditions (seizures, paralysis/paresis, difficulty in talking, rapid deterioration of vision, neck stiffness)
6. Unable to walk unaided
7. Any other condition that requires emergency management
Yes, for any symptoms
Appropriate diagnosis, management/ Expert consultation/ Referral, if required
Day 1
No
Comorbid conditions
• Whether the patient has TB?
• Whether the patient has known history of kidney diseases or uncontrolled diabetes or hypertension
Yes, for any comorbid condition
No
Readiness assessment
• Preparedness counselling
• For PLHIV with psychosocial concerns or comorbid substance use, involve relevant persons like family members, relatives, peers, counsellors, etc. for enhanced counselling and support
Day 1 Preferably
Initiate ART- Preferably same day (if patient is ready)
• ART to be dispensed for one month
• Concurrently send samples for CD4 count and other baseline investigations as per NACO guidelines
Within 3–5 days preferably
Follow up
• Review test result: If test reports are not normal, PLHIV to be called back to ART centre (as soon as possible, within 2 weeks of ART initiation)
• ART counsellor to call all patients & ask about general wellbeing of patients within 2 weeks of ART initiation
• Medical officer should provide appropriate management of Advanced Disease, adjustments in ART regimen, OI prophylaxis, co-morbidity management, etc.
ART initiation as soon as appropriate action has been taken (as per NACO guidelines), depending on the reason for deferral (opportunistic infection, comorbidity, etc.)

- PLHIV who do not have any such conditions can be fast tracked for ART initiation giving them the benefits of timely ART initiation, such as reduction in incident TB and other OIs, achieving quick viral load suppression, prevention of transmission and better health outcomes. Additionally, it will also reduce travel inconvenience and financial burden for PLHIV.
- PLHIV who have any such symptoms would require further evaluation for diagnosis and management of common OIs/advanced HIV disease/comorbid conditions before ART initiation. For details of management of advanced HIV disease, refer to **Chapter 2.3 (Advanced Disease Management in PLHIV).**

Monitoring of Patients on ART

Follow-up and monitoring are essential in patients initiated on ART to track clinical progress, monitor well-being and to identify adverse drug reactions and toxicities.

ART monitoring includes clinical monitoring and laboratory monitoring. Clinical monitoring includes monitoring of adherence to ART as well. The client should be monitored every month for clinical progress, side effects of the ARVs and treatment adherence. Clinical and laboratory evaluations are carried out at specified intervals for patients on ART.

A combination of clinical and laboratory monitoring is to be carried out in all PLHIV after initiation of ART as depicted in Table 2.2.10.

Table 2.2.10: Monitoring and follow-up schedule for patients on ART

Monitoring Tool	When to Monitor
Body weight Height / length in children	Every visit
Treatment adherence	Every visit
Clinical monitoring and T-staging	Every visit
4-symptom TB screening	Every visit
Screening for common NCD; Hypertension, Diabetes mellitus	Every 6 months or symptom directed
Laboratory evaluation based on ART regimen	Every 6 months or symptom directed
CD4 Count	CD4 must be done every 6 months*
Viral load	At 6 months, 12 months and then every 12 months**

***CD4 Count:**

1. As routine virological monitoring is available, CD4 testing should be done every 6 months and can be discontinued in PLHIV (except those with HIV-2 infection) when CD4 count reaches greater than 350 cells/mm^3 and viral load is less than 1000 copies/ml (when both tests are conducted at the same time).
2. CD4 monitoring should be restarted for any patient if
   a. the patient has been switched due to treatment failure, that is, virologic failure (Plasma Viral Load ≥1000 copies/ml) or
   b. when deemed necessary for clinical management by the clinician at any point in time

**For patients on second/third-line ART, Plasma Viral Load testing to be done every 6 months

The various monitoring indicators are listed below:

Clinical monitoring

- Monthly clinical evaluation
- Body weight, overall well-being, any new symptoms/signs, 4-symptom screening for TB at every visit
- Monthly treatment adherence evaluation, pill count, self-reported adherence
- Adherence to ART must be assessed at each visit and adherence must be reinforced through counselling at each visit.
- Adverse reactions of ART/OI drugs
- Drug–drug interactions, look for all concomitant drug use (prescribed and over the counter)
- Look for IRIS

Immunological monitoring

- CD4 testing should be done every 6 months.
- As routine virological monitoring is available, CD4 testing should be done every 6 months and can be discontinued in PLHIV (except those with HIV-2 infection) when CD4 count reaches greater than 350 cells/mm3 and plasma viral load is less than 1000 copies/ml (when both tests are conducted at the same time).

Virological monitoring: At 6 months and 12 months after ART initiation and then every 12 months

Interpretation of Plasma Viral Load testing results

- PLHIV with plasma viral load report <1000 copies/ml should continue the same ART regimen. Next viral load testing should be done as per guidelines.
- PLHIV with plasma viral load report ≥1000 copies/ml should undergo step-up enhanced adherence counselling for three months. ART centre counsellor should provide intensive support to improve adherence.
- Repeat viral load testing should be done once treatment adherence is > 95% for three consecutive months.

    If repeat plasma viral load report is <1000 copies/ml, patient should be continued on same ART regimen.
    If repeat plasma viral load report is ≥1000 copies/ml, patient should be referred electronically to SACEP (e-SACEP) for further management.
- In case of PLHIV with high viral load, declining CD4 counts and poor clinical conditions, ART Medical Officer may refer the patient to SACEP, even based on a single viral load report, for further management. For more details, including viral load algorithm, please refer to **Chapter 2.7 (ART Treatment Failure in Adults and Adolescents: When and What to Switch).**

Laboratory Monitoring

The laboratory monitoring of PLHIV on ART is also very important. Regular monitoring of the patient's laboratory parameters is crucial to identify ARV-related toxicities, inter-current illnesses, drug–drug interactions and other metabolic abnormalities. The frequency of monitoring and the parameters to be monitored depend on the components of the regimen. The summary of the laboratory monitoring recommended under the programme is presented in Table 2.2.11. Additional laboratory tests outside this schedule may be performed as clinically indicated by the ART medical officer.

Table 2.2.11: Laboratory monitoring of individual ARV drugs

For all patients on ART, we need to do CD4, Hb, TLC, DLC, ALT (SGPT) and serum creatinine once every six months								
Tests for monitoring patients on ART (Follow-up tests): Drug-specific tests frequency as below								
Monitoring ARV drug in regimen	Monitoring test	Baseline	15th Day	First month	Third month	Sixth month	Then every 6 months	At 12 months
On Tenofovir-based ART	Serum creatinine	Yes	–	–	–	Yes	Yes	–
	Urine for protein	Yes	–	–	–	Yes	Yes	–
On Zidovudine-based ART	CBC	Yes	Yes	Yes	Yes	Yes	Yes	–
Efavirenz-containing ART	Lipid profile	Yes	–	–	–	–	–	Yes
Atazanavir-containing ART	LFT Lipid profile	Yes	–	–	–	Yes	Yes	–
Lopinavir-containing ART	Lipid profile & Blood sugar	Yes	–	–	–	Yes	Yes	–
Dolutegravir- containing ART	ALT (SGPT) & blood sugar	Yes				Yes	Yes	–

The prevalence of lipid abnormalities is significantly frequent in patients on ART, particularly if they are on Stavudine, Efavirenz or boosted PIs. In case of these patients and those with significant risk factors for coronary artery disease, a fasting lipid profile should be done at 6 months or earlier as required. Otherwise, yearly evaluations suffice. This is expected to decrease since DTG is not known to have significant lipid abnormalities.

Fasting blood sugar is recommended as part of the baseline screening of all patients to be started on ART, as currently one of the major causes of morbidity in India is diabetes mellitus.

More frequent visits or additional laboratory monitoring may be required if the patient develops any symptoms or side effects of the ARVs or experiences difficulties in adherence to ARVs due to any reason, including clinically indicated reasons as per the discretion of the medical officer.

Once the patient has stabilized and CD4 starts improving, the patient does not have any OI or adverse events and has been adherent to ART for at least 6 months, the frequency of visits can be reduced to once in 3 months.

What to Expect in the First Six Months of Therapy?

Taking ART is a lifelong commitment, and the first 6 months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART. However, certain OIs and/or IRIS and/or early adverse drug reactions such as drug hypersensitivity may develop, especially in the first 3 months of treatment. ART significantly decreases the overall mortality, but death rates are highest in the first 3 months of ART initiation in PLHIV with advanced HIV disease. As the immune system recovers, there may be exacerbation of previously sub-clinical coexisting infections (e.g., TB), resulting in an apparent worsening of the disease. It is to be remembered that this is not due to failure of therapy, but due to the success of the therapy and resulting immune reconstitution. Complications are most common during the first few weeks of treatment, especially among people starting ART with advanced HIV disease, those with severe immunodeficiency and existing co-infections and/or comorbidities, very low haemoglobin, low BMI, very low CD4 counts or those who are severely

malnourished. Poor adherence during this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

CD4 recovery

In most adults and children, CD4 cell counts rise by 40 to 60 cells/year when ART is initiated, and immune recovery starts. Generally, this increase occurs during the first year of treatment, achieves a plateau and then continues to rise further during the second year. However, severe immunosuppression may persist in some individuals who do not experience a significant rise in CD4 cell count with treatment, especially those with a very low CD4 cell count at the time of initiation of ART. Failure to achieve some CD4 recovery should alert the healthcare provider to potential adherence problems or primary non-response to ART and consideration should be given to continue prophylaxis for OIs such as CPT.

Several other factors can influence CD4 cell counts apart from laboratory-related variables. These include the following:

- Concurrent infections, specifically hepatitis;
- Leukopenia of varying aetiology, especially caused by ART itself and steroids or other immunosuppressive therapies;
- Pregnancy can also lead to lower values.
- Diurnal variation occurs; CD4 cells are lower at noon, and highest in the evening around 8 pm.
- Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Several factors can influence the extent of immune reconstitution during ART. The degree of viral suppression is crucial: the lower the viral load, the more pronounced the effect. The absolute increase in CD4 count is higher if CD4 counts were high at the start of ART. Presence of naive CD4 T-cells at the time of ART initiation is a particularly important factor for long-term immune reconstitution/recovery. Hence CD4 response may vary widely, and we need to focus on viral suppression.

Patients with declining CD4 but undetectable plasma viral load should be evaluated for recent viral infection, immunization and CD4 variability; if all these have been ruled out, one may consider the possibility of HIV-2 or HIV-1 and HIV-2 co-infection.

Plasma Viral Load

Within the first few weeks of therapy, the plasma viral load should start decreasing and after 6 months, a plasma viral load test should be done to evaluate the response to ARVs. Plasma viral load testing should be done at 6 months after initiation of ART, again at 12 months and once the viral load is suppressed, every 12 months. Most people will achieve viral suppression at 24 weeks of initiation of treatment.

Virological suppression in the context of the national programme means a plasma viral load of less than 1000 copies/ml after at least 6 months on ART.

Stable Adults and adolescents (≥10 years)

Definition

PLHIV (Adult/Adolescent) shall be termed ‘stable’ if they fulfil all the following criteria:

- On ART for at least 6 months;
- No adverse effects of ART that require regular monitoring;
- No current illness/OI/medical condition that requires management or regular monitoring;

- Suppressed plasma viral load (in the absence of viral load monitoring, rising CD4 cell counts or CD4 cell counts exceeding 200 cells/mm3 and adherence ≥ 95% consecutively over the last 3 months).

Applicability of 'Stable' definition

- The definition of stable patient shall be applicable for patients on any ART regimen (first, second and third line) after being on that line of regimen for at least 6 months.
- This definition shall be applicable across various differentiated care models like multi-month dispensation (MMD), decentralized and community-based dispensations (such as link ART centre [LAC], Community ART Refill Groups [CARG]).
- Benefits of MMD may also be extended to patients availing services at LAC and LAC plus.
- PLHIV who have completed 3 months on TPT could also be provided benefits of service delivery models for stable PLHIV, if fulfilling above criteria.

They should be provided after proper counselling on adherence and side effects (for more details refer to NACO Operational Guidelines Guidelines for ART Services 2021).

Early ARV toxicity

First-line drug toxicities fall into two categories. Early toxicity usually presents in the first few weeks to months of ART initiation. Early and potentially severe toxicities such as skin rashes, neuropsychiatric side effects to NNRTIs (EFV and NVP) normally occur within the first few weeks of therapy, which are expected to reduce further as NACO is phasing in DTG-based regimens. AZT-related anaemia and GI side effects like severe vomiting and occasional diarrhoea typically present in the first few months of therapy whereas some toxicities may occur years after initiation of treatment like TDF-induced toxicities. For further reading, refer to **Chapter 2.6 (First-line ART in Adults and Adolescents: Management of ARV Toxicities).**

Mortality on ART

Although ART significantly decreases mortality, the risk of death is higher in the first 6 months than during the subsequent period on therapy, particularly when patients start ART with clinical stage 4 events, such as diagnosed with TB meningitis at baseline, low BMI during follow-up, severe immunosuppression and/or very low CD4 counts.

Immune Reconstitution Inflammatory Syndrome

Definition

"The worsening of signs and symptoms due to known infections" or "the development of disease due to occult infections that result from an inflammatory response by a reinvigorated immune system following the initiation of ART."

This is a condition that can occur shortly after a person starts ART for the first time. It is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. The suppression of CD4 T-lymphocyte cells by HIV causes a decrease in the body's normal response to certain infections. ART partially restores the immune defects caused by chronic HIV infection, including the restoration of protective pathogen- specific immune responses. If the CD4 count rapidly increases (due to effective treatment of HIV), a sudden increase in the inflammatory response produces non-specific symptoms such as fever and, in some cases, a paradoxical worsening of pre-existing symptoms of infective or non-infective conditions, e.g., TB, MAC or CMV. In general, people

with profound immunosuppression before starting HIV therapy are the most at risk for IRIS. It occurs in 10% to 30% of patients initiating ART, usually within the first 4–8 weeks. However, late IRIS can be observed up to 6 months of initiating ART. Some risk factors for IRIS are as follows:

- People with CD4 counts below 100 cells/mm^3 before starting therapy (lower CD4 counts at ART initiation) or lower CD4:CD8 ratio at ART initiation;
- People with rapid initial fall in HIV viral load due to therapy;
- People with diagnosis of another infection before starting therapy; the closer the appearance or diagnosis is to starting therapy, the higher the risk (shorter interval between OI therapy initiation and ART initiation);
- Severity of TB disease, especially high pathogen burden, and short interval between initiation of ATT and ART;
- Male sex;
- Younger age;
- Higher HIV RNA at ART initiation;
- Genetic susceptibility.

Working definition of IRIS in Programme Conditions

"The worsening of signs and symptoms due to known infections, or the development of disease due to occult infections within 6 weeks to 6 months after initiating ART, with an increase in CD4 count."

The various categories of IRIS along with the possible antigen are mentioned in Table 2.2.12.

Table 2.2.12: Categories of IRIS

Categories	Antigen Target
Infection – unmasking	Viable replicating infective antigen
Infection – paradoxical	Dead or dying organisms
Auto immune	Host
Malignancies	Possible tumour or associated pathogen

Source: Devesh J. Dhasmana et al[1]

Unmasking IRIS refers to, for e.g., the initial clinical expression of active TB occurring soon after ART is started. **Paradoxical IRIS** refers to, for e.g., the worsening of TB, clinical manifestations after the initiation of ART in patients, who are receiving anti-TB treatment. IRIS should be considered only when the presentation cannot be explained by a new infection, expected course of a known infection or drug toxicity. IRIS should be diagnosed by excluding the following:

- Active OI
- Treatment failure
- Side effect from ARV
- Failure to Antimicrobial Therapy

The clinical spectrum of IRIS is diverse in terms of early or delayed onset, atypical symptoms, generalized or localized infection, variation in severity and it may be infectious or non-infectious.

The following can help in the diagnosis of IRIS:

- Temporal association between the initiation of ART and the development of new clinical event (mostly within 3 months);

    Typically, IRIS occurs within 2–12 weeks of the initiation of ART, although it may present later (usually between 6 weeks to 6 months).
    The incidence of IRIS is estimated to be 10% among all patients in whom ART has been initiated and up to 25% among those initiated on ART having CD4 cell count of below 50 cells/mm^3.
- Unusual clinical manifestations in patients responding to ART include the following:

    Unexpected, localized disease, e.g., lymph nodes (appearance or enlargement and/or suppuration), or involving liver or spleen or development of pleural effusion;
    Exaggerated inflammatory reaction, e.g., severe fever, with exclusion of other causes;
    Painful lesions;
    Atypical inflammatory response in affected tissues, e.g., granulomas, suppuration, necrosis;
    Perivascular lymphocytic inflammatory cell infiltrate;
    Progression of organ dysfunction or enlargement of pre-existing lesions;
    Development or enlargement of cerebral space-occupying lesions after treatment, for e.g., cerebral cryptococcosis or toxoplasmosis;
    Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary TB or PCP;
    Onset or worsening of uveitis/vitritis after the resolution of CMV retinitis;
    Fever and cytopaenia after treatment for disseminated MAC.

The most serious and life-threatening forms of paradoxical IRIS are TB and Cryptococcosis. BCG vaccine–associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is a routine.

The most important steps to reduce the development of IRIS include earlier HIV diagnosis and initiation of ART before decline of CD4 below 200 cells/mm3; improved screening for OIs before ART, especially TB, Cryptococcus, CMV and optimal management of OIs before initiating ART. Timing of ART in people with OIs requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

IRIS Management

IRIS is generally self-limiting and interruption of ART is rarely indicated, but people may need to be reassured in the face of protracted symptoms to prevent discontinuation of ART or poor adherence to ART.

- Mild form (with ongoing ART)

    Observation
- Localized IRIS (with ongoing ART)

    Local therapy such as minor surgical procedures for lymph node abscesses (drainage)
    As per system involvement e.g., neurological, respiratory
- Most of the situations (with ongoing ART)

    Recognition and management of ongoing infections
    Antimicrobial therapy is required to reduce and to eliminate the triggering pathogen (antigenic load)
- Reconstituting immune reaction to non-replicating antigens

    No antimicrobial therapy is required

Short-term therapy with corticosteroids or non-steroidal anti-inflammatory drugs can be given to reduce

the inflammation – Prednisolone at 1.5 mg/kg orally for two weeks followed by 0.75 mg/kg orally for two weeks and then tapered off.

Temporary cessation of ART must be considered, only if potentially life-threatening forms of IRIS develop.

2.3 Advanced Disease Management in PLHIV

Introduction

India has an estimated 25.44 lakhs (21.68–30.38) PLHIV with a national HIV prevalence of 0.20% in the adult population.[1] Recent estimates suggest that about 30% to 40% of PLHIV starting ART in low- and middle-income settings have a CD4 cell count of less than 200 cells/mm^3, and 20% have a CD4 cell count of less than 100 cells/mm^3; in some settings, up to half of people present to care with advanced HIV disease.

Overall, the estimated adult HIV prevalence (15–49 years) has been declining in India since the epidemic's peak in 2000 when it was estimated at 0.56%, decreasing to 0.32% in 2010, and further reducing to an estimated 0.20% in 2023. Similar consistent declines were noted among both males and females at the national level. AIDS related death (ARD) per 1,00,000 population was estimated to have declined from 25.75 in 2005 to 14.34 in 2010 and reduced further to an estimated 2..61 in 2023.[1] These declines were largely due to the rapid scale-up of ART.

However, it is estimated that at least a third of patients present late to HIV care with advanced immunosuppression, and the HIV-associated morbidity and mortality remain high in this group. Even after initiating ART, people with advanced immunosuppression or CD4 <200 cells/mm^3 at baseline have a 50% higher rate of mortality as compared to people with a CD4 count > 200 cells/ mm^3 at the time of ART initiation.[2,3] Mortality in this group is mostly related to complications from HIV-associated OIs. In line with the WHO Guidelines, NACO's Technical Resource Group on ART recommended providing tailored differentiated care package to meet the unique needs of different patient populations.

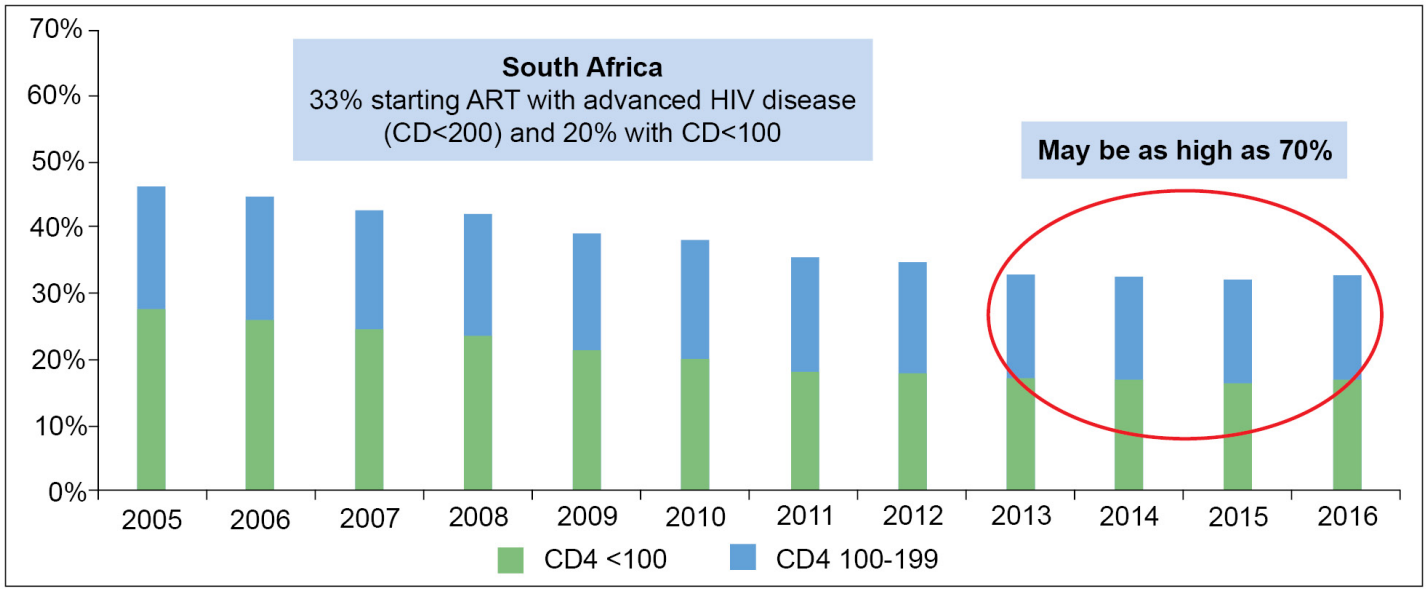
Advanced HIV Disease Definition

Burden of Advanced HIV Disease

Advanced HIV disease has been defined as, for adults, adolescents and children of 5 years or more of age, living with HIV, as having a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 disease. Measuring CD4 count at baseline remains essential as relying on clinical stage alone risks missing substantial number of PLHIV with severe immunosuppression. People presenting with advanced HIV disease at the time of registration at the ART centre are at high risk of death, even after ART is started, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count <100 cells/mm^3.

Data from IeDEA-COHERE[4] of 9,51,855 adults from 55 countries indicates that 37% of patients were started on ART at CD4 less than 200 cells/mm^3 (Figure 2.3.1).

Figure 2.3.1: Globally advanced disease is a challenge



In India, the trend of median baseline CD4 cell count at registration depicts upward trend (Figure 2.3.2). However, **around 35% of PLHIV still present to care with advanced disease based on CD4 criteria of less than 200 cells/mm^3** (Table 2.3.1). CD4 count at baseline remains essential as relying on clinical stage alone risks missing substantial number of PLHIV with severe immunosuppression.

Figure 2.3.2: Trend of median CD4 count at the time of registration at the ART Centre, over the years (NACO, IMS)

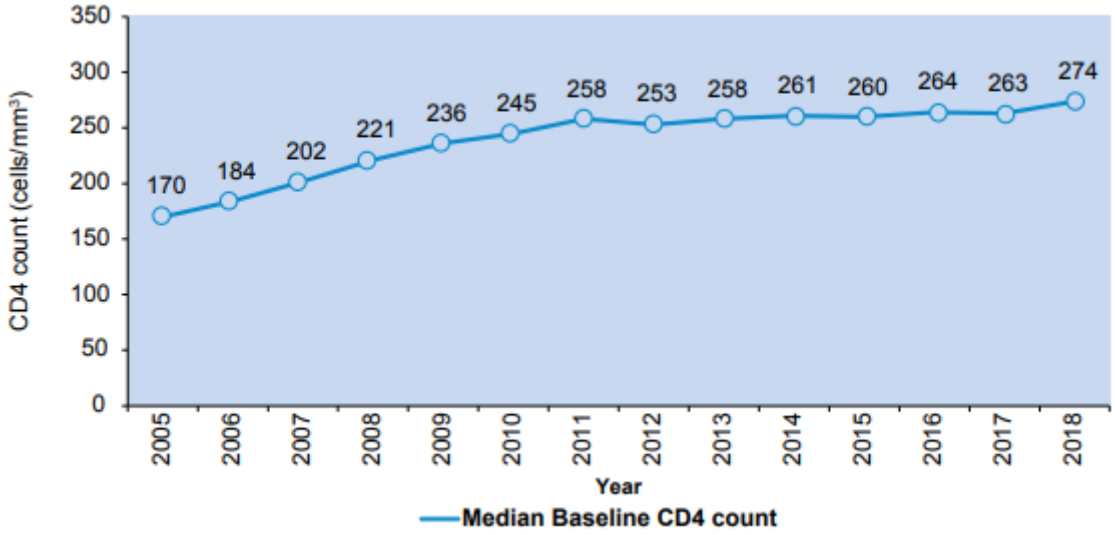


Table 2.3.1: Baseline CD4 count distribution in 2019 (NACO, IMS)

Baseline CD4 Count Range	Patients (%)
Patients with CD4 count <200 cells/mm^3	35
Patients with CD4 count between 200 and 349 cells/mm^3	26
Patients with CD4 count between 350 and 499 cells/mm^3	18
Patients with CD4 count ≥ 500 cells/mm^3	21

Mortality in Advanced Disease

Advanced HIV disease is associated with increased risk of OIs, IRIS, incomplete immune reconstitution, increased risk of AIDS-related and non-AIDS-related comorbidities and more frequent monitoring needs leading to significant economic burden to PLHIV as well as the health system. Leading causes of mortality among adults with advanced HIV disease, globally, include tuberculosis, severe bacterial infections, cryptococcal meningitis, toxoplasmosis, and PCP. Among children, TB, severe bacterial infections, PCP, diarrhoeal diseases, malnutrition and wasting are the leading causes of death.

In India, OIs remain the most common cause of death with TB being the most common OI. In a study published in 2011 by ICMR-NARI,5 causes of death were ascertainable in 49 (59%) out of 83 total deaths. Of these, 24 (49%) patients had pulmonary or extra-pulmonary TB prior to death and their baseline median CD4 count was 67 cells/mm^3 (IQR: 42-107); 23 (47%) patients had causes unrelated to TB (toxoplasmosis, cryptococcal meningitis, septicaemia, PCP, acute gastroenteritis, disseminated intravascular coagulation, myocardial infarction, lactic acidosis, PML and hepatorenal syndrome and their baseline median CD4 count was 96 cells/mm^3 (IQR: 50-231). TB and bacterial infections were reported as significant contributors in another study from Bangalore (2015).[6]

A systematic review[7] of 60 observational studies indicate a pooled 6.4% (95% CI 5.7–7.2%; 55 studies) and 2.0% (95% CI 1.2–2.7%; 21 studies) prevalence of cryptococcal antigen among PLHIV with a CD4 cell count ≤ 100 cells/mm^3 and 100–200 cells/mm^3, respectively. The findings of this review support the recommendations to screen all PLHIV who have a CD4 count ≤ 100 cells/mm3 for cryptococcal antigen (CrAg) and suggest that screening may be considered at CD4 cell count ≤ 200 cells/mm^3.

In a prospective study,[8] Guha et al reported 12.56% CrAg positivity among 390 ART-naive HIV-seropositive PLHIV with CD4 count ≤100 cells/mm^3 screened for CrAg, and it was found that this was comparatively higher in those with CD4 ≤50 cells/mm^3.

Another study from a public sector hospital in Pune indicated high prevalence of CrAg positivity among asymptomatic advanced HIV patients and 8% CrAg positivity among HIV-infected adults presenting with CD4 count <100 cells/mm^3. One-fifth of those with CrAg positivity had laboratory□confirmed cryptococcal meningitis and a high 6-month all-cause fatality rate was among those CrAg positive.[9]

Package of Advanced HIV Disease Management

This package of differentiated care includes key evidence-based interventions such as prophylaxis, diagnosis using point-of-care testing (POCT) and treatment to reduce morbidity and mortality among these patients with advanced disease. The benefits of these interventions have been well demonstrated in the REALITY[10] and REMSTAR[11] trials. The package of interventions as recommended by WHO includes the following minimum interventions:

- Screening for active TB with NAAT and TB-LAM assay (when indicated, if available) and prompt initiation of anti-TB treatment or TPT, as indicated;
- Systematic screening for CrAg; fluconazole pre-emptive therapy for CrAg-positive people without evidence of meningitis;
- Cotrimoxazole prophylaxis
- Rapid initiation of ART
- Adapted adherence support

Intensified adherence support is recognized as benefiting people with advanced HIV disease; such support may be provided at the time of diagnosis and initiation of ART and during episodes of acute illness both while hospitalized and during the immediate discharge period.

People with advanced HIV disease are likely to have an increased pill burden during the treatment of an acute OI and during ongoing maintenance prophylaxis and may also have significant physical challenges in attending clinic appointments. For these people, OIs affecting the central nervous system and HIV encephalopathy may pose a further challenge to comprehending and remembering adherence messages. Hence, an adapted approach to providing treatment support, including an option for home- or community-based follow-up, should be considered wherever feasible, with the consent of the patient. Early tracing of anyone who misses an appointment should also be implemented.

Components of the Package of Advanced Disease Management

Table 2.3.2: Components of the package of interventions for people presenting with advanced HIV disease

Components of the package	Intervention	CD4 Cell Count	Adults and adolescents	Children
Screening and diagnosis	4S TB screening in children and adults Sputum NAAT (CBNAAT/ Truenat) as the first test for TB diagnosis among symptomatic people	Any	Yes	Yes
	TB LF-LAM* to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children with signs and symptoms of TB or seriously ill or irrespective of signs and symptoms of TB	With a CD4 cell count <200 cells/mm^3 OR Any seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths/ minute; heart rate ≥120 beats/ minute; or unable to walk unaided	Yes	Yes
	Cryptococcal antigen (CrAg) screening**	<200 cells/ mm^3	Yes	No
Prophylaxis and pre-emptive treatment	Cotrimoxazole prophylaxis	≤350 cells/mm^3 or clinical stage 3 or 4 (Any CD4 count in settings with high prevalence of malaria or severe bacterial infections)	Yes	Yes
	TB preventive treatment	Any	Yes	Yes
	Fluconazole pre-emptive therapy for CrAG–positive people without evidence of meningitis	Any	Yes	Not applicable (screening not advised)
ART initiation	Rapid ART initiation	Any	Yes	Yes
	Defer initiation if clinical symptoms suggest meningitis (TB or cryptococcal)	Any	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced disease package, including home visits if feasible	<200 cells/mm^3	Yes	Yes

*TB LF-LAM testing is currently not available in the programme.
**CrAg screening for cryptococcal infection is currently not available in the programme.

Patient Management under Advanced Disease Management

A stepwise approach to any patient with advanced disease is useful. Following the stepwise approach would make sure that we do not miss any important aspect.

Initial screening and triaging

- The first step is to screen all PLHIV regularly to identify if they have advanced HIV disease.
- Staff nurse is then to do 4S screening and look for persistent headache and any other signs of serious illness as listed:

    Temperature ≥ 39°C with headache
    Respiratory rate ≥ 30 per minute
    SpO2 < 90% as per pulse oximeter
    Heart rate ≥ 120/minute
    Unable to walk unaided
    Altered sensorium, seizures, paralysis, difficulty in talking, rapid deterioration of vision, signs of cranial nerve involvement
- Medical officer should assess the patient for signs of serious illness. If signs of serious illness are present, then the patient should be referred to specialist, if available, in the same institution or referred to higher or tertiary centre.
- In the absence of signs of serious illness, further assessment is required for evaluation of other components:

    Screen for TB
    Screen for meningitis

In those admitted: mortality is highest in the first 48 hours after admission[10]. Initial screening and triaging should be completed as soon as possible on the same day of presentation to segregate the seriously sick cases. Based on clinical assessment, start TB and opportunistic infection therapies as soon as possible among those who are seriously ill.

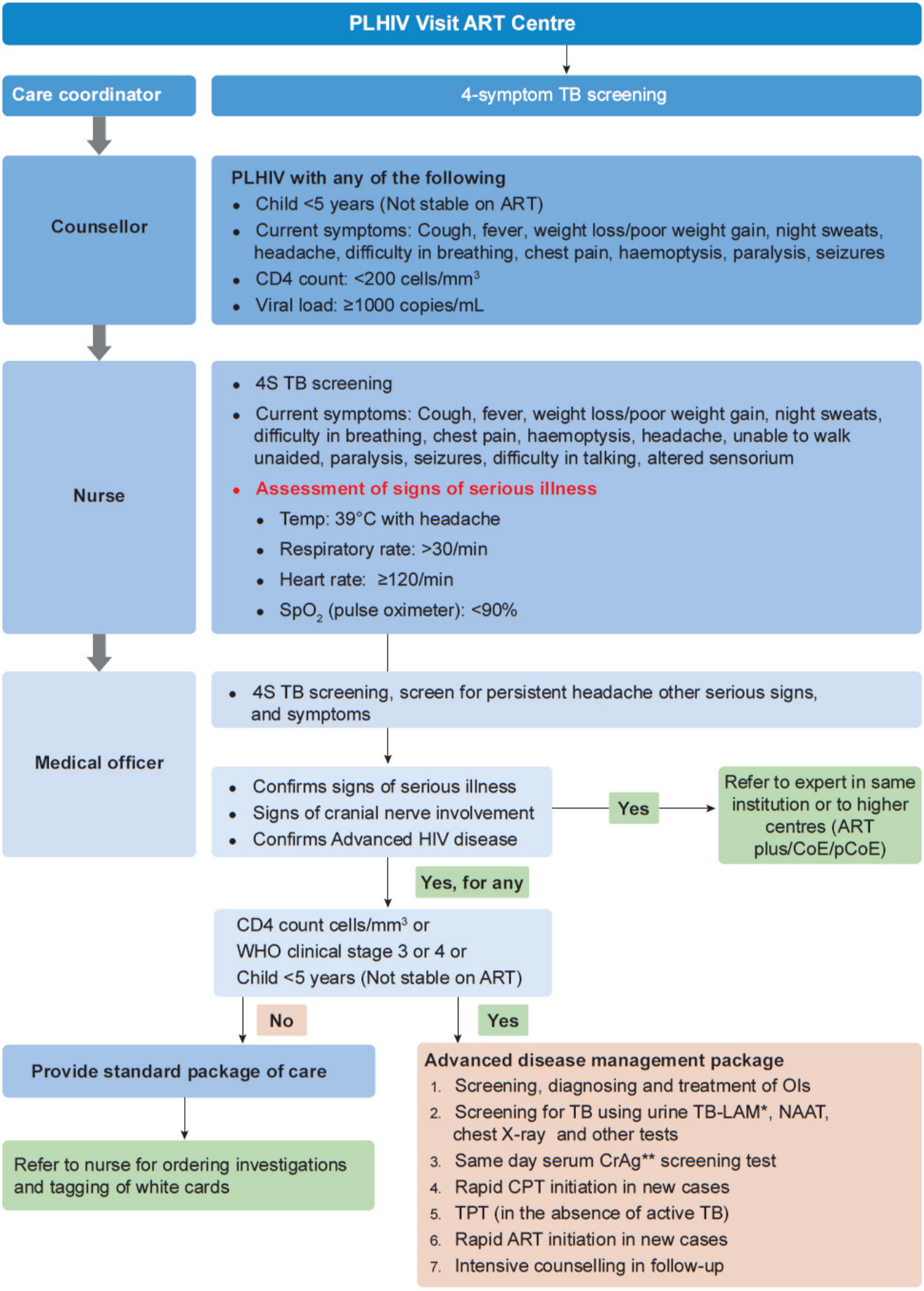
Screening and Triaging

This is an important step and in addition to identifying the PLHIV with advanced disease, it also helps identify those who are seriously ill. Any person who has signs of serious illness as mentioned above should be referred for expert evaluation and management.

Screen for Symptoms of Tuberculosis

Since TB has been well documented to be the leading cause of mortality, it is of utmost importance to screen all PLHIV for TB. Diagnosis of TB becomes difficult as immunosuppression worsens, and the spectrum of extra-pulmonary manifestations increases as the CD4 count falls. The algorithm of advanced disease management of TB and the need for using TB-LAM urine assay are described in the TB section of **Chapter 4.3 (Respiratory System).**

Figure 2.3.3: Identification and enrolment of PLHIV for advance disease management


PLHIV Visit ART Centre
Care coordinator
4-symptom TB screening
Counsellor
PLHIV with any of the following
Child <5 years (Not stable on ART)
Current symptoms: Cough, fever, weight loss/poor weight gain, night sweats, headache, difficulty in breathing, chest pain, haemoptysis, paralysis, seizures
CD4 count: <200 cells/mm3
Viral load: ≥1000 copies/mL
Nurse
4S TB screening
Current symptoms: Cough, fever, weight loss/poor weight gain, night sweats, difficulty in breathing, chest pain, haemoptysis, headache, unable to walk unaided, paralysis, seizures, difficulty in talking, altered sensorium
Assessment of signs of serious illness
Temp: 39°C with headache
Respiratory rate: >30/min
Heart rate: ≥120/min
SpO2 (pulse oximeter): <90%
Medical officer
4S TB screening, screen for persistent headache other serious signs, and symptoms
Confirms signs of serious illness
Signs of cranial nerve involvement
Confirms Advanced HIV disease
Yes
Refer to expert in same institution or to higher centres (ART plus/CoE/pCoE)
Yes, for any
CD4 count cells/mm3 or
WHO clinical stage 3 or 4 or
Child <5 years (Not stable on ART)
No
Yes
Provide standard package of care
Refer to nurse for ordering investigations and tagging of white cards
Advanced disease management package
1. Screening, diagnosing and treatment of OIs
2. Screening for TB using urine TB-LAM*, NAAT, chest X-ray and other tests
3. Same day serum CrAg** screening test
4. Rapid CPT initiation in new cases
5. TPT (in the absence of active TB)
6. Rapid ART initiation in new cases
7. Intensive counselling in follow-up
If the available CD4 count result is not within 3 months, order fresh CD4 testing.
Repeat viral load after completion of 3 months of Enhanced Adherence Counseling.
Currently *TB-LAM screening test and **CrAg screening test for cryptococcal infection are not available in the programme.
Refer to Fig 4.2.2 for CrAg test results and Fig 4.3.3 for urine TB LAM test results.

ART should be initiated in all PLHIV with TB regardless of CD4 count; however, the timing of ART in relation to TB treatment needs to be carefully considered. Section 2 of **Chapter 2.6 (First- line ART in Adults and Adolescents: Management of ARV Toxicities)** gives detailed guidance on the regimens, special situations and drug interactions. However, salient points that should be reiterated are in Table 2.3.3.

Table 2.3.3: ART initiation in PLHIV co-infected with TB

Patient's details	Timing of ART in relation to initiation of TB treatment	ART recommendations
HIV-TB co-infected patients	• ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among PLHIV (except when signs and symptoms of meningitis are present). • Among PLHIV with TB meningitis, ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered as adjuvant treatment for TB meningitis.	Appropriate ART regimen

Assess for symptoms of meningitis

Fever, chronic severe headache, altered mental status (confusion, strange behaviour, reduced consciousness), other neurological problems (seizures, paralysis, difficulty in talking, rapid deterioration of vision), unable to walk unaided.

Cryptococcal disease is an OI that occurs primarily among people with advanced HIV disease. The most common presentation of cryptococcal disease is cryptococcal meningitis. Cryptococcal meningitis is a serious manifestation and a major cause of morbidity and mortality among PLHIV with advanced disease. For details, please refer **Chapter 4.2 (Central Nervous System).** The flow chart 4.2.2 'Identification and management of cryptococcal meningitis' has been added in the same for easy reference.

Treat Opportunistic Infections

Several OIs can be found in a patient who is severely immunocompromised. It is not uncommon to have more than one OI at the same time in PLHIV with advanced HIV disease.

Treat other OIs including possible bacterial infections. Treatment of Pneumocystis or bacterial pneumonia should be considered in patients with severe respiratory distress as detailed in **Chapter 4.3. (Respiratory System).**

Start Prophylaxis as per Indication

All patients who have advanced disease should receive the prophylaxis as per the indications and once the active disease has been ruled out.

- Cotrimoxazole prophylaxis to prevent severe bacterial infections and PCP.
- TPT to prevent development of TB.
- Fluconazole pre-emptive treatment to prevent the development of cryptococcal meningitis (if CrAg positive without meningitis) or Fluconazole Primary Prophylaxis when CrAg screening test is not available and CD4 count is <100 cells/mm3.

CPT has been established to have many benefits. CPT must be initiated in all HIV-infected adults and adolescent with CD4 count <350 cells/mm3 or those with WHO clinical stage 3 and 4. A flow diagram is appended in **Annexure 20** for easy follow-up. For further details, refer **Chapter 2.9 (Prevention of Opportunistic Infections) and Annexure 20.**

TB Preventive Therapy

All patients who do not have active TB should be considered for prophylaxis as per the guidelines. Currently in the National Programme, TPT is given to all PLHIV who are negative for all four symptoms used for TB screening and those who do not have active TB to prevent latent TB from progressing to active TB. It also prevents reinfection after exposure to an open case of TB. If a patient becomes 4S positive during the TPT, TPT should be stopped, and the patient should be evaluated for TB. If found positive for TB, anti-TB treatment should be started.

ART by itself is the biggest armament in the fight against the OI by virtue of its effect on the immune system recovery. Hence, it is vital to know if the patient is currently receiving ART. Accordingly, there can be three scenarios. To learn more on when and what ART should be initiated, refer **Chapter 2.2 (ART in Adults and Adolescents).**

Provide Adherence Support

PLHIV with advanced disease, who have been diagnosed with OIs, face several difficulties to maintain adherence to treatment. This is true not only for ART but also for the treatment of OIs. The frequency of medications, pill burden, drug–drug interactions, side effects, poor morale, travel costs and expenses have all been documented to have an adverse impact on adherence. Hence, there is a need to provide intensified adherence support to these patients. Many of these patients might present when they are admitted in the hospital, and the ART centre will have to ensure that they are well counselled and have the required treatment literacy. Wherever possible, involving the relative or treatment supporter as well as providing peer support and outreach through Care and Support Centres (CSCs) can be critical. These should be undertaken as an additional measure for all patients with advanced disease after taking their informed consent.

Intensified adherence support for both OI medication and ART with constant monitoring of condition should be offered. Home visits should be considered, and mechanisms for rapid tracing of patients who miss subsequent appointments through existing resources/manpower (CSC, Vihaan, TB Programme incentive for patient having TB, SVA, etc.) should be put in place and documented.

Arrange Referrals/Discharge

Several complicated cases might be referred from lesser equipped centres to the higher centres (like the ART Plus and CoE) for better management of patients. Also, most of the cases might be managed as indoor patients. Once they stabilize, ensure communication for referral back to the parent ART centres after discharge for continuation of ART and/or OI medication, as indicated. They should also be linked to appropriate differentiated care services under the programme, so that it facilitates their retention in care, and ensures good and desired level of treatment adherence.

Rapid Initiation of ART and Advanced Disease Management

NACO guidelines on advanced disease recommend the following:

- Rapid ART initiation should be offered to all PLHIV following a confirmed HIV diagnosis and clinical assessment.
- Rapid initiation is defined as within 7 days from the day of HIV diagnosis; people with advanced HIV

disease should be given priority for assessment and initiation.

- ART initiation should be offered on the same day to people who are ready to start after appropriate preparedness counselling.

Rapid ART Initiation to Ensure Timely ART Initiation in PLHIV/CLHIV

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation within 7 days of registration at the ART centres wherever possible, after appropriate preparedness counselling, including the option of same-day initiation. Rapid ART initiation is especially important for people with very low CD4 cell count, for whom the risk of death is high. People should not be forced to start immediately and should be supported in making an informed choice regarding when to start ART. Further, the same-day initiation of ART may lead people, especially CLHIV, to start ART before they are ready, with adverse consequences for adherence and treatment outcomes. Keeping these things in mind, for children 'Rapid initiation of ART' is advised, preferably within 7 days of registration at the ART centres, wherever possible, after appropriate preparedness counselling.

People who have no clinical signs and symptoms of TB or other OIs and whose CrAg test is negative may be initiated on ART the same day in combination with their package of prophylaxis. For the operational flow of rapid initiation of ART at the ART centre, refer **Chapter 2.2. (ART in Adults and Adolescents).**

2.4 Adherence to ART

Adherence

"Extent to which a person's behaviour – the taking of medication and following healthy lifestyle including a healthy diet and other activities – corresponds with the agreed recommendations of the healthcare providers" (WHO, 2003).

Though the terms 'adherence' and 'compliance' are synonymously used, adherence differs from compliance. Compliance is the extent to which a patient's behaviour matches the prescriber's advice. Compliance implies patient's obedience to the physician's authority, whereas adherence signifies that the patient and physician collaborate to improve the patient's health by integrating the physician's medical opinion and the patient's lifestyle, values and preferences to care.

Assessing a patient's ART readiness is the first step to successful ART adherence. Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence.

For ART, a high level of sustained adherence is necessary to (1) suppress viral replication and improve immunological and clinical outcomes; (2) decrease the risk of developing ARV drug resistance; and (3) reduce the risk of transmitting HIV (WHO, 2013).

Adherence should be assessed and routinely reinforced by everyone in the HIV care team (treating physicians, counsellors, nurses, pharmacists, peer educators, care coordinator, Care and Support Centre [CSC] staff and others) at each of the patient's visit to the ART centre. Studies indicate that >95% of adherence is required for optimal viral load suppression. Lesser degree of adherence is often associated with virological failure.

Factors associated with poor adherence include the following:

- Poor patient–clinician relationship
- Medication-related factors may include (1) adverse events; (2) drug toxicity; (3) complexity of dosing regimens; and (4) pill burden.
- Dietary restrictions
- Health system factors may include requiring PLHIV to (1) visit health services frequently to receive care and obtain refills; (2) travelling long distance to reach health services; and (3) bearing the direct and indirect costs of care (financial problems).
- Lack of caregiver
- Lack of patient education:

    inability of patients to identify their medications;
    lack of clear information or instruction on medication;
    limited knowledge on the course of HIV infection and treatment;
- Home or job work responsibilities
- Frequent travel
- Forgetfulness, mental illness, psychological factors
- Substance abuse
- Cultural factors (e.g., religious fasting)
- Beliefs about treatment – faith in traditional faith healers
- False perception of good health and thus no need for ART
- Impression of being too ill for treatment
- Lack of continuity of care – interrupted ARV drug supply
- Absence of supportive environments for PLHIV
- HIV-related stigma and discrimination

Pregnant and Postpartum Women

Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Other challenges during this period include coping with the diagnosis of HIV infection (many women learn about their HIV infection during routine antenatal screening), concerns about ART affecting the health of the foetus, pill burden, the number of clinic visits during pregnancy, fear of disclosure of HIV status to partners and long waiting times at clinics.

Adolescents Living with HIV (ALHIV)

Adherence challenges faced by adolescents include a potentially large pill burden if they are treatment-experienced, stigma and fear of disclosure, concerns about safety of medication, adverse effects, peer pressure and perceived need to conform, not remembering to take medications and inconsistent daily routine.

The transition from paediatric to adolescent care presents several challenges that may affect treatment adherence in adolescents. These include assuming increased responsibility for their own care (which may lead to treatment interruptions because of forgetfulness), an inability to navigate the healthcare system, lack of links between adult and paediatric services, lack of health insurance and inadequately skilled healthcare providers. Depression and substance use have also been shown to present challenges in adolescents.

Refer Chapter 3.7 (Counselling for Children and Adolescents Living with HIV) for additional information on issues related to ALHIV.

Infants and Children

Adherence among children is a special challenge. The limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence. Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of CLHIV may themselves be living with HIV; suboptimal HIV care and treatment for family members could result in suboptimal care for the child. (**Refer Chapter 3.7 [Counselling for Children and Adolescents Living with HIV**] for additional information on issues related to CLHIV**)**.

Incarceration (Confinement in a jail or prison)

Incarceration may negatively affect continuity of care. People who are incarcerated have the additional risk of acquiring TB, resulting in high morbidity and mortality rates in the absence of efficacious HIV and TB treatment.

At least two to three preparatory adherence counselling sessions should be taken up with PLHIV. The steps of preparatory counselling are provided in Table 2.4.1.

Table 2.4.1: Counselling for treatment preparation and adherence

Step 1	• Establish rapport and a relationship of trust with the patient.
	• Provide necessary information and guidance.
	• Encourage peer participation and help identify treatment support persons.
	• Encourage disclosure to an identified family member.
	• Encourage positive living and positive prevention.
	• Provide information about cough hygiene and TB prevention.
	• Perform 4S screening.
	• Develop an individual treatment plan, fitting ART into the patient's lifestyle/daily events and identifying treatment reminders.
	• Assess patient's readiness for and commitment to ART; readiness to commence ART may be assessed by the following:
	  ▪ Ability to attend ART centre regularly and not miss appointments
	  ▪ Ability to take OI prophylaxis, e.g., Cotrimoxazole
	  ▪ Ability to complete full course of TB therapy if patient co-infected with TB
	• List barriers to adherence and develop strategies to overcome these barriers.
	• Ensure adequate understanding of ARV adverse drug effects.
	• There should be strict adherence to treatment. Adherence to recommended regimens should be >95% to avoid development of ARV drug resistance.
	• If patients have difficulty in adhering to regular doses, reinforce adherence counselling.
	• Enlist community outreach teams and peer support groups of PLHIV, as appropriate.
	• Inform that treatment is lifelong.
	• The timing of drug intake is critical (e.g., drugs taken twice daily must be taken every 12 hours, whereas drugs to be taken once daily must be taken at 24-hour interval). Missed doses can be taken up to 6 hours later in a twice-daily regimen. If more than 6 hours elapse, skip the dose and take the next normal dose. If the pill of a once-daily regimen of TLE or TLD is missed, then it should be taken as soon as patient remembers within 12 hours.
	• Dietary requirements with ARV drugs: Some drugs are taken with food, some on an empty stomach, fatty food needs to be avoided before some drugs and some require an increased intake of water.
	• The side effects of the drugs must be explained to and understood by the patient before commencing ART. Consider giving an information sheet to patients about the ART regimen they are taking.
	• People on ART need to continue using condoms regularly and practise safe injecting drug use (IDU).
	• Other medications, including herbal/traditional products, may interact with ART.
	• Patients need careful counselling about which medications are allowed and which are not with their ART.
	• Regular clinic attendance for monitoring of efficacy, side effects and adherence is essential.

Step 2	**Counselling (in one or more individual sessions)** • Help the patient explore his/her feelings. Many patients are preoccupied with problems related to family, job, relationships, etc. and cannot focus on strict adherence until negative feelings about these problems are sorted out. • Many have no private place to store their medicines and are not able to take them in privacy. Not wanting others to know their HIV status is by far the most common reason for poor adherence by patients. Patients must be realistic about whom to confide their HIV status in and how to tell them. **Check for any financial difficulties the patient may be experiencing** • Some patients may not follow up if they do not have money to travel to the centre, or their health maybe affected by a poor diet. • Help patients develop secondary support systems for themselves.
Step 3	**Solving practical problems and creating a treatment plan** • Where will the ARV drugs be stored? • At what time will they be taken? • How will the patient remember or who will remind him/her to take the medication if he/she forgets? • What will the patient do if his/her normal routine is interrupted? • A time should be agreed upon to meet or telephone the patient within a few days of starting ART to discuss any problems. • If patients cannot keep the appointment, counsellors should make phone calls and or arrange home visits through CSC.

The counsellors shall follow the checklists displayed in Table 2.4.2.

Table 2.4.2: Checklists to be used for identifying treatment adherence

No.	Checklists for treatment adherence
1	On-time pill pick up
2	Number of doses missed since the last visit
3	Whether doses are taken at correct time interval (if not, ask about delay in hours)
4	Reasons for missing/incorrect dosing/non-adherence
5	Timings and dosage of concurrent medications

Checklist for Adherence Counselling

Checklist for first visit at ART centre:

- Introduce self and ask for the client's introduction.
- Find out the purpose of the visit and check the HIV report.
- Assess the knowledge of HIV/AIDS, routes of transmission and risk reduction.
- Assess if the client is mentally prepared about the result.
- Check how you can give emotional and social support.
- Find out about his/her lifestyle and if he/she are willing to change.
- Assess if there are any suicidal ideations and/or frustrations.
- Check for prior ART exposure.
- Check for any addictions.
- Check his/her living, financial, psychological and social conditions.
- Risk assessment
- Check about the HIV status of his/her family members.
- Explain the difference between HIV and AIDS and clarify that it is not necessary that a HIV- positive client is an AIDS client.
- Check for common OIs.
- Conduct 4S TB screening.
- Referral and linkages as required.
- Provide IEC/behaviour change communication materials and condoms.
- As per client's need, provide information regarding other district and state ART centres.
- It is necessary to take address and ID proof of the client.
- Register the client and fill the white card, green book, consent form and pre-ART register.
- Provide space for the clients to ask queries and answer the questions.
- Schedule an appointment for a follow-up counselling session.

Checklist for Subsequent Adherence Counselling

- Recall the client's understanding about the previous session/visit.

- Check client's CD4 count, viral load
- Check knowledge of client/caregiver about HIV/AIDS/CD4 count and importance of ART.
- Inform client's eligibility for ART and need for lifelong ART.
- Provide information on the role of ART in HIV treatment.
- Explain about the importance of regular visit to ART centre and the need for regular CD4 testing.
- Conduct 4S screening.
- Identify potential barriers/factors affecting adherence (related to treatment, client, attitudes and behaviour of providers and environmental and social) and suggest possible solutions for these barriers/factors affecting adherence.
- Inform that regular clinical follow-up and laboratory investigations are necessary.
- Identify the support services required for the client.
- Requirement of follow-up visit should be explained and decided accordingly.

Checklist for ART Preparedness Counselling

- Review and recap the client's understanding about previous session/visit.
- Check whether client has accepted his/her HIV status.
- Identify caregiver/guardian and check acceptance of child's HIV status.
- Check caregiver's understanding about need for ART.
- Check understanding and importance of CD4 count, need for ART initiation.
- Check whether the client has accepted lifelong treatment.
- Conduct 4S screening.
- Make the client understand the importance and need for monthly visits.
- Check feasibility of monthly drug pickup.
- Check readiness to start ART.
- Check preparedness to initiate ART.
- Give information about possible ART side effects and their management.
- Inform about importance of regular clinical follow-up and laboratory investigation.
- Identify support services required.
- Plan for follow-up visit.

Checklist for Adult ART Adherence Counselling

- Review the client's adherence to treatment.
- Conduct 4S screening.
- Physical verification and cross-checking of drug (pill counting)
- Check when they missed a dose last time
- Discuss the reasons for not taking/giving the pills
- Discuss the importance of timing in taking ART
- Check side effects as per client's experience
- Identify treatment or side effects in a private / government sector
- Explain the importance of adherence and work out fresh strategies for adherence
- Check for psychological symptoms such as depression, anxiety, etc.

- Discuss diet plan, nutrition, exercise, positive living, etc.
- Discuss how treatment has affected other areas of their life
- Check the client's supply of medicine for the coming month and ensure that they do not have any problems with taking the medicine.
- Discuss about ongoing treatment issues.
- Monitor about failure of ART treatment.
- Fix an appointment for the next visit.

Checklist for Paediatric Adherence Counselling

- Review the client's adherence to treatment.
- Conduct 4S screening.
- Physical verification and cross-checking of drugs (pill counting).
- Check when they missed a dose last time.
- Use of colour, drawing, storytelling and role play for maintaining adherence.
- Discuss the reasons for not taking the pills.
- Check whether dose was taken at correct time and discuss importance of timing.
- Explain the importance of adherence and work out fresh strategies for adherence.
- Discuss diet plan, nutrition, exercise, positive living, etc.
- Review social and family support on a regular basis.
- Discuss about ongoing treatment issues.
- Monitor about failure of ART treatment.
- Fix an appointment for the next visit.

The key to successful adherence is educating the patient before the initiation of therapy, supporting ARV initiation as the patient first starts taking medications and continuously monitoring and supporting adherence. The reinforcement of the principles of adherence by treatment supporters (guardian), relatives, friends and community support personnel is of great help. Providing PLHIV with an information sheet on the ART regimen they are taking will facilitate adherence and education.

Calculating Adherence

There are a number of ways to measure adherence like self-reporting by patient, pill count, home visit, patient diary etc. Pill count is the most used method to assess adherence. In each follow-up visit, the patient should be asked to bring the pill box with the unconsumed remaining pills. For more than one type of pill, adherence needs to be calculated for all drug combination separately and reasons for different adherence patterns to different drugs should be explored.
The following formula is used to calculate the adherence:

Adherence (in %) = (Total number of pills the patient has actually taken / Total number of pills should have taken in that period) *100

This is equal to (Number of pills given to the client – Number of pills balance in the bottle / Number of pills the client should have taken) *100

Examples

- Tab TLD (Single pill daily) = Number of pill balance 9, patient returns on 28th day. Adherence calculation: (30-9) / 28 X 100 = 75%
- ALD Regimen: Tab AL (one tablet once a day) + Dolutegravir (one tablet once a day) Number of pill balance AL 5; Dolutegravir 5; patient returns on 25th day. Adherence calculation: (30-5)/(25x1) x 100 = 25 / 25 x 100 = 100%
- TL+ATV/r Regimen: TL once a day; ATV/r once a day; patient returns on 32nd day; Pill box: Remaining tablets TL: Nil; ATV/r 1.

    TL Adherence = (30-0) / 32 x 100 = 30 / 32 x 100 = 94%

    ATV/r adherence = (30-1) / 32 x 100 = 29 / 32 x 100 = 91%

    Whenever a combination of two separate drugs is given, calculation has to be done for individual tablet and whichever adherence is lower, that has to be considered for reporting purpose as 'overall adherence'.

    Overall adherence in this patient is 91%

- Tab ZL +LPV/r (ZL one pill twice daily and LPV/r two pills twice daily dose) = Number of pill balance = 11 ZL and 25 LPV/r, patient returns on 25th day.

    ZL Adherence = (60-11) / (25x2) x 100 = 49 / 50 x 100 = 98%

    LPV/r adherence = (120-25) / (25x4) x 100 = 95 /100 x 100 = 95%

    Adherence calculation: Individual drug combination adherence needs to be calculated and whichever is lower can be considered for reporting purpose.

    Overall adherence in this patient is 95%.

Refer to consolidated NACO's HIV Counselling Training Modules for ICTC, PPTCT and ART Counsellors, for more details on treatment adherence.

Role of Care and Support Centre (CSC) in improving adherence of PLHIV

The overall goal of CSC is to improve the survival and quality of life of PLHIV. To improve treatment adherence and education for PLHIV is one of the specific objectives of CSC, because adherence education and support by CSC can help PLHIV sustain and manage their treatment regimes. The CSC serves as a comprehensive unit for treatment support, retention, adherence, positive living and referral linkages to need-based services and strengthening enabling environment for PLHIV.

The day-to-day functioning of the CSC is supported by a team comprising of project coordinator, counsellor, peer counsellor and outreach workers. All of them have different roles in improving adherence of PLHIV by providing treatment education and adherence counselling at the CSC or during outreach activities. The CSC can arrange a support group meeting with a thematic area of ART adherence for a specific group of clients with compromised adherence. The main reasons for suboptimal or poor adherence need to be identified by counsellor/peer counsellor or outreach worker during home visit to the client or during their visit at CSC. An effective outreach should bridge these gaps by providing comprehensive information to enhance the knowledge and ultimately result in improved adherence and better quality of life.

Refer to NACO Operational Guidelines for ART services and NACO guidelines on Care and Support Centres for more details about role of CSC in improving treatment adherence of PLHIV.

2.5 PPTCT and ART in Pregnant Women

Introduction

Parent to child transmission (PTCT) is a major route for transmission of new HIV infections in children. PTCT contributes to about 4% of HIV infections in India. The Prevention of Parent to Child Transmission (PPTCT) programme is being implemented under NACP to achieve the goal of Elimination of Mother to Child Transmission (EMTCT). Children born to women living with HIV acquire HIV infection from their mother, either during pregnancy, labour/delivery or through breastfeeding which is largely preventable with appropriate intervention, by providing ART to mothers and ARV prophylaxis to infants (Table 2.5.1). In 2023, 63,000 children (0-14) are estimated to be living with HIV accounting for 2.5% of the estimated 25.44 lakh PLHIV in India.[1]

PPTCT of HIV under the NACP involves provision of free counselling and testing services, detection of HIV-positive status and administration of ART to all HIV-positive pregnant women, respectively, and ARV prophylaxis to their infants to prevent vertical transmission of HIV. Nationally, in 2023, there were an estimated 19.96 thousand pregnant women requiring ART to prevent MTCT of HIV. MTCT of HIV is a key commitment under the NACP. However, HIV estimation 2023 also showed that the progress on EMTCT, though significant, is still far from the target. A significant achievement is evidenced by around 81.5% decline of annual new HIV infections among children between 2010 and 2023. The final MTCT rate (including breastfeeding period) in 2023 was estimated at 11.75%(7.93-17.66), down from around 40.2% in 2010. Still, the MTCT rate continues to be on the higher side as against the target of 5%.[1]

This is a significant challenge considering the NACP's commitment to the ART coverage target of ≥95% among pregnant women to achieve the EMTCT goal. All HIV-infected pregnant women must be provided with timely ART to reduce MTCT and ultimately eliminate paediatric HIV. Globally, there were 1.2 million [940 000–1.5 million] pregnant women with HIV in 2022, of which an estimated 82% [64–98%] received antiretroviral drugs to prevent mother-to-child transmission. (WHO data).

Table 2.5.1: Risk of HIV transmission from mother to child with or without interventions[2]

ARV Intervention	Risk of HIV Transmission from Mother to Child
No ARV; breastfeeding	30–45%
No ARV; no breastfeeding	20–25%
Short course with one ARV; breastfeeding	15–25%
Short course with one ARV; no breastfeeding	5–15%
Short course with two ARVs; breastfeeding	5%
3 ARVs (ART) with breastfeeding	2%
3 ARVs (ART) with No breastfeeding	1%

There has been a significant scale-up of HIV counselling and testing, PPTCT and ART services across the country over the last few years. The number of pregnant women tested annually under the PPTCT programme has significantly increased over the last decade. However, the HIV testing rates for antenatal

clinic attendees is still far from universal coverage.

PPTCT Services in India

The PPTCT services provide access to all pregnant women for HIV diagnostic, prevention, care and treatment services and have the reach to a wide area, including sub-district level. As such, the key objective is to ensure integrated PPTCT services delivery with existing Reproductive and Child Health (RCH) programme.

Vision: Women and children, alive and free from HIV

Goal: To work towards elimination of paediatric HIV and improve maternal, newborn and child health and survival in the context of HIV infection

The programme will strive to detect HIV-infected pregnant women and provide ART to all of them. Further, it will ensure access to early infant diagnosis (EID) to HIV-exposed infants, ARV prophylaxis or ART.

India's Commitment to EMTCT

India is committed to achieving the EMTCT goal of HIV so that no child is born with HIV and the mothers are kept alive.

Targets for process indicators for validation of EMTCT (to be maintained for at least 2 years) are as follows:

- >95% of all estimated pregnant women are registered for antenatal care and receive at least 1 antenatal care check-up;
- >95% of all estimated pregnant women are tested for HIV;
- >95% of all HIV positive pregnant women are on ART.

The Essential Package of PPTCT Services includes[3] the following:

- Offer Routine HIV counselling and testing to all pregnant women enrolled in antenatal care with 'opt out' option.
- Ensure involvement of spouse and other family members and move from an 'antenatal care- centric' to a 'family-centric' approach.
- Provide lifelong ART, as per national guidelines to all pregnant and breastfeeding HIV- infected women regardless of CD4 count and clinical stage.
- Provide care for associated conditions (like, STI/RTI, TB and other OIs, hypertension, diabetes).
- Promote institutional deliveries of all HIV-infected pregnant women (ANMs/ ASHAs, community workers to accompany to institutions; reduction of stigma and discrimination among healthcare providers through sensitization and capacity building).
- Perform plasma viral load testing at 32–36 weeks of gestation to determine the risk of HIV transmission to the baby.
- Provide ARV prophylaxis to infants as per national guidelines.
- Provide nutrition counselling and psychosocial support to HIV-infected pregnant women (linkages with ANMs, ASHAs, Community outreach workers, District level networks to advise them on the right foods to take and go to Anganwadi centres for nutritional support and to the district level network of Positive

People for peer counselling and psychosocial support).

- Provide counselling and support for initiation of exclusive breastfeeding within an hour of delivery as the preferred option and continue for 6 months. After 6 months, complementary feeding should be given along with breastfeeding. Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond, like the general population, while being fully supported for ART adherence.
- Integrate follow-up of HIV-exposed infants into routine healthcare services including immunization.
- Ensure initiation of CPT and EID using HIV-TNA PCR at 6 weeks of age onwards as per NACO EID guidelines (Refer to **Annexure 1** and **1x**).
- Strengthen community follow-up and outreach through local community networks to support HIV-positive pregnant women and their families.

(Refer Guidelines for PPTCT of HIV using Multi-Drug Antiretroviral Regimen in India, December 2013.)

Four-Pronged strategy for PPTCT

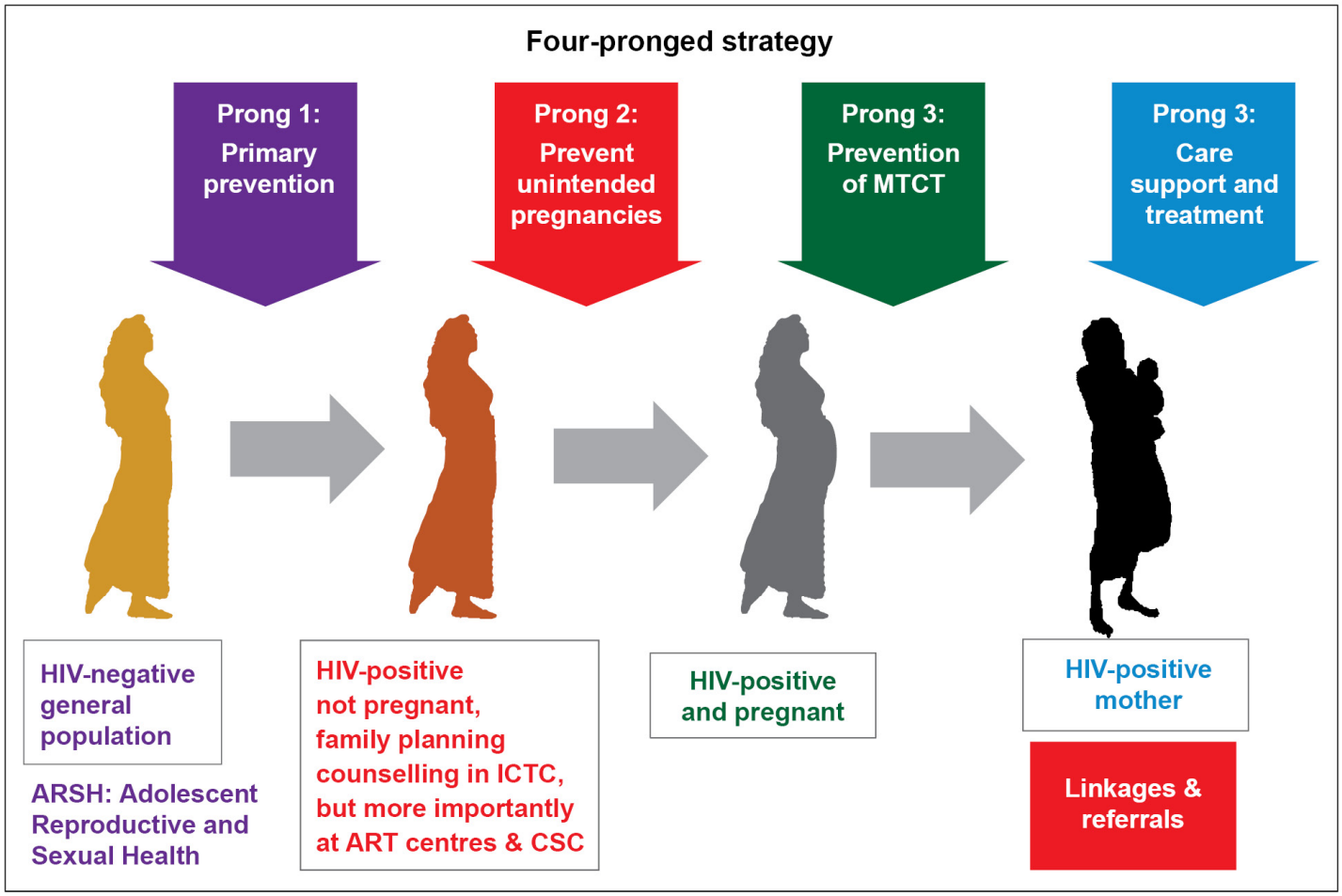
The National PPTCT programme recognizes the four elements (Figure 2.5.1) integral to preventing HIV transmission among women and children. These include the following:

- **Prong 1: Primary prevention of HIV, especially among women of childbearing age**
- The first prong is primary prevention of HIV among women of childbearing age. This can be achieved by implementation of the general population-based HIV prevention strategy and the Adolescent Reproductive and Sexual Health (ARSH) programme. Some components of primary prevention include promoting condoms through social marketing and community-based distribution system, behaviour change communication and social mobilization campaigns and prevention, diagnosis and treatment of STIs.
- **Prong 2: Prevention of unintended pregnancies among women living with HIV**
- The second prong focuses on preventing unintended pregnancies in HIV-positive women. This strategy aims at educating all HIV-positive women on available options of contraception and family planning methods. HIV-positive women should be assisted in making decisions regarding planning a pregnancy and childbirth by the staff of ICTC, ART centre and CSC.
- **Prong 3: Prevention of HIV transmission from pregnant women infected with HIV to their children**
- The third prong is to implement interventions to prevent PTCT of HIV from positive pregnant mothers to their babies. This includes linking of HIV-positive pregnant mothers to ART centre for ART initiation, counselling for adherence to ART and safe sex practices, referral for plasma viral load testing between 32 and 36 weeks of pregnancy to determine the risk of HIV transmission to the baby and decision on type of infant ARV prophylaxis.
- Institutional deliveries and ARV prophylaxis to their babies with infant feeding counselling
- **Prong 4: Provide care, support and treatment to women living with HIV and to their children and families**
- The fourth prong focuses on care, support and treatment given to HIV-positive women and their children and family. This includes treatment support, feeding counselling, immunization, linking their children to the PPTCT centre for care of HIV-exposed infant including the EID programme.

The national PPTCT programme adopts a public health approach to provide these services to pregnant women and their children. Currently, the major activities focused under PPTCT services have been prongs 3 and 4. However, Prongs 1 and 2 are also emphasized to achieve the overall results of the PPTCT

programme.

Figure 2.5.1: Four-Pronged strategy for PPTCT



Risk Factors Associated with Increase in Parent to Child Transmission of HIV

There are various risk factors contributing to vertical transmission of HIV to the baby. These may be maternal and obstetrical risk factors, infant risk factors or infant feeding risk factors.

Maternal and obstetrical factors that increase the risk of HIV transmission:

- Recent HIV infection in the mother
- High viral load, advanced HIV disease in mother
- STIs
- Obstetric procedures:
- Forceps/vacuum delivery
- Prolonged labour
- Invasive foetal monitoring
- Maternal malnutrition
- Conditions of breasts (sore nipple, breast abscess, mastitis etc.)

Infant-related factors that increase the risk of HIV transmission

- Preterm/low birth weight baby

- Condition of baby's mouth (oral ulcers, thrush)
- Mixed feeding

PPTCT interventions

- Interventions during pregnancy:

  Provide HIV information to all pregnant women.
  Antenatal visits are opportunity for PPTCT.
  Prevention of PTCT through ART
  Referral for viral load between 32 and 36 weeks of pregnancy to determine the ARV prophylaxis of the child depending on the risk
  Counselling for institutional delivery so that interventions for PPTCT can be undertaken
  Counselling on infant feeding practices and ARV prophylaxis for the child
  Safe obstetric practices
- Interventions during labour and delivery:

  Under the cover of Maternal ART, the care given to HIV-infected mothers and their babies is like the care given to uninfected mothers and their babies. When delivering HIV-infected women, follow safe delivery techniques as follows:

- Standard work precautions
- Minimize vaginal examinations and use aseptic techniques.
- Avoid prolonged labour; consider oxytocin to shorten labour.
- Avoid artificial rupture of membranes.
- Use non-invasive foetal monitoring and avoid invasive procedures.
- Support perineum and avoid routine episiotomy.
- Avoid instrumental delivery as much as possible unless indicated. If indicated, low cavity outlet forceps delivery is preferable to a ventouse delivery because it is generally associated with lower rates of foetal trauma than a ventouse delivery.
- **Considerations in mode of delivery:** In India, normal vaginal delivery is considered unless the woman has obstetric indications (like foetal distress, obstructed labour) for a Caesarean section.
- Suctioning the newborn with a nasogastric tube should be avoided unless there is meconium staining of the liquor. If suctioning the baby is a must, then we need to keep the suction pressure below 100 mm Hg pressure or use a bulb suction.
- Avoid milking the cord and delayed cord clamping. Cord clamping after it stops pulsating and after giving the oxytocin injection immediately after delivery as part of active management of third stage of labour
- Infants should be handled with gloves until all blood and maternal secretions have been washed off. Always cover the cord with gloved hands and gauze before cutting the cord to avoid blood splattering.
- Wipe and clean the baby's mouth and nostrils as soon as the head is delivered.
- **Initiate feeding within the first hour of birth according to the preferred and informed choice of the couple.**

Infant Feeding

- The two infant feeding options available for the HIV-positive mother are **exclusive breastfeeding (EBF) or exclusive replacement feeding (ERF).**
- Counselling for infant feeding should begin in the antenatal period itself. All HIV-positive pregnant women should be informed about infant feeding options, namely EBF or ERF. Pros and cons of both options must be discussed with the parents so that they can make an informed choice.
- **EBF** means giving a baby only breast milk and no other liquids or solids, not even water. Drops or syrups consisting of vitamins, mineral supplements, medicines or vaccines are permitted.
- EBF provides the infant with all required nutrients and immunological factors that help to protect them against common infections. Breastfeeding is to be started within one hour, both in a normal vaginal delivery and in a Caesarean-section delivery.
- EBF maximizes the chances of survival of these infants and is recommended as the preferred choice of infant feeding for HIV-exposed infants in India.
- **ERF** is the process of feeding a baby, who is not breastfeeding, with a diet that provides the baby its nutrient requirements.
- Replacement feeding includes feeding the baby animal milk, dairy milk, and infant formulas. It is important to counsel parents that the feed must be prepared in a hygienic manner and should be given with a spoon and bowl. Avoid bottle feeding.
- **Mixed feeding increases the risk of transmission of HIV and should be avoided.**
- When EBF is not possible for any reason (maternal sickness, twins), mothers and HCWs can be reassured that maternal ART reduces the risk of postnatal HIV transmission in the context of mixed feeding as well.
- Healthcare providers and counsellors should be trained to help pregnant women/couple in reaching the right decision and to support them in implementing their preferred choice.

For more details on infant feeding, EBF and ERF, please refer **Chapter 3.1 (Management of HIV-exposed Infants and Children).**

Current National Guidelines for Infant Feeding in HIV-exposed and Infected Infants Less Than 6 Months of Age

- EBF for the first 6 months of life is recommended.
- Beyond 6 months of age, breastfeeding should continue while complementary feeds are introduced.
- Breastfeeding should only stop once a nutritionally adequate and safe diet without breast milk can be provided to the child.
- Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond, like the general population, while being fully supported for ART adherence.
- If the HIV-positive mother plans to return to work, she can be reassured by HCWs that shorter duration of breastfeeding of less than 12 months is better than never initiating breastfeeding at all.
- Breastfeeding is made SAFE by giving ART to the mother and ARV prophylaxis to the baby.
- With optimal adherence to ART and a suppressed maternal viral load, there remains no difference in infant feeding guidelines for HIV-exposed versus unexposed infants.
- Mothers should follow safe-sex practices and ART adherence to reduce risk of HIV transmission to their babies.

Under the national programme, it is recommended to provide lifelong ART for all pregnant and

breastfeeding women living with HIV, where all pregnant women living with HIV receive a 'Fixed Drug Combination (FDC)' triple-drug ART regimen regardless of CD4 count or clinical stage, both for their own health and to prevent vertical HIV transmission and for additional HIV prevention benefits. Presently as per national guidelines, TLD is the preferred regimen for pregnant women.

Box 1: ARV for Pregnant Women and Exposed Infant

- All HIV-positive pregnant women including those presenting in labour and breastfeeding should be initiated on a triple-drug ART regardless of CD4 count and clinical stage (Treat all), for preventing MTCT and should continue lifelong ART.
- ARV Prophylaxis is advised to the infant based on the risk of HIV transmission. Single-drug ARV Prophylaxis is advised in infants with low risk for HIV transmission for 6 weeks (regardless of type of feeding). Dual-drug ARV Prophylaxis is advised in infants with high risk for HIV transmission, the duration of which depends on the type of feeding (for 6 weeks if on replacement feeding and 12 weeks if on breastfeeding). (Refer Table 2.5.7). Details of the ARV Prophylaxis is discussed later in the chapter.

Evaluating HIV-Infected Pregnant Women under Different Case Scenarios

The decision tree (Figure 2.5.2) shows some of the steps taken as part of the evaluation process of HIV-infected and breastfeeding women at the ART Centre:

What ART to Start?

ART in Pregnant and Breastfeeding Women

ART works for PPTCT by

- Reducing the maternal viral load
- Loading the foetus with ARVs that prevent the transmitted virions from replicating
- Improving overall health of mother
- Reducing the risk of transmission to the HIV-exposed infant

Mothers need to be repeatedly counselled on adherence to ART throughout the period of pregnancy and breastfeeding to reduce the risk of HIV transmission to the baby. Counselling should be done for care of breast and nipples if mother is opting for breastfeeding.

Table-2.5.2 describes the specific groups to which the pregnant and breastfeeding women belong and guides the medical officer in selecting the regimen.

Figure 2.5.2: Decision tree for ART in pregnant and breastfeeding women with HIV

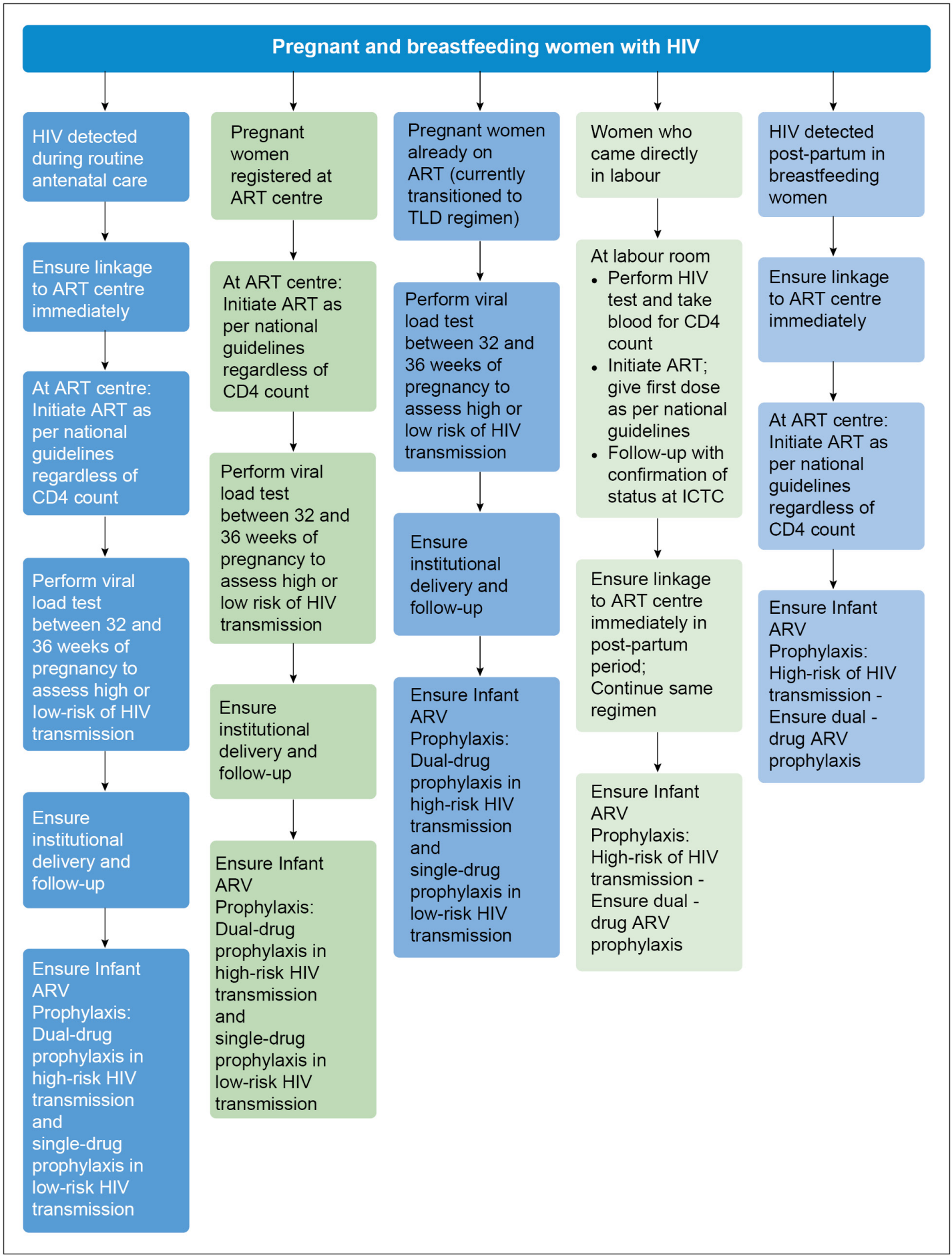


Table 2.5.2: ART regimen in pregnant and breastfeeding women with HIV

Target Population	Preferred ART Regimen	Remark
Pregnant or breastfeeding women with HIV	Tenofovir + Lamivudine + Dolutegravir TDF + 3TC + DTG (TLD)	• FDC of TDF (300 mg) + 3TC (300 mg) + DTG (50 mg) • To be given once daily • Including HIV-1, HIV-2, HIV-1 & 2, women exposed to single-dose NVP in the past and co-infected with TB or Hepatitis • Pregnant women with HIV should be educated about the benefits and risks of DTG to help informed choice

Care and Assessment of Women Presenting Directly in Labour

- Labour room nurse will offer bedside counselling and HIV screening test.
- If the woman consents, screen for HIV using the 'Whole Blood Finger Prick Test' in delivery room or labour ward.
- If reactive for HIV, the medical officer in charge will initiate ART as per the guideline (TDF + 3TC + DTG) and ensure HIV confirmation at ICTC.
- Labour room nurse informs the ICTC counsellor and laboratory technician for further confirmation of HIV status as per guidelines.
- If tested negative at ICTC, the ART is stopped. If HIV-positive status is confirmed at ICTC, ensure linkage to ART centre, collect blood for CD4 count and continue the ART as per guidelines.

Table 2.5.3: Pregnant women presenting in active labour

Maternal Status	Intra-partum	Post-partum
Presenting in active labour, no prior ART	Initiate TLD TDF (300 mg) + 3TC (300 mg) + DTG (50 mg)	Continue TLD TDF (300 mg) + 3TC (300 mg) + DTG (50 mg)

Infant ARV Prophylaxis

Appropriate and adherent maternal ART reduces the HIV viral load to suppressed levels within a few months of treatment. Appropriate infant ARV prophylaxis will reduce the risk of HIV exposure during labour, delivery and breastfeeding period. The level of viral load during the last trimester of pregnancy is key risk factor for HIV transmission during labour, delivery and breastfeeding. Recognizing the importance of knowing viral load of HIV-infected pregnant women, it is recommended that HIV risk categorization in the infants should be done based on viral load suppression in HIV-positive pregnant women. Therefore, viral load testing of all HIV- positive pregnant women should be done during 32 to 36 weeks of pregnancy (regardless of duration of ART). The HIV-exposed infants are categorized as low risk or high risk and their prophylaxis options are given in Table 2.5.4.

Table 2.5.4: HIV risk assessment of infants born to HIV-infected mothers and infant ARV Prophylaxis options

HIV Risk Status	Option for ARV Prophylaxis
Low-risk infants • Infants born to mothers with suppressed viral load (<1000 copies/ml) done any time after 32 weeks of pregnancy up to delivery	1. Syrup Nevirapine (NVP) or 2. Syrup Zidovudine# (in situations where NVP will not be effective): • Infant born to a mother with confirmed HIV-2 or HIV-1 and HIV-2 combined infections • Infant born to a mother who had received single dose of NVP during earlier pregnancy or delivery • Infant born to a mother who is on PI-based ART regimen due to treatment failure **Duration of ARV prophylaxis:** From birth till 6 weeks of age
High-risk infants • Infants born to HIV-positive mother not on ART • Maternal viral load not done after 32 weeks of pregnancy till delivery • Maternal viral load not suppressed between 32 weeks of pregnancy till delivery • Mother newly identified HIV positive within 6 weeks of delivery	**Options for dual prophylaxis:** Syrup NVP + Syrup Zidovudine## **Duration of Dual ARV Prophylaxis:** • In case of Exclusive Replacement Feeding (ERF): From birth till 6 weeks of age • In case of Exclusive Breastfeeding (EBF): From birth till 12 weeks of age
#When Zidovudine syrup is not available, syrup Lopinavir (LPV)/ritonavir should be used after 14 days of birth. ##When Zidovudine syrup is not available, syrup NVP should be used for the first 14 days after birth and after that add syrup LPV/ritonavir till 6 weeks in case of ERF or 12 weeks in case of EBF. ##Another alternative that may be used in this situation is AZT+3TC+NVP (ZLN) paediatric formulation. **In exceptional scenarios** and **for high-risk infants** born to HIV-2-positive mothers or for high-risk infants born to mothers who had received single dose of NVP during earlier pregnancy or delivery, **opinion of SACEP should be sought**	

Low-risk infants shall receive single ARV prophylaxis whereas those with high risk will receive dual ARV prophylaxis, as shown in Table 2.5.4. Doses of drugs used are given in Tables 2.5.5 and 2.5.6.

Table 2.5.5: Dose of syrup Nevirapine (10 mg/ml)

Infant Age	Daily Dosing
Birth* to 6 weeks • Birth weight 2000–2500 g • Birth weight >2500 g	 10 mg (1 ml) once daily 15 mg (1.5 ml) once daily
>6 weeks – up to 6 months#	20 mg (2 ml) once daily
>6 months – up to 9 months#	30 mg (3 ml) once daily
>9 months – until breastfeeding ends	40 mg (4 ml) once daily
*Infants weighing <2000 g, the suggested starting dose is 2 mg/kg once daily. #NVP dose for older infants is provided in a situation where HIV exposure is identified during infancy, the mother is breastfeeding and the infant is either HIV uninfected or the status is yet to be determined after taking opinion from SACEP/ pCoE. Any HIV-exposed breastfeeding baby beyond 6 weeks of age will need SACEP/pCoE opinion for indication of dual prophylaxis.	

Table 2.5.6: Dose of syrup Zidovudine (10 mg/ml)

Infant Birth Weight	Zidovudine Daily Dosage (in mg)	Zidovudine Daily Dosage (in ml)	Duration
<2000 g	5 mg/dose twice daily	0.5 ml twice daily	6 weeks
2000–2500 g	10 mg/dose twice daily	1 ml twice daily	6 weeks
>2500 g	15 mg/dose twice daily	1.5 ml twice daily	6 weeks

Syrup LPV/ritonavir should be used for infant prophylaxis in certain specific situations. It should be used infants only after 14 days of their birth.

- When Zidovudine syrup is not available, syrup Lopinavir/ritonavir (LPV/r) should be used after 14 days of birth.
- When Zidovudine syrup is not available, syrup NVP should be used for first 14 days after birth and then add LPV/r till 6 weeks in case of ERF or 12 weeks in case of EBF.

The dosages of LPV/r syrup must be administered twice daily according to the body weight of the infant as detailed in Table 2.5.7.

Table 2.5.7: Dose of syrup LPV/r (80 mg/20 mg per ml of solution) for infant ARV prophylaxis

Infant Age	Weight of Baby	Daily Dosing
Birth to 2 weeks	**Do not use LPV/r solution for infants aged younger than 2 weeks of age**	
2 weeks to 4 weeks	Weight 2000–2999 g	0.6 ml twice daily
	Weight 3000–3999 g	0.8 ml twice daily
	Weight 4000–4999 g	1.0 ml twice daily
> 4 weeks	Weight 3000–5999 g	1.0 ml twice a day
	Weight 6000–9999 g	1.5 ml twice a day

- Dosage: Once-daily dosing of LPV/r is not recommended.
- LPV/r 300 mg/75 mg/m² of body surface area per dose, given twice daily. This approximates to LPV/r 16 mg/4 mg (both per kg body weight) per dose given twice daily.

Infant ARV prophylaxis should be started immediately after birth or at their first encounter with health services. It can be started even if more than 72 hours have passed since birth, though its efficacy in preventing perinatal transmission will be lower. It will, however, still be protective towards transmission by breastfeeding. Daily infant ARV prophylaxis should continue for a minimum of 6 weeks, during which the mother should be linked to appropriate ART services. A longer duration (12 weeks) of prophylaxis is needed for infants on breastfeeding as described earlier.

Table 2.5.8: Duration of infant ARV prophylaxis

Type of Infant	Type of Feeding Option	Duration of ARV Prophylaxis
Infant with low risk for HIV transmission	Exclusive breastfeeding (EBF)	6 weeks, regardless of feeding option
	Exclusive Replacement feeding (ERF)	
Infant with high risk for HIV transmission	EBF	12 weeks
	ERF	6 weeks

Specific Interventions during Infancy:

- Observe for signs and symptoms of HIV infection.
- All HIV-exposed infants should receive Cotrimoxazole at 6 weeks of age.
- Follow standard immunization schedule.
- Routine well-baby visits
- Early Infant Diagnosis: TNA PCR (NAT) test
- 18-month visit for HIV antibody testing

ART requires ongoing adherence monitoring and reduces risk of PTCT in the following ways:

- Reduces viral replication and maternal viral load
- Loads foetus with ARVs that prevent placentally transmitted virions from replicating
- Treats maternal infection
- Protects the HIV-exposed infant from HIV infection
- Improves overall health of mother

As India embarks on the goal of EMTCT of HIV, it is evident that good coverage with antenatal care, high rates of HIV testing, effective ART for pregnant and breastfeeding mothers and ARV prophylaxis to infants will remain key factors contributing to the success of preventing the vertical transmission.

Case Scenarios on PPTCT and Infant ARV Prophylaxis

Table 2.5.9: PPTCT case scenarios

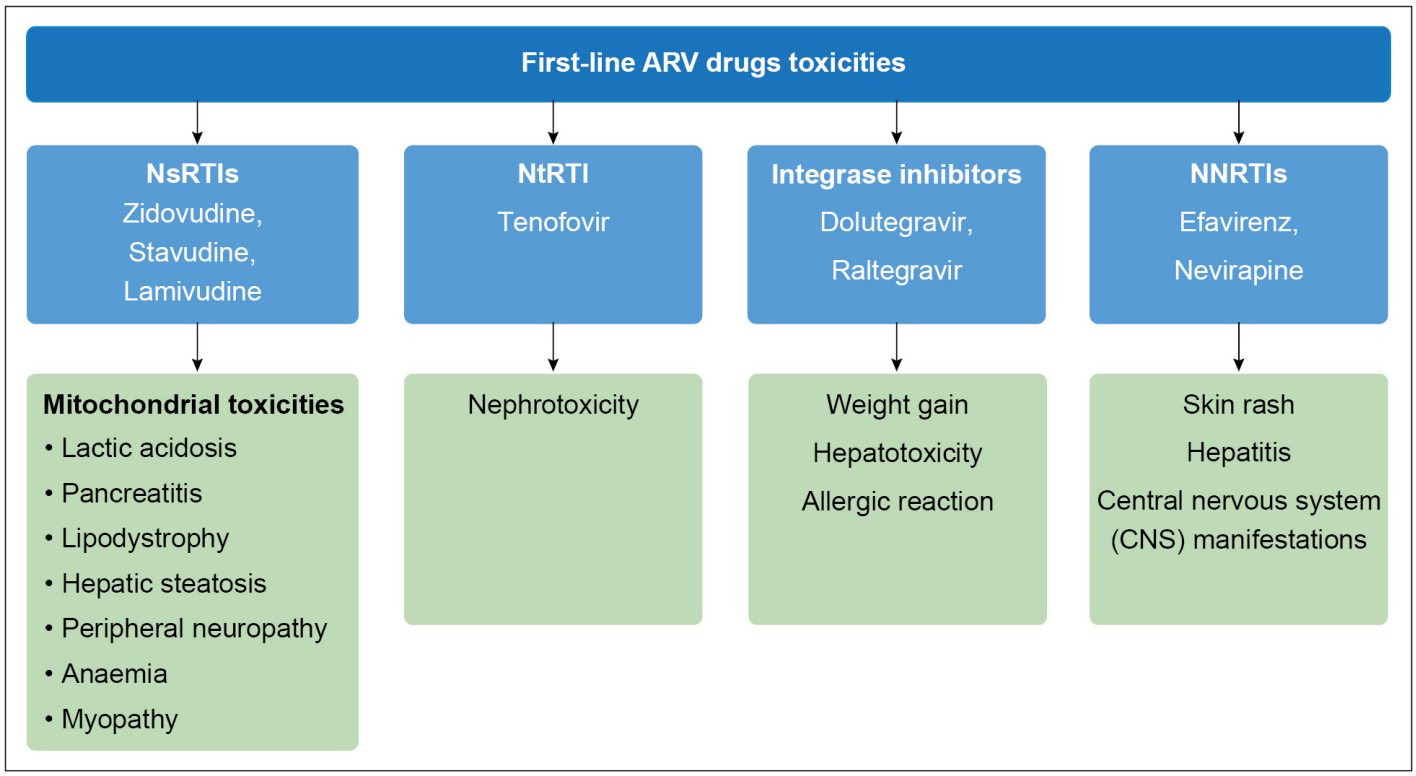
Case	Scenario & Question	Answer and Explanation
1	Mrs. A was initiated on ART in 2018 on TLE. She is adherent to ART. She has now reported to the ART centre and informs that she is 2 months pregnant. Her latest result of viral load testing was 1NO (Target Not Detected). **Question:** As the med-cal officer, what actions will you take?	**Counsel her with respect to** • Transitioning to TLD regimen • ART adherence • Linkage to PPTCT programme • Safe-sex practices to avoid fresh HIV infection • Institutional delivery for interventions during labour and delivery and timely ARV prophylaxis to the baby • Feeding practices and care of breast and nipples • Nutritional supplementation • Regular antenatal visits • Iron, folic acid and calcium supplementation
2	Mrs. B was initiated on ART in October 2020 on TLD and she reported that she was 2 months pregnant. She missed an ART visit in February 2021. She was linked back to the ART centre in March 2021 by the CRW. **Question:** As the ART MO, what actions will you take?	This may not have happened if mother had been adequately counselled about role of adherent ART in preventing HIV infection in her baby. Resume TLD regimen. **Counsel her with respect to** • Role of ART adherence for her health and preventing transmission of HIV infection to her baby • Linkage to PPTCT programme • Protected sex practices to avoid fresh HIV infection • Institutional delivery • Feeding practices and care of breast and nipples • Nutritional counselling • Regular antenatal visits • Iron, folic acid and calcium supplementation • Mrs C needs to be started on ART immediately, after explaining the need for lifelong ART adherence. • Hence, recommend Mrs C to be initiated on TLD (one tablet once a day).
3	Mrs. C received triple-drug ARV prophylaxis in 2012 during her first pregnancy. She was advised TLE once a day as prophylaxis and it was stopped 7 days after discontinuation of breastfeeding. Now she reports to the ART centre with 2 months of pregnancy. Her latest CD4 count is 420 cells/mm³. **Question 1:** What ART regimen should she be advised? **Question 2:** Mother's viral load result done at 34 weeks of gestation was 500 copies/ml. She plans to breastfeed the baby. What infant prophylaxis should be advised and for what duration?	**Infant Prophylaxis:** Give syrup Nevirapine (NVP) once a day for 6 weeks. **Explanation** • As she was on triple drug ART, chances for archived resistance to NNRTIs are minimal. • As mother's viral load result done at 34 weeks of gestation was 500 copies/ml, the baby becomes a low-risk infant for HIV Transmission **Duration** • 6 weeks regardless of type of feeding in low-risk infants
4	Mrs. D has reported to ART centre at 7 months of pregnancy. She is ART naive and her CD4 is 365 cells/mm³. **Question 1:** What ART regimen should she be initiated on?	• Mrs D needs to be started on ART immediately, after explaining the need for lifelong ART adherence. **Advice** • TLD one tablet once a day
	Mother's viral load report done at 36 weeks of gestation was 20,000 copies/ml. She plans to breastfeed the baby. **Question 2:** What infant prophylaxis should be advised and for what duration?	• Baby should be advised dual ARV Prophylaxis: Syrup NVP once a day and syrup Zidovudine twice a day, both to be given for a duration of 12 weeks **Explanation** • Mother's viral load report done at 36 weeks of gestation was unsuppressed (more than 1000 copies/ml). The baby becomes a high-risk infant for HIV transmission. • Hence the baby will be advised two drugs for ARV Prophylaxis i.e., NVP and Zidovudine. **Duration** • 12 weeks as mother has opted for breastfeeding and has not taken adequate duration of ART for optimal viral suppression in breast milk
5	Mrs. E was advised a single dose of NVP as prophylaxis in her previous pregnancy in 2011. She was later initiated on TLE in 2014. She has now reported to ART centre at 3 months of pregnancy. **Question 1:** What ART regimen should she be initiated on?	• Transition ART regimen from TLE to TLD, after explaining the benefits of DTG in achieving faster viral suppression. **Explanation** • TLD is effective in women with history of single dose NVP previously.
	Question 2: Mother's viral load report done at 33 weeks of gestation was 250 copies/ml. She plans to breastfeed the baby. What infant prophylaxis should be advised and for what duration?	Baby should be advised syrup Zidovudine twice a day for 6 weeks. **Explanation** • There is history of single-dose NVP in the previous pregnancy. Hence likely presence of archived resistance to NNRTI in the mother and subsequent transmission to infant. Hence Zidovudine twice a day will be advised.Duration of ARV prophylaxis- 6 weeks • As mother's viral load report done at 36 weeks of gestation was 250 copies/ml, the baby becomes a low-risk infant for HIV transmission. **Duration** • 6 weeks, regardless of type of feeding, in low-risk infants
6	Mrs. F is an asymptomatic postnatal PLHIV, who presents at the ART Centre 3 days after delivery; her CD4 count is 550 cells/mm³. She has opted for EBF. The weight of the baby is 2.4 kg. **Question 1:** What is the next step in the management of the mother?	• Mrs. F needs to be started on ART immediately, after explaining the need for lifelong ART adherence. **Advice** • TLD one tablet once a day • Linkage to PPTCT programme • Feeding practices and care of breast and nipples • Nutritional counselling • Protected sex practices
	Question 2: What is the next step in the management of the baby?	• Baby should be advised dual ARV Prophylaxis: Syrup NVP once a day and syrup Zidovudine twice a day, both to be given till 6 weeks of age • Dose: Syrup NVP 1ml once a day + Syrup Zidovudine 1ml twice a day **Explanation** • ARV prophylaxes may work even after 72 hours of perinatal exposure to HIV virus in the baby. • As the mother is ART naive, her baby becomes a high-risk infant for HIV transmission. Hence the baby will be advised two drugs for ARV Prophylaxis i.e., NVP and Zidovudine. **Duration** • 6 weeks as mother has opted for replacement feeding
7	Mrs. G was screened for HIV and found to be reactive by finger prick test performed in the labour room. She was immediately given a single tablet of TLD. She was linked to an ART centre the next day after her confirmatory test report for HIV was positive. Weight of the baby is 2.8 kg. **Question 1:** What is the next step in the management of the mother?	• Mrs. G needs to be started on ART immediately, after explaining the need for lifelong ART adherence. **Advice** • TLD one tablet once a day • Linkage to PPTCT programme • Feeding practices and care of breast and nipples • Nutritional counselling • Safe sex practices
	Question 2: What advice needs to be given for the baby if mother opts for breastfeeding?	• Baby should be advised dual ARV Prophylaxis: Syrup NVP once a day and syrup Zidovudine twice a day, both to be given for a duration of 12 weeks. • Dose: Syrup NVP 1.5 ml once a day + Syrup Zidovudine 1.5 ml twice a day **Explanation** • As the mother is ART naive, her baby becomes a high-risk infant for HIV transmission. • Hence the baby will be advised two drugs for ARV Prophylaxis i.e., NVP and Zidovudine. **Duration** • 12 weeks as mother has opted for breastfeeding and has not taken adequate duration of ART for optimal viral suppression in breast milk
8	Mrs. H is a 24-year-old newly diagnosed HIV-positive pregnant woman linked to the ART centre. She has confirmed HIV-1 & HIV-2 co-infections. She is 3 months pregnant and her CD4 count is 700 cells/mm³. **Question 1:** What ART regimen should be started for Mrs. H?	• Mrs. H needs to be started on ART immediately after explaining the need for lifelong ART adherence. **Advice** • TLD one tablet once a day **Explanation** • TLD is effective in HIV 1 & HIV-2 co-infections
	Question 2: Mother's viral load report done at 36 weeks of gestation is Target Not Detected. She plans to breastfeed the baby. What infant prophylaxis should be advised and for what duration?	Syrup Zidovudine twice a day is the drug of choice for infant Prophylaxis. **Explanation** • NVP will not be effective ARV prophylaxis for HIV-2 infection . • Zidovudine is the choice of ARV prophylaxis in babies born to confirmed HIV-2 or HIV-1 & HIV-2 co-infected mothers. • As mother's viral load report done at 36 weeks of gestation was suppressed (less than 1000 copies), the baby becomes a low-risk infant for HIV transmission. **Duration** • 6 weeks, regardless of type of feeding, in low-risk infants
9	Mrs I, a newly diagnosed PLHIV, has been recently linked to an ART centre with her 3 months old baby who is breastfeeding. **Question 1:** How will we manage her?	Initiate Mother on TLD after preparedness Counselling. **Advise mother regarding** • Care of nipples and breast • Feeding Counselling • Protected sex practices
	Question 2: How will we manage the baby of this PLHIV?	• Send DBS sample for TNA PCR-HIV as per EID algorithm. • Start CPT • Ideally, the baby should be evaluated by a Paediatrician for presence of clinical signs of HIV infection. • E-referral to SACEP/pCeE for opinion on management of the HIV-exposed baby. • Immunization of baby as per schedule If TNA PCR is negative, keep under regular follow-up and at 6 months of age perform rapid antibody test and subsequently TNA PCR (if necessary), as per EID algorithm and take further decision accordingly. Confirm at 18 months of age as per the guidelines.
10	Mrs L is a newly diagnosed PLHIV linked to an ART centre. She has a 20 days old baby, who is breastfeeding. Weight of the baby is 3.2 kg. **Question 1:** How will we manage the PLHIV?	• Initiate mother on TLD after preparedness counselling. • Feeding counselling to parents **Advice** • EBF and to avoid mixed feeding • Linkage to PPTCT programme • Care of breast and nipples • Nutritional counselling • Protected sex practices
	Question 2: How will you manage the baby of this PLHIV?	• Baby should be advised dual ARV Prophylaxis: Syrup NVP once a day and syrup Zidovudine twice a day, both to be given for 12 weeks. • Dose: Syrup NVP 1.5 ml once a day + Syrup Zidovudine 1.5 ml twice a day **Explanation** • As the mother is ART naive, her baby becomes a high-risk infant for HIV transmission. • Hence the baby will be advised two drugs for ARV Prophylaxis i.e., NVP and Zidovudine. **Duration** • 12 weeks, as mother has opted for breastfeeding and has not taken adequate duration of ART for optimal viral suppression in breast milk
11	Mrs K was diagnosed HIV infected recently. She has reported to an ART centre and informs that she is 6 months pregnant. Her CD4 is 285 cells/mm³. **Question 1:** What ART regimen should be started in this PLHIV?	• Mrs K needs to be started on ART immediately, after explaining the need for lifelong ART adherence and preparing her to accept ART initiation. **Advice** • TLD once a day • She needs to be started on CPT also as her CD4 is less than 350 cells/mm³.
	Mother's viral load report done at 36 weeks of gestation is 55,000. She plans to breastfeed the baby. **Question 2:** What infant prophylaxis should be advised and for what duration if syrup Zidovudine is not available?	Baby should be advised dual ARV Prophylaxis: Syrup NVP + Syrup LPV/r (to be started after 14 days of life), as follows: • Syrup NVP once a day started immediately after birth and continued till 12 weeks of age + Syrup LPV/r twice a day and started at 15 days of age and continued till 12 weeks of age **Explanation** • Mother's viral load report done at 36 weeks of gestation was unsuppressed (more than 1000 copies/ml). The baby becomes a high-risk infant for HIV transmission. Hence the baby will be advised two drugs for ARV Prophylaxis i.e., NVP and Zidovudine. As Zidovudine is not available, Syrup LPV/r can be given as the second ARV drug. LPV/r cannot be advised in the first 14 days of life. Hence, we will be advising Syrup NVP + Syrup LPV/r (to be started after 14 days of life). **Duration** • 12 weeks as mother has opted for breastfeeding and has not taken adequate duration of ART for optimal viral suppression in breast milk.
12	Mrs. L, 26 years, was registered at the ART centre in 2012. She was initiated on ART (TLE) in 2015. She became lost to follow-up after 1 year as she shifted to her village. She has now reported in active labour. **Question 1:** How should we manage this patient?	• She is to immediately be given a single tablet of TLD. She should be linked to the ART centre the next day for restarting lifelong ART. **Advice** • Role of ART adherence for her health and preventing transmission of HIV infection to her baby • Care of nipples and breast • Feeding counselling • Safe sex practices
	Mrs L delivered a baby by normal delivery with a weight of 3.2 kg and has opted for breastfeeding. **Question 2:** What is the next step in the management of the baby if syrup Zidovudine and syrup LPV/r are both not available?	• Baby should be advised dual ARV Prophylaxis: As both syrup Zidovudine and LPV/r are not available, baby can be advised paediatric ZLN (FDC) tablets as per weight band twice a day till 12 weeks of age. • Dose: ZLN-60 mg one dispersible tablet twice a day for 12 weeks **Explanation** • As the mother is ART naive, her baby becomes a high-risk infant for HIV transmission. Hence the baby will be advised two drugs for ARV Prophylaxis. As both syrup Zidovudine and LPV/r are not available, baby can be advised paediatric ZLN (FDC) tablets as per weight band. **Duration** • 12 weeks as mother has opted for breastfeeding and has not taken adequate duration of ART for optimal viral suppression in breast milk
Referral to SACEP for opinion on infant Prophylaxis		
In exceptional scenarios and for high-risk infants born to HIV-2 positive mothers or for high-risk infants born to mothers who had received single dose of NVP during earlier pregnancy or delivery, opinion of SACEP should be sought.		

2.6 First line ART in Adults & Adolescents: Management of ARV Toxicities

Introduction

ARV drugs used in first-line ART regimens for adults and adolescents in the national ART Programme in India are Zidovudine, Tenofovir, Abacavir, Lamivudine, Efavirenz and NVP. These drugs are associated with toxicities, which may be class specific and/or drug specific. The class-specific drug toxicities to Nucleoside Reverse Transcriptase Inhibitors (NsRTIs and NtRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are depicted in Figure 2.6.1

Figure 2.6.1: First-line ARV toxicities in adults and adolescents



ARV drugs may be associated with a broad range of toxicities, ranging from low-grade intolerance, which may be self-limiting, to life-threatening adverse reactions. Differentiating between complications of HIV disease and ART toxicity is sometimes difficult. The toxicities of ARVs need to be differentiated from manifestations of a new OI and IRIS. Alternative explanations should be considered before it is concluded that the manifestations are related to ART toxicity. The factors to be considered include inter-current illness (e.g., hepatitis A and malaria) and reactions to medications other than ARV drugs (e.g., isoniazid-induced hepatitis or Cotrimoxazole-induced rash). Most of the toxicities/side effects can be adequately co-managed with efficient clinical monitoring at all levels of the healthcare system.

The management of ARV toxicities is based on clinical and laboratory monitoring. The frequently encountered adverse drug effects (ADEs) for the first-line ARV drugs are provided in Table 2.6.1.

Table 2.6.1: Adverse drug effects of commonly used first-line ARVs in adults and adolescents

Class of ARV Drugs	Drugs	Adverse Drug Effects
Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	**Tenofovir (TDF)**	Renal toxicity, bone demineralization
	Zidovudine (AZT)	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis, hyperpigmentation of skin and nail
	Lamivudine (3TC)	Minimal toxicity, rash (very rare)
	Abacavir (ABC)	Hypersensitivity reaction* in 3% to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath); rechallenging after reaction can be fatal.
Integrase Strand inhibitors (INSTI)	**Dolutegravir (DTG)**	Hepatotoxicity, weight gain, allergic reaction, insomnia
	Raltegravir (RAL)	Hepatotoxicity, allergic reaction, myalgia/rhabdomyolysis/ myopathy when used concomitantly with other drugs increasing risk, severe skin rashes/hypersensitive reactions in a few patients
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	**Efavirenz (EFV)**	Central nervous system symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation) and personality change. Rash occurs, but less common than with NVP. Avoid taking EFV after heavy fatty meals.
	Nevirapine (NVP)	Hepatitis (usually within 12 weeks), sometimes life-threatening hepatic toxicity; skin rash occasionally progressing to severe conditions, including Stevens-Johnson's syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes while being treated with NVP should not be rechallenged.
Protease Inhibitors (PIs)	**Atazanavir/ ritonavir (ATV/r)**	Hyperbilirubinaemia, less lipid problems than with LPV/r; hyperglycaemia, fat maldistribution, nephrolithiasis
	Lopinavir/ritonavir (LPV/r) Heat stable tablet	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance. PIs should not be prescribed with Simvastatin as they significantly increase the level of Simvastatin leading to rhabdomyolysis, resulting in severe kidney failure.

*Abacavir hypersensitivity is linked to the presence of the HLA-B 5701 gene. It is associated with <5% of adults and children in India. Hypersensitivity usually occurs during the first 6 weeks of therapy but may occur at any time; it can potentially be fatal. Whenever hypersensitivity reaction is noticed, abacavir must be discontinued immediately; never rechallenge or use it again.

Clinicians approach commonly observed ARV drug toxicities in relation to the time of their occurrence after initiating first-line ART. The toxicities can be termed 'short-term', 'medium term' and 'long-term' and are classified according to the class of ARV drugs in Table 2.6.2.

Table 2.6.2: Common ARV drug toxicities

Class of ARV Drugs	Drugs	Short-term Toxicities	Medium-term Toxicities	Long-term Toxicities
NRTIs	**Zidovudine**	Headache, nausea, vomiting, malaise diarrhoea Bone marrow suppression, anaemia (macrocytic)	Bone marrow suppression, anaemia, (macrocytic), hyperpigmentation, lactic acidosis, proximal myopathy	None
	Lamivudine	Skin rash (rare)	None	None
	Stavudine	None	Lactic acidosis, pancreatitis, peripheral neuritis	Lipodystrophy, dyslipidaemia
	Abacavir	Hypersensitivity reaction in 3% to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath)		
	Tenofovir	Nephrotoxicity (low incidence), Fanconi's syndrome and rarely Acute Renal Failure, can reduce bone mineral density		
Integrase Strand inhibitors	**Dolutegravir**	Nausea, diarrhoea, insomnia, rashes, hepatotoxicity		None
	Raltegravir	Nausea, diarrhoea, insomnia, rashes, hepatotoxicity		None
NNRTIs	**Efavirenz**	Drowsiness, dizziness confusion, vivid dreams skin rashes, hepatotoxicity (very rare)	None	None
	Nevirapine	Skin rashes, hepatotoxicity	None	None

Clinicians and other supporting staff of ART centres (counsellors, nurses and pharmacists) should be well versed with overlapping toxicities exhibited by ARVs and other co-administered drugs used for other co-existing conditions or for prophylaxis for certain OIs. Some conditions are provided in Table 2.6.3.

Table 2.6.3: Overlapping toxicities

Overlapping Toxicities	Drugs
Bone marrow suppression	Zidovudine, Co-trimoxazole, Dapsone, Pyrimethamine, Ganciclovir, Amphotericin B, Ribavirin
Hepatotoxicity	Nevirapine, Atazanavir, Lopinavir, Ritonavir, Isoniazid, Rifampicin, Pyrazinamide, Fluconazole, Cotrimoxazole, Dolutegravir
Peripheral neuropathy	Stavudine, Isoniazid
Pancreatitis	Stavudine, Cotrimoxazole

Dolutegravir Toxicity

DTG-based regimens are now the preferred first-line drug in India for all new patients to be enrolled in national ART programme. It has a good overall safety profile, with fewer metabolic side effects. Minor side effects like insomnia, GI intolerance and skin rashes are reported in initial phase of starting DTG and may not require change of drug.

The major areas of concern usually raised with use of DTG have been the following:

- Neural tube defects in the foetus when used in pregnancy
- Weight gain.

There were some concerns initially regarding its safety for use in pregnant women. However, it is now understood that the risk of neural tube defects associated with DTG use at the time of conception is no longer statistically significant when comparing the prevalence of neural tube defects between preconception DTG and preconception non-DTG ART regimen. In a large study, the incidence of neural tube defects was found to be ≤ 0.2%.

Other adverse pregnancy outcomes (miscarriage, stillbirth, preterm birth, low birth weight, small for gestational age and neonatal mortality) were not increased with maternal DTG compared with EFV-containing regimens when the regimens were started preconception or during pregnancy.

A woman-centred and a rights-based approach should be applied to ART delivery. Concern about the risk of neural tube defects and other pregnancy outcomes has highlighted the importance of both access to reproductive health services, including contraceptives, for women and adolescent girls living with HIV and the importance of the rights of women and adolescent girls living with HIV to make informed choices about their health, including their sexual and reproductive health and choice of ART.

DTG and Weight Gain

The concern of weight gain has been noted with use of DTG. However, it is worth noting that the weight gain was mostly seen when ART backbone with TAF was used along with DTG.

Both low CD4 and high HIV RNA were highly prognostic of higher weight gain, whereas the effects of gender on weight gain appear to be ethnicity dependent, with higher rates among African women compared with men.

Reporting on serious adverse events of hyperglycaemia or diabetes was limited across studies. An expert think tank convened by WHO in March 2020 concluded that more data was required to better document long-term body weight gains with DTG with and without TAF, including in different populations and geographical regions and how this relates to metabolic consequences.

The following are useful to consider:

- Adequate counselling on lifestyle and dietary changes for all PLHIV;
- Measurement of blood pressure to detect hypertension, with special attention to the risk of hypertension during pregnancy;
- Monitoring and treating metabolic complications – glucose and lipid profile monitoring;
- Monitoring weight and associated complications as part of toxicity monitoring.

Tenofovir Toxicity

TDF is also a commonly used drug under the programme. It has a good overall safety profile, with fewer metabolic side effects and mitochondrial toxicities. TDF has a relatively long half-life, allowing once-daily dosing and making compliance easier for patients. The major side effects of TDF are

- Renal toxicity
- Decrease in bone mineral density.

However, out of these, the most significant is TDF-related renal toxicity, though overall incidence may be only 3% to 5%. The renal proximal tubule (PT) is the main target of TDF toxicity. For additional information on TDF toxicity, refer **Annexure 3 (Additional Guidance on Tenofovir- related renal toxicity).**

Management of Toxicities

Management of Toxicities

Regardless of severity, toxicities may affect adherence to therapy. A proactive approach is required to manage them

- Discuss potential side effects of the ART regimen with the patient before initiation and during the early stages of treatment. This must be part of preparedness counselling for the patient and the caregiver.
- Differentiate any new clinical event after the initiation of ART from IRIS.
- Always assess the toxicity and grade its severity. The management of toxicity depends on the grade of severity.
- Offer support during minor and major adverse events.
- Ensure that the patient is familiar with the signs and symptoms of toxicities that are serious and require immediate contact with the clinical team, especially in the case of EFV-associated Stevens-Johnson's syndrome, hepatitis, NRTIs-led lactic acidosis or Abacavir-associated hypersensitivity reaction.

Clinicians should be able to recognize drug toxicities during the scheduled or unscheduled visits of PLHIV at the ART centres and be able to manage them as described in Table 2.6.4.

Table 2.6.4: Clinical signs, symptoms and management of adverse effects of antiretroviral drugs

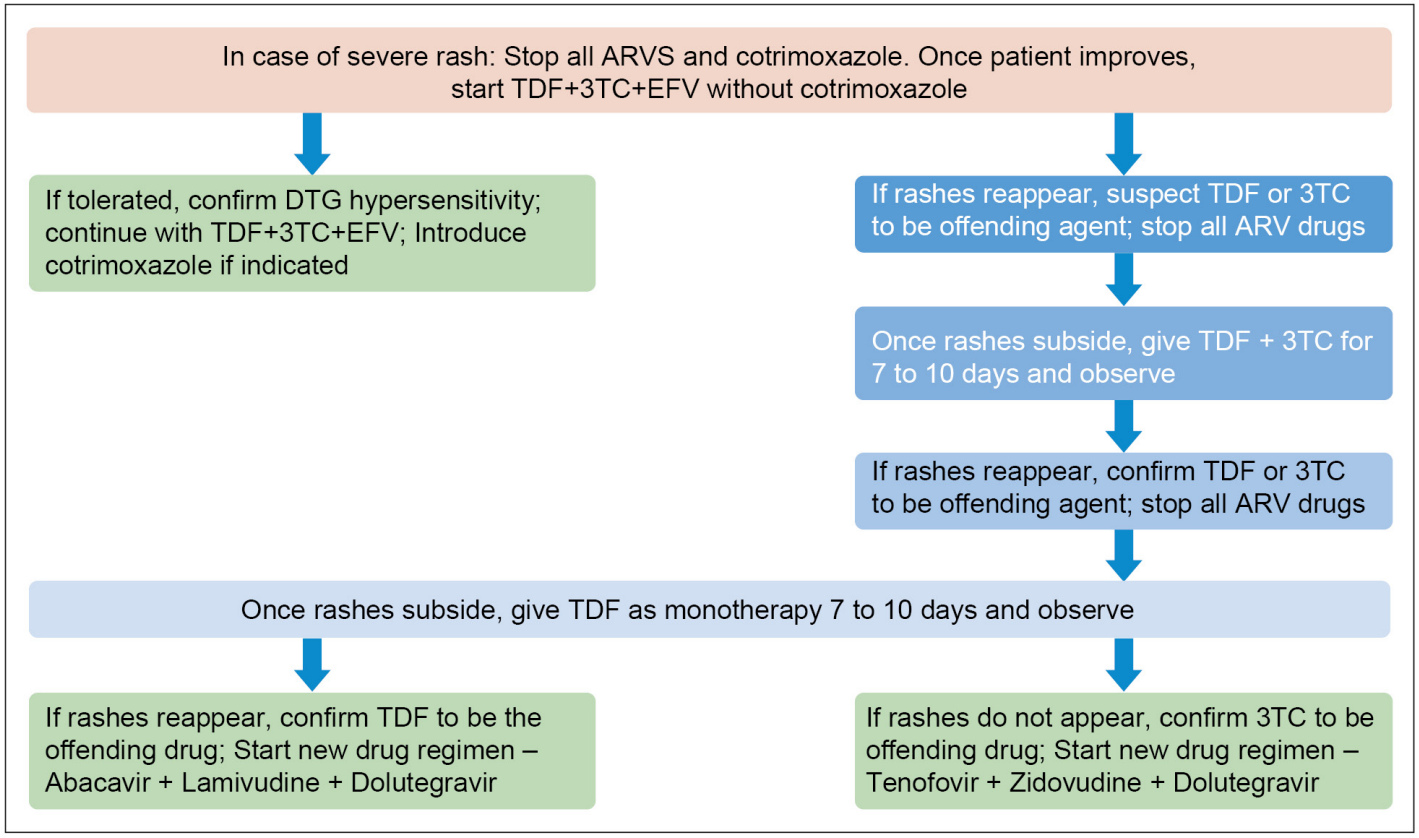
Adverse Effect	Possible Offending Drug(s)	Clinical Signs/ Symptoms	Management
Acute hepatitis	Nevirapine (NVP) and PI/r; Efavirenz (EFV) less common Uncommon with Zidovudine (AZT), Stavudine (d4T) (<1%)	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia, NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	Monitor serum transaminases and bilirubin. If ALT >5 times the baseline level, stop ARVs until symptoms resolve. NVP should be permanently discontinued. Substitute the most likely offending ARV drug.
Acute pancreatitis	Stavudine (d4T); Lamivudine (3TC) - infrequent	Nausea, vomiting and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ARVs should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., AZT, TDF, ABC).
Lactic acidosis	All Nucleoside reverse transcriptase inhibitors, particularly Stavudine (d4T)	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea), abdominal pain, hepatomegaly, anorexia, and/ or sudden unexplained weight loss, respiratory symptoms (tachypnoea and dyspnoea) or neurological symptoms (including motor weakness)	Discontinue all ART; symptoms may continue or worsen after discontinuation of ART. Give appropriate therapy. Resume ART by replacing offending ART with either ABC or TDF.
Hypersensitivity reaction	Abacavir (ABC) Nevirapine (NVP)	ABC: Constellation of acute onset of symptoms including fever, fatigue, myalgia, nausea / vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea (with or without rash). Although these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever, myalgia, arthralgia, hepatitis, eosinophilia with or without rash	Discontinue all ART until symptoms resolve. The reaction progressively worsens with drug administration and can be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ART with a change to different NRTI if ABC-associated or to PI- or NNRTI–based regimen if NVP-associated.
Rash/drug eruptions including Stevens-Johnson's Syndrome or Toxic Epidermal Necrolysis (TEN)	Nevirapine; Efavirenz Rarely: Dolutegravir, Lamivudine	Rash usually occurs during the first two to four weeks of treatment. The rash is usually erythematous, maculopapular, confluent; most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson's syndrome or TEN has been reported in ~0.3% of infected individuals receiving NVP	In mild cases, give antihistamines. If rash is moderate, non-progressing and without mucosal or systemic symptoms, consider substituting NVP to EFV after rash resolves. In moderate and severe cases, discontinue all ARVs until symptoms resolve and give supportive treatment.
			Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or Stevens-Johnson's syndrome or TEN. Once resolved, switch ART regimen to different ARV class (e.g., two NRTIs and PI).
Peripheral Neuropathy	Stavudine (d4T)	Pain, tingling, numbness of hands or feet, distal sensory loss, mild muscle weakness and areflexia can occur	Stop suspected NRTI early and switch to different NRTI that does not have neurotoxicity (e.g., AZT, ABC). Symptoms usually resolve in two to three weeks.
Diarrhoea	Lopinavir/ritonavir (LPV/r)	Loose or watery diarrhoea	Usually self-limited. No need to discontinue ART. Offer symptomatic treatment; if diarrhoea is not controlled, switch to ATV/r, as dose of RTV is less in ATV/r (mostly Ritonavir is responsible for diarrhoea).
Dyslipidaemia, Insulin resistance and hyperglycaemia	PIs, EFV		Consider replacing the suspected PI by drugs with less risk of metabolic toxicity.
Gastrointestinal intolerance	All ARVs	Gastritis, indigestion, etc	Usually self-limited. No need to discontinue ARVs. Offer symptomatic treatment.
Haematological toxicities, e.g., anaemia, leucopoenia	Zidovudine (AZT)	Fatigue, breathlessness, palpitation	If severe (Hb <6.5 g/dl and/or absolute neutrophil count <500 cells/mm^3), substitute with an NRTI that has less effect on bone marrow, e.g., d4T, ABC or TDF. Consider blood transfusion.
Lipoatrophy Lipodystrophy	All NRTIs; particularly Stavudine (d4T)	Lipodystrophy syndrome: dyslipidaemia consisting of elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides; insulin resistance with hyperglycaemia; central fat accumulation (visceral, breast, neck) and local fat accumulation (lipomas, buffalo-hump); generalized diminution of subcutaneous fat mass (lipoatrophy). Lipoatrophy includes loss of subcutaneous fat in the face, extremities and buttocks.	Early replacement of suspected ARV drugs (e.g., d4T) with TDF or ABC. Consider aesthetic treatment and physical exercises.
Neuropsychiatric changes	Efavirenz (EFV)	High rates of central nervous system effects in the first 2 weeks, e.g., confusion, abnormal thinking, nightmares, impaired concentration, depersonalization, abnormal dreams, dizziness, insomnia, euphoria, hallucinations, suicidal ideation. Severe depression has been reported in 2.4%	Usually self-limited. No need to discontinue unless severe psychosis. Counsel to take EFV at night before bedtime.
Renal Toxicity (Renal Tubular Dysfunction)	TDF	Features of Fanconi's syndrome, i.e., hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria. Acute renal failure has been reported. Risk factors—low body weight and pre-existing renal disease (Refer Annexure 3 for more details.)	Discontinue TDF and give supportive treatment. After resolution, replace with another ARV.

Note: Discontinuing the offending agent would mean substituting with an alternative drug to ensure efficacy of ART regimen.

Whenever rash/drug eruptions including Stevens-Johnson's syndrome or TEN occur during first- line ART in adults and adolescents, it is usual to condemn an NNRTI drug (EFV/NVP) as the causative agent. To hold EFV/NVP as the offending agent may not be always right. Clinicians always need to be alerted to suspect other offending agents as well.

- Cotrimoxazole can be an offending agent.
- Many ART centres have identified Lamivudine to be the offending drug in a limited number of patients.
- There are sporadic reports on skin rashes induced by Zidovudine/LPV/ATV/ritonavir/ Darunavir/Raltegravir/DTG/Lamivudine.
- Therefore, in this situation, it is essential to identify the offending drug before appropriate action is initiated. The clinicians are advised to follow the guiding algorithm given in Figure 2.6.2.

Figure 2.6.2: Algorithm for patients starting with ART regimen (TDF+3TC+DTG) with Cotrimoxazole prophylaxis



As a general principle, mild toxicities do not require the discontinuation of ART or drug substitution. Symptomatic treatment may be given. Moderate or severe toxicities may require substitution of the drug with another of the same ARV class, but with a different toxicity profile. Severe life-threatening toxicity requires discontinuation of all ARV drugs until the patient is stabilized and the toxicity is resolved. The patient may require hospitalization.

Grading of Toxicities

Toxicity to ARV drugs can be identified by clinical manifestations (symptoms, signs) and/or by abnormal laboratory parameters. Division of AIDS, National Institute of Allergy and Infectious Diseases (Version 1.0 December 2004) had categorized ARV drug toxicities into four grades:

- Grade 1: Mild
- Grade 2: Moderate

- Grade 3: Severe
- Grade 4: Potentially life-threatening

Grading of selected clinical and laboratory toxicities are given in Table 2.6.5. Refer Annexure 4 for more details.

Table 2.6.5: Grading of selected clinical and laboratory toxicities

Estimating Severity of Grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially Life-threatening Grade 4
Clinical adverse events NOT identified elsewhere in the table	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability, or death
Note: This clarification includes addition of Grade 5 toxicity, which is death.				

Source: Division of AIDS, National Institute of Allergy and Infectious Diseases. Version 1.0 December 2004 clarification August 2009

According to grading of toxicities, as reflected by severity of clinical adverse events, patients must be managed as guided with advisories given in Table 2.6.6.

Table 2.6.6: Grading of toxicities and management advisories

ARV Drug Toxicity	Grading of ARV Drug Toxicities			
	Grade 1	Grade 2	Grade 3	Grade 4
Severity	Mild	Moderate	Severe	Potentially Life-threatening
Clinical adverse events	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability or death
Advice	Changes of ART should be avoided. Observe.	Changes of ART should be avoided; observe.	It will usually be necessary to discontinue the suspected drug until the condition resolves. Subsequently, it may be possible to cautiously re-administer the drug (under close monitoring).	Discontinue all the drugs and hospitalize the patient. The offending drug should not be re-administered. After improvement, institute the alternate. ART regimen comprising of a drug substituted for the offending drug.

Drug Substitution

Definition

Substitution refers to replacement of ARV drug(s) in a PLHIV due to adverse effects of drug, drug–drug interactions or programme policy. This does not indicate change of regimen due to treatment failure.

It is different from ‘switch’, which indicates ‘treatment failure’, refers to the loss of antiviral efficacy to current regimen and triggers the switch of the entire regimen from first-line to secondline or second-line to third-line ART.

It is identified by clinical and/or immunological criteria and confirmed by the virological criteria. Drug regimen or single-agent substitutions may be required to manage drug toxicity and to avoid drug–drug interactions. Delaying substitutions when there are severe adverse drug reactions may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure.

When drug interruptions are required, such as for severe and life-threatening adverse reactions, it is important to consider the various half-lives of ARV drugs. For example, when an NNRTI needs to be discontinued, a staggered approach should be followed, in which the use of the NRTI backbone is prolonged for 2–3 weeks. Alternatively, the NNRTI could be temporarily replaced with a boosted PI.

General Guidance

- The general principle is that single-drug substitution for toxicity should be made within the same ARV class.
- If a severe or life-threatening toxicity occurs, all ART should be stopped until the toxicity has resolved, and a revised regimen commenced when the patient has recovered.
- Whenever an ARV toxicity is suspected, rule out other OIs or other conditions that may be responsible. Always grade the toxicity according to its severity: refer Table 2.6.5 and for more details refer **Annexure 4.**
- For patients with dual toxicity to NVP and EFV needing substitution with PIs, these (PI-based) regimens must be started by CoE/ART plus centre after the review and approval of e-SACEP.

Table 2.6.7 provides guidance on what to change (drug substitution) in case of toxicity manifestation.

Table 2.6.7: Drug toxicity and drug substitution

ARV	Most Frequent Significant Toxicity for ARV drug	Suggested First-line ARV Substitution Drug
Zidovudine (AZT)	Patients on older regimens (ZLN/ ZLE) – severe anaemia or neutropenia lactic acidosis; severe gastrointestinal intolerance	Tenofovir
Abacavir (ABC)	Hypersensitivity reaction	Tenofovir (Zidovudine, if TDF contraindicated)
Tenofovir (TDF)	Renal tubular dysfunction (Fanconi's syndrome), bone mineral density loss	Abacavir
Efavirenz (EFV)	Persistent and severe central nervous system toxicity; acute symptomatic hepatitis; severe or life-threatening rash (Stevens-Johnson's syndrome)	Dolutegravir (DTG)
	Severe neuropsychiatric manifestations	Dolutegravir (DTG)
Both EFV and Nevirapine	Persistent and severe central nervous system toxicity; acute symptomatic hepatitis; severe or life-threatening rash (Stevens-Johnson's syndrome); severe neuropsychiatric manifestations	Dolutegravir (DTG)
Dolutegravir (DTG)	Complication or toxicity to DTG – Women in child bearing age group or pregnant women opting out of DTG-based regimen	EFV-based regimen with appropriate two NRTIs (example: TLE) Please refer to following table for additional management information.
Atazanavir/ritonavir (ATV/r)	Intolerance	DTG
Lopinavir/ritonavir (LPV/r)	Intolerance	DTG
Multiple NRTIs (AZT, ABC, TDF)	Toxicities/Intolerance	DTG in combination with appropriate boosted PI

Table 2.6.8 provides specific toxicities of DTG and the remedial measures for hepatotoxicity, hypersensitive reactions and insomnia.

Table 2.6.8: Dolutegravir: Management of adverse drug effects including substitution

Toxicity	Risk Factors	Management
Hepatotoxicity/ Hypersensitivity reactions	Co-infection with Hepatitis B or C	• Substitute another therapeutic class • EFV or boosted PI
Insomnia	Older than 60 years	• Consider morning dose or substitute with EFV or boosted PI or RAL
Weight gain	• Older than 60 years • Low CD4 counts or high viral load • Female • Tenofovir alafenamide (TAF)	• Monitor bodyweight and promote anti-obesity measures (such as diet and physical exercise) • If significant increase despite measures, consider substituting EFV or boosted PI

Guidance in Impaired Renal Function

Preferred drug regimen: Abacavir + Lamivudine + Dolutegravir with dose adjustment of Lamivudine according to creatinine clearance

- For patients with creatinine clearance >30 ml/min, full dose of Abacavir (600 mg) + Lamivudine (300 mg) can be given;
- For patients with creatinine clearance <30 ml/min, if lamivudine 100 mg single tablet is not available, full dose of Abacavir (600 mg) + Lamivudine (300 mg) may be given with close monitoring with renal functions with repeated tests, till creatinine clearance improves. If creatinine clearance worsens, then the ART must be stopped, and the case must be referred immediately for SACEP opinion.

TB can manifest while patient is on ART. Table 2.6.9 summarizes the management plan in those situations. Sometimes, substitution of ARV drug may be necessary.

- When a patient already on 2NRTIs + 1NNRTI (EFV)–based regimen has to be given 2HREZ + 4HRE–based ATT for the newly detected TB, same ART regimen can be continued without any modification.
- When a patient already on 2NRTIs + DTG–based regimen has to be given Rifampicin-based ATT for the newly detected TB, same ART regimen can be continued, since co-administered rifampicin reduces bioavailability of DTG, which can be overcome by an additional tablet of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) till the completion of ATT. Once the ATT is completed, additional tablet of DTG 50 mg should be stopped 2 weeks after stoppage of Rifampicin-containing treatment regimen.
- When a patient already on 2NRTIs + PI–based regimen develops TB, ART regimen has to be modified if 2HREZ + 4HRE–based ATT is co-administered.
- Whenever a patient on boosted PI–containing first-line ART regimen develops TB, we have two options:

  Consider changing from boosted PI–based ART regimen to DTG-based ART regimen if patient has not received DTG earlier. Continue the same 2NRTIs with DTG 50 mg BD as shown in Table 2.6.9. Additional dose of DTG 50 mg should be continued for 2 weeks after completion of Rifampicin-containing ATT-2HREZ + 4HRE.
  If DTG-based regimen could not be given for any valid reason and boosted PI(ATV/r or LPV/r or DRV/r)–based ART regimen has to be continued, the ATT regimen has to be modified. Rifampicin, being a CYP inducer, suppresses bioavailability of PIs, thereby decreasing the efficacy of boosted

PI–based ART. Rifampicin should be replaced by Rifabutin 150 mg daily for the entire course of anti-TB treatment. Rifabutin is a derivative of Rifamycin and does not interact with boosted PIs.

Table 2.6.9: Management recommendations for TB diagnosed in patients already receiving ART

It is different from 'switch', which indicates 'treatment failure', refers to the loss of antiviral efficacy to current regimen and triggers the switch of the entire regimen from first-line to secondline or second-line to third-line ART.

ART Regimen When TB Is Diagnosed	Management Options
(AZT or TDF or ABC) + 3TC + EFV	Continue with (AZT or TDF or ABC) + 3TC + EFV ATT: 2HREZ + 4HR
(AZT or TDF or ABC) + 3TC + NVP	Substitute NVP with EFV and continue EFV thereafter even after TB treatment is completed. ATT: 2HREZ + 4HRE
Two NRTIs (AZT or TDF or ABC) + ritonavir-boosted PI	ART: Consider changing to DTG-based regimen if patient has not received or not failed on DTG. (Same 2NRTIs) + *DTG 50 mg bd (Additional dose of *DTG 50 mg should be continued for 2 weeks after completion of Rifampicin-containing ATT) ATT: 2HRZE + 4HRE daily regimen **ART: If the same PI-containing regimen has to be continued, modify ATT.** **ATT: Rifampicin must be replaced with Rifabutin 150 mg in anti-TB treatment regimen.**
TDF 300 mg + 3TC 300 mg + DTG 50 mg morning	TDF 300 mg + 3TC 300 mg + DTG 50 mg at morning + DTG 50 mg* at night

*Rifampicin in FDC can be used with a DTG-based ART regimen with an extra dose of DTG 50 mg (at an interval of 12 hrs with the regular dose of DTG) till the completion of ATT.

*DTG 50 mg extra dose should be stopped 2 weeks after the completion of Rifampicin-containing ATT.

2.7 ART Treatment Failure in Adults and Adolescents: When and What to Switch

Introduction

This chapter is applicable to all adults and children (10 years and older). For management of treatment failure in children below 10 years, please refer to Chapter 3.5 (Treatment Failure and Switch to Second-line ART in Children with HIV).

The most important goal of ART is to ensure maximal and sustained suppression of viral replication while maintaining future therapeutic options for PLHIV. Consistent high-level adherence to ART is the key to

achieve this goal of Viral Load suppression and to maintain patient on first-line ART for as long as possible.

Expected Response to Antiretroviral Therapy

Virological response to ART: The plasma viral load done 6 months after initiation of ART should come down to <1000 copies/ml and should be maintained at undetectable or <1000 copies/ml throughout the treatment course.

Immunological response to ART: CD4 counts of the patients should increase after initiation of ART. This increase is usually 50–100 cells/mm^3 within 6–12 months of ART initiation in ARV-naive patients, who are fully adherent to ART. Immunological response is defined as an increase of at least 50 CD4 cells/mm3 at 6 months of ART.

Clinical response to ART: Clinical monitoring should be done at every visit to the ART centre. Clinical monitoring should include evaluation of weight, general well-being (functional status), adverse reaction to drugs and keeping an eye out for IRIS, especially in patients with low CD4 count. Each visit should be taken as an opportunity to evaluate adherence through pill count to reinforce treatment adherence and provide nutritional counselling.

Various laboratory monitoring parameters with frequency of testing have been described in **Chapter 2.2 (ART in Adults and Adolescents).**
It is important to keep a high index of suspicion for treatment failure. **The following issues should raise suspicion of suspected treatment failure among patients who are on first-line ART for at least 6 months:**

- New OIs/recurrence/clinical events after 6 months on ART (after ruling out IRIS)
- Progressive decline in CD4 and counts
- Unsuppressed viral load
- Slow/no clinical improvement over 6–12 months, associated with stationary CD4 count, despite good adherence. In cases of suboptimal rise in CD4 count at 6 months, despite good adherence and no clinical symptoms, one may repeat CD4 count at 3 months.

Chronology and Identifying Treatment Failure

Treatment failure

Treatment failure refers to the loss of antiviral efficacy to the current regimen. Treatment failure can be identified through three different criteria: virological (identified through plasma viral load testing), immunological (identified through CD4 testing) and clinical (through clinical monitoring).

The sequence of treatment failure is virological failure followed by immunological and clinical failures, as depicted in Figure 2.7.1. As a person fails on the current ARV regimen, HIV viral load starts rising, which is followed by a decline in CD4 count and thereafter clinical signs or OIs occur or recur. There is a time lag of around 6 months or more between the two and this is followed again after a few months with some clinical stage 4 manifestations, which indicate clinical failure. Hence, to detect treatment failure, a viral load test can give indication much earlier than CD4 count decline or appearance of clinical symptoms and signs indicative of failure.

Virological failure

Virological failure means incomplete suppression of viral replication. Under the national programme, it is defined as a plasma viral load value of ≥1,000 copies/ml at or after 6 months of ART with >95% treatment adherence. Viral rebound after being undetectable is also considered virological failure. A low-level viral rebound (<1000 copies/ml), termed 'blips', usually indicates a statistical variation in the determination of Plasma viral load and this does not require switch in therapy. In such cases, a repeated viral load needs to be done after 3 months with enhanced adherence reinforcement. Plasma viral load remains the most sensitive indicator of ART failure. Recognizing failure early facilitates the decision to switch drugs before multiple resistance mutations develop to first-line drugs.

In general, the clinical status and serial CD4 cell counts should be used in an integrated fashion to suspect treatment failure while the patient is on ART. However, the switch of a regimen from the first-line to second-line therapy should be made on the basis of virological failure only.

It is important to note that the current clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. Compared to clinical or immunological monitoring, plasma viral load provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes. Measuring viral load can also help to distinguish between treatment failure and non-adherence. Studies suggest that around 70% of patients on first-line ART, who have a first high plasma viral load, will be suppressed following an adherence intervention, indicating non-adherence as the reason for the initial high plasma viral load in most cases.

Immunological failure

NACO has adapted following WHO criteria1 for immunological failure (any one of the following two):

- CD4 count at 250 cells/mm3 following clinical failure OR
- Persistent CD4 cell count below 100 cells/mm^3

One should keep in mind the phenomenon of virological-immunological discordance. Even though declining CD4 count helps in suspecting treatment failure, virological failure is essential for decision-making in switching over to second-line ART.

Clinical failure

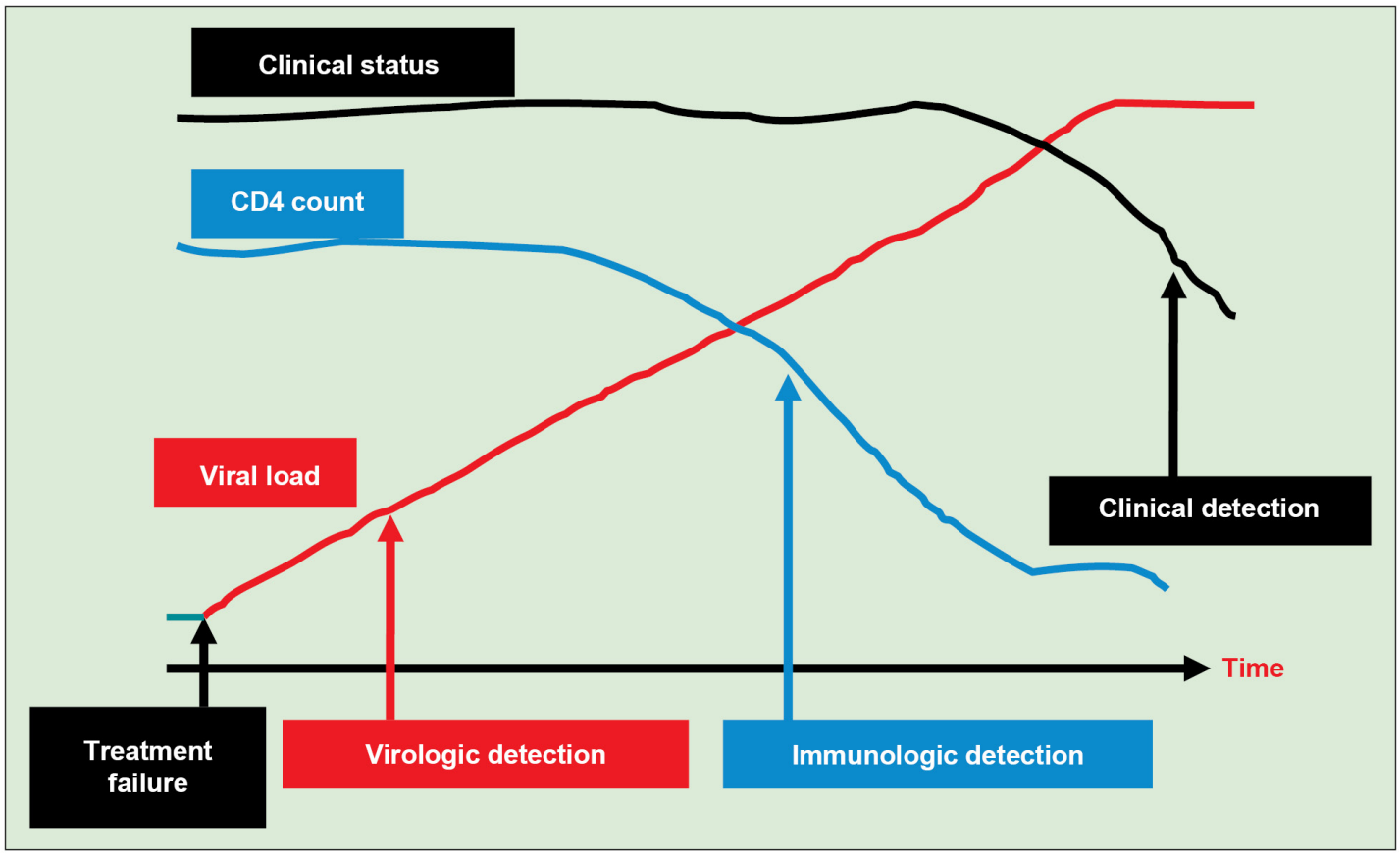
There should be a reasonable trial of first-line therapy lasting for at least 6 months before suspecting that the ARV regimen is failing based on clinical criteria. Adherence should be assessed and optimized, inter-current OIs treated and resolved and IRIS excluded before drawing such a conclusion.

The development of new or recurrent WHO stage 3 or 4 conditions while on treatment (after the first 6 months) is considered functional evidence of the progression of HIV disease. The assumption is that with immune restoration on ART, the subsequent progressive immunodeficiency means a failing ART regimen, the new clinical events signalling immune failure. This will be the same as those marking advanced and then severe immunodeficiency without ART, e.g., WHO clinical stage 3 and 4 conditions. TB can occur at any CD4 level and does not necessarily indicate treatment failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extra-pulmonary TB (e.g., simple lymph node TB or uncomplicated pleural disease), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. This also applies to severe and/or recurrent bacterial infections (as stage 3 or 4 events) or oesophageal candidiasis; they respond well to therapy. ('Switching' decision should be based on plasma viral load.).

Table 2.7.1: Definitions of treatment failure

Failure	Definition	Comments
Virological failure	Plasma viral load >1000 copies/ml	An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed
Immunological failure	• CD4 count at 250 cells/ mm^3 following clinical failure • Persistent CD4 cell count below 100 cells/mm^3	Concomitant or recent infection may cause a transient decline in the CD4 cell count. Some experts consider persistent CD4 counts of below 50 cells/mm^3 after 12 months of ART to be more appropriate.
Clinical failure	New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment	• The condition must be differentiated from IRIS. • Some WHO clinical stage 4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure. • For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure.

Figure 2.7.1: Chronology of treatment failure



Hence, compared to clinical or immunological monitoring, viral load monitoring provides an early and more accurate indication of treatment failure and the need to switch from first-line ART to second-line drugs, which can reduce the accumulation of drug-resistant mutants and thus improve clinical outcomes.

Identifying the cause of failure is important before deciding to modify the ART regimen. The following factors need to be assessed:

1. **Treatment adherence:** A detailed assessment of adherence needs to be made. The reasons for non-adherence need to be explored. Unless these reasons are identified, a patient will find it difficult to adhere to the second-line regimen.
2. **Drug–drug interactions:** Assessing whether the patient is concomitantly taking medications that interfere with ARV activity is important. For example, many patients may not reveal that they take herbal treatments along with the prescribed ART regimen.
3. Certain OIs and occult malignancies may lead to decline in the CD4 count, which may revert after treating those conditions.

   When failure is suspected or confirmed, a thorough assessment of the above-mentioned factors needs to be done. There could be one or more factors involved. Generally, causes of failure can be identified through history-taking and focused discussion with patient; however, in some cases these might not be obvious. Distinguishing among the causes of virological failure is important because the approaches to subsequent therapy may differ depending on the cause. Potential causes of failure should be explored in depth. Once failure is confirmed, steps should be taken to improve virological outcomes.

Confirming treatment failure

Plasma viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.

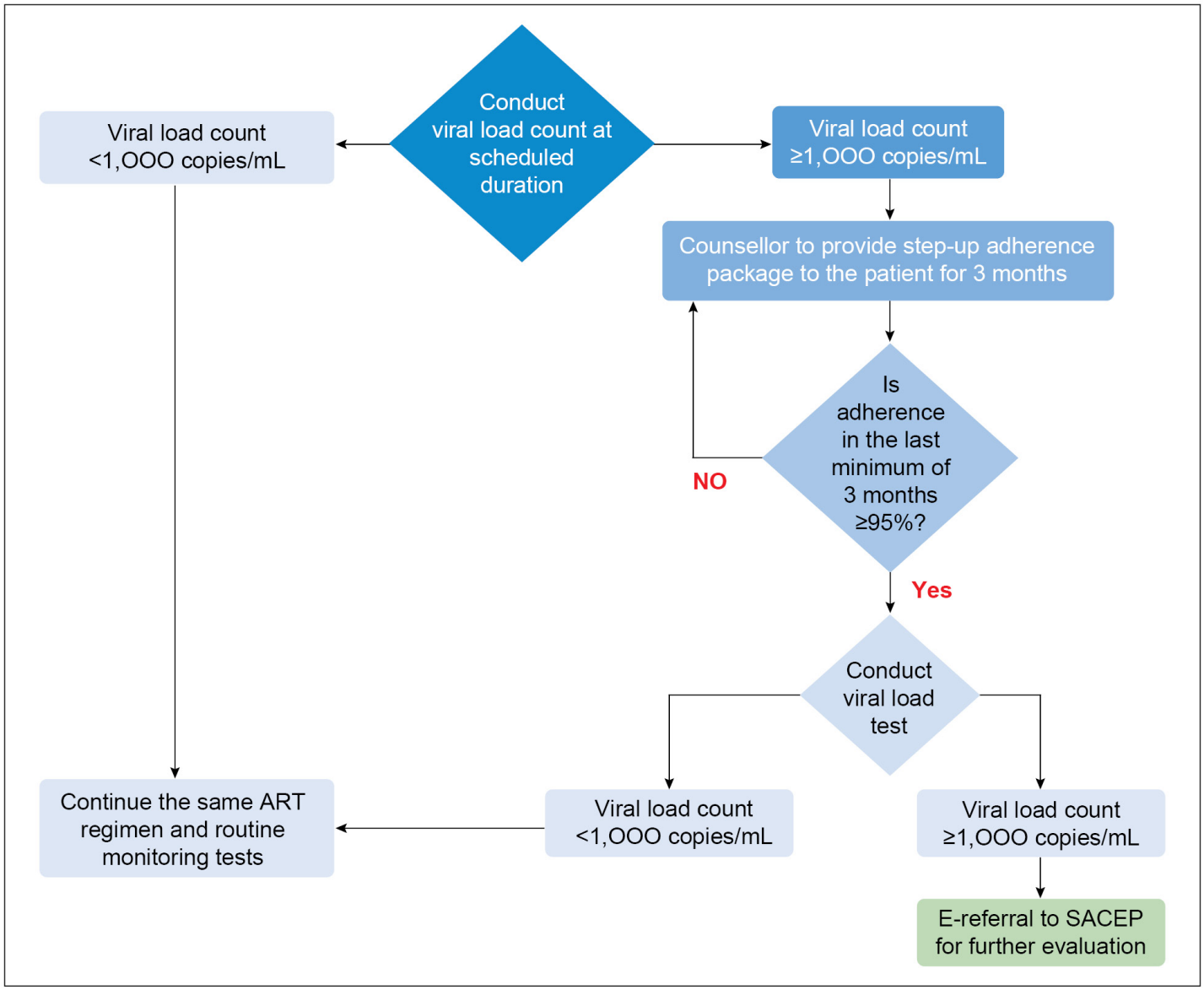
Timing of viral load test

1. For all patients on first-line ART, plasma viral load testing should be done at 6 months and 12 months after ART initiation and thereafter annually.
2. For all patients on second- or third-line ART, plasma viral load testing should be done every 6 months after initiation of second- or third-line ART.
3. The medical officer can request for additional plasma viral load test when deemed necessary for clinical management (e.g., during one drug substitution, new clinical event).
4. Plasma viral load testing is recommended for all HIV-positive pregnant women during 32 to 36 weeks of pregnancy (regardless of duration of ART) to determine the risk of HIV transmission to the baby (Refer Table 2.5.4).

Virological failure is identified by the detectable plasma viral load ≥1000 copies/ml during routine viral load monitoring, at least 6 months after ART, with >95% of treatment adherence for each of the last 3 months.

Currently under the national programme, plasma viral load testing is available only for HIV-1. Hence patients infected with HIV-2 should be monitored through CD4 testing and clinical monitoring. The immunological and clinical criteria for identifying failure shall be utilized for these patients.

Figure 2.7.2: Viral load testing algorithm



Poor adherence to ART is the most common cause of treatment failure. Adherence should be assessed and routinely reinforced by everyone in the ART team (physicians, counsellors, nurses, pharmacists, peer educators, NGO workers etc.) at each of the patient's visits to the ART centre.

Please refer **Chapter 2.4 (Adherence to ART) for more details on adherence counselling.**

Step-up adherence in patients with non-adherence or suspected treatment failure: Step-up adherence counselling is important in understanding possible reasons for non-adherence in a patient and then providing guidance to form an adherence plan. The counsellors should try to review psychological, behavioural, emotional and socioeconomic factors that may lead to non-adherence in a patient and provide customized counselling with the objective of improving adherence to treatment.

A minimum of three sessions are recommended for step-up adherence counselling but additional sessions can be conducted as needed. (Table 2.7.2 provides details of each session.) If adherence of patient is found to be adequate, a repeat viral load test is conducted 3 months after suspected treatment failure point to assess the benefits of step-up adherence counselling.

It is preferred that all counselling sessions are done by the same counsellor to ensure consistency, continuity and proper documentation of issue resolution. These sessions can be conducted when the patient visits to collect his/her medication.

Table 2.7.2: Overview of step-up adherence counselling sessions

Counselling Session	Counselling Issues to be Handled
Session 1 (Just after receiving the test results indicating suspected treatment failure)	• Review patient's understanding of viral load and discuss possible reasons for high viral load. • Assess possible barriers to adherence: ▪ Knowledge of medication – dosage and timing ▪ Motivation to take medicines ▪ Patient response to side effects (if any) ▪ Mental health (check for depression and other reasons) • Discuss patient's support systems. • Check patient's history with referral services such as support groups, medical clinics and evaluate their response to such services. • Support patient in developing an adherence plan that addresses the identified issues. • Check the patient treatment adherence (both pill adherence and appointment adherence) in the treatment card to create a baseline.
Session 2 (15 days or 1 month – as deemed fit by the counsellor at ART centre after Session-1)	• Review patient adherence between first and second sessions and discuss any emerging issues or gaps. • Follow up on any referral services that the patient undertook post the first session. • Support patient in modifying the adherence plan to tackle the identified issues. • Check patient treatment adherence again, and record it in the white card on a regular basis.
Session 3 (15 days or 1 month as deemed fit by the counsellor at ART centre after Session- 2)	• Review patient adherence between second and third sessions and discuss any emerging issues or gaps. • Support patient in modifying the adherence plan to tackle the identified issues. • Decide next course of action based on adherence: ▪ If adherence is good, plan a repeat plasma viral load test post 3 months of good adherence. ▪ If adherence is not adequate, plan further sessions with the patient before repeating Plasma viral load test. Explain the importance of adhering to the treatment and risk of treatment failure due to non-adherence.
Session after 'repeat plasma viral load test'	• Discuss results of the repeat Plasma viral load test. • Decide next steps based on repeat Plasma viral load test results: ▪ If Plasma viral load count <1000 copies/ml, appreciate the patient for his/her success and suggest continuation of current regimen; repeat Plasma viral load as per the scheduled frequency of the patient* ▪ If Plasma viral load count ≥1000 copies/ml, prepare the patient for a change in regimen.

On a case-by-case basis, in critically ill patients with high Plasma viral load, all the counselling sessions may need to be completed over a shorter span of time.

***Please note**

• Next Viral load test to be done after 12 months of the last viral load test in PLHIV on first line ART

• Next Viral load test to be done after 6 months of the last viral load test in PLHIV on second line ART

Adherence Support Systems

Support systems play a pivotal role in helping the patient being adherent. They need to be adaptable to patient needs. Children, adolescents, patients with mental disorder and substance users need special attention.

Treatment Failure to First-line and Second-line ART

Definitions

The working definitions of first-line and second-line ART regimens are as follows:

- **First-line ART:** First-line ART is the initial regimen prescribed for an ART-naive patient.
- **Second-line ART:** Second-line ART is the subsequent regimen used in sequence immediately after first-line therapy has failed.
- **Third-line ART:** Third-line ART is the subsequent regimen used in sequence immediately after second-line therapy has failed.

Substitution versus Switch

Any change of ARVs prescribed should be carefully distinguished between substituting a drug within a given regimen and switching an entire ART regimen:

- **SUBSTITUTION:** Substitution refers to replacement of ARV drug(s) in a virally suppressed PLHIV due to adverse effects of drug, drug–drug interactions or programme policy. This does not indicate change of regimen due to treatment failure. **Any substitution after 6 months should be preceded by viral load** testing. This helps to understand to whether a single drug substitution is enough (if Plasma viral load <1000 copies/ml) or whether the patient must be checked for treatment failure (if Plasma viral load ≥1000 copies/ml).
- **SWITCH:** Treatment failure refers to the loss of antiviral efficacy (Plasma viral load ≥1000 copies/ml) to the current regimen. When the regimen is changed because of ARV treatment failure, it is referred as the **switch** of the entire regimen.

Broad Principles and Objectives

All patients initiated on first-line ART need to be monitored carefully at every visit as per standard protocol on clinical and laboratory monitoring indicators. As emphasized earlier, a high index of suspicion is needed to detect first-line failure early.

One must start suspecting the possibility of failure of the regimen whenever a patient is found to have

- Increasing trend of plasma viral load (just around 1000 copies/ml);
- Static/declining trend in CD4 counts;
- New clinical manifestations (symptoms and/or signs)/worsening of existing condition.

Issues related to undetected OIs, and sub-optimal treatment adherence need to be addressed.

It is important to make appropriate pre-work-up and timely referral to SACEP for evaluation of such patients following the SACEP guidelines. Once the patient has undergone viral load test and been

evaluated by SACEP, if required, one of the following possible decisions will be conveyed by the SACEP of CoE/PCoE/ ART Plus centre to the referring ART centre:

- Switch to 'prescribed' second-line or third-line ART
- Regimen change not required
- Continue current ART, reinforce adherence and re-evaluate.
- Evaluate for HIV-2.

Once the decision has been made to change the regimen, the decision will be communicated to the referring centre. The second line can be initiated at the ART centre while for third line, initiation will be done at CoE/ART Plus Centre.

The objective of the second- and third-line ART is to prolong the survival of the PLHIV as much as possible with complete suppression of viral replication. This requires regular monitoring with viral load every 6 months for all patients on second/third-line ART.

Formulation of Second-line ART for PLHIV Failing First-line ART

Formulation of second-line ART is discussed in this section based on the following:

- Current NACO treatment guidelines for first-line ART (**Chapter 2.2 ART in Adults and Adolescents) in adults and adolescents** recommend a three-drug combination therapy from two classes of ARV drugs for initial treatment, i.e., 2NRTI + 1INSTI.
- Recently, NACO has adopted a strategy of treatment optimization, wherein patients on 2NRTI + 1NNRTI have been transitioned to INSTI-based regimen after viral load testing.
- It is important to document all changes in drugs/regimen taken by a patient during course of treatment to identify most optimum regimen for second/third-line regimen.

Current Recommendation for Second-line ART is based on the following

- A new class of ARV
    - an integrase strand transfer inhibitor (INSTI) (DTG), if first line was NNRTI based
    - a Ritonavir-boosted PI (Atazanavir/ritonavir or Lopinavir/ritonavir), if first line was INSTI based
- Supported by at least one new and unused NRTI (Zidovudine or Tenofovir)
- Continued Lamivudine administration ensures reduced viral fitness.

The steps to be followed in initiating second-line ART are given in Table 2.7.3.

Table 2.7.3: Steps in initiating second-line ART

STEP 1	Define treatment failure.	Define treatment failure by virological testing; see if adherence to treatment is adequate. Counsel and support. (SACEP will see these and take decision on providing second-line ART)
STEP 2	Decide on NRTI component of the second-line regimen.	• If Zidovudine (AZT) is used in first line, NRTI choice in second line is Tenofovir (TDF). If TDF/ABC is used in first line, NRTI choice could be AZT, unless contraindicated. • Continuing Lamivudine reduces viral fitness and must be part of second-line ART.
STEP 3	Decide on the other component • INSTI • PI	• If patient had NNRTI in first line, INSTI (Dolutegravir) will be preferred. • For patient who had INSTI in first line, give boosted PI (ATV/r) in combination. Use LPV/r in case of pregnant women or HIV-2.
STEP 4	Patient education and agreement on treatment plan including follow-up and monitoring	Include counselling for adherence, linkages to specialist care and follow-up monitoring plan

If failure has been identified/confirmed with delay or through clinical or immunological criteria, many patients can be expected to have significant NRTI resistance at the time of switching. Thus, in the decision-making for a second-line regimen with maximal antiviral activity, one must consider nucleoside class cross-resistance and drug interactions. The following facts must be considered for planning appropriate subsequent treatment regimen:

- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but often retains activity against nucleoside-resistant viral strains.
- TDF/ABC may facilitate evolution of the K65R drug resistance mutation, which mediates resistance to non-AZT NRTIs.
- NNRTI (such as EFV and NVP), usually there is complete cross-resistance.

The details of certain expected mutations with different NRTIs are provided in Table 2.7.4.

Table 2.7.4: Expected resistance mutations with different ARVs

Expected Resistance Mutations with Different NRTI Backbone	
Failing ARVs	**Mutations**
AZT or d4T + 3TC and AZT + 3TC + ABC	M184V and then successive NAMs (Cumulative, the longer one waits to switch)
TDF + 3TC	K65R and/or M184V
ABC + 3TC	L74V >K65R and/or M184V
AZT or d4T	TAMs, Q151M, T69ins
TDF + ABC and TDF	K65R
DTG	R263K, G118R, N155H and Q148H/R, with R263K and G118R
ATV/r	I50L, I84V, N88S
LPV/r	V32I, I47V/A, I50V, I54V/L/M, L76V, V82A/F/T/S, I84V
DRV/r	I47V, I50V, I54M/L, L76V, I84V

Once it is decided to switch the ART regimen, the following various scenarios should be considered for switching:

A. Second line recommendation for patients who had 2NRTI + NNRTI as first-line regimen:

This group may include the following patients:

- Women opting out of Tenofovir + Lamivudine + Dolutegravir (TLD) and are initiated/ continued on Tenofovir + Lamivudine + Efavirenz (TLE)
- Patients on NNRTI-based regimen not yet transitioned to DTG-based regimen.
- Patients substituted with NNRTI due to toxicity/contraindication to DTG

Table 2.7.5: Recommended ART regimens for patients failed to first-line ART containing NNRTI-based regimens

Failing First line ART	Recommended Regimens
TDF + 3TC + EFV/NVP	**Hb ≥9 g/dl** • AZT + 3TC + DTG (TDF to be maintained if the patient is co-infected with HBV*) **Hb <9 g/dl** • DTG + ATV/r + existing NRTI backbone
AZT + 3TC+ NVP/EFV	• TDF + 3TC + DTG (Use ABC if TDF contra-indicated)
Multi NRTI exposed + 3TC + EFV/NVP	• ATV/r + DTG + existing NRTI backbone (TDF to be maintained if the patient is co-infected with HBV*)

AZT - Zidovudine; ABC - Abacavir; TDF - Tenofovir

3TC - Lamivudine; EFV - Efavirenz; NVP - Nevirapine; ATV/r - Atazanavir/ritonavir; LPV/r - Lopinavir/ritonavir; DTG - Dolutegravir

*Refer to appropriate physician for further monitoring such as HBV DNA load and use of entecavir (Referral-linkage with NVHCP for optimal HBV treatment).

B. Second line recommendation for patients who had 2NRTI + Dolutegravir-based first-line regimens (TLD, ALD):

This group may include the following:

- All patients who have been initiated on TLD as per recent guidelines and have not been exposed to any other regimen
- All patients who have been on other regimen (ZLN/ZLE/TLN/TLE/ALE/ALN) and have been transitioned to TLD for treatment optimization with documented viral suppression prior to transition
- All patients who have been initiated on TLD and substituted with alternative option like (Abacavir) due to contraindication/toxicity of Tenofovir
- All patients who have been on 2NRTI +PI (TL/ZL/AL + ATV/r or LPV/r) as first line and transitioned to TLD based on documented viral suppression prior to transition

Table 2.7.6: Recommended ART regimens for patients failed to first-line ART containing Dolutegravir

Failing First line ART	Recommended Regimens
TDF + 3TC + DTG or ABC + 3TC + DTG	**Hb ≥9 g/dl** • AZT + 3TC + ATV/r • Use LPV/r in case of pregnant women or HIV-2 • TDF to be maintained if the patient is co-infected with HBV* **Hb <9 g/dl** • DTG BD + ATV/r + existing NRTI backbone • TDF to be maintained if the patient is co-infected with HBV*
AZT + 3TC + DTG	• TDF + 3TC + ATV/r • Use LPV/r in case of pregnant women or HIV-2 • Use ABC in place of TDF if use of TDF is contraindicated.
AZT - Zidovudine; ABC - Abacavir; TDF - Tenofovir; 3TC - Lamivudine; EFV - Efavirenz; NVP - Nevirapine; ATV/r - Atazanavir/ritonavir; LPV/r - Lopinavir/ritonavir; DTG - Dolutegravir *Refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir (Referral-linkage with NVHCP for optimal HBV treatment).	

C. Second line recommendation for patients who had 2NRTI + PI (TL/ZL + ATV/r or LPV/r) as first-line regimen:

This may include following patient group:

- All patients with HIV-2 who have been initiated on PI-based regimen and not transitioned to DTG-based regimen
- Patients initiated on PI-based regimen as first line outside national programme and later joined programme under universal access strategy
- Patients who were initiated on NNRTI-based regimen but due to toxicity/contraindication to NNRTI were shifted to PI-based regimen
- Women exposed to single dose NNRTI under PPTCT and then initiated on ART with PI- based regimen

Table 2.7.7: Recommended ART regimens for patients failed to first-line ART containing boosted PI-based regimens

Failing First line ART	Recommended Regimens
TDF + 3TC + ATV/r or TDF + 3TC + LPV/r or ABC + 3TC + ATV/r or ABC + 3TC + LPV/r	**Hb ≥9 g/dl** • AZT + 3TC + DTG • TDF to be maintained if the patient is co-infected with HBV **Hb <9 g/dl** • DTG + DRV/r BD + existing NRTI backbone • TDF to be maintained if the patient is co-infected with HBV
AZT + 3TC + ATV/r or AZT + 3TC + LPV/r	• TDF + 3TC + DTG • Use ABC in place of TDF if use of TDF is contraindicated.
AZT, Zidovudine; ABC, Abacavir; TDF, Tenofovir; 3TC, Lamivudine; EFV, Efavirenz; NVP, Nevirapine; ATV/r, Atazanavir/ritonavir; DTG, Dolutegravir; LPV/r, Lopinavir//ritonavir *Refer to appropriate physician for further monitoring like HBV DNA load and use of entecavir (Referral-linkage with NVHCP for optimal HBV treatment).	

Table 2.7.8: Comprehensive second-line ART regimens for PLHIV failing on first-line ART

Failing First line ART regimen		Second-line ART regimen
Tenofovir/ Abacavir containing	INSTI-based first-line ART (DTG)	**Hb ≥9 g/dl** • Zidovudine 300mg + Lamivudine 150mg (FDC)–BD + Atazanavir 300 mg + Ritonavir 100 mg (FDC)–OD **Hb <9 g/dl** or past H/O Zidovudine induced Anaemia • Dolutegravir 50mg BD + Atazanavir 300 mg + Ritonavir 100 mg (FDC)–OD+ existing NRTI backbone*
Zidovudine containing	INSTI-based first-line ART (DTG)	• Tenofovir (300 mg) + Lamivudine (300 mg) (FDC)–OD + Atazanavir (300 mg) + ritonavir (100 mg) (FDC)–OD
Zidovudine containing	NNRTI/PI-based first-line ART	• Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) – (FDC) - OD • If patient has contraindication to TDF, Abacavir (600 mg) + Lamivudine (300 mg) (FDC)–OD + Dolutegravir (50 mg) - OD
Tenofovir/ Abacavir containing	NNRTI-based first-line ART	**Hb ≥9 g/dl** • Zidovudine 300mg + Lamivudine 150mg (FDC)–BD+ Dolutegravir 50mg–OD **Hb <9 g/dl** or past H/O Zidovudine induced Anaemia • Atazanavir 300 mg + Ritonavir 100 mg (FDC)–OD + Dolutegravir 50 mg–OD+ existing NRTI backbone*
	Boosted PI-based first-line ART	**Hb ≥9 g/dl** • Zidovudine 300mg + Lamivudine 150mg (FDC)–BD + Dolutegravir 50mg OD **Hb <9 g/dl** or past H/O Zidovudine induced Anaemia • Darunavir 600 mg BD + Ritonavir 100 mg BD + Dolutegravir 50 mg–OD + existing NRTI backbone*
Multi NRTI exposed	NNRTI-based first-line ART	• Atazanavir 300 mg + Ritonavir 100 mg (FDC)–OD + Dolutegravir 50 mg–OD + existing NRTI backbone*
Multi NRTI exposed	PI-based first-line ART	• Darunavir 600 mg–BD + ritonavir 100 mg–BD + Dolutegravir 50 mg–OD + existing NRTI backbone*

- NRTI=TDF/AZT/ABC; NNRTI=EFV/NVP; Boosted PI=ATV/r/LPV/r
- Any PLHIV co-infected with TB and on Rifampicin-based treatment receives BD dose of DTG until 2 weeks after the completion of anti-TB treatment and subsequently OD dose is continued.
- Any PLHIV co-infected with Hepatitis B will receive TL if not already receiving entecavir.
- For those with HIV-2 or HIV-1 and 2 infection, pregnant women and toxicity to ATV/r, use LPV/r instead of ATV/r
- *If contraindicated, use another NRTI backbone.

Second-line ART Failure and Third-line ART

As the HIV (virus) is prone to error during replications, some patients on second-line ART may also develop resistance to their regimen. This happens particularly when the adherence of the patients was not

good, or they underwent late switching to second-line drugs and there were either few Thymidine Analogue Mutations (TAMS) while on NRTIs or K65R while on NtRTI-based regimen. These patients will eventually require third-line ARV drugs. The stepwise guidance for screening, referral, initiation and follow-up of patients failing to second-line ART is given below:

Monitoring of patients on second-line ART

- All patients on second-line ART need to undergo viral load testing every 6 months.
- The viral load algorithm shall be followed based on the result.
- Patients with unsuppressed viral load should undergo enhanced adherence counselling.
- Once optimum adherence is achieved for 3 consecutive months, repeat viral load test should be done.

Work-up of patients with suspected second-line failure

- All cases with suspected second-line failure need to be thoroughly evaluated for treatment adherence and presence of any major OI. If adherence is good and there is no major OI, such patients with second-line treatment failure should be referred to Centres of Excellence (CoE)/ART Plus first electronically with referral form containing latest relevant reports and complete history of treatment.
- If treatment adherence is poor or major OI is identified, utmost steps need to be taken to improve adherence and/or treat OI. Such patients should be closely monitored clinically, immunologically and virologically. If no improvement is seen by 3 months, the case should be referred to CoE/ART Plus for further assessment.

    Prescription of third-line regimen can be done by SACEP at CoE and selected ART Plus centres (selection based on capacity and functioning of SACEP by SACS in consultation with the linked CoE) after e-review (e-referral/telemedicine).
    In view of introduction of DTG and optimization of ART, initiation and dispensation of third-line ART is being decentralized to all the ART centres.

Initiation of third-line ART

- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens such as INSTIs and second-generation NNRTIs and PIs.
- Under the national programme, it has been decided to provide INSTI (Dolutegravir) and a new boosted PI (Darunavir/ritonavir). Accordingly, the regimen is Dolutegravir (50 mg) one tablet once a day + Darunavir (600 mg) + ritonavir (100 mg), one tablet each twice daily
- As per WHO recommendations, in some cases the existing NRTI backbone can also be continued for the possible retention of some ARV activity; however, it is to be used judiciously for the possible risk of cumulative toxicities of NRTI backbone. Therefore, the third-line prescription must be a more balanced one for long-term management and acceptance.
- In cases with difficulty in assessment of second-line failure, complicated prior treatment regimens, patients referred from private, multi-NRTI exposed cases, any intolerance to third- line drugs, cases requiring these third-line drugs as alternate within the second-line ART or any other query, SACEP at CoE can obtain expert opinion from National AIDS Clinical Expert Panel (NACEP) electronically, by addressing nacep.naco@gmail.com.

The following guidance is to be utilized. Various scenarios that can be encountered while prescribing third-line regimen and respective guidance is provided below (Table 2.7.9).

Table 2.7.9: Third-line ART regimens

Scenarios	Failed First Line	Failing Second Line	Recommended Regimen for Third Line
Patients who failed on 2 NRTI + NNRTI as first line, and now failing on PI-based second line	AZT/d4T / TDF / ABC + 3TC + NVP/ EFV	AZT / d4T / TDF / ABC + 3TC + ATV/r or LPV/r	DRV/r (BD)** + DTG OD + existing NRTI backbone* TDF to be maintained if the patient is co-infected with HBV
Patients who had 2 NRTI + NNRTI as first line, failed on it and are on INSTI-based second line	AZT / d4T / TDF / ABC + 3TC + NVP/ EFV	AZT / d4T / TDF / ABC + 3TC + DTG	DRV/r (BD)** + DTG 50 BD + existing NRTI backbone*
Patients who had 2 NRTI + PI as first line, failed on it and are on INSTI-based second line	AZT / d4T / TDF / ABC + 3TC + ATV/r or LPV/r	AZT / d4T / TDF / ABC + 3TC + DTG	DTG 50 mg (BD) + DRV/r (BD)** + existing NRTI backbone*
Patients who had 2 NRTI + PI as first line, failed on it and are on NNRTI-based second line	AZT / d4T / TDF / ABC + 3TC + ATV/r or LPV/r	AZT / d4T / TDF / ABC + 3TC + NVP/ EFV	DRV/r (BD)** + DTG 50 mg (OD) + existing NRTI backbone*
Patients who had 2 NRTI + PI as first line, failed on it and are on DRV/r BD second line	AZT / d4T / TDF / ABC + 3TC + ATV/r or LPV/r	AZT / d4T / TDF / ABC + 3TC + DRV/r (BD)	DTG 50 mg (OD) + DRV/r (BD)** + existing NRTI backbone*

*If contraindicated, use another NRTI backbone. TDF to be maintained for PLHIV with HBV coinfection

If viral suppression is not achieved on third-line therapy, then there is still benefit in continuing failing ART regimen because of the residual partial activity and 'crippling' effect of such ART.

** DRV/r (600/100 mg)

There could be some patients who failed on NNRTI-based regimen, were provided PI-based regimen as second line and then were transitioned to DTG-based regimen based on suppressed viral load.

Monitoring of patients on second/third-line ART

The protocol for laboratory monitoring of patients on second-line ART is described in Table 2.7.10..

Table 2.7.10: Monitoring of patients on second/third-line ART

Tests	Months						
	0	1	3	6	12	18	24
Hb, CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete LFT	Yes		Yes	Yes	Yes	Yes	Yes
Renal function test	Yes		Yes	Yes	Yes	Yes	Yes
Fasting blood sugar	Yes				Yes		Yes
Fasting lipid profile	Yes				Yes		Yes
Viral load	Yes			Yes	Yes	Yes	Yes
CD4 count	Yes			Yes	Yes	Yes	Yes

Timing for CD4 testing: CD4 testing should be done at 6 months.

A baseline CD4 count at the time of ART initiation is necessary to understand the presence of OIs and to determine immunological failure in the future.

- CD4 testing should be done every 6 months till CD4 count reaches >350 cells/mm3 and plasma viral load is <1000 copies/ml (when both tests are conducted at the same time).
- CD4 monitoring should be restarted for any patient if the patient has suspected treatment failure, i.e., virological failure (Plasma viral load ≥1000 copies/ml or if the patient has undergone a switch in regimen).
- The treating doctor can request for a CD4 test or viral load test when deemed necessary for clinical management.

HIV-TB in Second-line/Third-line ART Patients

TB is the most common OI among PLHIV. Although tuberculosis must be treated appropriately and on priority, in the context of second-line ART, drug–drug interactions must be considered.

Second/third-line regimens containing PIs

- Rifampicin alters the metabolism of PIs, including Lopinavir, Atazanavir, Darunavir and Ritonavir, and reduces effectiveness of standard doses.
- However, another Rifamycin, Rifabutin can be administered in the presence of PI-containing second-line ART regimen without compromising the efficacy of ART or anti-TB treatment.
- Therefore, NACP and NTEP have recommended the substitution of Rifampicin with Rifabutin for the entire duration of anti-TB treatment.
- The dosage of Rifabutin during the administration of Atazanavir/ritonavir or Lopinavir/ ritonavir or Darunavir/ritonavir-based second-line or third-line regimen shall be 150 mg daily for all patients weighing >30 kg for the entire period of co-administration of anti-TB treatment and second-line ART, as presently NACO ART centres provide daily anti-TB treatment regimens for drug-sensitive TB patients.
- Whenever Rifabutin is prescribed, instead of the usual FDC packs, individual anti-TB drugs (without rifampicin) must be dispensed to the patients as per weight band.

- Some of the common side effects of Rifabutin include orange-brown discolouration of skin, tears, saliva, sweat, urine and stools during Rifabutin administration
- The ART centre SMO/MO should be contacted as and when the patient experiences chest pain, muscle aches, severe headache, fatigue, sore throat, flu-like symptoms, vision changes, unusual bruising or bleeding, nausea/ vomiting and/or yellowing of the skin or eyes.

Initiation of PI-based ART in Patient Already on Anti-TB Treatment

- If a patient is already on anti-TB treatment and needs to be initiated on PI-based second-line or third-line ART, then substitute Rifampicin with Rifabutin for 2 weeks prior to initiation of the second-line ART. This should be done to allow hepatic metabolism (induced by Rifampicin) to normalize prior to initiation of PI-containing regimens. While the patient is counselled and prepared for initiation of second-line or third-line regimen, the patient should still be given the existing ART regimen.

Initiation of anti-TB treatment in patients already on PI-based ART

- If the patient is already on PI-based ART (Atazanavir/ritonavir or Lopinavir/ritonavir or Darunavir/ritonavir-containing regimens) and detected to have TB, substitute rifabutin for rifampicin within the prescribed anti-TB regimen from the start of TB treatment.

Second/third-line regimens containing integrase inhibitors

- DTG can be safely co-administered with rifampicin.
- However, the dose of DTG, while being co-administered with rifampicin, is 50 mg twice daily.

Drug toxicity of drugs used in second/third line

- The major toxicities of the second-line drugs are depicted in Table 2.7.11.

Table 2.7.11: Management of side effects related to the second- and third-line regimens

Antiretroviral	Side Effect/Toxicity	Management
Tenofovir (TDF)	• Usually well tolerated • Minor: weakness and lack of energy, headache, diarrhoea, nausea, vomiting and flatulence • More serious side effects include kidney failure and pancreatitis • TDF can reduce bone mineral density.	• Monitor renal function test as per NACO protocol. • Symptomatic management of minor side effects • Calcium supplements may be used in patients with osteoporosis.
Dolutegravir (DTG)	• Usually well tolerated; Reported adverse effects include • Insomnia, headache • Depression and suicidal ideation (rare; usually occurs in patients with pre-existing psychiatric conditions) • Weight gain • Hepatotoxicity • Potential for increased risk of Neural tube defects in infants born to individuals who received DTG around the time of conception is lower than previously reported. • Hypersensitivity reactions, including rash, constitutional symptoms and organ dysfunction (including liver injury) can occur rarely.	• Symptomatic management of minor side effects • Informed consent from women in reproductive age group
Atazanavir (ATV	• Apart from the PI-class specific side effects like hyperglycaemia, fat maldistribution, hyperlipidaemia (especially with Ritonavir [RTV] boosting), increased bleeding episodes in haemophiliacs etc., the unique side effects of Atazanavir include indirect hyperbilirubinemia (producing yellow discolouration of eyes), skin rash, nephrolithiasis and cholelithiasis (rare). **Unique drug interaction involving Atazanavir:** • In addition to all the drug interactions involving PI class, ATV has significant drug interaction with antacids, H2 Receptor antagonists and proton pump inhibitors*	• The patients need to be counselled that they may appear to be jaundiced with yellow eyes, but they should not be afraid as it would only be a cosmetic problem (like Gilbert's disease). It should not be taken as hepatotoxicity. However, LFT must be done should someone appear to have jaundice. Also, they should be advised to consume plenty of water. • Refer to Annexure 5 for management of Atazanavir induced Unconjugated Hyperbilirubinemia. • Antacid: Give Atazanavir at least 2 hours before or 1 hour after antacids or any buffered medications (For details please refer Table 2.7.12).
Lopinavir boosted with ritonavir (LPV/r)	• Side effects include abdominal pain, abnormal stools or bowel movements, diarrhoea, feeling weak/tired, headache and nausea • In addition, patients taking Lopinavir should be monitored for possible liver problems. • People who have liver disease, such as hepatitis B or hepatitis C, may experience a worsening of their liver condition. A small number of patients have experienced severe liver problems.	• Symptomatic management of minor side effects • Supportive counselling and use of other drugs to manage gastrointestinal effects should be done. These symptoms improve after a few weeks. • Monitor LFTs, lipid profile and blood sugar regularly
Lamivudine (3TC)	• Very minimal side effects. They include cough, diarrhoea, dizziness, headache, loss of appetite, mild stomach cramps or pain. • More serious side effects include burning, tingling or pain in the hands, arms, feet or legs; chills; ear, nose or throat problems; fever, muscle aches, nausea, pale skin, severe stomach pain, skin rash are seen rarely.	• Symptomatic management of minor side effects
Darunavir (DRV)	• **Skin Rash:** DRV has a sulphonamide moiety; however incidence and severity of rash are similar in those with or without a sulphonamide allergy; Stevens-Johnson's syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and erythema multiforme have been reported. • Other adverse effects can be Hepatotoxicity, gastrointestinal intolerance, Headache, Hyperlipidaemia, Serum transaminase elevation, Hyperglycaemia • Fat maldistribution	• Symptomatic management of minor side effects • Supportive counselling and use of other drugs to manage gastrointestinal effects should be done. These symptoms improve after a few weeks. • Monitor LFTs, lipid profile and blood sugar regularly.

Table 2.7.12: Drug-drug interactions with second/third-line ART

Antiretroviral Drug	Major Drug–Drug Interactions
Dolutegravir (DTG)	• Al, Mg, +/- Ca-containing Antacids: Administer DTG at least 2 hours before or at least 6 hours after antacids that contain polyvalent cations • Polyvalent Cation Supplements: Mg, Al, Fe, Ca, Zn, including multivitamins with minerals: Administer DTG and supplements that contain Ca or Fe together with food, or administer DTG at least 2 hours before or at least 6 hours after supplement. Do not co-administer DTG under fasting conditions simultaneously with, or 2 hours after, supplements that contain Ca or Fe. • Rifampicin: Rifampicin can decrease concentration of DTG. Use DTG 50 mg twice daily instead of DTG 50 mg once daily while co administering with Rifampicin • Carbamazepine: Carbamazepine can decrease concentration of DTG. Increase DTG dose to 50 mg twice daily. • Metformin: DTG increases concentration of metformin. Start metformin at lowest dose and titrate based on glycaemic control. Monitor for adverse events of metformin. The dose of metformin should not exceed 1 gm/day.
All Protease Inhibitors (PIs)	• Avoid concurrent use of Astemizole, Cisapride, Fluticasone, Indinavir, Lovastatin, Simvastatin, Midazolam and Terfenadine. • Rifampicin: Decreases concentration of boosted PIs. Should not be used concomitantly • Atorvastatin: Increased concentration of Atorvastatin is possible; administer the lowest effective atorvastatin dose while monitoring for adverse events
Atazanavir (ATV)	Atazanavir (ATV) needs an acidic environment to be absorbed. The bioavailability of Atazanavir may decrease when given with antacids. Use ATV/r at least 2 hours before or 1 hour after antacids. **H2 Receptor Antagonist** • Administer ATV at least 2 hours before or 1 hours after the H2 receptor antagonist Example: if PLHIV is on ZL ATV/r: If a patient on Zidovudine + Lamivudine + Atazanavir/ritonavir requires to be treated with Famotidine 20 mg BID or Ranitidine 150 mg BID, she/he should be advised to take Tablet Famotidine/Ranitidine with Zidovudine + Lamivudine in morning at 8.00 am and take ZL and ATV/r at 8 pm in the evening. It has to be ensured that there is a gap of at least 2 hours before or 1 hours after Famotidine/Ranitidine evening dose. H2 receptor antagonist dose should not exceed a dose equivalent to Famotidine 40 mg BID in ART-naive patients or 20 mg twice daily (BID) in ART-experienced patients. **Proton Pump Inhibitors (PPIs)** PPIs are not recommended in ATV/r. Other drugs: • Carbamazepine: There is possible increase concentration of Carbamazepine. Carbamazepine dose reduction may be necessary. Concentrations of PI may reduce substantially. Consider alternative ARV or anticonvulsant. If co-administration is necessary, consider monitoring concentrations of both drugs and assess virological response. Carbamazepine dose reduction may be necessary. • Contraceptives: Decrease in concentration of oral contraceptives is expected. When co-administered, Oral contraceptive should contain at least 35 mcg of ethinyl oestradiol. • Buprenorphine: Area under the curve (AUC) ↑66% • Norbuprenorphine (active metabolite) Area under the curve AUC ↑105% • Monitor for sedation and other signs or symptoms of overmedication. Buprenorphine dose reduction may be necessary. It may be necessary to remove implant and treat with a formulation that permits dose adjustments. • Methadone: Opioid withdrawal is unlikely but may occur. Monitor for opioid withdrawal and increase methadone dose as clinically indicated.

2.8 HIV-TB Co-infection: Case Finding, Management and Prevention of Tuberculosis

Introduction

People living with HIV are 16 (uncertainty interval 14–18) times more likely to fall ill with TB disease than people without HIV.[1] TB accelerates HIV disease progression and HIV paves the way for clinical TB and Mycobacteremia. TB is the most common OI in PLHIV. It is also well recognized that HIV and TB make a fatal combination with extremely high death rates. TB is a primary and leading cause of AIDS-related death among PLHIV. India accounted for TB incidence of 53,000 (36,000 - 72,000); 3.8% (2.6-5.2%) among PLHIV in 2022.[1] Early diagnosis, effective TB treatment, prompt linkage to HIV care and early initiation of ART and TPT are key factors for reducing the negative impact of TB in PLHIV.

Effective linkages between the NACP and NTEP promoting intensified TB case finding and TPT in PLHIV, airborne-infection control (AIC) in HIV care settings and early initiation of ART in HIV/ HIV–TB cases are strategies targeted at mitigating morbidity and mortality due to TB. NACP and NTEP continue to provide seamless single window services to PLHIV for prevention and management of HIV-TB co-infection at ART centres.

Understanding TB

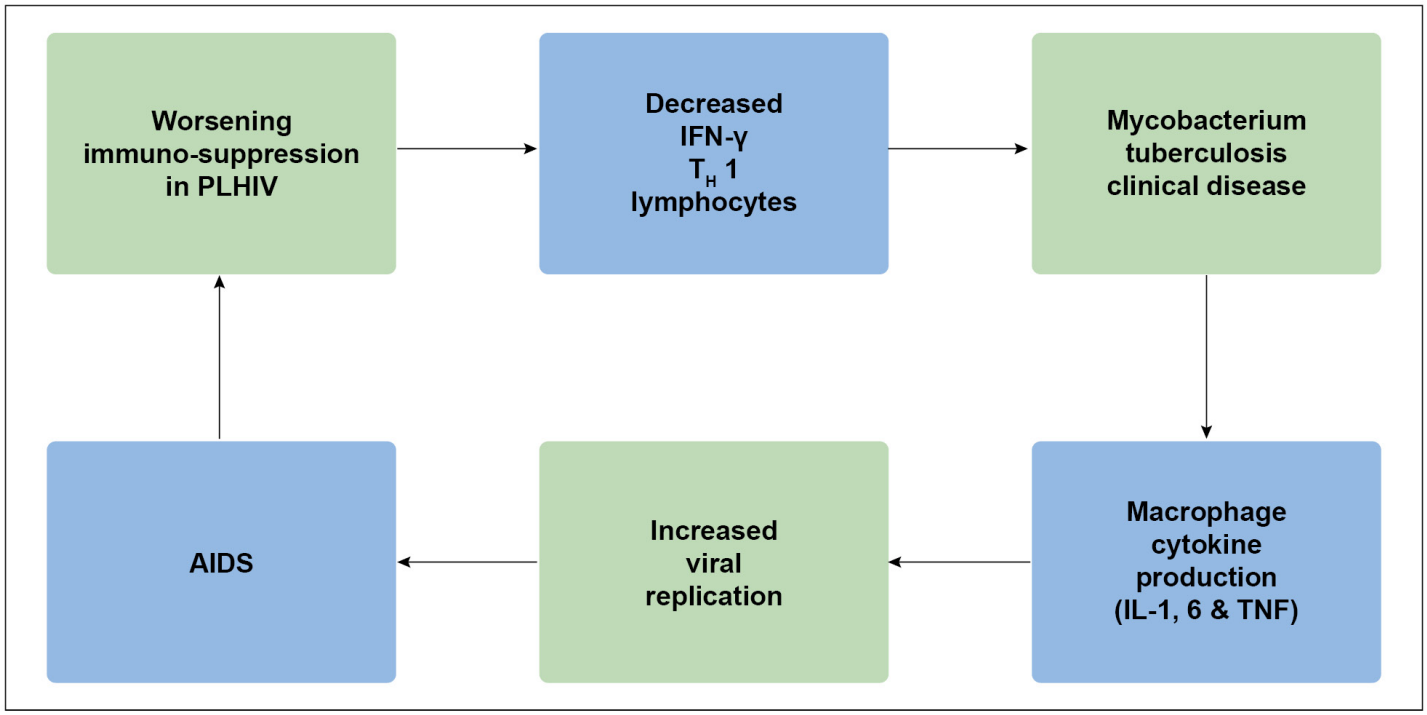
TB is caused by the bacilli, Mycobacterium tuberculosis (MTB). TB is an airborne infection and occurs when a person inhales MTB-containing droplet nuclei. Usually 2–12 weeks after infection, the multiplication of the bacilli is limited by body's immune responses and goes on to the development of the asymptomatic condition known as Latent TB infection (LTBI). In LTBI, though viable bacilli persist in the body for years, there are no symptoms or signs of disease, and the person is not infectious. On the other hand, active TB disease is a symptomatic illness requiring treatment. It may develop soon after exposure to MTB (primary disease), or more commonly after reactivation of the existing Latent TB infection. Active TB disease may be confined to the lung parenchyma and airways (pulmonary TB), or may involve organs other than the lungs (extra pulmonary TB) e.g., pleura, lymph nodes, abdomen, central nervous system, bone, joints, skin, etc. A TB patient may have lung (pulmonary) involvement, with or without involvement of one or more extra pulmonary organs.

HIV-associated TB

HIV and TB have a bidirectional interaction, with each disease worsening the other. HIV affects Th-1 (T helper type 1) responses in the body (i.e., cell-mediated immune responses), which are the central immune defences against MTB. As a result of this immune compromise, advancing HIV infection increases the risk of reactivation of Latent TB infection into progressive primary TB disease and later endogenous reinfection TB disease.

On the one hand, HIV infection leads to higher TB caseloads and deaths, and on the other, active TB also worsens HIV disease. TB-induced systemic immune activation leads to secretion of pro-inflammatory markers like Interleukin 6, TNF alpha leading to progression of HIV infection. Active TB also causes an increased number of HIV viral entry co-receptors (CCR5 and CXCR4) on human target cells allowing increased viral entry and thus viral replication (Figure 2.8.1). These factors lead to rapid increase of viral load by 6-7 times in an HIV-TB patient, leading to a rapid decline in the CD4 counts and the health of the patient.

Figure 2.8.1: HIV and TB interaction in human host



If depleted immune response is not taken care by early and appropriate ART, recurrent TB (reinfections and relapses) and treatment failure are inevitable. This increased risk for TB is seen throughout the course of HIV disease but decreases significantly with ART and TPT. Once PLHIV get active TB, due to deficient cell-mediated immunity, the disease is often disseminated and has unusual presentations. Therefore, though pulmonary TB is still the most common form of active TB in PLHIV, frequent involvement of extra pulmonary organs (often in multiple sites) is seen in PLHIV when compared to HIV-negative population.

HIV-TB co-infection also merits special consideration because of various issues encountered when co-managing HIV and TB. Treatment of dual disease is complicated by drug interactions between ATT and ART, additive drug toxicities of ATT and ART, TB-associated immune reconstitution inflammatory syndrome, adherence to dual treatment and issues of pill burden. For better understanding of the multiple concepts involved in HIV–TB treatment and care, this chapter has been broadly divided into two sections:

I. General principles for management of HIV–TB coinfected patients
A Diagnosis and management of Drug-Sensitive TB (DS-TB) and Drug-Resistant TB (DR- TB) in PLHIV
B. Diagnosis and management of DS-TB and DR-TB in CLHIV
II. General principles for prevention of TB in PLHIV

General Principles for Management of HIV-TB Coinfected Patients

Management of HIV-TB broadly includes early diagnosis of TB, prompt initiation of effective and appropriate TB treatment and its monitoring and timely administration of ART and CPT.
The following are the general principles for management of HIV-TB coinfected patients:

- Intensified Case Finding (ICF) using 4S Complex, fast tracking and referral of symptomatic patients for rapid molecular diagnostics Nucleic Acid Amplification Test (NAAT, CBNAAT or Truenat), and other appropriate investigations, as required, for TB diagnosis;
- Prompt and effective treatment of active TB in PLHIV in accordance with the NTEP guidelines;

- Early initiation and continuation of ART in PLHIV with TB co-infection;
- Cotrimoxazole Preventive Therapy (CPT) in all PLHIV with TB co-infection. They must receive CPT for the entire duration of TB treatment and beyond till CD4 count crosses >350 cells/mm3 and sustains at that level even beyond 6 months.
- Early initiation and continuation of ART in PLHIV coinfected with TB.

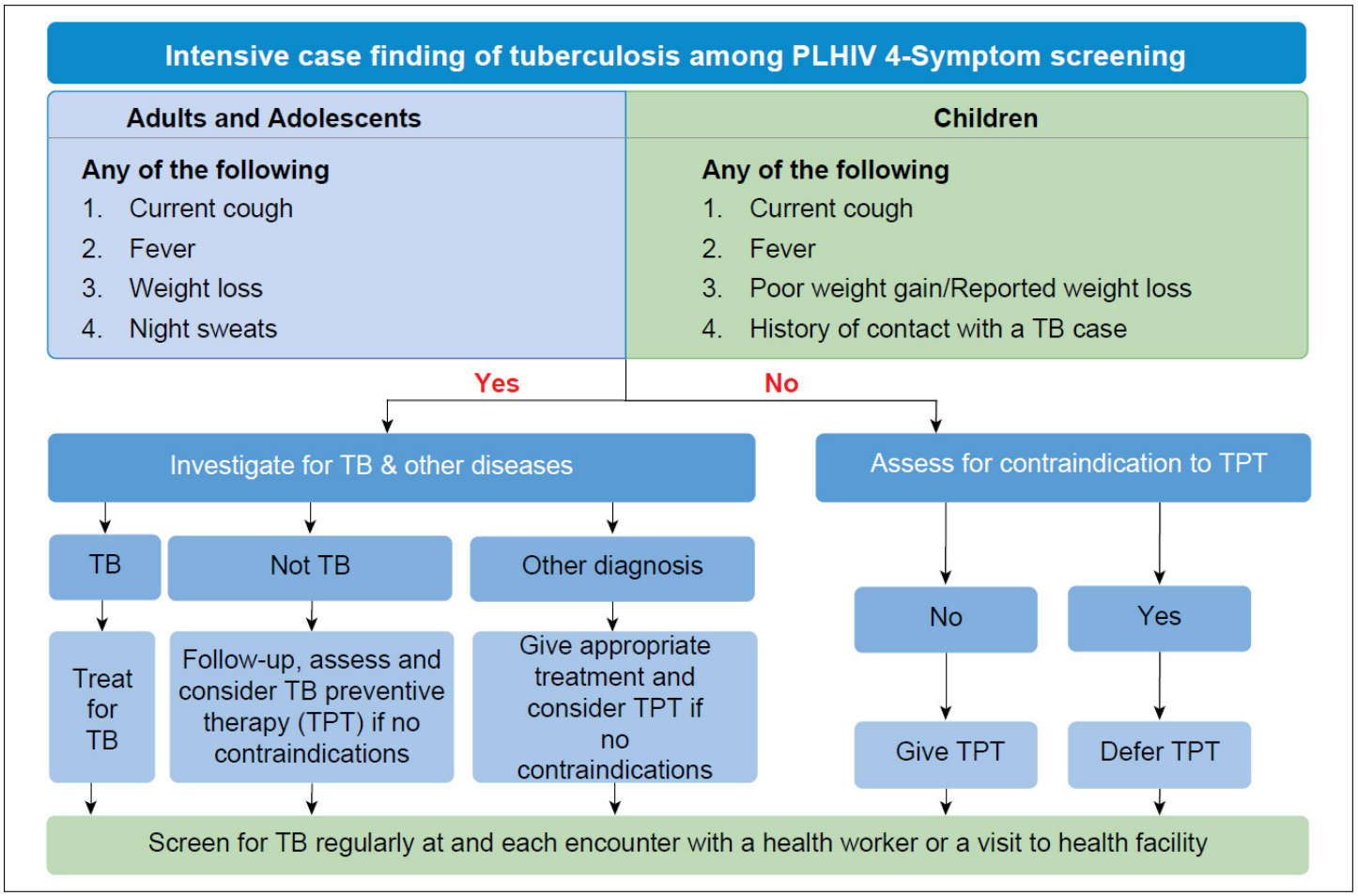
Intensified Case Finding at ART Centres Using 4S Complex, Fast Tracking and Referral for TB Diagnosis

Intensified case finding (ICF) involves systematic screening for active TB among PLHIV, both new and those on follow-up at each visit to the ART Centre. ICF is one of the critical interventions for increased TB case detection. It is an important step towards early diagnosis and TB treatment to reduce mortality, prevention of ongoing TB transmission and an initial step to rule out active TB disease to enable early TPT initiation.

All PLHIV should be regularly screened for TB during every visit to the ART Centre looking for the presence of any of the 4-symptoms—current cough, fever, weight loss and/or night sweats among adults and adolescents. In children, the 4-symptom TB screening includes current cough, fever, poor weight gain and/or history of contact with a TB case. PLHIV with all forms of TB showed that the sensitivity of 4S complex (current cough, fever, weight loss and night sweats) was 85%. Figure 2.8.2 presents the algorithm for ICF at ART centres. It may be noted that for all PLHIV newly registered in HIV care, use of chest x-ray alongside 4 TB symptom screening is recommended at the medical officer level.

PLHIV/CLHIV found positive for any of the four symptoms (4S+), should be considered presumptive TB and fast-tracked for TB diagnostic work-up.

Figure 2.8.2: Algorithm of ICF-four symptoms (4S) screening at the ART centre



Diagnosis of TB in PLHIV

PLHIV found positive for any of the four symptoms (4S) screened should be referred for molecular diagnostics NAAT and/or other appropriate investigations. A presumptive TB case once fast- tracked to the ART MO, must undergo detailed history taking for symptoms other than 4S – loss of appetite, chest pain, shortness of breath, haemoptysis, as well as organ specific symptoms and signs for extra pulmonary TB (EPTB) like swelling of lymph node, pain in abdomen, pain and swelling in joints, convulsions, neck stiffness, disorientation, etc.

To diagnose TB, appropriate diagnostic tools must be used. Microbiological tests are the mainstay of aetiologic TB diagnostic work-up. Microbiological tests not only provide confirmatory diagnosis of TB but also help in reliable monitoring of treatment outcome; they also provide vital information about drug resistance. Therefore, a microbiological confirmation of TB disease from a biological specimen like sputum, induced sputum, bronchoalveolar lavage (BAL), fine needle aspirate, CSF, pleural fluid or gastric aspirate must always be sought from every presumptive TB case.

TB-LAM (Lipoarabinomannan) lateral flow assay test is a promising point-of-care immunochromatographic dipstick assay that detects mycobacterial lipoarabinomannan in urine. It is used for patients with signs and symptoms of TB (pulmonary and/or extra pulmonary) or patients with advanced HIV disease or who are seriously ill or patients with CD4 count less than 200 cells/mm^3.

Please refer Chapter 4.2 (Central Nervous System) (Respiratory system for more details on diagnostic tools).

As per NTEP guidelines, rapid molecular diagnostic test/NAAT (CBNAAT or Truenat) is the preferred diagnostic technique for TB testing in PLHIV wherever appropriate biological specimen from site is available for testing. Where biological specimens are not available, the patients should be referred for other appropriate investigations based on symptoms and signs. Approach to TB diagnosis in PLHIV is illustrated in Figure 2.8.3.

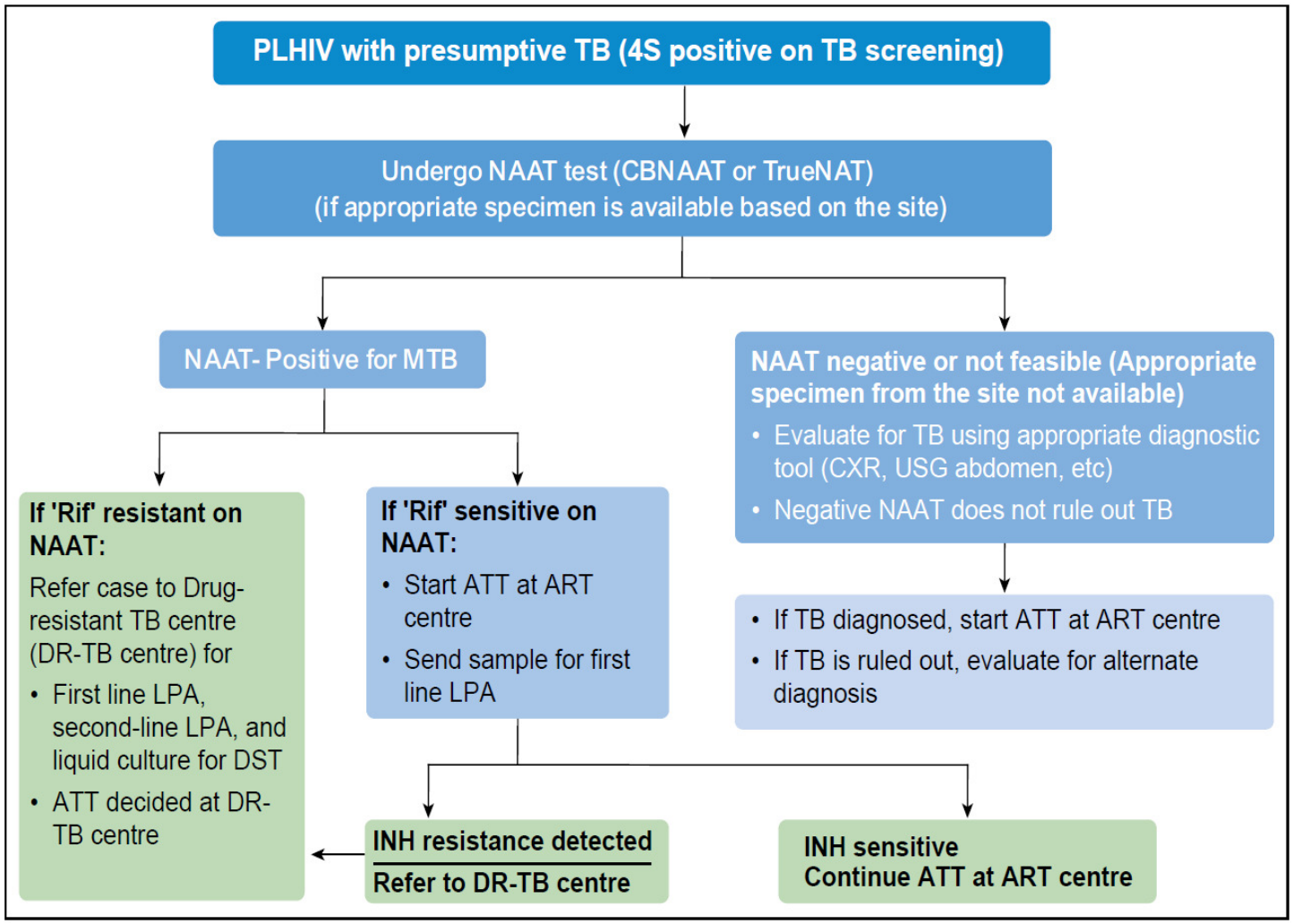
Rapid molecular diagnostic test/ Nucleic Acid Amplification Test (NAAT): NAAT is a molecular test that detects the DNA of the TB bacteria in PLHIV. It uses sputum or any other biological specimen like induced sputum, pleural aspirate, gastric aspirate, bronchoalveolar lavage, CSF (except blood and blood-contaminated specimens) and can give a result in less than 2 hours. It can also detect the genetic mutations associated with resistance to the drug rifampicin. As per studies, the median sensitivity of smear microscopy was 52.8% (range 22.2%–68.9%), compared to 84% (58.3%–91.7%) with NAAT. It may be noted that for non-respiratory specimens, sensitivity ranges from 34% to 93%. However, the specificity both in respiratory as well as non-respiratory specimens is around 99%. Therefore, a positive test provides useful confirmation so that ATT can be started promptly but a negative NAAT test does not always rule out TB.

All PLHIV detected for TB should undergo drug susceptibility testing (for first and/or second line ATT drugs as described in Figure 2.8.3.

Other supportive investigations for the clinical diagnosis of TB: Symptomatic PLHIV who test negative for TB by NAAT/Truenat or who did not undergo CBNAAT/Truenat test because of non-availability of biological specimen should be investigated for TB using other appropriate diagnostic tools.

Given below are the other supportive tests required to reach a diagnosis of TB in some cases, mostly EPTB:

Figure 2.8.3: Recommended approach to TB diagnosis in PLHIV



Source: Adapted from NTEP Guidelines on Management of DR-TB 2019

- **Radiological tests:** In addition to microbiological testing, the chest X-ray (CXR) is an important investigation for the diagnosis of pulmonary TB. Other radiological tests like ultrasound (abdomen), CT/ MRI scans of brain, spine, joints, etc. are useful tools for diagnosis of TB.
- Biochemical examination of body fluids (cerebrospinal, pleural, ascitic fluid, etc.)
- Cytological study of body fluids and fine needle aspirates from lymph nodes/cold abscess, etc.
- Histopathological examination (HPE) of tissue samples
- Fibre-optic bronchoscopy for intra-thoracic lymph nodes, ophthalmoscopy for ocular TB, arthroscopy for joint TB, etc.

Based on the diagnostic workup in Figure 2.8.3, a patient diagnosed as a case of active TB further needs to be classified for the purpose of TB management under the NTEP (Table 2.8.1):

- Type of diagnostic tool used (microbiologically confirmed or clinically diagnosed TB case)
- Anatomical site of disease (pulmonary or extra-pulmonary TB)
- History of previous treatment (new, previously treated or recurrent case or treatment after failure or treatment after lost to follow-up or others)
- Drug resistance (Drug Sensitive TB or Drug Resistant TB)

Table 2.8.1: Classification of TB and definitions

No	Classification based on	Type	Definition
1	Microbiological confirmation	**Microbiologically confirmed TB**	A presumptive TB patient with biological specimen positive for AFB, or positive for MTB on culture, or positive for TB through Quality Assured Rapid Diagnostic molecular test (NAAT or Truenat)
		Clinically diagnosed TB case	• A presumptive TB patient who is not microbiologically confirmed but diagnosed with active TB by a clinician based on X-ray, histopathology or clinical signs with a decision to treat the patient with a full course of anti-TB treatment. • (In children, this is based on the presence of abnormalities consistent with TB on radiography, history of exposure to an infectious case, evidence of TB infection (positive TST) and clinical findings suggestive of TB in the event of negative or unavailable microbiological results
2	Anatomical site of disease	**Pulmonary TB (PTB)**	Any microbiologically confirmed or clinically diagnosed case of TB involving lung parenchyma or tracheo-bronchial tree. Miliary TB classified as PTB because there are lesions in the lungs
		Extra-pulmonary TB (EPTB)	Any microbiologically confirmed or clinically diagnosed case of TB involving organs other than lungs e.g., pleura, lymph nodes, intestine, genitourinary tract, joint and bones, meninges of the brain, etc.
3	History of previous treatment	**New**	A TB patient who has never had treatment for TB or has taken anti-TB drugs for less than 1 month
3	History of previous treatment	**Previously treated patients**	Those who have received 1 month or more of anti-TB drugs from any source in the past
		Recurrent case	A TB patient previously declared as successfully treated (cured/treatment completed) and is subsequently found to be microbiologically confirmed TB
		Treatment after failure	Those patients who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment
		Treatment after lost to follow-up	A TB patient previously treated for TB for 1 month or more and was declared lost to follow-up in their most recent course of treatment and subsequently
		Others	Other previously treated patients are those who have previously been treated for TB but who cannot be classified into any of the above classification.
4	Drug resistance	For types of DR-TB, please refer to the section on “Treatment of drug resistant TB.”	

Management of Active TB disease in PLHIV

For managing TB, it is essential to understand the concept of drug resistance at the outset. An important classification of active TB disease is based on the susceptibility of TB bacilli to available anti-tubercular drugs. A TB case in which the isolated MTB is susceptible to all first-line drugs (rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E)) is said to have drug sensitive TB. Drug resistant TB is defined as TB disease where the bacilli is resistant to one or more anti-TB drugs; multi-drug–resistant TB (MDR-TB) is a subset of DR-TB wherein the TB bacilli are resistant at least to isoniazid and rifampicin (H&R) with or without resistance to other first-line drugs. Inadequate or poorly administered anti-TB drug regimen (monotherapy, irregular consumption, frequent interruptions or trial therapy) is the most common cause of acquired drug resistance.

Appropriate ATT for active TB in PLHIV will depend on whether the case is diagnosed as drug- sensitive or drug-resistant TB (based on Rapid molecular tests/Culture and Drug Sensitivity Testing). ATT shall be initiated in PLHIV diagnosed with Drug-Sensitive TB (H and R Sensitive) or cases with unknown sensitivity pattern at the ART centre itself by the ART MO as per details given in Table 2.8.2. PLHIV diagnosed with DR-TB will be referred to DR-TB centres for management of TB.

Treatment of Drug Sensitive TB

All HIV-infected TB cases must follow the NTEP guidelines for treatment. In NTEP, all PLHIV, who are with H and R sensitive TB and all PLHIV whose H and R resistant status is not known are initiated on first-line anti-TB treatment. The principle of treatment for TB is to administer daily dose combinations of first-line anti-tuberculosis drugs in appropriate weight bands.

The first line anti-TB treatment regimen for Drug-Sensitive TB cases is a combination of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) as given in Table 2.8.2.

Treatment is given in two phases

Intensive phase: The Intensive phase (IP) consists of 8 weeks (56 doses) daily of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) given under direct observation in daily dosages as per weight band categories.

Continuation phase: The Continuation phase consists of 16 weeks (112 doses) of isoniazid, rifampicin and ethambutol in daily dosages.

The CP may be extended by 12–24 weeks in certain forms of TB like CNS TB, skeletal TB, disseminated TB, etc. based on clinical decision on case-to-case basis. Extension beyond 12 weeks should only be on the recommendation of specialists. Steroids as an adjunctive therapy is useful in patients with TB pericarditis and meningeal TB, with an initial high dose tapered downwards gradually over 6–8 weeks.

Table 2.8.2: Regimen for new and previously treated Drug Sensitive TB patients (H and R Sensitive/unknown)

Type of TB case	Treatment Regimen in Intensive Phase	Treatment regimen in Continuation Phase
New and previously treated cases (H and R Sensitive/ unknown)	2HRZE daily (Total 56 doses)	4HRE daily (Total 112 doses)

- *Prefix to the drugs stands for number of months*
- *H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutol*
- *Doses are to be given every day.*

ATT is provided as Fixed Dose Combinations (FDCs) under the NTEP. Table 2.8.3 provides details of the daily dosage schedule for adult patients. (Adult TB patient: ≥18 years will be given ATT doses as per adult weight bands.)

Table 2.8.3: Daily dose schedule for adults (≥18 years) as per weight bands

Weight category	Number of Tablets–Fixed-dose Combination	
	Intensive Phase 4-FDC, HRZE (75/150/400/275)	Continuation Phase 3-FDC HRE (75/150/275)
25-34 kg	2	2
35–49 kg	3	3
50–64 kg	4	4
65–75 kg	5	5
>75 kg	6	6

- Fixed-Dose Combinations (FDCs) for adults: 4-FDC (given in IP) consists of HRZE and 3-FDC (given in CP) consists of HRE.
- If the weight of the patient increases by more than 5 kg and crosses the next weight band category during treatment, then patient should be given the next higher weight band FDC drugs.

Important points to remember

- TB patient ≥18 years will be given ATT doses as per adult weight bands (Table 2.8.3).
- TB patient <18 years will be given ATT doses as per children's weight bands (Tables 2.8.12 and 2.8.13).
- If the weight of the patient increases by more than 5 kg and crosses the next weight band category during treatment, then the patient should be given the next higher weight band FDC drugs.
- Loose anti-TB drugs can be used for substitutions in case of adverse drug reaction or drug- drug interaction in comorbid conditions. Major side effects of first-line anti-TB drugs are given in Table 2.8.4.
- Streptomycin is now considered a second-line drug. It is used in treatment of drug sensitive TB only in certain situations, like TB meningitis or if any first-line drug needs to be replaced due to adverse drug reaction as per weight of the patient.
- Administration of fluconazole with ATT can also result in hepatotoxicity and needs liver function test monitoring.

Table 2.8.4: Adverse drug effects of first-line anti-TB drugs

Drug	Main Effects	Rare Effects
Isoniazid	Peripheral neuropathy Skin rash Hepatitis Sleepiness and lethargy	Convulsion Psychosis Arthralgia Anaemia
Rifampicin	Gastro-intestinal: Abdominal pain, nausea, vomiting Hepatitis General cutaneous reactions Thrombocytopenic purpura	Osteomalacia Pseudomembranous colitis Pseudo-duodenal crisis Acute renal failure Haemolytic anaemia
Pyrazinamide	Arthralgia Hepatitis Gastrointestinal problems	Cutaneous reactions Sideroblastic anaemia
Ethambutol	Retrobulbar neuritis	Generalized cutaneous reactions Arthralgia Peripheral neuropathy Hepatitis (very rare)
*For further details of side effects and their management, please refer to NTEP 'Training Modules (1-4) for Programme Managers and Medical Officers, July 2020		

Refer to **Annexure 6** for adverse effects and drug interactions of anti-TB drugs, management of drug-induced Hepatitis, dosage adjustment in renal impairment and algorithm for reintroduction of TB drugs with stepwise increase in the dosage.

Follow-up of first-line anti-TB treatment: The TB patient should be closely monitored for treatment progress and disease response. There are two components of follow-up: clinical and laboratory.

Clinical follow-up: The SMO/MO-ART should clinically follow up every patient at least monthly. Improvement of clinical symptoms, increase in weight and control of comorbid conditions like diabetes by appropriate treatment are essential for getting a better prognosis to TB treatment. Symptoms and signs of adverse reactions to drugs should be specifically asked for, recorded in TB treatment card and appropriately managed. Chest X-ray may be a good tool to assess the progress of clinically diagnosed TB and it is to be offered whenever required and available. In cases of EPTB, response to treatment may be best assessed clinically based on parameters like weight gain and decrease in symptoms and signs. Help of radiological and other relevant investigations may be taken.

Laboratory follow-up: In case of pulmonary tuberculosis, **sputum smear microscopy** should be done at the end of intensive phase (IP) and end of treatment. One sputum sample is to be collected, preferably early morning. It must be ensured that patients undergo the follow-up sputum smear examination as scheduled and the last follow-up sputum examination is done before the completion of the last dose of treatment. *NAAT should not be done as a follow-up sputum examination, as it can pick up genes of dead MTB to give positive result.*

A negative sputum smear microscopy result at the end of IP may indicate good prognosis, and patient is shifted to CP. However, if sputum result is positive at the end of IP, then too CP will be initiated and continued till the drug susceptibility test (DST) results are available. ATT would then be modified, if warranted, after the results of DST.

On completion of treatment, a sputum smear examination should be done for every patient. The follow-up sputum smear examination at the end of treatment is very important for evaluating the results of treatment. However, in the presence of clinical deterioration, the SMO/MO of ART centre may consider repeating sputum smear microscopy even during CP. This will provide the patient an additional

opportunity to undergo DST if he/she is found to be sputum smear positive.

Long-term follow-up

After completion of treatment, the patients should be followed up clinically at the end of 6, 12, 18 and 24 months. In the presence of any clinical symptom, sputum microscopy and/or culture of the biological specimen should be considered. This is important for detecting recurrence of TB at the earliest. NAAT is contraindicated for assessment of symptomatic patients in long-term follow-up.

Determination of DS-TB Treatment Outcome

Once a TB case completes TB treatment, the relevant outcome (along with date) is to be recorded. A TB patient will have only one of the following outcomes at a time, as shown in Table 2.8.5.

Table 2.8.5: Types of treatment outcome and definitions

Treatment Outcome	Definition
Cured	Microbiologically confirmed TB patients at the beginning of treatment who were smear or culture negative at the end of the complete treatment
Treatment completed	A TB patient who has completed treatment without evidence of failure or clinical deterioration BUT with no record to show that the smear or culture results of biological specimen in the last month of treatment was negative, either because test was not done or because result is unavailable, or a clinically diagnosed patient, pulmonary or EP, who has received full course of treatment with no positive smear or culture at the end of treatment
Treatment success	TB patients either cured or treatment completed are accounted in treatment success, but it is an indicator and not an outcome.
Failure	A TB patient whose biological specimen is positive by smear or culture at end of treatment
Failure to respond	A case of paediatric TB who fails to have microbiological conversion to negative status or fails to respond clinically or deteriorates after 12 weeks of compliant treatment shall be deemed to have failed response provided alternative diagnosis/reasons for non-response have been ruled out.
Lost to follow-up	A TB patient whose treatment was interrupted continuously for ONE month or more
Not evaluated	A TB patient for whom no treatment outcome is assigned: this includes former “transfer-out”
Treatment regimen changed	A TB patient who is on first-line regimen and has been diagnosed as having DR-TB and switched to drug resistant TB regimen prior to being declared as failed
Died	A patient who has died during anti-TB treatment

ART in PLHIV with TB Co-infection

ART reduces the incidence and recurrence of TB, as well as case fatality rates. It also facilitates immunological reconstitution and decreases AIDS-defining illness and mortality. This benefit is seen across different ranges of CD4 counts.

All PLHIV diagnosed with active TB are to be initiated on ART regardless of CD4 count, after initiation of TB treatment in accordance with the NTEP guidelines discussed above. ART is to be started as soon as possible, keeping in mind the time needed for acceptance of the diagnosis, counselling needs, pill burden, drug interactions/additive toxicities with ATT and TB-associated IRIS (TB-IRIS). The timing of initiation of ART in relation to ATT and the recommended ART regimens in HIV-TB cases in adults and adolescents are given in Tables 2.8.6 to 2.8.8.

Table 2.8.6: Timing of ART in relation to initiation of TB treatment

Patient details	Timing of ART in Relation to Initiation of TB Treatment	ART Recommendations
HIV-TB coinfected patients	• ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV (PLHIV) (except when signs and symptoms of meningitis are present) • Among PLHIV with TB meningitis, ART should be delayed for at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered as adjuvant treatment for TB meningitis.	Appropriate ART regimen

*WHO Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring, July 2021

ART Regimen in PLHIV Receiving First-line (Rifampicin-containing) anti TB treatment

- DTG-based regimen (with NRTI backbone) is the preferred regimen for all PLHIV on first- line (Rifampicin-containing) ATT. However, Rifampicin (RIF) is a potent inducer of drug metabolizing enzymes and drug transporters, and co-administration with dolutegravir reduces bioavailability of DTG, which can be overcome by doubling the DTG dose to 50 mg twice daily. Therefore, patients on Rifampicin-containing ATT should receive an additional tablet of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) till the completion of ATT. Once the ATT is completed, additional tablet of DTG 50 mg should be stopped 2 weeks after stoppage of Rifampicin-containing treatment regimen.
- Rifampicin is a CYP inducer and suppresses bioavailability of PIs, thereby decreasing the efficacy of ART. Therefore, if a patient coinfected with HIV on first-line ATT needs to be co- administered boosted PI (ATV/r or LPV/r or DRV/r)-based ART regimen, Rifampicin should be replaced by Rifabutin for the entire course of ATT.

Table 2.8.7: Recommended ART regimens in PLHIV (adults and adolescents) infected with Drug Sensitive TB receiving Rifampicin-containing anti-TB treatment

First-line ART Regimen		Management of HIV-TB Co-infection
Preferred ART regimen (PLHIV with body weight >30 kg)	TDF 300 mg + 3TC 300 mg + DTG 50 mg at bedtime	TDF 300 mg + 3TC 300 mg + DTG 50 mg at bedtime + DTG 50 mg* in the morning (if TB treatment schedule has Rifampicin) to be given for the entire duration of ATT)* ATT: 2HRZE + 4HRE daily regimen
PLHIV with body weight ≤30 kg	ABC 600 mg + 3TC 300 mg, one tablet + DTG (50 mg) at bedtime	ABC 600 mg + 3TC 300 mg, one tablet + DTG (50 mg) twice daily* ATT: 2HRZE + 4HRE daily regimen
PLHIV with high (above ULN for lab) serum creatinine values (Calculate Creatinine clearance)	ABC 600 mg OD, Lamivudine (as per creatinine clearance**) + DTG 50 mg once daily	ABC 600 mg OD, Lamivudine (as per creatinine clearance) + DTG 50 mg twice daily* ATT: 2HRZE + 4 HRE daily regimen
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling**	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600mg)	TDF (300 mg) + 3TC (300 mg) + EFV (600 mg) ATT: 2HRZE + 4HRE daily regimen
	If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]	TDF (300 mg) + 3TC (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily] **Rifampicin must be replaced with Rifabutin 150** mg in anti-TB treatment regimen

*Rifampicin in FDC can be used with a DTG-based ART regimen with an extra dose of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) for the entire duration of ATT. Additional dose of DTG 50 mg is to be continued for 2 weeks after completion of Rifampicin-containing anti-TB treatment.

**Women of childbearing potential receive full information and medical guidance that is appropriate to their situation and are supported in making an informed decision.

Considerations in PLHIV Already on ART at Time of Diagnosis of Active TB

Following points to be considered in PLHIV if TB is diagnosed in patients already receiving ART:

- In PLHIV who are already on ART at the time of TB diagnosis, appropriate modification of ART/ATT needs to be done to maintain optimal efficacy of ATT as well as ART.
- When a patient on ART presents with active TB, there is a possibility of suspecting treatment (ART) failure. NACO recommends the following guiding principles in this context:
- If an episode of TB occurs within the first 6 months of the initiation of ART, it should not be considered as failure of the treatment and IRIS should be suspected and managed accordingly.
- If an episode of TB develops more than 6 months after the initiation of ART, PLHIV should be assessed for possibility of treatment failure (based on CD4 counts and viral load) with special focus on adherence.
- When a patient already on 2NRTIs + 1NNRTI (EFV)–based regimen has to be given 2HREZ + 4HRE–based ATT for the newly detected TB, same ART regimen can be continued without any modification.

- When a patient already on 2NRTIs + DTG–based regimen has to be given 2HREZ + 4HRE–based ATT for the newly detected TB, same ART regimen can be continued with one modification. Since co-administered rifampicin reduces bioavailability of DTG, this can be overcome by the additional tablet of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) till the completion of ATT. Once the ATT is completed, additional tablet of DTG 50 mg should be stopped 2 weeks after stoppage of rifampicin-containing treatment regimen.
- When a patient already on 2NRTIs + PI–based regimen develops TB, ART regimen has to be modified if 2HREZ + 4HRE–based ATT is co-administered. There are two options as described in Table 2.8.8.
- Whenever a patient on first-, second- or third-line ART has to be inevitably on PI- containing ART regimen, instead of rifampicin-based anti-TB regimen, rifabutin-based regimen must be given

Table 2.8.8: Management recommendations for TB diagnosed in patients already receiving ART

Current ART Regimen	Management Options for HIV-TB
(AZT or TDF or ABC) + 3TC + DTG	**ART:** Same ART to be continued Dolutegravir 50 mg additional tablet (at an interval of 12 hours with the regular dose of DTG) is to be given for the entire duration of anti-TB treatment (ATT). Additional dose of DTG 50 mg should be continued for 2 weeks after completion of Rifampicin-containing ATT. ATT: 2HRZE + 4HRE daily regimen
(AZT or TDF or ABC) + 3TC + EFV	ART: No change is required in ART regimen. ATT: 2HRZE + 4HRE daily regimen
(AZT or TDF or ABC) + 3TC + PI*	**ART:** Consider changing to DTG-based regimen if patient has not received or not failed on DTG. (Same 2NRTIs) + DTG 50 mg bd (Additional dose of DTG 50 mg should be continued for 2 weeks after completion of Rifampicin-containing anti-TB treatment.) ATT: 2HRZE + 4HRE daily regimen
	ART: If the same PI-containing regimen has to be continued, modify anti-TB treatment. ATT: Rifampicin must be replaced with Rifabutin 150 mg in anti-TB treatment regimen
PI* + DTG	**ART:** Same ART to be continued Dolutegravir 50 mg additional tablet (at an interval of 12 hours with the regular dose of DTG) is to be given for the entire duration of anti-TB treatment and not beyond (since patient had Rifabutin) ATT: Rifampicin must be replaced with Rifabutin 150 mg in anti-TB treatment regimen.
*PI=Lopinavir/r, Darunavir/r, Atazanavir/r	

Treatment of Drug Resistant TB in PLHIV

Drug resistant TB is treated with regimens containing second-line TB drugs. Second-line drugs are agents reserved for the treatment of drug-resistant -TB. Effective management of DR-TB relies on detection of drug resistance followed by appropriate and timely treatment. The molecular testing methods (i.e., NAAT and Line Probe Assays-LPA) are rapid tests based on detection of genes indicative of drug resistance and are much faster than culture and sensitivity testing that are growth-based tests. Rapid molecular tests facilitate timely diagnosis and prompt treatment initiation in DR-TB cases.

DR-TB regimens require a longer course, have higher pill burden and higher toxicity profile, resulting in lower adherence and poorer treatment outcomes, including more deaths as compared to DS-TB management. The average success rate of DR-TB treatment has significantly increased with addition of newer TB drugs in DR-TB regimens, namely Bedaquiline (Bdq) and Delamanid (Dlm).

Classification of Drug-Resistant TB

- **Mono-resistant TB (MR-TB):** A TB patient whose biological specimen is resistant to one first- line anti-TB drug only
- **Isoniazid-resistant TB (HR-TB):** A TB patient whose biological specimen is resistant to isoniazid and susceptibility to rifampicin has been confirmed. HR-TB requires treatment other than that for DS-TB.
- **Rifampicin-resistant TB (RR-TB):** A TB patient whose biological specimen is resistant to rifampicin, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR. RR-TB (mono) is taken as MDR-TB for treatment purposes.
- **Poly-Drug Resistant (PDR):** A TB patient whose biological specimen is resistant to more than one first-line anti-TB drug, other than both INH and Rifampicin.
- **Multi-Drug Resistant (MDR-TB):** A TB patient whose biological specimen is resistant to both Isoniazid and Rifampicin with or without resistance to other first-line anti-TB drugs; MDR-TB patients may have additional resistance to any/all Fluoroquinolone (FQ) or any other anti-TB drug.
- **Pre-extensively drug resistant TB (Pre-XDR-TB):** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and is also resistant to any Fluoroquinolone.
- **Extensively drug resistant TB (XDR-TB):** TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and is also resistant to any Fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either Bedaquiline or Linezolid [or both]).

Table 2.8.9: Groups of second line anti-TB drugs

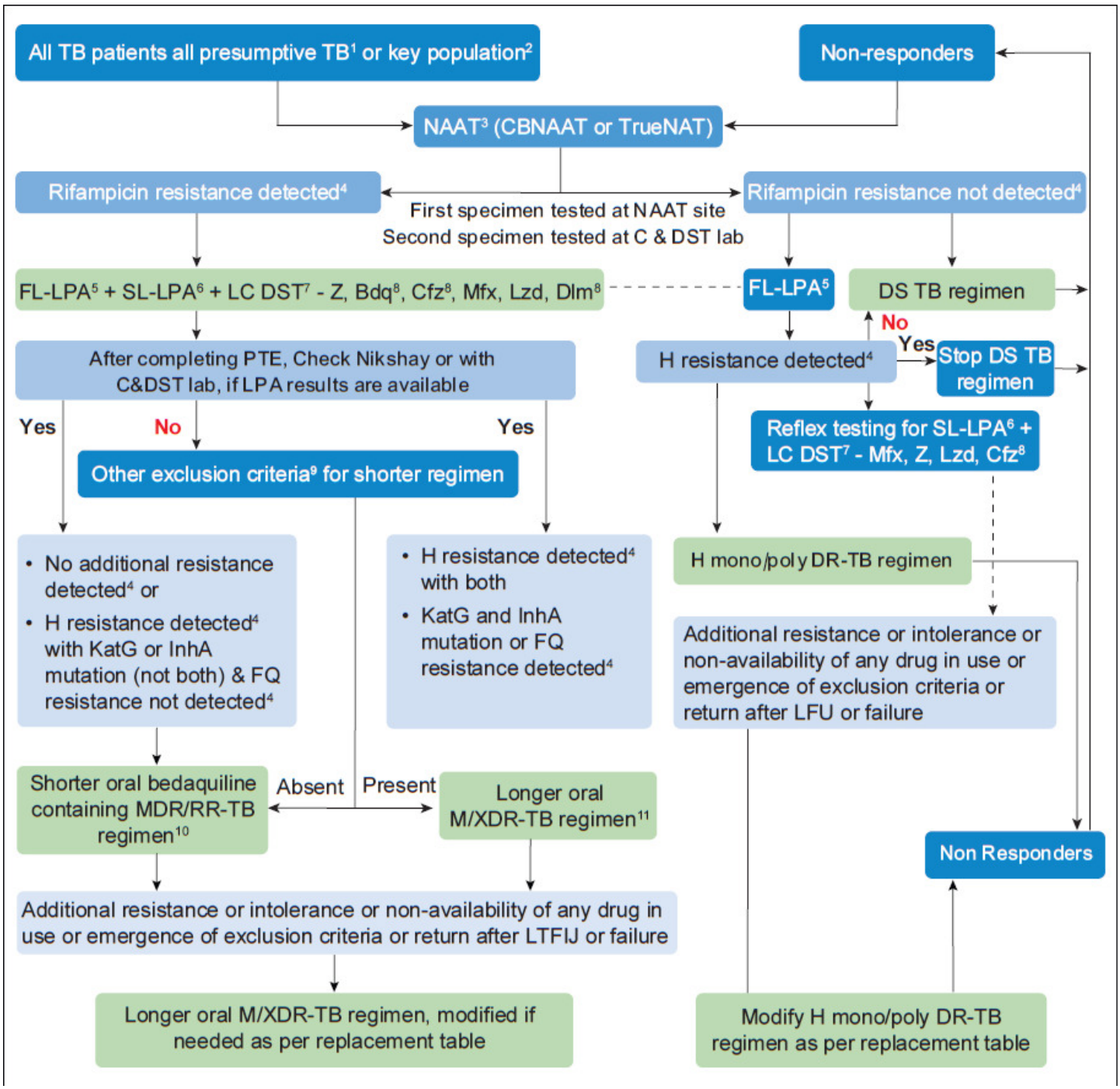
Groups of second line anti-TB drugs		
Group A **Include all three medicines**	Levofloxacin or Moxifloxacin Bedaquiline Linezolid	Lfx Mfx Bdq Lzd
Group B **Add one or both medicines**	Clofazimine Cycloserine or Terizidone	Cfz Cs Trd
Group C **Add to complete the regimen and when medicines from Group A and B cannot be used**	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin or Meropenem Amikacin (or) Streptomycin Ethionamide or Prothionamide p-aminosalicylic acid	EE Dlm Z Ipm-Cln Mpm Am S Eto Pto PAS

Table 2.8.10: Groups and side effects of second-line anti-TB drugs

Group	Name of Drug	Main Side Effects
Group A	**Levofloxacin (Lfx)**	Seizures, headache
	Moxifloxacin (Mfx)	Q-Tc prolongation with moxifloxacin, especially high dose
	Bedaquiline (Bdq)	Gastritis, hepatotoxicity, Q-Tc prolongation, dyselectrolytemia, myopathy
	Linezolid (Lzd)	Peripheral neuropathy, optic neuritis, bone marrow depression
Group B	**Clofazimine (Cfz)**	Reddish discoloration of skin, Q-Tc prolongation, phototoxicity
	Cycloserine (Cs)	Psychosis, depression, insomnia
	Terizidone (Trz)	Headache, tremors, insomnia, depression, convulsions, altered behaviour and suicidal tendencies
Group C	**Ethambutol (E)**	Ocular toxicity (retrobulbar neuritis)
	Delamanid (Dlm)	Q-Tc prolongation
	Pyrazinamide (Z)	Joint pains and severe hepatotoxicity
	Imipenem + Cilastatin (Ipm-Cln)	Diarrhoea, nausea, vomiting, seizures (rare)
	Meropenem (Mpm)	Fever, chills, light-headedness, dizziness, sweating, rapid shallow breathing, skin rash
	Amikacin (Am)	Nephrotoxicity, ototoxicity
	Streptomycin (S)	Nephrotoxicity, ototoxicity
	Ethionamide (Eto)	Gastritis, hypothyroidism
	Prothionamide (Pto)	Gastritis, hypothyroidism
	P-aminosalicylic Acid (PAS)	Gastritis, hypothyroidism

*For details of side effects of second-line anti-TB drugs, please refer to NTEP 'Guidelines for Programmatic Management of drug resistant TB in India', March 2021

Figure 2.8.4: Integrated drug resistant TB algorithm (PMDT Guidelines 2021)



Footnotes:

1. In areas transitioned to NAAT for TB diagnosis
2. Key population includes PLHIV, children, EPTB, smear negative/NA with CXR suggestive of TB, contacts of DR-TB patients, other vulnerable groups.
3. CBNAAT or TrueNAT. All EPTB specimen except fine needle aspiration cytology (FNAC) of peripheral lymph nodes and CSF to be sent directly to Culture and Drug Susceptibility Testing (DST) laboratory for further processing.
4. As per mutation pattern, includes resistance inferred
5. Discordance in RR results between NAAT and FL-LPA to be resolved with a repeat NAAT at Culture and DST laboratory and microbiologists will provide the final decision. InhA mutation associated with Ethionamide resistance. Use other exclusion criteria to decide regimen if FL-LPA is done on culture isolates for patients with smear-negative specimen.
6. To assess Lfx, Mfx and Am resistance
7. Start treatment based on LPA results and modify based on LC & DST results later.
8. Whenever DST is available
9. Other exclusion criteria for shorter oral Bedaquiline-containing MDR/RR-TB regimen include the following:
   - History of exposure for >1 month to Bdq, Lfx, Ethionamide or Cfz, if result for DST (Bdq, FQ, Inh A mutation, Cfz & Z) is not available;
   - Intolerance to any drug or risk of toxicity from a drug in the shorter oral Bedaquiline-containing MDR/RR-TB regimen (e.g., drug–drug interactions);
   - Extensive TB disease – presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography;
   - In children under 15 years of age, presence of cavities or bilateral disease on chest radiography;
   - Severe EPTB disease – presence of miliary TB or TB meningitis or CNS TB. In children under 15 years of age, extra-pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression);
   - Pregnant and lactating women (with conditional exceptions)
   - Children below 5 years of age
10. This portion applies as states move to shorter oral Bedaquiline-containing MDR/RR-TB regimen under guidance of NTEP.
11. Patients, who were initiated on longer oral M/XDR-TB regimen based on history of exposure for >1 month and in whom resistance is not detected to H or FQ, may be switched to shorter oral Bedaquiline containing MDR/RR-TB regimen based on the FL and SL LPA results, if the duration of longer oral M/XDR-TB regimen drugs consumed is <1 month.

Once a person living with HIV is diagnosed as a case of DR-TB (R-R or mono–H) on CBNAAT or

TrueNAT/FL-Line Probe Assay (LPA), the patient is to be referred to the District TB Officer (DTO) of NTEP, for further resistance testing (SL-LPA, D&CST), diagnosis of MDR /pre-XDR/XDR TB and initiation of the appropriate DR-TB regimen.

Though the DR-TB regimen is initiated and supervised by the NTEP, the patient continues to get ART and HIV care from ART Centres and the ART Centre medical officers must be aware of the drugs and regimens used in DR-TB, their toxicities and drug interactions with concomitant ART.

Anti-TB Regimens for DR-TB in PLHIV

The NTEP recommends standardized treatment regimens for different types of DR TB cases. These are detailed in Table 2.8.11.

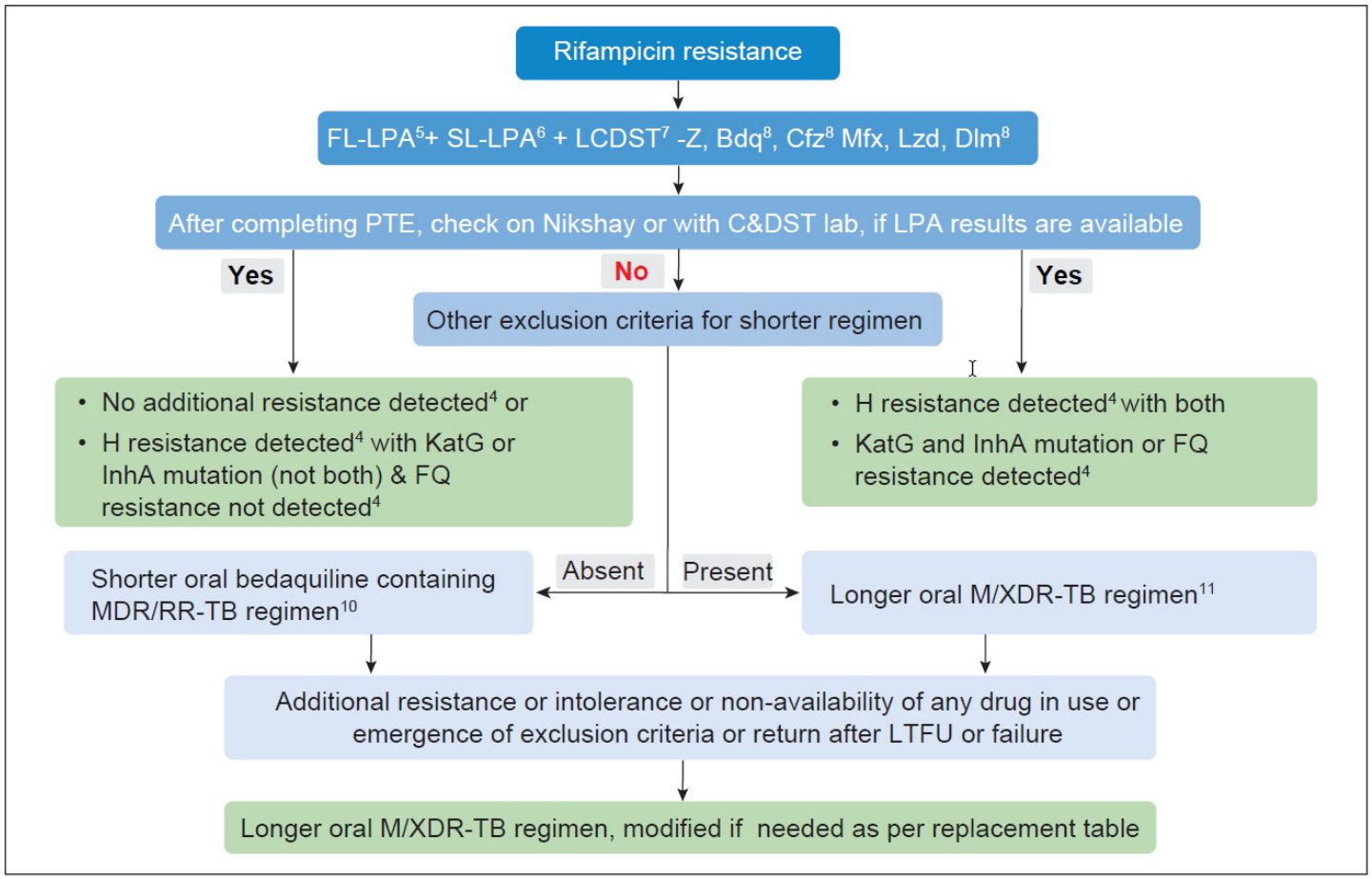
Table 2.8.11: Standard DR-TB regimens available under NTEP

Type of DR-TB	Standard DR-TB regimen under NTEP	
	Intensive Phase	Continuation Phase
H mono / Poly DR-TB	All oral H mono/poly DR-TB regimen (6) Lfx R E Z	
MDR-TB/RR-TB	**Shorter oral Bedaquiline-containing MDR/RR-TB regimen[1,2]**	
	(4-6) Bdq$^{(6\ m)}$,Lfx, Cfz, Z, E, Hh, Eto	(5) Lfx, Cfz, Z, E
MDR TB/ RR-TB	**Shorter injectable-containing regimen[3]**	
	(4-6) Mfx^{h}, Km/Am, Eto, Cfz, Z, H^{h}, E	(5) Mfx^{h}, Cfz, Z, E
M/XDR-TB	**Longer oral M/XDR TB regimens[4,5]** (18-20) Lfx, Bdq (6 m or longer), Lzd, Cfz, Cs	

Footnotes

1. Shorter oral Bedaquiline-containing MDR/RR-TB regimen is recommended in patients with confirmed MDR/RR-TB, who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to Fluoroquinolones has been excluded.
2. Shorter oral Bedaquiline-containing MDR/RR-TB regimen is being introduced in the country in a phased manner to gain programmatic experience to guide future expansion.
3. Till the above regimen has complete geographical coverage, the states yet to transition implementing shorter oral Bedaquiline-containing MDR/RR-TB regimen will continue to use shorter injectable-containing regimen.
4. Longer oral MDR/XDR-TB regimen is recommended for MDR/RR-TB patients who are excluded from shorter oral Bedaquiline-containing MDR/RR-TB regimen including for the XDR-TB patients.
5. For XDR-TB patients, the duration of longer oral XDR-TB regimen would be for 20 months. Pyridoxine to be given to all DR-TB patients as per weight band.

Figure 2.8.5: Treatment algorithm for Rifampicin-resistant tuberculosis (MDR/RR-TB) (adapted from NTEP 'Guidelines for programmatic management of DRTB' March 2021)



Refer to footnotes given below Fig 2.8.4

Monitoring of DR-TB and Declaration of Outcome

DR-TB cases initiated on treatment are monitored clinically, and by follow-up sputum microscopy and sputum cultures by the NTEP/ District TB Centre (DTC) staff, who will determine the outcome of DR-TB treatment as Cured, Treatment completed, Failure, Not evaluated, Regimen changed, Lost to follow-up or Died in accordance with NTEP guidelines.

ART for TB-HIV Co-infected Patients on Bedaquiline or Delamanid

- DTG-based regimen should be the ART regimen of choice for PLHIV on Bedaquiline / Delamanid-containing DR-TB regimens. Dolutegravir can be used safely and at the usual dose.
- If PLHIV are already on NRTI + DTG regimen, the same is to be continued with BDQ/DLM- containing DR-TB regimen.
- If PLHIV is on NNRTI/PI-based ART regimen, a DTG-based ART regimen must be used in place of NNRTI/PI-based ART regimen when co-prescribing with BDQ/DLM containing DR- TB regimens due to drug–drug interactions.
- TB-HIV co-infected PLHIV requiring a PI-based second-/third-line ART need coordination between SACEP and the linked DR-TB centre for considering a non-BDQ/DLM DR-TB regimen.
- In case an effective DR-TB regimen cannot be made without Bedaquiline/ Delamanid, the necessary DR-TB regimens using new TB drugs may be given with PI-based ART but with intensive monitoring for toxicities of Bedaquiline/ Delamanid.
- PLHIV on ARV regimens with boosted PI, if treated with Bedaquiline-based ATT, should be monitored closely.
- No dose adjustments are needed when Delamanid is used with Tenofovir, Efavirenz and

Lopinavir/Ritonavir.

- There is no impact on NNRTI or PI exposures with concomitant use of Delamanid, but more frequent ECG monitoring is advised.
- Also, use of Efavirenz had no impact on Delamanid after multiple doses in healthy subjects, and may be used concurrently without dose adjustment.
- PLHIV who will be receiving Delamanid as part of DR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

Management of CLHIV Infected with Tuberculosis

Clinical Presentation of TB in Children

Diagnosis of TB in an HIV-infected child is more difficult since the symptoms are often non- specific and may overlap with symptoms of HIV disease (Table 2.8.12). CLHIV should be screened for TB using the 4-symptom screening.

HIV-infected children have an increased risk of the following:

- Primary progressive TB
- EPTB
- Multi Drug Resistant TB
- Higher case fatality rate

Table 2.8.12: Clinical manifestations in CLHIV – Pulmonary TB vs. Extra Pulmonary TB

Clinical Features of Pulmonary TB	Clinical Features of Extra-pulmonary TB
• Fever • Cough • Failure to thrive • Weight loss: loss of more than 5% body weight as compared to highest weight recorded in last 3 months • Poor weight gain: no weight gain in past 3 months • Contact with a TB case: contact with a person with any form of active TB within last 2 years	• Lymph node enlargement • Headache/confusion (brain TB) • Backache, joint pain or spinal deformity (bone TB) • Chest pain, tightness in the chest, respiratory distress (pleural, pericardial) • Abdominal pain, swelling, discomfort and respiratory distress (abdominal, peritoneal) • Contact with a TB case

Diagnostic Tools Available for TB Among Children: (Ref: NTEP Training Modules 1–4, July 2020)

1. Clinical evaluation
2. Xray chest

3. Sputum/gastric aspirate/gastric lavage/induced sputum/bronchoalveolar lavage can be used for CBNAAT.

    - All attempts to be made to collect an appropriate and good quality specimen, though there are practical difficulties.

Gastric aspirate sampling is done in children less than 3 years of age. Two early morning samples of gastric aspirates through nasogastric tubes are to be collected. Samples need to be buffering with bicarbonate for children younger than 3 years.

Induced Sputum Sampling

- Two early morning samples of sputum may be induced with 3% saline nebulization for children older than 3 years.
- Sample should be of 2–5 ml in volume. It should be collected in a sterile container after rinsing of the oral cavity with clean water.
- The collected specimens should be transported to the laboratory as soon as possible.

4. Tuberculin skin test (TST) or Mantoux test using standard tuberculin as an adjunct tool in the diagnosis of TB among children. 2 TU PPD solution injected intradermally. Induration is read between 48 and 72 hours.

5. Ultra-Sonography for Abdominal Tuberculosis

6. Fine Needle Aspiration Cytology (FNAC), Excision/Biopsy of specimen, Fluid for cytology from the involved site can also be used.

7. Neuroimaging used for CNS TB

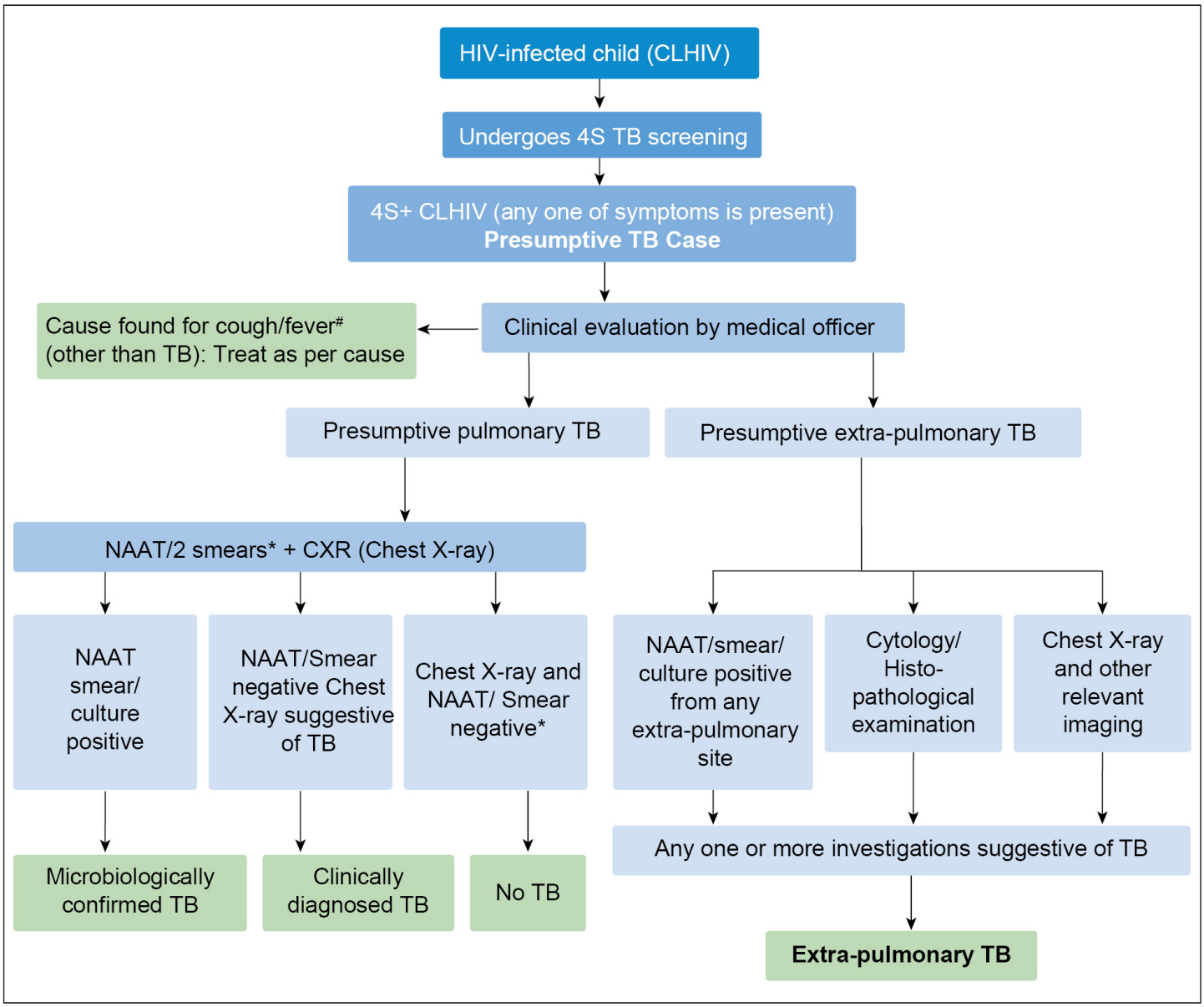
Tuberculin skin test (TST) or Mantoux test using standard tuberculin as an adjunct tool in the diagnosis of TB among children. 2 TU PPD solution injected intradermally. Induration is read between 48 and 72 hours.

Ultra-Sonography for Abdominal Tuberculosis

Fine Needle Aspiration Cytology (FNAC), Excision/Biopsy of specimen, Fluid for cytology from the involved site can also be used.

Neuroimaging used for CNS TB

Figure 2.8.6: Diagnostic algorithm for TB in CLHIV (both pulmonary and extra-pulmonary)



#**Cause found for fever:** Short duration fevers / malaria / dengue / URI / viral fevers

Presumptive Extra Pulmonary TB: Refers to the presence of organ specific symptoms and signs like swelling of lymph nodes, pain & swelling in joints, neck stiffness, disorientation etc.

Chest Xray-Non-specific shadows: Consolidations, patchy or non-homogenous shadows or signs of bronchopneumonia, etc.

Chest Xray highly suggestive of TB: Miliary shadows or lymphadenopathy (hilar or mediastinal), or chronic fIbro-cavltary parenchymal lesions

*May need to refer to paediatrician for induced sputum/gastric aspirate

Treatment of Drug sensitive TB in CLHIV

All children and adolescents less than 18 years of age are to be treated using paediatric weight bands and those weighing more than 39 kg are to be dispensed anti-tuberculous drugs with adult weight bands. According to the current NTEP guidelines, all TB patients, whether a new TB case or a previously treated TB case, shall be advised the daily anti-tubercular treatment. ATT course shall comprise of 2 months of Intensive Phase (IP) using four drugs namely Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. This shall be followed by 4 months of Continuation Phase with three drugs: Isoniazid, Rifampicin and Ethambutol.

Based on clinical decision of treating physician and specialist, continuation phase may be extended by 12–24 weeks in case of CNS TB, skeletal TB and disseminated TB.

Pyridoxine may be given at a dosage of 10 mg per day to all children receiving INH.

ATT is provided as Fixed Dose Combinations (FDCs) under the NTEP. Tables 2.8.13 and 2.8.14 provide details of the daily dosage schedule for paediatric patients.

Table 2.8.13: Anti-Tuberculous Treatment- daily drug dosage in children

Name of Drug	Daily Dose (mg/kg body weight)	Maximum Dose
Isoniazid	10 mg/kg (7-15 mg/kg)	300 mg
Rifampicin	15 mg/kg (10–20 mg/kg)	600 mg
Ethambutol	20 mg/kg (15–25 mg/kg)	1500 mg
Pyrazinamide	35 mg/kg (30–40 mg/kg)	2000 mg

Table 2.8.14: Daily dose schedule for paediatric patients up to the age of 18 years (as per weight band)

Weight Band	Number of Tablets (Dispersible FDC)			
	Intensive Phase (IP)		Continuation Phase (CP)	
	HRZ 50/75/150 mg	E 100 mg	HR 50/75 mg	E 100 mg
4–7 kg	1	1	1	1
8–11 kg	2	2	2	2
12–15 kg	3	3	3	3
16–24 kg	4	4	4	4
25–29 kg	3+1A	3	3+1A	3
30–39 kg	2+2A	2	2+2A	2

For paediatric patients, dispersible 3 FDC consists of HRZ and Dispersible 2 FDC consists of HR
A=Adult 4FDC (HRZE = 75/150/400/275) in IP and 3FDC (HRE = 75/150/275) in CP
Change in weight bands to be effective upon crossing of weight bands irrespective of the quantum of weight gain/loss.

ART in CLHIV with TB Co-infection

In TB coinfected HIV children, initiation of anti-TB treatment is priority. ATT is to be started first. CLHIV with all forms of TB shall be given ART after 2 weeks and not later than 8 weeks after ATT initiation. ART regimens in CLHIV during the treatment drug-sensitive TB are given in Table 2.8.15

Table 2.8.15: ART drug regimens for CLHIV during co-treatment of Drug-Sensitive TB (2HRZE+ 4HRE regimen)

Weight and Age of CLHIV	Recommended Regimen in TB Co-infection
Weight: Less than 20 kg or Age below 6 years	FDC of Abacavir + Lamivudine twice daily as per weight band + Lopinavir /ritonavir + super-boosting with additional ritonavir, twice daily as per weight band
Weight: Between 20–30 kg and Age: Between 6–10 years	FDC of Abacavir +Lamivudine twice daily as per weight band + Dolutegravir (DTG) 50 mg twice daily
Weight: Above 30 kg and Age: Above 10 years	FDC of Tenofovir + Lamivudine + Dolutegravir (DTG) once daily with an additional dose of Tab Dolutegravir 50 mg after 12 hours

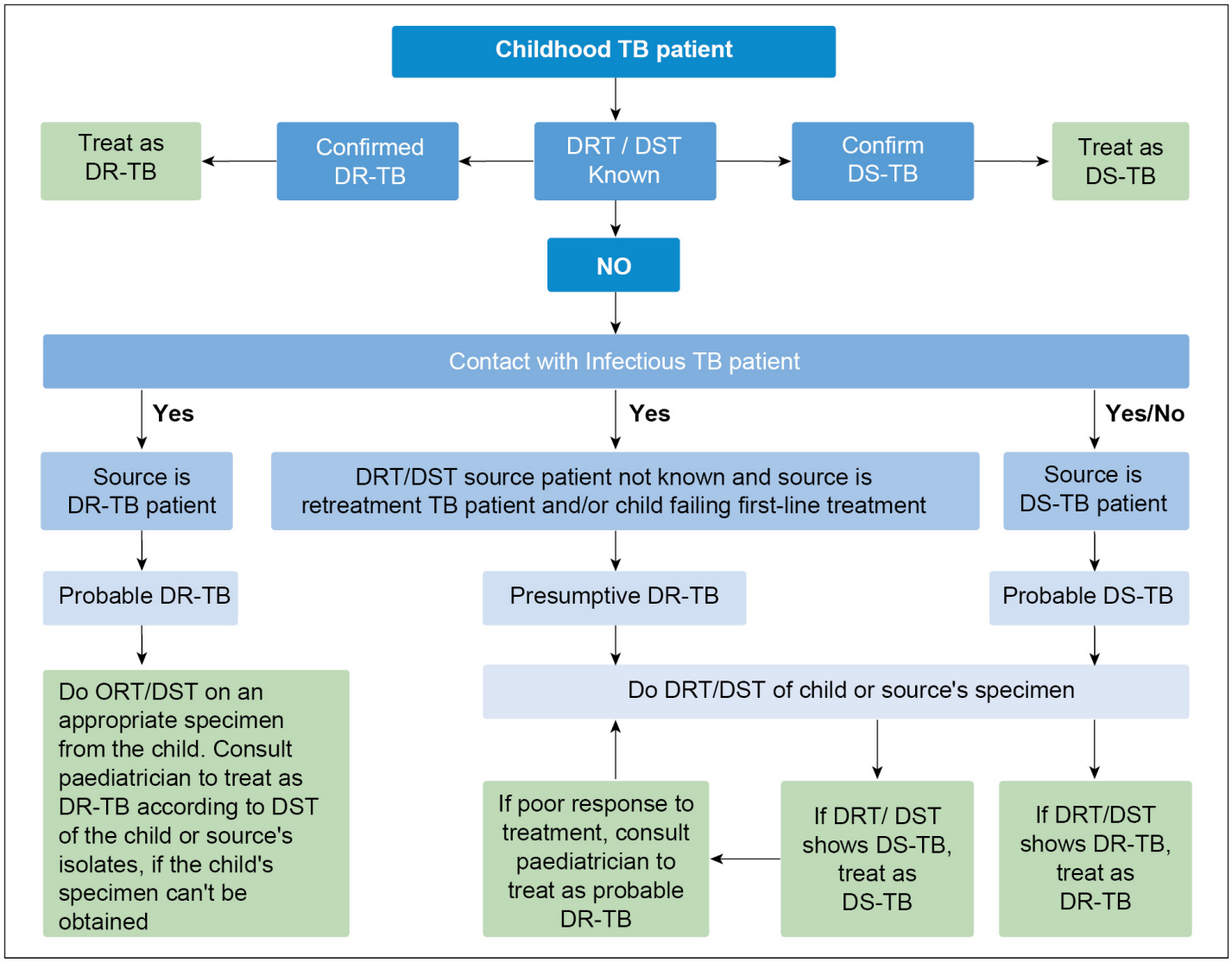
Note:

- DTG dose will need to remain twice daily for 2 weeks after stopping rifampicin-containing anti-TB treatment
- Super-boosting of LPV with ritonavir to continue for 2 weeks after stopping rifampicin-containing anti-TB treatment.
- Any infant or child initiated on any regimen must be based on body weight; Refer to Annexure 2 for dosage charts to determine the appropriate doses.

MDR-TB: Diagnosis and Treatment in Children with HIV

In children, very limited data is available for MDR-TB, which largely results from transmission of drug-resistant bacilli by the source case, usually adolescents and adults. It can result from previous inadequate TB treatment too, though not frequently.

Figure 2.8.7: Algorithmic approach to diagnosis of DR-TB children (PMDT Guidelines 2021)



Presumptive MDR-TB in children: Children who are contacts of adults with MDR-TB /DR-TB, who are lost to follow-up after initiating treatment, those who present with recurrence of disease after previous treatment, those who do not respond to treatment with first-line drugs and those living with HIV (CLHIV).

It is important to get appropriate specimens for both pulmonary and EPTB patients for mandatory bacteriological confirmation and drug susceptibility testing. For this, sputum or other relevant samples (e.g., gastric aspirate, induced sputum, bronchoscopy lavage, lymph node aspiration, CSF, tissue biopsies) must be collected in all children with presumed DR-TB for NAAT or LPA and culture and drug susceptibility.

Criteria for diagnosis of 'Probable MDR-TB' include children with signs and symptoms of active TB disease who in addition have the following risk factors:

- Close contact with a known case of MDR-TB
- Close contact with a person who died while on TB treatment
- Close contact with a person who failed TB treatment
- Non-response or failure of a first-line regimen
- Previous treatment with second-line medications

Regimen and duration:

- A shorter oral Bedaquiline-containing MDR/RR-TB regimen of 9–11 months' duration is recommended in

eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with DR-TB drugs used in this regimen for more than 1 month, and in whom resistance to Fluoroquinolones has been excluded.

- Shorter oral Bedaquiline-containing MDR/RR-TB regimen will be introduced in the country in a phased manner to gain programmatic experience to guide future expansion.

Until complete geographical coverage, the states yet to transition implementing shorter oral Bedaquiline-containing MDR/RR-TB regimen will continue to use shorter injectable-containing regimen for MDR/RR-TB. **(See box below.)**

(4-6) BDQ $_{(6\ mon),}$ Lfx, Cfz, Z, E, Hh, Eto	(5) Lfx, Cfz, Z, E

The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bdq is used for a duration of 6 months.

The composition or the duration of the initial or continuation phase cannot be changed.

Management of HIV-TB Coinfection in Specific Situations

Table 2.8.16 provides information on the ATT regimen and ART for specific situations.

Table 2.8.16: Treatment of HIV-TB in specific situations

SCENARIO	ACTION	
TB treatment in PLHIV on Protease Inhibitor (PI)-based ART	• Rifampicin suppresses bioavailability of boosted PIs (Atazanavir/ritonavir, Lopinavir/ritonavir, Darunavir/ritonavir). However, rifabutin, an effective anti-TB derivative of rifamycin group, does not inhibit effectiveness of these drugs. • Rifabutin is not available in FDC and hence should be provided as a loose drug. Substitute rifampicin with rifabutin (150 mg daily) for the entire duration of anti-TB treatment in such cases. • Anti-TB treatment initiation should be done as soon as TB is diagnosed, even in patients on PI-based ART. If substitution of rifampicin with rifabutin cannot be done immediately, one should not consider super boosting of PIs (in 1:1 proportion) as in children. With higher ritonavir dose in adults, toxicities will be very high and hence these are not recommended. Rifabutin availability must be ensured. • Replace rifampicin with rifabutin (150 mg) whenever rifabutin is available. • If rifampicin is continued for longer duration, this will make the boosted PI-based regimen ineffective and will hasten the emergence of drug-resistant mutants and eventual ART failure.	
TB treatment in children living with HIV (CLHIV) on Protease Inhibitor (PI)-based ART	• Super boosting of Lopinavir with Ritonavir is recommended in children in proportion of 1:1. • If age >6 years and weight 20 kg, replace boosted PI with DTG, given twice daily dose.	
Pregnant and lactating women	• All the primary anti-TB drugs (H, R, Z, E) are safe during pregnancy and lactation. **Among the second-line anti-TB drugs,** • Second-line injectables (Amikacin, Streptomycin) are contraindicated throughout pregnancy due to their effect on the 8th cranial nerve (auditory) of the foetus. • Use of Fluoroquinolone in pregnancy can affect cartilage development of foetus. • Ethionamide is contraindicated during the first 32 weeks of pregnancy due to teratogenic effects. • Bedaquiline and Delamanid are best avoided in pregnancy till there is more evidence available on their safety. • Shorter oral Bedaquiline-containing MDR/RR-TB regimen cannot be administered during pregnancy with DR-TB. • Among the ART, DTG/EFV-containing regimens are safe in pregnant women. However, they can exercise opt-out option for Dolutegravir.	
Renal impairment (Creatinine clearance <30 ml/min or for patients receiving haemodialysis)	**Modification in dose and frequency**	
	Isoniazid	No adjustment necessary
	Rifampicin	No adjustment necessary
	Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
	Ethambutol	15–25 mg/kg per dose three times per week (not daily)
	DR-TB drugs	Please refer Guidelines for PMDT in India 2021.

TB-associated IRIS

TB-IRIS may occur in up to one third of patients who have been diagnosed with TB and have been started

on ART. It typically presents within 3 months of the initiation of ART but can occur as early as 5 days. Patients with TB-IRIS most commonly present with appearance of new or worsening of existing TB signs and symptoms, like increased/reappearance of fever, cough, shortness of breath, appearance of neck rigidity etc. This symptomatic deterioration may be accompanied with increase in size or number of enlarged lymph nodes, appearance of new sites of TB, worsening x-ray picture etc. The symptoms are like the paradoxical reactions seen in immuno-competent patients on ATT but occur more frequently in HIV infected. Most cases resolve with symptomatic treatment or without any intervention and ART can be safely continued. At times, serious reactions such as meningeal TB, respiratory distress, massive adenopathy causing tracheal compression may occur. Such cases would require the use of anti-inflammatory drugs, including corticosteroids. For details on IRIS, please refer **Chapter 2.2 (ART in Adults and Adolescents).**

Cotrimoxazole Preventive Therapy in HIV-TB Cases

Cotrimoxazole is a fixed dose combination of sulfamethoxazole and trimethoprim, given routinely for the prevention of OIs in HIV-infected persons, as it has been shown to reduce morbidity and mortality of HIV-infected patients in general and HIV-infected TB patients in particular.

Note: For details on CPT, please refer **Chapter 2.9 (Prevention of Opportunistic Infections).**

General Principles for Prevention of TB in PLHIV at ART Centres

- Intensified Case Finding using 4-symptom complex
- TB Preventive Therapy (TPT) – Isoniazid Preventive Therapy (IPT)
- Airborne infection control

Intensified Case Finding using 4S Complex

As already discussed, Intensified Case Finding (ICF) is one of the critical interventions for prevention of ongoing TB transmission and the initial step to exclude the TB disease and initiate TPT. (Please refer Figure 2.8.2.)

TB Preventive Therapy/Isoniazid Preventive Therapy

Isoniazid Preventive Therapy (IPT) entails the administration of Isoniazid (INH) to PLHIV to prevent progression of latent TB to active TB disease.

- Isoniazid is one of the most effective bactericidal anti-TB drugs that protect against progression of latent TB infection to active disease (against endogenous reactivation).
- It also prevents TB reinfection post exposure to an open case of TB (against exogenous reinfection/super infection/nosocomial transmission). Several studies have shown that IPT administration in PLHIV prevents incidence and relapse of TB and is, therefore, a key public health intervention for TB prevention in PLHIV.
- The effects of IPT augment the effects of ART on reducing the incidence of TB. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of TBspecific immunity by ART and the beneficial effect of IPT may be prolonged.
- IPT does not promote Isoniazid resistance when used to treat latent TB infection. In latent TB, the Mycobacterium tuberculosis bacilli are fewer in number and are dividing slowly, resulting in an extremely

low risk of selecting drug-resistant mutants.

Note: For details on Isoniazid Preventive Therapy (IPT), please refer Chapter 2.9 (Prevention of Opportunistic Infections).

Airborne Infection Control (AIC) Activities at ART Centres

The presence of immuno-compromised patients in healthcare and congregate settings lacking effective infection control measures creates a favourable environment for TB transmission. The national Guidelines on Airborne Infection Control in Healthcare and Other Settings (April 2010)2 have identified ART centres as one of the high-risk settings for TB transmission. The presence of robust systems and policies is vital to control airborne transmission of TB infection in PLHIV at ART centres. Effective implementation of AIC measures involves four recognized controls in a hierarchy:

Guidelines on Airborne Infection Control in Healthcare and Other Settings



April 2010
Directorate General of Health Services
Ministry of Health & Family Welfare
Nirman Bhawan, New Delhi

1. **Managerial measures** are steps taken for promotion of AIC at national, state and hospital administration levels and by local health officials.
2. **Administrative controls** are to be done at the level of the ART Centre and broadly include fast tracking of 4S positive and HIV-TB patients through the ART Centre, educating PLHIV on cough

etiquette and respiratory hygiene, providing face masks to coughers and segregation of patients with respiratory symptoms in waiting areas.

3. **Environmental Controls** pertains to provision of adequate natural ventilation and maximization of air changes per hour (ACH) in ART centres by use of mixed natural and mechanical ventilation methods.
4. **Personal respiratory protection** may be provided to healthcare workers (like N95 masks) as per individual hospital policy.

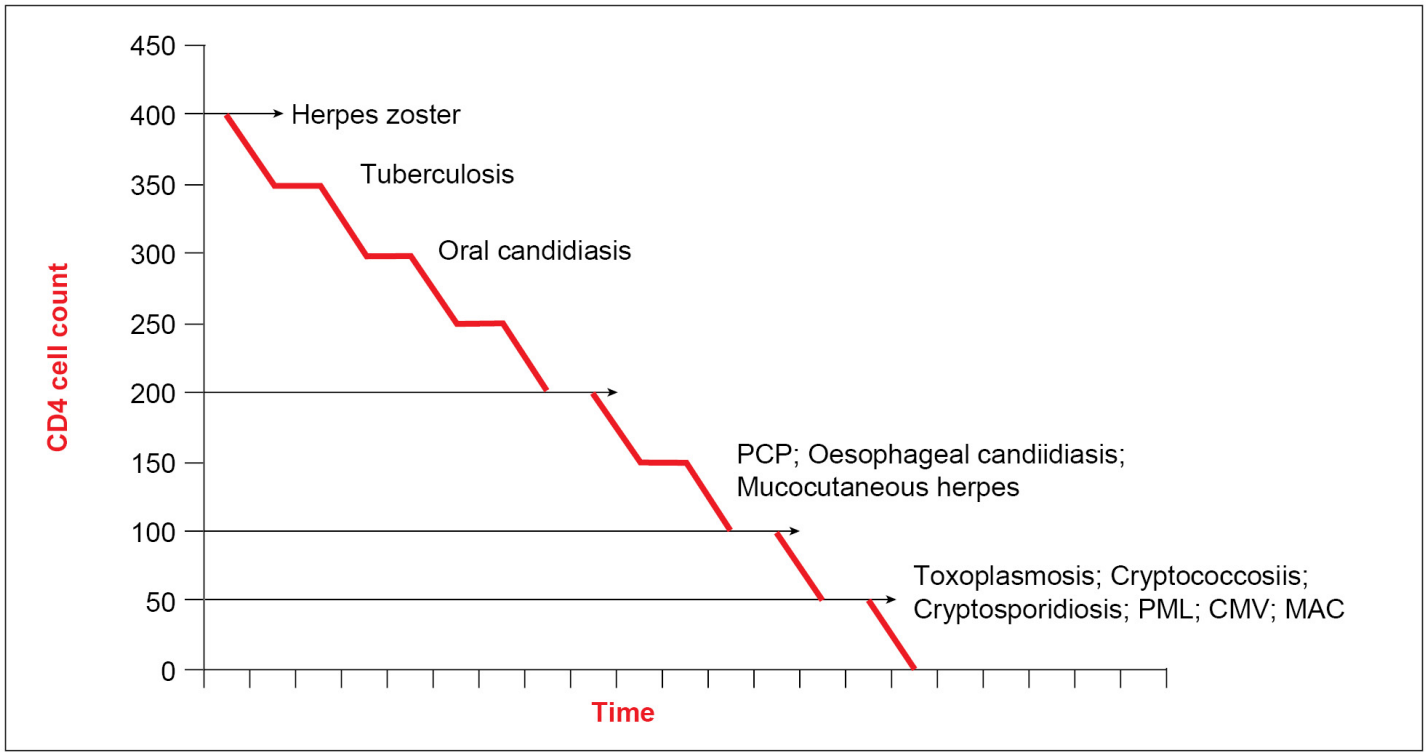
Note: For more details, refer to NTEP Training Modules (1-4) for Programme Managers and Medical officers, July 2020.

2.9 Prevention of Opportunistic Infections

Background

Opportunistic infections (OIs) are intercurrent infections that occur in People living with HIV. They are susceptible to a multitude of opportunistic micro-organisms including protozoa, fungi, virus and bacteria, which are generally innocuous in healthy individuals. OIs have been the major cause of morbidity and mortality among PLHIV. PLHIV tend to contract OIs during the disease, which mostly corroborates with the CD4 cell counts (Fig 2.9.1).

Figure 2.9.1: Association between CD4 counts and common opportunistic infections



Many of the common OIs are preventable but most can be prevented with early/rapid ART initiation. Since opportunistic events tend to recur, sometimes prophylaxis or preventive therapy needs to be continually given even after previous successful treatment until the patients achieve immune restoration.

The incidence of OIs has markedly declined in recent years because of the widespread availability of ART and early ART initiation in PLHIV. Along with ART, appropriate prevention and management of OIs make an additional and desirable impact. Simple preventive measures such as eating properly cooked food,

drinking boiled water, handwashing after toilet use, avoiding situations with a high risk of infection and appropriate and timely immunizations will aid in decreasing the disease burden of OIs.

The prophylaxis or preventive therapy of preventable OIs is recommended based on prevalence of OIs, immune status of the patient as well as access to ART. The prophylaxis/preventive therapy for common OIs in India has been included in this chapter.

Prevention of OIs under National AIDS Control Programme (Table 2.9.1)

- Prophylaxis for PCP
- Preventive treatment for MTB
- Preventive treatment for Cryptococcal meningitis

Prevention can be either primary or secondary.

- Primary prevention:

  Prophylactic or preventive drug given before the appearance of an OI is called primary prophylaxis/prevention.
- Secondary prevention

  Prophylactic or preventive drug given after the successful completion of treatment of OI is called as secondary prophylaxis/prevention.

Table 2.9.1: Prevention of OIs under National AIDS Control Programme

Type of Prevention	Opportunistic Infection	Drug
Primary	To prevent PCP	Cotrimoxazole
	To prevent tuberculosis (TB)	Isoniazid
	To prevent Cryptococcal infection (if CrAg test is not available in PLHIV with CD4 count <100 cells/mm^3)	Fluconazole
Secondary	To prevent recurrence of PCP	Cotrimoxazole
	To prevent recurrence of TB	Isoniazid
	To prevent recurrence of Cryptococcal infection	Fluconazole

Cotrimoxazole Preventive Therapy

Cotrimoxazole: (Sulfamethoxazole–Trimethoprim [SMX–TMP])

Cotrimoxazole needs special mention as one double strength (DS) tablet (800 mg/160 mg) orally once daily in adults and adolescents is effective in preventing multiple infections like:

- PCP
- Toxoplasmosis
- Bacterial pneumonias

- Nocardiosis
- Isosporiasis (caused by enteric pathogen isospora)

In case of allergy to Cotrimoxazole, an alternative for primary prophylaxis against PCP and Toxoplasmosis is Dapsone 100 mg once daily. Desensitization may be suggested for sulpha allergy.

Indication for primary prophylaxis in adults and adolescents:
CD4 counts <350 cells/mm3 or WHO Clinical stage 3 and 4

Indication for secondary prophylaxis in adults and adolescents
For all patients who have completed successful treatment for PCP until CD4 is >350 cells/ mm3 (at least on two occasions, done 6 months apart)

Regimen:

- Cotrimoxazole one DS tablet (SMX 800 mg/TMP 160 mg), each day or two single strength (SS) tablets daily
- Alternative: If allergic or intolerant to Cotrimoxazole (rash, anaemia, neutropenia), Cotrimoxazole desensitization may be tried; if severe, Dapsone 100 mg/day

Discontinuation: When CD4 count >350 cells/mm3 on two different occasions 6 months apart with an ascending trend and devoid of any WHO clinical stage 3 and 4 conditionss

Table 2.9.2: Cotrimoxazole preventive therapy for adults and adolescents

Prophylaxis	Recommendations
Commencing primary CPT	Cotrimoxazole prophylaxis must be initiated in PLHIV with CD4 count <350 cells/mm^3 or with WHO clinical stage 3 and 4
Timing the initiation of Cotrimoxazole in relation to initiating ART	• Start Cotrimoxazole prophylaxis first • Start ART after starting Cotrimoxazole or as soon as CPT is tolerated, and the patient has completed the 'preparedness phase' of counselling
Commencing secondary CPT	For all patients who have completed successful treatment for PCP until CD4 is >350 cells/mm^3 (at least on two occasions, done 6 months apart)
Dosage of Cotrimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily – total daily dose of 960 mg (800 mg SMZ + 160 mg TMP)
Cotrimoxazole for pregnant and breastfeeding women	• Women who fulfil the criteria for CPT should continue it throughout pregnancy. • If a woman requires CPT during pregnancy, it should be started regardless of the stage of pregnancy. • Breastfeeding women should continue CPT when indicated.
Patients allergic to sulpha-based medications	• Dapsone 100 mg per day • Cotrimoxazole desensitization may be attempted but not in patients with a previous severe reaction to Cotrimoxazole or other sulpha-containing drugs.
Monitoring	No specific laboratory monitoring is required in patients receiving Cotrimoxazole.
Discontinuation of Cotrimoxazole Prophylaxis	When CD4 count is greater than 350/mm^3 on two different occasions tested 6 months apart, with an ascending trend and devoid of any WHO clinical stage 3 or 4 conditions
Restarting of Cotrimoxazole Prophylaxis	In PLHIV, whose CD4 counts reached >350 cells/mm^3, may likely fall <350 cells/mm^3 afterwards due to ART treatment failure or due to any other immunosuppressive conditions or due to the administration of long-term immunosuppressive drugs. In those patients, Cotrimoxazole prophylaxis has to be restarted immediately and sustained till CD4 counts reached >350 cells/mm^3 on two different occasions tested 6 months apart, with an ascending trend and devoid of any WHO clinical stage 3 or 4 conditions

Cotrimoxazole desensitization

If the patient reports a history of hypersensitivity to sulpha-containing drugs, start him/her on a desensitization regimen as an in-patient. Desensitization can be attempted 2 weeks after a non- severe (grade 3 or less) Cotrimoxazole reaction that has resulted in temporary interruption in its usage. Cotrimoxazole desensitization (Table 2.9.3) has been shown to be successful and safe in approximately 70% of the patients with previous mild to moderate hypersensitivity.

Table 2.9.3: Protocol for Cotrimoxazole desensitization (adults and children)

Step	Dosage
Day 1	80 mg SMX + 16 mg TMP 2 ml oral suspension
Day 2	160 mg SMX + 32 mg TMP 4 ml oral suspension
Day 3	240 mg SMX + 48 mg TMP 6 ml oral suspension
Day 4	320 mg SMX + 64 mg TMP 8 ml oral suspension
Day 5	400 mg SMX + 80 mg TMP (one single – strength SMX-TMP tablet)
Day 6	800 mg SMZ + 160 mg TMP (two single-strength SMX-TMP tablets or one double-strength tablet)
Note: Cotrimoxazole oral suspension contains SMX 200 mg + TMP 40 mg per 5 ml	

Desensitization should not be attempted in individuals with a history of severe Cotrimoxazole or any other sulphonamide reaction. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone at a dosage of 100 mg per day may be tried.

Cotrimoxazole Prophylaxis in Children

All HIV-exposed infants should receive Cotrimoxazole prophylaxis from the age of 6 weeks until HIV is reliably excluded. In all those confirmed to be HIV infected, CPT should be continued till 5 years of age. The recommended dose is 5 mg/kg/day of Trimethoprim (TMP) + 25 mg of Sulfamethoxazole (SMX) combination once daily in syrup or tablet form according to age and bodyweight Table 2.9.5.

Children with history of severe adverse reaction (grade 4 reaction) to co-trimoxazole or other sulpha drugs as well as children with glucose-6-phosphate dehydrogenase deficiency (G6PD) should not be initiated on CPT. The alternative drug, in this case, is Dapsone 2 mg/kg once daily (not to exceed 100 mg/day) orally

Table 2.9.4: Indications for CPT in children

Group	When to Start Cotrimoxazole?	When to Discontinue CPT Prophylaxis?
All HIV-exposed infants/children	From 6 weeks of age (or at first encounter with health services)	HIV infection has been reliably excluded by a negative antibody test at 18 months, regardless of ARV initiation.
All HIV-infected infants and children up to 5 years of age	Regardless of WHO stage or CD4 counts or CD4%	At 5 years of age, when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e., in a child >5 years of age with a WHO T- stage 1 or 2 and CD4 count of >350 cells/ mm^3 on two occasions not less than 6 months apart
All HIV-infected children >5 years of age	WHO Stages 3 and 4 regardless of CD4 count or CD4 <350 cells/mm^3 regardless of WHO staging	When clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e., in a child >5 years of age with a WHO T-stage 1 or 2 and CD4 count of >350 cells/mm^3 on two occasions not less than 6 months apart
As secondary prophylaxis	After completion of treatment for PCP	• <5 years old: do not stop • >5 years old: with a WHO T- stage 1 or 2 and CD4 count of >350 cells/mm^3 on two occasions not less than 6 months apart

Table 2.9.5: Weight- and age-based dosing for Cotrimoxazole in PCP prophylaxis

Cotrimoxazole (TMP/SMX) Prophylaxis					
Weight (kg)	Approx. Age	Cotrimoxazole once a day			
		Syrup 5 ml (40 TMP / 200 SMX)	Child tablet (20 TMP / 100 SMX)	Single- strength adult tablet (80 TMP/ 400 SMX)	Double- strength adult tablet (160 TMP/ 800 SMX)
<5	**6 weeks–2 months**	2.5 ml	1 tablet	-	-
5–10	**2–12 months**	5 ml	2 tablets	½ tablet	-
10–15	**1–2 years**	7.5 ml	3 tablets	½ tablet	-
15–22	**2–5 years**	10 ml	4 tablets	1 tablet	½ tablet
>22	**>5 years**	15 ml	-	1½ tablets	½ to 1 tablet depending on weight

- Dosage: 5 mg/kg of TMP/day orally once daily;
- It should be emphasized to patients and families that Cotrimoxazole does not treat and cure HIV infection;
- Counsel caregivers well for side effects of CPT;
- Discontinue CPT if Stevens-Johnson's syndrome, severe liver disease, severe anaemia, severe pancytopenia or completely excluded HIV infection.

Splitting the tablets into quarters is not recommended unless there is no syrup available.

Cryptococcal Disease

Cryptococcal meningitis can be diagnosed through CSF culture, microscopy or by detection of CrAg. Diagnosis is said to be confirmed when Cryptococcus is identified in the CSF or CNS tissue. Serum CrAg

is usually positive in both meningeal and non-meningeal infections and may be present weeks to months before onset of symptoms. A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease

Primary prophylaxis: It is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance and cost.

In case CrAg test is not available, primary prophylaxis may be given to HIV-positive adults and adolescents who have CD4 cell count <100 cells/mm^3. For this, the recommended dosage shall be Fluconazole 100 mg OD. The criteria for discontinuing Fluconazole primary prophylaxis should take into consideration ALL the following criteria:

- Person is adherent to ART and free of cryptococcal disease
- Fluconazole given for at least 1 year
- CD4 cell count ≥100 cells/mm3
- Suppressed plasma viral load (Plasma viral load <1000 copies/ml)

Secondary prophylaxis or maintenance therapy:

Indications: Recommended after 2 weeks of successful treatment of cryptococcal disease (meningeal and non-meningeal) and 8 weeks of consolidation phase with fluconazole (400–800 mg daily for adults; 6–12 mg/kg/day for children/adolescents, up to maximum of 800 mg daily)

Maintenance (secondary prophylaxis): Fluconazole (200 mg daily for adults; 6 mg/kg/day for children/adolescents)

Discontinuing Fluconazole maintenance treatment: It is recommended that, after successful treatment of Cryptococcal disease (meningeal and non-meningeal) and consolidation phase treatment, the criteria for discontinuing Fluconazole maintenance treatment should take into consideration ALL the following:

- Person is adherent to ART and free of cryptococcal disease
- Fluconazole maintenance treatment given for at least 1 year
- CD4 cell count ≥100 cells/mm3 mm
- Suppressed plasma viral load (Plasma viral load <1000 copies/ml))

Pre-emptive treatment for PLHIV with asymptomatic cryptococcal infection in relation to CrAg test results is described in greater detail in Chapter 4.2 (Central Nervous System).

Tuberculosis Preventive Therapy

Isoniazid Preventive Therapy

Isoniazid Preventive Therapy (IPT) entails the administration of Isoniazid (INH) to individuals with latent TB infection to prevent progression to active TB disease. Isoniazid is one of the most effective anti-mycobactericidal TB drugs that protect against progression of latent TB infection to active disease (against endogenous reactivation). It also prevents TB reinfection post exposure to an open case of TB (against exogenous reinfection/super infection/ nosocomial transmission).

Several studies have shown that IPT administration in PLHIV prevents incidence and relapse of TB and is, therefore, a key public health intervention for TB prevention in PLHIV. The effects of IPT augment the effects of ART on reducing the incidence of TB. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of TB-specific immunity by ART and the beneficial effect of IPT may be prolonged. IPT does not promote INH resistance when used to treat latent TB infection.

In latent TB, the MTB bacilli are fewer in number and are dividing slowly, resulting in an extremely low risk of selecting drug-resistant mutants. A study conducted in 2010 reflected that the prevalence of INH resistance among IPT-exposed persons was like the background population.

Ruling Out Active TB

Adults and adolescents living with HIV should be screened for active TB with a clinical algorithm. The absence of all the four symptoms of current cough, night sweats, fever and weight loss (4S Symptoms negative i.e., 4S -ve) can identify a subset of adolescents and adults living with HIV who have a very low probability of having TB disease and who can be reliably initiated on IPT. This 4S TB screening has a very high negative predictive value of 99.3% in PLHIV on ART and 99.6% in PLHIV not on ART at 1% TB prevalence. CLHIV (more than 12 months of age) who do not report current cough, fever, poor weight gain and history of contact with a TB case (4S -ve) are unlikely to have active TB. Chest X-ray can not only pick up non-tuberculous pulmonary diseases like pneumonia (PCP) but can also help rule out active TB in certain situations. Tuberculin Skin test (TST) may be of some use in CLHIV.

Eligibility for TPT

All adults and adolescents living with HIV should be screened for TB with a clinical algorithm. Those who do not report any one of the four symptoms of current cough, fever, weight loss and night sweats are unlikely to have active TB and should, therefore, be assessed for IPT initiation. All children living with HIV more than 12 months of age, who do not report with current cough, fever, poor weight gain and history of contact with a TB case, are unlikely to have active TB and should, therefore, be assessed for IPT initiation. Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. If there is any doubt about the TB status of a patient, IPT should be delayed.

Contraindications to IPT

IPT should not be provided to patients in the following conditions:

- Active TB disease
- Active hepatitis
- Signs and symptoms of peripheral neuropathy such as persistent tingling, numbness and burning sensation in the limbs; regular and heavy alcohol consumption and symptoms of peripheral neuropathy
- Concurrent use of other hepatotoxic medications
- Contact with MDR-TB case
- PLHIV who have completed DR-TB treatment

IPT Work-up

The patient should be evaluated for signs of liver disease (yellowness of eyes) and neuropathy (persistent numbness and burning sensation in feet and hands) and examined for jaundice and tenderness in the right upper quadrant of the abdomen. Wherever available, routine liver function tests (LFTs)/ALT should be performed, but lack of LFTs/ALT results should not delay the initiation of IPT in asymptomatic patients. If

the patient does not have any abnormality based on the assessment above, assess for adherence using the criteria noted behind the ICF/IPT card.

IPT Regimen Plan

The regimen plan and dosing chart are provided in Table 2.9.6.

Table 2.9.6: Paediatric dosage chart for IPT

Weight Range (Kg)	Number of 100 mg Tablets of INH to be Administered Per Dose (Total Dose 10 mg/kg/day)	Dose (mg)
<5	½ tablet	50
5.1–9.9	1 tablet	100
10–13.9	1½ tablets	150
14–19.9	2 tablets	200
20–24.9	2½ tablets	250
>25	3 tablets or one adult tablet	300
Adults and Adolescents: Isoniazid 300 mg + Pyridoxine 50 mg (Vitamin B6) per day for 6 months		

Non-availability of pyridoxine should not be a reason to withhold TB preventive treatment. Alternatively, the multivitamin/B-complex formulations with the requisite prophylactic dose of pyridoxine available within the general health system may be considered.

IPT Initiation and Follow-up

All the 4S -ve patients should be assessed by SMO/MO to determine eligibility for IPT. IPT should be considered for both on-ART and pre-ART patients (if found 4S -ve). IPT should be initiated if not contraindicated. IPT drugs must be provided monthly (30 days) to all eligible patients.

4S screening should be done for all the patients (on ART and pre-ART) on IPT during every visit to exclude active TB. In case a patient becomes 4S +ve during the IPT course, he/she should be investigated for TB and if found positive, IPT should be stopped, and appropriate anti-TB treatment should be initiated.

IPT in Specific Situations

IPT provision in special circumstances, such as for patients who are previously treated for TB, patients with ART, pregnant patients and those with MDR-TB, is summarized in Table 2.9.7.

Table 2.9.7: IPT provision in specific situations

Scenario	Action
Patients previously treated for TB (secondary prophylaxis)	All CLHIV/PLHIV, who had successfully completed treatment for TB disease earlier, should receive INH for 6 months.
IPT with ART (secondary prophylaxis)	• Combined use of IPT with ART is recommended for all CLHIV/PLHIV regardless of ▪ degree of immunosuppression ▪ previous treatment for TB ▪ pregnancy. ART should not be delayed while starting or completing a course of IPT.
IPT and pregnancy	• A pregnant woman living with HIV should not be excluded from symptom-based TB screening and receiving IPT. • Isoniazid is safe in pregnancy. Start IPT in all HIV-positive pregnant women regardless of their gestation period. • Advise women to complete IPT if they become pregnant while taking IPT. Assure patient that IPT is safe while breastfeeding.
IPT in children born to microbiologically confirmed TB mothers	• If a baby is born to a microbiologically confirmed TB mother, assess the newborn for active TB. • Non-specific features suggestive of neonatal TB include fever, low birth weight, hepatosplenomegaly, irritability, feeding intolerance • Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.
IPT and MDR-TB	Contacts of MDR-TB and PLHIV who have completed DR-TB treatment are not eligible for IPT.
Patients develop TB during IPT treatment	• If a patient develops TB symptoms during IPT treatment, evaluate the patient for TB and conduct DST. Based on DST results, the appropriate treatment should be provided. • If the patient is sensitive to all the drugs, then based on history of ATT and duration of IPT decide on the following: ▪ If the patient has not received anti-TB treatment in the past and has taken IPT for less than 1 month, then provide the patient with treatment for new case. ▪ If the patient has received anti-TB treatment in the past OR if the patient has taken IPT for more than 1 month, then provide the patient with retreatment regimen. ▪ If the patient is found to have DR-TB, refer the patient to the DR-TB centre.
Patients develop TB after IPT treatment	Treat the TB episode as new or previously treated case based on previous TB treatment history and Rifampicin resistance pattern (whenever available). **IPT is not to be considered as past history of TB in such cases.**
If a patient had taken IPT for less than 1 month in total and discontinued for any reason (like toxicity or loss to follow-up)	• Conduct adherence counselling, address reasons for discontinuation, conduct ICF and, if asymptomatic, restart INH afresh. • Ensure they have completed a 6-month course.
After taking IPT for more than 1 month: If the patient had discontinued IPT for less than 3 months	• Conduct adherence counselling, conduct ICF and, if asymptomatic, restart INH afresh. • Ensure they complete a 6-month course within a 9-month period.
After taking IPT for more than 1 month: If the patient discontinued for more than 3 months or had discontinued more than once	• Do not re-initiate IPT.

2.10 Post Exposure Prophylaxis for HIV

Introduction

Healthcare providers are prone to accidental exposure to blood and other body fluids or tissues while performing their work duties. Avoiding occupational exposure to blood-borne pathogens is the key to prevent transmission of HIV, Hepatitis B, Hepatitis C and others in healthcare settings. Standard workplace precautions are likely to mitigate the occupational risk of blood-borne pathogens like HCV, HBV, HIV in healthcare personnel. With the scale-up of HIV testing and ART services, PLHIV survive longer and are increasingly utilizing healthcare facilities and the services of the healthcare personnel. Increased risk of accidental exposure to HIV-infected blood and other body fluids continues to be an important issue, despite the implementation of standard workplace precautions. Thus, the post-exposure management protocols form an important element of workplace safety. NACO guidelines describe the risks of infection, the preventive measures and the steps to be followed to deal with accidental occupational exposure to HIV and other blood-borne pathogens.[1]

The term 'healthcare personnel' is defined as any person, paid or unpaid, working in healthcare settings who are potentially exposed to infectious materials (e.g., blood, tissue and specific body fluids and medical supplies, equipment or environmental surfaces contaminated with these substances). Healthcare personnel include emergency care providers, laboratory personnel, autopsy personnel, hospital employees, medical and nursing students and healthcare professionals at all levels. Persons who are not directly involved in patient care but may be potentially exposed to blood or body fluids include clerical staff, dieticians, housekeeping staff, maintenance staff and others, including security personnel and volunteers. If required, PEP can also be given to public safety workers, including law enforcement personnel, sanitary workers, prison staff, firefighters, workers involved in needle exchange programmes, healthcare providers in private setting and even to attendants of patients after proper evaluation of exposure.

'Exposure' that may place an healthcare personnel at risk for blood-borne infection is defined as a percutaneous injury (e.g., needlestick or cut with a sharp instrument), where the risk of acquisition of HIV from a hollow-bore needle with blood from a known HIV seropositive source is between 0.2% and 0.5%, based on a prospective study[1] of occupational needlestick injuries.

- Contact with the mucous membranes of the eye or mouth
- Contact with non-intact skin (when the exposed skin is chapped skin or afflicted with dermatitis)

Occupational exposure refers Occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV and HCV) that occur during performance of job duties.

Non-occupational exposure refers to exposure to potential blood-borne infections (HIV, HBV, HCV) outside of the workplace setting like unprotected sex, sexual assault.

Post exposure prophylaxis (PEP) refers to the comprehensive management instituted to minimize the risk of infection following potential occupational exposure to blood-borne pathogens (HIV, HBV, HCV). PEP under the national programme also covers sexual assault victims, even though they are classified under non-occupational category.

This includes first aid, counselling, risk assessment, relevant baseline laboratory investigations based on informed consent of the source person (when possible) and exposed person, depending on the risk assessment, the provision of short term (28 days) of antiretroviral drugs, with follow- up and support including maintaining confidentiality.

The term **'Needle Stick Injury'** is a broad term that includes injuries caused by needles or other sharp objects (e.g., glass vials, surgical blades, forceps) that accidentally puncture the skin.

An **'Exposed Person'** is a person who is potentially at risk for acquiring HIV infection due to exposure to blood or potentially infectious body fluids in his or her occupation.

A **'Source Person'** is the person who is (either identified or not identified as) the possible source of contamination through blood or potentially infectious body fluids. If the sero status of the source person is unknown, he/she may be counselled to get tested for HIV under informed consent. The source person may be a patient if a healthcare provider is exposed or is the perpetrator in the case of sexual assault.

The decision regarding provision of PEP should be based on clinical consideration within 72 hours. Providers should give information, services and education without discrimination. The provision of information regarding PEP should be confidential including information about HIV testing, PEP provision and the reasons for seeking PEP.

Written informed consent needs to be obtained while providing PEP. Consent for HIV testing of source/exposed person in the context of HIV exposure and/or taking PEP needs to be done in accordance with national HIV counselling and testing guidelines.

In special situations, where the individual has limited or no capacity to consent (e.g., children or unconscious or mentally ill adults), a legally acceptable representative (e.g., parent/guardian/ caretaker) may be able to provide consent, without delay, as PEP must be provided within 72 hours.

NACP provides PEP services for all occupational exposures and victims of sexual assault but not for those following unprotected sexual behaviour or having other high-risk exposure.

Who is at Risk?

Professions with high risk of exposure to potential blood-borne infections include the following:

- Nursing staff and students
- Emergency care providers
- Labour and delivery room personnel
- Surgeons and operation theatre staff
- Laboratory technicians
- Physicians
- Interns and medical students
- Dentists
- Health facility cleaning staff, mortuary staff and clinical waste handlers

Table 2.10.1: Risk of exposure from different body fluids

Exposure to Body Fluids Considered 'at Risk'	Exposure to Body Fluids Considered 'Not at Risk', unless these Fluids Contain Visible Blood
Blood	Tears
Semen	Sweat
Vaginal secretions	Urine and faeces
Cerebrospinal fluid	Saliva
Synovial, pleural, peritoneal, pericardial fluid	Sputum
Amniotic fluid	Vomitus
Other body fluids contaminated with visible blood	(Unless these secretions contain visible blood)

Any direct contact (i.e., contact without barrier protection) to concentrated virus in a research laboratory requires clinical evaluation. For human bites, clinical evaluation must include the possibility that both the person bitten and the person who inflicted the bite were exposed to blood-borne pathogens.

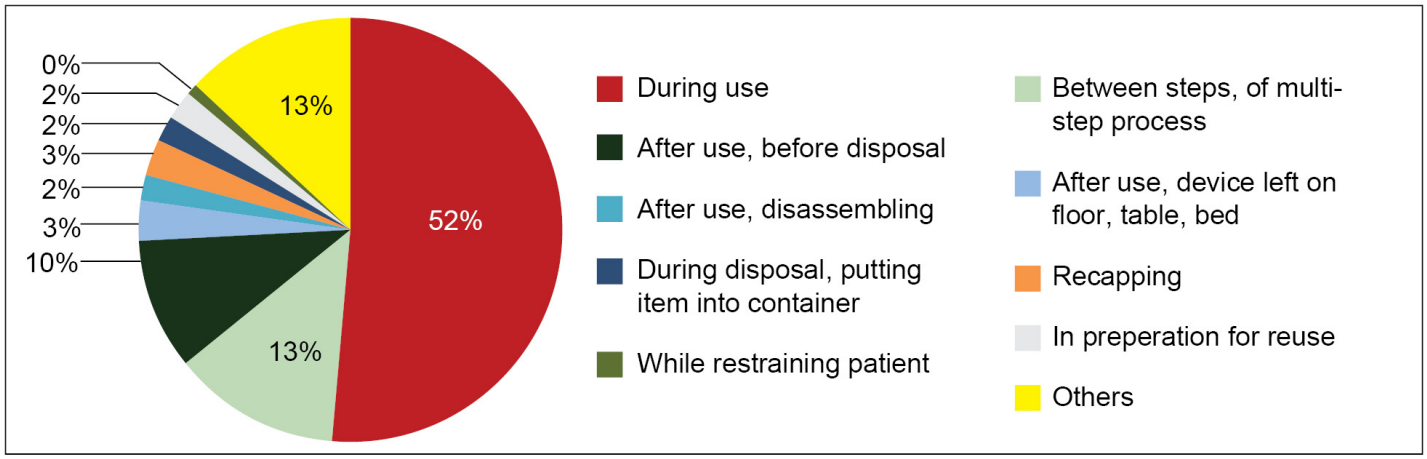
Average Risk of Acquiring HIV, Hepatitis B, Hepatitis C after Occupational Exposure

The average risk of acquiring HIV infection following different types of occupational exposure is low compared to the risk of acquiring infection with HBV or HCV. In terms of occupational exposure, the important routes (Table 2.10.2) are needlestick exposure (0.3% risk for HIV, 9–30% for HBV, and 1–1.8% for HCV) and mucous membrane exposure (0.09% for HIV).

Table 2.10.2: HIV transmission risk by different routes (WHO data)

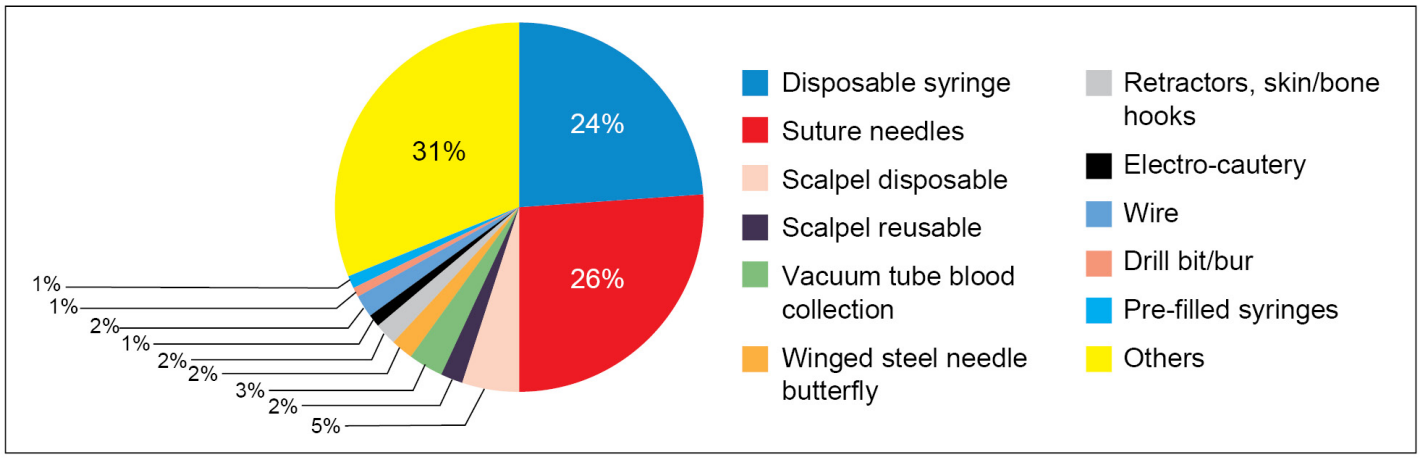
Exposure Route	HIV Transmission Rate
Blood transfusion	>98%
Perinatal (without any intervention)	20 - 40%
Sexual intercourse	0.1–1%
Vaginal	0.05–0.1%
Anal	0.065–0.5%
Oral	0.005–0.01%
Injecting drugs use	0.67%
Needle Stick exposure	0.3%
Mucous membrane splash to eye, oro-nasal	0.09%
Comparative risk after needle-stick injury for HBV is 9% to 30% and for HCV is 1% to 1.8%.	

Figure 2.10.1: Activities associated with needlestick or sharp object injury



Source: International Safety Center EPINet Report for Needlestick and Sharp Object Injuries, 2016.

Figure 2.10.2: Devices associated with percutaneous injuries by percentage of total percutaneous injuries reported



Source: International Safety Center EPINet Report for Needlestick and Sharp Object Injuries, 2016

Practices that influence and reduce the risk of occupational exposure

Certain work practices such as the following increase the risk of needlestick injury:

- Recapping needles (most important)
- Transferring a body fluid between containers
- Handling and passing needles or sharps after use
- Failing to dispose of used needles properly in puncture-resistant sharp containers
- Poor healthcare waste management practices

How to protect oneself from needlestick/sharp injuries:

- Strict compliance to standard workplace precautions
- Avoid the use of injections where safe and effective alternatives are available e.g., oral drugs.
- Avoid recapping needles.
- Plan for safe handling and disposal of needles after use.
- Promptly dispose used needles in appropriate sharps disposal containers.
- Report all needlestick and sharps-related injuries promptly to ensure that you receive appropriate

follow-up care.

- Participate in training related to infection prevention.
- Use devices with safety features provided by the institute (wherever possible).
- Record and monitor injuries with an injury register in each location of healthcare setting.

Figure 2.10.3: 'Do Not Recap Needle'



Performing activities involving needles and sharps in a rush increases the likelihood of an accidental exposure.

Preventing exposure to and transmission of HIV and other viruses

All categories of healthcare personnel within the hospital should be trained on how to protect themselves against HIV and other pathogens transmitted by blood or body fluids. The information must be reinforced on a regular basis. All the staff members share an individual and collective responsibility in this regard. The Medical Superintendent (MS)/Dean/Principal/In-charge of the hospital must constitute a hospital infection control committee that should conduct regular trainings and monitor hospital infection control including universal precaution, post-exposure prophylaxis implementation and quality control. The Medical superintendent must ensure that the hospital has a written protocol and Standard Operating Procedures (SOPs) to handle occupational exposure and that those are disseminated to all relevant personnel and departments.

The Medical superintendent /medical officer/in-charge of the hospital has the responsibility of informing the staff about the following:

- Standard workplace precautions to be followed in health services (Table 2.10.3)
- Use of personal protective equipment (Figure 2.10.4)
- SOPs to be followed in case of accidental exposure to blood and body fluids
- Round the clock availability of PEP drugs: Drugs must be kept in at least three locations – emergency room/casualty, labour room and ICU/OT complex

All hospital staff members must know whom to report for PEP and availability of PEP drugs in case of occupational exposure.

Minimize the use of sharps/injections: All the medical staff should try to minimize the use of invasive interventions, e.g., oral drugs must be used in place of injections wherever possible. Whenever the use of sharps is indicated, try to use safer alternatives that are practical and possible, within the limitations of the system.

Protection against Hepatitis: All healthcare personnel should be vaccinated against the Hepatitis B virus. The vaccination for Hepatitis B consists of three doses: baseline, 1 month and 6 months. Most of the recipients (99%) seroconvert after completing the full course. There is no vaccine or prophylaxis against Hepatitis C.

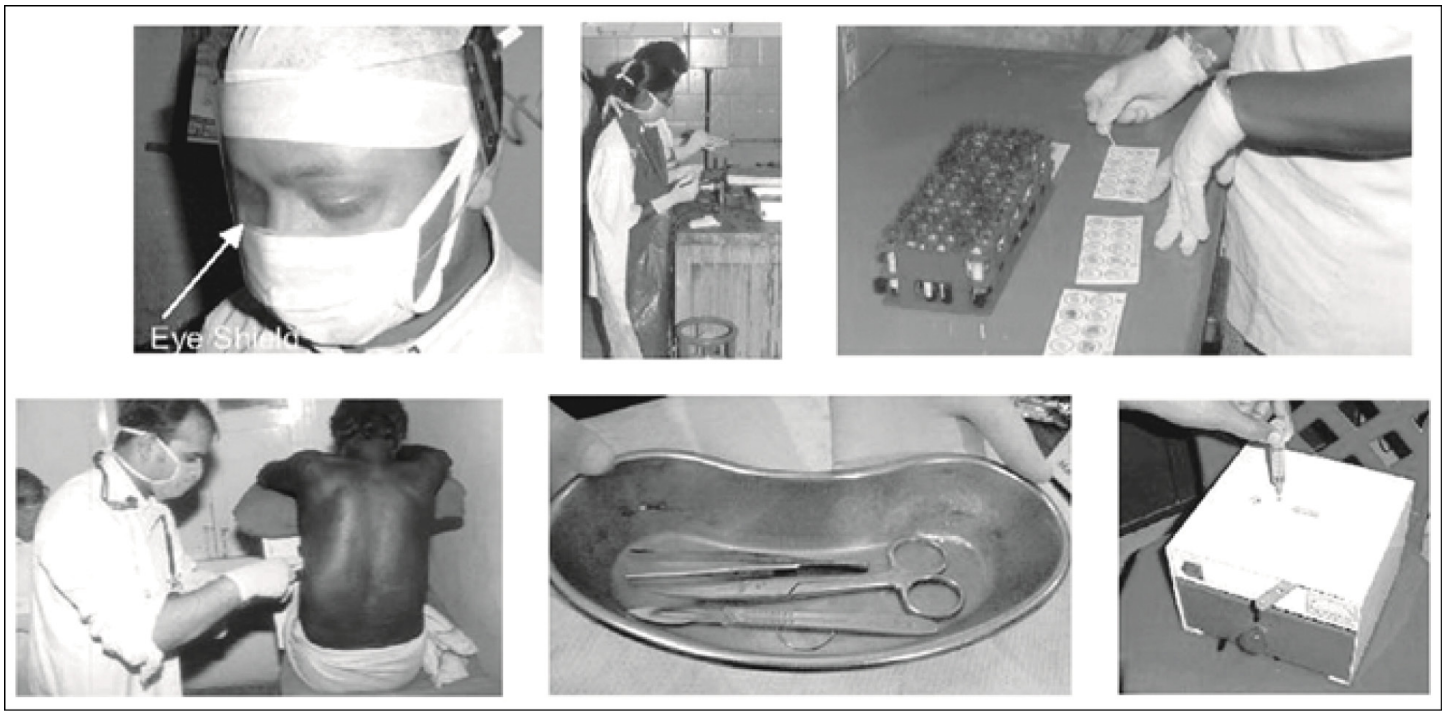
Table 2.10.3: Standard workplace precautions

Standard precautions are intended to prevent the exposure of healthcare workers and patients to blood-borne pathogens. These must be practised regarding the blood and body fluids of all patients, regardless of their infection status.

Standard precautions include the following:

- Handwashing before and after all medical procedures
- Safe handling and immediate safe disposal of sharps: not recapping needles; using special containers for sharps disposals; using needle cutter/destroyers; using forceps instead of fingers for guiding sutures; using vacutainers where possible
- Safe decontamination of instruments
- Use of protective barriers whenever indicated to prevent direct contact with blood and body fluid such as gloves, masks, goggles, aprons and boots. An healthcare personnel who has a cut or abrasion should cover the wound before providing care.
- Safe disposal of contaminated waste

Figure 2.10.4: Standard workplace precautions



Always use protective gear; consider all blood samples as infectious; follow universal precautions; practise safe handling of sharp instruments; use needle destroyers.

Management of the Exposed Person

Step 1: Management of Exposure Site – First Aid

Figure 2.10.5: Management of exposure site



Skin

If the skin is pierced by a needlestick or sharp instrument**:**

- Immediately wash the wound and surrounding skin with water and soap and rinse
- Do not scrub
- Do not use antiseptics or skin washes.
- Do not use bleach, chlorine, alcohol, betadine.

After a splash of blood or body fluids:

- Wash the area immediately.
- Do not use antiseptics.

Unbroken skin

- Wash the area immediately.
- Do not use antiseptics

Eye

- Irrigate exposed eye immediately with water or normal saline.
- Sit on a chair, tilt head back and ask a colleague to gently pour water or normal saline over the eye.
- If wearing contact lenses, leave them in place while irrigating, as they form a barrier over the eye and will help protect it. Once the eye is cleaned, remove the contact lenses and clean them in the normal manner. This will make them safe to wear again.
- Do not use soap or disinfectant on the eye.

Mouth

- Spit fluid out immediately.
- Rinse the mouth thoroughly using water or saline and spit again. Repeat this process several times.
- Do not use soap or disinfectant in the mouth.

Consult the designated physician of the institution for management of the exposure immediately.

Step 2: Establish Eligibility for PEP

A designated person/trained doctor must assess the risk of HIV and HBV transmission following an Accidental Exposure to Blood (AEB). This evaluation must be made rapidly, to start any treatment as soon as possible after the accident. This assessment must be thorough (because not every AEB requires prophylactic treatment).

The first dose of PEP should be administered ideally within 2 hours (but preferably within the first 72 hours) of exposure and the risk evaluated as soon as possible. If the risk is insignificant, PEP could be discontinued if already commenced. PEP needs to be started as soon as possible after the exposure and within 72 hours. In animal studies, initiating PEP within 12, 24 or 36 hours of exposure was more effective than initiating PEP 48 hours or 72 hours following exposure. Thus, PEP is more effective when given within 72 hours after exposure.

PEP must be initiated as soon as possible, preferably within 72 hours.

Two main factors determine the risk of infection: type of exposure and the HIV status of the source patient

Assessing the severity of exposure and risk of transmission

Severity of occupational exposure for healthcare personnel can be categorized and described based on the amount of blood/fluid involved and the entry port (Table 2.10.4). The average rate of HIV seroconversion after an Accidental Exposure to Blood (for percutaneous exposure) is 0.3%. The real risk of transmission

depends on the amount of HIV transmitted (= amount of contaminated fluid and the viral load). These three categories are intended to help in assessing the severity of the exposure but may not cover all possibilities. The risk is increased with higher viral inoculum, which is related to the amount of blood introduced and the concentration of virus in that blood. The size of the hollow bore needle, the depth of penetration and whether blood was injected are also important considerations. The risk of transmission is much lower in mucous membrane splash.

Table 2.10.4: Categories of exposures

Category of Exposure	Definition and Example
Mild exposure	Exposure to mucous membrane/non-intact skin with small volumes, contact with the eyes or mucous membranes or subcutaneous injections following small-bore needles
Moderate exposure	Exposure to mucous membrane with large volumes or percutaneous superficial exposure with solid needle. e.g., a superficial cut or needlestick injury penetrating glove
Severe exposure	Percutaneous exposure with large volume e.g. • an accident with a high-calibre needle (>18 G) visibly contaminated with blood • a deep wound (haemorrhagic wound and/or very painful); transmission of a significant volume of blood • an accident with material that has previously been used intravenously or intra-arterially
Note: The wearing of gloves is one of the standard workplace precautions, but glove punctures do happen. In case of an AEB with material such as discarded sharps/needles, dried contaminated blood, the transmission risk remains for a week for HIV; the risk remains more significant for HBV and HCV, as they survive longer than HIV outside the body.	

Assessing the HIV Status of the Source of Exposure

A baseline rapid HIV testing of the source of exposure should be done before starting PEP, if possible. Informed consent should be obtained before testing of the source as per national HIV testing guidelines. Initiation of PEP, where indicated, should not be delayed while waiting for the results of HIV testing of the source of the exposure. PEP shall be preferably initiated within 72 hours of exposure..

Table 2.10.5: Categories of situations depending on results of the source

Source HIV Status	Definition of Risk in Source
HIV negative	Source is not HIV infected; but consider HBV and HCV
Low risk	HIV positive and clinically asymptomatic
High risk	HIV positive and clinically symptomatic

Routinely used HIV tests that detect antibodies will not detect HIV during the ‘window period’, which is 21 to 28 days, as the antibody level is still too low for detection, but the person can still have a high viral load. This implies that a positive HIV test result (of source) can help in taking the decision to start PEP, but **a negative test result does not exclude HIV infection.** In districts or some population groups with a high HIV prevalence, a higher proportion of HIV-infected individuals are found in the window period. In these situations, it is important to understand local epidemiology and HIV prevalence for decision-making on PEP.

Assessment of the Exposed Individual

The exposed individual should have confidential counselling and assessment by an experienced physician. The exposed individual should be assessed for pre-existing HIV infection (see Step 5) intended for people who are HIV negative at the time of their potential exposure to HIV. Exposed individuals who are known or discovered to be HIV positive should not receive PEP. They should be offered counselling and information on the prevention of transmission and referred for clinical and laboratory assessment for subsequent linkage to comprehensive HIV services. Besides the medical assessment, counselling (see Step 3) of exposed healthcare personnel is essential to allay fear and start PEP (if required) at the earliest.

Step 3: Counselling for PEP

For an informed consent, exposed persons (clients) should receive appropriate information about what PEP is and the risk and benefits of PEP. It should be clear that PEP is not mandatory. The client should understand details of window period, baseline test, drugs that are used, their safety and efficacy and issues related to these drugs during pregnancy and breastfeeding. He/she should be counselled on safe sexual practices till both baseline and 3 months HIV test are found to be negative.

Psychological support: Many people will feel anxious after exposure. Every exposed person needs to be informed about the risks and the measures that can be taken. This will help to relieve part of the anxiety, but some may require further specialized psychological support.

Documentation on record is essential. Special leave from work, if required, should be considered for a period of, say, 2 weeks (initially), then as required based on assessment of the exposed person's mental state, side effects and requirements. For recording and reporting framework, please refer to NACO operational guidelines for ART services.

Step 4: Assessing Need for PEP and Prescribing PEP

Deciding on PEP Regimen

The decision on the need for PEP for HIV (following an occupational exposure in healthcare worker) will depend on the exposure, the source person's HIV status and the extent of disease if the source has been confirmed positive. It is decided based on exposure code and source code. Under NACP in India, programme managers and medical staff are being trained to assess the exposed person and the source person as detailed in the following two algorithms (Figures 2.10.6 & 2.10.7)

Figure 2.10.6: HIV exposure codes

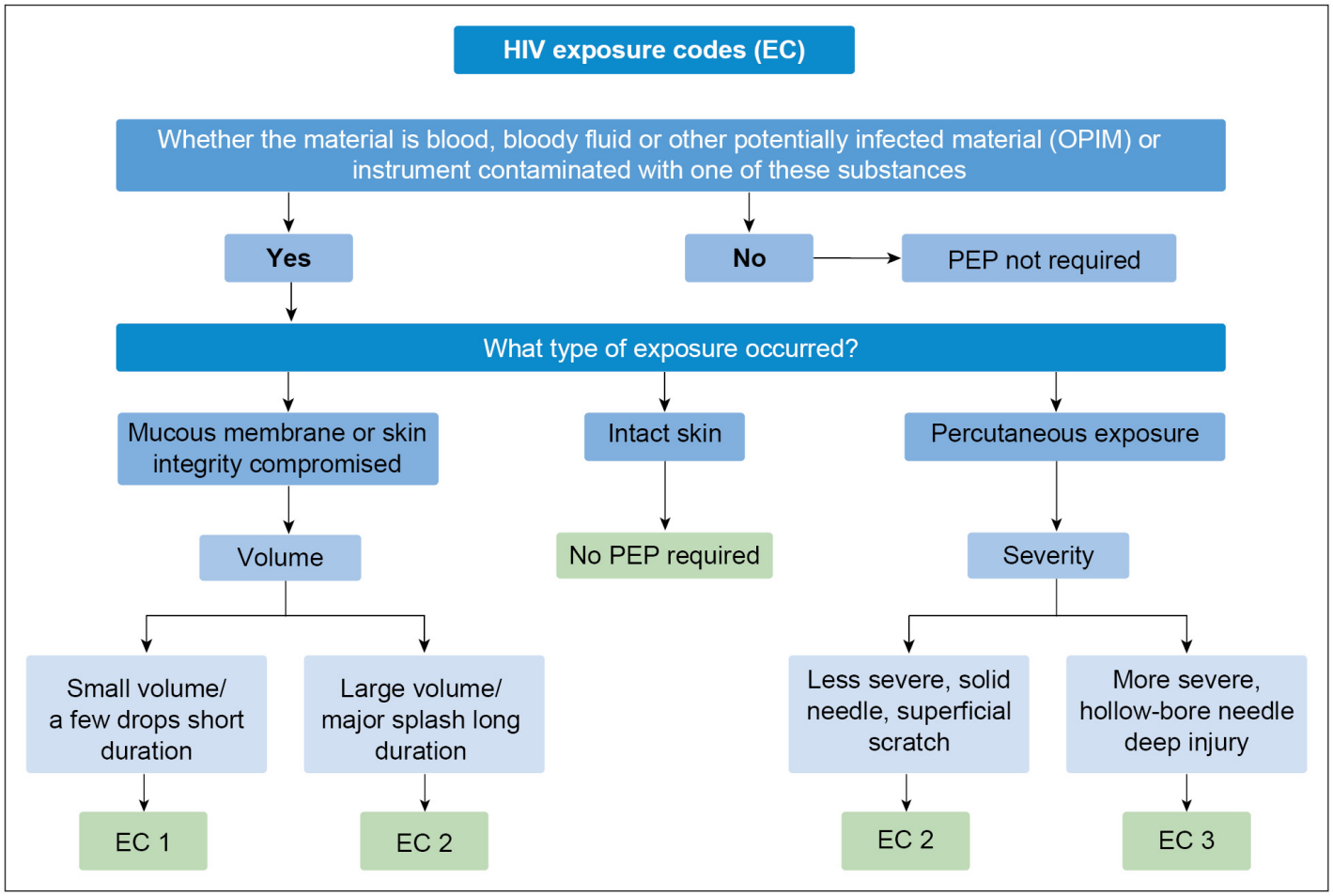
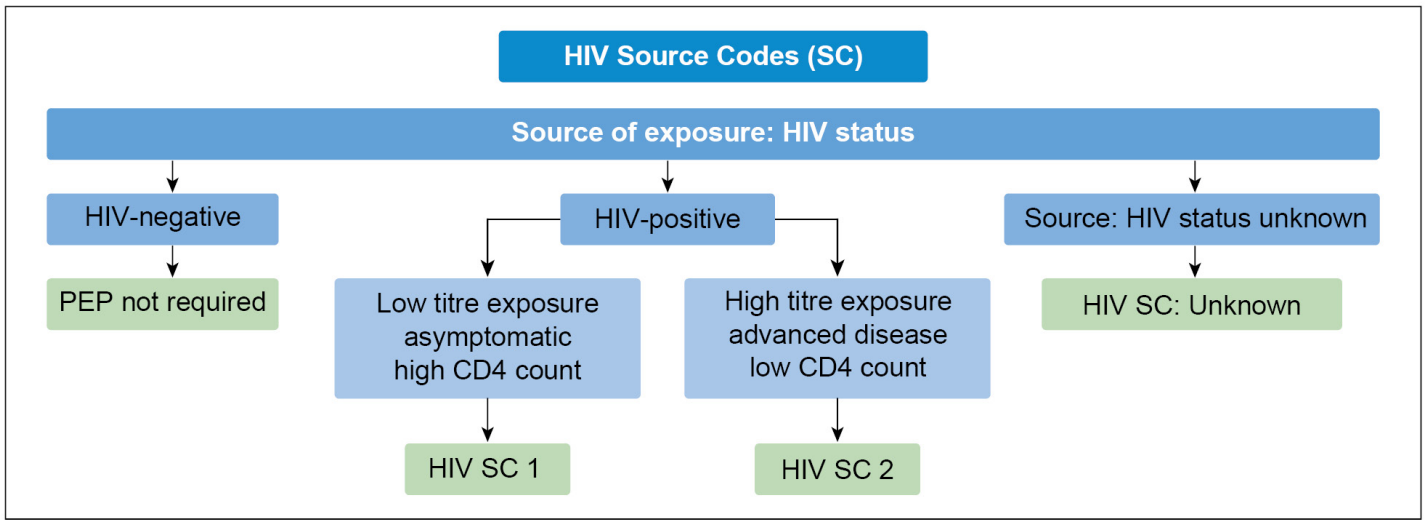


Figure 2.10.7: Source codes



Depending on the exposure and source codes, the decision to offer or defer PEP should be considered as provided in Table 2.10.6.

Table 2.10.6: NACO recommendations for PEP for healthcare personnel based on exposure and HIV source codes

Exposure Code	Source Code	Recommendation for PEP	Duration
1	1	Not warranted	
1	2	Recommended PEP	PEP is recommended for 28 Days
2	1		
2	2		
3	1 or 2		
2/3	Unknown	Consider PEP if HIV prevalence is high in given population in the region and risk categorization	28 days

In cases of sexual assault, PEP should be given to the exposed person as a part of the overall package of post sexual assault care.

- HIV testing of the source patient should not delay the decision about whether to start PEP. Start PEP first if required, then refer for consultation.
- In the case of a high-risk exposure (occupational or non-occupational) from a source patient who has been exposed to or is taking ARV medications, consult an expert to choose the PEP regimen, as the risk of drug resistance is high and a change of regimen may be required.

Key Considerations while Prescribing PEP

- PEP should be started preferably within 72 hours of exposure.
- If healthcare personnel presents after 72 hours of exposure, PEP can still be used after counselling about its effectiveness.
- PEP should be made available in the emergency department, labour room, Intensive Care Units and Operation Theatres (OTs).
- The exposed person should go to the designated clinic/officer, at the earliest, for a complete risk assessment, HIV counselling, testing and PEP.
- All hospital staff members must know whom to report to for PEP and where PEP drugs are available

Expert opinion may be obtained for the following situations:

- Delay in reporting exposure (>72 hours)
- Unknown source: Use of PEP to be decided on case-to-case basis after considering the severity of exposure and the epidemiologic likelihood of HIV transmission. Do not delay PEP initiation if indicated.
- Source patient is on ART or possibly has HIV drug resistance: Refer/consult as soon as possible.
- Major toxicity of PEP regimen: Minor side effects may be managed symptomatically. Refer to expert for non-tolerance or non-adherence.
- Refer/consult if in doubt or complicated cases (e.g., major psychological problem).

PEP must be initiated as soon as possible, preferably within 72 hours.

What Regimen to Give for PEP?

As PEP for HIV has its greatest effect if begun within 2 hours of exposure, it is essential to act immediately. There is little benefit if more than 72 hours have lapsed but PEP can still be used if the healthcare worker presents after 72 hours of exposure. The prophylaxis needs to be continued for 28 days

- Report exposure immediately to appropriate authority.
- Never delay the start of therapy due to debate over regimen. In cases with exposure from patient on ART, start available three drug regimens and seek opinion after that.
- PEP is indicated for healthcare providers based on exposure and HIV source codes. NACO's recommended PEP regimens are tabulated in Table 2.10.7

Table 2.10.7: Recommended PEP regimens

Exposed Person	Preferred Regimen for PEP Drugs and Dosages	Alternate Regimen (If the Preferred Regimen is not available or Contraindicated)
Adolescents and Adults (>10 years of age and >30 kg weight)	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) (FDC: One tablet OD)	Tenofovir (300 mg) + Lamivudine (300 mg), (FDC: One tablet OD) + Lopinavir (200 mg)/Ritonavir (50 mg) (two tablets BD), OR,Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600 mg), (FDC: One tablet OD)
Children (>6 years of age and >20 kg weight)	Zidovudine + Lamivudine (Dosage as per weight band) + Dolutegravir (50 mg) (One tablet OD)	If Hb <9 g/dl: Abacavir + Lamivudine (dosage as per weight band) +, Dolutegravir (50 mg), (One tablet OD)
Children (<6 years of age and <20 kg weight)	Zidovudine + Lamivudine + Lopinavir/ritonavir (Dosage as per weight band)	If Hb <9 g/dl: Abacavir + Lamivudine + Lopinavir/ritonavir (Dosage as per weight band)
• The first dose of PEP should be administered immediately (within 2 hours) and preferably within 72 hours of exposure. • Healthcare personnel should be counselled about the safety of the PEP drugs. • Duration of PEP is 28 days, regardless of PEP regimen.		

In case of highly treatment-experienced source, initiate first dose as per above guidelines and expert opinion should be sought urgently by phone/e-mail from CoE/ART Plus centre.

In cases of sexual assault, the same principles need to be followed in adults and adolescents. For children who have suffered assault and must be administered PEP, the dosage should be as per age and weight bands and haemoglobin levels.

In all cases, appropriate and adequate counselling must be provided regarding possible side effects, adherence and follow-up protocol.

In practice and from healthcare personnel studies, it has been observed that many healthcare personnel do not complete the full course of PEP because of side effects. With the currently recommended PEP regimen (Tenofovir + Lamivudine + Dolutegravir), the compliance rate will be very high. However, it is important that side effects (e.g., gastritis) of alternate drug regimen and boosted PI should be explained before initiating PEP so that the symptoms are not confused with symptoms of seroconversion to HIV.

Adherence information is essential with psychological support. More than 95% adherence is important to maximize the efficacy of the medication in PEP. Table 2.10.8 gives guidance on management of common side effects of PEP drugs.

Table 2.10.8: Management of minor ARV drug side effects

Sign or Symptom	Management at health facility
Nausea	Take with food; reassure that this is usually self-limited. Treat symptomatically.
Headache	Give paracetamol. If on Efavirenz, reassure that this is common and usually self-limited. If persists more than 2 weeks, call for advice or refer.
Diarrhoea	Hydrate. Follow diarrhoea guidelines. Reassure patient that if it is due to ARV, it will improve in a few weeks. Follow up in 2 weeks. If it does not improve, call for advice or refer.
Fatigue	This commonly lasts 4 to 6 weeks. Take 'sick leave' from work. If severe or longer than this, call for advice or refer.
CNS side effects: Anxiety, nightmares, psychosis, depression	This may be due to EFV. Take EFV at night before sleeping. Counsel and support (usually lasts <3 weeks). The initial difficult time can be managed with amitriptyline at bedtime. Call for advice or refer if severe depression or suicidal tendencies or psychosis (stop EFV)
Rash	If on EFV, assess carefully. Is it a dry or wet lesion? Call for advice. If generalized or peeling, stop drugs and refer for expert opinion
Fever	Assess clinically for Hepatitis; see if this could be primary (acute) HIV infection or other non–HIV-related infections, e.g., concurrent common cold. Call for advice or refer.
Jaundice, abdominal or flank pain	Stop drugs; call for advice or refer. If jaundice or liver tenderness is present, send for ALT test and stop ARVs; call for advice or refer.

Availability and Prescription for PEP

All clients starting on PEP must take 4 weeks (28 days) of medication. In all cases, the first dose of PEP should be offered as soon as possible, once the decision to give PEP is made. HIV testing of the client or results of the source HIV test can come later. As usage of PEP drugs is not frequent and the shelf life is 1 to 1.5 years, drugs for PEP should be made available in the emergency department, labour room and intensive care unit. Instructions must be given to the patient/client to go to the designated clinic/officer at the earliest for a complete risk assessment, HIV counselling and testing, receipt of the remaining medications and further management. It is important to monitor and regularly follow-up the patient/client once PEP is started (see Step 6).

Table 2.10.9: HBV vaccination after an accidental exposure to blood

HBV Vaccination after an Accidental Exposure to Blood (AEB)	
HBV Vaccination Status of Exposed Persons	**Action after AEB**
Never vaccinated	Give complete Hepatitis B vaccine series
Vaccinated, anti-HBsAg not known	Give Hepatitis B vaccine booster
Vaccinated more than 5 years ago	Give Hepatitis B vaccine booster
Note: If not available, testing for the antibody level (anti-HBsAg) is not necessary. Hepatitis B vaccine should be given as soon as possible after the exposure. Do not wait for anti-HBsAg results if the test is done. Adequate levels of serum Ab to HBsAg (i.e. anti- HBsAg) is > 10 IU/L	

Vaccination for Hepatitis B

- All healthcare personnel must be immunized for Hepatitis B.
- ART staff can be immunized using contingency fund.

Hepatitis C:

Presently no prophylaxis is available against Hepatitis C. There is no evidence that interferon, pegylated or not, with or without Ribavirin is more effective when given during this time than when given at the time of disease. Post-exposure management for HCV is based on the early identification of chronic HCV disease and referral to a specialist for management.

Step 5: Laboratory Evaluation

The reason for HIV testing soon after an occupational exposure is to establish a 'baseline' against which future test results can be compared. When offered HIV testing, the exposed person should receive standard pre-test counselling according to the national HIV testing and counselling guidelines and should give informed consent for testing. Confidentiality of the test result must be ensured. There are possibly different reasons for delaying HIV testing: the healthcare personnel may be unable to give informed consent immediately after the exposure due to anxiety or the exposure occurs outside working hours or in settings where HIV testing is not readily available. The HIV test may be done up to several days after the exposure, depending upon the informed consent and with pre- and post-test counselling, ensuring confidentiality.

Do not delay PEP if HIV testing is not available

Table 2.10.10: Recommended baseline laboratory investigations

Baseline Laboratory Investigations		
Timing	In person taking PEP (standard regimen)	In persons not taking PEP
Baseline	HIV, HCV, anti-HBs Ag*, complete blood count, serum transaminases	HIV, HCV, anti-HBs Ag*
*HIV, HBV and HCV testing of exposed staff within 6 days of an AEB is recommended (baseline sero status). Offer an HIV test in case of an AEB, as a positive HIV status may indicate the need to discontinue PEP. The decision to test for HIV or not should be based on the informed consent of the exposed person. Exposed persons not taking PEP need to be counselled for repeat testing of HIV, HCV, anti HBsAg at 6 weeks, 12 weeks and 24 weeks from date of exposure.		

HIV RNA testing by polymerase chain reaction (PCR) during PEP has a very poor positive predictive value and should be strongly discouraged. Pregnancy testing should also be available, but its unavailability should not prevent the provision of PEP. Other laboratory testing such as haemoglobin estimation should be available, especially when Zidovudine is used for PEP in areas where anaemia is common. Testing for other blood-borne diseases such as syphilis, malaria and kala azar may also be useful, depending on the nature of risk, symptoms of the source patient, local prevalence and laboratory capacity.

Step 6: Follow-up of an Exposed Person

Whether or not PEP has been started, follow-up is indicated to monitor possible infections and to provide psychological support.

Clinical follow-up: In addition, in the weeks following an AEB, the exposed person must be monitored for

the eventual appearance of signs indicating an HIV seroconversion: acute fever, generalized lymphadenopathy, cutaneous eruption, pharyngitis, non-specific flu symptoms and ulcers of the mouth or genital area. These symptoms appear in 50% to 70% of individuals with a primary (acute) HIV infection, almost always within 3 to 6 weeks after exposure. When a primary (acute) infection is suspected, referral to an ART centre for an expert opinion should be arranged immediately.

An exposed person should be advised to use precautions (e.g., avoid blood or tissue donations, breastfeeding, unprotected sexual relations or pregnancy) to prevent secondary transmission, especially during the first 3 months following exposure. Condom use is essential.

Counselling regarding adherence and side effects should be provided and reinforced at every follow-up visit. If PEP is prescribed, the exposed healthcare personnel should be followed up every week with laboratory tests recommended below; psychological support and mental health counselling are often required.

CLINICAL MONITORING IN POST-EXPOSURE PROPHYLAXIS

- Monitor for acute seroconversion illness
  - Within 3–6 weeks after exposure
  - If suspected, refer to ART centre
- Avoid
  - Blood donation
  - Breastfeeding
  - Pregnancy
- Person should use precautions
  - Sexual relationship (condom protection)
- • Adherence and adverse drug reaction counselling

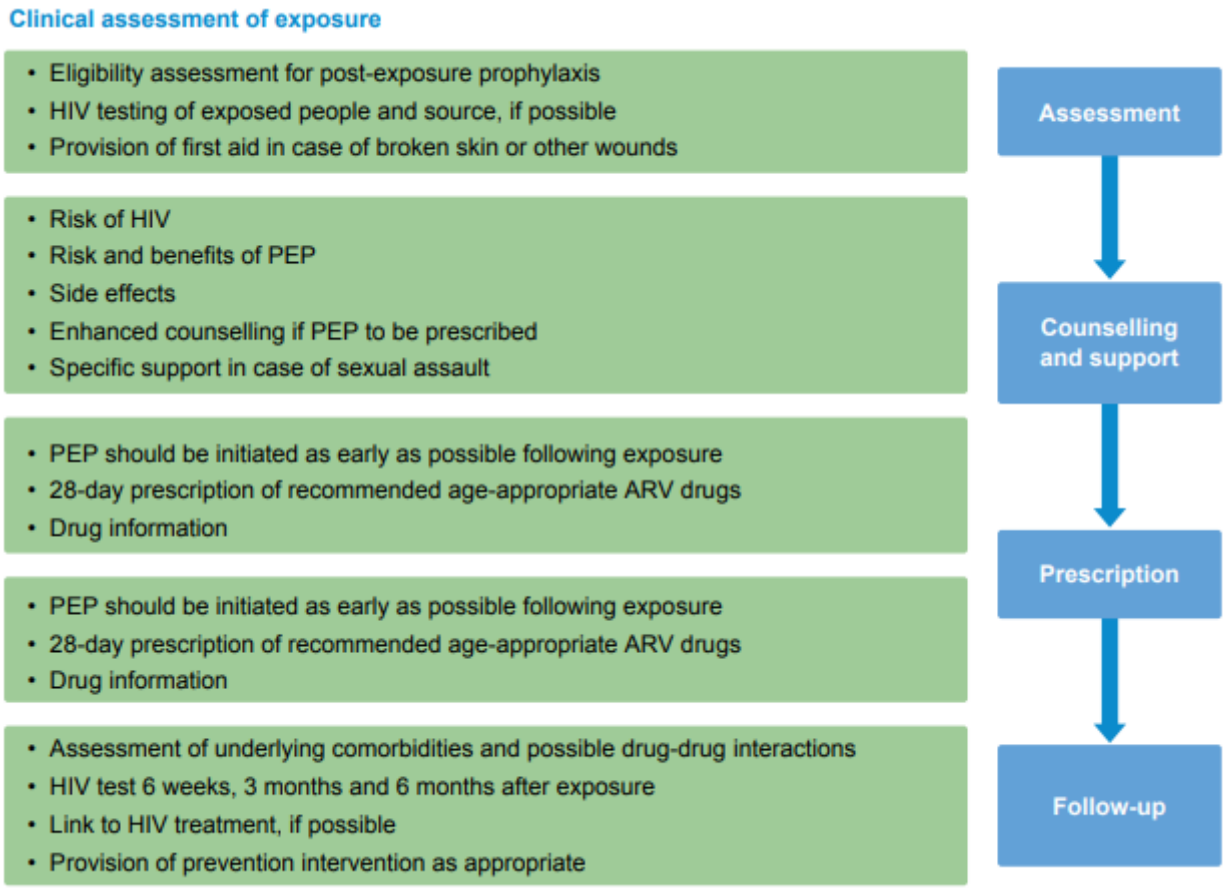
Laboratory follow-up: The exposed person should have follow-up HIV tests post PEP (Table 2.10.12). Testing at the completion of PEP may give an initial indication of seroconversion outcome if the available antibody test is very sensitive. However, testing at 4–6 weeks may not be enough as the use of PEP may prolong the time required for seroconversion and there is not enough time to diagnose all persons who seroconvert. Therefore, testing at 3 months and again at 6 months is recommended. Very few cases of seroconversion after 6 months have been reported. Hence, if the HIV test at 6 months is negative, no further testing is recommended.

Table 2.10.11: Recommended follow-up laboratory monitoring (during and after PEP)

Minimum Laboratory Follow-up Recommended for HIV PEP*	
Timing	**In person taking PEP (standard regimen)**
Weeks 2 and 4	Complete blood count (for patients on AZT, this is particularly useful.) Fasting blood sugar/Random blood sugar (for patients on Dolutegravir) Serum creatinine
Week 6	HIV-Ab
Week 12 (Month 3)	HIV-Ab
Week 24 (Month 6)	HIV-Ab

*It is important to remember that the person exposed to the risk of transmission of HIV is also at risk of getting infected with HBV and HCV. Hence, that too needs to be addressed.

Figure 2.10.8: Care pathway for PEP



"*Adapted from "HIV and the use of Cotrimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: Recommendations for a public health approach December 2014 supplement to the 2013 consolidated guidelines on the use of Antiretroviral drugs for treating and preventing HIV infection"*

Section 3

Paediatrics

3.1 Management of HIV Exposed Infants and Children

Background

The term '***HIV-exposed infants/children***' is used to refer to infants/children born to mothers infected with HIV, until HIV infection can be reliably excluded or confirmed in them. According to the India HIV estimates In 2023, 63,000 children (0-14) are estimated to be living with HIV accounting for 2.5% of the estimated 25.44 lakh PLHIV in India. Around 3.4% of the total new HIV infections in 2023 were estimated among children (aged <15 years), with an estimated 81.5% decline in annual new infections between 2010 and 2023[1]

Table 3.1.1: National summary of the HIV/AIDS epidemic in 2023[1]

Indicators	Desaggregation	Value
Number of People Living with HIV (In Lakh)	**Total**	25.44 (21.68 - 30.38)
	Adult (15+ years)	24.81 (21.15 - 29.61)
	Women (15+ years)	11.22 (9.56 -13.32)
	Children (<15 years)	0.63 (0.51- 0.79)
	Young people (15-24)	1.63 (1.27 - 2.17)
AIDS-related Deaths (in Thousand)	**Total**	35.87 (24.32-54.40)
	Adults (15+ years)	34.68 (23.56 - 52.26)
	Women (15+ years)	11.32 (6.44 - 19.09)
	Children (<15 years)	1.19 (0.60 - 2.45)
	Young people (15-24)	0.90 (0.56 - 1.47)

Mother-to-child-transmission (MTCT), occurring during pregnancy, labour or during breastfeeding accounts for over 90% of all HIV infections in children. Nationally, in 2023, there were an estimated 19.96 thousand pregnant women, requiring ART to prevent mother to child transmission of HIV. The final MTCT rate (including breastfeeding period) in 2023 was estimated at 11.75%(7.93-17.66), down from around 40.2% in 2010. Still, the MTCT rate continues to be on the higher side as against the target of 5%.[1]

Conventionally, MTCT is referred to as Parent to child transmission in India to emphasize the role of the father in the transmission of the virus as well as management of the infected mother and child.

Table 3.1.2 shows risk of HIV transmission through PTCT with and without any intervention

Table 3.1.2: Risk of HIV transmission through PTCT with and without any intervention

Intervention	Risk of Mother to Child HIV Transmission
No ARV, breastfeeding	30–45%
No ARV, no breastfeeding	20–25%
Short course with 1 ARV, breastfeeding	15–25%
Short course with 1 ARV, no breastfeeding	5–15%
Short course with 2 ARVs, no breastfeeding	5%
3 ARVs (ART), with breastfeeding	2%
3 ARVs (ART), no breastfeeding	1%

Source: Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Towards universal access, Recommendations for public health approach – 2006 version – WHO

Why are HIV-exposed infants a vulnerable group?

Regardless of their own HIV status, HIV-exposed infants are at a high risk of malnutrition, growth failure, developmental delay, and repeated infectious diseases-related morbidity by common as well as unusual organisms. Adverse social and economic factors associated with parental HIV infection like poverty, broken families, parental sickness/drug abuse and stigmatization by society are major reasons for this. Increased likelihood of replacement feeding that may often be inappropriate and over-diluted, poor environmental sanitation and delayed introduction and poor quality of complementary feeds may further increase this vulnerability.

Exposed infants who themselves acquire HIV infection are even more vulnerable to repeated infections, malnutrition and developmental delay. HIV disease progresses very rapidly in young children, especially in the first few months of life, often leading to death. If HIV exposure is not captured during pregnancy/labour, HIV-infected infants frequently present with clinical symptoms in the first year of life. Without care and treatment, about one third of infants living with HIV will die in their first year of life and almost 50% of children by the second year of life.

Thus, it is very important to follow all HIV-exposed infants with a structured plan to minimize risk of HIV transmission, ensure timely detection and management of HIV infection, and to give optimal comprehensive care to improve their overall outcome. With the rapid and significant expansion of the national HIV programme, i.e., the PPTCT, ICTC, ART (for adults and children) programmes, including access to early diagnosis for HIV testing of infants and children <18 months of age, it is now possible to ensure that HIV-exposed infected infants and children receive the required essential package of care. Recent studies indicate that given optimal care, the outcome of HIV-exposed infants in India can match that observed from more developed nations.

Care of HIV-exposed Infant/Child

Components of Care

The main components of care of HIV-exposed infants are presented in Table 3.1.3.

Table 3.1.3: Components of Care of HIV-exposed Infant/Child

- Immediate care at birth
- Infant feeding
- Antiretroviral prophylaxis
- Immunization and vitamin A supplementation
- Cotrimoxazole prophylaxis
- Growth and development
- Early infant diagnosis
- Follow-up

Immediate Care at Birth

Care of HIV-exposed infants should follow standard neonatal care according to safe motherhood guidelines, including the following:

- The baby's mouth and nostrils should be wiped as soon as the head is delivered.
- Infants should be handled with gloves until all blood and maternal secretions have been washed off.
- The cord should be clamped soon after birth, and milking should be avoided. Cover the cord with gloved hand and gauze before cutting to avoid blood splattering.
- Initiate feeding within the first hour of birth according to the preferred and informed choice.

Infant Feeding

Feeding guidelines for infants <6 months of age

Breastfeeding provides the infant all the required nutrients and immunological factors that help to protect against common infections. However, it does carry a risk of transmission of HIV infection from HIV-infected mothers to their infants. In accordance with WHO recommendations, NACO has been providing free and lifelong ART to all pregnant and lactating women regardless of their clinical and immunological stage since January 2014. Use of concomitant maternal ART not only decreases the maternal viral load, but also, upon transmission to the infant through placenta and breast milk, provides an effective pre-exposure prophylaxis to the infant preventing replication of any transmitted virions. Thus, the chances of HIV transmission to the foetus and the infant are greatly reduced, and breastfeeding is rendered even safer. Breastfeeding with concurrent ARV intervention offers HIV-exposed infants the greatest chance of HIV-free survival. In concurrence with the current WHO guidelines, this is the recommended feeding strategy for HIV-exposed infants in India.[2]

In concordance with the recommendation for HIV-unexposed infants, it is therefore recommended that

exclusive breastfeeding (EBF) be provided to all HIV-exposed infants; and at 6 months of age, these infants should be offered complementary foods along with breast milk.

However, given the fact that breastfeeding still carries some risk of HIV transmission, however slight it may be, individual pregnant women should also be informed about alternative infant- feeding options and their advantages and disadvantages as compared to breastfeeding **(Table 3.1.4).**

Exclusive Replacement Feeding (ERF) is not a viable public health strategy in India and other developing nations for HIV-exposed infants due to increased chances of non–HIV related morbidity and mortality negating the benefits of reduced HIV transmission. Thus, it cannot be recommended and promoted as the optimal infant-feeding strategy for HIV-infected mothers in India.

Table 3.1.4: Benefits and risks of exclusive breastfeeding and exclusive replacement feeding

	Exclusive Breastfeeding (EBF)	Exclusive Replacement Feeding (ERF)
Benefits	• Breast milk contains all the nutrients the baby needs in the first 6 months. • Breast milk is easy to digest. • Breast milk protects the baby from diarrhoea, pneumonia, and other infections. • Breast milk is readily available, does not require preparation. • Breastfeeding helps develop mother-infant bonding. • EBF helps the mother to recover from childbirth early. • EBF protects the mother from getting pregnant again too soon.	• No risk of HIV transmission through feeding • Other family members may be involved in feeding when mothers need help
Risks / Demerits	• Risk of acquiring HIV infection as long as the baby is breastfed	• Expense of obtaining appropriate milk, water, fuel, added task of cleaning utensils • Babies are at higher risk of contracting diarrhoea, pneumonia and other infections. • Mother may be questioned about not breastfeeding her baby.

The current national guidelines for feeding of HIV-exposed and infected infants <6 months age are as follows:

- EBF[#] for first 6 months of life is recommended. In a situation where the mother is practising mixed feeding, healthcare workers (HCWs) and counsellors should motivate her to exclusively breastfeed.
- When exclusive breastfeeding is not possible for any reason (i.e., maternal death, sickness, twins), mothers and HCWs can be reassured that maternal ART reduces the risk of postnatal HIV transmission in the context of mixed feeding as well.
- Mothers known to be HIV infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter and continue breastfeeding.
- Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. Mothers living with HIV should breastfeed for at least 12 months and may continue

breastfeeding for up to 24 months or beyond (like the general population), while being fully supported for ART adherence.

- Exclusive Replacement feeding may be considered only in situations where breastfeeding cannot be done* or upon individual mother's choice, only if all the six criteria for replacement feeding are met (Table 3.1.5).

#EBF means that infants are given only breast milk and nothing else: no other milk, food, drinks and no water. The infant receives only breast milk and no other liquids or solids except for drops or syrups consisting of vitamins, mineral supplements or medicines, as advised by authorized medical attendant.

*Maternal sickness/death, twins etc.

Table 3.1.5: The six criteria to assess suitability for replacement feeding

Mothers known to be HIV infected should give replacement feeding to their infants only when ALL the following conditions are met:

1. Safe water and sanitation are assured at the household level and in the community.
2. The mother, or any other caregiver, can reliably afford to provide sufficient and sustained replacement feeding (milk) to support normal growth and development of the infant.
3. The mother or caregiver can prepare it frequently enough in a clean manner so that it is safe and carries a low risk of diarrhoea and malnutrition
4. The mother or caregiver can, in the first 6 months, exclusively give replacement feeding.The family is supportive of this practice
5. The family is supportive of this practice.
6. The mother or caregiver can access healthcare that offers comprehensive child health services.

Counselling Mothers Regarding Choosing Feeding Strategy

A discussion with the parents should take place well before delivery regarding choice of infant feeding strategy. While clearly recommending EBF as the feeding option of choice, the counsellor should provide the family information about risk of HIV transmission associated with breastfeeding as well as stressing good adherence to ART as a tool for minimizing it. Benefits and risks of replacement feeding should also be provided, and family situation assessed as described above. Since each mother is different from the others in terms of education, financial situation and social support, counselling as well as the final decision regarding feeding option needs to be customized for everyone's unique need. Most importantly, the counsellor must support the family in executing the chosen feeding option in a correct manner.

Counselling mothers who decide to breastfeed infants

Mothers who decide to breastfeed their infants should be counselled to give breastfeeds as often as the child wants, day and night, at least eight times in 24 hours. The mother should be advised to continue breastfeeding if the child is sick. She should not give any other food, fluids or water to her infant during the first 6 months of life. Counselling should also include steps for appropriate breast care. The counsellor should stress upon the importance of breastfeeding exclusively, since even a small amount of mixed feeding makes a child vulnerable to gastrointestinal and other infections.

Counselling mothers who decide to give Replacement feeding to infants

The options of Replacement feeding include unmodified animal milk or pre-packed processed toned milk (containing 3% fat, 3.1% protein and providing 58 Kcal/100 ml) or suitable infant formula reconstituted as

per recommendation of the manufacturer. Although animal milk is not ideally suited to meet the complete nutritional requirements of an infant below 6 months, it is easily available, economical and culturally acceptable. Infants receiving animal milk should additionally receive multivitamin and iron supplementation.

Mothers who decide to give ERF to their infants need to be counselled about the hygienic way to prepare feeds and about the amount of feeding the child will need at different ages. They should wash their hands with soap and water before preparing the feed and use clean utensils. The child should be fed using katori–spoon or paladai. **Bottle feeding should be strictly avoided since it carries a higher risk of causing diarrhoea.**

Mixed Feeding

It was earlier recommended that giving an infant a combination of breastfeeding and replacement feeding is to be avoided since an artificially fed or breastfed child is at less risk of acquiring HIV than the child who receives mixed feeding. Use of animal milk/formula feed increases the chance of causing inflammation of gut mucosa due to allergy and infections, making it easier for the HIV in breast milk to gain access and cause HIV infection in the infant. However, current evidence suggests that in continued presence of maternal ART, mixed feeding is also rendered safe and may be preferred over no breastfeeding at all. Thus, although EBF is still recommended during first 6 months, practising mixed feeding is not a reason to stop breast-feeding in the presence of ARV drugs. Thus, with ongoing maternal ART during pregnancy and lactation, there remains no difference in the feeding guidelines related to feeding of HIV-exposed versus unexposed infants.

Feeding guidelines for infants and children 6–18 months of age

For all infants more than 6 months of age, complementary feeding should be started regardless of HIV status and initial feeding options.

Breastfeeding beyond 6 months

Beyond 6 months of age, breastfeeding should continue while complementary feeds are introduced. If an infant is confirmed to be HIV infected, the mother is encouraged to continue breastfeeding up to 2 years of age or beyond as per the norm for general population. For HIV- uninfected infants, it was earlier recommended that breastfeeding be stopped by 12 months of age. However, in the current era of universal ART for all pregnant and lactating women, and resultant increased safety of breastfeeding, this recommendation may not be valid. The WHO, in its 2016 guidelines on feeding HIV-exposed infants recommend that **"**In settings where health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women living with HIV, the duration of breastfeeding should not be restricted. Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (like the general population) while being fully supported for ART adherence. Also, if a mother living with HIV plans to return to work, she and health-care workers can be reassured that shorter duration of breastfeeding of less than 12 months are better than never initiating breastfeeding at all.**"** NACO has endorsed this recommendation for use in India.

Complementary Feeding

The 10 guiding principles of complementary feeding are presented in Table 3.1.6. For further reading, refer **Chapter 3.6 (Nutritional Care of HIV-infected Children)**

Table 3.1.6: Guiding principles of complementary feeding

1. Introduce complementary foods at 6 months of age (180 days), while continuing to breastfeed.
2. Start at 6 months of age with small amounts of food and increase the quantity and frequency as the child gets older, while maintaining frequent breastfeeding.
3. Gradually increase food consistency and variety as the infant grows older, adapting to the infant's requirements and abilities.
4. Feed a variety of nutrient-rich and energy-dense food from the family pot to ensure that all nutrient needs are met; use iron-rich complementary foods or vitamin/mineral supplements for the infant, as needed.
5. Practice responsive (active) feeding, applying the principles of psychosocial care, good hygiene and proper food handling.
6. All breastfeeding should stop only when a nutritionally adequate and safe diet, without breast milk, can be provided by complementary feeds.
7. Assess the child's nutritional status regularly and, for HIV-positive children, classify appropriately as one of the three: growing, poor weight gain/conditions with increased nutritional needs or severe acute malnutrition.
8. In addition to age-specific needs, HIV-positive children who are growing appropriately will require additional 10% energy, based on actual weight.
9. In addition to age-specific needs, HIV-positive children who have poor weight gain or have conditions with increased nutritional needs will require additional 20%–30% energy, based on actual weight.
10. In addition to the age-specific needs, HIV-positive children who have severe acute malnutrition will need therapeutic feeding to provide 50%–100% additional calories and should be referred to appropriate facility for management of Severe Acute Malnutrition (SAM).

Infant ARV Prophylaxis

In addition to maternal ART, the HIV-exposed infant must also be given prophylactic ARV drugs to further reduce chances of HIV transmission during perinatal period and breastfeeding. The key factors for consideration when deciding the duration of prophylaxis are assessing the risk of the infant at delivery based on viral load test result available within 4 weeks prior to delivery and time to viral suppression with Dolutegravir (DTG) or non–DTG-based maternal ART regimens. In accordance with WHO guidelines, NACO recommends use of dual ARV prophylaxis for infants at high risk of HIV transmission and a single drug ARV prophylaxis for infants at low risk of HIV transmission. As per the current guidelines,

- Plasma viral load should be done in all pregnant women between 32 and 36 weeks of pregnancy (regardless of the duration of maternal ART), to assess the risk of HIV transmission to the infant.
- Infants born to mothers with suppressed plasma viral load assessed any time after 32 weeks of pregnancy up to delivery should be considered as 'low-risk infants'.

- All other infants will be considered ‘high-risk infants’, including the following
- Born to HIV-positive mother not on ART
- Maternal viral load not done after 32 weeks of pregnancy
- Maternal plasma viral load not suppressed after 32 weeks of pregnancy up to delivery
- Mother newly identified as HIV positive within 6 weeks of delivery

High-risk infants shall receive dual ARV prophylaxis while those with low risk will receive single ARV prophylaxis (table 3.1.7). Doses of drugs used are given in Tables 3.1.8 and 3.1.9.

Table 3.1.7: HIV risk assessment of infants born to HIV-infected mothers and infant ARV prophylaxis options

HIV Risk Status	Option for ARV Prophylaxis
Low-risk infants • Infants born to mothers with suppressed plasma viral loads (<1000 copies/ml) assessed any time after 32 weeks of pregnancy up to delivery	1. Syrup Nevirapine or 2. Syrup Zidovudine# (in situations where Nevirapine will not be effective): ▪ Infant born to a mother with confirmed HIV-2 or HIV-1 and HIV-2 combined infections ▪ Infant born to a mother who had received single dose of Nevirapine during earlier pregnancy or delivery ▪ Infant born to a mother who is on PI-based ART regimen due to treatment failure **Duration:** From birth till 6 weeks of age
High-risk infants • Infants born to HIV-positive mother not on ART • Maternal viral load not done after 32 weeks of pregnancy • Maternal plasma viral load not suppressed after 32 weeks of pregnancy • Mother newly identified HIV positive within 6 weeks of delivery	**Options for dual prophylaxis** Syrup Nevirapine + Syrup Zidovudine## **Duration** • In case of exclusive replacement feeding: From birth till 6 weeks of age • In case of exclusive breastfeeding: From birth till 12 weeks of age
#When Zidovudine syrup is not available, syrup Lopinavir/ritonavir should be used after 14 days of birth. ##When Zidovudine syrup is not available, syrup Nevirapine should be used for first 14 days after birth and then added syrup Lopinavir/ritonavir should be used after 14 days of birth. ##Another alternative that may be used in this situation is Zidovudine + Lamivudine + Nevirapine (ZLN) paediatric formulation.	
In exceptional scenarios as for high-risk infants born to HIV-2–positive mothers or for high-risk infants born to mothers who had received single dose of Nevirapine during earlier pregnancy or delivery, opinion of SACEP should be sought.	

Table 3.1.8: Dose of syrup Nevirapine (10 mg/ml solution) for infant ARV prophylaxis

Infant age	Daily dosing
Birth* to 6 weeks • Birth weight 2000–2500 g • Birth weight >2500 g	 10 mg (1 ml) once daily 15 mg (1.5 ml) once daily
>6 weeks – up to 6 months#	20 mg (2 ml) once daily
>6 months – up to 9 months#	30 mg (3 ml) once daily
>9 months	40 mg (4 ml) once daily

*Infants weighing <2000 g; the suggested starting dose is 2 mg/kg once daily.

#NVP dose for older infants is provided for the situation where HIV exposure is identified during infancy, the mother is breastfeeding and the infant is either HIV uninfected or the status is yet to be determined after taking opinion from SACEP/ pCoE.

Any HIV-exposed breastfeeding baby beyond 6 weeks of age will need SACEP/pCoE opinion for dual prophylaxis to be given or not.

Table 3.1.9: Dose of syrup Zidovudine (10 mg/ml solution) for infant ARV prophylaxis

Infant Birth Weight	AZT Daily Dosage (in mg)	AZT Daily Dosage (in ml)	Duration
<2000 g	5 mg/dose twice daily	0.5 ml twice daily	6 weeks
2000–2500 g	10 mg/dose twice daily	1 ml twice daily	6 weeks
>2500 g	15 mg/dose twice daily	1.5 ml twice daily	6 weeks
Older infants requiring dual prophylaxis may be given AZT syrup in a dose of 4 mg/kg/dose twice daily.			

Infant ARV prophylaxis should be started immediately after birth or at first encounter with health services. It can be started even if more than 72 hours have passed since birth, though its efficacy in preventing perinatal transmission will be lower. It will, however, still be protective towards transmission by breastfeeding. Daily infant ARV prophylaxis should continue for a minimum of 6 weeks, during which the mother should be linked to appropriate ART services. A longer duration (12 weeks) of prophylaxis is needed for infants on breastfeeding as described earlier.

Duration of infant ARV prophylaxis as per risk of HIV transmission in the infant is summarized in Table 3.1.10

Table 3.1.10: Duration of infant ARV prophylaxis

Type of Infant	Type of Feeding Option	Duration of ARV Prophylaxis
Infant with low risk for HIV transmission	Exclusive Breastfeeding (EBF)	6 weeks, regardless of feeding option
	Exclusive Replacement Feeding (ERF)	
Infant with high risk for HIV transmission	Exclusive Breastfeeding (EBF)	12 weeks
	Exclusive Replacement Feeding (ERF)	6 weeks

Immunization and Vitamin A Supplementation

HIV-infected infants and children are more susceptible to infections and more likely to develop serious complications thereof. Thus, there is an increased need for vaccination against all vaccine- preventable diseases endemic in the area. However, the success of vaccination may be suboptimal, depending upon the extent of immunodeficiency at the time of immunization. All recommended childhood immunizations should be administered to HIV-exposed infants. If HIV infection is confirmed, guidelines for the HIV-infected child should be followed. In a child with HIV infection, all inactivated vaccines can be administered safely, the decision to administer and the timing depend upon an assessment of likelihood of benefit. Live attenuated vaccines are contraindicated in severely immunocompromised infants and children with HIV infection (CD4 <15% in children up to 5 years, and CD4 count <200 cells/mm^3 in children aged >5 years) because of the risk of disease caused by the vaccine strain. CLHIV and their caregivers should be counselled about not accepting any vaccination given during immunization campaigns in schools or otherwise without first seeking opinion of the medical officer of ART centre.

HIV-exposed infants and children should be immunized according to the routine national immunization schedule (Table 3.1.11) with a few exceptions detailed below. It is important to give all the recommended vaccines at the correct age, as delay may not only increase susceptibility of the child to illness, but also decrease the immune response to the vaccine as the child's immune status deteriorates.

Specific points to be kept in mind:

- HIV-exposed infants, like all other infants, should be given BCG at birth. If BCG has not been given at birth, or for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be immunologically stable (CD4 >25%). For Children who are receiving ART, and have not received BCG earlier, it may be given once they are clinically well and immunologically stable (CD4% >25% for children aged <5 years or CD4 count ≥200 cells/mm^3 if aged >5 years).
- Severely immunocompromised HIV-infected infants, children, adolescents and young adults as defined above should not receive measles virus-containing vaccine, because vaccine- related pneumonia has been reported. WHO recommends that an additional dose of measles containing vaccine be administered to HIV-infected children receiving ART following immune reconstitution (CD4 count 20%–25%). Likewise, a supplemental dose of measles containing vaccine may be considered in HIV-exposed infants or soon after diagnosis of HIV infection in children older than 6 months who are not receiving ART and for whom the risk of measles is high, with the aim to provide partial protection till they are revaccinated.
- Rotavirus vaccine, though a live vaccine, is recommended for use in HIV-exposed infants due to their vulnerability to diarrhoea. The vaccine virus is a highly attenuated virus and immunization with the vaccine is given in early infancy when diagnosis of HIV infection is not confirmed in most infants. Moreover, even those who are infected but not diagnosed yet are unlikely to have severe immune deficiency. Nevertheless, like all live vaccines, it should not be given in children with known severe immunodeficiency.
- Pneumococcal conjugate vaccine (PCV13) is given at 2, 4 and 6 months, with booster at 12–15 months. This vaccine is being introduced in the National Immunization programme currently in a phased manner. It is recommended that Pneumococcal polysaccharide vaccine (PPSV23) should be administered at least 8 weeks after the last dose of PCV to children with HIV infection aged 2 years or older.
- Inactive Japanese Encephalitis (JE) vaccine is safe for use in children with HIV infection. A reduced immune response may be seen in HIV-infected children. However, most children with immune recovery after antiretroviral therapy develop a protective antibody response. A live attenuated JE vaccine is also now made available. This is to be avoided in children with HIV.
- It is desirable to check for seroconversion and give boosters as required especially for hepatitis B. A 4-dose, double-quantity schedule for hepatitis B has been recommended in view of poor seroconversion with

routine immunization.

- Vitamin A supplementation should be as per the national immunization schedule.

Desirable vaccines not currently available through the national schedule include the following:

- Inactivated Hepatitis A vaccine (two doses 6 months apart between 12–23 months)
- Inactivated influenza vaccine (starting at 6 months of age: two doses 1 month apart; 9 years and above: single dose; annual booster with single dose)
- Varicella vaccine: Administer the first dose at age 15–18 months and the second dose at age 4–6 years. Since this is a live attenuated vaccine, it is given only to asymptomatic children who are not severely immunocompromised.
- A single dose of Hib is indicated in unimmunized children >5 years of age (those who have not completed the primary series and the 15-month booster of Hib earlier).
- Meningococcal conjugate vaccine (MenACWY) should be administered two doses at least 8 weeks apart between 9–23 months of age, and a booster 2–5 years after the primary series.
- The three-dose series of human papillomavirus vaccine; tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine; and meningococcal conjugate vaccine all are indicated in HIV-infected adolescents.

It is worthwhile to note that since these children may not have an adequate response to vaccines, they may remain susceptible to infections despite having been immunized. Positive serologic test results in these children are not always reliable markers of protection. This should be kept in mind while managing children with HIV infection.

Table 3.1.11: Current national immunization schedule

Age	Vaccines
Birth	BCG, OPV-0, Hepatitis B birth dose
6 weeks	OPV-1, Rota-1, fIPV-1, Pentavalent-1, & PCV-1#
10 weeks	OPV-2, Rota-2, Pentavalent-2
14 weeks	OPV-3, Rota-3, fIPV-1, Pentavalent-3 & PCV-2#
9–12 months	MR-1, JE1,* PCV booster#
16–24 months	MR-2, JE2,* DPT booster 1, OPV booster
5–6 years	DPT booster 2
10 years	Td
16 years	Td
Pregnant mother	Td 1, 2 or Td booster**

*In endemic districts only
**One dose if previously vaccinated within 3 years
Being introduced in a phased manner in different states

BCG; Bacillus Calmette-Guerin; DPT: Diphtheria-Pertussis-Tetanus; Hep B: Hepatitis B; Pentavalent vaccine: DPT+ HepB + Hib (Haemophilus influenza type b); JE: Japanese encephalitis: MR: Measles–Rubella; OPV: Oral Polio Vaccine; TT: Tetanus Toxoid; IPV: Inactivated Poliovirus Vaccine; FIPV: Fractional Inactivated Polio Vaccine; RVV: Rotavirus Vaccine, Td: tetanus, reduced dose diphtheria

Cotrimoxazole Prophylaxis for HIV-Exposed/Infected Infants and Children

Cotrimoxazole prophylaxis is an effective and proven strategy for reducing morbidity and mortality in children with HIV infection. It not only protects the infants and children from Pneumocystis jiroveci infection, but also from malaria, diarrhoea due to Isospora and Cyclospora, toxoplasmosis and other bacterial diseases. All HIV-exposed infants should get Cotrimoxazole prophylaxis from the age of 6 weeks. The recommended dose is 5 mg/kg/day as a single daily dose. For details related to Cotrimoxazole prophylaxis, refer **Chapter 2.9 (Prevention of Opportunistic Infections).**

Growth and Development

Growth monitoring

Frequency of growth monitoring

The child's weight should be recorded at every visit to the ART centre. Length should be recorded once in 3 months for all HIV-exposed infants. It is recommended that the WHO growth reference standard be used for assessing a child's growth parameters. These are available as growth charts as well as reference tables for boys and girls separately (refer annexures 7, 8 and 11). In a child growing normally, a serial recording of these parameters in a growth chart over time should yield a curve parallel to one of the standard growth curves on the growth chart. When the child's growth parameters falter, serial recordings on a growth chart will no longer be parallel to the standard growth curves. For practical purposes, weight-for-age chart should be maintained for every child for serial weight monitoring. Z scores for other parameters like length for age and weight for length may be checked from the graph/table as required for assessment of nutritional status.

If the child's growth curve is flattening, one should intensify the assessment of HIV-related features and screen for treatable causes, e.g., nutritional deficiency, chronic infections such as respiratory, gastrointestinal and urinary tract infections and TB.

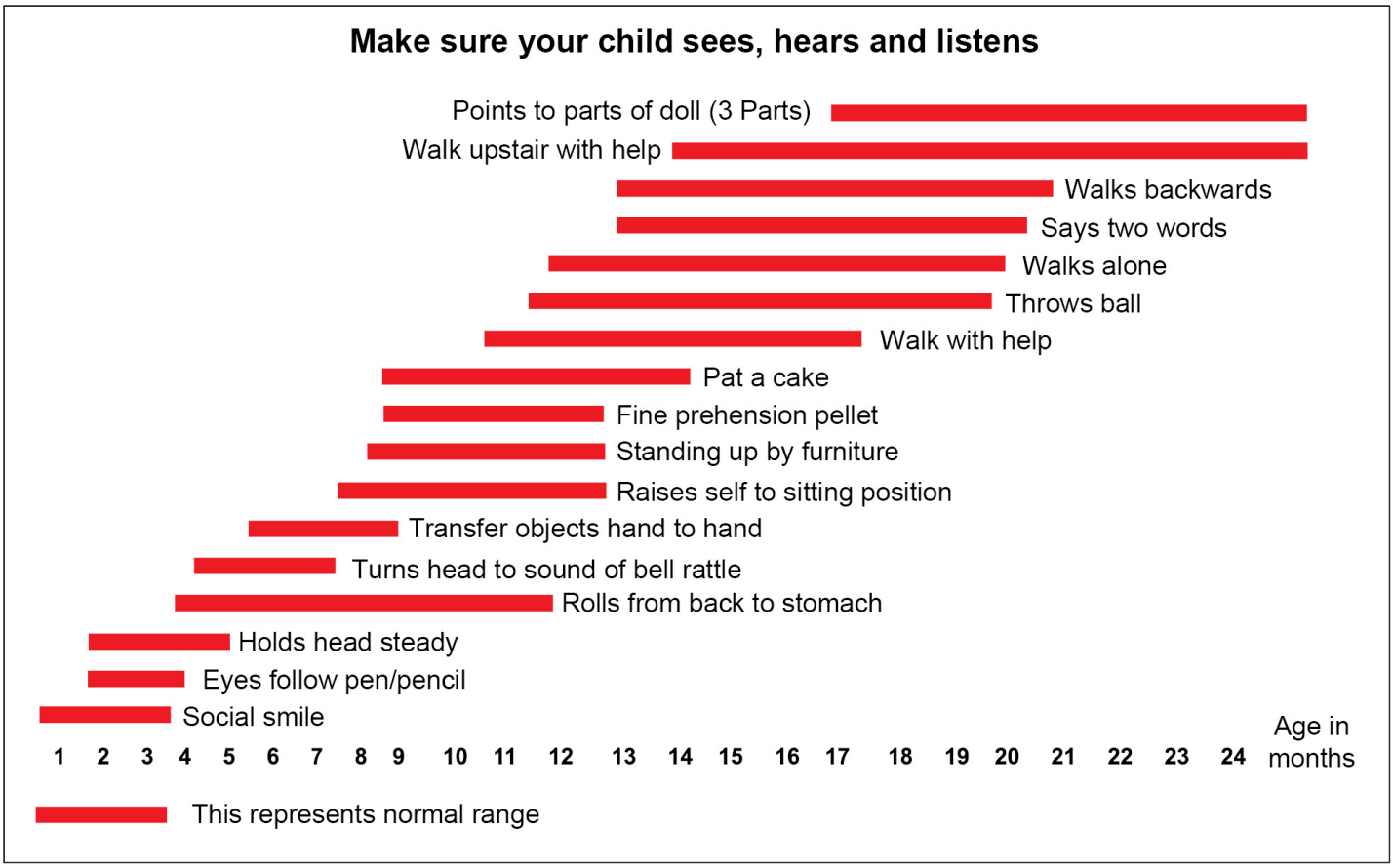
Developmental Assessment

Developmental milestones help in assessing development or maturation of the brain of an infant/ child. They refer to abilities that children are expected to possess at different ages. Delayed development or loss of milestones after attaining them may be the first sign of HIV infection suggesting HIV encephalopathy if other common causes are ruled out. Early identification of developmental delay and neurological abnormalities can facilitate intervention and suitable remedial actions. Therefore, it is crucial to assess the development in an HIV-exposed or HIV- infected infant/child.

Developmental assessment at each visit should include assessment of the cognitive, motor, language and social skills by asking appropriate history from the mother, and observing the child during the examination, using a developmental checklist.

The chart (Figure 3.1.1) given below can be used to assess whether the exposed infant is achieving various milestones within the expected time frame.

Figure 3.1.1: Development chart



Note: To use this chart, keep a pencil vertically on the age of the child. All milestones falling to the left of the pencil should have been by the child. Based on BSID Baroda norms & Trivandrum Development Screening Chart.

Diagnosis of HIV Infection in Infants and Children

Early infant diagnosis

Maternal HIV antibodies transferred passively to the infant during pregnancy usually persist for nearly 9–12 months in the infant. In some children, they may persist for as long as 18 months. Thus, children born to HIV-infected mothers will test positive for HIV antibodies regardless of their own infection status. A positive ELISA or rapid test that detects antibodies to HIV, therefore, does not necessarily indicate the presence of HIV infection in the infant/child. Rather, a positive ELISA or rapid test indicates exposure to HIV. More reliable indicators of the status of HIV infection of the infant are tests that detect HIV DNA or antigens. The current test of choice is HIV- 1 Total Nucleic Acid (TNA) PCR test that detects HIV pro-viral DNA and RNA.

NACO Protocol for Diagnosis of HIV-1 Infection in Infants and Children <18 Months of Age

NACO recommends the use of TNA PCR test on a dried blood sample (DBS) from the infant for diagnosis of HIV-1 infection. This is a qualitative nucleic acid test that detects viral nucleic acids from both HIV RNA and pro-viral DNA. This test has a sensitivity of 99% and specificity of 98% and has replaced the earlier used DNA PCR test that was based on conventional PCR and hybridization of pro-viral DNA. The window period for this test is 6 weeks after exposure. The available kits for TNA PCR include Abbott Real Time

HIV-1 kit with an RNA detection limit of 2500 copies/ml and Roche COBAS AmpliPrep/COBAS TaqManHIV-1 (Ver. 2) kit with a detection limit of 300 copies/ml; an excellent correlation exists between the two tests.

Limitations of Nucleic Acid-based Testing

The TNA-PCR is a highly sensitive test, and therefore has an inherent risk of false positivity. This false positivity rate rises as the mother to child transmission rate of HIV gets successively lower; with a mother-to-child transmission rate of less than 5%, the positive predictive value of the nucleic acid–based technologies may decrease to nearly 70%. Thus, a relatively higher proportion of infants may be wrongly diagnosed to have HIV infection and receive lifelong ART. To offset this limitation, WHO has introduced the concept of 'indeterminate range'. The indeterminate range refers to a range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infected. The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV- 1 Qualitative Test v2.0 assay. It is recommended that all indeterminate tests should be repeat tested on the same specimen or on a fresh sample to decrease the chance of false positive test. The use of indeterminate range is currently not being followed under the NACO testing protocol.

NACO Testing Protocol for Early Infant Diagnosis

NACO recommended early infant diagnosis (EID) protocol be used for the following categories of infants:

1. HIV-exposed infants
2. Infants who are sick with clinical features suggestive of HIV but with unknown HIV exposure status.

As per the protocol, the TNA PCR test is first performed at 6 weeks of age and thereafter until 18 months of age. At age of >6 months, TNA PCR must be performed after screening for HIV antibodies, as depicted in the algorithm (Annexure-1). It is also important to take breast-feeding into consideration in the HIV testing algorithm. Since breastfed children have ongoing risk of HIV acquisition, they are retested 3 months after complete cessation of breast-feeding to reliably exclude HIV-1 infection. The choice of test(s) depends upon the age of the child at the time of re-testing. Thus, if cessation of breastfeeding occurs beyond 18 months of age, rapid tests for HIV antibodies will suffice; a child between 6 and 18 months would first be screened for HIV antibodies followed by TNA PCR if found positive for antibodies.

As per the EID protocol of NACO, HIV-exposed infants are tested for HIV infection status as follows:

- The first HIV TNA PCR test for HIV-1 infection using a DBS method is conducted at 6 weeks of age. If the DBS test is positive for HIV, the test is repeated on another DBS sample as early as possible for confirmation. In case the second DBS tests negative for HIV, the laboratory will request for another DBS sample for a second confirmatory HIV -1 TNA PCR test from the ICTC and rely on the result of this test for final diagnosis.
- If the first PCR is negative (before 6 months of age), the child is screened for HIV antibodies (rapid test) at 6 months of age. Infants testing positive on rapid test are retested with a PCR test using DBS.
- TNA PCR can be repeated earlier if the infant becomes symptomatic.
- If the child is breastfed and initial PCR tests are negative, retesting is carried out 3 months after cessation of breastfeeding.
- If the infant is seen for the first time after 6 months of age, an HIV serology is performed as a screening test. A PCR on a DBS sample is performed only if serology for HIV is positive.
- In 74% and 96% of HIV-uninfected exposed children, HIV antibody test will be negative at age 9 and 12

months, respectively. Thus, if in a HIV-exposed child older than 6 months of age HIV antibody test is negative, there are two situations:

- If the infant/child is not breastfed in the last 3 months, the infant/child is probably not infected and does not need HIV TNA PCR testing.
- In an infant/child with negative HIV antibody test but receiving breastfeeding, HIV antibody test should be repeated after 3 months of complete cessation of breastfeeding to rule out HIV infection.

If symptoms develop at any time, the child should be tested appropriately (TNA PCR or Antibody test If by ELISA/rapid) at that age.

For National Testing Algorithm for HIV-exposed infants and children younger than 18 months of age, refer to **Annexures 1 and 1x**.

- Cotrimoxazole Preventive Therapy to be initiated for all HIV-exposed babies from 6 weeks of age and continued until proven HIV negative on all three serological tests at 18 months of age or later if still being breastfed. In case the baby is found to be HIV infected at any stage, LPV/r- based ART should be initiated and CPT should be continued until 5 years of age.
- Initiate babies on exclusive breastfeeding/ ERF till 6 months of age; add complementary food thereafter.

Presumptive diagnosis where no virologic testing (TNA PCR) available

If the child is aged <18 months and has symptoms and signs that are suggestive of HIV infection and there is no virologic testing available, it is possible to make a presumptive diagnosis by addressing the following issues:

- Does the child meet the clinical criteria for presumptive diagnosis of severe HIV infection?
- Is there evidence of HIV exposure – does mother or baby's serology show positive HIV antibody?
- Is there evidence of immune suppression (low CD4 count/CD4%) and/or symptoms or illnesses consistent with HIV infection?

Table 3.1.12 shows the clinical criteria for presumptive diagnosis of HIV infection in children aged <18 months when virological tests are not available. In a child meeting the presumptive criteria, ART may be initiated after sending the confirmatory virological test even if the report of the same is not available yet.

Table 3.1.12: Clinical criteria for presumptive diagnosis of severe HIV disease in infants and children less than 18 months of age requiring ART in situations where virological testing is not immediately available/report is pending

A presumptive diagnosis of severe HIV disease should be made in the following situations:

The infant's HIV antibody test is reactive

and

Diagnosis of any AIDS-indicator condition(s) can be made

or

The infant is symptomatic with two or more of the following:*

- Oral thrush
- Severe pneumonia
- Severe sepsis

Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include the following:

Recent HIV-related maternal death; or advanced HIV disease in the mother; CD4 in the child <20%.

Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

Notes

*As per IMCI definition:

1. Oral thrush: Creamy white to yellow soft small plaques on red or normally coloured mucosa that can often be scraped off (pseudo membranous), or red patches on tongue, palate or lining of mouth, usually painful or tender
2. Severe pneumonia: Cough or difficult breathing in a child with chest in-drawing, stridor or any of the IMCI general danger signs, i.e., lethargic or unconscious, not able to drink or breastfeed, vomiting and presence or history of convulsions during current illness; responding to antibioticss
3. Severe sepsis: Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest in-drawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

IMCI: Integrated Management of Chidhood Illness[3]

Final testing of HIV-exposed infants

All HIV-exposed children should undergo the HIV antibody test for definitive diagnosis, using all three serological tests, at ICTC, at 18 months of age and 3 months after cessation of breastfeeding, whichever is later. In a rare situation, there may be serological discordance at final testing, i.e., if a child is diagnosed HIV infected by two PCR-TNA tests, started on ART, and later at 18 months of age the child tests negative for HIV antibody test, i.e., negative report in any one or more of the serological tests performed. It is important for medical officers to remember to continue ART in these children and evaluate further, as per the algorithm for management of babies with sero- discordance at 18 months.

Discordance among the EID results and rapid tests at 18 months or beyond

As per the current recommendations, in case of discordance between EID result and rapid test at 18 months or beyond, ART is to be continued while the baby is tested with all the following five tests:

a. All three rapid diagnostic tests done in parallel
b. HIV-1 ELISA
c. Qualitative HIV TNA PCR
d. Quantitative HIV1 PCR (plasma viral load)
e. Western Blot Test

In case any one of these tests is positive, ART is to be continued. If the child tests negative on all the tests, ART is to be interrupted and the child followed as per the revised algorithm (**Annexure 1-X**). The case should be referred to National AIDS Clinical Expert Panel (NACEP).

Diagnosis of HIV infection in Children >18 Months

Children aged ≥18 months are tested according to the national adult testing strategies:

Two positive HIV antibody test results (done sequentially) in a clinically symptomatic child (symptoms suggestive of HIV infection) more than 18 months of age indicate HIV infection in the child. Three positive HIV antibody test results (done sequentially) in a clinically asymptomatic child aged more than 18 months old indicate HIV infection in the child.

Two positive HIV antibody test results and one negative result (done sequentially) in an asymptomatic child more than 18 months of age is indeterminate HIV status. Follow-up testing should be done in such a child to resolve the HIV status.

Diagnosis of HIV infection in an infant with suggestive symptoms

For symptomatic infants less than 6 months of age: If the mother is available and her HIV status is not known, a rapid serological test is done for the mother. If the mother is positive, HIV TNA PCR of the child is done. If the mother is not available, due to any reason, serological testing of the child is to be done with simultaneous sample taken for HIV TNA PCR. If the child is positive for HIV in serological test, sample for qualitative HIV TNA PCR is to be sent. For symptomatic children 6 to 18 months of age, a rapid serological test is to be done for the child irrespective of availability of the mother while taking simultaneous DBS sample for NAT. For symptomatic children >18 months of age, current protocol for testing as for older children and adults using rapid antibody test is to be followed.

- For infants <18 months of age: Confirm with PCR and check status of breastfeeding.
- For infants >18 months of age: Antibody testing as per NACO HIV testing guideline

Follow-up of HIV-exposed infants and children

HIV-exposed infants are a vulnerable group irrespective of their own HIV status due to a combination of various adverse socioeconomic and family factors including poverty, stigma, increased exposure to sickness due to parental ill-health/death, exposure to ARV drugs and, in some cases, replacement feeding. A structured follow-up plan gives the opportunity to clinically evaluate these children at regular intervals and give them comprehensive care including delivery of all the components discussed above.

Exposed infants and children should be followed up at ICTCs beginning at 6 weeks of life. Prior to this, they should have been given BCG, hepatitis B and OPV vaccine at birth. At the first visit at 6 weeks of age, the following activities are undertaken:

- Initiation of Cotrimoxazole prophylactic therapy
- Checking adherence of infant NVP prophylaxis for the past 6 weeks and decision regarding continuation of NVP till 12 weeks depending upon duration of maternal ART
- First DBS for HIV TNA PCR
- Growth monitoring/development assessment
- Referral of any infant with medical problems for medical assessment

- For exclusively breastfed infants, the pattern of feeding, attachment and positioning and mother's breast condition is enquired about.
- For infants on replacement feeding, parents/family are asked about any problems faced in infant feeding. The nature, frequency and amount of replacement feeds being given are enquired about and feed hygiene is emphasized.
- Assessment of maternal health and her adherence to ART

The subsequent visits are at 10, 14 weeks, 6, 9, 12, 15 and 18 months of age, synchronized with the immunization visits. The activities at these visits are similar to those described for the 6-week visit. At any time, an infant is detected to be infected with HIV on laboratory testing or by presumptive WHO criteria, he/she is referred to the ART centre without delay. Infants may also require a medical review during an acute episode of sickness, or if they show growth faltering over serial visits. At every visit, information is given to the mother or caregiver on potential common HIV- related features, about availability of EID, and the importance of follow-up and adherence to ARV prophylaxis or treatment. Any psychosocial concerns are addressed and need for CPT is reinforced. Age-appropriate guidelines are given for infant feeding. At the 18-month visit, HIV serology is tested for all infants. In case the infant is breastfeeding beyond 18 months of age, he/ she should be followed up till complete cessation of breastfeeding. An HIV test must be performed 3 months after complete cessation of breastfeeding.

The follow-up protocol of HIV-exposed infants is summarized in table 3.1.13

Table 3.1.13: Follow-up protocol of HIV-exposed infant

Care of HIV-exposed Infants and Children									
Activities at Each Follow-up Visit									
Visit	**Birth**	**6 Wks**	**10 Wks**	**14 Wks**	**6 Mths**	**9 Mths**	**12 Mths**	**15 Mths**	**18 Mths**
Cotrimoxazole Preventive Therapy (CPT)		• Start from 6 weeks (or first immunization visit) for all HIV-exposed infants and children • Continue CPT: for those tested to be HIV infected • Stop Cotrimoxazole: for those tested to be HIV uninfected							
Counselling for infant feeding	√	√	√	√	√	√	√	√	√
Growth monitoring	√	√	√	√	√	√	√	√	√
Developmental assessment	√	√	√	√	√	√	√	√	√
Immunization & vitamin A supplement	BCG OPV-0 Hep B birth dose	OPV-1 RVV-1 fIPV-1## Pentavalent-1	OPV-2 RVV-2 Pentavalent-2	OPV-3 RVV-3 fIPV2/IPV Pentavalent-3		MCV-1 Vit A* JE-1 #		MCV-2	DPT-B1 OPV-B JE-2# Vit A*
Clinical assessment	√	√	√	√	√	√	√	√	√
HIV testing (√ if required)		√			√		√		√
Maternal health and ART adherence	√	√	√	√	√	√	√	√	√

Counselling and Psychosocial Support

The success of any public health programme depends upon effective and ongoing counselling. Parents and caregivers of HIV-exposed infants need ongoing counselling beginning right from pregnancy through labour, post-natal period and beyond. The key counselling areas are PPTCT, maternal ART and infant ARV prophylaxis, infant feeding, nutrition, EID, Cotrimoxazole initiation, vaccination, awareness of signs of sickness in an infant and adherence to ART (mother) and ARV prophylaxis (infant). The key persons responsible for counselling are the PPTCT and ART counsellors, ART centre MO, the paediatrician and the obstetrician. It is critical that all the key persons are well informed about the current national guidelines so that a consistent message is given to the affected family by anyone who interacts with them. For further reading, refer **Chapter 3.7 (Counselling for Children and Adolescents Living with HIV).**

3.2 Management of Newly Diagnosed HIV Infection in Children Including ART Initiation

Introduction

The diagnosis of HIV infection in a child marks the beginning of HIV care. The continuum of care through life cycle approach is key for the success of the management of these children. The primary aim of management of CLHIV is to prevent morbidity and mortality, thereby promoting the quality of life. At the beginning of the care, which starts as soon as the diagnosis of HIV is made, a thorough clinical, laboratory and psychosocial assessment of the child as well as the family should be performed. The key objectives of such assessment include the following:

- Determining the clinical and immunological staging
- Providing appropriate pre-ART care
- Appropriate counselling to the child and family to prepare them for lifelong ART
- Initiation of ART

Determining Clinical and Immunological Staging

Assessment of a newly diagnosed child with HIV

- Growth assessment
- Clinical assessment (History/Physical Examination)
- Developmental assessment
- Laboratory assessment
- Psychosocial assessment

Growth assessment

Growth is an important indicator of nutritional status of CLHIV, active/latent OI, advanced HIV disease, treatment response as well as treatment failure. HIV-infected children are at particular risk for problems related to growth. There are many factors that influence growth of CLHIV including maternal HIV infection and nutrition, OIs, HIV infection itself, neurodevelopmental status and socioeconomic factors. Early detection of growth faltering facilitates timely intervention to prevent further deterioration.

Anthropometric assessment is a valuable tool for assessing growth and nutritional status of children. It also helps in determining the appropriate dosage of the ARV medications. It involves measuring a child's weight, length/height, head circumference and mid-upper arm circumference (MUAC) and comparing these measurements to growth reference standards. The purpose is to determine whether a child is growing 'normally', or his/her growth pattern is different from the expected. It is recommended that WHO growth reference standards be used for assessing a child's growth up to 5 years of age. These are available as growth charts as well as reference tables for boys and girls separately (see **Annexures 7, 8, 11** and **Chapter 3.1 [Management of HIV-exposed Infants and Children])**. For children beyond 5

years of age, Indian Academy of Paediatrics (IAP) growth charts based on growth reference data from Indian children are recommended (**Annexures 9, 10, 12 and 13**). Refer **Chapter 3.6 (Nutritional Care of HIV-infected Children)** for details on anthropometric assessment and its interpretation. For adolescents, the assessment of pubertal growth and development is important.

Clinical Assessment

History

Ask for:

- History of bacterial, fungal and viral infections, such as otitis media, sinusitis, and pneumonia,candidiasis (thrush) or superficial skin fungal infection, herpes simplex or zoster infection or cytomegalovirus (CMV) retinitis – their frequency, severity and response to standard treatment;
- 4S screening for TB – current cough, fever, poor weight gain and contact history of TB
- History of TB and any treatment for it
- Key age-appropriate developmental milestones: Failure to attain typical milestones at the appropriate age suggests a developmental delay; such delays, particularly impairment in the development of expressive language, may indicate HIV encephalopathy. Ask also about loss of any pre-acquired milestones.
- Behavioural abnormalities (in older children), such as loss of concentration and memory, may also indicate HIV encephalopathy.
- Review relevant medical documents for coexisting medical conditions and concomitant use of any medication that may have drug interactions with ART.
- Assess immunization status.

Physical Examination

Look for:

- Visible severe wasting and/or oedema in extremities
- Anaemia and signs of vitamin deficiencies
- Fever, respiratory distress, decreased activity or altered sensorium
- Jaundice
- Thrush in the oral cavity and posterior pharynx (observed in approximately 30% of HIV-infected children)
- Linear gingival erythema and median rhomboid glossitis, Oral Hairy Leucoplakia and aphthous ulcers
- Parotid enlargement
- Herpetic infection with herpes simplex virus (HSV) that may manifest as herpes libialis gingivo-stomatitis,oesophagitis or chronic erosive,vesicular and vegetating skin lesions; the involved areas of the lips, mouth, tongue and oesophagus are ulcerated
- HIV dermatitis: An erythematous, papular rash observed in about 25% of children with HIV-infection
- Dermatophytosis: Manifesting as an aggressive tinea capitis, corporis, versicolor or onychomycosis
- Digital clubbing: As a result of chronic lung disease or pulmonary hypertension
- Generalized cervical, axillary or inguinal lymphadenopathy
- Hepatosplenomegaly
- Otitis media

Perform a thorough systemic examination for any evidence of associated systemic disease.

Developmental Assessment

Developmental milestones help in assessing development or maturation of the brain of an infant/ child. They refer to the abilities that children are expected to possess at different ages. Delayed development, or loss of milestones after attaining them, may be the first sign of HIV infection suggesting HIV encephalopathy if other common causes are ruled out. Early identification of developmental delay and neurologic abnormalities can facilitate intervention and suitable remedial actions. Therefore, it is crucial to assess the development in an HIV-infected infant and child.

A thorough history including the pre-natal, perinatal and post-natal factors, which can affect the development of the child, should be ascertained. A complete examination including physical examination, anthropometric parameters, assessment of vision and hearing and other factors that affect development should be undertaken.

Developmental assessment at each visit should include assessment of the cognitive, motor, language and social skills by asking appropriate history from the mother and by observing the child during the examination, using a developmental checklist. Certain red flags suggest that development is seriously disordered and needs prompt referral.

Red Flags in Developmental Screening

Positive indicators (the presence of any of the following):

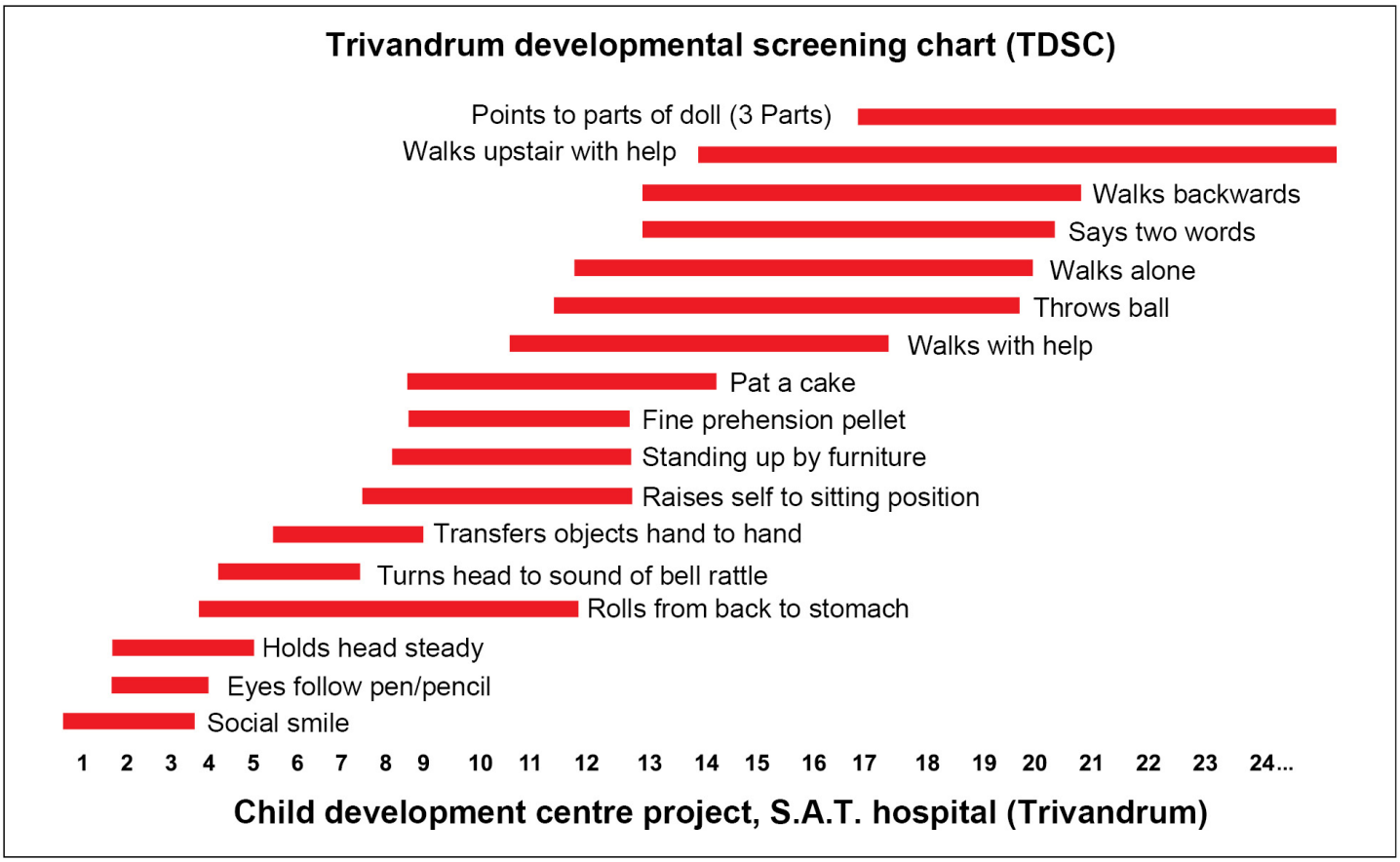
- Loss of previously acquired developmental skills at any age
- Parental or professional concerns about vision, fixing or following an object or a confirmed visual impairment at any age (simultaneous referral to paediatric ophthalmology)
- Hearing loss at any age (simultaneous referral for expert audiologic or ear, nose and throat assessment)
- Persistently low muscle tone or floppiness
- No speech by 18 months of age, especially if the child does not try to communicate by other means such as gestures (simultaneous referral for urgent hearing test)
- Asymmetry of movements or hand preference before 18 months of age or other features suggestive of cerebral palsy, such as increased muscle tone
- Persistent toe walking
- Complex disabilities
- Head circumference above +3 SD or below -3 SD. Also, if the circumference has crossed 2 centiles (up or down) on the appropriate chart or is disproportionate to the parental head circumference
- An assessing clinician who is uncertain about any aspect of the assessment but thinks that development may be disordered

Negative indicators (activities that the child cannot do)

- Sit unsupported by 12 months of age
- Walk by 18 months of age (check creatine kinase urgently)
- Walk other than on tiptoes
- Run by 2.5 years of age
- Hold object placed in hand by 5 months of age (corrected for gestation)
- Reach for objects by 6 months of age (corrected for gestation)

Use of development screening tools helps detect developmental delay (Figure 3.2.1). Children with developmental disorders are at increased risk for behavioural problems. For example, temper tantrums or disruptive behaviour may be a manifestation of language delay.

Figure 3.2.1: Trivandrum development screening chart



Adapted from Journal of Paediatric Association of India. New Indian Journal of Paediatrics. Development and Validation of Trivandrum Development Screening Chart for Children aged 0-3 Years by TDSC (0-3). Chauhan VH, Vilhekar KY, Kurundwadkar M.

Clinical Staging

Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS. These stages are defined by specific clinical conditions or symptoms.

The clinical stage is useful for baseline assessment of patients and, also in the follow-up of patients in care and treatment programmes. It should be used to guide decisions on when to start Cotrimoxazole prophylaxis and other HIV-related interventions. Refer Table 2.3.3: WHO Clinical Staging in Adults, Adolescents and Children of **Chapter 2.1 (Assessment of Adults and Adolescents with HIV Infection).**

Laboratory Assessment

The purpose of the baseline laboratory evaluation is to:

- determine the stage of the disease,
- identify concomitant OIs and
- determine baseline safety parameters.

The following are recommended tests for CLHIV at ART centres (Table 3.2.1):

Table 3.2.1: Baseline laboratory tests recommended for newly diagnosed CLHIV at ART centre

Baseline Investigations: Essential tests for all patients registering in HIV care at ART Centre
• Haemogram/CBC • Urine for routine and microscopic examination • Fasting/Random blood sugar • Blood urea, serum creatinine • Serum bilirubin, ALT (SGPT) • VDRL • CD4 count and CD4% • HBsAg and Anti-HCV IgG (if available) • X-ray chest PA view • Pregnancy test (if required in adolescents) • rK-39 strip test to confirm or rule out leishmaniasis (especially in patients with HIV infection who live in or travel to endemic areas i.e., Bihar, Eastern Uttar Pradesh, Jharkhand and West Bengal)
Additional tests at baseline as per physician's decision
• Symptoms and signs directed investigations for ruling out OIs, including M. tuberculosis by testing sputum or appropriate specimen by NAAT (CBNAAT or Truenat) and/or other required investigations • Complete LFT (liver function test) for those being initiated on anti-TB treatment and for patients with Hepatitis B or C co-infection • Lipid profile (if available and when child is planned to be initiated on PI-based ART regimen) • Ultrasonogram whole abdomen
NON-AVAILABILITY/NON-FEASIBILITY OF ANY OF THESE TESTS SHOULD NOT DELAY THE INITIATION OF ART Note: All the above investigations other than CD4 estimation shall be done from the health facility where the centre is located, with support from State Health Department

Additional tests

Depending on clinical presentation

- Sputum/gastric aspirate/other body fluids as applicable for smear microscopy/ NAAT (CBNAAT or Truenat)
- USG abdomen/CT scan chest/CT scan brain
- CSF analysis

Tests for special situations

- For patients with Hepatitis B or C co-infection: further tests may be required to assess for chronic active hepatitis.
- For patients started on PI-based regimen: Baseline investigations including blood sugar, LFT (SGPT) and lipid profile to be done.

Cascade screening

- Screen the family for HIV and other OIs.

Immunological staging

Due to relative lymphocytosis in infants and young children, normal CD4+ counts are higher in them than in adults. These decline over the first few years of life and reach adult level by 6–8 years of age. A value of 1500 CD4 cells/mm3 in children <1 year of age is indicative of severe CD4 depletion and is comparable to <200 CD4 cells/mm3 in adults. As a result, young children may develop OIs at higher CD4+ levels than adults. Meanwhile, the CD4% (proportion of CD4 cells with respect to total lymphocyte count) remains constant during these years of life. Hence CD4% is a more useful surrogate marker of HIV and immunosuppression in infants and young children. Classification based on age-specific CD4 levels (Table 3.2.2) is useful for describing the immunologic status of HIV-infected children.

Table 3.2.2: Revised classification of immune suppression in children (CD4 levels in relation to severity of immune suppression)

Classification of HIV-associated Immunodeficiency	Age-related CD4 Cell Values			
	<11 months	12-35 months	36-59 months	>5 years
Not significant	>35%	>30%	>25%	>500 cells/mm^3
Mild	30–35%	25–30%	20–25%	350–499 cells/mm^3
Advanced	25–30%	20–25%	15–20%	200–349 cells/mm^3
Severe	<25% or <1500 cells/ mm^3	<20% or <750 cells/mm^3	<15% or <350 cells/mm^3	<200 cells/mm^3 or (<15%)

Source: WHO 2007, Case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children.

Utility of CD4 measurement in the context of 'Treat All' and viral load as monitoring tool

Baseline CD4 is important to monitor treatment response, identify complications like IRIS, anticipate OI infections, identify the need for OI prophylaxis and offer immunization advice. Serial CD4 measurements are more informative than individual values as they reflect trends over time. Where possible, these assessments should compare the same parameter. The CD4 measurement may be discontinued in a stable CLHIV above 5 years of age on ART where regular viral load monitoring is advised.

Pre-ART Care

Pre-ART period is the period between a child testing positive for HIV and initiation of ART as per the national guidelines. In the current era of 'test and treat' and rapid initiation of ART, the pre-ART period is very short, just the time taken for complete assessment, evaluation and initiation of the management of comorbidities and stabilizing the general condition. This is also the phase when the child and caregivers are counselled regarding the need for ART, its benefits and limitations and the need for lifelong adherence.

Pre-ART care of the infected child with support to the family, as well as comprehensive care for the family unit, is important as this sets the stage for future care and response to treatment.

Management of opportunistic infections and HIV-related illness

Table 3.2.3 lists the OIs and HIV-related illnesses that need treatment or stabilization during pre-ART care before commencing ART

Table 3.2.3: Management of clinical conditions before ART initiation

Clinical Picture	Action
Any undiagnosed active infection with fever	Diagnose and treat first; start ART when stable.
Tuberculosis	ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among CLHIV (except when signs and symptoms of meningitis are present) Refer Table 3.2.6.
Pneumocystis pneumonia (PCP)	Treat PCP first; start ART when PCP treatment is completed.
Invasive fungal diseases: oesophageal candidiasis, cryptococcal meningitis, penicilliosis, histoplasmosis	Treat oesophageal candidiasis first; start ART as soon as the patient can swallow comfortably. Treat cryptococcal meningitis, penicilliosis, histoplasmosis first; start ART when patient is stabilized or OI treatment is completed.
Bacterial pneumonia	Treat pneumonia first; start ART when treatment is completed.
Malaria	Treat malaria first; start ART when treatment is completed.
Drug reaction	Do not start ART during an acute drug reaction.
Acute diarrhoea which may reduce absorption of ART	Diagnose and treat first; start ART when diarrhoea is stabilized or controlled.
Non-severe anaemia (Hb <9 g/dl)	Start ART if no other causes for anaemia are found (HIV is often the cause of anaemia); avoid Zidovudine.
Skin conditions such as pruritic papular eruption and seborrhoeic dermatitis, psoriasis, HIV- related exfoliative dermatitis	Start ART (ART may resolve these problems).
Suspected Mycobacterium avium complex (MAC), cryptosporidiosis and microsporidiosis	Start ART (ART may resolve these problems)
Cytomegalovirus infection (CMV)	Treat CMV; start ART after induction phase of treatment for CMV.
Toxoplasmosis	Treat; start ART after 6 weeks of treatment and when patient is stabilized.
Severe acute malnutrition	ART should be started as soon as possible after stabilization of metabolic complications and sepsis (after establishment of F-100 diet, i.e., usually after 7 days).

Prevention of Opportunistic Infections

It includes appropriate prophylaxis (please refer **Chapter 2.9 [Prevention of Opportunistic Infections])** and childhood immunization (please refer **Chapter 3.1 on Management of HIV- exposed Infants and Children).**

Counselling and Timely Referrals for Psychological/Social Support If Needed

HIV infection affects all dimensions of a person's life: physical, psychological, social and spiritual. Counselling and social support can help CLHIV and their caregivers cope more effectively with each stage of the infection and enhance the quality of life. With adequate support, they are more likely to be able to respond adequately to the stress of being infected and are less likely to develop serious mental health problems.

Need for Counselling

HIV infection can also result in stigma and fear for those living with the infection, as well as for those caring for them, and may affect the entire family. Psychosocial support can assist people in making informed decisions, coping better with the illness and dealing more effectively with discrimination. It improves the quality of their lives and prevents further transmission of HIV infection.

For people with HIV/AIDS who must adhere to multi-drug therapy including TB treatment, long-term prophylaxis and ART, ongoing counselling can be critical in enhancing adherence to treatment regimens.

Psychosocial Assessment before ART Initiation

The physician must realize that initiating ART is never an emergency. The child and the caregiver need to be prepared for ART by giving the pre-treatment information and plan including benefits and limitations of ART and the need for lifelong treatment adherence.

The following issues are to be considered during this preparedness counselling:

- Identify primary caregiver as well as backup second informed caregiver for the child and his/her ability and willingness to adhere to follow-up and to administer medications, especially ART.
- Assess family members' understanding of HIV disease and treatment (i.e., lifelong therapy, importance of adherence and mode and frequency of drug administration, toxicities and storage of drugs).
- Assess child's adherence to previously started medication including anti-TB treatment.
- Assess the family's financial status including its ability to pay for transportation to clinic and to afford adequate food/nutritional supplements for the child.
- Assess disclosure of HIV status within the family (whether the child knows his/her status or whether anyone else knows; also, whether the child knows the parent/s' HIV status)

Further details on counselling children and their caregivers and appropriate psychological interventions are given in Section 3.7 on 'Counselling for Children and Adolescents Living with HIV'.

Promoting Healthy/Positive living

CLHIV and their caregivers should be counselled regarding basic healthy habits that will help them to stay healthy and avoid infections such as the following:

- Eating healthy/nutritious foods
- Washing hands well and often
- Maintaining good dental hygiene
- Getting enough sleep
- Doing moderate exercise

With ‘Treat All policy’ in place, it is important to realize that the term ‘Pre-ART Care’ remains relevant. In fact, all the activities listed under this head would still need to be carried out, or at least initiated before starting ART and continued alongside ART.

Evaluation of an Adolescent Living with HIV (ALHIV)

Adolescents, defined as young persons between the age of 10 and 19 years, with HIV are a unique subset of individuals with HIV infection. As per UNICEF, in 2022, about 1.65 million adolescents between the ages of 10 and 19 were estimated to be living with HIV worldwide.[1] Adolescents account for about 4% of all PLHIV and about 10% of new adult HIV infections. In 2020 alone, the estimated number of adolescents newly infected with HIV in ages of 10–19 years was 15 lakhs (girls 120,000 and boys 36,000). Estimated number of adolescents dying of AIDS-related causes in 2022 was 27,000 globally. As per UNAIDS 2018 estimates,[2] in India, an estimated 1,20,000 children and adolescents aged between 0 and 19 years were living with HIV in 2017. NACO includes adolescents till age 15 years in the paediatric age group, while those older than 15 years are pooled with adult patients. Thus, data pertaining to adolescents has been difficult to access and collate.

Assessment of ALHIV

Adolescents may not volunteer information about a health problem. They may be embarrassed or scared to do so or may be uncomfortable with the health worker. The HEADS assessment proposed by WHO (Table 3.2.4) is a structured tool that offers step-by-step guidance to the counsellor/medical officer for assessing ALHIV, starting with the most non-threatening issues. It begins by examining non-threatening issues like the home and the educational/employment setting. It then goes on to issues related to eating and activities. Only subsequently does it deal with more sensitive issues such as drugs, sexuality, safety and suicide/depression. Using the HEADS assessment, the healthcare worker can get a full picture of the adolescent as an individual. It helps identify the behaviours and the factors in the adolescent’s environment that need to be addressed.

Table 3.2.4: Step-by-step guidance for comprehensive assessment of an ALHIV

Home	Where and with whom do they live? Any recent changes in their home situation? How do they perceive their home situation?
Education/ Employment	Whether they study/work and how they are doing How are the relations with their teachers/employers/colleagues? What they do during their breaks?
Eating	How many meals do they have in a day? What do they eat at each meal? What do they think and feel about their bodies?
Activity	What activities are they involved in other than study/work? What they do in their free time? Do they spend some time with family members and friends?
Drugs	Whether they use tobacco, alcohol or other substances Whether they inject any substances If yes, how much do they use? When, where and with whom do they use them?
Sexuality	What knowledge do they have about sexual and reproductive health? Do they have any questions regarding this? Are they sexually active? If yes, are they taking steps to avoid sexual and reproductive health problems (unwanted pregnancy, infection, sexual coercion)? What is their sexual orientation?
Safety	Whether they feel safe at home, in the community, in their place of study or work; on the road (as drivers and as pedestrians) etc. If they feel unsafe, what makes them feel so?
Suicide/ Depression	Is their sleep adequate? Do they feel unduly tired? Do they eat well? How do they feel emotionally? Have they had any mental health problems such as depression? If yes, have they received any treatment for this? Do they have suicidal thoughts? Have they attempted suicide?

Source: WHO (2010), 'IMAI one-day orientation on adolescents living with. HIV. Participants' manual and facilitator guide'; accessed at http://whqlibdoc.who.int/publications/ 2010/9789241598972_eng.pdf

Physical examination of ALHIV

The examination needs to be carried out after obtaining consent of the adolescent. If the adolescent is below the legal age of giving consent, the same needs to be obtained from a parent or guardian along with an assent from the child. Nature of the examination should be explained, and adolescent asked whom he/she would like/would not like to be present during examination. Ensure privacy and presence of a male/ female colleague while a male doctor/nurse examines a female patient and vice versa. Watch for signs of discomfort or pain and stop the examination if needed.

Apart from the head-to-toe assessment as recommended for any PLHIV, care should be taken to assess growth by recording weight, height and calculating BMI. The same should be plotted on a growth chart as also recommended for CLHIV. It is expected that ALHIV already on ART for several years will grow along their previous established growth trajectory. In these adolescents, deviation from their previous growth curve may indicate presence of treatment failure. Vertically infected ALHIV newly initiated on ART are likely to have wasting as well as stunting at presentation. Serial growth monitoring in them is expected to show a robust catch-up first in weight and then also in height as they are initiated on and respond to ART (Refer **Chapter 3.6 [Nutritional Care of HIV-infected Children]** for further details). Apart from growth monitoring, onset and progression of pubertal development should also be monitored, since puberty is often delayed in ALHIV, especially those initiated late on ART or failing on ART. Pubertal

development is assessed using the Tanner staging.

Antiretroviral Therapy for Children

Paediatric formulations of ARV drugs have greatly improved the care of CLHIV. ART is the cornerstone in the management of CLHIV. Initiation of ART at the earliest is crucial in reducing mortality and morbidity for infants and children. ART is a lifelong therapy and with its benefit, HIV-infected infants and children are surviving to adolescence and adulthood today.

When to start ART for infants and children?

ART should be initiated in all children and adolescents living with HIV, regardless of age, CD4 count and WHO clinical staging.

ART should generally be deferred until acute infections have been treated, whenever possible. In the case of confirmed or presumptive TB disease, initiating TB treatment is the priority. In such children, ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among CLHIV (except when signs and symptoms of meningitis are present). After deciding to start ART, one should also consider the child's social environment, including identification of a clearly defined caregiver who understands the prognosis of HIV and the requirements of ART.

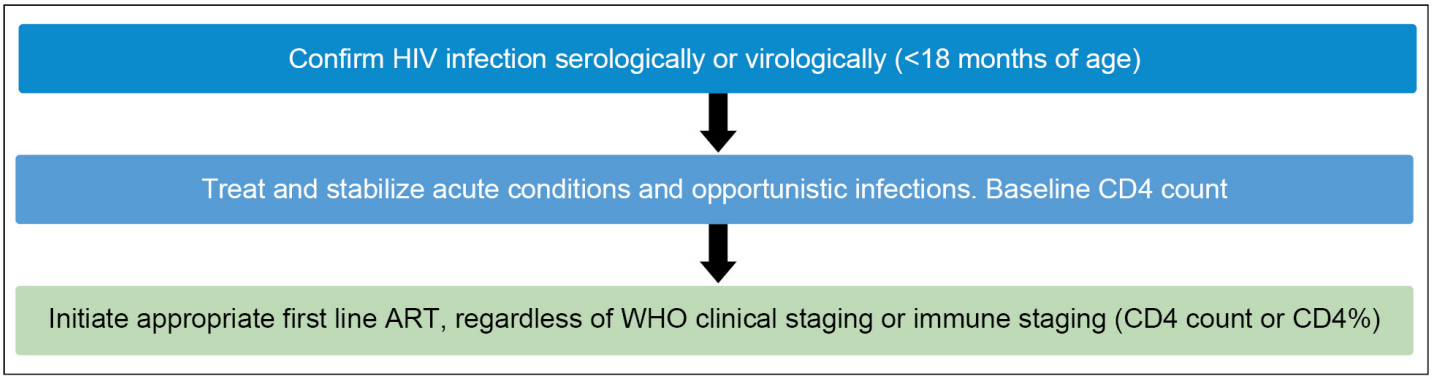
Rapid initiation of ART

Often, ART initiation is considered a non-emergency intervention, and treatment preparedness and management of active OIs are given priority over ART. There is definite evidence pointing to high rate of loss to follow-up when the duration between HIV diagnosis and ART initiation is increased.

However, concerns remain that accelerated or same-day initiation of ART may lead people to start before they are ready, with adverse consequences for adherence and treatment outcomes. Keeping these things in mind, 'rapid initiation of ART' is advised for children at the earliest, after appropriate preparedness counselling. For seriously ill and hospitalized children, ART should be started after the child is stabilized (preferably a few days before discharge from the hospital).

ART Initiation

Figure 3.2.2: Steps in ART initiation in CLHIV



Recommended first-line ARV regimens for infants and children

ARV drugs are not a cure for HIV; but they reduce mortality and morbidity and help to improve quality of life for HIV-infected infants, children and their families. The current standard treatment for HIV infection uses three ARV medications (triple-drug therapy) to suppress viral replication as much as possible and to arrest the progression of HIV disease. It is important to actively support adherence to first-line regimen to maximize the durability and efficacy of the regimen.

Drug formulations and doses for infants and children

Important considerations for ART regimens for infants and children include the availability of suitable paediatric drug formulations that can be taken in appropriate doses; simplicity of the dosage schedule; and the taste and palatability. All these are potential factors for better treatment adherence in young children.

Fixed-dose combinations are increasingly available for younger children and are preferred to syrups and individual multiple drugs because they promote and support treatment adherence. Adult formulations that require breaking into half, one third, etc. can result in under dosing or overdosing when given to children and this may lead to an increased risk of drug resistance or toxicity. In view of the availability of paediatric formulations, use of adult formulations is usually not resorted to in young children and those with lower bodyweight.

Dosing of ARV drugs in children is usually based on either body surface area, or weight, or more conveniently by weight band (as in the National Programme **Annexure 2**). As these children gain weight, drug doses must be adjusted/re-adjusted to avoid under/overdosing. For further reading on clinical pharmacology of ARV drugs, refer **Chapter 2.2 (ART in Adults and Adolescents).**

Paediatric first-line ART regimens

The choice of drugs depends on the child's age and body weight. Abacavir (ABC) is the preferred NRTI for initiation in children less than 10 years of age and body weight of less than 30 kg at present. For all children above 10 years and above 30 kg body weight, Tenofovir (TDF) is the preferred drug for initiation. This is the simplest, most potent and least toxic regimen that offers the advantage of a decentralized service delivery and monitoring as it harmonizes with adult ART regimen. It also simplifies the supply chain and minimizes the monitoring requirements.

Lopinavir/ritonavir is recommended as the preferred third drug in all children less than 6 years of age and less than 20 kg body weight till the availability of paediatric formulations of Dolutegravir under the national programme. For children older than 6 years of age and body weight of more than 20 kg, DTG is recommended as the preferred third drug.

Table 3.2.5: First-line ART regimens for infants and children with HIV-1 and HIV-2 infection

Particulars	Recommended Regimen
Age less than 6 years and body weight less than 20 kg	Abacavir + Lamivudine + Lopinavir/ritonavir (AL+LPV/r)
Age between 6 and 10 years and body weight between 20 kg and 30 kg	Abacavir + Lamivudine + Dolutegravir (ALD)
Age more than 10 years and body weight more than 30 kg	Tenofovir + Lamivudine + Dolutegravir (TLD)

Please note:

- Any infant or child initiated on any regimen must be based on body weight; refer Annexure 2 for dosage charts to determine the appropriate doses.
- On every visit, check body weight of the infant/child before writing the prescription. Even though the drug regimen remains the same, drug dosages have to be modified according to change in body weight.

Rationale of using Dolutegravir-based regimen in children aged more than 6 years and weighing 20 kgs

An updated systematic review showed DTG-based regimen was more effective, with less serious adverse effects, lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic barrier to developing drug resistance when compared to EFV-based regimen. Because of long half-life, it is feasible to be used as once-daily fixed-dose combination. DTG has also documented in vitro and clinical activity against HIV-2 infection, which is naturally resistant to EFV.

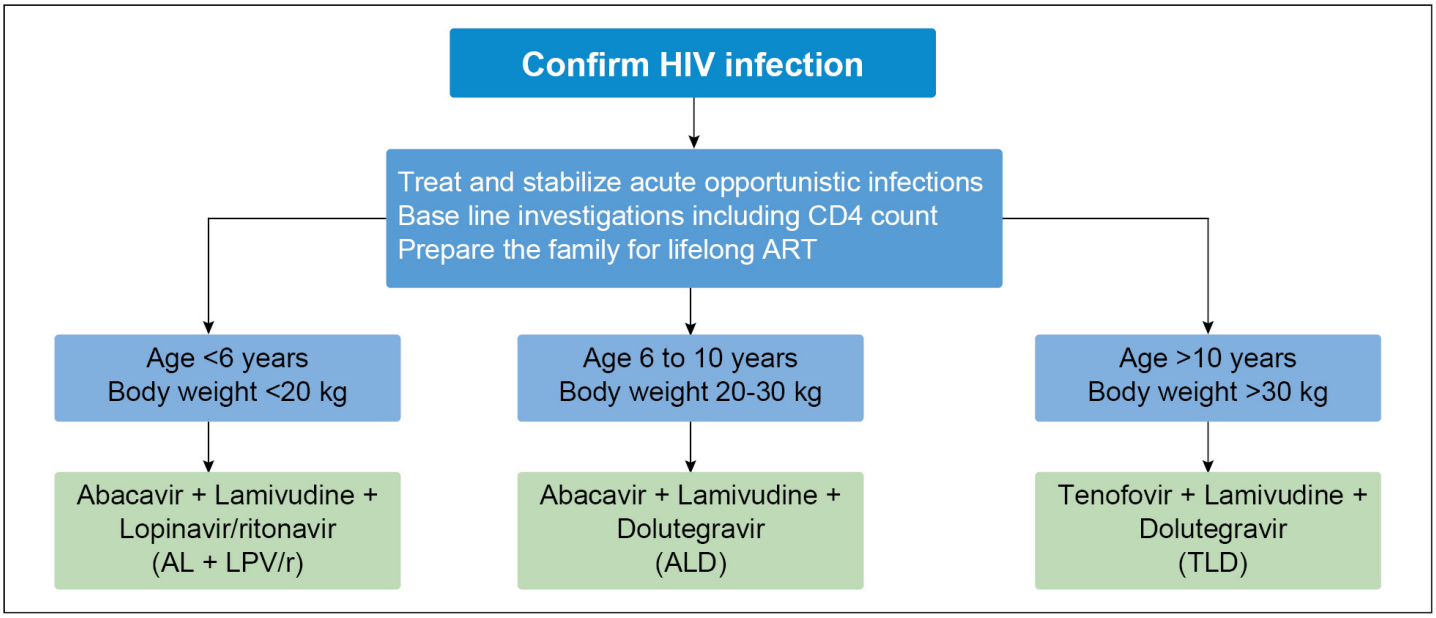
The most common adverse effects of DTG include insomnia and other neuropsychiatric adverse reactions. Compared with other ARV drugs, incidence of the other short-term serious adverse events including cardiovascular events, IRIS or suicidal behaviour are low.

The safety, tolerability, efficacy and favourable pharmacokinetics of DTG for children older than 6 years of age have been demonstrated in the short term. Due to lack of paediatric study comparing DTG-based regimen with EFV-based or LPV/r-based regimen, adult data was analysed, which showed DTG being superior to an LPV/r-based regimen in terms of viral suppression at 48 and 96 weeks, discontinuation and emergent serious adverse events.

For these reasons, the Paediatric Technical Resource Group recommended DTG as the preferred first-line regimen for children older than 6 years of age and weighing at least 20 kg. Because of the limited experience with DTG among children, the Technical Resource Group also advised that steps be taken to implement routine active toxicity monitoring.

Recently, DTG has been approved by the FDA for use in infants and children ≥4 weeks of age and weighing ≥3 kg. This recommendation is based on Pharmacokinetic and safety data from two ongoing clinical trials (IMPAACT P1093 and ODYSSEY), as well as a study of treatment- experienced (but INSTI-naive) older children.[3] However, paediatric DTG formulations are not available currently in India. Till such date, LPV/r-based regimen will be used as preferred first line for children less than 6 years of age and body weight less than 20 kgs.

Figure 3.2.3: Choice of ART regimen in children



ART in special situations: HIV-TB Co-infection

In TB coinfected CLHIV, initiation of anti-TB treatment is the priority.
For details on treatment of Drug sensitive TB and Drug resistant TB in CLHIV, refer **Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis).**
Timing of ART initiation in relation to TB treatment initiation is summarized in Table 3.2.6.

Table 3.2.6: Timing of ART in relation to initiation of TB treatment

Patient's details	Timing of ART in relation to initiation of TB treatment
CLHIV coinfected with TB	• Initiate anti-TB treatment first. • ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among children living with HIV (except when signs and symptoms of meningitis are present).
	• Among children living with HIV with TB meningitis, ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated. • Corticosteroids should be considered adjuvant treatment for TB meningitis.

ART regimens in CLHIV receiving Rifampicin-based ATT

All CLHIV receiving rifampicin-based ATT, the ART regimen needs to be modified. WHO policy brief, 1 July 2020, recommends that children weighing more than 20 kg who are receiving DTG- based regimens should continue their ART regimen using an increased dose of DTG 50 mg twice daily for the duration of TB treatment, as supported by data generated by the ongoing ODYSSEY trial. The FDA has approved the use of DTG 5 mg twice daily when used in infants and children weighing 3 kg and older than 4 weeks who are being treated for TB.[3]

CLHIV with drug sensitive TB requiring LPV/r-based ART initiation is given super-boosted Lopinavir/ritonavir. Super boosting of LPV means giving additional ritonavir to make the ratio of Lopinavir to ritonavir equal (1:1). Super boosting of LPV with ritonavir should continue for 2 weeks after stopping rifampicin. For CLHIV requiring DTG-based regimen, dose of DTG is increased to 50 mg twice daily. Additional dose of DTG 50 mg is to be continued for 2 weeks after completion of Rifampicin-containing

ATT regimen. Efavirenz based ART does not require any modification with Rifampicin-based ATT. This is summarized in Tables 3.2.7 and 3.2.8.

Table 3.2.7: Modification of ART regimen in CLHIV receiving rifampicin-based ATT

Current Regimen	ART Modification While Receiving Rifampicin-Based Regimen
DTG-based regimen	Double the dose of DTG. DTG dose will need to remain twice daily for 2 weeks after the last dose of rifampicin.
LPV/r-based regimen	Super boosting of LPV with ritonavir (the ratio of LPV:r is 1:1). Super boosting of LPV with ritonavir to continue for 2 weeks after stopping rifampicin.
EFV-based regimen	No modification is required.
DTG + LPV/r regimen	Double the dose of DTG (DTG 50 mg twice daily). In addition, super boosting of LPV with ritonavir (the ratio of LPV:r is 1:1). Both double dose of DTG and super boosting of LPV with ritonavir to continue for 2 weeks after stopping rifampicin

Table 3.2.8: ART regimens in CLHIV on first-line ART with TB co-infection

Weight and Age of CLHIV	Recommended Regimen in TB Coinfection
Weight less than 20 kg or Age below 6 years	FDC of Abacavir + Lamivudine twice daily as per weight band plus Lopinavir /ritonavir + super boosting with additional ritonavir, twice daily as per weight band
Weight between 20–30 kg and Age between 6–10 year	FDC of Abacavir +Lamivudine twice daily as per weight band plus DTG 50 mg twice daily
Weight above 30 kg and Age above 10 years	FDC of Tenofovir + Lamivudine + Dolutegravir once daily with an additional dose of Tab Dolutegravir 50 mg after 12 hours
Note: DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin. Super boosting of LPV with ritonavir to continue for two weeks after stopping rifampicin. Please refer Annexure 2 for drug dosing details.	

ART is lifelong and optimal adherence is key to success of the management of CLHIV. As these children after starting ART gain weight rapidly, the dose of ART needs to be constantly upgraded. However, the ART regimen remains unchanged unless the child develops intolerance to any of the ARV drugs used. ART dose modification is also required when concomitant rifampicin-based ATT is used. With the introduction of DTG, the ART regimen in children has become simpler and more potent.

ART in ALHIV

In general, an ALHIV already initiated on ART during childhood will continue on the same regimen, with weight-adjusted dosing, as long as she/he is virologically suppressed. For an ALHIV newly initiated on ART, failing on previous regimen, the choice of regimen and dosing (adult or paediatric) of ART should be based on both weight and age of the adolescent and prior ARV exposure. Special attention needs to be paid to adherence to ART as it is more likely to falter during this period. Disclosure of HIV status would be an important determinant of adherence to ART and would need to be assessed and addressed in every adolescent on every visit to ART centre.

3.3 Advanced Disease Management in CLHIV less than 5 Years of Age

Introduction

WHO defines advanced HIV disease for adults and adolescents (and children 5 years and older) as having a CD4 cell count of less than 200 cells/mm3 or WHO clinical stage 3 or 4.[1] All children less than 5 years (who are not already receiving ART and clinically stable) are considered to have advanced disease because evidence shows that 80% of all children initiating ART have severe immune-suppression. In a study of 1,289 CLHIV from southern India, the mortality rate was found to be 28.2% among children less than 5 years, 38.6% in children with advanced WHO clinical staging, 35.2% among severely immunosuppressed children and 22.3% in severely malnourished children.[2] Age less than 5 years and advanced clinical and immunological disease at the baseline are associated independently with high mortality in CLHIV. It is also known that younger children have an increased risk of disease progression and mortality regardless of clinical and immune condition. Advanced HIV disease includes:

- Newly diagnosed CLHIV aged less than 5 years
- Severe immune suppression following treatment failure
- Re-engaging with the care after treatment interruption

However, children older than 2 years of age, who have been receiving ART for more than 1 year, are established on ART and are clinically stable should not be considered to have advanced disease.

Major causes of morbidity and mortality

The major causes of morbidity and mortality among CLHIV less than 5 years of age are pneumonia (including PCP), TB, bloodstream infections, diarrhoeal disease and severe acute malnutrition. An Indian study reported[2] the major causes of mortality in CLHIV were pneumonia (38% including PCP), TB (28%), sepsis (20%) and diarrhoeal disorders (10%).

Package of Advanced Disease Management in CLHIV under 5 Years of Age

All CLHIV less than 5 years of age are categorized as having advanced disease regardless of CD4 cell counts (CD4%) and clinical disease. Hence, all these children should be offered advanced disease package and evaluated for pneumonia, TB, bloodstream bacterial infections, diarrhoeal disease and malnutrition.

No randomized controlled trial has included children to determine the optimal package of care for advanced HIV disease for children. The main interventions as recommended by WHO known to reduce morbidity and mortality among CLHIV can be summarized as Screen, Treat, Optimize and Prevent AIDS (STOP AIDS). These recommendations include screening for TB, severe acute malnutrition and cryptococcal meningitis (if there are signs of meningitis); treatment of TB, severe pneumonia, severe bacterial infections and malnutrition (as well as cryptococcal meningitis when present); rapid ART initiation unless there are signs of meningitis or severe acute malnutrition, with appropriate measures to prevent TB disease, pneumococcal disease and other vaccine- preventable diseases. In addition, routine interventions recommended for children in general such as deworming, iron and vitamin A supplementation and growth monitoring should be provided.

Table 3.3.1: STOP AIDS

Screen	**Tuberculosis (TB)**	• Screen for TB using the 4S screening tool and paediatric TB clinical algorithm. • Use the following diagnostic tests to confirm TB as applicable: ▪ Rapid molecular diagnostic (with NAAT) on (induced) sputum, gastric aspirate or other extra-pulmonary samples if relevant ▪ Lateral flow urine lipoarabinomannan (TB-LAM) assay (if available) as per the guidelines
	Cryptococcal infection among (>10 years)	Serum or plasma or blood cryptococcal antigen screening followed by lumbar puncture if positive or symptomatic
	Malnutrition	• Weight-for-height • Height-for-age • Mid-upper arm circumference among children 6 months–5 years of age
Treat		• TB, severe pneumonia, severe bacterial infections, cryptococcal meningitis and severe acute malnutrition as per national guidelines
Optimize		• Rapid antiretroviral therapy at the earliest or before discharge in hospitalized children with optimal regimens • Antiretroviral therapy preparedness and adherence counselling
Prevent		• Bacterial infections and Pneumocystis pneumonia – Cotrimoxazole prophylaxis • TB preventive treatment for children above 1 year of age • Cryptococcal meningitis among adolescents – Fluconazole pre-emptive therapy for adolescents (Refer **Chapter 4.2 Central Nervous System**) • Immunization as per the national immunization schedule • Routine childhood interventions like deworming, vitamin A and iron supplementation and growth monitoring • Appropriate nutritional counselling to prevent malnutrition

Initial assessment, screening and triage

All children less than 5 years of age with newly diagnosed HIV infection, or with severe immunosuppression following treatment failure or re-entering care after a period of loss to follow-up should be assessed for advanced HIV disease. These children if found to have any general signs of serious illness, severe acute malnutrition, severe pneumonia, diarrhoea with severe dehydration or meningitis should be referred for further evaluation and management.

- Assess the child for any of the following general signs of serious illness:
- Able to drink or breastfeed?
- Vomiting everything?
- Convulsions
- Lethargic or unconscious
- Stridor in a calm child

- Screen the child for presence or absence of severe acute malnutrition (SAM) by using the following tools
- Oedema of both feet OR

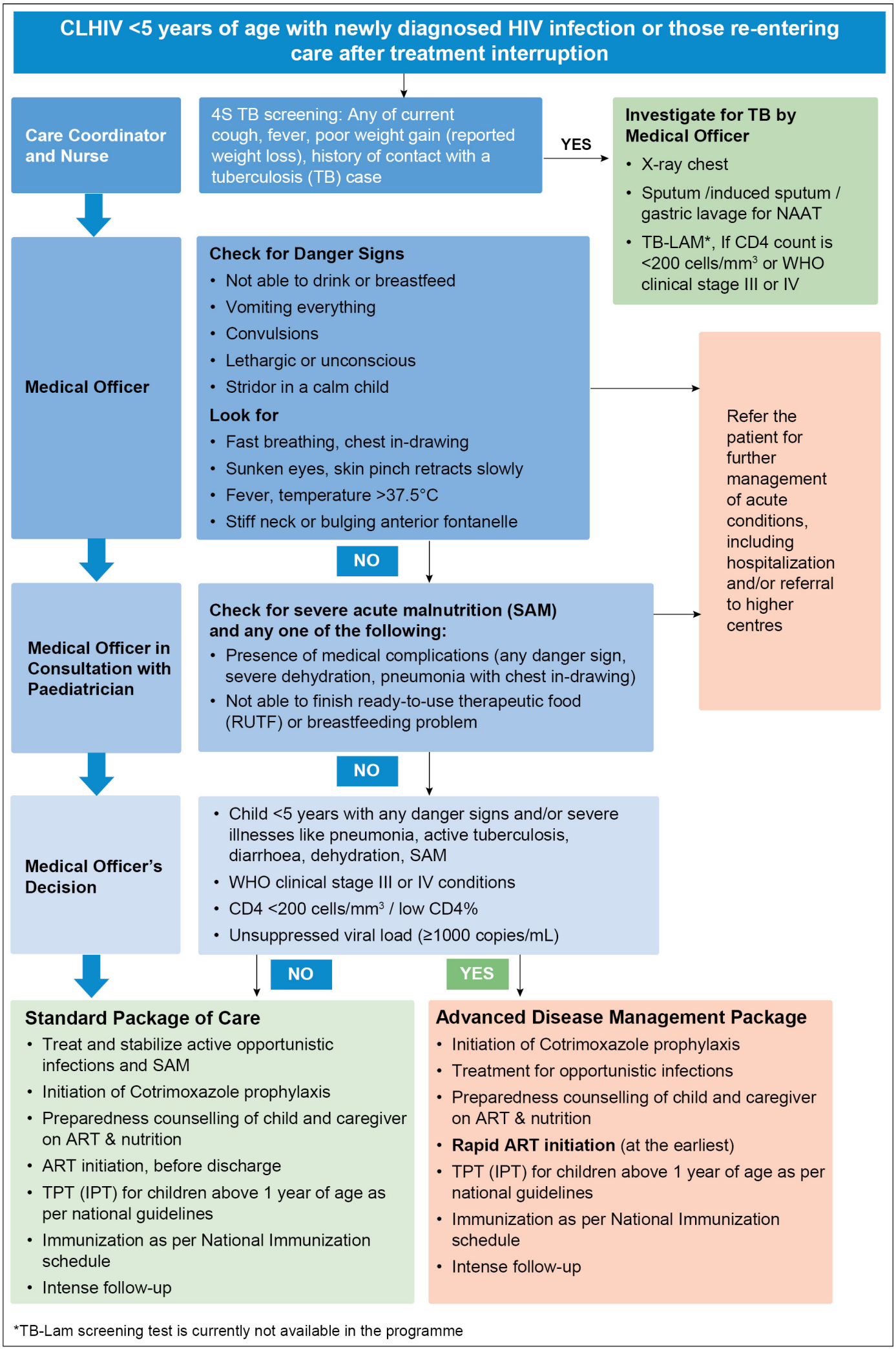
- Weight for height or length: <-3 Z-scores OR
- Mid-upper arm circumference (MUAC) <115 mm

AND

- Any one of the following:
- Medical complication present (any general danger signs, severe dehydration, pneumonia with chest in-drawing)
- Not able to finish Ready to Use Therapeutic Food
- Breastfeeding problem

- Apart from general danger signs, the medical officer should also look for any signs of pneumonia (fast breathing and/or chest in-drawing), severe dehydration (sunken eyes and/or skin pinch goes very slowly), fever (temperature >37.5^{0}C) and for meningitis (neck stiffness or bulging anterior fontanelle). In infants aged between 2 months and 12 months, respiratory rate of >50/minute and in children between 1 year and 5 years, a rate of >40/minute is considered fast breathing. Subcostal, intercostal and suprasternal retractions should be looked for in any child with fast breathing. To assess severity of dehydration apart from general danger signs and sunken eyes, skin turgor is assessed by pinching the skin over anterior abdominal wall. If skin pinch goes back very slowly (>2 sec), it is considered a sign of severe dehydration.3 A child's anterior fontanelle should be examined in upright position to determine bulging anterior fontanelle, which would indicate raised intracranial pressure.

Figure 3.3.1: Algorithm for assessment of CLHIV for advanced disease management


CLHIV <5 years of age with newly diagnosed HIV infection or those re-entering care after treatment interruption
Care Coordinator and Nurse
4S TB screening: Any of current cough, fever, poor weight gain (reported weight loss), history of contact with a tuberculosis (TB) case
YES
Investigate for TB by Medical Officer
• X-ray chest
• Sputum /induced sputum / gastric lavage for NAAT
• TB-LAM*, If CD4 count is <200 cells/mm3 or WHO clinical stage III or IV
Medical Officer
Check for Danger Signs
• Not able to drink or breastfeed
• Vomiting everything
• Convulsions
• Lethargic or unconscious
• Stridor in a calm child
Look for
• Fast breathing, chest in-drawing
• Sunken eyes, skin pinch retracts slowly
• Fever, temperature >37.5°C
• Stiff neck or bulging anterior fontanelle
Refer the patient for further management of acute conditions, including hospitalization and/or referral to higher centres
NO
Medical Officer in Consultation with Paediatrician
Check for severe acute malnutrition (SAM) and any one of the following:
• Presence of medical complications (any danger sign, severe dehydration, pneumonia with chest in-drawing)
• Not able to finish ready-to-use therapeutic food (RUTF) or breastfeeding problem
NO
Medical Officer's Decision
• Child <5 years with any danger signs and/or severe illnesses like pneumonia, active tuberculosis, diarrhoea, dehydration, SAM
• WHO clinical stage III or IV conditions
• CD4 <200 cells/mm3 / low CD4%
• Unsuppressed viral load (≥1000 copies/mL)
NO
YES
Standard Package of Care
• Treat and stabilize active opportunistic infections and SAM
• Initiation of Cotrimoxazole prophylaxis
• Preparedness counselling of child and caregiver on ART & nutrition
• ART initiation, before discharge
• TPT (IPT) for children above 1 year of age as per national guidelines
• Immunization as per National Immunization schedule
• Intense follow-up
Advanced Disease Management Package
• Initiation of Cotrimoxazole prophylaxis
• Treatment for opportunistic infections
• Preparedness counselling of child and caregiver on ART & nutrition
• Rapid ART initiation (at the earliest)
• TPT (IPT) for children above 1 year of age as per national guidelines
• Immunization as per National Immunization schedule
• Intense follow-up
*TB-Lam screening test is currently not available in the programme

Screening for TB

All children should be screened for TB using 4S screening tool, which includes current cough, fever, reported weight loss or confirmed weight loss >5% since last visit or growth curve flattening or weight for age <-2 Z-scores and history of contact with a person with any form of active TB within last 2 years. If a child has any one of these four symptoms, he/she should be further investigated for active TB (both pulmonary and extra-pulmonary TB) using diagnostic algorithm with chest x-ray, NAAT on (induced) sputum, gastric aspirate or other extra-pulmonary samples if relevant or any other relevant investigations (refer Chapter 2.8 HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis and Figure 2.8.6: Diagnostic algorithm for TB in CLHIV (both pulmonary & extra pulmonary).

NACO's Technical Resource Group recommends based on WHO's recent guidance, using TB- LAM to assist in diagnosing active TB among any CLHIV less than 5 years of age with signs and symptoms of TB (pulmonary and/or extra-pulmonary) or those seriously ill regardless of signs and symptoms of TB.

Screening for cryptococcal disease

The main differences in the package of care for children compared with adolescents and adults is that routine cryptococcal antigen screening and pre-emptive therapy are not recommended for children less than 10 years of age because of the low prevalence of cryptococcal meningitis in this age group. However, if a child less than 10 years of age presents with signs and symptoms of meningitis, cryptococcal meningitis should still be considered and the appropriate investigations and treatment for this should be implemented.

Screening for malnutrition

Severe acute malnutrition is common at HIV diagnosis and carries a high risk of mortality. All children should be assessed for presence or absence of malnutrition at the time of HIV diagnosis and during each visit. Anthropometric measurements like weight, height and MUAC, are important tools in identification of malnutrition. Weight-for-Height or Weight-for-Length should be determined by using the WHO growth standards charts and MUAC is measured using MUAC tape in all children 6 months of age or older.

Treatment

All CLHIV less than 5 years of age presenting with any general danger signs categorized as having severe illness should be immediately referred for management. All these CLHIV with severe illness should be evaluated for TB regardless of signs and symptoms of TB. In CLHIV with active TB co- infection, the treatment of TB is the priority and should be started at the earliest (Refer **Chapter 2.8 HIV-TB Co-infection: Case Finding, Management and Prevention of Tuberculosis**). Drug–drug interactions between Rifampicin and LPV/r or DTG need to be considered and ART dosing adjusted accordingly (Refer **Chapter 3.2 Management of Newly Diagnosed HIV-infection in Children Including ART Initiation**).

The most common bacterial pathogens causing severe pneumonia in CLHIV are Streptococcus pneumoniae and Staphylococcus aureus. These pathogens are sensitive to commonly available and recommended antibacterial medications. The severity of illness and need for hospitalization should be classified according to the WHO integrated management of childhood illness algorithms. As a definitive diagnostic test for PCP is not available, it is advised to empirically treat all these infants with HIV infection with severe pneumonia with oral Cotrimoxazole, (20 mg of trimethoprim and 100 mg of sulfamethoxazole per kg per day), every 6 hours for 21 days. This reduces mortality from PCP among young infants with HIV. The early use of steroids in infants with a clinical diagnosis of PCP in addition to

Cotrimoxazole therapy significantly reduces mortality. For children between 1 and 5 years of age, Cotrimoxazole is not empirically recommended in CLHIV with severe pneumonia as prevalence of PCP in this age group is low.

Severe bacterial bloodstream infections are reported in CLHIV especially at the time of diagnosis or within the first 3 months of ART initiation. The most common pathogens causing community- associated infections are Streptococcus or Staphylococcus and in hospital-associated infections predominantly gram-negative organisms. The antibiotic to treat severe bacterial bloodstream infections should be guided by the blood and/or cerebrospinal fluid culture and sensitivity. If culture is not available, local microbiological drug sensitivity profile should be used to start the treatment. The treatment should be based on current standard guidelines and tailored according to age.

Severe acute malnutrition is common at HIV diagnosis and carries a high risk of mortality. These children should be appropriately linked to nutritional rehabilitation services available locally.

Optimize

Although rapid ART initiation within 7 days of diagnosis is a priority, children who require hospitalization for severe acute malnutrition, TB, meningitis or other illnesses need to be clinically stabilized first. However, initiating ART is encouraged as part of the child's hospital admission, since referral after discharge may lead to loss to follow-up and failure to initiate ART. Among children with signs of or confirmed TB meningitis, the start of ART should be delayed in accordance with existing guidelines. Similarly, ensuring linkage to the facility in which the child will receive ongoing HIV care on discharge is critical.

Prevent

Prevention of OIs in advanced HIV disease among children consists mostly of rapid and optimal ART initiation, preventing severe TB disease with BCG and TB preventive treatment, preventing PCP with Cotrimoxazole prophylaxis (refer **Chapter 2.9 Prevention of Opportunistic Infections**) and administering age-appropriate vaccinations as per national immunization schedule and catch-up vaccine administration when indicated. Additional measures like deworming, vitamin A Prophylaxis and iron supplementation should be provided.

3.4 Care of CLHIV: Post ART Initiation

Introduction

Care of CLHIV following initiation of ART is an essential component of comprehensive management of HIV infection in children. Since ART is lifelong and initiated at an early age in children, CLHIV and their families need continuous care and support to avail the maximum benefit of ART. The normal growth and development of children pose unique challenges in delivering the care and support. The objectives of post ART care of CLHIV are ensuring the safety of the CLHIV on ART, optimizing the benefit of ART, monitoring the response to ART and early identification of treatment failure and comorbidities/co-infections. The following are different components of post ART initiation care of CLHIV:

- Monitoring after initiation of ART
- Adverse events of ARVs – identification and substitution
- Identification of treatment failure
- Adherence counselling

What to expect in the first 6 months following ART initiation?

The factors influencing the events during the first 6 months after ART initiation are age of the child, baseline clinical, immunological and nutritional status and presence or absence of active or latent OIs. The first 6 months on ART are critical and clinical, nutritional and immunological improvement is expected. There may be poor clinical response or even deterioration in some children. The various reasons for apparent failure to clinical response include baseline advanced HIV disease and very severe immunosuppression, slow viral suppression, recovery of immature immune system in children, untreated malnutrition, overlapping drug toxicities, immune reconstitution inflammatory syndrome, vulnerability to OIs including TB, pre-existing comorbidities like bronchiectasis, pulmonary hypertension and suboptimal adherence. It is important to allow sufficient time on therapy before judging the effectiveness of a regimen. Supporting adherence during this period is critical and, in such cases, hasty switching of ARV regimen would be inappropriate. It is well documented in the literature that though mortality is reduced after starting ART, it can still be high in the first 6 months. The risk factors for this high mortality in the early post ART period are baseline advanced HIV disease and severe immunosuppression. These children gain weight rapidly during the first few months after ART initiation. As a result, there is continuous need to modify the doses of the ARV drugs during this phase.

Table 3.4.1: What happens to CLHIV in first six months of therapy

- Viral suppression
- Clinical and immunological improvement
- Improvement in quality of life and decrease in morbidity and mortality
- Certain opportunistic infections may appear
- Immune reconstitution inflammatory syndrome (IRIS) may develop
- Early adverse drug reactions, such as drug hypersensitivity may occur

Monitoring after Initiation of ART in CLHIV

Follow-up of clinical adherence and laboratory monitoring are essential in children initiated on ART. The regular monitoring, when required, aids in initiation of appropriate remedial measures like dosage modification of ARVs, substitution of ARV causing adverse effects, recognizing Immune Reconstitution of Inflammatory Syndrome, initiation/stopping of any prophylaxis and switching the ART regimen in the event of treatment failure. To achieve these objectives, well- structured clinical and laboratory evaluations are advised at specified intervals in these children.

Table 3.4.2: Parameters to monitor during follow-up after ART initiation

Clinical monitoring: • Clinical evaluation/overall well-being • Any new clinical event • 4S screening for TB • Treatment adherence • Adverse drug reactions	**Laboratory monitoring to identify** • ARV-related toxicities • Inter-current illnesses • Drug–drug interactions • Other metabolic abnormalities
Immunological monitoring • CD4 testing	**Viral load monitoring** • Viral load testing

Clinical monitoring

At each monthly visit, the patient should be reviewed for clinical symptoms, nutritional and developmental assessment, screened for any new OI and adverse drug reaction. After clinical evaluation, the clinical T staging of every child should be confirmed.

Nutritional/growth assessment includes weight, height (length in children less than 2 years of age), head circumference (in children up to 3 years of age) and mid upper arm circumference (age between 6 months to 5 years); it should also enquire about the diet, mode of feeding and supplements received. The anthropometric measurements are plotted on appropriate growth charts (refer **Chapter 3.6 Nutritional Care of HIV-infected Children**). The growth flattening can be an early sign of treatment failure and latent OIs and thus help in initiating early interventions.

Developmental assessment should be performed at every visit especially in children less than 5 years of age as described in the previous chapters (**Chapters 3.1 Management of HIV-exposed Infants and Children and chapter and 3.2 Management of Newly Diagnosed HIV-infection in Children Including ART Initiation**). Any delay in development or regression of already attained developmental milestone warrants prompt referral to experts. In older children, scholastic performance may be assessed. A poor or deteriorating scholastic performance may be an early sign of HIV-associated encephalopathy.

At every clinical visit, CLHIV should be screened for OIs especially TB. 4S screening for TB is an essential tool for early detection of TB. (Please refer C**hapter 2.8 HIV-TB Co-infection: Case Finding, Management and Prevention of Tuberculosis for details**). Appropriate symptom-directed physical examination and investigations will also help in early identification of other OIs.

Adherence to ART must be assessed at each visit and adherence must be reinforced through counselling at each visit. Suboptimal adherence is the single most important cause of early treatment failure. Most frequently, the immediate adverse effects of the ARV drugs result in poor adherence in the first few months of ART initiation. A proactive approach involving the caregivers by appropriate pre-emptive counselling about the possible adverse effects of ARV will mitigate the risk of poor adherence. Review of concomitant medications and their potential interactions with ART should be done during clinical visits. This helps in optimizing the benefit of ART by reducing drug interactions and lessening the severity of overlapping adverse effects.

Calculating the child's ARV dosage as per body weight at every visit is essential. Even though the drug regimen remains the same, drug dosages must be modified according to the change in body weight. The caregiver should be counselled whenever the dose is increased due to weight gain by the child. At every visit, the counsellor should speak to the child also to confirm the dose of medicine given. Medical officer should reinforce the dosage change to caregiver and child. The pharmacist should also reinforce the dosage, preferably write it on the bottle with a marker.

The Clinical Monitoring and Follow-up schedule of a CLHIV is summarized in Table 3.4.3.

Table 3.4.3: Clinical monitoring and follow-up schedule

Parameter	When to Monitor?
Growth and nutrition	Every visit
Developmental progress	Every visit
4S screening for TB	Every visit
Clinical monitoring for opportunistic infections and T-staging	Every visit
Treatment adherence	Every visit
Calculate ARV dose	Every visit

Warning signs of a new clinical event

The ART staff needs to be vigilant about warning signs that may indicate occurrence of a new clinical event. These include weight loss, sudden onset of fatigue or loss of appetite, repeated episodes of vomiting, diarrhoea and repeated episodes of fever, which may suggest the appearance of a new opportunistic infection or an adverse drug reaction. One should also keep a note on recurrent adherence issues if the children/caregivers are repeatedly missing pill pick-up dates, a viral load ≥1000 copies/ml, sudden fall in CD4 counts and signs suggestive of IRIS.

Laboratory monitoring

The laboratory monitoring of CLHIV on ART is also very important. Regular monitoring of The patients' laboratory parameters is crucial to identify ARV-drug related toxicities, inter-current illnesses and drug–drug interactions. The frequency of monitoring and the parameters to be monitored depend upon the ARV drugs used in the regimen, clinical symptoms and duration of ART exposure. The summary of the laboratory monitoring recommended under the programme is presented below in the tables. Additional laboratory tests outside this schedule may be performed as clinically directed.

Table 3.4.4: Laboratory parameters for HIV-infected infants and children at baseline and monitoring during ART

Tests	Day 0	At 15days	At 1 month	At 2 months	At 3 months	At 6 months & Every 6 months thereafter
Hb/CBC	Yes	Yes (if on AZT)	Yes (if on AZT)	Yes (if on AZT)	Yes	Yes
Blood urea	Yes					Yes
LFT/ALT[a]	Yes					Yes
Urinalysis	Yes					Yes (if on TDF)
Creatinine	Yes (if planning for TDF					Yes (if on TDF)
Lipid profile	Yes[b] (If planning for PI)				Yes	Yes[b] (if on PI)
Random blood sugar	Yes[b] (If planning for PI or DTG[d])				Yes[b]	Yes (if on PI or DTG[d])[b]
CD4%[c] **or counts**	Yes					Yes
Screening for TB[e]	Yes	Yes	Yes	Yes	Yes	Yes
Plasma viral load	At 6 months and 12 months after ART initiation and then every 12 months					

Other symptom-directed biochemistry tests can be done based on the availability of such tests.

[a]ALT at baseline is the minimum monitoring for possible liver impairment. Children with high ALT (>5 times upper limit of normal) should have full liver function test performed as well as assessment for hepatitis B, hepatitis C or other hepatic disease. For HBV and/or HCV coinfected patients, 3-monthly screening of liver function is recommended. In this case, further tests may be required to assess for chronic active hepatitis.

[b]For children to be started on PI- or DTG-based regimen, blood sugar, LFT and lipid profile are to be done at baseline.

[c]CD4% is used in children less than 5 years of age. For children >5 years of age, CD4 count is used.

CD4 monitoring can be stopped for children aged more than 5 years if CD4 count is greater than 350 cells/mm^3 and viral load count is <1000 copies/ml (when both tests are conducted at the same time.)

[d]Pregnancy test is advised in adolescent girls especially when DTG-based ART is initiated.

[e]As and when children develop signs and symptoms of TB (4S screening) or history of contact with TB, they should be investigated for the presence of active TB.

More frequent visits or monitoring may be required, if the patient develops any symptoms, side effects of the ARVs or experiences difficulties in adherence to ARVs because of any reason, including clinically indicated reason as per the discretion of the Medical Officer.

Virological monitoring

Serial plasma viral load monitoring is done in all children initiated on ART. The time points when this is done are at 6 months and 12 months after starting ART and annually thereafter. If plasma viral load is less than 1000 copies/ml, then that CLHIV is considered as virologically suppressed. If plasma viral load is ≥1000 copies/ml, clinical evaluation for OIs and step-up adherence counselling are advised under close clinical supervision for 3 months. Even after optimal adherence, if repeat plasma viral load is ≥1000 copies/ml, treatment failure should be considered provided CLHIV has received ART for more than 6

months.

For viral load algorithm, please refer **Chapter 3.5 Treatment Failure and Switch to Second-line ART in Children with HIV.**

Interpretation of Viral Load Test Results

Target not detected (TND) or Undetectable

- Means that the level of HIV is too low to be detected or measured by the test
- Does not mean that HIV has disappeared
- HIV is still present in reservoirs.
- Continue current regimen

Plasma viral load <1000 copies/ml

- Under current national guidelines, this is considered suppressed viral load.
- Continue the same ART regimen.
- Next viral load testing must be done as per guidelines.

Plasma viral load ≥1000 copies/ml

- At least three sessions of 'Step-up adherence'/enhanced adherence counselling
- Repeat viral load testing when treatment adherence is >95% for three consecutive months.
- If repeat plasma viral load is <1000 copies/ml, patient must be continued on same ART regimen.
- If repeat plasma viral load is ≥1000 copies/ml despite step-up counselling, patient needs to be referred to SACEP for further evaluation.

For step-up adherence counselling process in CLHIV with poor adherence to ART, refer **Chapter 3.5 Treatment Failure and Switch to Second-line ART in Children with HIV.**

Stable Child

Since CLHIV have been started on ART at a young age, they have a lifetime of ART management ahead of them. To facilitate the retention in care and avoid treatment fatigue, various service delivery options like multi-month dispensation (MMD) are explored. This facilitates retention on ART by limiting time in health facilities, uninterrupted school attendance and increased time with peers. One of the prime concerns for MMD is requirement of dosage modification with the growth of these children. Growth may be rapid in the initial few months after starting ART. Butthereafter, when growth slows down and hence ART doses do not have to be adjusted frequently, dosage changes may only be required three times until a child reaches 10 years of age. To facilitate MMD, the following definition of 'Stable Child' has been adapted:

For children >2 years to 10 years of age satisfying ALL the following criteria:

- Receiving ART for at least 6 months
- Viral load is suppressed (Plasma viral load <1000 copies/ml).
- Should be on the same regimen (with no dose or formulation change) for at least 3 months
- Should not have any active illnesses/medical condition that requires further management
- Treatment adherence >95% in each of last 3 months

- Weight for age is more than -2SD OR weight for height/length is more than -2SD.

For children >10 years of age, the definition is the same as adult and adolescents. (Please refer Chapter 2.6 on First-line ART in Adults and Adolescents: Management of ARV Toxicities).

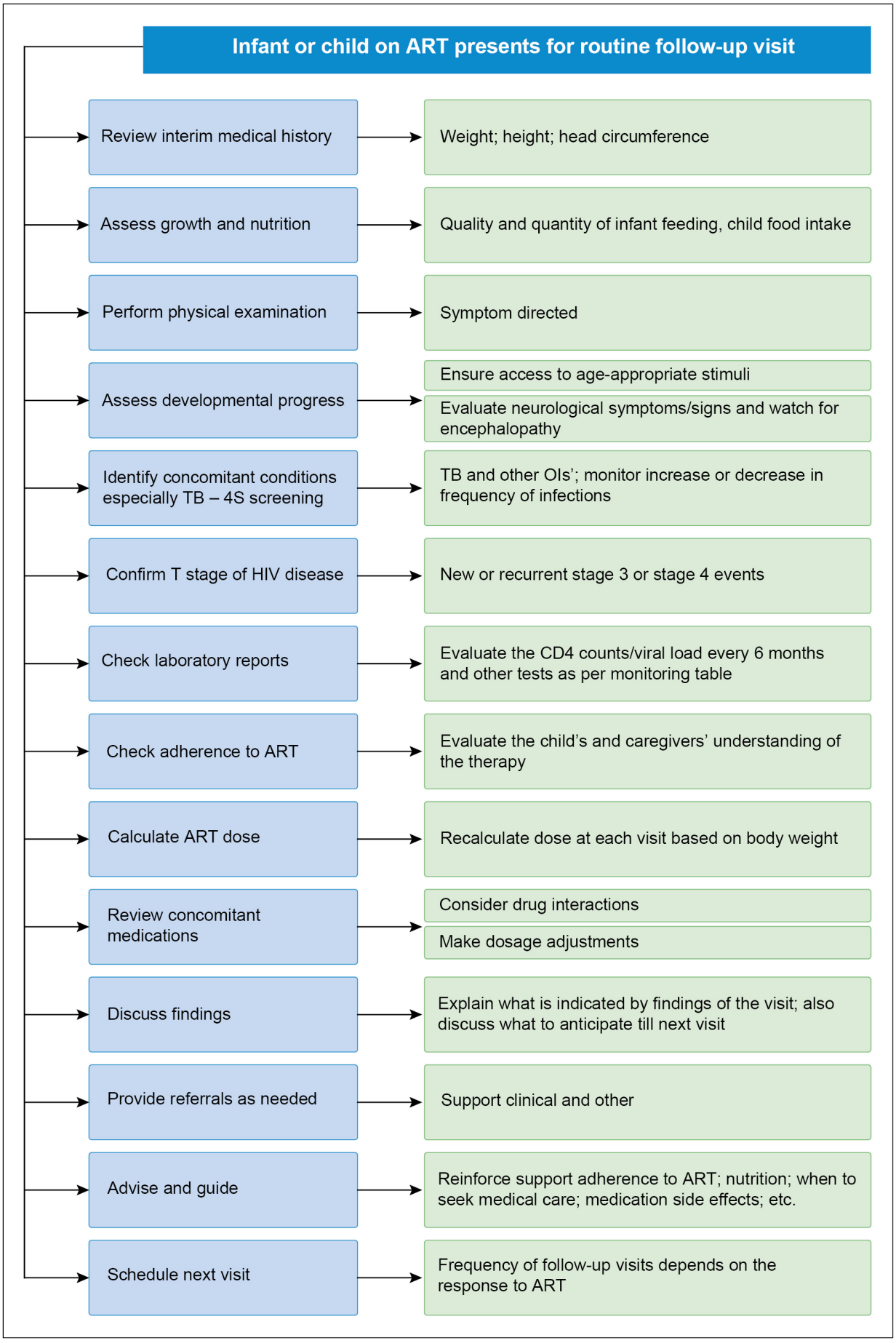
For children >10 years of age satisfying ALL the following criteria:

- On ART for at least 6 months
- No adverse effects of ART that require regular monitoring
- No current illness/OI/medical condition that requires management or regular monitoring
- Suppressed viral load (in the absence of viral load monitoring, rising CD4 cell counts or CD4 cell counts exceeding 200 cells/mm^3 and adherence ≥95% consecutively over the last 3 months)

Adverse Effects of ARV Drugs and their Management

'Adverse events' is the term used to describe side effects due to normal dose of medications as well as toxicities due to abnormal dose of medications. It is, however, not uncommon to use side effects to describe both types of events. The manifestations of ARV-related adverse events may overlap with many HIV-associated conditions including organ dysfunction, opportunistic infections, Immune Reconstitution Inflammatory Syndrome, other common childhood diseases or similar side effects of concomitant medications. Hence, the differentiating ARV-related adverse events from these conditions pose a great challenge. There remains limited data in children when it comes to drug adverse events, and much is extrapolated from adult studies. Most common ARV-related side effects are self-limiting and resolve on continued ARVs with simple supportive measures. It has been found in adults that ARV-related adverse events are the most important barrier for optimal adherence, especially in the early phase of ART initiation. Hence a 'proactive' approach is required to limit non-adherence. A proper counselling of an understanding child and caregiver before initiation of ART explaining the self-limiting nature of ARV-related adverse events reassures the patient and caregiver, and supports adherence to medications.

Figure 3.4.1: Monitoring of children on ART – Routine follow-up visit



Severity of adverse events

Depending on the temporal relationship between the initiation of ART and onset of ARV-related adverse events, the severity of adverse events can be described as follows:

Table 3.4.5: Type of adverse events

Type of Adverse Event	Duration of ART
Acute	Immediately after drug use
Sub-acute	A few weeks up to 6 months after drug use
Late	More than 6 months' (prolonged) drug use

The severity of these ARV-related adverse events or side effects required for effective management can be described as follows:

Table 3.4.6: Severity of adverse events

Grade	Type of reaction	Features
Grade 1	**Mild reactions**	• Symptoms are mild and transient • Do not require medical intervention/therapy
Grade 2	**Moderate reactions**	• Mild to moderate limitation of activity • Some assistance needed, no or minimal medical intervention/therapy required • In most cases, consider continuation of ART as long as feasible. • Consider single drug substitution: ▪ If patient does not improve on symptomatic therapy ▪ Some moderate reactions (e.g., lipodystrophy or peripheral neuropathy)
Grade 3	**Severe reactions**	• Significant limitation of activity • Some assistance required usually; medical intervention/therapy required with possible hospitalization • May need substitution of the offending drug without discontinuing ART
Grade 4:	**Severe life-threatening reactions**	• Extreme limitation of activity • Significant assistance required, significant medical intervention/ therapy needed; hospitalization or hospice care needed • Immediate discontinuation of all ARV drugs is recommended. • Manage the medical event (i.e., symptomatic and supportive therapy) and reintroduce ARVs using a modified regimen (i.e., with an ARV drug substitution for the offending drug) when patient is stabilized.

Adverse effects of ARVs

The adverse effects of ARV are the most important cause for poor adherence and discontinuation of therapy. Hence, management of these events help in maintaining optimal adherence and obtaining maximum benefit from ART. Meanwhile, hasty and irrational substitution of ARVs for mild to moderate non-life-/organ-threatening adverse events will lead to loss of future pharmacological options for the child. As only a few paediatric formulations of ARVs are available, substitutions should be done by balancing the risk of morbidity and mortality with the preservation of future therapeutic options.

Need to differentiate Adverse Drug Effects from the following:

- Opportunistic Infections
- Hepatitis A in a CLHIV with symptoms of hepatitis
- Malaria in a CLHIV with severe anaemia
- Other common childhood diseases
- Complications of HIV infection
- Immune Reconstitution Inflammatory Syndrome
- Reactions to medications other than ARV drugs
- Isoniazid-induced hepatitis in CLHIV on treatment for TB
- Rash induced by Cotrimoxazole

Table 3.4.7: Adverse effects of ARVs

ARV drug	Toxicity	Frequency	Risk factors
ABC	Nausea, vomiting, fever, headache, diarrhoea, rash, anorexia	Most common	
	Serious and sometimes fatal hypersensitivity reactions, which is a multi-organ clinical syndrome usually characterized by rash or signs or symptoms in two or more of the following groups: • Fever and constitutional symptoms, including malaise, fatigue or achiness • Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhoea or abdominal pain • Respiratory signs and symptoms, including dyspnoea, cough or pharyngitis • Pancreatitis can occur. • Severe hepatomegaly with steatosis, including fatal cases	Less common (more severe)	Presence of HLA-B*5701 allele
	• Laboratory and radiologic abnormalities: Abnormal LFT, elevated CPK and creatinine, lactic acidosis lymphopenia and pulmonary infiltrates. • Hypersensitivity reactions generally occur during the first 6 weeks of therapy, but they have also been reported after a single dose of ABC. • If an hypersensitivity reaction is suspected, ABC should be stopped immediately and not restarted as hypotension and death may occur upon re-challenge.		
	Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS) syndrome	Rare	
AZT	Hematologic toxicity, including neutropenia and anaemia, particularly in patients with advanced HIV disease	Most common	CD4 cell count of ≤200 cells/mm^3
	Headache, malaise, nausea, vomiting and anorexia	Most common	
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	Less common (more severe)	BMI >25 kg/m^2 - Prolonged exposure to NRTIs
	Cardiomyopathy	Rare	
TDF	Nausea, diarrhoea, vomiting, flatulence	Most common	
	Bone toxicity (osteomalacia and reduced bone mineral density [BMD])	Rare (severe)	History of rickets (in children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency
	Renal toxicity, including increased serum creatinine, glycosuria, proteinuria, phosphaturia and/or calcinuria and decreased serum phosphate	Rare (very severe)	
	Lactic acidosis or severe hepatomegaly with steatosis	Rare (very severe)	Prolonged exposure to nucleoside analogues Obesity Liver disease
LPV/r	Diarrhoea, headache, asthenia, nausea and vomiting, rash	Most common	
	Hyperlipidaemia, especially hypercholesterolemia and hypertriglyceridemia Insulin resistance	Common	More pronounced in girls than in boys.
	ECG abnormalities (PR and QRS interval prolongation, torsades de pointes)	Rare (very severe)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia
	Hepatotoxicity	Less common	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs
	• An increased risk of toxicity in premature infants • Transient symptomatic adrenal insufficiency • Life-threatening bradyarrhythmia and cardiac dysfunction (including complete atrioventricular block, bradycardia and cardiomyopathy) • Lactic acidosis • Acute renal failure • Central nervous system (CNS) depression • Transient asymptomatic elevation in 17-hydroxyprogesterone levels has also been reported in term newborns treated at birth with LPV/r.		Seen in neonates, these toxicities may be caused by the drug itself and/or from the inactive ingredients in the oral solution, which include propylene glycol 15.3% and ethanol 42.4%
DTG	Insomnia and headache	Most common	Consider morning dose of Dolutegravir; in intractable situation, consider substitution.
	Weight Gain	Very common	Patients need to be monitored for obesity and counselled for lifestyle management and exercise
	• Hypersensitivity reactions characterized by rash, constitutional symptoms • Hepatotoxicity • Neuropsychiatric symptoms	Rare	Especially in patients with a history of psychiatric illness
	A very small significant increase in the risk of neural tube defects has been observed among infants born to women who were receiving DTG at the time of conception.		Medical Officer should discuss with female adolescents, who plan for pregnancy this very small potentially increased risk of neural tube defects with patients receiving or have been initiated on DTG and their caregivers so that they can make informed decisions about its use.
EFV	Persistent CNS toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Less common	Depression or other mental disorder (previous or at baseline)
	Convulsions	Rare	History of seizure
	Hepatotoxicity	Less common	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs
	Severe skin and hypersensitivity reactions	Uncommon	Risk factor(s) unknown
	Gynaecomastia	Less common	Risk factor(s) unknown
NVP	Hepatotoxicity • Severe skin rash and hypersensitivity reaction, including Stevens-Johnson's syndrome	Common	Underlying hepatic disease HBV and HCV co-infection Concomitant use of hepatotoxic drugs High baseline CD4 cell count (CD4 count >250 cells/mm^3 in women or >400 cells/mm^3 in men)

Monitoring Abacavir toxicity in adolescents and children

The use of Abacavir (ABC) has been limited due to its toxicity profile, including an increased risk of hypersensitivity reaction in children. Serious and sometimes fatal Hypersensitivity Reactions have been observed in approximately 3%–5% of adults and children. Monitoring for hypersensitivity reactions in children initiated on first-line/second-line ART especially within the first 6 weeks of treatment is important to hypersensitivity reactions. The risk of hypersensitivity reactions is increased with the presence of the HLA-B*-5701 allele. However, the prevalence of the HLA-B*-5701 allele genotype in people of Asian origin was reported to be 4.0%. In the meantime, because hypersensitivity reactions remains rare and HLA-B*5701 screening is not feasible under the national programme, appropriately trained clinical staff should manage patients clinically, with education provided to caregivers and older children.

The Hypersensitivity Reaction to ABC is a multi-organ clinical syndrome that is usually characterized by rash or signs or symptoms in two or more of the following groups:

- Fever
- Constitutional symptoms, including malaise, fatigue or achiness
- Gastrointestinal signs and symptoms, including nausea, vomiting, diarrhoea or abdominal pain
- Respiratory signs and symptoms, including dyspnoea, cough or pharyngitis
- Pancreatitis can occur.
- Severe hepatomegaly with steatosis, including fatal cases
- Laboratory and radiologic abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine, lactic acidosis lymphopenia and pulmonary infiltrates

Abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible and regardless of HLA-B*5701 status. Abacavir SHOULD NOT be restarted because more severe symptoms may occur within hours, including **life-threatening hypotension and death.**

Monitoring Tenofovir toxicity in adolescents and children

Systematic review indicates that TDF toxicity among children and adolescents could be like that seen in adults. However, data are still lacking and renal and bone toxicities in growing children and adolescents remain a concern. Increasing monitoring for TDF toxicity should be considered especially in adolescents receiving TDF.

Dual-energy X-ray absorptiometry testing is not possible in most settings, but careful growth monitoring is recommended while adolescents are receiving TDF. When serum phosphate testing is available, by extrapolation, low serum phosphate should give rise to concern about bone mineral density loss. Increasing dosing accuracy in children and adolescents is extremely important for reducing toxicity.

Principles of Management of Adverse Events

The identification of ARV-related adverse events and determination of its severity are important steps in their management. However, distinguishing ARV-related adverse events from other HIV-related conditions or adverse events due to other concurrent drugs poses a great challenge.

If the ARV-related adverse event is severe and potentially life threatening, then consider stopping ART immediately and symptomatic/supportive management should be provided. Never reintroduce the drug

responsible for such a severe life-threatening complication. Alternative ART regimen with substituted new ARV is reintroduced after complete resolution of life-threatening adverse event.

If the ARV-related adverse event is severe but not life-threatening, then substitute the offending drug without stopping ART. In case the ARV-related adverse event is moderate, continue ART and provide symptomatic/supportive management. If non-resolving, substitute the drug responsible for moderate ARV-related adverse events or side effects. With mild ARV-related adverse events or side effects, continue ART and provide symptomatic/supportive management. The symptomatic management of adverse events and ARV substitution are mentioned in Tables 3.4.8 and 3.4.9

Table 3.4.8: Symptomatic management of adverse effects

Adverse Event	Symptomatic/ Supportive Measures	Specific Measures
Headache	• Rest • Hydration	• Step 1: Non-opioid +/- adjuvants Paracetamol • Step 2: Weak opioid +/- adjuvants Paracetamol (Codeine) • Step 3: Strong opioid +/- adjuvants (Morphine)
Peripheral Neuropathy	• Rest • Warmth	• Step 1: Non-opioid +/- adjuvants Paracetamol • Step 2: Weak opioid +/- adjuvants Paracetamol (Codeine) • Step 3: Strong opioid +/- adjuvants +/- Anticonvulsants
Nausea and Vomiting	• Depends on cause • Environment • Smell • Food • Calm • Small frequent feeds	• Step 1: Select anti-emetics Domperidone/Metoclopramide/ Haloperidol • Step 2: Select broad or combination anti-emetics Ondansetron, Cyclizine + Haloperidol
Insomnia	• Depends on cause • Review day activity • Environment • Warm milk • Restrict frightening TV programmes • Story telling • Parent/Guardian's presence	• Melatonin • Sedatives • Benzodiazepine • Chloral hydrate

Drug Substitution

Definition: Single-drug replacement of individual ARV (usually within the same class) for toxicity, drug–drug interactions or intolerance refers to SUBSTITUTION of individual (offending) drug and this does not indicate that a second-line regimen is being used even if second-line drugs like boosted PIs are used for substitution.

It is different from a ‘Switch’, which indicates ‘Treatment Failure’; refers to the loss of antiviral efficacy with the current regimen and it triggers the switch of the entire regimen from first to second line. It is identified by clinical and/or immunological criteria and confirmed by the virological criteria.

Drug Substitution: General Guidance

- The general principle is that single-drug substitution for toxicity should be made within the same ARV class.
- If a life-threatening toxicity occurs, all ART should be stopped until the toxicity has resolved, and a revised regimen should commence when the patient has recovered.
- Whenever an ARV toxicity is suspected, rule out other OIs or other conditions, like IRIS that may be responsible. Always grade the toxicity according to its severity.
- Patients with Dual Toxicity should be referred to PCoE/ART Plus centre for the review and approval of SACEP.

Table 3.4.9: Substituting with alternative first-line ARV drugs

First line ARV causing the toxicity	Patient characteristics	Alternative substitute
ABC	Age <10 years and body weight <30 kg; Hb >9 g /dL	AZT
	Age >10 years and body weight >30 kg	TDF
	Age <10 years and body weight <30 kg; Hb <9 g/dl	Refer the patient to PCoE/paediatric experts for evaluation
TDF		ABC
AZT	Age <10 years and body weight <30 kg	ABC
	Age >10 years and body weight >30 kg	TDF
LPV/r	Age >6 years and body weight >20 kg	DTG
	Age between 3 and 6 years and body weight between 10 kg and 20 kg	EFV
	Age <3 years and body weight <10 kg	NVP
EFV	Age >6 years and body weight >20 kg	DTG
	Age <6 years and body weight <20 kg	LPV/r
NVP	Age >6 years and body weight >20 kg	DTG
	Age <6 years and body weight <20 kg	LPV/r
Dual Toxicities		
ABC and AZT	Age >10 years and body weight >30 kg	TDF
	Age between 6 and 10 years and body weight between 20 kg and 30 kg	LPV/r + DTG This effectively moves the child to third line. A step-up adherence counselling should be done.
	Age <6 years and body weight <20 kg	Please refer to PCoE/paediatric experts.
NVP and EFV	Age >6 years and body weight >20 kg	DTG
	Age <6 years and body weight <20 kg	LPV/r
EFV/NVP and LPV/r	Age >6 years and body weight >20 kg	DTG
	Age is <6 years and body weight <20 kg	Please refer to PCoE/paediatric experts.

Transition to more optimal regimen

With increasing evidence of high rates of NNRTI resistance, it has become critical to ensure that children be initiated on or transitioned to optimal new ARV drugs that are more potent to rapidly achieve and maintain viral suppression, which will prolong the duration of first-line or second- line treatment and support adherence through easier administration. DTG-based regimens are more robust, prevent long-term toxicities, have less pill burden, are less costly and have better viral suppression rates (as compared to Efavirenz-based regimens). The long-term, especially metabolic, consequences of use of LPV/r are debilitating. Therefore, transitioning to DTG-based regimens if the children were stable and doing well on LPV/r-based regimens is advised. This transition will also make the paediatric regimen simpler and harmonize with adult ART regimens. Before transitioning to DTG-based regimens, viral load testing (within 6 months) should be done. Any child above 6 years of age and body weight of more than 20 kg

whose Plasma viral load values are <1000 copies/ml (virologically suppressed) is eligible for transition to DTG-based regimens.

Table 3.4.10: Transition plan for virologically suppressed children

Current Regimen	Weight	Optimal Regimes for Transitioning	Considerations
ZLN / ZLE / ALN	<20 kg	AL+ LPV/r	Transition to DTG when weight becomes ≥20 kg
	>20–30 kg	AL+ DTG	Transition to TL+ DTG when they reach >30 kg (in virologically suppressed children)
	>30 kg	TL+ DTG	Continue same regimen
ALE	<20 kg	No change until they reach ≥20 kg, unless there is treatment failure	Transition to DTG-based regimens once they reach >20 kg weight
	>20–30 kg	AL+ D	Transition to TL+ DTG when they reach >30 kg (in virologically suppressed children)
	>30 kg	TL+ D	Continue same regimen
AL + LPV/r ZL + LPV/r	<20 kg	No change until they reach >20 kg unless there is treatment failure	Transition from ZL+ LPV/r can also be considered to reduce the pill burden and preserve the antiretroviral advantage of NRTI sequencing.
	>20–30 kg	AL+ DTG	If virologically suppressed, children can be transitioned to TL+ DTG when they reach >30 kg.
	>30 kg	TL+ DTG	Continue same regimen.

Please refer **Annexure 2** for drug dosing details.

Post ART initiation care is an important step in the management of CLHIV and for the success of ART. This care ensures safety of the CLHIV while on ART, optimizes the benefits of ART and monitors the treatment response and adverse events. It also helps in maximizing adherence with continued support. Early identification of ART adverse effects, OIs and treatment failure help in prompt initiation of appropriate measures leading to prevention of morbidity and mortality in CLHIV.

3.5 Treatment Failure and Switch to Second-line ART in Children with HIV

Introduction

ART has reduced morbidity and mortality in CLHIV and thus improved the quality of life and survival. One of the important goals of ART is continued virological suppression while adverse events are minimal. The key for achieving this goal is optimal adherence to the ART regimen and to have a sustained response to the first-line ART regimen as long as possible. Continued monitoring and supporting adherence to the CLHIV and family are required. The challenges for sustaining long-term virological suppression in children are unusually high baseline viral load, intrauterine and perinatal exposure to ARVs, immature/developing immune system, dependency on caregiver for adherence support, dynamic dosing

with weight and non-availability of child- friendly formulations. However, CLHIV on long duration of ART despite optimal adherence may also develop treatment failure. In such children, accumulation of drug resistant mutations resulting from unusually high replication rate, error-prone reverse transcriptase and naturally due to selective pressure from drugs or from the immune system leads to treatment failure.

In some cases, treatment failure develops within a few months or years of ART initiation. Suboptimal adherence, under-dosing, drug interaction, inappropriate choice of ART regimens and pre-treatment/primary drug resistance are important among the many reasons for early treatment failure. Early recognition of treatment failure and prompt switch to appropriate second- line ART can prevent morbidity and mortality. The pharmacological options for second-line ART in children are limited by the non-availability of paediatric formulation of many ARVs as well as perinatal exposure to the ARVs. Hence, it is appropriate for the healthcare professionals associated with the care of the CLHIV to support and promote the factors that facilitate and sustain the response to the first-line ART regimen as long as possible.

Treatment Response

Virological response to ART

The plasma viral load done 6 months after initiation of ART should be less than 1000 copies/ml. However, in HIV-infected infants and young children with high baseline plasma viral load, it may take longer than 6 months to achieve complete viral suppression. In such cases, other factors like clinical, nutritional and immunological parameters should be considered before taking a decision on treatment failure.

Immunological response to ART

CD4 counts of patients should increase after initiation of ART. In general, the quantum of this increase is usually 50–100 cells/mm3 within 6–12 months of initiation of ART in older children (age above 5 years). But this increase may be higher in younger children (less than 5 years of age) as there is physiological high lymphocyte count in this age group.

Clinical response to ART

After ART initiation, most children become asymptomatic and start gaining weight between 12 and 24 weeks. This response is hastened by the effective treatment of concurrent OIs. Clinical monitoring should be done at every visit to the ART centre. Clinical monitoring should include anthropometric evaluation, general well-being, neurocognitive developmental assessment, adverse reaction to drugs and drug interaction and features of Immune Reconstitution Inflammatory Syndrome. Each visit should be taken as an opportunity to evaluate adherence through pill count to reinforce treatment adherence and to provide nutritional counselling. Further, 4S screening for TB on each and every visit and provision of psychosocial support, as required, must be taken care of. For older children and adolescents, disclosure status of HIV infection should be checked, and caregivers should be encouraged to disclose the infection status to these children. Please refer **Chapter 3.4 (Care of CLHIV: Post ART Initiation)** for complete discussion on monitoring and follow-up.

With the availability of viral load monitoring in the programme, it is imperative to identify treatment failure before the appearance of clinical and immunological failure. This early identification of treatment failure and prompt switch to second-line ART will prevent further emergence and accumulation of drug resistant mutants. This is especially important in children as pharmacological options are limited and they have a long lifetime ahead of them requiring ART. The following clinical and immunological features of suspected treatment failure among CLHIV who are on first-line ART for at least 6 months should be

watched for:

- New OIs /recurrence/clinical events after 6 months on ART (after ruling out IRIS)
- Failure to thrive or weight loss
- Developmental regression/delay
- Progressive decline in CD4 counts or increment lesser than severe immunosuppression level over 6–12 months. In cases of suboptimal rise in CD4 count at 6 months, despite good adherence and absence of clinical symptoms, one may repeat CD4 count at 3 months. (Immunological response is defined as an increase of at least 50 CD4 cells/mm3 at 6 months of ART.)

Treatment failure refers to the loss of antiviral efficacy and triggers the SWITCH of the entire first-line regimen to the second line or beyond. It can be suspected by immunological and/or clinical indicators but needs the confirmation of unsuppressed viral load.

Second-line ART is the next regimen used in sequence immediately after the failure of the first- line therapy. Before identifying treatment failure, certain factors like duration of ART, new OI or IRIS and treatment adherence need to be considered.

The appropriate timing of switching of ART regimen is critical. Early switching leads to loss of precious period of any potential survival benefit from an effective first-line therapy, whereas late switching can compromise the effectiveness of second-line therapy and increases morbidity and mortality.

Identifying Treatment Failure

The virological criteria, immunological criteria and/or T-staging–based clinical criteria while on treatment should be considered for identification of treatment failure. A switch to a second-line regimen is recommended only after consulting SACEP at Paediatric Centres of Excellence (PCoE), Centres of Excellence (CoE) or ART Plus centres. The following factors need to be considered before failure of existing treatment regimen is concluded:

- The child should have received the regimen for at least 6 months.
- Adherence to therapy should be assessed and should be optimal (>95%).
- Any active opportunistic infections should have been treated and resolved before interpreting CD4 counts.
- Immune Reconstitution Inflammatory Syndrome must be excluded.
- Primary malnutrition that can mimic clinical treatment failure should be ruled out.
- Adverse effects of drugs manifesting like clinical treatment failure should be ruled out.
- All suspected clinical and immunological treatment failure should be confirmed by virological criteria for treatment failure.

Table 3.5.1: Definitions of treatment failure in children

Type of failure	Defining factors
Virological failure	**Two consecutive HIV-1 plasma viral load values of ≥1000 copies/ml with the following criteria:** • After 6 months of ART initiation and • After giving three sessions of step-up adherence counselling and • Adherence in each of last 3 months was >95%
Immunological failure*	**Children between 12 and 35 months:** • CD4 percentage falls below 15% • Persistent CD4 levels below 200 cells/mm^3 after 12 months of ART **Children between 36 and 59 months:** • CD4 percentage falls below 10% • Persistent CD4 levels below 200 cells/mm^3 • **Children aged 5 years and above: At least one of the following three criteria:** • Fall of CD4 count to pre-therapy level • 50% fall from peak 'on treatment' level • Persistent CD4 levels below 100 cells/mm^3 after 12 months of ART
Clinical failure#	• New or recurrent WHO stage 4 condition, after at least 6 months of ART • Progressive neurodevelopmental deterioration • Growth failure

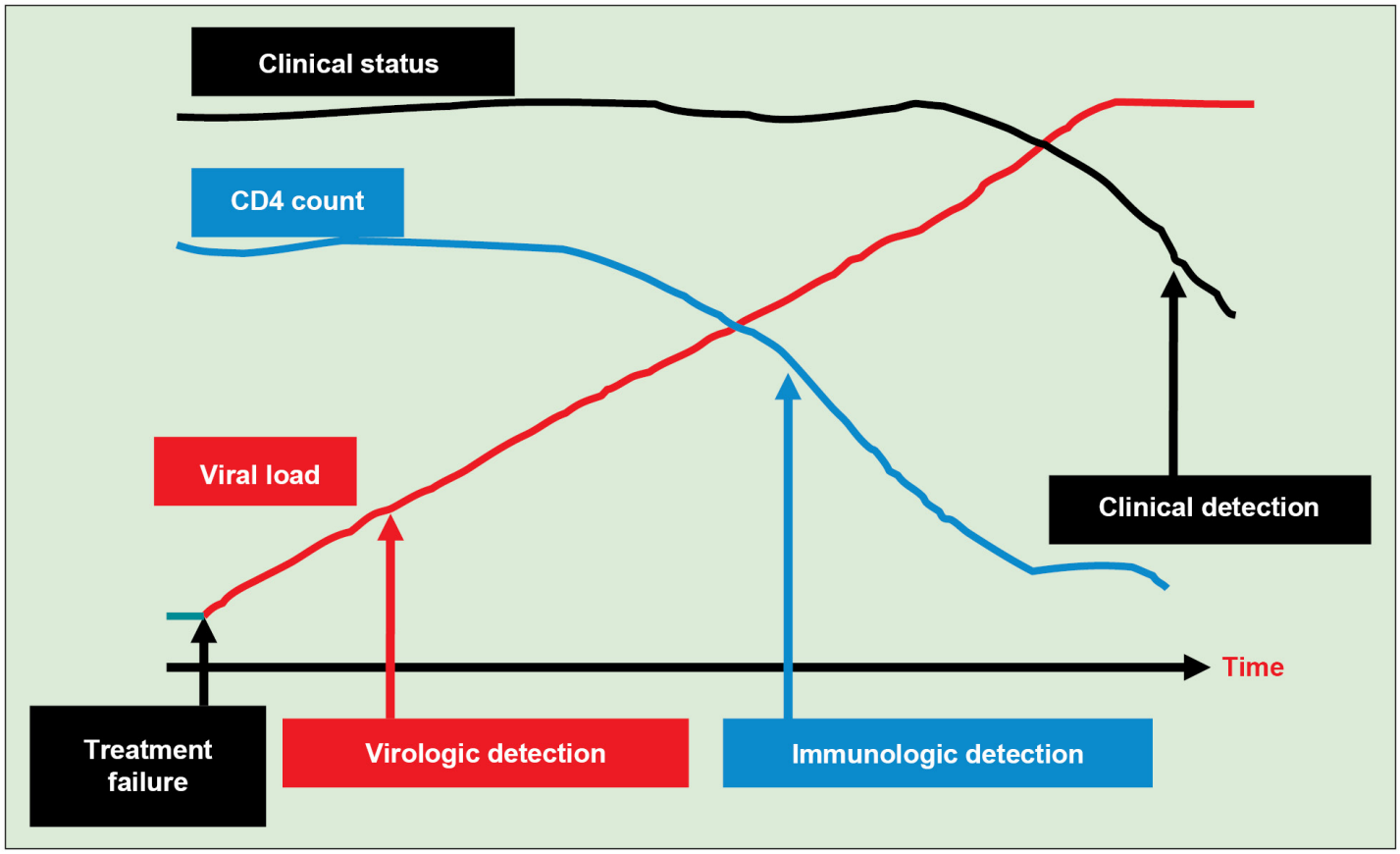
*Concomitant or recent infection may cause a transient decline in the CD4 cell count.

#The condition must be differentiated from IRIS. Some WHO stage 3/4 conditions (lymph node TB, uncomplicated TB pleural disease, oesophageal candidiasis, recurrent bacterial pneumonia) may not indicate treatment failure.

Virological treatment failure

Virological treatment failure is defined by Plasma Viral Load value ≥1,000 copies/ml in any child on treatment for 6 months or more. This indicates incomplete suppression of the virus. Viral rebound after being undetectable is also considered virological failure. A low-level viral rebound termed 'blip' usually indicates a statistical variation in the determination of Plasma viral load and not the need to alter therapy. Plasma viral load remains the most sensitive indicator of ART failure. In the sequence of treatment failure, virological failure is the earliest and precedes immunological and clinical failures. Hence, by routine virological monitoring, it is possible to identify treatment failure much before the decline of CD4 counts and further before the occurrence of AIDS-defining clinical features, as shown in Fig 3.5.1.

Figure 3.5.1: Chronology of treatment failure



Confirming failure early facilitates the decision to switch drugs much before multiple resistance mutations to drugs of the first-line regimen are accumulated.

Immunological treatment failure

The CD4 cell count is the strongest predictor of HIV-related complications, even after the initiation of therapy. However, with the availability of routine viral load testing in the programme, treatment failure can be recognized even before the fall in the CD4 counts. In the context of any new clinical events occurring after 6 months of ART initiation, immunological criteria assist in differentiating clinical treatment failure from other overlapping conditions like IRIS, OIs and drug toxicities. The baseline pre-treatment value is informative; lower baseline CD4 counts are associated with smaller and slower improvements in the count over time.

Poor immunologic response despite virologic suppression is uncommon in children. Immune recovery may take longer than 1 year to achieve in children with baseline severe immunosuppression (i.e., a CD4 T lymphocyte [CD4] cell count <500 cells/mm^3), despite prompt virologic suppression. During this early treatment period of persistent immunosuppression, additional clinical disease progression can occur. The most common cause for such cases of poor immunologic response despite virologic suppression is laboratory error in CD4 values or viral load measurements. As CD4 values decline physiologically in the first 5 to 6 years of life, they need to be interpreted correctly in young children. The routine viral load assays used in the programme may not amplify HIV-2, resulting in falsely low or negative viral load results. After ruling out laboratory errors, evaluate CLHIV for adverse events, medical conditions and other factors that can cause CD4 values to decrease. Several drugs (e.g., corticosteroids, chemotherapeutic agents) and conditions (e.g., Hepatitis C virus [HCV], tuberculosis, malnutrition, Sjogren's syndrome, sarcoidosis, syphilis, cirrhosis, acute viral infections) are independently associated with low CD4 values. In some children, a drop in or low CD4 count is also seen in drug-induced bone marrow suppression. Children who have very low baseline CD4 values before initiating ART are at higher risk of an impaired CD4 response to ART. These children, despite virologic suppression, may be at higher risk of death and AIDS-defining illnesses, which needs to be prevented. However, it is not recommended to modify an ART regimen based on lack of immunologic response if virologic suppression is complete.

Clinical Treatment Failure

Treatment failure should be considered if the child has been on therapy for at least 6 months. Before diagnosing clinical treatment failure, suboptimal adherence, inter-current OIs and IRIS should be excluded. The development of new or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical conditions except for TB) after 6 months of effective treatment is considered functional evidence of the progression of HIV disease.

Children with poor clinical response despite adequate virologic and immunologic responses should be carefully evaluated as all such cases may not represent ART failure. The clinical deterioration seen after initiation of ART may be due to paradoxical worsening of a known OI, or unmasking of a previously undiagnosed OI because of profound immune response (IRIS) related to successful viral suppression. IRIS does not represent ART treatment failure and does not generally require ART discontinuation or a change in ART. An apparent lack of clinical improvement is also seen in children who have suffered irreversible damage to their lungs (bronchiectasis, chronic lung diseases), brain (HIV encephalopathy) or other organs especially during prolonged and profound pre-treatment immunosuppression. These children may continue to have recurrent infections or symptoms, as ART and consequent immunologic recovery may not reverse the damage caused to their organs. Again, such cases do not represent ART failure, and these children would not benefit from a change in ARV regimen. Before clinical treatment failure is confirmed, a child should also be evaluated to rule out (and, when indicated, treat) other causes or conditions that can occur with or without HIV-related immunosuppression, such as pulmonary TB, malnutrition and malignancy. TB can occur at any CD4 level and does not necessarily indicate ART failure. The response to TB therapy should be used to evaluate the need to switch ARV drugs. In the case of pulmonary TB and some types of extra-pulmonary TB (e.g., simple lymph node TB), the response to TB therapy is often good and the decision to switch ARV drugs can be postponed and monitoring can be stepped up. The clinical criteria as per T-staging while on treatment should be considered for a switch to the second-line regimen only after confirming with viral load validation and SACEP (PCoE/CoE/ ART Plus centre) approval.

Standard Operating Procedures for Determining Failure

Before diagnosing ‘treatment failure’ and switching the ART regimen, the following factors need to be considered:

Adherence: Optimal adherence to ART is the single most important factor determining the success of ART. As poor adherence is responsible for treatment failure in majority of cases, a detailed assessment of adherence should be done. The factors influencing poor adherence and barriers for optimal adherence should be explored and addressed before switching to second-line ART. Unless these factors and other barriers are addressed, a patient will find it difficult to adhere to the second-line regimen also. In clinically stable children, a step-up treatment adherence counselling should be done, and adherence should be closely monitored and supported for 3 months before a repeat plasma viral load testing is done.

Step-Up Adherence Counselling in CLHIV

General guidance

- A minimum of three sessions are recommended for step-up adherence counselling (additional sessions may be needed to ensure that treatment adherence is >95% for three consecutive months).
- All counselling sessions are to be taken preferably by the same counsellor.
- Effort to be made to build a rapport with the caregiver and the child
- Both caregiver and the child should be counselled together and individually, in all the sessions.

- These sessions are to be conducted during the child's visit to ART Centre along with the caregiver.
- Counsellor needs to review all the barriers that led to poor adherence and provide customized counselling.
- A customized adherence plan should be developed with involvement of both the caregiver and the child.
- Ensure weight documentation in white card and green book on each visit and check if the correct dose is given as per the weight band.
- CSC to be involved for counselling and supporting the caregiver and the child to help them achieve required adherence.
- Group counselling should be taken up for tailoring support for children in different age groups at ART Centre and CSC.
- To allay fear of side effects of ARV (which is the most common cause of poor adherence), assurance should be given to the caregiver and the child that they will be taken care of at the ART centre if reported in time.
- Assessment of mental health of the caregiver and the child and timely referral for appropriate management (for depression, anxiety, aggressive nature)
- **Assessment of five 'As' of treatment adherence in all sessions:**

1. **Assess:** The problem/effects on individual and family/probable consequences
2. **Assist:** In addressing the barrier/planning what, when and how to do
3. **Advice:** Importance of adherence/how to continue treatment in difficult situations
4. **Arrange:** Necessary referrals (medical, psychological)/admission in ward/ follow-up sessions
5. **Agree:** Treatment adherence plan/plan to address the barrier

Table 3.5.2: General counselling messages in step-up adherence counselling

CLHIV	Caregiver
• Child-centric counselling is recommended: • Building rapport with CLHIV is very important. • Involve child in all decisions along with the caregiver. • Probe for palatability issues related to ARV: if any, suggest solutions. • Check the pill swallowing capacity of the child. • The child should be counselled for taking all the pills prescribed with emphasis on benefits of ART ("You will be strong/active/playful/with good growth.") This may be important and challenging in younger children due to high pill burden. • Ensure that the ART timing does not clash with child's school and other extracurricular activities. • Suggest reminders, if not used. • Encourage proper nutrition and increased activity. • Probe for any barriers to adherence.	• Ensure that the caregiver has adequate finances to travel to ART centre along with the child for his/her HIV care and treatment. If required, try to link to existing welfare schemes/NGOs for financial support. • Issues of long-distance travel can be addressed by linking them to the nearest facility for HIV care and ART pill pick-up. • Caregiver should be counselled for age-appropriate disclosure of status to the child, if not already done. Counsellor or the medical officer to support in the process if required by the caregiver. • Counsellors to ensure that ART is given under direct observation of a responsible caregiver. • Enquire about the frequency, number of pills and timings of ART. • Ensure that the ART timing does not clash with caregiver's work timings and timing of child's school and other activities. • Suggest reminders for pill intake, if not using any. • Ensure that the weight is documented on white card and green book on each visit and the dose is given as per the weight band. • Proper nutritional counselling to caregivers is essential for maintenance of a good nutritional status and nutritional rehabilitation of CLHIV. Caregivers should be counselled about need for additional food, dietary modifications to meet the increased needs of child and correct nutrition practices. They should be informed about the relation between proper nutrition and improved tolerance to ARVs, which results in improvement of adherence. If needed, they may be linked to organizations/NGOs for nutritional support. • In case of double orphans, ensure that the extended family provides basic care and psychosocial support to the child. If not, option of institutional placements through child welfare committee referrals/NGOs should be given to caregivers in the best interest of the child.

Session 1: Just after receiving the viral load test results (Plasma viral load ≥1000 copies/ml)

- Check the child's treatment adherence to have a baseline adherence.
- Involve CSC to counsel and support the caregiver and the child in achieving required adherence.
- General counselling along with customized counselling to be done based on the identified issues

Table 3.5.3: Counselling messages in first session of step-up adherence counselling

CLHIV	Caregiver
• Try to build a rapport with CLHIV. • Explain the benefits of ART in age-appropriate words. • Assess the barriers leading to poor adherence. • Motivate to take medicines in the prescribed dose with full adherence and suggest reminders. • Ensure documentation of weight at each visit in white card and green book. • Ensure that the child is receiving appropriate ART dose as per the weight band • Assess for OI or any co-infection and refer for appropriate management. • Assess mental health of CLHIV and refer for appropriate management. • Review for any adverse effects of drugs. • Assess nutrition status and provide nutritional counselling.	• Review caregiver's understanding of adherence, pill intake and viral load suppression. • Assess 5 As of treatment adherence. Assess possible barriers to adherence and suggest solutions. • Check ARV medicines given to the CLHIV: What, when, how and who. • Inquire about pill intake frequency, timing and regularity. • Check if reminders are being used: if not, then suggest one. • Discuss risk of treatment failure due to non-adherence. • Motivate for age-appropriate disclosure of status to child, if already not done. • Assess mental health of the caregiver and refer for appropriate management. • Develop an adherence plan with involvement of the child to address the identified issues.

Session 2: One month after previous session

(For a close follow-up: If the caregiver cannot visit the ARTC along with the CLHIV after 15 days of first session, a telephonic communication may be made at 15 days of first session to check and remind the CLHIV/caregiver for adherence.)

- Review child's adherence between the first and second sessions.
- General counselling and reassessment for any new barriers. Check if the previous barriers are addressed and solved.
- Involve CSC to counsel and support the caregiver and the child in achieving required adherence.

Table 3.5.4: Counselling messages in second session of step-up adherence counselling

CLHIV	Caregiver
• Praise and reward the child if adherence >95%. • Encourage to continue the good effort. • Reassess the child's understanding of importance and benefits of ART (according to age). • Remotivate to take medicines regularly, in full dose, and use reminders. • Reassess mental health of CLHIV and refer for appropriate management. • Assess for any new barriers and modify the adherence plan accordingly in discussion with the caregiver and the child.	• Discuss any new barriers in adherence. Discuss risk of treatment failure due to non-adherence. • Remotivate for age-appropriate disclosure of status to child, if not already done. • Re-emphasize the importance of directly observing taking of ART by the child and reminders. • Modify the adherence plan with involvement of both caregiver and the child to tackle newly identified issues. • Re-assess mental health of the caregiver and refer for appropriate management. • If adherence improved >95%, appreciate the efforts made.

Session 3: Usually one month after the second session

Review the child's adherence between the second and third sessions.

- If adherence is >95% in last three consecutive months:

  Plan a repeat Plasma viral load test;
  Explain to the caregiver to keep Plasma viral load appointment and return for viral load report;
  Praise the caregiver and the CLHIV and motivate to maintain adherence.
- If adherence is not adequate:

  Plan further sessions with caregiver and child;
  Involve CSC to counsel and support the caregiver and the child in achieving the required adherence;

Table 3.5.5: Counselling messages in third session of step-up adherence counselling

CLHIV	Caregiver
If adherence improved to >95% • Praise and reward the child if adherence >95%. • Encourage to continue the good effort. • Remotivate to take medicines regularly and use reminders. • Re-emphasize the benefits of adherence on ART. **If adherence not improved to >95%:** • Reassess the child's understanding of importance and benefits of ART (according to age). • Remotivate to take medicines regularly, in full dose, and use reminders. • Rule out opportunistic infections or co-infections and provide appropriate treatment. • Re-assess mental health of CLHIV and refer for appropriate management. • Assess for barriers (pre-existing and new) and modify adherence plan accordingly in discussion with the caregiver and the child.	**If adherence improved to >95%:** • Appreciate and encourage to continue the good efforts. • Re-emphasize the direct supervision of pill intake by CLHIV. • Re-emphasize the significance of adherence and its close relation with treatment success. **If adherence not improved to >95%:** • Discuss risk of treatment failure due to non-adherence. • Look for barriers (pre-existing and new) to adherence. • Reassess 5 As of treatment adherence. • Along with general counselling, do a customized counselling to address the identified barriers. • Modify adherence plan with involvement of both the caregiver and the CLHIV to tackle the identified issues. • Motivate for age-appropriate disclosure of status to child, if not already done.

Counselling Session after Repeat Viral Load Test

(Repeat Plasma viral load test is done when after the step-up counselling, the adherence is >95% for last three consecutive months.)

Discuss the results of the repeat Plasma viral load test with the caregiver and CLHIV.

If Plasma viral load result is <1000 copies/ml

- Appreciate both the caregiver and CLHIV for maintaining adherence.
- Advise to continue the same regimen.
- Re-emphasize adherence, importance of directly observing pill intake, proper nutrition, psychosocial support to the child and caregiver and achieving viral load suppression.
- Involve CSC to counsel and support the caregiver and the child in maintaining good adherence.
- Repeat Plasma viral load test as per guidelines.

If Plasma viral load result is ≥1000 copies/ml

- Counsel the caregiver/CLHIV to prepare them for SACEP referral, and for a possible change in ART regimen if recommended by SACEP.
- If the caregiver is unable to take the child physically to visit SACEP, explain the process of e-SACEP referral and arrange for one.
- Re-emphasize adherence and educate the caregiver and child on importance of directly observing pill intake, proper nutrition, psychosocial support to the child and caregiver, adherence and achieving viral load suppression.
- Ensure documentation of weight and check the ARVs prescribed and their dose as per the weight band.

- Involve CSC to counsel and support the caregiver and the child in treatment adherence.
- Repeat Plasma viral load test as per guidelines.

Drug–drug interactions

Assessing whether the patient is concomitantly taking medications that interfere with ARV activity is important. For example, many patients may not reveal that they take herbal treatments along with the prescribed ART regimen. These drugs reduce the efficacy of ART due to increased metabolism of ARVs. Some of these drugs can have overlapping toxicities, which may lead to poor adherence. Some of the **drug toxicities** like bone marrow suppression due to AZT may mimic treatment failure. This needs to be differentiated before switch to second-line ART.

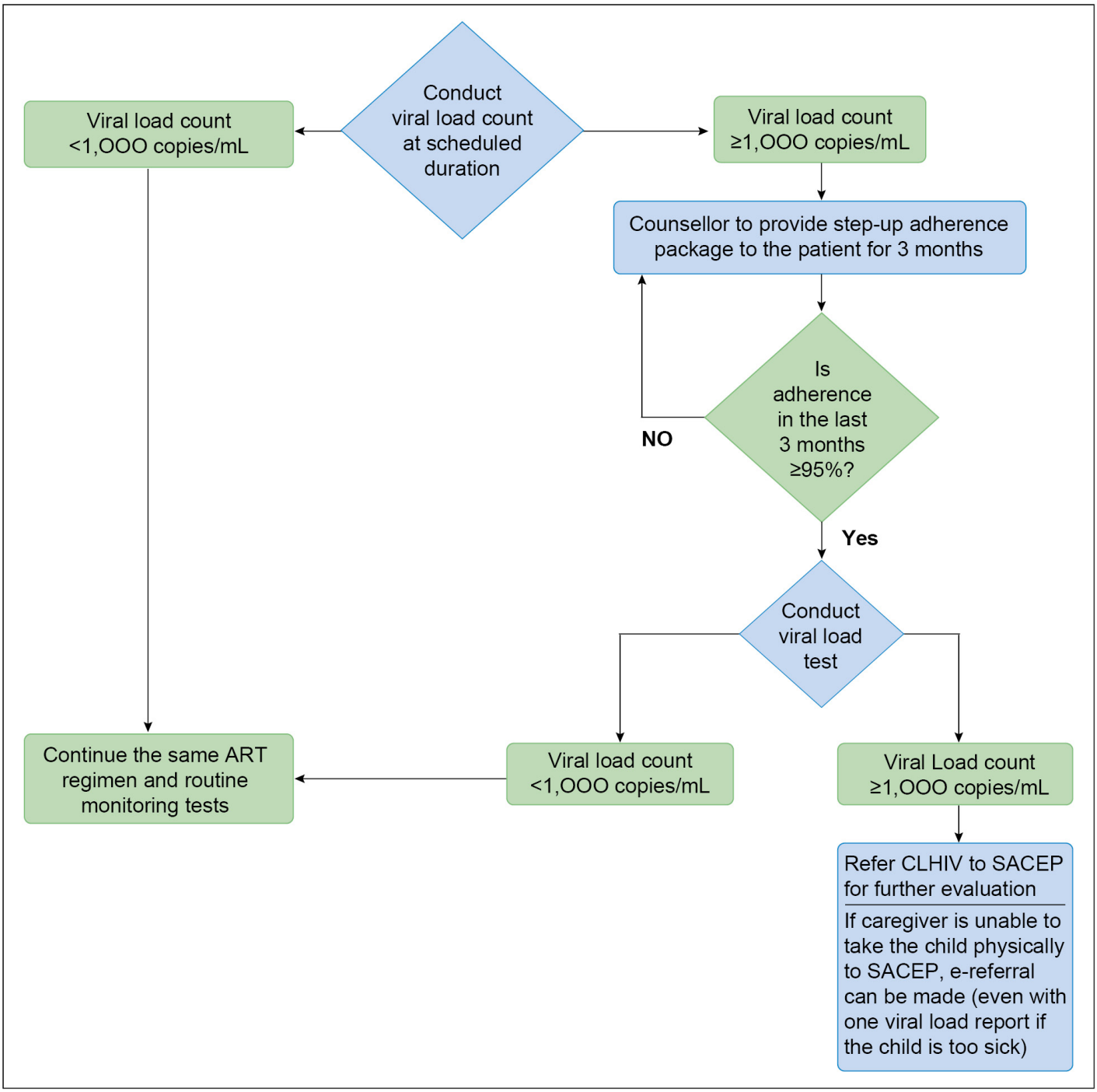
Certain **Opportunistic infections** may lead to decline of the CD4 count, which may revert after treating those infections. **Immune Reconstitution Inflammatory Syndrome** needs to be identified and managed appropriately before diagnosing treatment failure.

In children, **severe acute malnutrition** may sometime mimic treatment failure due to similarities in the clinical features. Hence, it is advised to adequately treat nutritional deficiency and initiate nutritional rehabilitation before diagnosing treatment failure.

Importance of routine viral load monitoring

The sequence of treatment failure starts with virological failure followed by immunological and clinical failure (Fig. 3.5.1). The time lag between virological and immunological failure is around 6 months, and a few months later clinical failure may set in. Hence, compared to clinical or immunological monitoring, viral load provides an early and more accurate indication of treatment failure. This early identification of treatment failure and subsequent switch from first- line to second-line drugs reduces the accumulation of drug resistance mutants and improves clinical outcomes. Measuring viral load can also help to distinguish between treatment failure and non-adherence (Figure 3.5.2). Studies suggest that around 70% of patients on first-line ART who have a high viral load will be suppressed following interventions to improve adherence.

Figure 3.5.2: Viral load testing algorithm



Formulating Second-line Regimen in Children

Definitions

First-line and Second-line ART Regimen

The working definitions of first-line and second-line ART regimens are as follows:

First line ART: First-line ART is the initial regimen prescribed for ART-naive children as soon as HIV infection is diagnosed. Before initiating first-line ART, stabilize any concurrent illness and ensure adequate preparedness.

Second line ART: Second-line ART is the subsequent regimen used in sequence immediately after first-line therapy has failed.

SWITCH: Treatment failure refers to the loss of antiviral efficacy to the current regimen. It triggers the SWITCH of the entire regimen from the first to the second line. It can be identified by clinical and/or immunological criteria and confirmed by virological criteria.

Broad Principles and Objectives

All patients initiated on first-line ART need to be monitored carefully at every visit as per the standard protocol on clinical and laboratory monitoring indicators. During routine viral load monitoring, as soon as a child's viral load suggests virological failure (Plasma viral load ≥1000 copies/ml), a detailed evaluation should be done to identify OIs and adherence. A step-up treatment adherence counselling for 3 months is done, and viral load testing is repeated after 3 months. It is important to identify treatment failure before clinical and immunological failure set in. It is important to follow the protocol for all patients with 'suspected treatment failure' and make appropriate timely referrals to SACEP for evaluation of such patients. Once the decision has been made to start second-line ART, the decision will be communicated to the referring centre where the ART SMO/MO will initiate second-line treatment as per the guidelines given by CoE/ pCoE/ART Plus centre.

The objective of second-line ART earlier was to prolong the survival of CLHIV rather than complete viral suppression as no further regimens were available. Now, with the availability of third-line ART, the objective is complete suppression of viral replication just as in the first-line ART; this requires regular monitoring with plasma viral load every 6 months.

What to Switch?

When failure has been confirmed, virologically, many patients can be expected to have significant NRTI resistance at the time of switching. Thus, in the decision-making for a second-line regimen with maximal antiviral activity, one must consider nucleoside class cross-resistance and drug interactions. Some points to note :

- Cross-resistance exists between AZT and d4T.
- High-level AZT/3TC resistance reduces susceptibility to ABC.
- TDF can be compromised by multiple nucleoside analogue mutations (NAMs) but TDF often retains activity against the nucleoside-resistant viral strains.
- TDF/ABC may facilitate evolution of the K65R drug resistance mutation, which mediates resistance to non-AZT NRTIs.
- NNRTI (such as EFV and NVP) together: usually there is complete cross-resistance.
- NNRTI exposure (single drug) to children through infant ARV prophylaxis can result in archived NNRTI-resistant mutations.

Once it is decided to switch the regimen, the four steps outlined in Table 3.5.6 need to be followed for decision making.

Table 3.5.6: Steps to be followed for review by SACEP for suspected treatment failure

STEP 1	Define treatment failure	Define treatment failure by virological testing; see if adherence to treatment is adequate: counsel and support. (SACEP will see these and take decision on providing second-line ART) (Table 3.5.7)
STEP 2	Decide on NRTI component of the second-line regimen.	Select NRTI backbone as per Table 3.5.7.
STEP 3	Decide on the third component of the second-line regimen	Select the third drug as per Table 3.5.7.
STEP 4	Patient education and agreement on treatment plan including follow-up and monitoring	Including counselling for adherence, linkages to specialist care and follow-up monitoring plan

The current recommendation for second-line ART in children is based on previous exposure to ARV, age and body weight of the CLHIV. A new class of ARV, unused in the first-line ART, either a Dolutegravir or ritonavir-boosted PI (Lopinavir/ritonavir) or NNRTI (Efavirenz), supported by at least one new and unused NRTI (Abacavir or Zidovudine or Tenofovir) should be used. Lamivudine administration should be continued to ensure reduced viral fitness.

For children who failed on the first-line AZT-containing regimen, the recommended second- line regimen is ABC/TDF-based regimen. TDF as the second-line option is recommended for children aged >10 years with body weight >30 kg who were on AZT-based first-line ART. For those on ABC/TDF-based first-line regimen, the second line will be an AZT-based regimen if Hb is >9 g/dl.

For children older than 6 years and weight more than 20 kg body weight on LPV/r- or EFV- based first-line regimen, Dolutegravir can be used as the third drug in second-line regimen.

For children less than 6 years of age and less than 20 kg body weight receiving EFV-based first- line regimen, LPV/r can be used as the third drug in the second-line regimen. These children can be transitioned to a DTG-based regimen when they reach 6 years of age and 20 kg body weight. However, in children less than 6 years of age and less than 20 kg body weight receiving LPV/r-based first-line regimen experiencing virologic failure, there are often limited resistance mutations detected, indicating that poor adherence/tolerance of the regimen may be the cause of poor viral control. In such cases, an improved adherence may help in viral suppression. Despite good adherence if virologic failure is seen, EFV can be used for children between 3 and 6 years of age and body weight between 10 and 20 kg.

There are limited options of second-line drugs for children aged less than 3 years receiving LPV/r-based regimen with first-line treatment failure. These children should be continued on the existing regimen with careful monitoring, except in the case of advanced clinical disease progression or lack of adherence specifically due to poor palatability of LPV/r. In such cases, switching to a second-line NVP-based regimen should be considered. However, concerns remain about the effectiveness of this approach, given the potential for re-emergence of archived resistance because of NNRTI exposure during breastfeeding and post-natal ARV prophylaxis. Such children need to be referred to pCoE for further management.

For the children who have ABC-based first-line regimen and AZT is contraindicated due to anaemia (Hb<9 g/dl), there are limited options for the formulation of the second-line regimen. In such children less than 6 years of age and weight less than 20 kg, it is advised to continue the existing regimen and anaemia should be corrected. After correction of anaemia, these children can be switched to an AZT-based regimen. If anaemia is not corrected, then refer the patient to pCoE for further evaluation and decision. Children more than 6 years of age and weight more than 20 kg can be switched to DTG and LPV/r-based regimen. To give the advantage of the Lamivudine in such children, it is advised to continue recycled non–AZT-based NRTI backbone.

Table 3.5.7: Second-line ART regimens in children

Regimen	Age Less than 6 years and Weight Less than 20 kg	Age between 6 and 10 years and Weight between 20 and 30 kg	Age ≥10 years and Weight ≥30 kg
ZL + LPV/r	No change in regimen If child has advanced disease stage, then after consultation with pCoE/CoE or paediatric experts, shift to **ALN/ALE**	**ALD**	**TLD**
AL+ LPV/r	No change in regimen If child has advanced disease stage, then after consultation with pCoE/CoE or paediatric experts, shift to **ZLN/ZLE.** If Hb <9 g/dl Continue AL+ LPV/r till Hb is built up and then shift to ZLN/ZLE. If anaemia is persisting or develops after AZT-based regimen switch, refer the child to pCoE/CoE for paediatric expert consultation.	ZLD, if **Hb ≥9 g/dl** If **Hb <9 g/dl**, continue same regimen till anaemia is corrected. Then change to ZLD. If anaemia is persisting or develops after AZT-based regimen switch, refer the child to pCoE/CoE for paediatric expert consultation.	
ZLE	**AL + LPV/r** (till paediatric DTG formulations are available in the programme). Whenever child crosses 6 years of age and weighs >20 kg, then the child can be transitioned to DTG-based regimen.	**ALD**	**TLD**
ALE	**ZL + LPV/r,** if Hb ≥9 g/dl (till paediatric DTG formulations are available in the programme). If Hb <9 g/dl, continue same regimen till anaemia is corrected. Then change to ZL **+ LPV/r.** If anaemia is persisting, refer the child to pCoE / CoE for paediatric expert consultation. Whenever the child crosses 6 years of age and weighs >20 kg, the child can be transitioned to DTG-based regimen.	**ZLD,** if **Hb ≥9 g/dl** **DTG + LPV/r + recycled non–AZT-based NRTI backbone*** if Hb <9 g/dl. This effectively moves the child into third-line ART regimen. Hence adherence should be carefully monitored and supported.	
ALD		**ZL+ LPV/r**	
TLD		**ZL+ LPV/r**	

*Continue NRTI backbone to give the advantage of Lamivudine, unless contraindicated.
Please refer **Annexure 2** for drug dosing details.

ART Options for Multi-NRTI-exposed Patients

The options for children exposed to multiple NRTIs are limited. Hence it is important to assess the child in detail whenever a single drug substitution is contemplated due to drug toxicities. The formulation of second-line regimen in such children depends on the previous exposed ARVs, current failing regimen, age,

body weight and importantly availability of paediatric formulations in the programme. Another challenge in such children is the non-availability of drug resistance testing in the programme. Hence it is advised to consult paediatric experts in such complex situations where modified adult formulations may be used. Table 3.5.8 shows various options for such children.

Table 3.5.8: Second-line ART options for children exposed to multiple NRTIs

Multi NRTI exposed children					
Current Failing Regimen	**Previous Exposed Drug**	**Age ≤3 Years and Weight ≤10 kg**	**Age between 3 and 6 Years and Weight between 10 and 20 kg**	**Age between 6 and 10 Years and Weight between 20 and 30 kg**	**Age ≥10 Years and Weight ≥30 kg**
TDF/ABC-based regimen and third drug is PI	**AZT/d4T** (CD4 count was not suggestive of immunological failure at the time of substitution from AZT to TDF)	No change in regimen is recommended, unless in the case of advanced clinical disease progression. In this case, switching to a second-line NVP-based regimen with AZT re-challenge under close haematological monitoring of CLHIV should be considered after consultation with pCoE/CoE or paediatric experts. **ZLN** if Hb ≥9 g/dl. If Hb <9 g/dl, continue same regimen till anaemia is corrected. Then change to **ZLN.** If anaemia persists or appears after rechallenge of AZT, refer the child to pCoE/CoE for paediatric expert consultation.	**ZLE** if Hb ≥9 g/dl (till paediatric DTG formulations are available in the programme). Whenever child crosses 6 years of age and weighs >20 kg, then child can be transitioned to DTG-based regimen. If Hb <9 g/dl, no change in the regimen till anaemia is corrected. Then change to ZLE. If anaemia persists or develops after AZT-based regimen switch, refer the child to pCoE/CoE for paediatric expert consultation.	Re-challenge AZT if current HB is > or = ≥9 g/dl **AZT + 3TC + DTG.** If Hb <9 g/dl, no change in regimen till anaemia is corrected. Then change to **AZT + 3TC + DTG.** If anaemia persists or reappears after re-challenge, **DTG + LPV/r + recycled non–AZT-based NRTI backbone.*** This effectively moves the child into third-line ART regimen. Hence adherence should be carefully monitored and supported.	
TDF/ABC-based regimen and third drug is NNRTI	**AZT/d4T** (CD4 count was not suggestive of immunological failure at the time of substitution from AZT to TDF)	No change in regimen is recommended, unless in the case of advanced clinical disease progression. In this case, switching to a second-line regimen with AZT rechallenge under close haematological monitoring should be considered after consultation with pCoE/CoE or paediatric experts. **ZL + LPV/r** if Hb ≥9 g/dl. If Hb <9 g/dl, continue same regimen till anaemia is corrected. Then change to **ZL + LPV/r.** If anaemia persists or appears after the rechallenge of AZT, refer the child to pCoE/CoE for paediatric expert consultation.	**ZL + LPV/r,** if > or = ≥9 g/dl (till paediatric DTG formulations are available in the programme). Whenever child crosses 6 yrs. of age and weights ≥20 kg, then can be transitioned to DTG based regimen. If Hb <9 g/dl, no change in the regimen till anaemia is corrected. Then change to **ZL + LPV/r** If anaemia persists or develops after AZT-based regimen switch, refer the child to pCoE/CoE for paediatric expert consultation.	Re-challenge AZT if current HB is >or = ≥9 g/dl **AZT + 3TC + DTG.** If Hb <9 g/dl, no change in regimen till anaemia is corrected. Then change to **AZT + 3TC + DTG** If anaemia is persisting or reappears after re-challenge, **DTG + LPV/r + recycled non-AZT based NRTI backbone*** This effectively moves the child into third-line ART regimen. Hence adherence should be carefully monitored and supported.	
• **First line failure with history of multiple NRTI exposure** (CD4 count was suggestive of immunological failure at the time of substitution from AZT to ABC/TDF)		• No change in regimen is recommended, unless in the case of advanced clinical disease progression. Refer the child to pCoE/CoE for paediatric expert consultation.		**DTG + LPV/r + recycled non–AZT-based NRTI backbone*** This effectively moves the child into third-line ART regimen. Hence adherence should be carefully monitored and supported	
*Continue NRTI backbone to give the advantage of Lamivudine, unless contraindicated. Please refer Annexure 2 for drug dosing details.					

Second-line ART in HIV-TB Coinfected Children

Due to Rifampicin induced metabolism of many ARVs, the efficacy of these ARVs is reduced when used concomitantly. Hence, the modification of the ART is required while treating a child for HIV-TB co-infection. In HIV-infected adults co-infected with TB, Rifabutin is being used as a substitution for Rifampicin, if they have to be treated with Rifampicin containing anti-TB treatment. However, there is inadequate data on the pharmacokinetics, therapeutic levels and efficacy of Rifabutin in infants and children. Furthermore, there are no Rifabutin paediatric formulations available at present. In HIV-infected children on paediatric DTG-based second- line regimens, which require concurrent TB treatment, the dose of the DTG should be doubled (DTG 50 mg twice daily). If second-line regimens are LPV/r based, the current practice globally is 'super boosting of LPV/r' with additional doses of Ritonavir with the target ratio of LPV/r as 1:1. These measures will ensure adequate therapeutic levels during concurrent TB treatment with Rifampicin. In children receiving EFV-based second-line regimen, no modification in ART regimen is needed.

Table 3.5.9 shows the ART modifications required when receiving Rifampicin-based ATT.

Table 3.5.9: Modification of ART regimen in CLHIV receiving Rifampicin-based ATT

Current Second-line Regimen	ART Modification while Receiving Rifampicin-based Regimen
DTG-based regimen	Double the dose of DTG (DTG 50 mg twice daily)*
LPV/r-based regimen	Super boosting of LPV* with ritonavir (the ratio of LPV:r is 1:1)
EFV-based regimen	No modification is required
DTG + LPV/r regimen	Double the dose of DTG (DTG 50 mg twice daily).* In addition, super boosting of LPV with ritonavir (the ratio of LPV:r is 1:1)

*Rifampicin in FDC can be used with a DTG-based ART regimen with an extra dose of DTG 50 mg (at an interval of 12 hours with the regular dose of DTG) for the entire duration of ATT. Additional dose of DTG 50 mg is to be continued for 2 weeks after completion of Rifampicin-containing ATT.

Please refer Annexure 2 for drug dosing details and dosage of Ritonavir in Super boosting of LPV/r.

Initiation of second-line ART and anti-TB treatment in the presence of TB co-infection

In the event of a child being identified with first-line ART failure presenting with tuberculosis simultaneously, anti-TB treatment initiation is a priority. In such CLHIV, second-line ART regimen with appropriate modification, if necessary, should be started as soon as possible within 2 weeks of initiation of anti-TB treatment.

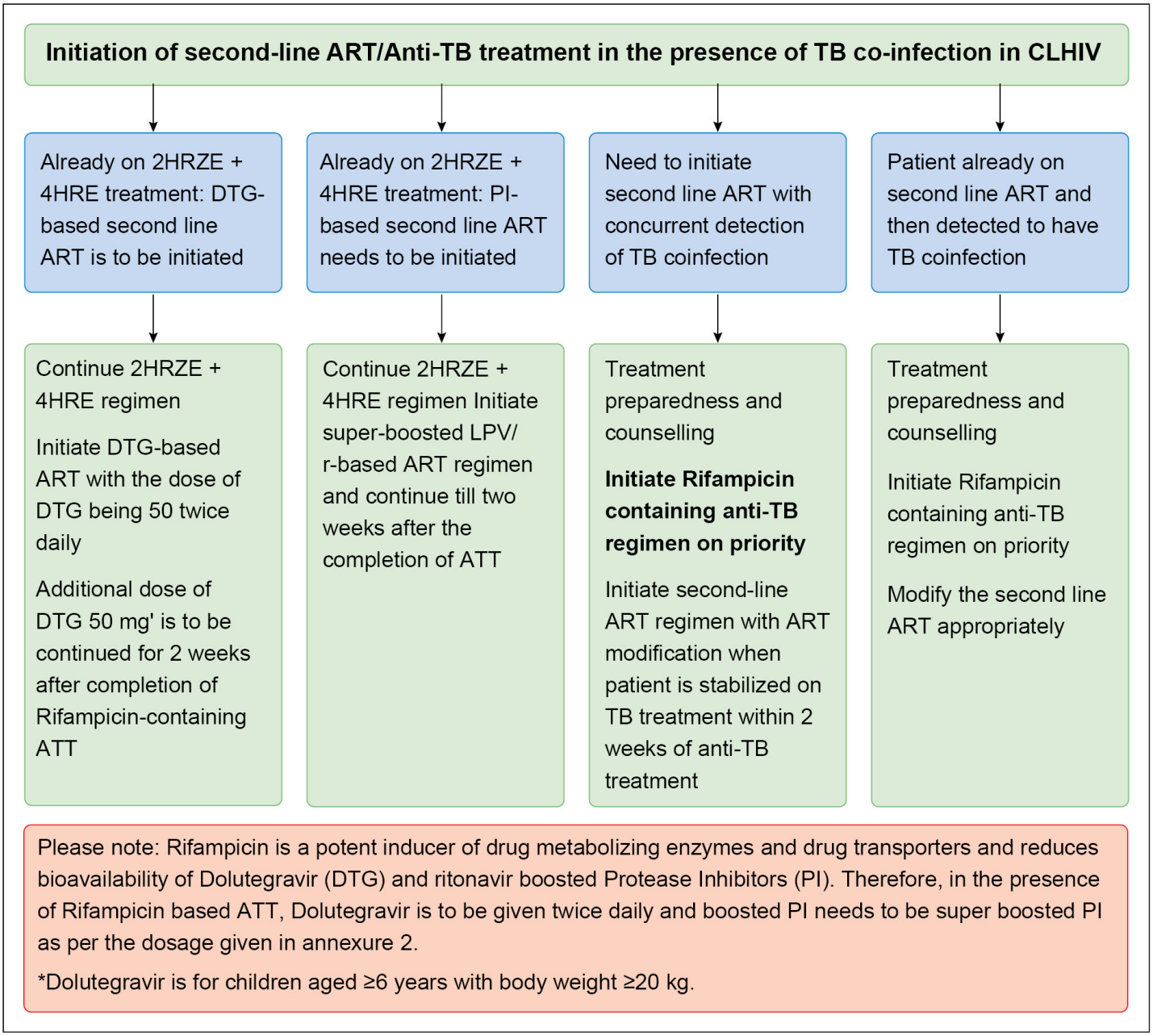
If the child is already on second-line ART regimen and develops TB, appropriate anti-TB treatment should be initiated immediately. ART regimen should be modified simultaneously.

Monitoring Children on Second-line ART

Children on second-line regimen should be monitored for clinical, immunological and virological recovery apart from the adverse effects of drugs. (Please refer Chapter 3.4 (Care of CLHIV: Post ART Initiation) for details of adverse events and their management.) All these children should be clinically screened for OIs

especially TB and evaluated for nutritional recovery. Routine investigations like complete blood count, lipid profile, renal and liver function tests should be done. CD4 count should be done every 6 months to assess immunological recovery. Plasma viral load must be repeated every 6 months (Table 3.5.10).

Figure 3.5.3: Initiation of second-line ART and anti-TB treatment in the presence of TB co-infection



Note:

- Patient should be counselled well for both anti-TB treatment and second-line ART. Pill burden is high. If patient is not started on second-line ART immediately, then continue first-line regimen till patient is switched to second-line ART.
- ART modifications should be reverted 2 weeks after stopping of Rifampicin-based anti-tubercular treatment

Table 3.5.10: Monitoring patients on second-line ART

Tests	Months						
	0	1	3	6	12	18	24
Hb, CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Complete LFT	Yes		Yes	Yes	Yes	Yes	Yes
Renal function test	Yes		Yes	Yes	Yes	Yes	Yes
Random blood sugar	Yes				Yes		Yes
Lipid profile	Yes				Yes		Yes
Viral Load	Yes			Yes	Yes	Yes	Yes
CD4	Yes			Yes	Yes	Yes	Yes

Second-line ART Failure and Third-line ART

Introduction

Some patients on second-line ART may also develop resistance to their regimens. Among the many reasons for the failure of second-line regimen, poor adherence, using modified adult formulations due to non-availability of appropriate paediatric formulations and late switching to second-line ART are important. The late switching leads to accumulation of drug resistance mutants and all these children will eventually require third-line ARV drugs. These drugs have been introduced in the national ART programme now. The stepwise guidance for screening, referral, initiation and follow-up of patients failing to second-line ART follows.

Monitoring of patients on second-line ART

All patients on second-line ART need to undergo viral load testing every 6 months.

Work-up of patients with suspected second-line failure

All CLHIV with suspected second-line failure need to be thoroughly evaluated for treatment adherence and presence of any major opportunistic infection. If adherence is good and there is no major OI, such patients with suspected second-line treatment failure should be referred to Paediatric Centres of Excellence first electronically with referral form, containing latest relevant reports and complete history of treatment.

When treatment adherence is poor or major OI is diagnosed in such children, step-up treatment adherence counselling should be done and all necessary steps should be taken to improve adherence. All active OIs should be appropriately treated. An intense clinical, immunological and virological monitoring should be done and if no improvement is seen by 3 months, the case should be referred to pCoE for further assessment.

During the visit to pCoE, SACEP members will thoroughly examine the patient for issues like clinical signs and symptoms, nutritional status, neurocognitive development, investigations, recent viral load and CD4 counts, adherence, OI treatment and prophylaxis.

All those with Plasma viral load >10,000 and more copies/ml will be switched to third-line ART. But if Plasma viral load is between 1000 and 10,000 copies/ml, a repeat Plasma viral load should be done after 3 months to confirm failure and exclude the possible blips in viral load readings.

Initiation of third-line ART

Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens such as Integrase strand transfer inhibitors and second-generation NNRTIs and PIs. Ideally, Drug Resistance Testing (DRT) is to be done in children failing second-line ARV regimens. But lack of adequate resources and prolonged turnaround time for DRT restricts its widespread use in the programme. DRV is approved for children more than 3 years of age but paediatric formulation of DRV is currently not available under the programme. Efforts are underway to procure paediatric formulation of DRV under the national programme. The guideline will be changed once paediatric Darunavir (DRV) formulations are made available in the national programme. However, for children above 12 years of and 40 kgs weight, adult formulation of DRV can be used. For such children, follow adult third-line recommendations. Table 3.5.11 provides drug regimens used as third-line ART for children with second-line ART failure.

Table 3.5.11: Third-line ART regimes in CLHIV

Age and Body Weight of Child	Failing Second-line Regimen	Recommended Third Line
Age <6 years and body weight <10 kg	AL + LPV/r; ZL + LPV/r. SL + LPV/r; ALN; SLN; ZLN	Continue the second line with emphasis on adherence to ART (However, it is better to continue a PI-based (LPV/r) failing regimen than NNRTI-based one (NVP/EFV) because of high genetic barrier of LPV/r as compared to NVP/EFV).
Age ≥6–10 years and body weight >20–30 kg	ALD; ZLD; DTG+LPV/r	DTG BD + LPV/r + existing NRTI backbone*
Age >10 years and body weight >30 kg	TLD	DTG BD + LPV/r + existing NRTI backbone*
*Continue NRTI backbone to give the advantage of Lamivudine, unless contraindicated.		

In cases with difficulty in assessment of second-line failure, complicated prior treatment regimens, patients referred from private, multi-NRTI-exposed cases, any intolerance to third-line drugs, cases requiring these third-line drugs as alternative within the second-line ART or any other query, SACEP at pCoE/CoE can obtain expert opinion from National AIDS Clinical Expert panel electronically, by addressing to nacep.naco@gmail.com.

Follow-up Protocol

Patients on third-line ART need strict monitoring for side effects at every visit as there is limited experience on the use of these drugs in the programme; one should keep eyes and the mind open for any new symptom and seek opinion if required. The guidelines for laboratory monitoring of patients on third line are given in Table 3.5.12.

Table 3.5.12: Laboratory monitoring of patients on third-line ART

Tests	Timeline			
	Baseline	1 Month after initiation	3 Months after initiation	Every 6 Months after initiation
Hb, CBC	√	√	√	√
Complete LFT	√		√	√
Renal function test	√		√	√
Fasting blood sugar	√			√
Fasting lipid profile	√			√
Viral Load	√			√
CD4 count	√			√

The options for second-line are limited in children especially in children exposed to multiple NRTIs. Treatment failure in children is usually due to poor adherence to first-line ART. Infants and children are dependent on adult caregivers for optimal adherence. All measures should be used to promote good adherence to achieve sustained virological suppression for longer duration. In children, if dosage of ART is not optimized as per their weight, virological suppression may not be achieved. This may lead to early treatment failure.

When substitution is considered in the event of an adverse effect of the drugs used in first-line ART, it is important to assess the child for treatment failure. If there is evidence of treatment failure, then the ART regimen must be switched rather than substituting a single drug.

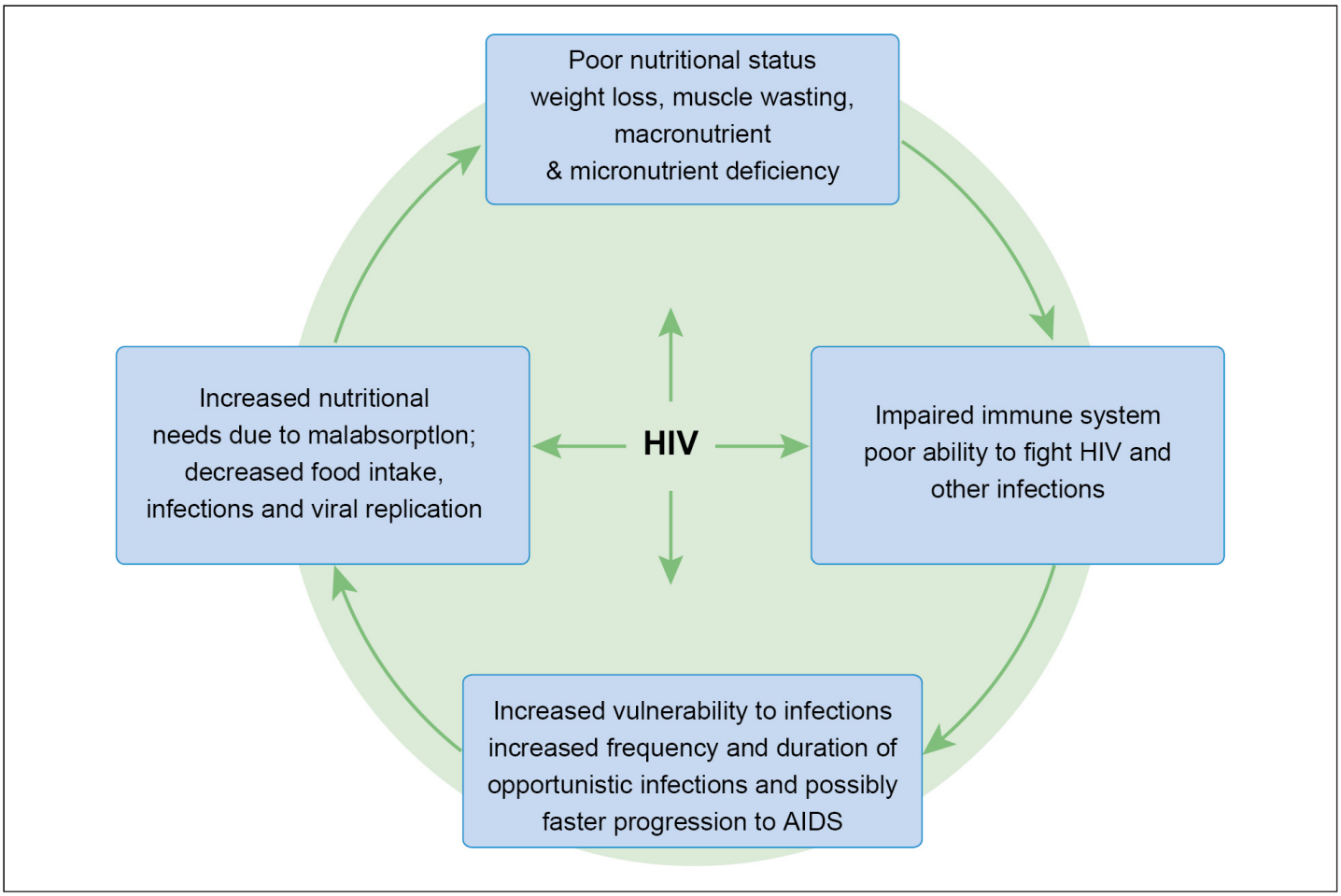
Formulating a third-line ART form for children is a challenge due to non-availability of paediatric formulation and requirement of ART for longer duration in children. Children with suspected second-line failure should be thoroughly evaluated before initiating third-line regimen.

3.6 Nutritional Care of HIV-Infected Children

Introduction: HIV and Nutrition Interplay

Childhood is a period characterized by rapid growth and development leading to increased nutritional needs. HIV and associated infections increase the need for energy, proteins and micronutrients like iron, zinc, vitamin C, etc. If these increased needs are not met, it may lead to malnutrition and weakening of the immune system. Weight loss and undernutrition are common in children living with HIV/AIDS and are likely to accelerate disease progression, increase morbidity and reduce survival. The child will be more vulnerable to OIs and increased nutritional needs. Children deserve special attention because of nutritional requirements necessary for growth and development, and because of their dependency on adults for adequate care. This will lead to a vicious cycle (Figure 3.6.1).

Figure 3.6.1: Malnutrition and HIV: A vicious cycle



Source: Adapted from RCQHC and FANTA 2003a.

Role of Nutrition in the Care of HIV-infected Children

Nutritional care is a crucial part of continuum of care for HIV-infected children. Appropriate nutritional support from early stages of HIV infection can prevent onset of malnutrition and other nutritional deficiencies. It will also help maintain the performance of immune system.

Given the important relationship between HIV, nutrition, growth and survival of CLHIV, nutritional assessment and support should be an integral part of the routine care of HIV-infected infant or child from the beginning. Assessing a child's growth provides valuable information about adequacy of his/her nutritional status and health.[1]

Assessment of Nutritional Status

Regular measurement of weight and height is an essential activity to be undertaken for every HIV-infected child. The assessment should be initiated at the time of diagnosis. Serial assessment and plotting of weight and height on a growth chart help in early detection of growth faltering. Faltering in growth, especially a weight lower than that expected for a child's height, often occurs even before OIs or symptoms are evident in a HIV-infected child. Early detection of growth faltering gives time for intervention to prevent further deterioration. Some children who do not gain weight or lose weight are at a very high risk for malnutrition.

Nutritional assessment should include the following to help in the early identification of growth faltering:

- Diet history
- An evaluation of the child's growth pattern
- Caregiving practices and family food security
- Opportunistic infections

Assessment of growth

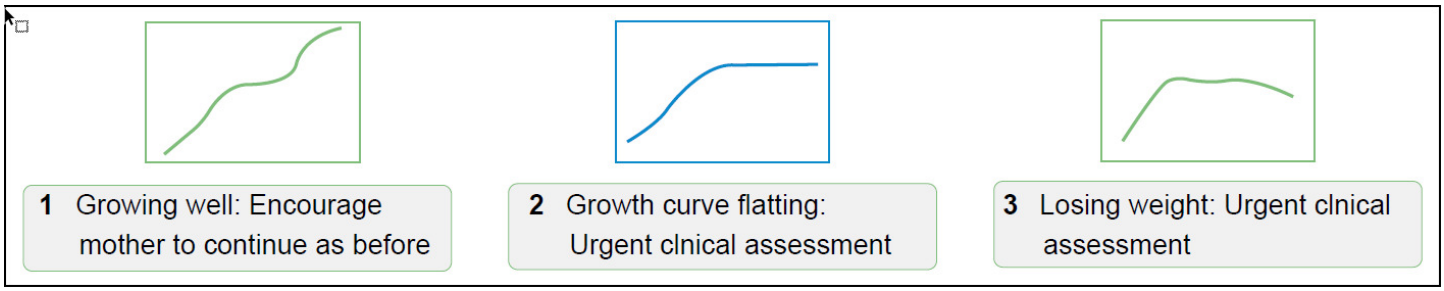
Growth is assessed by measuring weight and height (length for children less than 2 years of age) and interpreting these parameters in relation to age and sex of established reference standards. It is recommended that WHO growth reference standards be used for assessing a child's growth parameters.

These are available as growth charts as well as reference tables for boys and girls separately. The parameter ‘weight for age’ reflects body weight in relation to age. While a single reading gives limited information, serial recording of weight on a ‘weight for age' chart gives a good idea about the child's growth over a period. A weight for age chart is the most commonly used growth chart (refer **Annexures 7, 9, 10**).

‘Height for age' is a measure of linear growth. Plotting length/height on the ‘length/height for age’ chart helps in detecting stunting, a common finding in HIV-infected children (refer **Annexures 8, 9, 10**). The parameter ‘weight for length' reflects body weight in relation to linear growth. Evaluating weight for length for children up to 5 years of age helps in early detection of weight faltering refer **Annexure 11**).

For a child more than 5 years of age, BMI (weight [kg] / height [m]^2) is a better indicator than ‘weight for length' (refer **Annexures 12,13**). Weight for length/BMI is also used as a parameter to identify severe acute malnutrition, as described later. Mid-upper arm circumference is also a good indicator of a child's general nutritional status. At the anganwadi and sub-centre levels where it may not be feasible to measure length or height, MUAC is a useful tool for screening for malnutrition and identifying children at high risk of mortality..

Figure 3.6.2: Depiction of growth curve in different situations



Follow-up: On every visit, CLHIV should be examined for visible signs of malnutrition like loss of subcutaneous fat and muscles and bipedal oedema. The weight should be recorded at every visit and height (length for children upto 2 years of age) once in 3 months for all HIV- infected children up to 5 years of age. For children more than 5 years of age, height can be taken at 6-monthly intervals since the rate of growth is slower.

Classification of Nutritional Status of HIV-infected Children

Based on the anthropometric measures and presence of visible signs of malnutrition, the nutritional status of HIV-infected children can be classified as given in Table 3.6.1. Determination of the nutritional status will guide the dietary requirements and further management of these children as described later.

Table 3.6.1: Classification of nutritional status of HIV-infected children (0–14 years)

Signs	Classify As
Signs of severe visible wasting, or Oedema present in both feet, or Weight for height (BMI for children >5 years) less than -3 Z-score or MUAC less than115 mm in children 6–60 months 129 mm in children 5–9 years, 160 mm in children 10–14 years	**Severe Malnutrition**
Reported weight loss, or Very low weight (weight for age less than -3 Z-score), or Underweight (weight for age less than -2 Z-score), or Confirmed weight loss (>5%) since the last visit, or Growth curve flattening	**Poor weight gain**
Child is gaining weight (weight for age more than -2SD and gaining weight appropriately)	**Growing appropriately**
Chronic lung disease or TB or persistent diarrhoea or other chronic opportunistic infection or malignancy	**Conditions with increased nutritional needs**
Nurses, counsellors and other paramedical workers may classify a child as having 'severe malnutrition' based on the presence of visible severe wasting, oedema of both feet or MUAC criteria. However, medical officers should also use the additional criterion based on weight for height/BMI. Use BMI for age for children older than 10 years.	

Nutritional Needs of HIV-Infected Children 6 Months to 14 Years of Age

Energy and protein needs of HIV-infected children depend on their age, growth pattern and presence of associated complications. As mentioned earlier, these children have higher energy needs as compared to healthy children due to increased metabolic demands placed by HIV infection. Presence of associated OIs and other chronic conditions like chronic lung disease or persistent diarrhoea further increases the metabolic demand. Table 3.6.2 gives the total energy needs of HIV-infected children depending upon their nutritional status. HIV-infected children with chronic lung disease, TB, persistent diarrhoea or other chronic OIs or malignancy have increased nutritional needs despite a good nutritional status.

Table 3.6.2: Total energy needs of HIV-Infected children

Age of Infant/ Child	Daily Energy Needs of HIV Uninfected Children*	HIV-infected and Asymptomatic 10% Additional Energy	HIV infected and poor weight gain or other symptoms 20% additional energy	Severely malnourished and HIV infected (post-stabilisation) 50-100% additional energy**
6–11 months	690	760	830	150–220 kcal/kg/day
12–23 months	900	990	1080	150–220 kcal/kg/day
2–5 years	1260	1390	1510	150–220 kcal/kg/day
6–9 years	1650	1815	1980	75–100 kcal/kg/day
10–14 years	2020	2220	2420	60–90 kcal/kg/day

*Based on average of total energy requirements for light and moderate habitual physical activity levels for girls and boys by age group. Joint FAO/WHO/UNU Expert Consultation, October 2001. ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.df

**Management of Severe Malnutrition: a manual for physicians and other senior health workers. WHO,1999

Nutritional Management of HIV-infected Children: Practical Guidelines

In general, feeding guidelines for HIV-infected infants and children are the same as those for healthy children apart from the need for meeting increased energy needs. If an infant is confirmed to be HIV infected, the mother should be strongly encouraged to breastfeed exclusively for 6 months and continue breastfeeding up to 2 years or beyond as per the norm for general population. This will ensure optimum growth for the infant to provide protection from infections. For further reading on safe preparation of formula/animal milk and the amount of milk the child will need at different ages, please refer Annexure 14. Complementary foods are introduced at 6 months of age as recommended for all infants. The quantity and frequency of food is increased as the child grows older. Food consistency is also gradually made thicker, and variety introduced adapting to the child's requirement and abilities. The IMNCI guidelines for feeding healthy children of different age groups are available in Annexure 15. All infants diagnosed to be HIV infected are started on ART as per national recommendations.

Nutritional management of a HIV-infected child growing well

HIV-infected children who are growing well and are asymptomatic need about 10% extra energy as compared to uninfected children of their age to maintain normal growth, development and activities. For further reading on ‘age-related food intake standards for children’ refer Annexure 16. The additional energy is best given as additional household foods as part of a balanced diet.

Nutritional management of a HIV-infected child growing poorly or having conditions with increased nutritional needs

Children with poor weight gain should have a complete assessment including

- detailed dietary history and
- evaluation for comorbidities
- OIs, e.g., chronic lung disease, TB, persistent diarrhoea that may have an impact upon the nutritional

status.

These children require an extra 20%–30% energy each day. These are also best given through additional household foods. If this is not possible, specific nutritional supplements may be given till the underlying condition is effectively managed. Mother or caretaker should be given dietary counselling about meeting these increased nutritional needs at home.

Table 3.6.3 shows the additional energy requirements for children with different nutritional status and examples of dietary modification that would meet these increased needs.

Management of children with severe acute malnutrition

Children with severe acute malnutrition have signs of:

- visible wasting
- bilateral oedema
- severely impaired growth (below 2Z score)

They must be identified and managed correctly since they are at a very high risk of mortality.

These children should be evaluated at the ART Centre for the following:

- Anaemia
- Opportunistic infections including TB
- Drug side effects
- Treatment adherence
- Treatment failure
- IRIS

Unless associated complications are appropriately managed, improvement in diet alone may not result in normal growth, weight recovery or improvement in clinical status.

Children with SAM require 50%–100% extra energy every day after the period for stabilization till nutritional recovery (usual duration 6–10 weeks). They should be treated with therapeutic feeding. Children with no medical complications may be managed at home if they still have a good appetite. They can receive good supervision at home and therapeutic feeds can be provided. Children who are sick and have associated complications like infections, have a poor appetite or are unable to eat must be referred for inpatient care by trained staff with experience in nutritional rehabilitation. The nutritional management of HIV-infected severely malnourished children is largely the same as for any other severely malnourished child.[1]

Table 3.6.3: Additional energy requirements of HIV-infected children and means of providing them

Additional Energy Requirement in HIV-Infected Children			
Age of Child	Asymptomatic with Adequate Growth (10% additional energy)	Poor Weight Gain or Increased Nutritional Needs (20–30% additional energy)	Severely Malnourished (50–100% additional energy)
6-11 months			
Calories required in addition to usual requirement*	60–70 kcal/day	120–150 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 teaspoons of edible oil and 1 teaspoon of sugar to porridge in addition to normal diet	Add 2 teaspoons of edible oil and 1–2 teaspoons of sugar to porridge or other foods. Aim to add twice daily.	Therapeutic feeding as per national guidelines to provide 150–220 kcal/kg/ day based on actual weight.
12-23 months			
Calories required in additional to usual requirement*	80–90 kcal/day	160–190 kcal/day	-
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Add 2 teaspoons of edible oil and 2 teaspoons sugar to porridge, or 1 medium banana.	Extra cup (200 ml) of full-cream milk with 1 teaspoon sugar or 2 big idlis or 2 slices of bread with butter	Therapeutic feeding as per national guidelines to provide 150–220 kcal/kg/ day based on actual weight.
2-5 years			
Additional calories*	100–140 kcal/day	200–280 kcal/day	Based on actual weight 150–220 kcal/kg/day
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup of milk or sweetened curd or 1 extra roti with vegetables or 1 paratha	2 puris with vegetables or 1 cup porridge or 2 pieces of chikki	Therapeutic feeding as per national guidelines to provide 150–220 kcal/kg/ day based on the actual weight
6-9 years			
Additional Calories*	130–190 kcal/day total = 1815 kcal/day	260–380 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra cup (200 ml) of full-cream milk or 1 egg omelette or 1 extra roti with vegetables	Extra cup of full cream milk and one vegetable stuffed paratha, or 2 parathas with curd or halwa 100 gm (1/2 cup) or poha11/2 cups	Therapeutic feeding as per National guidelines to provide 75-100 kcal/kg/ day based upon the actual weight
10–14 years			
Additional calories*	170–230 kcal/day	340–400 kcal/day	Based on actual weight
Examples of ways to increase energy intake in addition to meals and snacks appropriate to age	Extra 1 roti at lunch and dinner with vegetable or 1 dosa with sambhar or 1 stuffed paratha	1 egg omelette with 2 slices of bread or 1 stuffed paratha and 1 cup milk	Therapeutic feeding as per National guidelines to provide 60–90 kcal/kg/day based on actual weight
*Calories in addition to that recommended for normal children in the same age group			

Supportive measures including micronutrient needs

The following measures support the improvement of nutritional status and health of HIV-infected children and should be provided to all children:

- Micronutrient supplements: Micronutrient intake at recommended level should be ensured through balanced diet. If the child's diet does not contain a variety of fruits, vegetables and food from animal sources, give a daily supplement that provides 1 RDA of vitamins and other micro¬nutrients. Investigate for presence of anaemia and give iron supplements if deficiency is confirmed
- Give vitamin A supplements every 6 months for children up to 5 years of age in the following dose:
- 6–12 months: 1,00,000 IU orally
- 1–5 years: 2,00,000 IU orally
- For children beyond 5 years of age, vitamin A should be provided through daily micronutrient supplement.
- Deworm every 6 months (albendazole 400 mg single dose orally every 6 months after first year of life).
- Continue Cotrimoxazole prophylaxis as indicated.
- In patients with recent history of diarrhoea, give Zinc 20 mg daily for 2 weeks.
- Encourage regular play and age-appropriate activities: Play helps maintain appetite and build muscles. Children who play are healthier and happier. Parents or caretakers should be encouraged to participate in age-appropriate activities with the children. This promotes child–caretaker interaction and is a source of happiness for both.
- Administer routine childhood immunizations.

Nutritional Counselling

Nutritional counselling of caretakers is essential for maintenance of a good nutritional status and nutritional rehabilitation. The mother or caretaker should be counselled about the following:

- Need for additional food
- Dietary modifications required to meet increased needs
- Safe food preparation
- Safe food and water storage methods
- Hygiene issues.

For five keys to safer food, **refer Annexure 17**.

Nutritional care of HIV-infected children with special needs

HIV-infected children commonly experience poor appetite and suffer from mouth sores and diarrhoea. Sick children need extra drinks and food during illness, e.g., if they have fever or diarrhoea. It is often difficult to feed such children. During these acute illnesses, they are likely to lose weight. All sick children should be offered appropriate foods unless there is a medical reason. For feeding recommendations during sickness and health, refer **Annexure18.**

Nutritional management of children with diarrhoea, mouth ulcers or poor appetite is discussed in detail.[1]

During the recovery period, therefore, it is important to do the following:

- Increase energy and protein consumed in everyday foods by adding one meal per day.

- Feed the child on demand day and night.
- Encourage the child in simple and loving ways.
- Make the child comfortable.
- Be patient and feed slowly.
- Feed small amounts frequently.
- Children may tire easily while eating, making it difficult to eat sufficient food at a sitting.
- Offering feeds frequently may be needed to increase food intake.
- Give foods that the child likes.
- Give a variety of foods and extra fluid.
- If the child is thirsty, give fluids that have some energy.
- Avoid commercial juices or fizzy drinks that have very little nutritional value.

Follow-up

Nutritional status is assessed at every follow-up visit for an HIV-infected child. The frequency and interval between visits depend upon the condition and needs of the child (Table 3.6.4).

Table 3.6.4: Follow-up of nutritional status of HIV-infected children

Condition	Nutritional Follow-up	Remarks
The child who is well and growing appropriately	2–3 months	May be monthly if receiving routine Cotrimoxazole/micronutrient or other support/ treatment, including ART
The child on ART	3 months	If gaining weight and no other problems
	2-4 weeks	If not gaining weight
The child who has chronic increased nutritional needs but investigated and no other active problems	2-3 months	Tell caregiver to return earlier if problems arise.
Child with poor weight gain	First visit 1–2 weeks, then 1–2 months	Tell caregiver to return earlier if problems arise.
The child who is unwell and/or showing signs of growth faltering or has had recent diarrhoeal illness	2–4 weeks	May require more frequent visits depending on clinical status and support offered or being provided
When the child is malnourished +/- other signs of disease progression e.g., history of recent severe weight loss or recent diarrhoea illness	Weekly	Only if fulfils criteria for management at home and no immediate need of other investigations that require hospitalization
When a child is severely malnourished with medical complications or no appetite	Refer for hospitalization	

Note: HIV-infected children who are followed up by the ART programme monthly should have their normal measurements done as per ART guidelines, e.g., weight. Follow-up of their nutritional status is as above.

3.7 ≫ Counselling for Children and Adolescents Living with HIV

Introduction and Scope

Care and support of CLHIV pose very different challenges compared with those for adults. Both the child client and his/her caregivers must be supported through sensitive and caring counselling. Counselling for CLHIV will be covered as follows:

- Challenges faced while counselling CLHIV
- Child-friendly ART centre
- Child-centric counselling
- Counselling the caregiver and child: Treatment preparedness, adherence and follow-up counselling

Challenges Faced while Counselling CLHIV

While all Persons Living with HIV need psychosocial support in living with the illness and managing treatment, care and support of CLHIV pose very different challenges. These challenges could be related to the child, the caregiver or the home environment (Table 3.7.1).

Table 3.7.1: Challenges faced while counselling children

Caregiver-related challenges	• Frequent sickness/mortality in parents • Frequent changes in caregiver • Attitudes, beliefs and habits of caregiver
Child-related challenges	• Dependency on adults for treatment • Poor attention span of child • Difficulty experienced by the child in communicating feelings or thoughts • Poor physical growth of the child and delayed developmental milestones • Changing understanding of the child with age
Home environment-related challenges	Higher chance of sickness, economic constraints, discrimination/stigma

These challenges can be addressed by the following means:

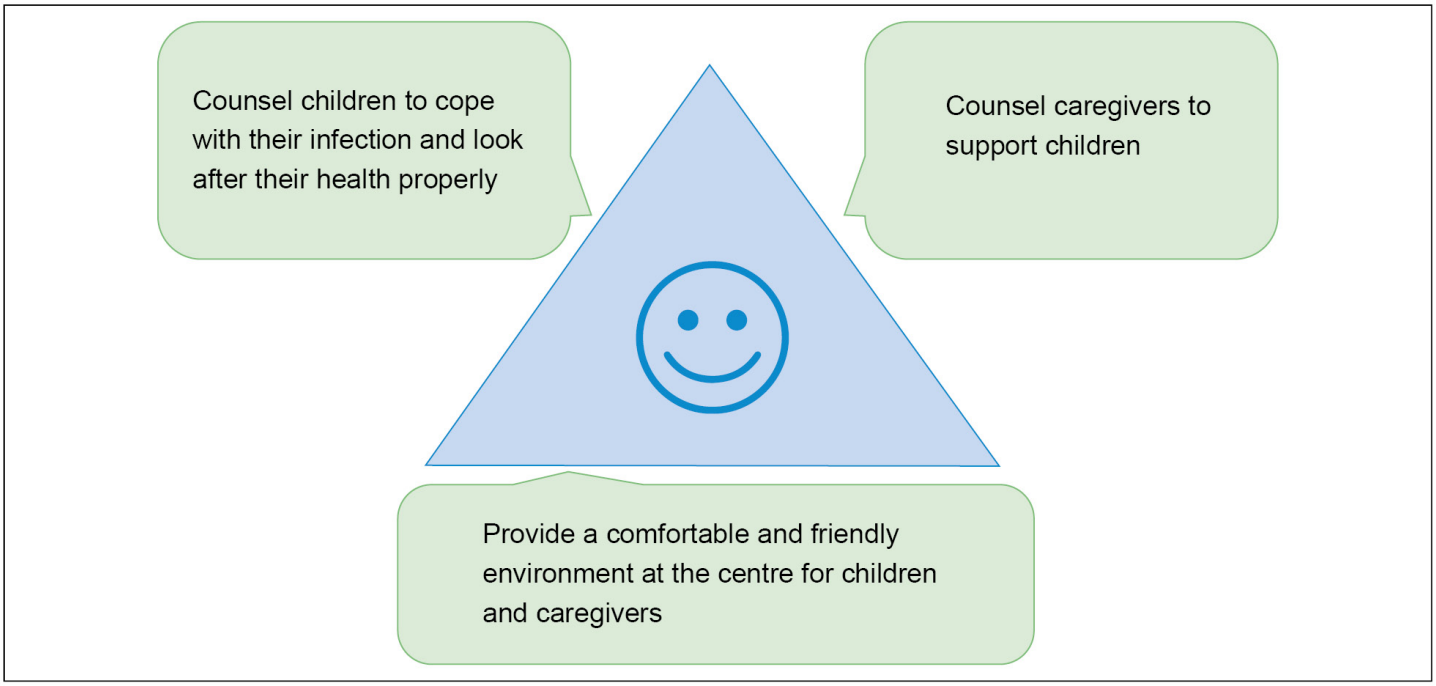
1. Both the child client and his/her caregivers need to be supported through sensitive and caring counselling.
2. Counselling messages should be tailored as per child's age, developmental status, ability to understand HIV disease and treatment and his/her social circumstances.
3. Counselling messages should be adapted to changing needs as the child grows older and progresses through various stages of child development.
4. Essential to identify the primary caregiver and a back-up secondary caregiver if the primary caregiver is not available.
5. Challenges of coping with adherence to lifelong treatment; issues of disclosure, confidentiality,

stigma and discrimination in their immediate environments, issues related to education, career, relationships, etc., all need to be sensitively addressed at appropriate times which may vary from child to child.

Creating a Child-friendly ART Centre

A child-friendly environment is necessary in the centre to support children and make them feel comfortable. The atmosphere at the ART centre is crucial for strengthening the trust between the ART team and the child, and to support adherence to treatment. This can change the perception of the child from viewing the ART centre as a 'hospital' to a 'friendly centre' that can help find solutions to the issues he/she is facing. Figure 3.7.1 depicts how ART staff can support CLHIV registered at their ART centre.

Figure 3.7.1: How can ART staff support children living with HIV?



The ART team must make efforts create a child-friendly corner using some portion of the contingency funds. Ideas for creating a child-friendly ART centre in resource-limited settings may be as follows:

- A separate room for counselling of children is ideal. If it is not available, then plan a child- friendly corner with wall cut-outs of cartoon characters such as from Panchatantra stories or a plastic playhouse.
- Small chairs for children
- Drawing papers, crayons and other art material
- Story books, games and toys for children
- Wall display of paintings done by CLHIV, such as calendars with complete adherence marked by children, or pictures drawn or coloured by them
- Blackboard and chalk placed at the child's eye level in a corner of the waiting area so that they may express their creativity

Child-Centred Counselling

Children are not just tiny adults. Their physical, emotional and psychosocial needs are different and

require different handling than that given to adults. The basic skills for counselling children and adults are the same. While counselling children, there should be use of age-appropriate language so that the children understand the information and are able to express their feelings. Interactive tools such as drawing, storytelling, plays and drama are media through which children can be helped to express themselves. Child-centred counselling is summarized in Table 3.7.2.

Table 3.7.2: Child-centred counselling

- Development of rapport between the child, caregiver and counsellor
- Focusing on the child's needs
- Tailored to the child's physical and psychological development
- Promoting the child's potential and abilities
- Building self-esteem
- Respecting the child's identity and emotions
- Protecting the 'best interest' of the child, including the right to:
  - participate in decisions that affect him/her
  - non-discrimination
  - confidentiality of information
- Always involve the child and the child's caregiver

Communication with the children depends on the developmental level and ability to express their feelings and issues themselves. Very young children have difficulty in expressing themselves verbally because they cannot use words to describe their emotions or thoughts. Hence, practical ways must be found to communicate with children and help them express their feelings. It is difficult to sustain a young child's attention. Thus, messages related to various aspects of their illness are best conveyed using tools like stories, drawings and games. Table 3.7.3 summarizes essential skills in child-centric counselling.

Table 3.7.3: Essential skills in child-centric counselling

Counselling Skills	Description of Skills
Rapport building	• Greeting the child, and introducing yourself/your role to the child, including how you will assist him/her • Clearing fears and misconceptions about counselling that the child may have and normalizing the process of seeking help • Setting the context—so that the child knows why and for what concerns he/she has been referred for counselling • Assuring the child of confidentiality • Neutral play and art activities to build a therapeutic relationship and a spirit of collaboration
Listening	• Listening involves paying attention to the child's verbal and non-verbal communications to encourage the sharing of stories and difficult experiences of the child • It also entails being supportive, i.e., without being argumentative and offering immediate solutions through the child's narrative
Recognizing and acknowledging emotions	• Validating children's (difficult) experiences and emotions; this assures children that you not only understand but also empathize with their predicament; this helps children feel supported and comforted (and is one of the main objectives of counselling). • Any suggestion or advice provided by the counsellor needs to be predicated on such understanding and acknowledgement of the child's emotions
Acceptance and non-judgemental attitude	• Although it is legitimate for us all to have personal views and opinions on various matters, being non-judgemental means to refrain from imposing these on children. • It means being non-critical and not blaming the child, whatever the behaviour may be. • Providing the space for children to examine and analyse their actions: such reflection serves as the basis on which they can make (more informed or thoughtful) decisions about their lives and actions. • Ultimately, the child takes the decisions for himself/herself – the counsellor's role is to be an enabler in the child's decision-making process.
Questioning and paraphrasing	• All inquiry should be embedded within counselling processes i.e., with the use of the child-centric counselling skills. • A combination of open and close-ended questions may be used to elicit information from children. • However, to best understand children's perspectives and allow them to tell their stories in ways that are descriptive, detailed and non-threatening, a greater use of open-ended questions is encouraged. • Paraphrasing ensures that the child's narrative is summarized in ways that reflect and validate children's experiences, and that the counsellor has understood the child's account accurately.

Source: Sheila Ramaswamy, Kritii Tikku and Shekhar Seshadri; Psychosocial Care & Mental Health

Concerns in Paediatric HIV; Dept. of Child and Adolescent Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore (unpublished).

Counselling the Caregiver and Child for Lifelong ART

Counselling for ART can be divided into three stages:

1. **Preparedness counselling:** Preparing the child and caregiver for treatment, which includes disclosure of the HIV status to the caregiver and then to the child (age-appropriate partial or complete disclosure) through the caregiver. This is a necessary step before starting ART.
2. **Adherence counselling:** Strengthening adherence to treatment by identifying barriers to adherence and developing adherence strategies.
3. **Follow-up counselling:** Providing ongoing psychosocial supportt

Treatment Preparedness Counselling

Preparedness counselling for paediatric ART includes educating and preparing the child and caregiver for lifelong therapy. Preparing for treatment is crucial for good adherence and a successful treatment outcome. Several counselling sessions maybe required to prepare the child and caregiver, keeping in mind that initiation of ARV medication is usually not an emergency.

Preparedness counselling messages for children are like those for adults. The major difference is that since children are dependent on caregivers for treatment, counselling for children includes the caregiver also. It is necessary to evaluate the child's social environment, including identifying a clearly defined caregiver who can understand the prognosis of HIV and the implications of ART.

Counselling the Caregiver

The first step is to identify the primary caregiver, usually parents but may be other family members or at times a caretaker from an orphanage. The caregiver must be explained the advantages and limitations of ART, implications of ART being lifelong therapy, importance of adherence, knowledge of drug toxicities and storage of drugs. It is also vital to identify a second caregiver for backup, especially if HIV-infected parents are primary caregivers.

Informing the caregiver about the HIV status of the child and acceptance of HIV infection in the child is a very emotive topic for family members. In most instances, the transmission has occurred from the parent to the child. So, acceptance of HIV infection in the child is complicated with guilt on the part of the parent and worry about being blamed by the child. Counselling the parents must help them deal with personal guilt and worry as well as acknowledge that the emotional needs of the parent cannot be a reason to ignore or subsume the needs and rights of the child. In situations where discovery of HIV infection in the child has led to subsequent discovery of infection in other family members including parents themselves, extreme sensitivity is required and family needs help understanding and accepting the illness and its implications in the family before treatment can be initiated.

It is also important to sensitize the caregiver about the disclosure of HIV status and disease information to the affected child. Disclosure to a child needs to be age-appropriate and according to his/her level of understanding. Disclosure of HIV status is discussed in detail later in the chapter.

The counsellor must assess the health status of parents and siblings and the family's access to adequate nutrition and support.

Preparedness counselling of caregivers should begin as soon as possible and before initiation of ART. The 5 As is a practical method to follow when preparing the child and caregiver for treatment. The 5 As in treatment preparedness are as follows:

ASSESS: the child's and caregiver's knowledge of HIV status, understanding of HIV disease and its treatment. It is also important to assess the potential barriers to adherence and their social support systems.

ASSIST: the child and caregiver in developing a treatment and adherence plan

ADVISE: about how ART works and the need for lifelong treatment, and importance of adherence and regular follow-up visits. It is important to advise the child and caregiver to aim for 100% adherence, and not miss even a single dose/visit.

ARRANGE: the ART team can arrange for medical investigations and appropriate referrals within and outside of the hospital since the children and caregivers do not know the hospital procedures for investigations and where to go for them.

AGREE: means that the patient and caregiver both understand, accept and agree to the formulated treatment and 100% adherence to lifelong treatment.

In addition, the caregiver should also be educated about the possible danger signs in a child such as lethargy, not accepting feeds orally, decreased urine output, repeated vomiting, blood in stools and drowsiness with high persistent fever. In the event of a child having one or more of the above signs, he/she needs to be brought to the hospital immediately.

The caregiver is the key player in the child's treatment adherence. The counsellors should explain the What, When, How and Who about ART medicines.

Explain WHAT medicines will be given. Are they pills or syrup? What is the colour or shape of the pill, which cover, etc.? Familiarize the caregiver and child with the medicines. Show them a picture or an actual sample. Explain that a dose must be repeated if the child vomits within 30 minutes of taking the medicine. Vomiting beyond 30 minutes will not affect the absorption of the medicine. Also explain what to do if the child has to attend a function or travel outstation on a holiday.

Specify WHEN the medicines should be given or taken and how frequently medicines should be given. The specific times and routines can be decided based on the age and responsibilities of the child and caregiver. The counsellor needs to ensure that this timing is linked with the routine of the child. If the pill is to be taken every 12 hours, explain that the child can take the medicines with breakfast or before going to school and in the evening. It is better to fix the timing, e.g., 7 a.m. and 7 p.m. Explain that any time the school timing changes, a new timing plan can be implemented in consultation with the counsellor.

Provide details on HOW the medicines will be given or taken. Details should include the number of tablets, which measuring spoons to be used for syrups and whether medicines can be taken with water before or after food. They can be taken as tablets or dispersed in water (boiled and cooled). The tablets can be halved as they are scored tablets. Advise to use clean utensils to prepare syrups out of dispersible tablets. Answers to all questions about drug timing, mode of preparation, dosage etc. should have been understood by the caregiver. Also plan on the reminders to use for reminding about pill timing. Reminders should be timed about 15 to 20 minutes before the time fixed for medicine, as children have to have food with the medicine.

Identify WHO will administer the medicines to the child, whether it is the mother, father, grandparent, an extended family member or a volunteer. It should not happen that the child is given medicine by two different people in the family on the same day. Hence, it is essential to identify the primary caregiver and a backup secondary caregiver if the primary caregiver is not available.

Pre-ART activities such as teaching a child pill swallowing with peppermint sweets or planning on giving first doses in the ART centre or hospital will help give confidence to the child and caregivers about swallowing pills.

Counselling caregiver about the side effects of ARV drugs and home based care

Prepare the caregivers for the possibility of minor side effects of ARV drugs like nausea, headache and abdominal discomfort and explain to them about home-based care of these common adverse events. This has been covered in detail in Chapter 5.7 (Palliative Care for Adults and Children with HIV). Provide IEC materials on side effects, if available. Counsel that mild side effects will recede over time or respond to change in diet or method and timing of medication administration.

Adherence Counselling

Adherence to ART is essential to achieve viral suppression. Hence, it is essential to educate both the CLHIV and the caregiver about adherence to ART at the time of ART initiation and during the subsequent visits. It is also important to check the regularity of the child's visits to the centre and adherence to other co-medications (e.g., anti-TB drugs) as well.

It is essential to involve the child in adherence assessment so that he/she also realizes that adherence is important. This also gives the child a sense of involvement in his/her disease management. As far as possible, interactive methods such as pill charts and storytelling should be used with children.

Various ART reminder tools including calendars, alarms, SMS reminders, refill boxes and pill charts can be suggested to improve adherence.

The ART team, especially the counsellor and the doctor, should build a rapport with the CLHIV so that they themselves inform about the doses missed and reasons for missing them.

Barriers to Adherence in CLHIV

The four broad categories of potential barriers to adherence in CLHIV are child-related, treatment-related, provider-related and environmental and social factors. This categorization helps the counsellor in addressing each barrier.

For example, a child-related barrier can be addressed by the CLHIV themselves. To overcome care provider-related barriers, support can be sought from family members or friends. Counsellors can gain a complete picture of the child's adherence and the caregiver's administration of the medicine by asking both child and caregiver about the process of taking medicine. Discrepancies in the reports of both sides should be discussed in counselling. When the barrier is related to a counsellor, the counsellor may need to modify the counselling approach to be more effective.

Treatment-related adherence issues could occur due to long-distance travel to and from hospital, loss of daily wages for travel, frequent changes in ART staff, high pill burden, etc. These issues can be addressed by the counsellor while designing the customized adherence plan. Issues related to social factors may be stigma discrimination at home, school, while living in an orphanage or with relatives and poor access to medical care facilities etc. In issues related to the society, the ART team may have limited scope for intervention. However, CLHIV should be helped to minimize the impact of the barrier on them and encouraged to continue the treatment.

Table 3.7.4: Common barriers to adherence in CLHIV

Child-related Factors	Caregiver-related factors
• Dependency on adults • Likes and dislikes for medicines (Taste, smell and colour of medicine) • Emotional issues • Using medicines to manipulate adults • Other infections and medications	• Knowledge and understanding of treatment and its implications • Misconceptions regarding treatment • Health beliefs • Daily routine, nature and timings of job • Attitude towards adherence • Repeated changes in caregivers • Relationship with the child

The child-related factors affecting adherence include children's dependence on adults, likes and dislikes for medicines. For example, they may have issues with the taste, smell and colour of medicine. They may have emotional issues like mood swings, dislike of the behaviour of caregivers, illness in a family member or death in the family. Children may be using medicines to manipulate adults emotionally. Counsellor should also enquire about other infections and medications the child may be taking. Counsellors need to patiently work with children to identify such factors and address them properly.

As mentioned before, caregivers are key people in a child's adherence to treatment. Since they are the care providers, they should have adequate understanding about the treatment and its implications. Apart from gaps in the knowledge, caregivers may have misconceptions about the HIV treatment or certain health beliefs that may manifest later. Counsellors should be vigilant about these factors too. The caregiver's daily routines, nature and timings of job, attitude towards adherence also affects the child's adherence.

Another important factor for poor adherence is frequent changes in caregivers. This is because the child may not be comfortable with the new caregiver. In such a situation, the counsellor may need to facilitate the development of bonding and closeness between the new caregiver and the CLHIV. At times, barriers to adherence may be due to non-disclosure of HIV status, food insecurity or other factors.

It is essential to monitor adherence during each visit and identify and address any identified barriers to adherence.

Follow-up Counselling

Adherence Fatigue in CLHIV

As time passes, the CLHIV may get tired of taking medicines. This usually occurs after an ART adherent period of about 2 years. There can be various signs of adherence fatigue in a child on ART. These may be in the form of marked change in the confidence level and attitude towards the treatment and expression of 'feeling bad' for being the only one to take medicines among his peers. Symptoms of psychological distress in the form of anxiety, depression and fears may be apparent and lead to poor school performance. Persistence of medication-related side effects may also contribute. The caregiver may also face adherence fatigue and feel tired of administering or supervising medication.

Some statements that a counsellor may hear from the CLHIV are "I can't take these medicines", "I don't like the taste of these pills", "My friends are not taking it, why should I?" Other statements from the CLHIV may be "My head is paining" or "I feel like vomiting". These statements from the child are indications that the child is getting tired of taking medicine daily and that adherence fatigue is setting in. Such complaints need to be taken seriously.

Disclosure of HIV Diagnosis to Children living with HIV

Disclosure of HIV diagnosis to infected children is a challenge for both the families and the healthcare providers. One of the most common barriers to disclosure is that the mothers/parents/ caregivers feel guilty and uncomfortable, and they are afraid of the consequences of disclosure. Many of the parents/caregivers do not know what to say to the child or they want to protect the child from bad news. Another barrier is the fear that the child may talk about their HIV status to others. Sometimes, there may be no caregiver available for disclosure as in the case of orphans.

Timing of Disclosure

Counsellors and doctors are often concerned about the right age for disclosure to the child. It is best to begin informing children about their status when they are between 5 and 7 years of age, depending on the child's ability to understand and with parents' consent. One could do this gradually until a child is 12–14 years of age.

Disclosure may be partial or complete depending on the age and level of functioning of the child. Partial disclosure aims to describe to the CLHIV what is happening to the body and how the treatments will help to resolve this, rather than naming the virus or illness. Complete disclosure involves open discussion about the virus, infection and all other issues relating to HIV infection. It is important that information given to the child, though not complete, should be true. This helps build the child's trust in the information provider. It is also important to answer any questions that a child may ask, in a language and to the extent the child can understand. This keeps communication channels open with the child and facilitates further exchange of information and experiences in subsequent visits.

Table 3.7.5: Type and timing of disclosure

Type of Disclosure	Time of Disclosure
Initiating disclosure (Age 4 to 6 years)	When the child is curious about many issues and concepts of illness and wellness can be introduced
Partial disclosure (Age 7 to 11 years)	When the child is aware that he/she or the parent has a chronic illness and is taking daily medications for it.
Full disclosure (Age 12 and above)	When the child can understand full disclosure of illness

It is important to monitor the short- and long-term effects of disclosure during counselling and understand that continuous psychosocial support needs to be given to the child after the disclosure.

How to explain HIV and ART to children?

Disclosure must be done together with the child and the parents/ caregivers/guardians. Disclosure to a child needs to be age appropriate and according to the level of understanding. Table 3.7.6 below gives an example of utilizing the understanding about child's growth in counselling using age-appropriate counselling messages about HIV infection.

Table 3.7.6: Age-appropriate counselling messages about HIV infection

Age Groups		Messages
3-6 years		"You are not well. If you want to play, you should be well and for that you need to take medicine."
6-9 years		"You have got germs inside your body. That germ is making you fall sick often. To kill that germ, you need to take medicine every day. The germ will become strong if you don't take medicine."
9-12 years		"There is a germ in your body. It reduces your body's ability to fight other infections. We cannot remove it from your body. But we can control it so that you stay healthy. For that, you must take medicine regularly."

Preparing the parents/caregivers for providing HIV disclosure

Parents/caregivers are the most appropriate persons for disclosure of HIV status to a child. They must be encouraged and supported through the process of disclosure of status to their child at a place and time of their choosing. They must be prepared to break the news gently to the child, answer any questions that the child may ask and support the child in accepting and coping with the knowledge related to the illness.

Some caregivers may request the counsellor/medical officer to carry out the disclosure. In such cases, it is strongly recommended to have common counselling sessions with the child and the caregiver. Caregivers' feedback on the preparedness of the child to receive such disclosure counselling should be duly considered. The counsellor can also gently offer her/his own assessment of the readiness of the child to hear this message.

One common fear of caregivers (and of counsellors) is that children who learn of their status may inadvertently blurt out this fact to other people, and thus increase the chances of being stigmatized. Parents may fear that the child may feel depressed and suicidal. The counsellor and other team members should address these issues by suggesting disclosure in stages based on the capacity of the child to understand the impact of the diagnosis. Further, the team should attempt to normalize the situation by comparing HIV to a chronic illness like diabetes, which also requires constant personal health-promoting behaviours from clients.

Caregivers and parents may be unwilling to share the child's HIV status with other people. This concern and worry could cause interruptions in treatment because of unwillingness to fill prescriptions locally, hiding or re-labelling medicine bottles to maintain secrecy within the family and missed doses when the parent is unavailable. These issues should also be discussed during counselling. Table 3.7.7 describes the process of preparing the caregivers for disclosure. Refer to **Annexure 14** of 'National Operational Guidelines for ART services 2021' for further details on disclosure counselling.

Table 3.7.7: Preparing the parents/caregivers for providing HIV disclosure

Preparing the Parent/Caregiver	
Understanding caregivers' fears and concerns	It is important to know what the level of knowledge of the caregiver is about the illness before planning HIV disclosure. Provide the basic information about HIV: How does one get HIV? What are the treatment options? How can one manage the symptoms? The importance of adherence to treatment. They will then have a chance to ask questions, clarify doubts and share their concerns,
Explaining the need to disclose	It is important to explain what the consequences can be of keeping the information from the child. Children, even when not provided the information directly, can sense stressful situations. They may sometimes ask directly; sometimes, they may not ask but they will try to process information and assign meanings to what they sense, see or hear about the situation around them. The unprocessed thoughts, doubts and questions will only make them anxious and fearful. Similarly, given the fact that there is a lot of stigma around HIV, in case the disclosure is not made by the parents but by a peer, neighbour or a stranger in an abrupt and sudden manner, it may be shocking and hard for the child to process. Therefore, it is best to prepare the child and provide authentic information to avoid unnecessary traumatization.
Addressing parents/ caregivers' fears and concerns	The parents may still have concerns and fears about disclosure. It is a common belief that children will not understand if told as they are not 'mature' enough. Or it will scare children if they are told about illness, it will cause worry and anxiety in them. Therefore, using diversionary methods or completely avoiding the subject feels like an easier option. Parents should be prepared to give limited age-appropriate information to the child without going into all possible implications at the time of disclosure.
Deciding how, when and by whom disclosure will be implemented	Disclosure can either be made by the counsellor or the parent. It depends on the circumstances and the comfort of the child. In case the parents carry out the disclosure process, the counsellor can prepare them with the right script to make disclosure to the child in an age-appropriate and graded manner in order to not overwhelm him/her. The counsellor remains in the background and helps manage any difficulties (emotional, behavioural) that may arise after the disclosure.

Source: Sheila Ramaswamy, Kritii Tikku and Shekhar Seshadri; Psychosocial Care & Mental Health Concerns in Paediatric HIV; Dept. of Child and Adolescent Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore (Unpublished)

Other Counselling Messages

Nutrition and Safe Food Handling

Dietary counselling is another important component of paediatric HIV-related counselling. It is important to instruct the caregiver and the child to include a variety of nutritious food items in the CLHIV's diet, to eat small frequent meals and have plenty of fluids. Further details on nutrition and safe food handling are given in **Chapter 3.6 (Nutritional Care of HIV-infected Children).**

Counselling for personal hygiene and measures for personal safety must also be given to the child and the caregiver. This includes advice to always wash their hands with soap and water, cover the nose and mouth while coughing, covering wounds and avoiding direct contact with other people's open wounds. Mosquito nets can be used to avoid infections such as dengue or malaria. Garbage should be always kept in covered bins to avoid flies.

Immunization Advisory

The counsellor should encourage and ensure timely immunization of children with HIV. In asymptomatic CLHIV with CD4 count above 15% can be safely immunized even with live vaccines. The SMO/MO should assess the child for the safety of immunization with live vaccines. This issue is discussed in detail in **Chapter 3.1 (Management of HIV-exposed Infants and Children).**

Planning for the future of the CLHIV

When caregivers are parents who are on ART themselves, it is important to alert them to the need to plan for the future of the child in case of their own untimely death. This includes financial and legal planning. It is also important to enable the parent to identify who will be the legal guardian and caregiver in such an eventuality.

Counselling for Adolescents Living with HIV (ALHIV)

Adolescents are the individuals in the age group of 10–19 years and are in transition from being children to adults and need to be treated in a very sensitive manner.

Adolescence is a phase of overall development and includes physical, emotional and behavioural development. Physical development is characterized by the appearance of secondary sexual characteristics, rapid growth in height, voice changes and interest in sexual relationships. Emotional development is affected by the surge of sex hormones. This may cause mood swings, impulsivity, feeling ‘indestructible’, that “it won’t happen to me”, and idealistic thinking: individuality and identity are key milestones of emotional development. Behavioural changes also occur including self-consciousness, sensitivity and concern over one's own bodily changes, a strong need for peer approval, high risk-taking behaviours and role confusion whether to behave as a child or an adult.

Adolescents are different from adults, and this has implications on counselling. Even though adolescents are moving towards cognitive independence, they are confused whether they could choose and be responsible for their actions. Adults are relatively free to make decisions and choices without excessive influence from family and others. This implies that the decision opted by an adolescent may not always be right and beneficial for them. HCWs must help the adolescent understand the risks and benefits of each decision. They should help them to analyse their desires and needs and may also need to facilitate an adolescent’s discussion with parents or family on critical matters and actions.

Adolescents are more vulnerable to HIV since they lack awareness about HIV and the risks associated with different behaviours. They tend to ignore their risk of HIV infection despite being informed. They lack social skills and experience, which compromises their ability to identify the potential risks and consequences of early sexual activities and sex with multiple partners. Adolescents experiment with sexual activity and have risk-taking behaviour. Peer pressure further influences the behaviours of adolescents causing risky practices. Traditional and social norms limit the options of adolescents in receiving information regarding HIV risk.

Further, due to traditional norms like maintaining virginity till marriage, they may engage in high- risk behaviours like oral and anal sex. Due to economic issues, some adolescents quit schooling and start working at early ages. Poverty may force them to live on the streets increasing chances of high-risk activities and alcohol and drug use.

Adolescents with HIV are a newly emerging population. Sensitization of paediatricians, early infant diagnosis and large-scale free availability of ART has resulted in a large number of children with HIV reaching adolescence. This makes it very important to focus on adolescents living with HIV.

Adolescents Living with HIV: Two Distinct Populations

Depending on the mode of acquisition of HIV, ALHIV may be classified into two distinct populations:

1. **Vertically infected adolescents:** Those who have acquired HIV through vertical route: The diagnosis of HIV infection in these children may be through the 'early infant diagnosis' protocol if maternal HIV exposure is known during pregnancy/delivery. Alternatively, they may be diagnosed later when symptomatic, or through contact tracing of infected parents/ siblings. They may or may not be on ART at the time of entering adolescence.
2. **Horizontally infected adolescents:** Those who have acquired HIV infection horizontally during childhood or adolescence through sexual transmission because of unprotected sex or sexual abuse, or through parenteral transmission due to injectable drug use, unsafe surgical procedures or injections or blood transfusion. These two groups differ in some important characteristics (Table 3.7.8).

Vertically infected adolescents: These ALHIV are likely to be in an advanced stage of HIV infection. They are more likely to have OIs. Their growth and development are usually affected, especially if ART was started late/not started and they may experience a higher mortality rate. Many of them would have been diagnosed during childhood at different ages, while a small proportion may present during adolescence. Those already on ART are also likely to be highly ART-experienced with multiple changes in ARVs and harbouring multiple mutations. Their HIV status may have been either partially disclosed or not disclosed to them at all. They may have faced multiple HIV-related losses. They usually experience stigma early in life, at school, home and healthcare. Those diagnosed during adolescence are likely to have chronic medical problems and developmental delay.

Horizontally infected adolescents: Most adolescents in this group are usually in the early stages of HIV infection. They are less likely to have OIs, lower impact on growth and development and a lower mortality. They are likely to know of their HIV status if they have accessed HIV care services. They are likely to lack familial, social and clinical support system. They usually face stigma later, which may be exacerbated by stigma related to drug use and sexuality. Some of these adolescents who have acquired infection in early childhood through blood transfusion/previous surgery/ unsafe injection practices, etc. are more likely to behave like vertically infected group.

Table 3.7.8: Characteristics of adolescents with HIV

Vertically Infected Adolescents	Horizontally Infected Adolescents
Likely to be in advanced HIV stage	Earlier stages of HIV
More likely to have opportunistic infections (OIs)	OIs less likely
Growth and development usually affected	Effect on growth and development less likely
Higher mortality rate	Lower mortality
Disclosure of HIV Status: Partial/None	If accessing HIV services, likely to know status
Likely to have experienced multiple HIV-related losses	Likely to lack familial, social and clinical support system
Experience stigma early in life (school/ home/healthcare	Experience stigma later, exacerbated by stigma related to drug use, sexuality, etc.

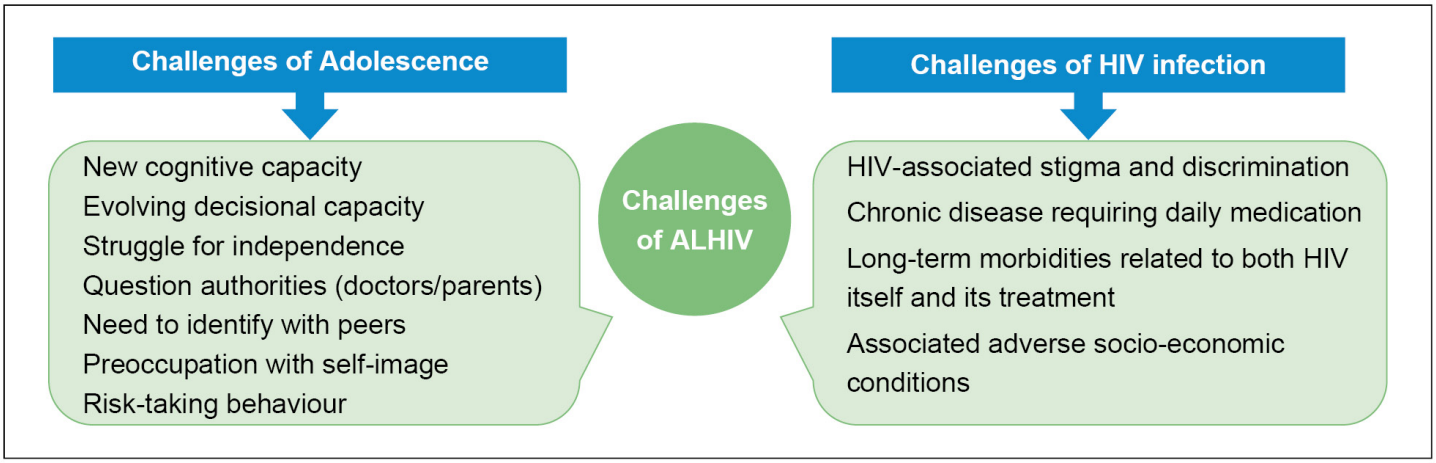
Source: USAID & PEPFAR. Transitioning of care and other services for adolescents living with HIV in Sub Saharan Africa, Technical brief, 2012. Accessed at: http://www.aidstar-one.com/sites/default/files/AIDSTAR-ne_TechnicalBrief_ALHIV_Transition.pdf

The vertically infected adolescent is a relatively newer population that has come into existence since progressively more potent and safer regimens of ART became widely available and accessible to CLHIV. These children, a large majority of whom would earlier succumb to their illness during infancy or childhood, now not only survive into adolescence but can look forward to leading a reasonably productive life as adults too. Although India has a robust care and support programme for PLHIV, providing optimum comprehensive care to these adolescents is an emerging priority. The horizontally infected adolescent, on the other hand, though vulnerable to acquire HIV, gets detected only infrequently during adolescence, the infection being usually detected during adulthood. Thus, for this group, prevention, access to safe and confidential testing and linking to HIV care services are important issues. They need to be provided accurate information about their diagnosis, care and treatment options.

Challenges Faced by ALHIV

ALHIV face challenges (Figure 3.7.2) of both adolescence and HIV infection. As adolescents, they are developing new cognitive capacity and their decision-making capacity is evolving. They struggle for independence and question the authority of doctors and parents. They feel the need for identifying themselves with peers and are often pre-occupied with self-image. This leads to risk-taking behaviour.

Figure 3.7.2: Challenges faced by ALHIV



Challenges Faced by Vertically Infected Adolescents

Vertically infected adolescents face many challenges. Unless started on ART early in childhood, they are likely to experience poor physical growth, delayed puberty and impaired bone health. They also may have delayed development and cognitive and memory impairment. They may not perform well in school, due to which dropping out of school is very common. Many long- term HIV-related morbidities including metabolic complications and those involving renal, cardiovascular or central nervous systems may become evident during adolescence. Prevalence of psychiatric and behavioural problems is also higher in these adolescents as compared to the general population. Many adolescents may not know their own HIV status and that of their parents. Some of them may have partial or even incorrect information about their disease. Many of them have development-related issues and will face challenges in transitioning from adult supervised care to self-led care expected to happen during adolescence. They are required to take daily medication for ART, the need for which they begin to question. Challenges related to long duration of ART including faltering adherence, treatment failure, treatment-related side effects and likely complex ART regimens are also commonly seen in this group. As HIV-infected patients, they face HIV-associated stigma and discrimination. They also may face adverse socioeconomic circumstances. As implications and impact of HIV infection on their life, career, relationships, etc. become evident, these adolescents are likely to suffer from many mental health-related issues.

Challenges Faced by Horizontally Infected Adolescents

Horizontally infected adolescents also face numerous, though different challenges. Many of them live on the fringes of society, hiding their sexuality, occupation or gender from their families and peers. They are difficult to reach due to criminalization of drug use, sex work, consensual sex between males and fear of arrest and abuse if their behaviour is discovered. They typically learn about their HIV status through healthcare providers but face challenge in disclosing this to caregivers or family. Transgender youth and adolescents with sexually transmitted infections (STIs) face greater challenge. Engagement and retention in HIV care is also a big challenge in these adolescents. Horizontally infected adolescents also face ART-related challenges. The detection of HIV infection gets delayed in them due to low index of suspicion in largely asymptomatic adolescents, lack of adequate youth-friendly voluntary testing facilities and requirement of parental consent for HIV testing before they reach the age of 18 years. Once they test positive, their linkage to HIV care and their retention remains poor and loss to follow-up is high between diagnosis and initiation of ART. These adolescents face familial constraints in disclosure, along with lack of emotional and financial support leading to delayed initiation of ART. Thus, they are likely to enter care late and with significant immune dysfunction.

Common challenges faced by both vertically and horizontally infected adolescents

Irrespective of the route of transmission and age at acquiring infection, there are many challenges common to all ALHIV, including the following:

- Increased likelihood of adverse family and social environment with poor support
- Difficulty in accepting and learning to cope with their diagnosis and its impact on various aspects of their life
- Increased mental stress and risk of acquiring deviant and aggressive behaviour
- Higher chance of hindered education and career-related challenges
- Difficulty in coping with relationships, following protected sexual practices and a greater risk of unwanted pregnancy

Most countries including India lack programmes tailored to meet specific requirements of ALHIV.

ALHIV and Mental Health

There is a two-way relationship between HIV infection and mental health problems. ALHIV are more prone to develop mental health problems due to social stressors such as stigma, financial difficulties and relationship difficulties. Adequate support structures are lacking for them. Mental health issues may also be associated with certain medications or with the direct effect of HIV on the brain.

Similarly, adolescents with mental health problems are more prone to acquire HIV because they are more likely to engage in risky behaviours like unprotected sex and substance abuse. They are also at risk of getting sexually abused..

Counselling ALHIV

ALHIV need long-term counselling and support not only to come to terms with their diagnosis, but also to discuss what it means to live with HIV, if and when to disclose their status to others and how to envision their future. It is important to involve adolescents in the counselling process. Many parents or guardians

continue to take key decisions without involving the adolescent. The adolescent is the primary client and focus should be on his/her needs. However, permission from the parent or guardian is essential before discussing issues with an adolescent under the age of 18 years.

Key Areas of Counselling ALHIV

Counselling needs of ALHIV can be grouped under three headings. The first group is related to 'care and treatment', which include understanding HIV, need for and living with lifelong ART, treatment adherence, disclosure of their HIV status, healthy living with HIV and nutrition. The second group of counselling needs is related to 'sex and HIV' which include growing up and changing behaviour, sex and relationships and pregnancy prevention. The third group of needs is related to 'life skills' including communication skills, handling stigma and discrimination, decision making and planning for the future. This is summarized in Table 3.7.9.

Table 3.7.9: Counselling needs of ALHIV

Care and Treatment	Sex and HIV	Life Skills
• Understanding HIV • Lifelong ART • Treatment adherence • Disclosure • Healthy living • Nutrition	• Growing up and changing behaviour • Sex and relationships • Pregnancy prevention	• Communication skills • Handling stigma and discrimination • Decision making • Planning for future

ALHIV need to have good understanding about HIV disease and how it spreads. It is important to give details about HIV infection and AIDS and discuss the role of medication and the need for lifelong therapy. Adolescents need to know about drug side effects and the importance of adherence to drug regimens. Knowledge about importance of regular follow-up is also essential.

The relationship of a counsellor/other HCWs with the adolescent is dynamic and changes as the adolescent himself/herself matures from a child to a responsible adult. As understanding develops, he/she gains new insights into his/her illness. It is important to build a strong rapport with the adolescent client and be responsive towards the ever-changing concerns the adolescent may have as he/she goes through this phase of life. Key principles of communicating with adolescents are presented in Table 3.7.10 and discussed in the following sections.

Understand their interests

One must understand their interests. Assure confidentiality of the information shared by them. Include questions about their friends, since peers are very important to them. Acknowledge their identity, as they do not want to be treated as children. Be open and non-judgemental towards their actions or behaviour.

Address their concerns

Adolescents have their own concerns. One common concern voiced by most adolescents is "Nobody understands me". The counsellor should explicitly acknowledge all their concerns.

Constructively respond to their feelings

Adolescent may feel shy, helpless, anxious, scared, defensive, resistant, embarrassed or worried. The counsellor should explain to them that it is normal to feel this way. It is important to constructively respond to their feelings as feelings may act as barriers to communication.

Help the adolescents with adherence to ART

Develop a good, open relationship with them to encourage trust and be aware of issues of alcohol/ substance use and depression. Connect them with other adolescents facing similar issues and help them practise with other drugs (vitamins, cotrimoxazole) before starting ART. It is also important to remind them to take drugs even if they are feeling well.

Table 3.7.10: Communicating with adolescents

What to Do and What to Avoid when Communicating with Adolescents	
DO	**AVOID**
• Be truthful about what you know and what you do not know.	• Giving inaccurate information (to scare them or make them "behave")
• Be professional and technically competent.	• Threatening to break confidentiality "for their own good"
• Use words and concepts that they can understand and relate to assess if they understand. • Use pictures and flipcharts to explain.	• Giving them only the information that you think they will understand • Using medical terms, they will not understand
• Treat them with respect in terms of how you speak and act.	• Talking down to them, shouting, getting angry or blaming them
• Give all the information/choices and help them decide what to do	• Telling them what to do because you know best, and they "are young"
• Treat all adolescents equally. • Be understanding and supportive even if you do not approve of their behaviour.	• Being judgemental about their behaviour, showing disapproval or imposing your own values
• Accept that they may choose to show their individuality in dress or language.	• Being critical of their appearance or behaviour, unless it relates to their health or well-being

Source- WHO (2010), 'IMAI one-day orientation on adolescents living with. HIV. Participants' manual and facilitator guide'; accessed at http://whqlibdoc.who.int/publications/ 2010/9789241598972_eng.pdf

Using the 5 As (Assess, Advise, Agree, Assist, Arrange) in ALHIV

These are a series of steps used in the integrated management of adult illness (IMAI) approach to chronic HIV care with ART, to guide health workers at each consultation.

Assess

- Assess the adolescent's goals for this consultation: assure him/her of confidentiality.
- Assess the patient's physical and mental status, understanding that HIV may progress more slowly in adolescents than in adults. Review current treatments and assess adherence.
- Assess whether they are sexually active or not (or planning to become sexually active), and whether they are using condoms and/or other contraception.

- Assess young women for pregnancy.
- Assess other risk behaviours/factors for HIV transmission (e.g., injecting drug use, alcohol use, orphan, sex worker).
- Assess the adolescent's knowledge, beliefs, concerns and daily behaviours in relation to HIV.
- Assess support structures and who knows about their HIV status (e.g., partner, family, friends).

Advise

- Advise using plain, neutral and non-judgemental attitude and language. Include parents or guardians in discussions if the adolescent is agreeable.
- Correct any inaccurate knowledge and fill gaps in the adolescent's understanding of his/her condition.
- Advise on being young and living with HIV (relationships, sex, alcohol/drug use).
- Advise on sexual activity, condom use, contraception and other aspects of positive prevention.
- Discuss couple counselling and the benefits of disclosing HIV status to chosen people to develop support structures.
- Advise on peer support from other ALHIV.
- Advise on adherence.

If developing a treatment plan

- Advise on options available to the adolescent (risk reduction, positive prevention, prophylaxis and treatment).
- Advise on the simplest regimen possible and evaluate the patient's confidence and readiness to adopt and adhere to treatment.
- Take the adolescent's developmental phase (using the Tanner scale) into consideration in prescribing ART.

Agree

- Agree where the adolescent should choose to receive treatment and support.
- Agree to whom they choose to disclose their HIV status.
- Agree on how and when they wish to disclose their status, and the support they may need.
- Agree on the roles that the adolescent and others will play in their care and treatment.
- Agree on the treatment plan that has been developed.
- Agree on goals that reflect the adolescent's priorities. Ensure that the negotiated goals are clear, measurable, realistic, under the adolescent's direct control and limited in number.

Assist

- Provide a written or pictorial summary of the plan.
- Provide referrals to adolescent-friendly health workers and services in the community, as required.
- Provide links to support services for young people living with HIV in the community.
- Provide treatments and other medications (prescribe or dispense).
- Provide condoms and contraception, as required.
- Provide skills and tools to assist with self-management and adherence, (e.g., pill box organized by day, a

calendar or other ways to remind and record the treatment plan).

- Address obstacles to adherence (e.g., side effects, weight gain, medication as a constant reminder of HIV status).
- Help patients to predict possible barriers to implementing the treatment plan and to identify strategies to overcome them.
- Assist with the patient's physical, mental and social health, including the provision of psychological support as needed; if an adolescent patient is depressed, treat for depression.
- Assist by strengthening the links with friends, family, peer support groups, community services and if possible, a treatment supporter/buddy or guardian.

Arrange

- Arrange what the adolescent will do in the time between visits to you.
- Arrange for the next appointment date: reinforce the importance of attending even if he/she feels well and has no problems.
- Arrange for referral for group counselling or reliable support group.

Disclosure in ALHIV

Disclosing the HIV status to an adolescent is important as it has a strong impact on the adherence and clinical outcomes, and adolescents need counselling support to decide when, how and to whom to disclose their HIV status.

Disclosure encourages adolescents to take more responsibility and participate in their own care. It also improves retention in care. Adolescents need ongoing support for disclosure of their own status and disclosure of parental status to them. Counselling for disclosure of their status to others would need to cover the risks and benefits of disclosure of their HIV status to others. Also, support should be provided to them while deciding when, how and to whom to disclose their HIV status.

It is important to ensure that the adolescent is ready for the process of disclosure. Encourage the parent or caregiver to assume responsibility for disclosure. One should tailor the disclosure process to meet the developmental needs and understanding of each adolescent according to age. Managing the barriers to disclosure is vital and it should be done with the support of the caregiver. Counsellors or other staff should be accessible and open to answering queries that may arise from the adolescent or caregiver during and after the disclosure. Disclosure is an ongoing process; each time the understanding of the disease improves.

Section 4

Opportunistic Infections

4.1 Introduction

Background

India had an estimated 25.44 lakhs (21.68lakh–30.38 lakh) PLHIV in 2023, with an adult (15– 49 years) HIV prevalence of 0.20%(0.17–0.25) and 35.87 thousand (24.32-54.40) AIDS-related deaths among PLHIV in 2023.[1] The national adult HIV prevalence continued to decline from an estimated peak level of 0.54% in 2000–2001 through 0.33% in 2010 to 0.22% in 2020 to 0.20% in 2023. This corresponds to a 33.3% decline in the last 10 years. Similar consistent declines were noted among both males and females at the national level. Nationally, HIV incidence was estimated at 0.05 (0.03–0.08) per 1,000 uninfected population in 2023 and it declined from 0.60 in 1996 to 0.10 in 2010 and reduced further to an estimated 0.05 in 2020. This level was maintained from 2020 to 2023.[1] This might have been due to increased number of PLHIV receiving ART, resulting in their overall well-being and significant overall reductions of OIs and related deaths, overtime. India had around 16,77,560 patients on ART as of 2022.[2]

The threat to the life of a person living with HIV is essentially due to life-threatening OIs, consequent to decline in immunity and not because of HIV per se. Thus, the major cause of morbidity and mortality among PLHIV are different OIs. Along with ART, appropriate prevention and management of OIs is as important as preventing mortality and morbidity among HIV- infected persons. The incidence of OI depends on the level of immunosuppression (occurring at CD4 cell counts of <200 cells/mm^3) and on the endemic prevalence of the causative agent.

Health-care workers involved in the care, treatment and support of PLHIV must recognize the characteristic symptom patterns of these serious and frequent OIs to be able to institute prompt and effective treatment. Early diagnosis of the HIV status and periodic interaction between HCWs and PLHIV are needed for providing appropriate preventive advice and for timely management of OIs. Screening for OIs in persons-at-risk particularly before starting ART will reduce the incidence of immune reconstitution inflammatory syndrome. Judicious use of chemotherapy and immune prophylaxis to prevent various OIs favourably impacts the survival of HIV-infected people and is necessary to maximize benefits from the ART roll-out. More widespread availability of ART is certain to reduce OI and decrease the hospitalization and mortality of HIV-infected persons. OIs remain the major driver of HIV-associated morbidity and mortality, accounting for the substantially higher mortality observed in low-to-middle income countries.

The incidence of OIs has markedly declined over the years because of the widespread availability of ARV drugs, but their impact on specific OIs has not been well documented, mainly due to low level of routine country-level monitoring for OIs.

However, OIs continue to contribute significantly to the morbidity and mortality, despite the increasing availability of ART, which will help to reduce this burden. It is important to emphasize the strategies for diagnosis of OIs, their management in patients on ART, timing of initiation of ART in the presence of an OI, recommendations during pregnancy, understanding of geographically distinctive OIs (penicilliosis and leishmaniasis) and drug interactions during concomitant administration of treatment for OIs and ART. Simple preventive measures such as eating properly cooked food, drinking boiled water, hand-washing after toilet use, avoiding situations with a high risk of infection, wearing face masks and keeping physical distancing in ‘COVID times’ and appropriate and timely immunizations go a long way in decreasing the disease burden of OIs.

Based on the systematic reviews done in various low-to-middle income countries, it was seen that ARTs have huge impact on the risk of developing OIs. In a systematic review,3 ART led to greatest reduction in incidence of all OIs during the first 12 months of ART (range 57%–91%) except for TB, and was the largest for oral candidiasis, PCP and toxoplasmosis. However, during the first year, there was also a non-

statistically significant reduction for cryptococcal meningitis, herpes zoster and oesophageal candidiasis.

Definitions of Opportunistic Infections

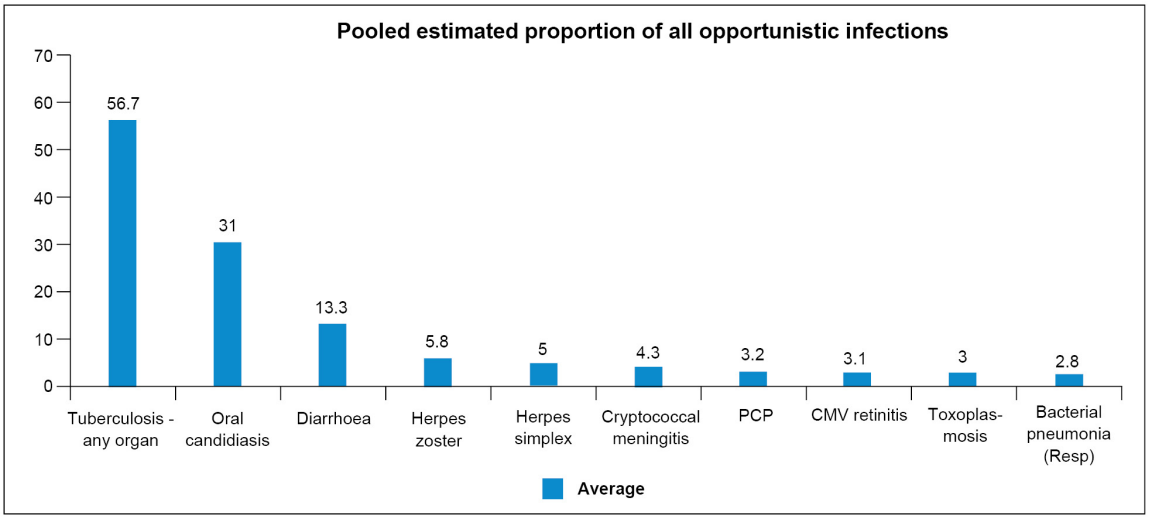
An OI is a disease caused by a microbial agent in a person with a compromised host immune system. Acquired immunodeficiency syndrome (AIDS) is defined as the occurrence of life- threatening OIs, malignancies, neurological diseases and other specific illnesses in patients with HIV infection and CD4 counts <200 cells/mm3. The appearance of many OIs correlates with the CD4 count. Tuberculosis generally develops at CD4 counts of 200–500 cells/mm3, as does Candida albicans infection. PCP generally occur at CD4 counts <200 cells/mm3 and cytomegalovirus (CMV) infection occurs when the CD4 count falls below 100 cells/mm3.

Opportunistic Infections in India

HIV disease in India has a diverse range of manifestations in multiple organ systems. Based on the review of region-specific data, range for the proportion of each OI was determined.

Figure 4.1.1 clearly shows that TB (including pulmonary and extra-pulmonary) is the most common OI presenting in PLHIV, followed by candidiasis and diarrhoea. The other OIs are herpes zoster, herpes simplex, cryptococcal meningitis, PCP, CMV retinitis, toxoplasmosis and bacterial pneumonias. Other uncommon OIs are not given in the figure as the proportions are not clear

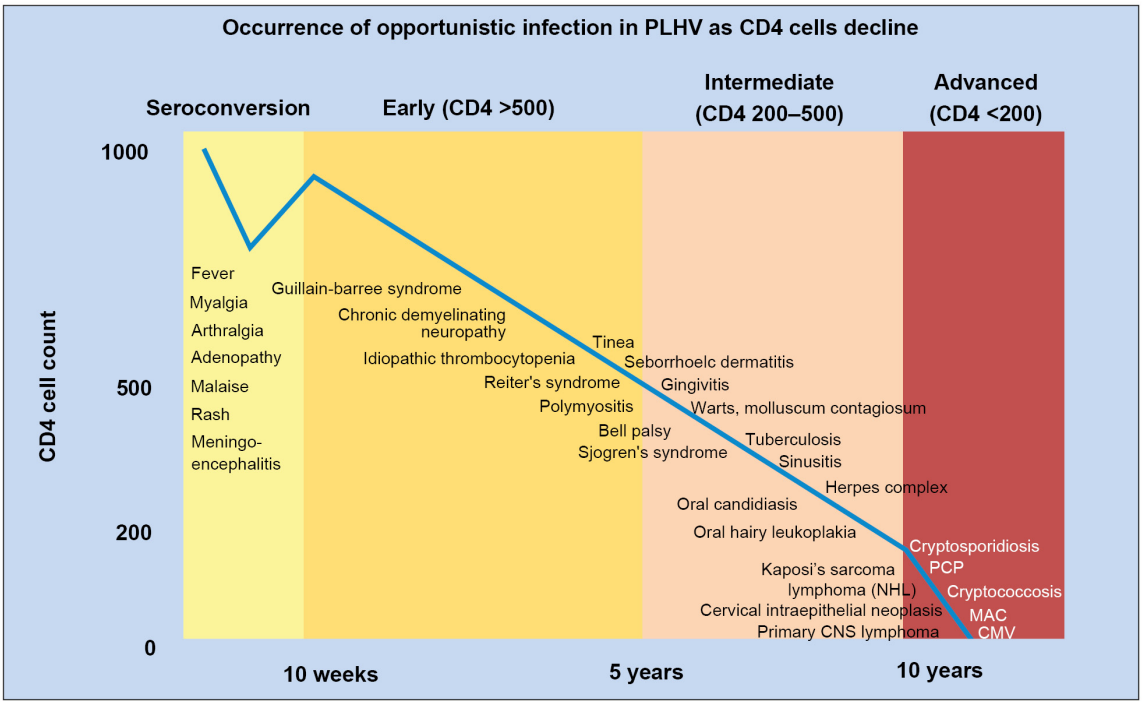
Figure 4.1.1: Proportions of opportunistic infections among PLHIV



Data on proportion of OIs is computed by comparing different geographical regions of India. (Source: Published articles in English between 2001 and 2021)

There is correlation between occurrence of OIs and CD4 count. As CD4 count decreases, there are some life-threatening OIs that make management of HIV difficult. Therefore, early identification of symptoms and adherence to appropriate treatment are extremely important. The classification of OIs based on CD4 levels is shown in Figure 4.1.2.

Figure 4.1.2: Classification of opportunistic infections based on CD4 levels



Source: Graeme JS, Irvine SS, Scott M, Kelleher AD, Marriott DJE, McKnight I, Pethebridge AM, Wodak A, Ziegler J.Editors. Strategies of care in managing HIV. Sydney: Australasian Medical publishing Company Limited 1997.

Table 4.1.1 gives the OIs according to pathogens that are possible in the Indian context.

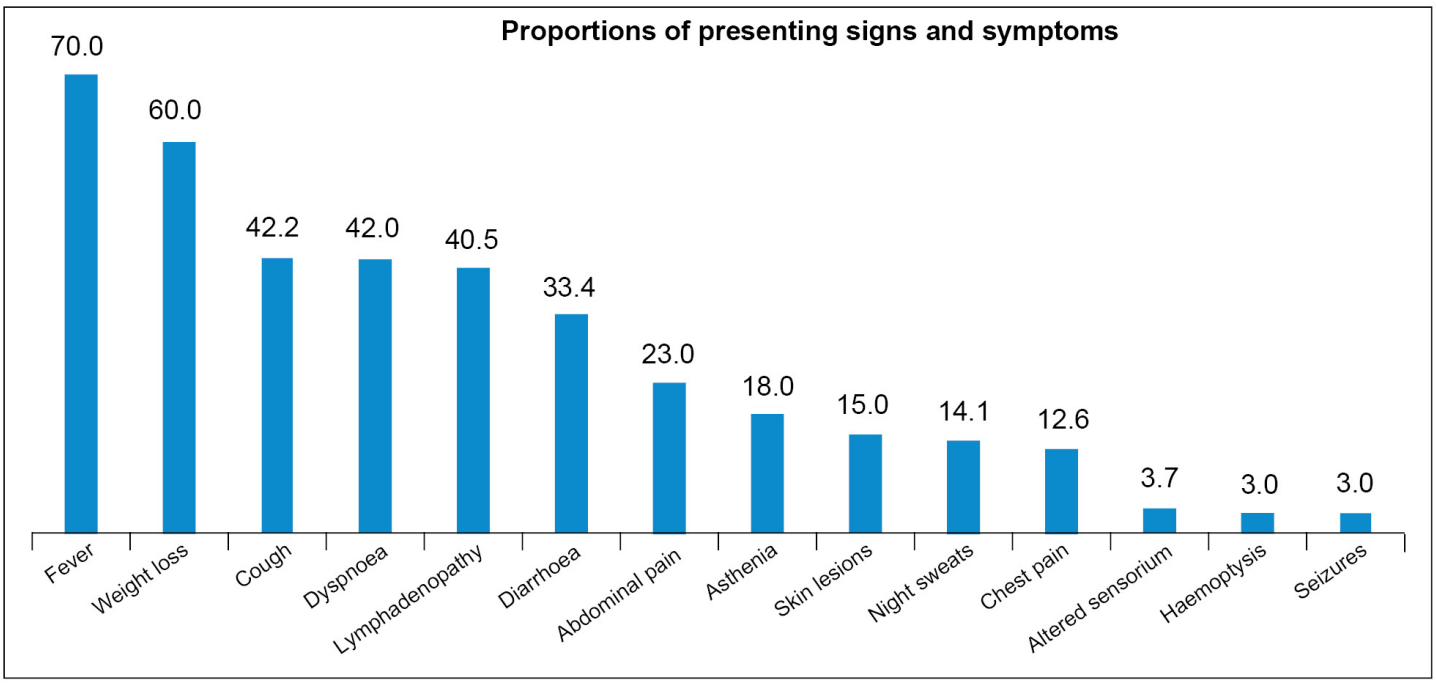
Table 4.1.1: Classification of opportunistic infections based on pathogen

Bacterial	Viral	Fungal	Parasites
Tuberculosis **Respiratory:** • Streptococcus pneumoniae • Haemophilus influenza • Staphylococcus aureus **Intestinal:** • Salmonella • Shigella • Escherichia coli • Clostridium difficile • Mycobacterium avium complex (MAC) disease	• Varicella zoster • Herpes simplex virus (HSV) • Cytomegalovirus (CMV) • Human papilloma (HPV) • Epstein Barr virus: ▪ Oral hairy leucoplakia ▪ Lymphoma • JC virus (PML) • Human herpesvirus-8 (HHV-8) ▪ Kaposi's sarcoma	• Candidiasis (Oral/ oesophageal/ vaginal) • Pneumocystis jiroveci pneumonia (PCP) • Cryptococcus meningitis • Talaromyces marneffei (Penicillium) • Histoplasma capsulatum	• Toxoplasmosis Intestinal: • Cryptosporidium • Isospora • Microspora • Giardia • Entamoeba histolytica

Common Symptoms and Signs of OIs in HIV

The most common symptoms and signs presented are weight loss, fever, cough, diarrhoea and lymphadenopathy. There are some specific signs and symptoms pertaining to a particular OI that are covered in subsequent chapters.

Figure 4.1.3: Presenting symptoms and signs among PLHIV



Data on proportion of presenting signs and symptoms is computed by comparing different geographical regions of India (Source: Published articles in English between 2001 and 2021)

Table 4.1.2: Various opportunistic infections based on presentation in different systems

Respiratory System	Gastrointestinal System	Central Nervous System	Skin and Mucous Membranes
• Mycobacterium tuberculosis • Bacterial pneumonia • Pneumocystis jiroveci pneumonia • Mycobacterium avium complex • Toxoplasmosis gondii • Penicillium marneffei (Talaromycosis) • Histoplasmosis • Nocardiosis • Aspergillosis	• Candidiasis (Oral and oesophageal) • Necrotizing gingivitis • HSV lesions • Epstein Barr infection (oral hairy leucoplakia) • Kaposi's sarcoma • Aphthous ulcer and oesophagitis • Acute and chronic diarrhoeas (including enteric pathogens/ parasitic infections)	• Toxoplasmosis • CMV disease • Bacterial meningitis • Tuberculous meningitis • Progressive multifocal leukoencephalopathy (PML) • Neurosyphilis	• Staphylococcal aureus (bullous impetigo, skin abscess or pyomyositis furunculosis or folliculitis) • Bacillary angiomatosis • Lupus vulgaris • Scrofuloderma • Cutaneous manifestations of syphilis • Candidiasis • Tinea infections • Systemic mycosis • HHV-8 (Kaposi's sarcoma) • Herpes zoster • Molluscum contagiosum • Orolabial herpes, genital herpes • Xerosis/Ichthyosis • Seborrheic dermatitis • Drug reactions/Pruritic papular eruptions

Common Diagnostics and Treatment-related Challenges of Opportunistic Infections

Diagnosis and treatment of OIs are important to reduce the morbidity and mortality due to OIs. Let us discuss some of the common diagnostics- and treatment-related challenges of the most common OIs.

Diagnostics-related challenges

Tuberculosis

- The diagnosis of TB is challenging due to paucibacillary TB forms and atypical clinical presentations of disseminated TB and poor sensitivity of existing screening tests available, especially in PLHIV with lower CD4 counts.
- It is difficult to get a good clinical specimen from extra-pulmonary site, especially in CLHIV for NAAT testing.
- Facilities for diagnosis of EPTB are not present in all ART centres like ultrasound and ophthalmoscopy and lead to multiple visits by patients to ART centres for diagnosis.
- **Candidiasis:** Oesophageal candidiasis is missed due to non-availability of referral facilities like endoscopy at some ART centres.
- **Pneumocystis jiroveci pneumonia (PCP):** Usually diagnosed clinically, hence there is an ongoing need to train medical officers to enable them to suspect PCP.
- **Cryptococcal meningitis:**
- CSF sample collection: Reluctance to perform lumbar puncture.
- Challenge to differentiating between new and relapse cases as culture testing is not available everywhere.
- **Toxoplasmosis:** Challenge to get brain imaging done on priority for early diagnosis.
- **Chronic diarrhoea (cryptosporidiosis/isosporiasis):** Lack of sensitization across all ART centres leads to lesser diagnosis.
- **CMV retinitis:** Ophthalmologist needed for confirmation.

Treatment-related challenges

- Cryptococcal meningitis:
- Long duration of follow-up during the maintenance phase of treatment.
- Treatment options in relapse cases are limited.
- Non-availability of certain OI drugs at ART centre.

4.2 Central Nervous System

Introduction

HIV is a neurotropic virus and has a predilection to infect the nervous system. HIV affects the nervous system in two ways: directly by the neurotropic effects of the virus itself and through the OIs of the nervous system as shown in Table 4.2.1. Any level of the neuroaxis can be involved, including the brain,

meninges, spinal cord, nerve and muscle.

Neurologic disease is the first manifestation of symptomatic HIV infection in roughly 10%–20% of people, whereas about 60% of patients with advanced HIV disease will have clinically evident neurologic dysfunction during their illness.

Table 4.2.1: Neurological manifestations of HIV infection

HIV Related	OI related
Acute aseptic meningitis	Cryptococcal meningitis
Chronic meningitis	Cerebral toxoplasmosis
HIV-associated neurocognitive disorder (HAND),	CMV retinitis and encephalitis
HIV encephalopathy (AIDS dementia)	Progressive multifocal leukoencephalopathy (PML)
Vacuolar myelopathy	Primary CNS lymphoma
Peripheral neuropathy (sensory)	Tuberculosis
Myopathy	Syphilis

Neurological Syndromes in PLHIV

Neurological manifestations can be broadly classified into global cerebral syndrome, focal neurological syndrome, encephalitis, myelitis and neurocognitive decline. The syndromes are classified primarily based on the part of the neuroaxis affected and the constellation of symptoms (Table 4.2.2).

Table 4.2.2: Key combination of symptoms in PLHIV and associated OIs

Syndrome	Clinical Features	Aetiology
Meningitis	Headache, fever with nausea/ vomiting, altered consciousness	Tuberculosis, cryptococcosis, syphilis and other bacterial infections
Focal cerebral lesions	Headache, focal neurological signs, convulsions	Tuberculoma, toxoplasmosis, Progressive multifocal leukoencephalopathy (PML), syphilis, primary CNS lymphoma, neurocysticercosis
Encephalitis	Cognitive impairment, psychiatric features, altered consciousness, convulsions	Cytomegalovirus, herpes simplex (HSV), toxoplasmosis
Myelitis	Sensory disturbances, paraparesis, sphincter disturbance	Cytomegalovirus, herpes virus (Herpes simplex and zoster), syphilis, toxoplasmosis, tuberculosis
Neurocognitive decline	Memory loss, behavioural abnormalities, motor function deterioration	HIV-associated neurocognitive disorder (HAND)

It is important to remember that there may be coexistent involvement of other organs/organ systems in patients with neurological manifestations and it is crucial to look at the complete clinical picture while making a differential diagnosis.

Cryptococcal Meningitis

Epidemiology

Cryptococcal disease is an opportunistic fungal infection that occurs primarily among people with advanced HIV disease and is an important cause of morbidity and mortality. It is caused by the encapsulated yeast of Cryp¬tococcus neoformans or C. gattii. Among these two, C. neoformans is more commonly associated with meningitis in immunocompromised patients. Cryptococcal anti¬genemia is considered an independent predictor of Cryptococcal meningitis (CM) in PLHIV with advanced immunosuppression. Cryptococcus, the causative agent of cryptococcal disease, is found in the environment worldwide. Exposure to the organism occurs through inhalation but rarely results in clinically significant invasive disease in the general population. Clinically significant invasive disease is thought to be primarily caused by reactivation of latent infection among immunocompromised individuals, such as PLHIV, months to years after initial exposure. Cryptococcal disease is far less common among children with HIV, even in areas with a high disease burden among adults.

By far, the most common presentation of cryptococcal disease is cryptococcal meningitis, which **accounts for an estimated 15% of all AIDS-related deaths** globally,[1] three quarters of which are in sub-Saharan Africa. Globally, an estimated 223,100 cases of Cryptococcal meningitis resulted in 181,100 deaths among PLHIV in 2014. A systematic review[2] of 60 observational studies done globally indicates that the pooled prevalence of Cryptococcal antigenemia was 6.4% (95% CI 5.7– 7.2%; 55 studies) among people with a CD4 cell count ≤100 cells/mm^3 and 2.0% (95% CI 1.2–2.7%; 21 studies) among people with a CD4 cell count of 100–200 cells/mm^3.

Mortality from CM is highest in developing low-income countries, accounting for around 70%– 80% in low-income versus only 20%–30% in high-income countries.[1]

A major reason for this high mortality is delay in diagnosis, largely because of limited access to lumbar puncture and rapid diagnostic assays. Further contributing factors are the limited availability and high cost of first-line antifungal drugs. Another important contributor to mortality is the limited ability in developing countries to monitor and manage treatment-limiting toxicities and the frequent complications of raised intracranial pressure (ICP) as well as immune reconstitution inflammatory syndrome associated with cryptococcal meningitis and ART.

Clinical Manifestations

Cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis. Most patients with early cryptococcal meningitis develop nonspecific symptoms consisting of fever and headache, and approximately 65%–75% do not have the classic signs of meningeal irritation early in their course of meningitis. As the disease progresses, more neurologic-specific manifestations typically develop, including altered mental status, neck stiffness or cranial nerve abnormalities.

Some patients experience encephalopathic symptoms, such as lethargy, altered mentation, personality changes and memory loss that are usually a result of increased intracranial pressure.

Box 1: Ask, look and investigate for Cryptococcal meningitis

- Ask for onset of symptoms suggestive of meningitis. Do not miss the non-specific symptoms; if patient is on ART, ask about the duration on ART to rule out IRIS.
- Look for the umbilication to differentiate between Molluscum and Cryptococcoma skin lesions.
- Serum CrAg is indicated in all PLHIV presenting with CD4 counts <200 cells/mm^3 with or without symptoms suggestive of cryptococcal meningitis.
- In patients presenting with severe headache while on Cryptococcal meningitis treatment, therapeutic cerebrospinal fluid tap is indicated.
- Refer all patients with positive serum CrAg for lumbar puncture.
- A negative result on India ink does not rule out cryptococcal meningitis.

Cryptococcosis usually is disseminated when diagnosed in an HIV-infected patient. Any organ of the body can be involved, and skin lesions may show myriad different manifestations, including **umbilicated skin lesions mimicking molluscum contagiosum** – Figure 4.2.1

Isolated pulmonary infection is also possible but rare; symptoms and signs include cough and dyspnoea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as an acute respiratory distress syndrome and mimic PCP.

Figure 4.2.1: Cutaneous cryptococcosis (*Courtesy CoE, BHU, Varanasi*)



Diagnosis

Cryptococcal meningitis can be diagnosed through cerebrospinal fluid (CSF) culture, microscopy or by detection of CrAg. Diagnosis is said to be confirmed when Cryptococcus is identified in the CSF or CNS tissue.

Cryptococcus may be occasionally identified on a routine Gram stain preparation of the CSF also. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases.

Analysis of CSF generally demonstrates mildly elevated levels of protein, low-to-normal glucose concentrations and pleocytosis consisting of mostly lymphocytes. The opening pressure in the CSF may be elevated, with pressures ≥25 cm H_2O occurring in 60%–80% of patients.

CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infections and may be present weeks to months before onset of symptoms. A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. (Please refer to the flow diagram in Figure 4.2.2) **The tests for the diagnosis of Cryptococcal disease are summarised in Table 4.2.3.**

Table 4.2.3: Tests for the diagnosis of Cryptococcal infection

Type of Test	Sample Required	Methods of Testing
Antigen detection	Serum or CSF	CrAg LFA*
Microscopy	CSF	Gram staining/India ink
Culture	CSF	Fungal culture media

*CrAg test is currently not available in programme. CSF: cerebrospinal fluid; LFA: lateral flow assay.

For PLHIV suspected of having CM, prompt lumbar puncture with measurement of CSF opening pressure and rapid CrAg assay is recommended as the preferred diagnostic approach. The following diagnostic approaches are recommended based on availability of testing facility:

A. Settings with access to and no contraindication for lumbar puncture:

1. If CrAg assay is available, lumbar puncture with rapid CSF CrAg assay is the preferred diagnostic approach.
2. If CrAg assay is not available, lumbar puncture with CSF India ink test examination is the preferred diagnostic approach.

B. Settings without access to lumbar puncture or when lumbar puncture is clinically contraindicated (such as significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs or recurrent seizures):

1. If CrAg assay is available, serum, plasma or whole blood CrAg are the preferred diagnostic approaches.
2. If a CrAg assay is not available, prompt referral for further investigation and treatment as appropriate.

Screening and Prevention

Screening for CrAg followed by pre-emptive antifungal therapy among CrAg-positive people to prevent the development of invasive cryptococcal disease is recommended under the national programme, before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <200 cells/mm^3.

Screening is not recommended for children (<10 years), given the low incidence of CM in this age group.

Use of serum CrAg test and its eligibility criteria: It has been documented that CrAg LFA is reliable, robust and easy to perform and should be used to diagnose cryptococcal infections among PLHIV. It is recommended to use it in any PLHIV with CD4 counts below 200 cells/ mm^3.

Table 4.2.4: Interpretation and management based on CrAg* in PLHIV with CD4 counts <200 cells/mm^3

	S. CrAg*	CSF CrAg	Recommendations
CD4 counts <200 cells/mm^3 with symptoms of meningitis	+ve	+ve	Treat as Cryptococcal meningitis
	+ve	-ve/not feasible	• If symptomatic, treat for Cryptococcal meningitis • If asymptomatic, pre-emptive treatment
	-ve		• If patient is symptomatic, consider evaluating for other causes. • If asymptomatic, standard package of care
	Not feasible		• If patient is symptomatic, consider evaluating for TB, Cryptococcal meningitis and bacterial meningitis. May consider presumptive treatment for Cryptococcal meningitis/bacterial meningitis based on symptoms or reports • If asymptomatic, Fluconazole primary prophylaxis if CD4 count <100 cells/mm^3
*CrAg test is currently not available in the national programme			

Pre-emptive treatment for PLHIV with asymptomatic cryptococcal infection:

It is important to offer pre-emptive antifungal treatment if asymptomatic PLHIV test positive for cryptococcal infection (CrAg test).

Everyone testing positive for serum or plasma (or whole blood) CrAg during screening should be carefully evaluated for signs and symptoms of meningitis to exclude active Cryptococcal meningitis, before initiating pre-emptive treatment.

The dosage and duration of pre-emptive antifungal treatment (as per NACO Technical Resource Group recommendation) is as follows:

Induction phase: Fluconazole (800 mg/day for adults; 12 mg/kg/day for adolescents) for 2 weeks

Consolidation phase: Fluconazole (800 mg daily for adults; 6–12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily) for 8 weeks

Maintenance phase: Fluconazole (200 mg daily for adults, 6 mg/kg/day for children and adolescents) until evidence of immune reconstitution

Criteria for discontinuing Fluconazole maintenance treatment should take into consideration of ALL the following:

- Person is adherent to ART and free of cryptococcal disease
- Fluconazole maintenance treatment given for at least 1 year
- CD4 cell count ≥100 cells/mm^3
- Suppressed plasma viral load (Plasma viral load <1000 copies/ml)

The pre-emptive antifungal treatment is recommended in pregnant women as well; however, proper counselling should be provided.

Timing of ART initiation: The NACO accepted the recommendation of WHO.

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have Cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment. Thus, ART should be initiated between 4 and 6 weeks after undergoing antifungal treatment.[3]

Primary prophylaxis: It is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance and cost.

In case CrAg test is not available, primary prophylaxis may be given to HIV-positive adults and adolescents who have CD4 cell count <100 cells/mm^3. For this, the recommended dosage shall be Fluconazole 100 mg OD and the criteria for discontinuing fluconazole primary prophylaxis should take into consideration ALL the following criteria:

- Person is adherent to ART and free of cryptococcal disease.
- Fluconazole given for at least 1 year
- CD4 cell count ≥100 cells/mm^3
- Suppressed viral load (Plasma viral load <1000 copies/ml)

Secondary prophylaxis: Also known as maintenance phase of treatment (See below)

Management

Treatment guidelines for Cryptococcal meningitis and its duration:

Dosage and duration of treatment for Cryptococcal meningitis are mentioned in Table 4.2.5.

Table 4.2.5: Recommendations for treatment of Cryptococcal meningitis

Treatment Phase	Preferred Regimen	Alternative 1	Alternative 2
Induction Phase	Amphotericin B* deoxycholate (1 mg/kg/day) and Flucytosine* (25 mg/kg QID) for 1 week **Followed by:** Fluconazole* (1200 mg/day for adults, 12 mg/kg/day for children/ adolescents up to a maximum dose of 800 mg/day) for 1 week	Two weeks of Fluconazole (1200 mg daily for adults; 12 mg/kg/ day for children/ adolescents and Flucytosine (25 mg/ kg QID)	Two weeks of Amphotericin B deoxycholate (1 mg/kg/day) and Fluconazole (1200 mg daily for adults; 12 mg/kg/day for children/adolescents
Consolidation phase	Fluconazole (400–800 mg daily for adults; 6–12 mg/kg/day for children/ adolescents, up to a maximum of 800 mg daily) for 8 weeks		
Maintenance (or secondary prophylaxis)	Fluconazole (200 mg daily for adults; 6 mg/kg/day for children/ adolescents)		
Discontinuing Fluconazole maintenance treatment	It is recommended that, after successful treatment of cryptococcal disease (meningeal and non-meningeal), the criteria for discontinuing fluconazole maintenance treatment should take into consideration ALL the following: • Person is adherent to ART and free of cryptococcal disease • Fluconazole maintenance treatment given for at least 1 year • CD4 cell count ≥100 cells/mm^3 • Suppressed viral load (Plasma viral load <1000 copies/ml)		

*Medication for the treatment of cryptococcal meningitis such as Amphotericin B, Flucytosine and Fluconazole will be made available from SACS/the institution. ART Medical Officer to request the SACS/Institution superintendent for procurement of these drugs.

ART Initiation

Timing of ART initiation: Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have CM because of the risk of increased mortality and should be deferred by 4 to 6 weeks from the initiation of antifungal treatment. Thus, ART should be initiated between 4 and 6 weeks after successful antifungal treatment.

Special Recommendations

Managing raised ICP

CM is often associated with increased ICP (opening pressure greater than 20 cm H_2O). Appropriate and timely management of increased ICP can improve survival and neurologic outcomes.

Following steps can be taken to manage raised ICP occurring in CM:

1. Lowering the opening pressure at initial lumbar puncture: If the opening pressure is elevated, the recommended approach is to remove ample CSF (20 to 30 ml) to reduce the opening pressure to a normal pressure (less than 20 cm H_2O), or at least by 50% if not able to achieve a normal pressure with removal of 20 to 30 ml.

2. Serial lumbar punctures: Serial lumbar punctures with CSF drainage may be required daily to maintain opening pressure less than 20 cm H_2O.
3. Use of lumbar drains or ventriculostomy: If the person initially has focal neurologic deficits, or serial lumbar puncture with removal of CSF fails to control increased ICP, a lumbar drain or ventriculostomy may be required.
4. Medical therapy for reducing ICP: For persons with acute CM, attempts to treat increased ICP with medical therapy, such as mannitol, acetazolamide or corticosteroids, is not effective and is not recommended.

Table 4.2.6: Managing Amphotericin B toxicity

Scenario	Recommendations
Administration of amphotericin B* deoxycholate	• Amphotericin B powder should be reconstituted in sterile water; add the calculated volume of reconstituted antifungal into 1 litre of 5% dextrose water and administer within 24 hours. • Amphotericin B can be administered via a peripheral intravenous (IV) line if the solution contains ≤0.1 mg of amphotericin B per 1 ml of 5% dextrose water. • The solution should be infused over at least 4 hours.
Prevention of amphotericin B deoxycholate-related toxicities	• Adults should be pre-hydrated with 1 litre of normal saline containing 1 ampoule of potassium chloride (20 mmol) infused over 2 hours before the amphotericin B infusion. • Twice-daily oral potassium and daily oral magnesium supplementation should be administered to adults. • To minimize the risk of phlebitis, lines should be flushed with normal saline immediately after the amphotericin B infusion is complete and the infusion bag should not be left attached to the IV administration set after the infusion is complete.
Monitoring of patients receiving amphotericin B	• Days 0, 3 and 7: Creatinine, sodium and potassium levels (and magnesium if available) • Days 0 and 7: Full blood count (with a differential count if available)
Management of amphotericin B-related toxicities	**Refer Annexure 19.9** • Febrile reactions can be treated with paracetamol 1 g 30 min before infusion (if severe, hydrocortisone 25 mg IV can be given before subsequent infusions).

*Liposomal Amphotericin B is preferred over the conventional amphotericin B formulation due to less incidence of adverse effects. However, it is much more expensive.

Managing relapse

Relapse is defined as recurring clinical features of CM because of recurrent or ongoing C.neoformans growth in the CNS, diagnosed by a positive CSF fungal culture.

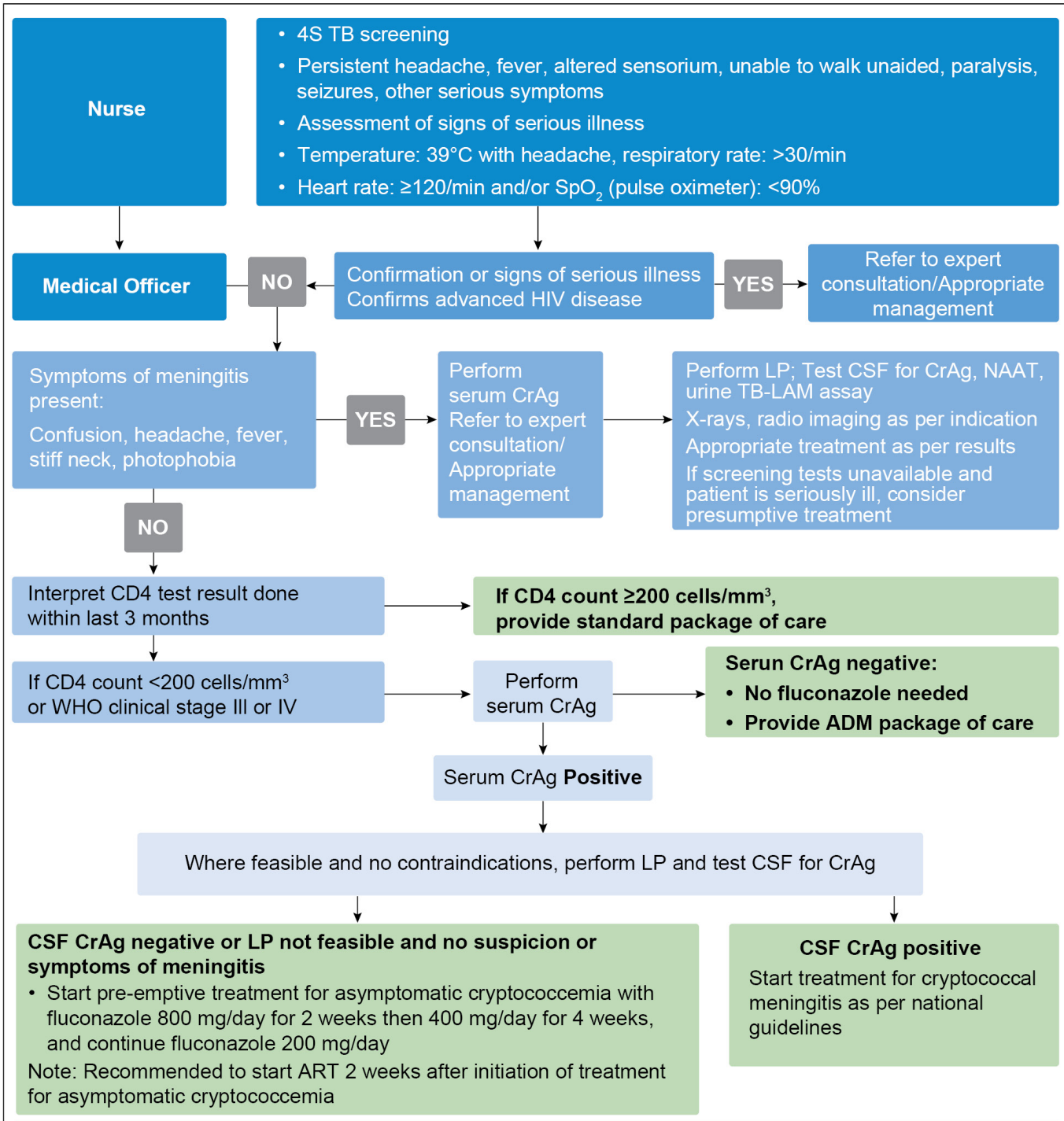
Table 4.2.7: Causes of relapses of cryptococcal meningitis

Aetiologies	Causes	Management
Possible causes of cryptococcal meningitis relapse	**Fungal** • Inadequate induction therapy (e.g., suboptimal amphotericin B deoxycholate administration because of toxicity) • Non-adherence to fluconazole consolidation or maintenance therapy • Fluconazole resistance (uncommon if preferred induction regimens are used) • Central nervous system (CNS) cryptococcomas or gelatinous pseudocysts (requiring prolonged induction therapy) • Immunological failure because of virological failure of ART	**Non-adherence** Patient should be treated as first episode and enhanced adherence counselling should be given.
Paradoxical immune reconstitution inflammatory syndrome (IRIS)	• Features of IRIS (most cases have negative cerebrospinal fluid [CSF] fungal culture) • Occurs weeks to months after ART initiation • Because of an inflammatory response directed at antigens of non-viable fungus • Associated with higher CSF white cell counts compared to the initial (culture positive) episode of cryptococcal meningitis • Frequently accompanied by raised intracranial pressure and can be associated with focal brain inflammation and/or mass lesions	In all patients with suspected paradoxical CM-IRIS, a lumbar puncture should be performed to measure pressure and obtain a fungal culture incubated for up to 14 days.
Persistently elevated intracranial pressure	• Thought to be mediated by occlusion of arachnoid granulations by fungi and fungal capsule; this does not necessarily imply cryptococcal meningitis treatment failure.	Refer to higher centres to rule out other causes
Unrelated to cryptococcal meningitis		
1. Tuberculous meningitis 2. Viral or bacterial meningitis 3. Space-occupying lesion with cerebral oedema (e.g., tuberculoma, CNS malignancy) or hydrocephalus 4. Non-infective (e.g., tension headache)		Treat according to causes

There is no role for India ink staining or CSF/blood CrAg assays in establishing the cause of recurrence, as these tests may remain positive for months to years in patients after successful treatment.

If the CSF is culture-positive and non-adherence does not appear to be the cause, then fluconazole susceptibility testing should be considered.

Figure 4.2.2: Operational flow for screening and management of Cryptococcal Meningitis



Management of cryptococcal meningitis

Treatment Phase	Drugs
Induction	Amphotericin B (0.7–1 mg/kg) + Fluconazole (1200 mg daily for adults); (children 12 mg/kg) for 1 week: followed by Fluconazole (1200 mg/day for adults, 12 mg/kg/day for children/adolescents, up to a maximum dose of 800 mg/day) for 1 week
Consolidation	Fluconazole (400–800 daily for adults: 6–12 mg/kg/day for childrel/adolescents, up to maximum of 800 mg daily) for 8 weeks
Maintenance	Fluconazole (200 mg daily for adults; 6 mg/kg/day for children/adolescents)
Discontinuation of mainteance phase	It is recommended that, after successful treatment of Cryptococcal disease (meningeal and non-meningeal), the criteria for discontinuing Fluconazole maintenance treatment should take into consideration ALL the following: • Person is adherent to ART and free of cryptococcal disease • Fluconazole maintenance treatment given for at least 1 year • CD4 cell count ≥100 cells/mm3 • Suppressed plasma viral load (PVL<1000 copies/mL)

CrAg test is not performed for children aged <1O years
*Currently TB-LAM screening and CrAg screening test for cryptococcal infection are not available in the programme

Toxoplasmosis

Epidemiology

Toxoplasma encephalitis (TE) is caused by the protozoan Toxoplasma gondii. T. gondii is an obligate intracellular parasite. Cats are the definitive host.

Transmission occurs **by eating food contaminated with oocytes from cat faeces** or from tissue cysts in undercooked meat from domesticated animals. Most cases of toxoplasmosis in persons with HIV result from reactivation of latent T. gondii cysts as immunity wanes. Primary infection occasionally is associated with acute cerebral or disseminated disease. Asymptomatic infection is common in immunocompetent adults (20%–50% normal adults are IgG seropositive). Latent infection (reflected by +ve IgG in serum) may become reactivated in immunocompromised patients.

Toxoplasma infection remains the **most common cause of focal brain lesions** among PLHIV despite the decline in OIs with the introduction of ARV treatment and prophylaxis for OIs.

A study done by PGIMER, Chandigarh, India,[4] from January 2004 to October 2014 depicted the percentage of toxoplasma seroprevalence over the 10-year study duration. A decline in seroprevalence from 2004 to 2014 was noted in HIV/AIDS patients (22.2% to 4.7%). Overall, 18.9% seroprevalence of toxoplasma among HIV/AIDS patients and 17.1% in post-transplant recipients was seen.

Clinical disease is rare among patients with CD4 count >200 cells/mm^3. Patients with CD4 counts <50 cells/mm^3 are at greatest risk. The organism is not transmitted through person-to-person contact.

Clinical Manifestations

Among patients with AIDS, the most common clinical presentation of T. gondii infection is focal encephalitis with headache, confusion or motor weakness and fever. Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms. Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, coma and death. Retinochoroiditis, pneumonia and evidence of other multifocal organ system involvement can occur but are rare in patients with AIDS.

Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will typically show multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated oedema. Toxoplasmosis also can manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies. This latter presentation tends to be rapidly progressive and fatal.

Box 2: Ask/Look for Toxoplasmosis

Ask for symptoms of headache and confusion.

Ask for symptoms of convulsions, stupor.

Look for motor weakness/focal deficits

On CT scan or MRI, multiple ring-enhancing lesions clinch the diagnosis of toxoplasma encephalitis.

Always perform imaging first, then a lumbar puncture (if indicated) in case of focal lesions to prevent coning

Diagnosis

Serum IgG and IgM anti-toxoplasma antibodies can be estimated, but do not indicate active disease. The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible.

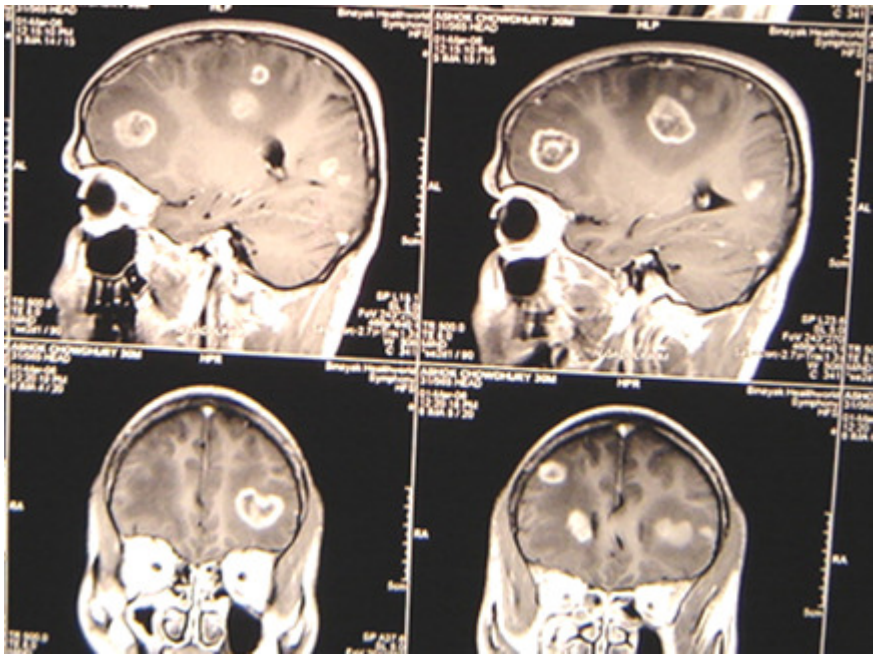
Polymerase chain reaction (PCR) tests have high specificity but low sensitivity and are not easily accessible.

CT or MRI scans showing focal lesions may be helpful in making a diagnosis. Lesions are usually ring-enhancing and have a predilection for the basal ganglia. Positron emission tomography or single - photon emission computed tomography scanning may be helpful in distinguishing between TE and primary CNS lymphoma, but no imaging technique is completely specific.

Stereotactic CT-guided brain biopsy is reserved for patients who fail to respond to therapy.

Definitive diagnosis of TE requires a compatible clinical syndrome; identification of one or more mass lesions by CT or MRI and detection of the organism in a clinical sample.

Figure 4.2.3: Multiple Toxoplasma in brain



(Image courtesy: CoE, STM, Kolkata)

Box 5: Clinical Profile of Progressive Multifocal Leukoencephalopathy

- Positron emission tomography or single-photon emission computed tomography scanning may be helpful in distinguishing between toxoplasmosis encephalitis and primary central nervous system (CNS) lymphoma, but no imaging technique is completely specific.
- The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leukoencephalopathy (PML).
- In the absence of immune reconstitution inflammatory syndrome, PML (but not lymphoma) can be distinguished based on imaging studies.
- PML lesions typically involve white matter rather than grey matter, are non-contrast enhancing, and produce no mass effects.
- Less common causes of focal neurologic disease in patients with AIDS include mycobacterial infection (especially tuberculosis); fungal infection, such as cryptococcosis; Chagas disease; and pyogenic brain abscess, particularly in IV drug abusers.

Suspected/symptomatic PLHIV should be tested for IgG antibody to toxoplasma soon after they are diagnosed with HIV to detect latent infection with T. gondii.

Management

Table 4.2.8: Management of toxoplasma encephalitis

Acute infection: Total duration is 6 weeks	
Preferred regimen	
Pyrimethamine 200 mg PO once, followed by dose based on body weight.	
Body weight ≤60 kg	Pyrimethamine 50 mg OD + Sulfadiazine 1000 mg QDS + Leucovorin 10–25 mg OD (can increase to 50 mg OD or BD)
Body weight >60 kg	Pyrimethamine 75 mg OD + Sulfadiazine 1500 mgQDS + Leucovorin 10–25 mg OD (can increase to 50 mg OD or BD)
Alternatives:	
Pyrimethamine plus clindamycin 600 mg IV or PO QDS; preferred alternative for patients intolerant to sulfadiazine or who do not respond to pyrimethamine– sulfadiazine (or) TMP–SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BD	
Chronic Maintenance Therapy for Toxoplasma gondii Encephalitis	
Preferred Regimen:	
Pyrimethamine 25–50 mg OD + Sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + Leucovorin 10–25 mg OD	
Alternatives:	
Clindamycin 600 mg TDS + (Pyrimethamine 25–50 mg + Leucovorin 10–25 mg) OD (or) TMP-SMX 1 tablet BD, or TMP-SMX DS 1 tablet OD	
Discontinuing chronic maintenance therapy: Patient who has successfully completed initial therapy, remains asymptomatic of signs and symptoms of toxoplasma encephalitis and CD4 count >200 cells/ mm^3 for >6 months in response to ART	

Prophylaxis

Prophylaxis for TE is classified as either primary prophylaxis (preventing the first episode of TE) or maintenance therapy (secondary prophylaxis) for preventing the recurrence of TE. CPT protects PLHIV from PCP, toxoplasmosis and other bacterial diseases. The double-strength-tablet once daily dose of Cotrimoxazole, which is the preferred regimen for PCP prophylaxis, is also effective against TE and is recommended. (Please refer **Chapter 2.9 [Prevention of Opportunistic Infections for more details]**).

In case of allergy to Cotrimoxazole, an alternative for primary prophylaxis against PCP and toxoplasmosis is dapsone 100 mg once daily. Desensitization may be suggested for sulpha allergy.

Cytomegalovirus Disease

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes virus family that can cause disseminated or localized end-organ disease in PLHIV with advanced immunosuppression. CMV can cause invasive disease, including CMV retinitis, colitis, esophagitis and neurologic disease. In persons with HIV, retinitis is the most common manifestation of CMV-related end-organ disease. Most clinical disease occurs in individuals previously infected with CMV (seropositive) who have a CD4 count <200 cells/mm^3 and therefore represents either re-activation of latent infection or re- infection with a novel strain.

Significantly, 35%–70% of PLHIV exhibit ocular manifestations, and the most notable OI is CMV retinitis, which has a reported incidence of 7%–20% higher in Asian settings.[5] CMV retinitis in PLHIV may remain asymptomatic or can cause either partial or total blindness in one third of the patients.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients. It can occur as unilateral disease in two thirds of patients at presentation, but disease ultimately is bilateral in most patients in the absence of therapy or immune recovery.

Peripheral retinitis may be asymptomatic or present with **floaters, scotomata** or **peripheral visual field defects.** Central retinal lesions or lesions impinging on the macula or optic nerve are associated with decreased visual acuity or central field defects. CMV retinitis is a full-thickness necrotizing retinitis. Its characteristic ophthalmologic appearance is of fluffy, yellow-white retinal lesions, with or without intraretinal haemorrhage, with little inflammation of the vitreous. ART induces immune recovery, which bring in changes in the ophthalmological appearances.

In the absence of ART or specific anti-CMV therapy, retinitis invariably progresses rapidly within 10 to 21 days after presentation. **CMV retinitis is a medical emergency because it can cause blindness if not treated promptly.** Ophthalmological examination may reveal the characteristic brushfire pattern, with white leading edge advancing before an atrophic gliotic scar.

Box 4: Ask, Assess and Look for Manifestations of CMV Retinitis

- **Ask: Any patient presenting with ART failure or CD4 count <100 cells/mm^3, ask for diminishing vision or floaters.**
- **Assess for visual acuity.**
- **Refer: Immediately refer to ophthalmology department for specialized care.**
- **Look: On indirect ophthalmoscopy, look for fluffy, yellow-white retinal lesions, with or without intraretinal haemorrhage.**

Patient may occasionally present with fever, cough or dyspnoea and diagnosis of CMV pneumonitis may be made with presence of diffuse pulmonary interstitial infiltrates in chest x-ray.

Colitis occurs in 5% to 10% of PLHIV with CMV end-organ disease. The most frequent clinical manifestations are weight loss, anorexia, abdominal pain, debilitating diarrhoea and malaise. In the colon, and especially in the caecum, CMV can cause perforations and patient presents with ‘acute abdomen’.

Oesophagitis occurs in a small percentage of patients with AIDS who experience CMV end- organ disease and causes odynophagia, nausea and occasionally mid-epigastric or retrosternal discomfort. Colitis and esophagitis may cause fever.

CMV neurologic disease includes dementia,ventriculo-encephalitis and poly radiculomyelopathies. Patients with dementia caused by CMV encephalitis typically have lethargy, confusion and fever. Patients with ventriculo-encephalitis have a more acute course with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement of computed tomography or magnetic resonance images is highly suggestive of CMV ventriculo-encephalitis rather than HIV-related neurologic disease.

CMV polyradiculomyelopathy causes a Guillain-Barre–like syndrome characterized by urinary retention and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia.

Diagnosis

CMV retinitis usually is diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis in that setting has a 95% positive predictive value.

Figure 4.2.4: CMV retinitis (fluffy, yellow retinal lesions, with intraretinal haemorrhage)



(Images Courtesy: CMC, Vellore)

CMV colitis is usually diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions.

CMV oesophagitis is diagnosed by presence of ulcers of the distal oesophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.

CMV pneumonitis is difficult and requires consistent clinical and radiological findings (i.e., diffuse pulmonary interstitial infiltrates, fever and cough or dyspnoea), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis.

Blood tests to detect CMV by antigen detection, culture or PCR are not recommended for diagnosis of CMV end-organ disease because of their poor positive predictive value. A negative serum or plasma PCR assay also does not rule out CMV end-organ disease. PCR assays are not standardized; therefore, sensitivity, specificity and intra-assay comparability are not clearly delineated.

Presence of serum antibodies to CMV is not diagnostically useful, although a negative IgG antibody level indicates that CMV is unlikely to be the cause of the disease process.

CSF typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels and normal-to-elevated protein levels.

Management

Table 4.2.9: Management of CMV

General Considerations

- Patients with suspected visual impairment may be referred to the ophthalmology department by the ART Medical Officer with a referral letter detailing the symptoms and the possible clinical and diagnostic evaluation as required from the specialist.
- Patients diagnosed and requiring treatment may be intimated to SACS for further support on treatment for CMV.
- CMV should be treated for at least 3–6 months and follow-up should be done to make sure that lesions are inactive with CD4 count >100 cells/mm^3 for 3 to 6 months in response to ART.
- Therapy should be discontinued only after consultation with an ophthalmologist, considering magnitude and duration of CD4 count increase, anatomic location of the lesions, vision in the contralateral eye and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended

Progressive Retinitis: Initial Therapy Followed by Chronic Maintenance Therapy

Preferred Therapy

- Valganciclovir 900 mg orally every 12h for 14–21 days, then 900 mg once daily.

Alternative Therapy

- Ganciclovir 5 mg/kg IV every 12h for 14–21 days, then 5 mg/kg IV daily
- Ganciclovir 5 mg/kg IV every 12h for 14–21 days, then Valganciclovir 900 mg orally daily; with or without intravitreous injections of Ganciclovir (2 mg/injection) or Foscarnet (2.4 mg/injection); repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady-state intraocular ganciclovir concentrations are achieved.

Note: IV Ganciclovir can be switched to oral Valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.)

- Foscarnet 60 mg/kg IV every 8h or 90 mg/kg IV every 12h for 14–21 days, then 90–120 mg/kg IV every 24h

Stopping Chronic Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3–6 months, and lesions are inactive and with CD4 count >100 cells/mm^3 for 3–6 months in response to ART.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or immune recovery uveitis and then periodically after sustained immune reconstitution.

Reinstituting Chronic Maintenance for CMV Retinitis

CD4 count <100 cells/mm^3

For Peripheral Lesions

- Administer one of the systemic antiviral therapies listed above for the first 3–6 months until ART-induced immune recovery. (Valganciclovir 900 mg PO BD for 14–21 days, then 900 mg once daily for the first 3–6 months until ART-induced immune recovery)
- Immune recovery uveitis might develop in the setting of immune reconstitution.
- Periocular corticosteroid or a short course of systemic steroid

CMV Esophagitis or Colitis: Duration is for 21–42 days or until signs and symptoms have resolved.

Preferred Therapy	Alternative Therapy
• Ganciclovir 5 mg/kg IV BD, may switch to Valganciclovir 900 mg PO BD once the patient can absorb and tolerate PO therapy	• Foscarnet 60 mg/kg IV TDS or 90 mg/kg IV BD—for patients with treatment limiting toxicities to Ganciclovir or with Ganciclovir resistance; or • Oral Valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption.

CMV Neurological Disease

- Doses are the same as for CMV retinitis.
- Treatment should be initiated promptly.
- Combination of Ganciclovir IV plus Foscarnet IV to stabilize disease and maximize response.
- Optimal duration of therapy has not been established.
- The role of oral Valganciclovir has not been established.
- Optimize ART to achieve viral suppression and immune reconstitution

CMV Pneumonitis

- Doses are the same as for CMV retinitis.
- Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV Ganciclovir or IV Foscarnet is reasonable.
- The role of oral Valganciclovir has not been established.
- The optimal duration of therapy has not been established.

Meningitis

The following are the main causes of meningitis among PLHIV:

• Cryptococcal meningitis (for details,please see above)
• Aseptic meningitis
• Bacterial meningitis
• Tuberculous meningitis

Aseptic meningitis

Aseptic meningitis is a clinicopathological syndrome, and its cardinal symptoms are headache, fever and meningism. Aseptic meningitis among PLHIV may be caused by HIV itself or by another opportunistic viral infection (CMV and JCV), mycobacterial infection, non-infectious inflammatory processes (immune reconstitution inflammatory syndrome, IRIS) or CNS neoplasia (lymphoma).

The illness takes typically a biphasic course with initial non-specific constitutional symptoms followed by the classic features usually associated with meningitis, namely, headache, malaise, fever, neck stiffness, rigors, photophobia, nausea and vomiting. Skin rash-like the eruptions of varicella zoster (VZV) may appear concurrently. Other less common manifestations are cranial neuropathies, confusion, decreased level of consciousness and seizures. Aseptic meningitis usually is a self-limited disease.

Diagnosis

The typical CSF profile in aseptic meningitis is that of a lymphocytic pleocytosis (of less than 500 cells/mm3), normal or mildly elevated protein, normal glucose concentration and negative bacterial antigen tests.

Management

Management is usually symptomatic and sometimes specific anti-viral may be required for for HSVs/ EBV etc.

Bacterial meningitis

Acute bacterial meningitis occurs with equal frequency in HIV-infected and uninfected persons. Common aetiological organisms include Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitides.

The symptoms and signs include fever, headache, stiff neck, photophobia, vomiting, malaise, irritability, drowsiness and coma. Symptoms tend to present within 1 week of infection and may be preceded by a prodromal respiratory illness or sore throat.

Diagnosis

On examination, the CSF shows increased pressure, a high cell count (100–10000/mm3), increased protein (>100 mg/dl) and decreased glucose (<40 mg/dl or <50% of the simultaneous glucose blood level). A Gram-stained smear of a spun sediment of the CSF may reveal the etiological agent. CSF culture examination and antibiotic sensitivity study may be rewarding for both diagnosis and management. A full blood count should also be done. Where available, CT scan or MRI may be performed to evaluate for any focal neurological deficits.

Management

Third generation cephalosporins (Ceftriaxone 2 g IV 12 hourly) is the preferred treatment for acute bacterial meningitis. Vancomycin 15–20 mg/kg IV every 8–12 hours may be added if indicated**.** Alternately, Penicillin (24 million units daily in divided doses every 2–3 hours) or ampicillin (12 g daily in divided doses every 2–3 hours) or chloramphenicol (4–6 g IV/day) can be given.

Treatment should be continued for 10–14 days.

Tuberculous meningitis

TB of the CNS may present as meningitis, tuberculous granulomas (tuberculomas) or tuberculous brain abscess.

Tuberculous meningitis (TBM) has a varying presentation where symptoms have been reported to vary from 1 day to 6 months, and consequently may present as either acute or chronic meningitis.

The non-specific symptoms of TBM include fatigue, malaise, anorexia and vomiting. The acute presentations may be indistinguishable from bacterial meningitis. Fever, headache, vomiting and weight loss are the most common symptoms. Occasionally, TBM may present as a progressive dementia, with social withdrawal and personality changes.

Cranial nerve palsies may be seen on presentation, most commonly involving the sixth cranial nerve, but the second, third, fourth and eighth nerves may also be involved. Seizures may occur at any point during the initial illness or during the treatment period. TBM may be complicated by vasculitis infarcts that may be present as hemiparesis or cranial nerve palsies. Cerebral oedema or brainstem infarctions may lead to pyramidal or cerebellar signs and are associated with a depressed level of consciousness. The end-stage illness is characterized by deep coma, along with spasticity and posturing.

Diagnosis

The diagnosis is established by examining CSF by doing LP. The CSF pressure is high, proteins are increased and the sugar is low. There is pleocytosis with a predominance of lymphocytes. Acid-fast staining may not demonstrate the organisms and culture of CSF take several weeks.

Treatment

ATT with the standard drugs should be given as per recommendations of the TB programme. Additionally, steroids in the initial phase are helpful in reducing complications like obstructive hydrocephalus and vasculitis. Measures to reduce ICP should be instituted when ICP is raised.

Table 4.2.10: *CSF findings in different neurological Infections

Organism	Cells	Biochemistry	Microbiology
Cryptococcus	Lymphocytic, may be normal	Protein elevated (30–150 mg/dl) Low sugar (50–70 mg/dl)	India ink staining positive Cryptococcal antigen (CrAg) test positive Organism isolated by Sabouraud dextrose agar culture
Mycobacterium tuberculosis (MTB)	Predominantly lymphocytic, A few hundred WBCs/ml (60–70% monocytes)	Protein elevated (40–100 mg/dl) Low to normal suga	Isolation of MTB in CSF CBNAAT and culture - occasionally positive
Pneumococcus	Predominantly neutrophilic, >1000 WBCs/ml	Protein very high (>100 mg/dl) Very low sugar (<40 mg/dl)	Gram stain and routine culture may reveal the organism
Syphilis	Lymphocytic, mildly elevated (10–400 cells)	Protein slightly high, (46–200 mg/dl) Sugar near normal	Venereal disease research laboratory positive
*Lumbar puncture to be done after ruling out papilloedema			

Progressive Multifocal Leukoencephalopathy

Epidemiology

PML is a viral infection of the CNS caused by a neurotropic human polyomavirus, John Cunningham virus. Primary infection by John Cunningham Virus is commonly acquired in childhood and is usually asymptomatic with the virus remaining latent. Immunosuppression, classically occurring in the setting of HIV infection, reactivates the virus, resulting in brain invasion, destruction of oligodendrocytes and a **debilitating demyelinating illness.**

An extremely rare disease, PML has an incidence rate of 3%–5% in HIV patients with AIDS.[6] Although its frequency decreased following the advent of ART, it is still significantly common in HIV patients. At present, approximately 80% of PML patients have underlying AIDS. Although most CNS OIs are almost wholly prevented when CD4 cell counts are maintained above 100 to 200 cells/mm^3, PML can still sometimes occur in patients treated effectively with ART.

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions (occipital lobes [with hemianopsia], frontal and parietal lobes [aphasia, hemiparesis, and hemisensory deficits] and cerebellar peduncles and deep white matter [dysmetria and ataxia]). Spinal cord involvement is rare, and the optic nerves are not involved.

Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis) as individual lesions expand concentrically or along white matter tracts. The time course of this evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral infarcts begin even more abruptly.

Nonetheless, PML is sometimes mistaken for an evolving stroke, which like PML is bright on diffusion weighted MRI. **Headache and fever are not characteristic of the disease,** and when present may indicate presence of another OI. Seizures develop in nearly 20% of PML patients and are associated with lesions immediately adjacent to the cortex.

Box 5: Clinical profile of Progressive Multifocal Leukoencephalopathy Diagnosis

- Progressive multifocal leukoencephalopathy (PML) is a viral infection caused by a neurotropic human polyomavirus, John Cunningham virus.
- PML manifests as focal neurological deficits.
- The time course of evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis with respect to infections causing focal lesions.
- Headache and fever are not characteristic of the disease, and when present may indicate presence of another opportunistic infection.
- There is no effective antiviral therapy for preventing or treating John Cunningham Virus infections or PML.
- The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.
- HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy.
- In ART-naive patients who are diagnosed with PML, ART should be started immediately.
- In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression.

Diagnosis

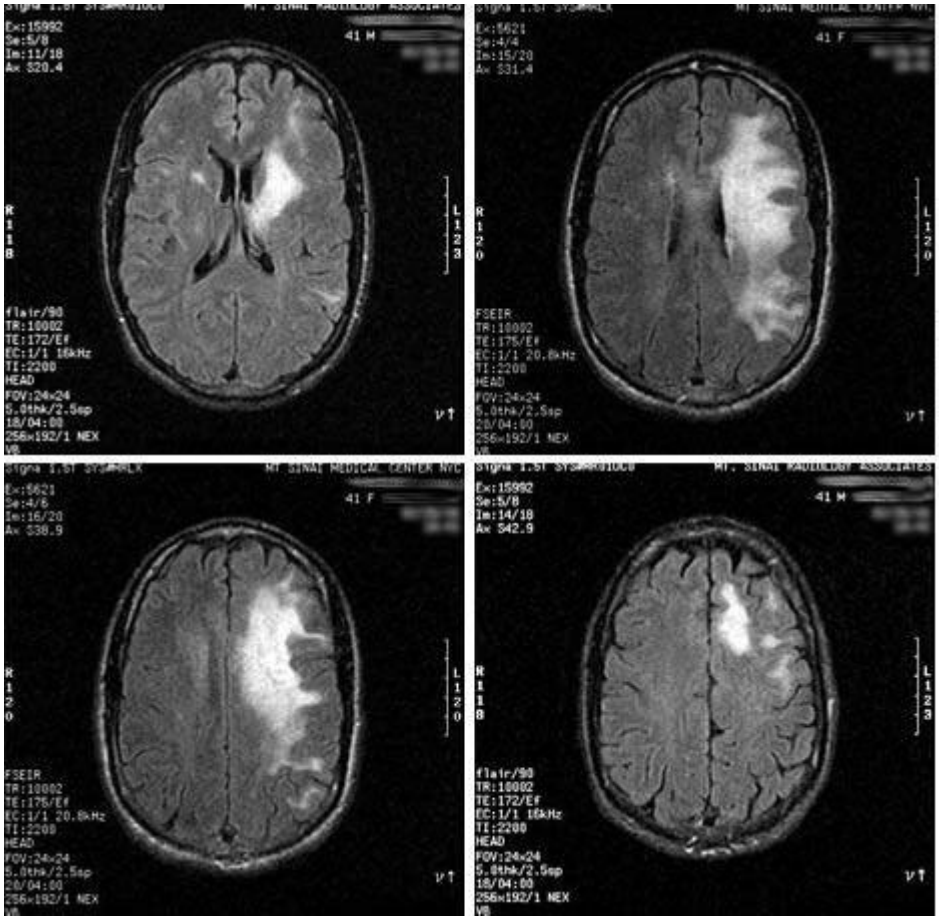
Diagnosis of PML relies on clinical and imaging findings. Steady progression of focal neurological deficits show typical imaging findings of single or multiple hypodense, non-enhancing cerebral white matter lesions. Lesions are hyperintense (white) on T2-weighted and fluid-attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences. No mass effect or displacement of normal structures is usually evident.

In most cases, this would be enough to support presumptive diagnosis.

To confirm the diagnosis, polymerase chain reaction (PCR) of CSF sample for the presence of JCV DNA can be done. In some instances, brain biopsy is required to establish the diagnosis.

Serologic testing is generally not useful.

Figure 4.2.5: MRI-T2 weighted image: PML



(Image courtesy: GHTM Tambaram-I-TECH Fellowship programme)

Management and Prevention

There is no effective antiviral therapy for preventing or treating John Cunningham Virus infections or PML. The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART. ART should be started in patients not on HIV treatment as soon as PML is recognized. Among PLHIV on ART, more than half of HIV- infected PML patients experience a remission in which disease progression stops.

HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy. In PML occurring in multiple sclerosis patients, younger age, more restricted unilobar disease and lower CSF JCV DNA copy numbers are associated with better outcomes. Peripheral blood CD4 cell count at presentation is the only variable that predicted survival in patients with CD4 counts <100 cells/mm3 compared with patients who had higher CD4 cell counts. Worse prognosis is also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART and the presence of lesions in the brainstem.

Table 4.2.11: CT Scan Findings in HIV-Related Neuropathology

HIV Encephalopathy	CNS Toxoplasmosis	Tuberculoma	PML (Progressive Multifocal Leukoencephalopathy
Cortical atrophy +/- bilateral basal ganglia calcifications	Single or multiple rings enhancing lesions with mass effect Leukoencepha-lopathy	Single ring-enhancing lesion, +/- hydrocephalus and basal meningitis	Single or multiple hypodense lesions in cortical white matter without contrast enhancement or mass effect (hyperintense on T2w MRI)

HIV-associated Neurocognitive Disorders

A common CNS manifestation of HIV is a chronic neurodegenerative condition characterized by cognitive, central motor and behavioural abnormalities.

HAND is stratified as shown in Table 4.2.12

Table 4.2.12: HIV-associated neurocognitive disorders

Asymptomatic neurocognitive impairment	Subclinical decline in cognition
Minor neurocognitive disorder	Mild decline in cognition in addition to mild everyday functioning impairment that affects the more difficult activities of daily living
HIV-associated Dementia (HAD)	Significant decline in cognition along with a significant degree of functional impairment that affects routine activities

There is no diagnostic marker or combination of markers for HAND. The diagnosis is made in PLHIV with cognitive impairment, after ruling out confounding conditions (CNS OIs, neurosyphilis, substance abuse, delirium, toxic-metabolic disorders, psychiatric disease, age- related dementias).

HIV-associated dementia (HAD) is different from other OIs in that the disease is caused by the HIV itself, which enters the brain as early as 2 days after infection.

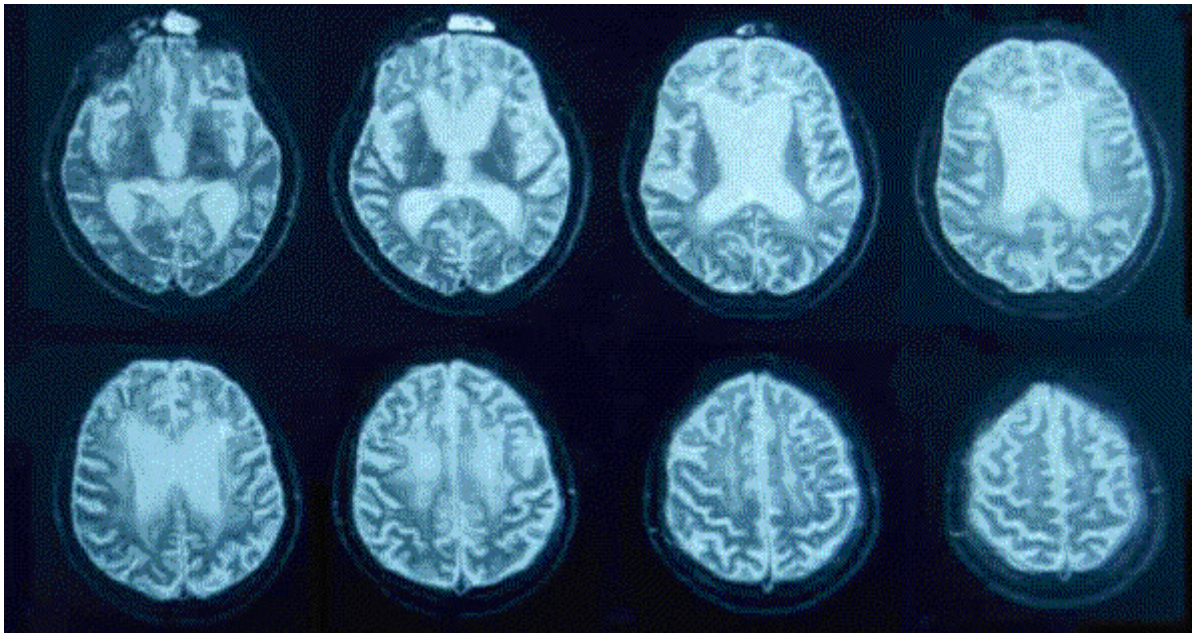
HAD is more likely with CD4 counts <200 cells/mm^3. Between 20% and 35% of all HIV-positive people eventually develop HAD at CD4 counts of 100–200 cells/mm^3.

There is acquired and slowly progressive cognitive decline, motor and behavioural changes, and non-focal or diffuse CNS signs. Signs of early dementia include trouble learning new things, difficulty remembering things that happened in the past, changes in behaviour, confusion and depression. Advanced dementia produces abnormalities of speech, balance, vision, gait and loss of bladder control. It can also lead to mania (exaggerated feeling of well-being) or psychosis (loss of contact with reality).

Diagnosis

HAD is a diagnosis of exclusion. The CSF findings are non-specific, and CT/MRI shows only cerebral atrophy and ventricular dilatation. Several AIDS-related diseases such as toxoplasmosis, lymphoma and PML can cause symptoms like those of HAD.

Figure 4.2.6: Contrast CT brain of patient with AIDS dementia.



(Image courtesy: CoE, GHTM Tambaram, Chennai)

Treatment

ART is the most effective treatment and ARV regimens should include agents that penetrate the CNS (AZT, d4T, ABC, NVP, 3TC, EFZ, TDF). Even though ART can treat the underlying cause, it may not effectively treat the symptoms and may worsen them in some cases. Additional supportive treatment strategies may be needed in some cases. Sedation is required for those who are agitated and aggressive, with smaller initial doses to avoid oversedation. Close monitoring to prevent self-harm, adequate nutrition, early diagnosis, treatment of other OIs and psychological support for caregivers are important accessories to therapy.

HIV-associated Vacuolar Myelopathy

It is the most common spinal cord disease in AIDS. It is mostly underdiagnosed and must be differentiated from other causes of myelopathy such as infection with human T-cell lymphotropic virus (HTLV) I or II; herpes simplex 1 or 2, varicella zoster, cytomegalovirus, enteroviruses, syphilis and TB, tumours and nutritional deficiencies such as B12.

Vacuolization of myelin sheath, accumulation of foamy macrophages and microglia with relative sparing of axons are the pathological manifestations.

Clinically, this presents with slowly progressive leg weakness, which may be asymmetric at first, spasticity, dorsal column (vibration, position) sensory loss, ataxic gait and urinary frequency and urgency. Erectile dysfunction is an early sign in men. Paraesthesias in the legs are common but neuropathic pain rarely rises to the level seen with peripheral neuropathy. There is prominent hyperreflexia and extensor plantar responses. In advanced cases, patients may become wheelchair- bound and doubly incontinent.

The diagnosis includes CSF analysis (to rule out other infectious causes) and thoracic spinal imaging (MRI) showing high signal hyperintense areas on T2-weighted imaging, primarily in the thoracic region and affecting the posterior columns, which do not enhance with contrast. **There is no specific treatment.**

Primary CNS Lymphoma (PCNSL)

Primary CNS lymphoma is rare in the general community but affects about 2% of PLHIV and it is the second most common mass lesion in AIDS.

PCNSL is almost always associated with EBV, a ubiquitous herpes virus. Most EBV infections are asymptomatic or present as acute mononucleosis. In PLHIV, the immortalized EBV-infected B cells are no longer held in check. Thus, the risk of PCNSL is greatly increased. The disease evolves over 2–8 weeks. It usually occurs when the CD4 count is <100 cells/mm^3.

The presenting symptoms of PCNSL include lethargy, confusion, impaired memory, headache, seizures or focal weakness. Many patients develop cranial neuropathies and/or ocular involvement. Increased ICP and herniation can result in papilloedema and coma if untreated.

Diagnosis

CT scan/MRI shows periventricular irregular lesions that appear solid on enhancement in one or more sites. There is prominent oedema. Lymphoma is suspected when the toxoplasma IgG is negative or there is failure to respond to empirical treatment for toxoplasmosis. Neuropsychological tests show subcortical dementia.

Mini-mental status examinations are not very sensitive. CSF analysis is normal in 30%–50% of patients. The CSF cytology is positive for malignant cells in <5% of patients.

Treatment

There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients but is considered palliative. Corticosteroids can also help some patients.

HIV-associated Neuropathies

Many peripheral neuropathic syndromes have been reported in the context of HIV infection. The following are some of the common neuropathies seen in HIV:

- Distal symmetric polyneuropathy (DSPN)
- Mononeuropathy multiplex
- Chronic inflammatory demyelinating polyneuropathy
- Progressive lumbosacral polyradiculopathy (CMV)

DSPN is the most common form. The risk factors are older age, history of alcohol abuse, advanced HIV disease, prior use of a neurotoxic ARV drug (e.g., didanosine, stavudine, zalcitabine) and diabetes.

The most common symptom is paraesthesia, usually beginning in the feet. Patients complain of burning, numbness, hot or cold sensations, and episodic electric shock-like sensations. Some complain of a sensation that they are walking on sand or glass. Many cannot bear to wear shoes. The symptoms ascend over time, as far as the thighs, and will also involve the hands in a glove- like fashion. Cramps and fasciculations may develop in the extremities. On examination, there are decreased or absent ankle jerks, diminished vibratory sensation in the legs and increased threshold to temperature and pinprick.

There is no specific treatment available.

Neurosyphilis

The interaction of syphilis and HIV infection is complex. It is well known that history of an STI, including syphilis, is associated with an increased risk of exposure because sexual behaviours that increase the risk of acquiring STIs also increase the risk of acquiring HIV. Furthermore, genital ulcerations and inflammation caused by STIs are implicated as cofactors for acquiring or transmitting HIV infection.

The conventional staging of syphilis is unaltered by HIV coinfection, and we will discuss the neurological involvement of syphilis in this chapter.

It usually presents in three forms:

- Asymptomatic CNS involvement
- Acute syphilitic meningitis usually occurs within the first 2 years of infection and some cases are diagnosed at the time of the secondary rash. Patients can present with headache, meningeal irritation and cranial nerve abnormalities typically involving cranial nerves at the base of the brain (especially 2, 6, 7 and 8).
- Meningovascular neurosyphilis occurs a few months to 10 years (average 7 years) after the primary infection. Prodromal symptoms include unilateral numbness, paraesthesia, extremity weakness, headache, vertigo, insomnia and psychiatric abnormalities such as personality changes. The focal deficits initially are intermittent or progress slowly over a few days.

Symptoms of neurosyphilis, principally of central origin, include personality change, ataxia, stroke, ophthalmic symptoms (e.g., blurred vision, reduced colour perception, impaired acuity, visual dimming, photophobia), bladder incontinence, dizziness, hearing loss and seizures.

Signs of neurosyphilis include hyporeflexia, sensory impairment, pupillary changes and optic atrophy.

HIV coinfection makes syphilis more severe and increases the likelihood of syphilitic CNS involvement. Ocular syphilis in HIV patients who are not receiving ART is more likely to involve both eyes and has more frequent posterior segment involvement. ART and periodic ophthalmological evaluations help prevent serious complications.

The diagnosis of neurosyphilis is based on CSF findings of a reactive VDRL, presence CSF pleocytosis (usually 10–400 cells/mm3) and mildly elevated protein (46–200 mg/dl).

Treatment includes Benzathine penicillin 4 MU IV 6th hourly for 10–14 days.

Follow-up: Follow-up of patients treated for neurosyphilis depends on the initial CSF findings. If pleocytosis was present, the CSF should be re-examined every 6 months until the white blood cell count is normal. Re-treatment should be considered if the CSF white blood cell count does not decline after 6 months or completely normalizes after 2 years.

The CSF also can be re-examined to look for serial decreases in antibodies on the VDRL test or serial decreases in protein levels, although the management of persistent abnormalities is not well established. It is expected that CSF parameters will normalize within 2 years. Failure to normalize may warrant re-treatment. Most treatment failures occur in immunocompromised patients.

4.3 ≫ Respiratory System

Introduction

Preventable and treatable respiratory infections are seen in up to two thirds of all HIV-infected individuals. Although HIV-associated respiratory diseases include upper respiratory infections, sinusitis and bronchitis, the pneumonias are the most diagnosed bacterial respiratory infection. In advanced stages of the disease, there is often more than one pathogen.

Respiratory symptoms are a frequent complaint among HIV-infected individuals. These include cough, dyspnoea and pleuritic chest pain, either alone or in combination. Symptoms usually are acute and present for 3–5 days. In an HIV-infected patient with a CD4 count of <200 cells/mm^3, the absence of purulent sputum and a duration of symptoms for a few weeks strongly favour a diagnosis of PCP rather than bacterial pneumonia. In contrast, the presence of purulent sputum and a duration of symptoms of a few days favour a diagnosis of bacterial pneumonia. Patients who have PCP and report a productive cough or purulent sputum often have a concurrent bacterial infection (bronchitis or pneumonia). Patients diagnosed with bacterial pneumonia who initially respond to antibiotics but subsequently worsen often have PCP that has become clinically symptomatic.

Table 4.3.1 gives a snapshot of association of infections with CD4 counts in PLHIV.

Table 4.3.1: Association of pulmonary infections with CD4 counts in HIV-infected patients

Pulmonary Infection/Disease	CD4 count- cells/mm^3
*Mycobacterium tuberculosis**	<400 cells/mm^3
Bacterial pneumonia	<250 cells/mm^3
Suppurative lung and sinus disease	<100 cells/mm^3
Pneumocystis jiroveci pneumonia	<200 cells/mm^3
Mycobacterium avium complex	<100 cells/mm^3
Cytomegalovirus	<100 cells/mm^3
*Tuberculosis can occur with any CD4 count, though common in PLHIV with <400 cells/mm^3.	

Source: Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIVInfected Adult and Adolescent May 2007

Mycobacterium Tuberculosis

Epidemiology

TB is the most common cause of death in people with HIV. In people with normal immune systems, initial contact with TB bacteria, usually in childhood, results in a robust granulomatous reaction and the infection is then contained and remains latent. In an HIV-infected person, because of immunosuppression, this response is modified leaving patients with a reduced ability to kill the bacteria. Simultaneously, active TB also promotes host HIV replication and progression to AIDS.

In India and other areas of the world where TB is endemic, TB infection is usually acquired in childhood. Roughly 5%–15% of adults with LTBI develop active TB disease; 5%–10% of those infected develop active TB disease over the course of their lives, usually within the first 2 years. Risk of TBI increases 16–21 times in case of HIV coinfection with or without ART.[1]

HIV-related TB can present with typical or atypical clinical and/or radiological features. In general population, TB and EPTB are divided in 80% and 20% approximately, wherein EPTB is almost 40% among PLHIV.[2,3]

HIV among TB patients

India had an estimated 25.44 lakh (21.68–30.38 lakh) PLHIV in 2023, with an adult (15–49 years) HIV prevalence of 0.20% (0.17%–0.25%).[4] In 2019, India accounted for an estimated 71,000 incident TB patients among PLHIV, which accounts to approximately 9% of the global burden. Based on available country data, it is estimated that 3% of incident TB patients in India were HIV positive in 2019.[5]

TB is the most common OI among HIV-infected individuals. It is a major cause of mortality among patients with HIV and poses a risk throughout the course of HIV disease, even after successful initiation of ART. In India, more than 50% of AIDS cases reported had TB at some time in their lifetime, and TB is one of the leading causes of death in PLHIV.

Impact of HIV on TB

The primary impact of HIV on TB is that the risk of developing TB becomes higher in patients with HIV. An HIV-infected person newly infected with TB has a 16–27 times higher chances of developing the disease than among patients infected with TB only.[6] Among TB-infected PLHIV, 3%–10% of persons develop TB per year.[6] Furthermore, HIV-infected TB patients suffer much higher mortality than HIV-negative TB patients. Even if TB is successfully treated, recurrence of TB and long-term post-TB mortality among PLHIV are extremely high.

Impact of TB on HIV

In a TB patient infected with HIV, inflammatory response to TB bacilli increases HIV replication. As a result of the increase in number of viruses in the body, there is rapid progression of HIV infection. The viral load can increase 6–7 folds. As a result, there is a rapid decline in CD4 count and the patient starts developing symptoms of various OIs. Thus, the health of the patient who has dual infection deteriorates much more rapidly than with a single infection. Among the AIDS cases, TB is the most common OI. The mortality due to TB in AIDS cases is also high.

Clinical Manifestations

Pulmonary TB (PTB) is the most common form of TB disease. HIV-positive and HIV-negative patients with active PTB generally manifest similar clinical features, namely **cough, fever, night sweats, haemoptysis and weight loss.**

The presentation may sometimes vary with the degree of immune suppression. In patients with mild immune suppression, the clinical picture often resembles usual adult post-primary PTB; i.e., the sputum smear is frequently positive for acid-fast bacilli (AFB), and the CXR typically may show unilateral or bilateral upper lobe infiltrates, cavitations, pulmonary fibrotic changes and/or volume loss.

Table 4.3.2: Manifestations of TB in relation to immunosuppression

Features of TB	HIV Immunosuppression	
	Early Phase	Late Phase
Clinical presentation	Often resembles post-primary TB (Adult type)	Often resembles primary TB
Sputum smear result	Often positive	Often negative
Chest X-ray appearance	Often shows cavities in upper lobes	Atypical presentation Often infiltrates Mid and lower lung-field lesions Intrathoracic lymph nodes Infrequent cavities

In immune-suppressed patients, the overall risk of TB is even higher, but it is more difficult to distinguish TB from other serious chest diseases. In persons with advanced HIV infection, disseminated and EPTB are more common than in early HIV infection, and may be as common as PTB. The most common forms of EPTB seen are lymphadenitis, pleural effusion, pericarditis, military disease and meningitis.

The chest x-ray in advanced HIV infection may show any pattern. Hilar lymphadenopathy is frequently observed, and interstitial infiltrates tend to be common, especially in the lower zones; features such as cavitation or fibrosis are less common. Infiltrates may be unilateral or bilateral and are seen more often in the lower lobes than in the upper lobes.

The most common symptom of PTB is a persistent cough of 2 weeks or more, with or without expectoration. It may be accompanied by one or more of the following symptoms: fever, night sweats, weight loss, chest pain, haemoptysis, shortness of breath, tiredness and loss of appetite. A person with extra-pulmonary TB may have symptoms related to the organs affected along with or without the constitutional symptoms.

Diagnosis

Intensified Case Finding at ART Centres using 4-Symptom Complex, Fast Tracking and Referral for TB Diagnosis

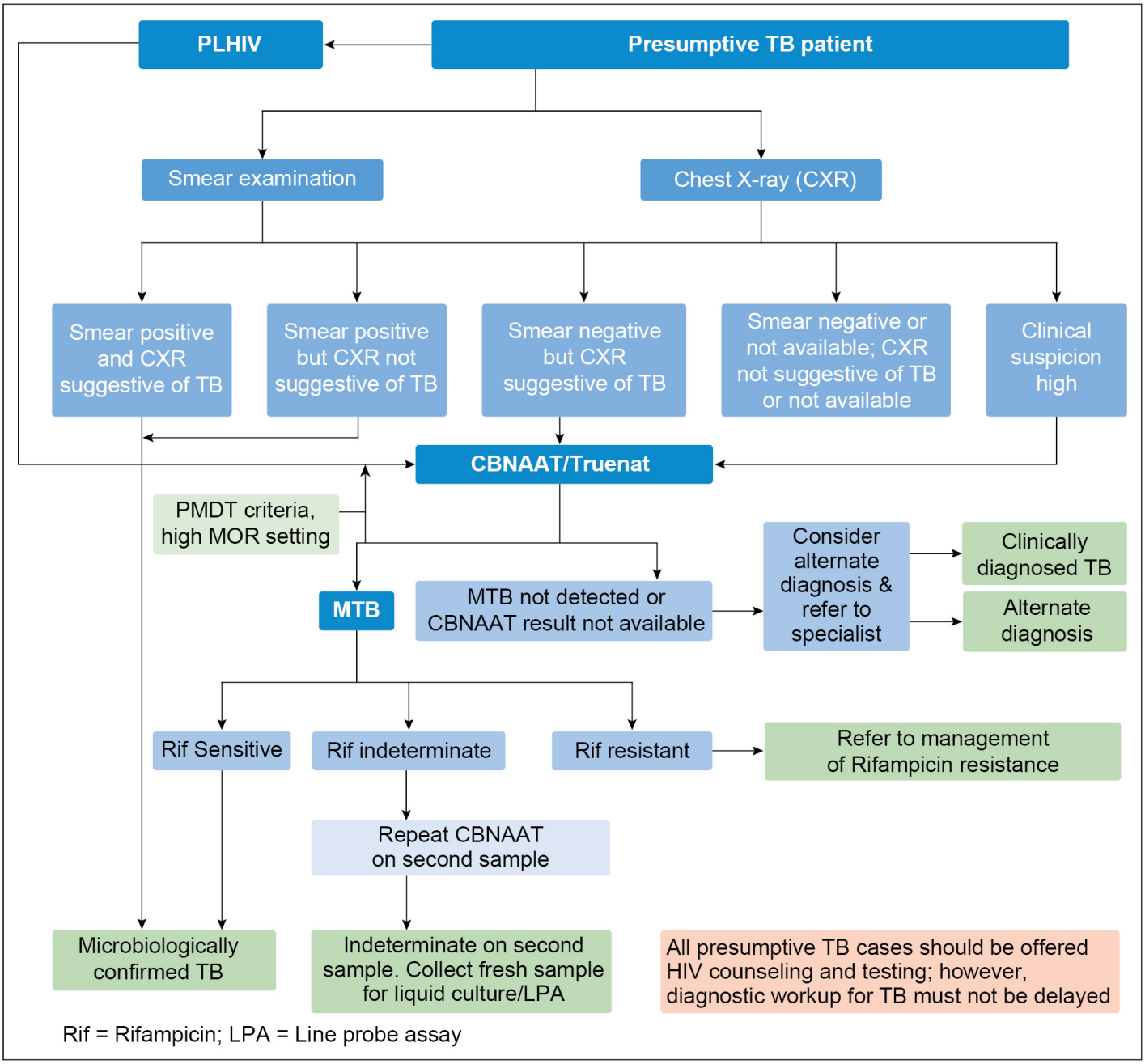
Intensified case finding (ICF) involves systematic screening for active TB among HIV-infected individuals and is one of the critical interventions for increased TB case detection. It is an important step towards earlier diagnosis and treatment of TB and an initial step to rule out TB disease so that TB preventive therapy can be initiated.

All PLHIV should be regularly screened for TB during every visit to the ART centres using the 4S complex – current cough, fever, weight loss and night sweats among adults and adolescents. In children, the 4S complex includes current cough, fever, poor weight gain and history of contact with a TB case. For more details on 4S TB screening, please refer **Chapter 2.8 (HIV-TB Co-infection: Case Finding, Management and Prevention of Tuberculosis).**

PLHIV found positive for any of the four symptoms (4S+) should be referred for molecular diagnostics (Nucleic Acid Amplification [NAAT] Test – CBNAAT or Truenat) and/or other appropriate investigations.

It may be noted that for all PLHIV newly registered in HIV care, use of chest x-ray alongside 4S screening is recommended at the medical officer level. In pulmonary tuberculosis, the features of the disease are frequently atypical, resembling those of primary TB. Smear-negative TB is as common as smear-positive TB.

Figure 4.3.1: Diagnostic algorithm for drug-sensitive pulmonary TB (adapted from NTEP Training module (1-4) for Medical Officers, July 2020)

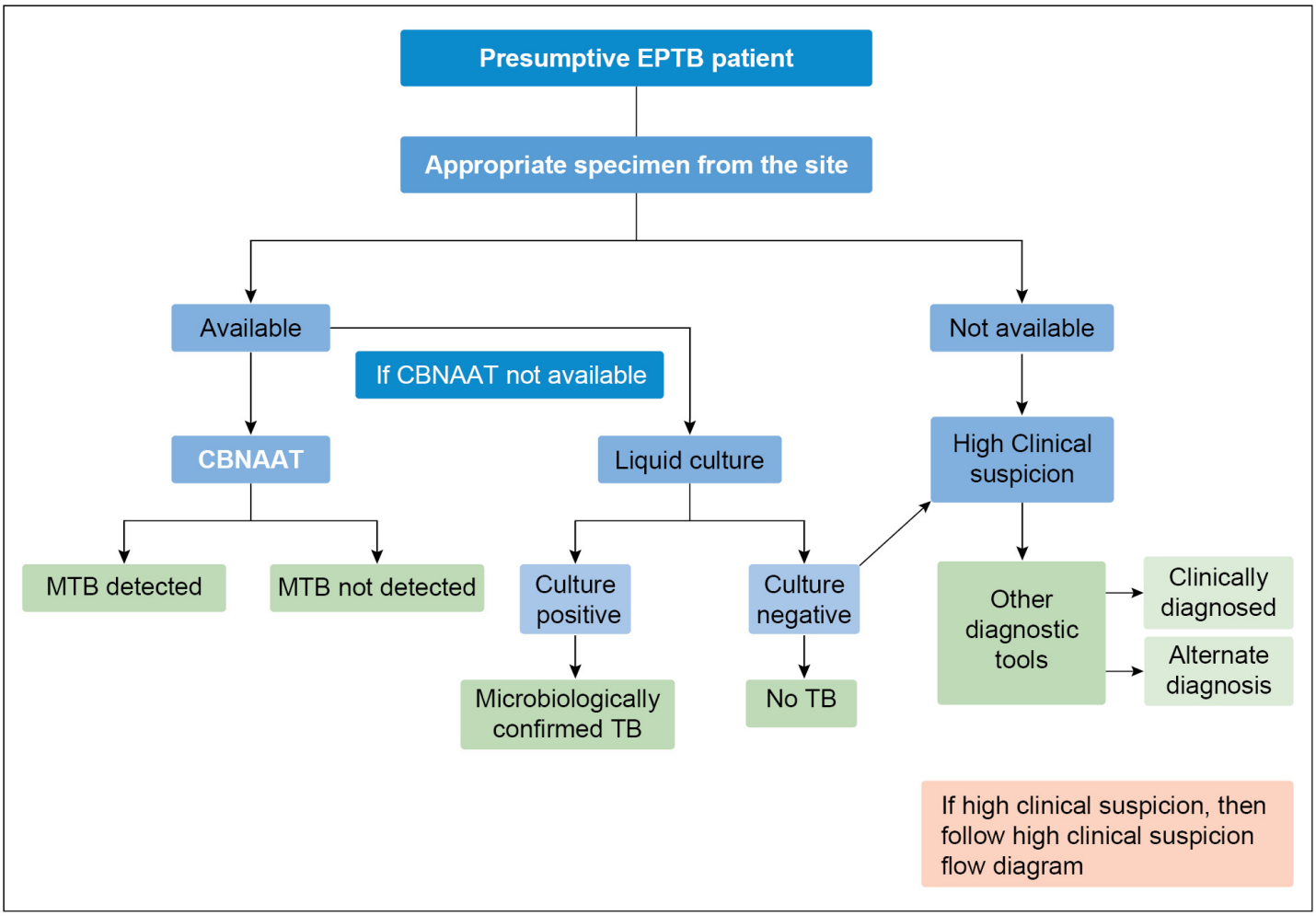


A person with EPTB may have symptoms related to the organs affected along with constitutional symptoms such as current fever, weight loss and/or night sweats.

- Enlarged cervical lymph nodes with or without discharging sinuses (TB lymphadenitis)
- Chest pain with or without dyspnoea in pleural TB
- Pain and swelling of the joints in bone TB (fever, backache, deformity in spinal TB)
- Signs of raised intracranial tension like irritability, headache, vomiting, fever, stiffness of the neck and mental confusion in TB meningitis
- Painless haematuria or sterile pyuria in renal TB and, infertility in genitourinary TB.

The medical officer must look for EPTB and ask for x-rays, CT/MRI scan, organ-specific ultrasonogram, FNAC and other procedures (e.g., pleural aspirate, pericardial aspirate, gastric aspirate) as the case may warrant. The specimens can be sent for NAAT as well as for cytological examination.

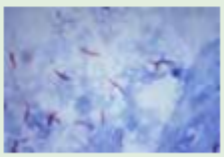
Figure 4.3.2: Diagnostic algorithm for extrapulmonary TB (adapted from NTEP Training module (1-4) for Medical Officers, July 2020)



A combined flow chart on the diagnostic approach for PTB and EPTB in PLHIV is provided in **Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis).**

Under the programme, acceptable methods for microbiological diagnosis of TB are provided in Table 4.3.3:

Table 4.3.3: Tools for microbiological confirmation of TB

Rapid molecular diagnostic tests	Line probe assay (LPA) for MTB complex and detection of RIF & INH resistance (FL LPA) and FQ and SLI resistance (SL LPA) Nucleic Acid Amplification Test (NAAT) (CBNAAT/Truenat)	
NAAT: CBNAAT & Truenat 	**Cartridge Based Nucleic Acid Amplification Test (CBNAAT)** No biosafety cabinet Closed system (no contamination risk) Performance specific for MTB, sensitivity close to culture Detection of Rifampicin-resistance via rpoB gene Simultaneously detects TB and Rifampicin drug resistance Provides accurate results in less than 2 hours so that patients can be offered proper treatment on the same day Has minimal biosafety requirements and training needs; Can be housed in non-conventional laboratories	
Culture Methods	Solid (Lowenstein Jensen) media Automated liquid culture systems e.g., BACTEC MGIT 960, BacT/ Alert or VersaTREK	
Lowenstein-Jensen Medium (LJ) **Solid medium**		Long duration Tedious Dedicated manpower Difficult to sustain quality
BACTEC **Liquid culture**		Turnover time: 8 days Agreement 99% for RIF 94% for INH & SM 91% for EMB
MGIT **Mycobacterium growth indicator tube assay**		More specific and sensitive than culture Turnover time: 8 days
Drug sensitivity testing	Modified Proportionate Sensitivity Testing for MGIT 960 system Economic variant of Proportion sensitivity testing (1%) using LJ medium	
Follow-up tests for patients on treatment for drug-sensitive TB (DS-TB)		
Sputum smear microscopy Ziehl-Neelsen staining Fluorescence staining		NAAT tests cannot be used, as they can pick up rpoB gene from dead bacilli in treatment follow-up sputum specimens
• For more details on follow-up sputum examination, please refer Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis).		

Management of Tuberculosis as per NTEP

Basic principles for management of tuberculosis are as follows:

- ICF using 4S complex for TB screening; fast-tracking and referral of symptomatic patients for CBNAAT test and other appropriate investigations, as required, for TB diagnosis, as detailed earlier in the chapter.
- If a patient with active TB is diagnosed with HIV, the priority is to start TB treatment in accordance with the National TB Elimination Programme guidelines.
- All HIV-TB coinfected persons are to be initiated on ART regardless of the CD4 count. ART reduces the incidence and recurrence of TB, as well as case fatality rates.
- Cotrimoxazole prophylaxis should be given to all HIV–TB patients

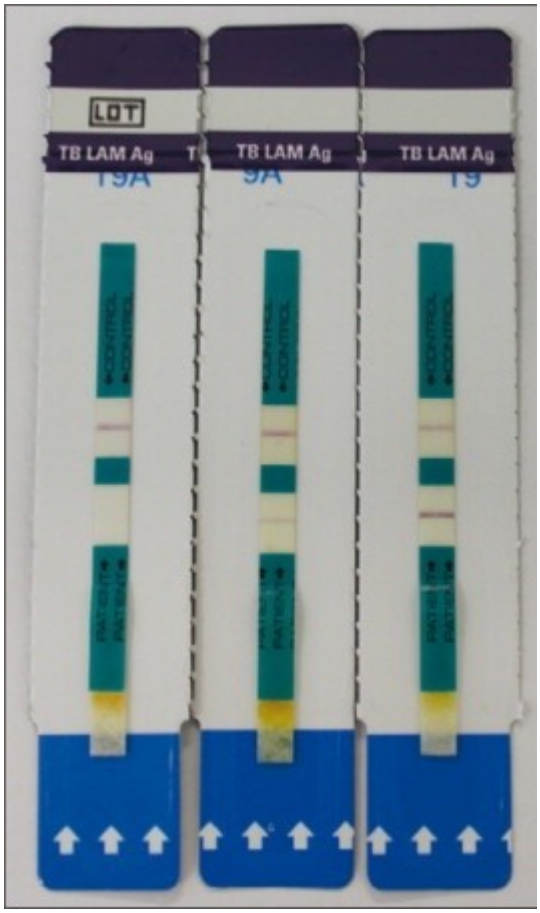
Please refer Chapter 2.8 (HIV-TB Coinfection: Case Finding, Management and Prevention of Tuberculosis) for more details on the following aspects:

- Classification of TB and definitions
- Adverse drug effects of DS-TB drugs
- Definitions of treatment completion
- Definitions for DR-TB
- DR-TB drugs and adverse drug effects of DR-TB drugs
- Management details of DS-TB and DR-TB in adults and children
- ART treatment details (First line, treatment failures and alternate regimens) in adults and children coinfected with HIV and TB

Screening and diagnosis of TB among PLHIV with advanced HIV disease TB-LAM (lipoarabinomannan) Test:

A promising development is a point- of-care immunochromatographic dipstick assay that detects mycobacterial lipoarabinomannan in urine. The assay seems limited to the diagnosis of HIV-associated TB in patients with advanced immunodeficiency (CD4 cell counts <200 cells/mm^3), such as those being

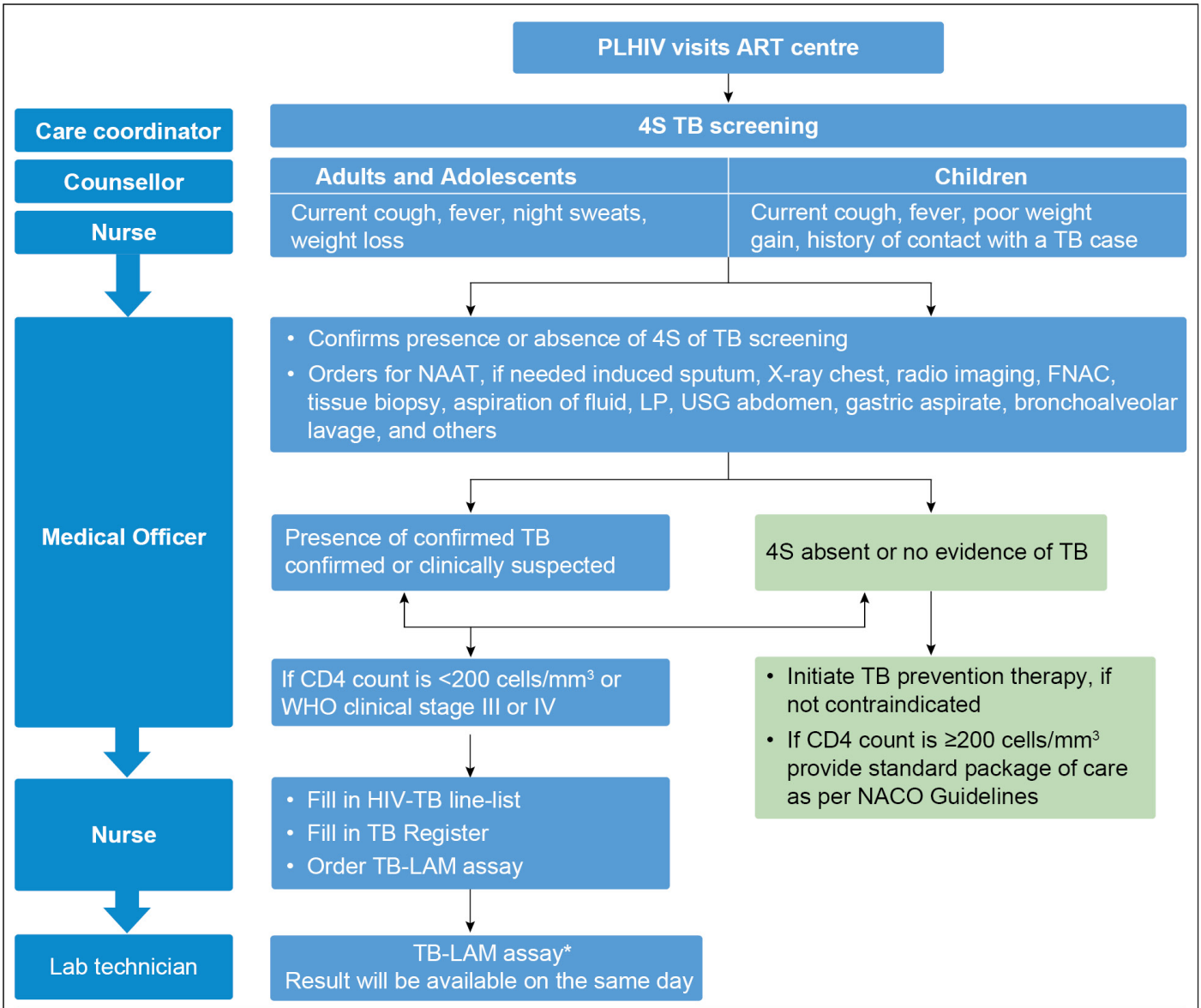
screened in ART centres.



Urinary LAM assays have shown greater sensitivity when used for the diagnosis of TB in people living with advanced HIV disease. The sensitivity increases significantly in patients with lower CD4 cell counts.

NACO Technical Resource Group recommends using urine Lateral Flow TB-LAM test (whenever made available in national programme) to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children (pulmonary and/or extra-pulmonary), or patients with CD4 count less than 200 cells/mm^3 (irrespective of the in-patient or out-patient setting).

Figure 4.3.3: Screening and advanced disease management of tuberculosis



Medical Officer: Management of TB

NAAT	TB-LAM*#	Interpretation	Action
Positive	Positive	Microbiologically confirmed TB case	Start ATT, exclude DR-TB
Positive	Negative		
Negative / Not available	Positive	Clinically diagnosed TB case	Start ATT
Negative / Not available	Negative	Will depend on correlation with TB signs and symptoms	• Consider Other diagnosis • If TB is unlikely, Start TPT

#Negative TB-LAM test does not rule out active TB

ART should be initiated as soon as possible within two weeks for initiating TB treatment, regardless of CD4 cell count (except when signs and symptoms of meningitis are present)

*Currently TB-LAM assay is not available in the programme

TB Preventive Therapy

Isoniazid preventive therapy (IPT) entails the administration of INH to individuals with LTBI to prevent progression to active TB disease. INH is one of the most effective bactericidal anti-TB drugs that protect against progression of LTBI to active disease (against endogenous reactivation). It also prevents TB reinfection post exposure to an open case of TB (against exogenous reinfection/ super

infection/nosocomial transmission).

Several studies have shown that IPT administration in PLHIV prevents incidence and relapse of TB and is, therefore, a key public health intervention for TB prevention in PLHIV. The effects of IPT augment the effects of ART on reducing the incidence of TB. With the concomitant administration of both ART and IPT, there is a likelihood of restoration of TB-specific immunity by ART and the beneficial effect of IPT may be prolonged. IPT does not promote INH resistance when used to treat LTBI.

In latent TB, the MBT bacilli are fewer in number and are dividing slowly, resulting in an extremely low risk of selecting drug-resistant mutants. A study conducted in 2010 reflected that the prevalence of INH resistance among IPT-exposed persons was like the background population.

Please refer **Chapter 2.8 (HIV-TB co-infection: Case Finding, Management and Prevention of Tuberculosis)** for more details.

Pneumocystis Jiroveci Pneumonia (PCP)

Epidemiology

PCP is caused by *Pneumocystis jirovecii*, a ubiquitous fungus. Initial infection with P. jirovecii usually occurs in early childhood; two thirds of healthy children have antibodies to P. jirovecii by age 2 years to 4 years.[7] Adult PCP results from reactivation of latent infection or new exposure to the organism. Person-to-person spread occurs by the airborne route.

The use of ART and prophylaxis for PCP have dramatically reduced the number of new and cases of PCP. However, PCP continues to occur among persons who are unaware of their HIV infection, and in patients who fail to seek medical care or adhere to or respond to ART or PCP prophylaxis.

PCP infection occurs in 20%–30% of AIDS patients.8 Even with treatment, PCP is associated with a mortality of 20%–40%.[8] Approximately 90% of PCP cases occurred in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm.[3,8] Other factors associated with a higher risk of PCP in the pre-ART era included CD4 cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss and higher plasma HIV RNA levels.

Clinical Manifestations

Most patients with PCP have danger signs, and, therefore, meet the criteria for admission to hospital. **PCP is a clinical diagnosis.**

PCP is common in HIV-infected children aged less than 1 year. In older children, it is seen mainly in severely immune-compromised children not on CPT. Suspect PCP if the child is <12 months old and has tachypnoea (>50 breaths/minute in children aged 2–12 months; 40 breaths/minute in children aged 12 months–5 years), cyanosis (in advanced stage) and few crepitations relative to the degree of cyanosis.

In PLHIV, the most common manifestations of PCP are **subacute onset of progressive dyspnoea, fever, non-productive cough and chest discomfort**, which worsen within days to weeks. In mild cases, pulmonary examination, while the patient is at rest, usually is normal. With exertion, tachypnoea, tachycardia and diffuse dry rales may be observed. Oral thrush (candidiasis) is a common coinfection. Fever is apparent in most cases and may be the predominant symptom in some patients.

Hypoxemia, the most characteristic laboratory abnormality, can range from:

- Mild (PaO_2 70–79 mm Hg*)
- Moderate (PaO_2 60–69 mm Hg*)
- Severe (PaO_2 <60 mm Hg*)

Table 4.3.4: Manifestations of PCP in adults and children

Adults	Children
• Dyspnoea (shortness of breath) caused by clogging of the alveoli is the main symptom. This is the key presenting feature of PCP. Initially, this occurs only on exertion, but later at rest also. The patient can progress to severe dyspnoea quite quickly. • Low blood oxygen levels (hypoxaemia) can be confirmed with the use of a pulse oximeter device but remember that a rapid respiratory rate can often compensate for hypoxaemia, resulting in reasonable oxygen saturation. • Dry cough (non-productive) • Tachypnoea (fast breathing), often with flaring of the nostrils • Temperature may be normal or high and may be over 40°C. • Chest x-ray characteristically shows a ground-glass (hazy) appearance that is more pronounced in the lower lung zones. (Intrathoracic lymph nodes are not a radiological feature of pneumocystis pneumonia.)	• Tachypnoea* • Dyspnoea (severe difficulty in breathing) • Cyanosis • Sudden onset of fever, although a fever may not always be present • Chest auscultation is less specific. • The intensity of respiratory distress is a more important sign. • The chest x-ray may show commonly bilateral diffuse parenchymal infiltrates with 'ground-glass' or reticulogranular appearance. In mild cases, parenchymal infiltrates predominantly perihilar and progressing peripherally to reach the apical portion of the lung are seen. Rarely, lobar, cavitary or miliary lesions, pneumothorax or pneumomediastinum may be seen.
* Tachypnoea in children is defined as respiratory rate: • More than 60/min in infants less than 2 months of age • More than 50/min in infants with age 2–12 months of age • More than 40/min in children aged between 1 and 5 years • More than 30/min in children older than 5 years	

The chest radiograph typically demonstrates diffuse, bilateral, symmetrical 'ground-glass' interstitial infiltrates emanating from the hila in a butterfly pattern; however, in patients with early disease, a chest radiograph may be normal. Atypical radiographic presentations, such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, intrathoracic adenopathy and pneumothorax occur.

Spontaneous pneumothorax in a patient with HIV infection should raise the suspicion of PCP. Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis or an additional pathology.

Diagnosis

Because clinical presentation, blood tests and chest radiographs are not pathognomonic for PCP (and because the organism cannot be cultivated routinely), histopathologic or cytopathologic demonstration of organisms in tissue, BAL fluid or induced sputum sample are required for a definitive diagnosis of PCP.

Presumptive diagnosis: A presumptive diagnosis can be made in the presence of clinical symptoms, low CD4 count, presence of oral candidiasis and suboptimal prophylaxis in the past. The PaO_2 can be used to grade the severity. CXR may support the diagnosis but may also be normal. Diagnosis should be confirmed by sputum examination, if available. However, treatment should not be withheld for want of confirmation.

Serum lactate dehydrogenase (LDH) is often raised. **A high LDH level is an unfavourable sign and**

indicates severe PCP. However, its use as a parameter for prognosis of the disease is limited.

Definitive diagnosis: The diagnosis of PCP is confirmed by **demonstration of the organism** in pulmonary secretions.

This may be achieved by

1. Sputum induction with hypertonic saline (50%–80% sensitive)
2. BAL (86%–97% sensitive)
3. BAL and transbronchial lung biopsy (99% sensitive)

Sputum is often difficult to obtain. However, it can be collected by inhalation of hypertonic saline or by nebulization. All material coughed out (2–3 ml) is collected and diluted with an equal volume of sterile water. The specimen is liquefied with dithiothreitol or used as such for preparing smears and staining. It is difficult to induce sputum in children <2 years of age and may cause nausea, vomiting and bronchospasm.

Staining techniques: The common staining techniques undertaken for demonstrating P. jiroveci include the following:

- Wright–Giemsa staining: Cysts and trophozoites of P. jiroveci are seen, which are thick- walled 5–8 mm structures, with up to eight intracystic bodies (1–2 mm) termed sporozoites. Trophozoites are thin-walled, free-living, pleomorphic organisms containing a small nucleus.
- Immunofluorescence staining: Organisms are visible either as a single cyst or aggregates of extracellular thick-walled cysts with a bright apple-green fluorescence. The cyst aggregates may or may not be embedded in a brightly stained extracellular matrix. Individual cysts may appear as comma-shaped or parenthesis-like structures.
- Silver impregnation: Gomori's methenamine silver stain is used.

PCR is an alternative method for diagnosing PCP. PCR is highly sensitive and specific for detecting Pneumocystis; however, PCR cannot reliably distinguish colonization from active disease, although higher organism loads as determined by quantitative PCR (Q-PCR) assays are likely to represent clinically significant disease.

1,3 β-D-glucan (β-glucan), which is a component of the cell wall of Pneumocystis cysts, is often elevated in patients with PCP. The sensitivity of the β-glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in patients with a low level of β-glucan (e.g., <80 pg/ml using the Fungitell assay). However, the specificity of β-glucan testing for establishing a PCP diagnosis is low, since many other fungal diseases, cellulose membranes used for haemodialysis and some drugs can elevate β-glucan levels.

However, PCP treatment can be initiated before a definitive diagnosis is established because P. jirovecii persist in clinical specimens for days or weeks after effective therapy is initiated.

Prophylaxis

Adult

Indication for primary prophylaxis:

- CD4 count <350 cells/mm^3
- WHO Clinical stage 3 and 4

Indication for secondary prophylaxis:

- For all patients who have completed successful treatment for PCP until CD4 count is >350 cells/mm^3 (at least on two occasions, done 6 months apart)

Regimen:

- Cotrimoxazole one double-strength tablet (TMP 160 mg/SMX 800 mg), each day or two single- strength tablets daily
- Alternative: If allergic or intolerant to Cotrimoxazole (rash, anaemia, neutropenia), TMP-SMX desensitization may be tried; if severe, Dapsone 100 mg/day

Discontinuation: When CD4 count is >350 cells/mm^3 on two different occasions 6 months apart with an ascending trend and devoid of any WHO clinical stage 3 and 4 conditions

Table 4.3.5: Cotrimoxazole preventive therapy for adults and adolescents

Prophylaxis	Recommendations
Commencing primary CPT	Cotrimoxazole prophylaxis must be initiated in PLHIV with CD4 count <350 cells/mm^3 or with WHO clinical stage 3 and 4
Timing the initiation of Cotrimoxazole in relation to initiating ART	Start Cotrimoxazole prophylaxis first. Start ART after starting Cotrimoxazole or as soon as CPT is tolerated, and the patient has completed the 'preparedness phase' of counselling
Commencing secondary CPT	For all patients who have completed successful treatment for PCP until CD4 is >350 cells/mm^3 (at least on two occasions, done 6 months apart)
Dosage of Cotrimoxazole in adults and adolescents	One double-strength tablet or two single-strength tablets once daily: total daily dose of 960 mg (800 mg SMZ + 160 mg TMP)
Cotrimoxazole for pregnant and breastfeeding women	Women who fulfil the criteria for CPT should continue it throughout pregnancy. If a woman requires CPT during pregnancy, it should be started regardless of the stage of pregnancy. Breastfeeding women should continue CPT, when indicated.
Patients allergic to sulpha-based medications	Dapsone 100 mg per day Cotrimoxazole desensitization may be attempted but not in patients with a previous severe reaction to Cotrimoxazole or other sulpha-containing drugs.
Monitoring	No specific laboratory monitoring is required in patients receiving Cotrimoxazole
Discontinuation of Cotrimoxazole prophylaxis	In PLHIV whose CD4 counts reached >350 cells/mm^3, may likely to fall <350 cells/mm^3 afterwards due to ART treatment failure or due to any other immunosuppressive conditions or due to the administration of long-term immunosuppressive drugs. In those patients, Cotrimoxazole prophylaxis has be restarted immediately and sustained till CD4 counts reach >350 cells/ mm^3 on two different occasions tested 6 months apart, with an ascending trend and devoid of any WHO clinical stage 3 or 4 conditions

Cotrimoxazole desensitization

If the patient reports a history of hypersensitivity to sulpha-containing drugs, start him/her on a desensitization regimen as an in-patient. Desensitization can be attempted 2 weeks after a non- severe

(grade 3 or less) Cotrimoxazole reaction that has resulted in temporary interruption in the use of the drug. Cotrimoxazole desensitization has been shown to be successful and safe in approximately 70% of the patients with previous mild-to-moderate hypersensitivity.

Table 4.3.6: Protocol for Cotrimoxazole desensitization

Step	Dosage
Day 1	80 mg SMX + 16 mg TMP 2 ml oral suspension
Day 2	160 mg SMX + 32 mg TMP 4 ml oral suspension
Day 3	240 mg SMX + 48 mg TMP 6 ml oral suspension
Day 4	320 mg SMX + 64 mg TMP 8 ml oral suspension
Day 5	400 mg SMX + 80 mg TMP (One single-strength SMX-TMP tablet)
Day 6	800 mg SMZ + 160 mg TMP (Two single-strength SMX-TMP tablets or one double-strength tablet)
Note: Cotrimoxazole oral suspension contains 40 mg TMP + 200 mg SMX per 5 ml.	

Desensitization should not be attempted in individuals with a history of severe Cotrimoxazole or any other sulphonamide reaction. If a reaction occurs, the desensitization regimen should be stopped. Once the patient recovers fully, Dapsone at a dosage of 100 mg per day may be tried.

Children

All HIV-exposed infants should receive CPT from the age of 6 weeks until HIV is reliably excluded. In all those confirmed to be HIV infected, CPT should be continued till 5 years of age. The recommended dose is 5 mg/kg/day of Cotrimoxazole (Sulfamethoxazole and Trimethoprim combination) once daily.

Children with history of severe adverse reaction (grade 4 reaction) to Cotrimoxazole or other sulpha drugs as well as children with glucose-6-phosphate dehydrogenase deficiency(G6PD) should not be initiated on CPT. The alternative drug in this case is Dapsone 2 mg/kg once daily (not to exceed 100 mg/day) orally.

Table 4.3.7: Indications for CPT prophylaxis in children

Group	When to Start Cotrimoxazole?	When to Discontinue CPT prophylaxis?
All HIV-exposed infants/children	From 6 weeks of age (or at first encounter with health services)	HIV infection has been reliably excluded by a negative antibody test at 18 months, regardless of ARV initiation
All HIV-infected infants and children up to 5 years of age	Regardless of WHO stage or CD4 counts or CD4%	At 5 years of age, when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e., in a child >5 years of age with a WHO T-stage 1 or 2 and CD4 count of >350 cells/ mm^3 on two occasions not less than 6 months apart
All HIV-infected children >5 years of age	WHO Stage 3 and 4 regardless of CD4 cell count OR CD4 <350 cells/mm^3 regardless of WHO staging	When clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e., in a child >5 years of age with a WHO T-stage 1 or 2 and CD4 count of >350 cells/mm^3 on two occasions not less than 6 months apart
As secondary prophylaxis	After completion of treatment for PCP	• <5 years of age: do not stop • >5 years of age: with a WHO T- stage 1 or 2 and CD4 count of >350 cells/mm^3 on two occasions not less than 6 months apart

Table 4.3.8: Dose of Cotrimoxazole for PCP prophylaxis in children

Weight- and Age-based Dosing for Cotrimoxazole (TMP/SMX) Prophylaxis					
Weight (kg)	Approx. Age	Cotrimoxazole once a day			
		Syrup 5 ml (40 TMP/ 200 SMX)	Child tablet (20 TMP/ 100 SMX)	Single strength adult (80 TMP/400 SMX)*	Double strength adult tablet (160 TMP/ 800 SMX)
<5	6 weeks–2 months	2.5 ml	1 tablet	-	-
5–10	2–12 months	5 ml	2 tablets	½ tablet	-
10–15	1–2 years	7.5 ml	3 tablets	½ tablet	-
15–22	2–5 years	10 ml	4 tablets	1 tablet	½ tablet
>22	>5 years	15 ml	-	1½ tablet	½ to 1 tablet depending on weight

- Dosage: 5mg/kg of TMP/day orally once daily
- *Splitting the tablets into quarters is not recommended unless there is no syrup available.
- It should be emphasized to patients and families that Cotrimoxazole does not treat and cure HIV infection.
- Counsel caregivers well for side effects of CPT.
- Discontinue CPT if Stevens-Johnson's syndrome, severe liver disease, severe anaemia, severe pancytopenia or completely excluded HIV infection.

Cotrimoxazole desensitization in children is same as mentioned above

Management of PCP

Duration of treatment: 21 days

Table 4.3.9: Treatment schedule for PCP

Severity of PCP	Preferred regimen	Alternative regimen	Adjunctive steroid therapy
Mild to Moderate	TMP–SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/ day, orally in three divided doses or TMP–SMX: (160 mg/800 mg or DS) two tablets orally three times daily	Dapsone 100 mg oral daily plus TMP 5 mg/kg orally thrice daily or Primaquine 30 mg (base) orally daily plus (clindamycin 450 mg orally every 6 hours or 600 mg oral every 8 hours), or Atovaquone 750 mg orally twice daily with food	**Indications** PaO_2 <70 mm Hg at room air, or alveolar-arterial DO_2 gradient >35 mm Hg Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy): • Days 1–5: 40 mg orally twice daily; 1 mg/kg/dose twice daily (children) • Days 6–10: 40 mg orally daily; 1 mg/ kg/dose once daily (children) • Days 11–21: 20 mg orally daily; 0.5 mg/ kg/dose once daily (children)
Moderate to Severe	TMP–SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/ day IV given every 6 hours or every 8 hours; may switch to oral formulations after clinical improvement	Pentamidine 4 mg/kg IV daily infused over ≥60 minutes; can reduce dose to 3 mg/kg IV daily in the event of toxicities or Primaquine 30 mg (base) orally daily plus (clindamycin 600 mg IV every 6 hours or 900 mg IV every 8 hours) or (clindamycin 450 mg oral every 6 hours or 600 mg PO every 8 hours) (AI)	

Table 4.3.10: High dose Cotrimoxazole for treatment of PCP in children

Weight (kg)	Dose given 4 times a day*		Dose given 3 times a day	
	Syrup/ disp. tablet*	SS tab*	Syrup*	SS tab*
<5	2.5 ml		4 ml	
5 - 9.9	5 ml		7 ml	
10 - 14.9	7.5 ml		10 ml	1 tab
15 - 21.9	10 ml	1 tab	15 ml	1 ½ tab
>22	15 ml	1½ tab		2 tabs

*Syrup: 200 mg SMX/40 mg TMP per 5 ml Dispersible (disp.) tablet: 100 mg SMX/20 mg TMP (1 disp. tablet = 5 ml syrup) Single-strength (SS) tablet: 400 mg SMX/40 mg TMP

Bacterial Pneumonia

Epidemiology

Bacterial respiratory diseases, including **sinusitis, bronchitis, otitis and pneumonia**, are among the most common infectious complications in PLHIV. Bacterial pneumonia is a common cause of HIV-associated morbidity. The incidence of bacterial pneumonia in individuals with HIV has decreased

progressively with the advent of ART.

Pneumonia is the most common pulmonary manifestation followed by TB and PCP. Incidence of bacterial pneumonia is 0.8–2 per 100-person year. Incidence of pneumonia increase by six times in untreated HIV patients.[9]

Bacterial pneumonia in individuals with HIV results from multiple risk factors, particularly immune defects. A CD4 count decrease, especially when below 100 cells/mm^3, continues to be a major risk factor for pneumonia due to routine bacterial pathogens. In CLHIV, bacterial pneumonia can develop at any level of immunosuppression regardless of CD4 count. Lack of ART or intermittent use of ART increases the risk for pneumonia, likely due to uncontrolled HIV viremia. Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include tobacco, alcohol and/or injection drug use and chronic viral hepatitis. Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency and congestive heart failure are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV. In CLHIV, underlying pulmonary disease like bronchiectasis and chronic lung diseases pose additional risks for the development of pneumonia. In individuals with HIV, S. pneumoniae and Haemophilus species are the most frequently identified causes of community-acquired bacterial pneumonia. Staphylococcus aureus (S. aureus) and S. pneumoniae are among the most common aetiologies of pneumonia in association with influenza infection. Atypical bacterial pathogens such as Legionella pneumophila, Mycoplasma pneumoniae and Chlamydophila species have been reported as infrequent causes.

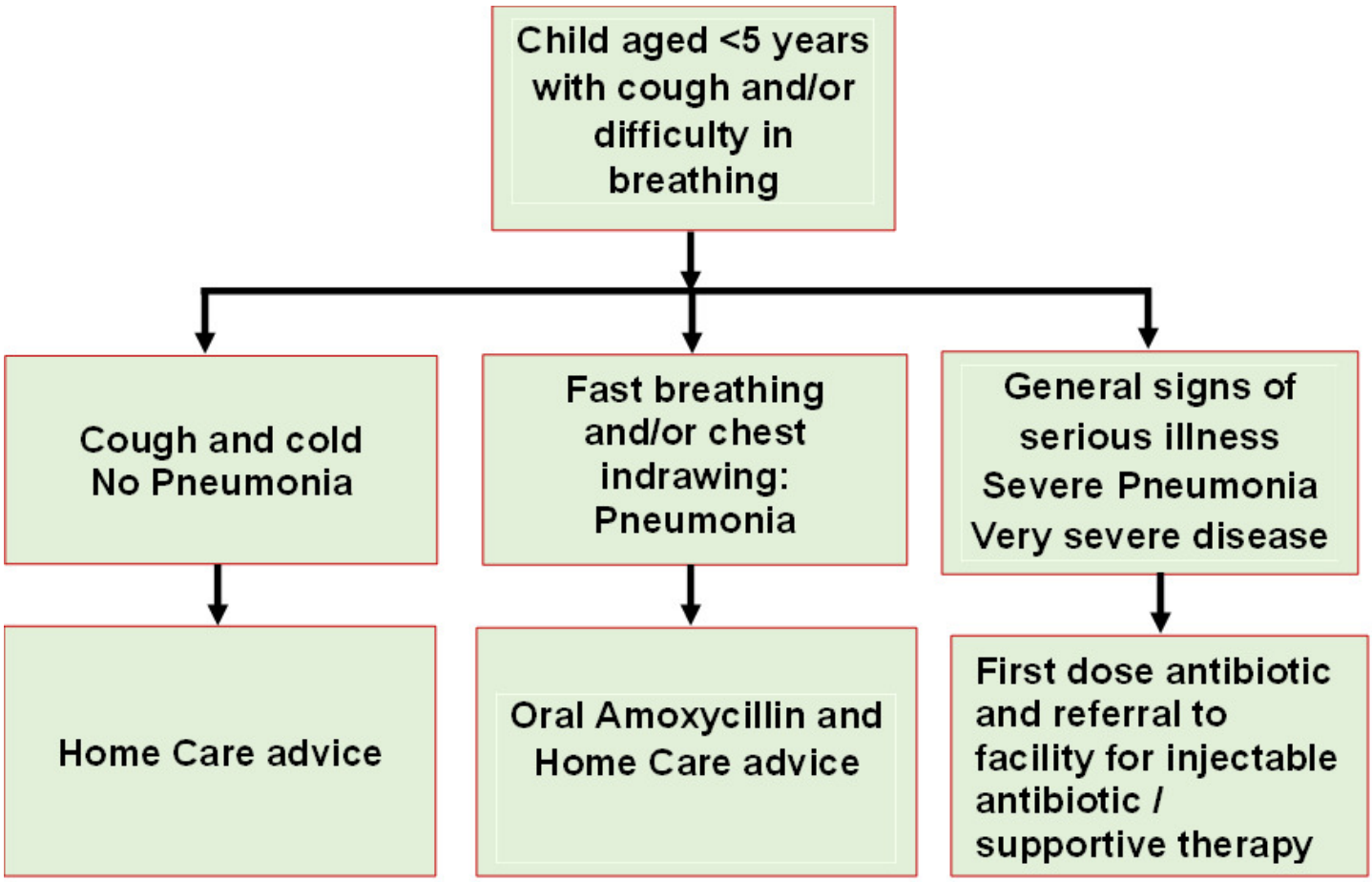
Respiratory viruses-associated pneumonias are less studied in individuals with HIV. Patients with advanced HIV disease (CD4 count ≤50 cells/mm^3) or underlying neutropenia, as well as pre- existing lung disease such as bronchiectasis or severe COPD have an increased risk of infection with **P. aeruginosa.**

Clinical Manifestations

Patients with pneumonia caused by bacteria such as S. pneumoniae or Haemophilus species characteristically have **acute onset (3–5 days) of symptoms**, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum and dyspnoea. The presence of fever, tachycardia and/or hypotension can be indicators of sepsis. Tachypnoea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia.

Most often in young CLHIV, acute bacterial pneumonia is associated with bacteraemia. Hence, many of these infants and young children can present with signs of general danger like not able to drink or breastfeed, persistent vomiting, convulsions (active or immediate past), poor sensorium (lethargic or unconscious) and stridor in a calm child. These children are classified as having very severe disease or severe pneumonia and should be referred immediately for further management. CLHIV presenting with fever and cough, if with tachypnoea (respiratory rate >60/min in infants less than 2 months of age; >50/min in infants 2–12 months of age; >40/min in children aged between 1 and 5 years; >30 in children older than 5 years) and/or chest in-drawing but no general danger signs, are classified as having severe pneumonia. Children with hyperactive airway disease or bronchial asthma can also present with fever (infection triggered exacerbations), cough and tachypnoea. Such children can be distinguished by the response to the inhaled rapidly acting bronchodilators.

Figure 4.3.4: Classification of pneumonia in CLHIV



#Not able to drink, persistent vomiting, convulsion, lethargic or unconscious, stridor in a calm child or malnutrition

Patients with bacterial pneumonia typically have signs of focal consolidation, such as egophony, and/or pleural effusion on lung examination. In patients with bacterial pneumonia, the white blood cell (WBC) count usually is elevated. The elevation may be relative to baseline WBC count in those with advanced HIV. Neutrophilia or a left shift in WBC differential may be present

Individuals with bacterial pneumonia characteristically exhibit **unilateral, focal, segmental or lobar consolidation on chest radiograph.** The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to S. pneumoniae or Haemophilus species typically present with consolidation, whereas cavitation may be a feature more suggestive of *P. aeruginosa or S. aureus.*

In individuals with HIV, the incidence of bacteraemia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to S. pneumoniae.

Table 4.3.11: Recurrent bacterial pneumonia and signs of severity

Recurrent Bacterial Pneumonia: Current Episode Plus One or More Previous Episodes in the Past Six Months		
Recurrences	**Adults**	**Children (<15 years)**
Severe recurrent bacterial pneumonia: Current episode plus one or more in previous six months	Respiratory rate >30 Hypoxia: Oxygen saturation <90%	Cough with fast breathing, chest in-drawing, nasal flaring, wheezing and grunting

Diagnosis

Generally, microbiological investigations should precede initiation of therapy. **Microscopy** alone can be performed at routinely available laboratory services at healthcare facilities. **Culture of common pathogens** may be possible at district- and tertiary-level health centres while bacterial isolation and antimicrobial susceptibility testing may be possible only at tertiary/referral centres.

Patients with clinical symptoms and signs suggestive of pneumonia should have posteroanterior and lateral chest radiographs. **CXR and WBC** count aid in making a diagnosis of bacterial pneumonia. PCP may coexist with bacterial pneumonia. An induced sputum examination for P. jiroveci should be done to rule it out. **AFB staining and TB cultures** of sputum samples (either expectorated or induced) should be performed on all PLHIV hospitalized patients with pulmonary infiltrates.

Table 4.3.12: Differentiating features between PCP and bacterial pneumonia

Findings		PCP	Pneumonia
Clinical	CD4 cell count	≤200 cells/mm^3	CD4 in any range
	Symptoms	Non-productive cough	High fever, cough with purulent sputum, chest pain
	Symptom duration	Over 2–4 weeks	Typically, 3–5 days
	Signs	Occasional inspiratory dry crepitations	Focal lung signs
	WBC Count	Varies	Elevated frequently; often neutrophilic leucocytosis
X-ray Chest	Distribution	Normal or diffuse	Lobar/Focal
	Location	Bilateral	Unilateral, lobar or segmental
	Pattern	Reticular/granular	Air space consolidation
	Pleural effusions	Very rare	In one third of patients
	Cysts	15%–20%	Rare

Procalcitonin (PCT) testing has been proposed as a tool to distinguish between bacterial and viral respiratory infections. In general, we do not have sufficient evidence for its recommendations.

Management

Always consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the below mentioned therapy.

General considerations

Duration

- 5–7 days. The patient should be afebrile for 48–72 hours and should be clinically stable before discontinuation of therapy.
- Longer duration of antibiotics is often required when severe pneumonia or bacteraemia is present, and particularly if due to S. pneumoniae or complicated S. aureus infection.
- Switch from IV to oral therapy: A switch should be considered for patients who have improved clinically, can swallow and tolerate oral medications, and have intact GI function.

Table 4.3.13: Treatment Protocol

Oral Regimens in Non-severe Cases	
Preferred therapy	**Alternatives**
Beta-Lactams: High-dose Amoxicillin or amoxicillin/clavulanate plus a macrolide (azithromycin or clarithromycin) **In children,** oral amoxicillin (40 mg/kg/dose) twice daily for 5 days	**Beta-Lactams:** Cefpodoxime or cefuroxime, or a respiratory fluoroquinolone (levofloxacin or moxifloxacin), especially for patients with penicillin allergies **In children,** alternatives are beta-lactam, Cotrimoxazole and azithromycin
Hospitalized Patients with Non-severe Cases	
Preferred Therapy	**Alternative Therapy**
An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) **Preferred Beta-Lactams:** Ceftriaxone, cefotaxime or ampicillin-sulbactam or An IV respiratory fluoroquinolone (levofloxacin or moxifloxacin), especially for patients with penicillin allergies **In children**: Ampicillin 50 mg/kg or benzyl penicillin: 50,000 units/kg IM/IV every 6 hours for at least 5 days along with Gentamicin 7.5 mg/kg IM/IV once a day for at least 5 days	An IV beta-lactam plus doxycycline IV penicillin may be used for confirmed pneumococcal pneumonia
Patients with Severe Pneumonia	
Preferred Therapy	**Alternative Therapy**
An IV beta-lactam plus IV azithromycin or An IV beta-lactam plus an IV fluoroquinolone (levofloxacin or moxifloxacin), **Preferred Beta-Lactams:** Ceftriaxone, cefotaxime or ampicillin-sulbactam	**For Penicillin-allergic patients:** Carbapenems (IV) plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin)
Patients at Risk of Pseudomonas Pneumonia	
Preferred Therapy	**Alternative Therapy**
An IV anti-pneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin IV or levofloxacin IV 750 mg/day) **Preferred Beta-Lactams:** Piperacillin-tazobactam, cefepime, imipenem or meropenem	An IV anti-pneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus IV azithromycin or An IV anti-pneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus an IV anti-pneumococcal fluoroquinolone (moxifloxacin or levofloxacin)
Patients at Risk for MRSA Pneumonia	
Vancomycin IV or linezolid (IV or PO)	

Mycobacterium Avium Complex Disease

Epidemiology

MAC can cause life-threatening symptoms in immunocompromised individuals. In PLHIV with advanced HIV disease, MAC usually causes disseminated disease. MAC is ubiquitous and is found in water, soil, food and in other animals.

The mode of MAC transmission is thought to be through inhalation, ingestion or inoculation of MAC bacteria via the respiratory or GI tract. MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3.

Clinical Manifestations

The patient may present with fever, night sweats, chills, weight loss, muscle wasting, abdominal pain, tiredness, pallor and diarrhoea. There may be enlargement of the liver, spleen and lymph nodes.

A clinical MAC syndrome consists of one or more of the following: persistent fever >38°C for more than 1 week, night sweats, diarrhoea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anaemia (haemoglobin <8.5 g/dl) and alkaline phosphatase more than twice the upper limit of normal.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph node, bone marrow or other normally sterile tissue or body fluids.

The diagnosis is confirmed if MAC is cultured from normally sterile body fluid, tissue or an organ. Diagnosis is considered probable if MAC is cultured from the bronchopulmonary, GI, skin surface or other non-sterile sites (as the sole pathogen) and histopathological confirmation of AFB/MAC is obtained from the tissue specimen from which the culture was obtained.

Prevention and Management

Routine prophylaxis for MAC is presently not recommended in India.

Management

Combination therapy is generally used to prevent resistance. Clarithromycin is the preferred agent and results in rapid clearance of MAC from the blood. Azithromycin is an excellent substitute in cases where drug interactions or side effects prevent the use of clarithromycin. Ethambutol is active against MAC and recommended as a second choice, but it must be combined with either clarithromycin or azithromycin. It has side effects such as cause nausea, vomiting and visual problems. To prevent drug resistance and increase the potency of anti-MAC therapy, a third and sometimes a fourth antibiotic can be added. Rifampicin is used but has drug interactions, particularly with PIs or non-nucleoside analogues used to treat HIV. Ciprofloxacin can also be used. Lifelong maintenance therapy may be necessary to prevent recurrence but may be discontinued at a CD4 count >100 cells/mm^3..

Table 4.3.14: Management of MAC

Preferred therapy	At least two drugs as initial therapy to prevent or delay emergence of resistance Clarithromycin 500 mg PO twice daily plus ethambutol 15 mg/kg PO daily or Azithromycin 500–600 mg plus ethambutol 15 mg/kg PO daily when drug interaction or intolerance precludes the use of clarithromycin
Alternatives	Rifabutin 300 mg PO daily or Fluoroquinolone (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily)
Criteria for discontinuing therapy	Completed at least 12 months therapy No signs and symptoms of MAC disease, and Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART

Talaromycosis (Previously known as Penicilliosis)

Epidemiology

Talaromycosis is caused by a thermally dimorphic fungus, Talaromyces (Penicillium) marneffei. It is geographically restricted to Southeast Asian countries including India (Northeast India). Majority of the cases in India have been reported from the state of **Manipur.** A few cases have been reported from Assam and other north eastern states, viz. Nagaland, Mizoram, Meghalaya and Sikkim.

Bamboo rats are known to be carriers of T. *marneffei.* In India, only two species of bamboo rats, viz. *Cannomys badius and Rhizomys pruinosus* are found. The infection is transmitted by bamboo rats and most commonly during rainy season.

Clinical Manifestations

The infection frequently begins as a subacute illness characterized by **fever, weight loss, hepatosplenomegaly, lymphadenopathy and respiratory and GI abnormalities.** These clinical features are non-specific and are indistinguishable from those of disseminated TB, other systemic mycoses or infections due to intracellular pathogens such as Salmonella species.

Skin lesions: Central necrotic papules with umbilication appearing on the face, trunk, and extremities occur in 40%–70% of patients.

Figure 4.3.5: Cutaneous manifestations of Talaromycosiss


'01 8 16



(Pictures' courtesy: CoE, RIMS, Imphal, Manipur)

Pulmonary involvement manifests as cough or shortness of breath.

GI involvement presents as diarrhoea or abdominal pain. Hepatosplenomegaly together with intra-abdominal lymphadenopathy causes abdominal distention and pain.

Meningoencephalitis is a rare manifestation and has a rapid disease course with mortality. Concurrent infections are also common, namely, oropharyngeal candidiasis and TB.

Patients have **anaemia and thrombocytopenia** due to bone marrow infiltration. Anaemia can be profound and may require multiple red cell transfusions. Elevation of aminotransferase is common, with serum aspartate aminotransferase (AST) over alanine aminotransferase (ALT) ratio of approximately 2. The chest radiographical findings are broad, ranging from diffuse interstitial disease to reticulonodular infiltrates to alveolar infiltrates causing respiratory failure.

Diagnosis

A diagnosis of talaromycosis should be considered in all patients with HIV with CD4 count <100 cells/mm^3 with positive travel history.

Skin lesions have typical central necrotic appearance and can be a diagnostic sign; however, these are late manifestations and absent in almost 60% of patients.

The current diagnostic methods are still based on conventional microscopy, histology and culture. Culture results usually return within 4 to 5 days but can take up to 14 days.

A presumptive diagnosis can be made based on the **microscopic examination** of Giemsa-, Wright- or Gomori methenamine silver-stained samples of skin lesion scrapings, lymph node aspirate, bone marrow

aspirate or tissue sections showing round to oval extracellular and intramacrophage yeast-like organisms measuring 3 to 6 µm in diameter. Identification of a clear midline septum in a dividing yeast cell is what distinguishes T. marneffei from Histoplasma or Candida species.

A definitive diagnosis can be made by the histopathologic demonstration of the organism in biopsy specimens. Antigen detection and PCR-based methods are promising rapid diagnostics currently being evaluated.

Prevention and management

Primary prophylaxis is not recommended.

Table 4.3.15: Management of Talaromycosis (Penicilliosis)

Preferred Therapy
Induction therapy with liposomal amphotericin B 3 to 5 mg/kg/day IV for 2 weeks; Followed by consolidation therapy with itraconazole 200 mg oral twice daily for 10 weeks; Followed by maintenance therapy or secondary prophylaxis with itraconazole 200 mg oral daily
Alternative Therapy
Induction therapy with deoxycholate amphotericin B 0.6 mg/kg/day IV for 2 weeks; Followed by consolidation therapy with itraconazole 200 mg oral twice daily for 10 weeks; Followed by maintenance therapy or secondary prophylaxis with itraconazole 200 mg oral daily **Criteria for Discontinuing Maintenance Therapy:** CD4 count >200 cells/mm^3 for ≥6 months in response to ART

Other Pathogens with Pulmonary Manifestations: The box below contains other pathogens having the pulmonary manifestations.

Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus Histoplasma capsulatum. Histoplasmosis is acquired by inhalation of microconidia that form in the mycelial phase of the fungus in the environment. This is not very common in India.

Table 4.3.16: Management of Histoplasmosis

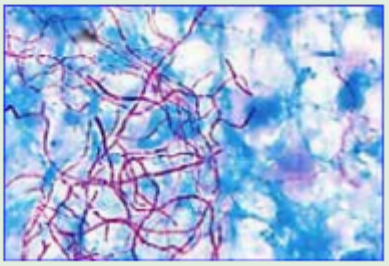
Clinical Manifestations	Diagnostics	Management
Progressive disseminated histoplasmosis presents with fever, fatigue, weight loss and hepatosplenomegaly. Pulmonary manifestations: Cough, chest pain and dyspnoea  *(Picture courtesy: CoE, STM, Kolkata)* CNS manifestations: Fever and headache, and if brain involvement is present, seizures, focal neurological deficits and changes in mental status GI manifestations: Diarrhoea, fever, abdominal pain and weight loss	CSF findings are lymphocytic pleocytosis, elevated protein and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases. H. capsulatum can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions or from samples from other involved sites in >85% of PLHIVs and disseminated histoplasmosis, but the organism requires several weeks to grow. Detection of Histoplasma antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated and acute pulmonary histoplasmosis but is insensitive for chronic forms of pulmonary infection.	Moderately severe to severe disseminated disease Induction Therapy: Liposomal amphotericin B 3 mg/kg IV daily for at least 2 weeks or until clinically improved or Deoxycholate amphotericin B 0.7–1.0 mg/kg IV daily for 2 weeks Maintenance Therapy: Itraconazole 200 mg oral three times a day for 3 days, then 200 mg oral twice a day Less severe disseminated disease Induction and Maintenance Therapy: Itraconazole 200 mg oral three times a day for 3 days, then 200 mg oral twice a day Duration of Therapy: At least 12 months

Nocardiosis

Nocardiosis is a localized or disseminated infection caused by an aerobic actinomycete.

It is often misdiagnosed as PTB since its clinical and radiological manifestations are like the latter. N. *asteroides* is the most common. Diagnosis of pulmonary nocardiosis can be made based on a positive sputum culture in an immunocompromised host.

Table 4.3.17: Management of Nocardiosis

Clinical Manifestations	Diagnostics	Management
The most common symptoms at presentation are chronic cough, chest pain, dyspnoea and haemoptysis. Pulmonary nocardiosis is a chronic disease which can rarely have an acute course as well. It rarely has skin involvement with sub-cutaneous ulcerated nodules and the disseminated form has nervous system involvement with symptoms like headache, altered mental status and ataxia.	Chest radiological findings of pulmonary nocardiosis in advanced HIV infection include alveolar infiltration, cavitation, pleural effusion and reticulonodular pattern. Computed tomography finding of chest shows multiple nodules in almost all patients and cavitation in majority of patients. Bronchial washings are shown to be useful for isolation of nocardia. Nocardia may take several days to weeks to grow in culture. Sputum smear with Kinyoun acid-fast stain reveals acid-fast branching filaments of Nocardia.	Treatment for 6 months + Cotrimoxazole + Amikacin or Imipenem *(Pictures courtesy: CoE, GHTM, Tambaram)*  

Aspergillosis

Aspergillus species are ubiquitous throughout the world. The fungus commonly grows in decaying vegetation and soil. Exposure to the fungus occurs through the inhalation of spores. A. fumigatus causes the most severe disease in humans. The major portal of entry for infection is the respiratory tract.

Table 4.3.18: Management of Aspergillosis

Clinical Manifestations 3 clinical syndromes:	Diagnostics	Management
1. Allergic bronchopulmonary aspergillosis 2. *Aspergillus mycetoma* or fungal balll 3. Invasive aspergillosis: This occurs in PLHIV mostly and presents with high fevers, pulmonary consolidation and haematogenous dissemination. Symptoms include fever, dyspnoea, cough, chest pain and haemoptysis	Chest radiographic findings include thick-walled cavities, most commonly in the upper lobes. Culture of organisms if possible	Liposomal amphotericin B or the combination of caspofungin and voriconazole should be considered.

COVID-19 in PLHIV

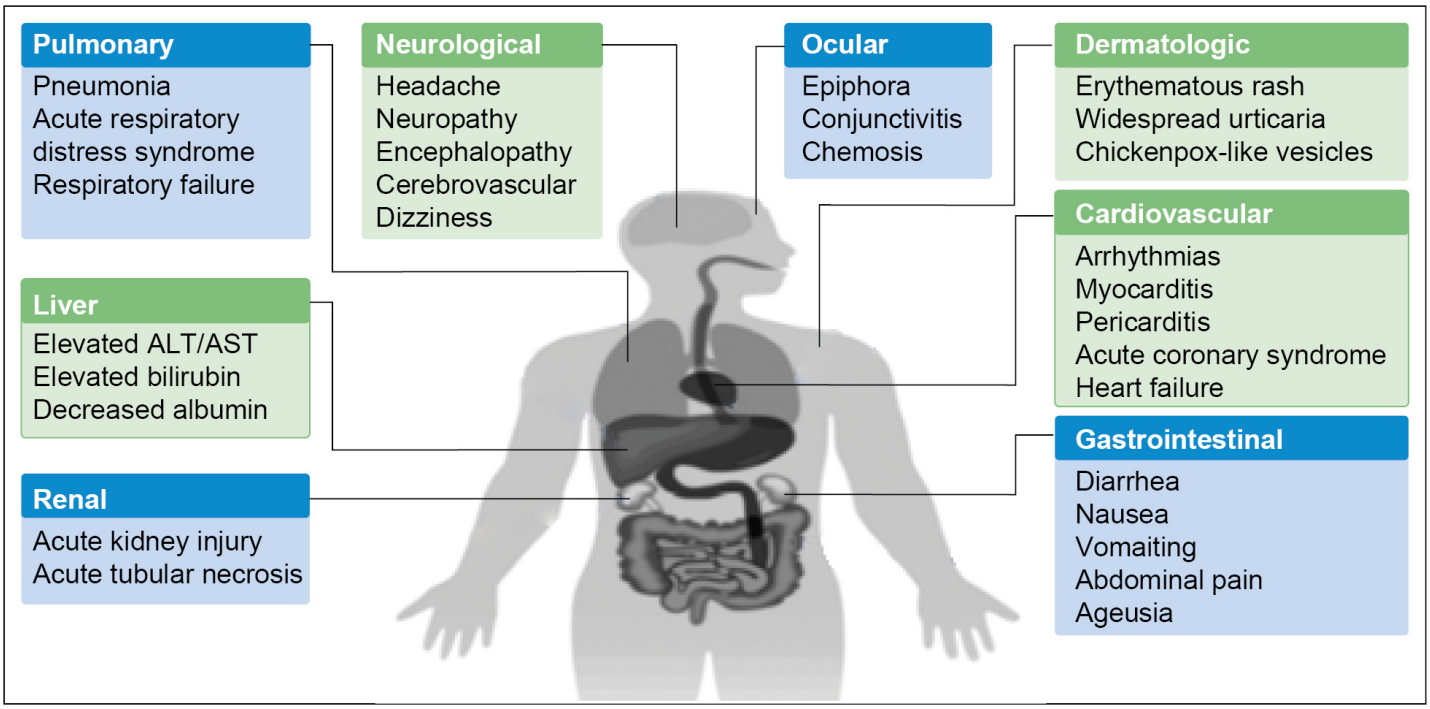
Over the last two decades, the coronavirus family has been identified as the source of several highly pathogenic global outbreaks. Some of the most notable was the 2003 severe acute respiratory syndrome coronavirus-1 (SARS-Coronavirus-1), which caused the severe acute respiratory syndrome (SARS) outbreak in China, and the 2012 Middle East Respiratory Syndrome coronavirus (MERS- Coronavirus),

which caused the MERS outbreak in Saudi Arabia. The most recent coronavirus outbreak started in China in December 2019 as a series of acute respiratory disorders (acute hypoxic respiratory failure, pneumonia, acute respiratory distress syndrome [ARDS]). The causative pathogenic agent was found to be an enveloped, non-segmented, positive- sense RNA β-coronavirus responsible for COVID-19 Respiratory Syndrome coronavirus-2 (SARS- Coronavirus-2), also referred widely as the coronavirus disease 2019 or COVID-19.

Manifestations of COVID-19

The most affected organ system by COVID-19 is the pulmonary system, with the most frequent clinical manifestations including cough, dyspnoea, fever and sore throat, like SARS and MERS.[10],[11] In the severe disease state, the patient's clinical course is complicated by the development of pneumonia with ARDS, acute hypoxic respiratory failure and/or death.[12]

Figure 4.3.6: Multiple system involvement in Covid 19



Multiple studies conducted in various countries have demonstrated that cough is the predominant pulmonary symptom in patients with COVID-19.[13,14,15] The main reason for the development of these symptoms is the presence of severe pneumonia in COVID-19 patients. COVID-19 is categorized into mild, moderate and severe disease based on the degree of severity.[16]

Mild disease is characterized by upper respiratory tract symptoms (and/or fever) WITHOUT shortness of breath or hypoxia.

Moderate disease is characterized by dyspnoea/evidence of lower respiratory disease with a SpO_2 of 90% to <93% on room air and respiratory rate ≥ 24/minute, whereas severe disease is characterized by tachypnoea (respiratory rate ≥30/minute, hypoxemia and lung infiltrates on imaging with an SpO_2 <90% on ambient air. Notably, some providers have reported patients with hypoxia but relatively mild or no dyspnoea. This phenomenon has been termed 'silent hypoxia' or 'happy hypoxia', and may mask the severity of the illness and delay medical care.ARDS is a known severe pulmonary complication of COVID-19, where patients experience severe hypoxia refractory to oxygen therapy. Further, COVID-19 patients with severe pneumonia can deteriorate and develop life-threatening acute respiratory failure and ARDS, requiring intensive medical care.

ARDS is a known severe pulmonary complication of COVID-19, where patients experience severe hypoxia

refractory to oxygen therapy. Further, COVID-19 patients with severe pneumonia can deteriorate and develop life-threatening acute respiratory failure and ARDS, requiring intensive medical care.

There are some risk factors responsible for severe disease or mortality among PLHIV, such as the following:

- Age >60 years
- Cardiovascular disease, hypertension and coronary artery disease
- Diabetes mellitus and other immunocompromised states
- Chronic lung/kidney/liver disease
- Cerebrovascular disease
- Obesity

For clinical guidance for management of adult and paediatric COVID-19 patients, please refer to MOHFW websites.[16,17]

PLHIV who are not taking antiretroviral treatment and have a low CD4 cell count, particularly those with advanced HIV disease, are at increased risk of OIs and AIDS-related complications.

PLHIV can have a greater prevalence of the known risk factors for COVID-19 acquisition and complications, such as heart disease, kidney disease, diabetes, chronic pulmonary disease, obesity, as well as other comorbidities and coinfections, like TB compared to the general population. Several case report series and small cohort studies[18,19] among hospitalized PLHIV with COVID-19 have shown comparable clinical outcomes and similar risk of SARS CoV2 infection when compared with general population, particularly in those with well-controlled HIV infection (on ART and with a CD4 count > 200 cells/mm^3 and suppressed viral load). These limited clinical data suggest that mortality risk in PLHIV is associated with known COVID-19 factors such as older age and presence of comorbidities including cardiovascular disease, diabetes, chronic respiratory disease and obesity.

Precautions to be taken by PLHIV

PLHIV are advised to take the same COVID-19 precautions as recommended for the general population: wash hands often; practice cough etiquette; ensure physical distancing; wear masks when appropriate and according to local regulations; seek medical care if symptomatic; self- isolate if one develops symptoms or has contact with a positive COVID-19 case and other actions per the local and government response.

Vaccines against COVID-19 and Vaccination Programme in India

Three vaccines that have been granted authorization for restricted use in emergency by the Central Drugs Standard Control Organization in India are Covishield (Astrazeneca's vaccine manufactured by Serum Institute of India), Covaxin (manufactured by Bharat Biotech Limited) and Sputnik V (developed by Gamaleya Research Institute, Russia, and the third vaccine to get approval from the Drugs Controller General of India. There are many other vaccines in the pipeline and waiting for the approval for usage.

The dose schedule of the three approved vaccines is as follows:

- Covishield: two doses at an interval of 12–16 weeks
- Covaxin: two doses at an interval of 4–6 weeks
- Sputnik: two doses at an interval of 3 weeks

Indication for vaccination: HIV remains a significant risk factor for acquiring COVID-19 infection and is associated with a higher risk of mortality from COVID-19. All PLHIV should be effectively counselled to get vaccinated on a priority consideration. COVID-19 vaccination is indicated only for people aged 18 years and above as of now. As per available global evidence till now, the second dose should also be of the same COVID-19 vaccine that was administered as the first dose.

COVID-19 affects all age groups; however, the morbidity and mortality is higher in adults, particularly those above 65 years. Children have either asymptomatic or mild infection. The currently available vaccines in the country have not been evaluated in children so far. There are some clinical trials now underway to test the effectiveness and safety of the COVID-19 vaccines in children.

COVID vaccination has been advised in all other special population groups as well, e.g., pregnant women, breastfeeding women.

4.4 Gastro-intestinal System

Introduction

Gastrointestinal (GI) disorders are among the most frequent complaints in patients with HIV infection. The common GI manifestations of HIV disease include diarrhoea, dysphagia,odynophagia, nausea, vomiting, weight loss, abdominal pain, anorectal disease, jaundice, hepatomegaly and GI bleeding.

Evaluation of GI symptoms is usually difficult as there are non-specific signs and symptoms that could be due to involvement of other systems. Multiple GI infections are also common at the same time. This chapter covers the most common presentations and focuses on the symptoms/signsbased approach for the management of these infections.

Oral Pathology

- Candidiasis (oral and oesophageal)
- Angular stomatitis
- Oral ulcers
- Kaposi’s sarcoma (KS)
- Necrotizing gingivitis

Candidiasis (oral and oesophageal)

Candidiasis is one of the most common infections to present in PLHIV. Approximately 30% of PLHIV present with some sort of candida infection.

Oral candidiasis (oral thrush)

Oral candidiasis is caused by a yeast called Candida albicans. It occurs commonly in HIV-negative people, such as in infants, the elderly, uncontrolled severe diabetics, persons on prolonged antibiotic therapy, high-dose systemic corticosteroids, immunosuppressants, cytotoxic drugs, etc. In PLHIV, it is a pointer towards more advanced immunodeficiency, with persisting oral thrush qualifying as stage 3 disease.

Figure 4.4.1. Oral thrush



Pictures courtesy: GHTM-I-TECH Fellowship programme

Clinical presentation

It It is commonly seen as **white patches (that can be easily removed by scraping with a tongue depressor) surrounded by a reddish border.** These involve mostly oral mucosa, pharynx and inner side of lips. Four clinical types of candidiasis are generally recognized: pseudomembranous (oral thrush), erythematous (atrophic), angular cheilitis and hyperplastic.
PLHIV often complain of having no taste. **Swallowing is frequently painful,** but just in the back of throat, not lower down behind the sternum.

Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leucoplakia, the **white plaques of oropharyngeal candidiasis can be scraped off the mucosa.** If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of Candida present.

Treatment

Nystatin oral suspension 1 ml swished around the mouth for a few minutes and then swallowed; 4 times a day for 5 days usually cures it. Alternative topical application is 1% Clotrimazole mouth paint. If the thrush persists or recurs, fluconazole 100–150 mg once daily (children 6 mg/kg/day) for 1 week is very effective.

Oesophageal Candidiasis

Oesophageal candidiasis is a WHO clinical stage 4 condition. It is usually diagnosed clinically based on the presence of oral candidiasis and associated subjective symptoms of difficulty in swallowing (dysphagia) and/or painful swallowing (odynophagia). Endoscopic examination reveals whitish plaques like those observed with oropharyngeal disease. Involvement of soft palate and posterior wall of pharynx on oral examination may give a clue**.** Anyone with complaints of dysphagia/odynophagia and having oral candidiasis should be treated presumptively for oesophageal candidiasis.

Clinical presentation

As oral candidiasis can cause pain in the throat on swallowing (odynophagia), the important question to ask when diagnosing oesophageal candidiasis is if the patient has pain behind the sternum on swallowing. Because of the extreme discomfort experienced, it is often associated with patients not eating and consequent weight loss. Children, unlike adults, often experience nausea and vomiting. Therefore, children with oesophageal candidiasis may present with dehydration and weight loss. Classic symptoms

and signs of oesophageal candidiasis may be absent in children with oesophageal candidiasis, particularly those receiving ART.

Figure 4.4.2: Endoscopic view of oesophageal candidiasis



(Picture courtesy: OI curriculum GHTM-ITECH Fellowship programme)

It is more commonly associated with lower CD4 counts, especially if oral thrush is present. Oesophageal thrush qualifies the patient to be in WHO clinical stage 4. Other possible causes of painful and difficult swallowing include the following:

- Gastro-oesophageal reflux disease (GORD)
- An oesophageal ulcer, which can be either idiopathic (i.e., aphthous ulcer) or related to HSV
- Ulceration of the oesophagus with CMV (consider this if CD4 count <50 cells/mm3)
- Kaposi's sarcoma
- Tbuberculosis ulcers (rare)

Oesophageal candidiasis often coexists with other stage 4 diseases, particularly disseminated TB. **Symptoms like loss of weight, lethargy or any danger signs should not be attributed to oesophageal candida alone.**

Diagnosis

The diagnosis is often made empirically based on symptoms and response to therapy, or visualization of lesions plus fungal smear or brushings without histopathologic examination. The definitive diagnosis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic Candida yeast forms in tissue and confirmation by fungal culture and speciation.

Treatment

- Fluconazole 200 mg daily for 14–21 days and check the response to treatment after 7 days; if there is a good response, continue the fluconazole for 10 days to 2 weeks.
- If fluconazole is not effective after 1 week, consider the other causes listed earlier:
- If not responding to fluconazole, treat for HSV with acyclovir 400 mg 3 times a day for 10 days.
- The majority of those with CMV-related oesophagitis will develop CMV retinopathy as well. Even though vision may deteriorate late in the disease, still ask about it and examine the fundi especially if CD4 count is less than 100 cells/mm3. The treatment of choice is Valganciclovir, and alternative is Ganciclovir.
- Ensure effective ART is being taken after screening for TB.
- Children: Fluconazole loading dose oral-6 mg/kg/dose once on day; maintenance – 3–6 mg/kg/ dose once daily for 4 to 21 days (maximum: 400 mg/day).

Angular Stomatitis

Angular stomatitis presents as inflamed, painful cracks at the corners of the mouth and is usually caused by candida; can also be caused by iron deficiency, and occasionally bacteria..

Management

It usually responds well to 10 days of a simple antifungal cream, such as Clotrimazole or even nystatin drops rubbed into the cracks.

Oral Ulcers

- Aphthous ulcers (canker sores)
- HSV
- Syphilis

Aphthous ulcers (canker sores)

- One or more ulcers on the mucosa of mouth, inner lips and sometimes tongue
- Cause unknown, presumed to be viral
- Often persistent and very painful, especially in patients with lower CD4 counts
- Treatment is effective with ART. If already on ART, ensure that the patient is virally suppressed.

Figure 4.4.3: Ulcer Tongue



(Picture courtesy: CoE, GHTM, Tambaram)

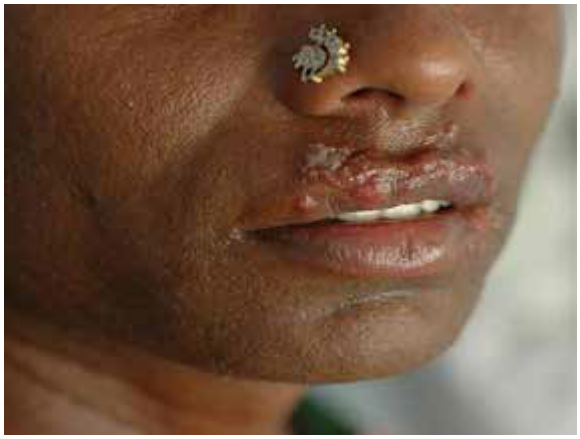
Herpes simplex virus

- May present as shallow ulcers and/or blisters that are painful, extensive and/or recurrent, often on lips as well

Treatment

- Avoid acidic foods.
- Pain relief: Paracetamol with Codeine or Tramadol
- Give Acyclovir 400 mg 3 times daily for 5–10 days orally
- Children: The dose of Acyclovir (15 mg/kg/ dose orally 5 times per day for 7–10 days; maximum 200 mg per dose) may decrease the duration of illness if started within 72 hours at the onset of symptoms. Topical Acyclovir is ineffective.

Figure 4.4.4: Herpes simplex



(Picture courtesy: CoE, GHTM, Tambaram)

Syphilis

- The ulcer of primary syphilis and a Chancroid look very similar, but the key difference is that it is almost always painless.
- Do VDRL to confirm.
- Treatment is Benzathine Penicillin 2.4 MU intramuscular weekly for 3 weeks.

Figure 4.4.5: Primary syphylis



(Picture courtesy: CoE, JJ Hospital, Mumbai)

Kaposi's Sarcoma

KS has varied presentations. For details, please refer **Chapter 5.6 (Guidelines for the Management of HIV-associated Malignancies).**

Clinical presentation

KS usually presents with purplish fleshy swelling on the roof of the mouth or gums, which may often

bleed. If KS is present on the palate or oral cavity, it may indicate pulmonary or GI tract (GIT) involvement as well. Investigate with a CXR, especially if any respiratory symptoms are present and check haemoglobin. It often results in anaemia from hidden (occult) GI bleeding.

Diagnosis

A diagnosis is usually made on history, appearance of the lesion and the distribution. For more details on KS, refer **Chapter 4.5 (Skin and Mucous Membrane)** and **Chapter 5.6 (Guidelines for Management of HIV-associated Malignancies)**.

Treatment

This is a WHO clinical stage 4 disease; the PLHIV needs to be on effective ART. If ART naive, start ART immediately. If the PLHIV is already on ART for more than 6 months, he/she must be evaluated for treatment failure. Request an urgent viral load; if failing first-line ART, switch to the second-/third-line treatment following NACO guidelines. In addition, the PLHIV is to be referred urgently for chemotherapy.

Necrotizing gingivitis

Clinical Presentation

This is an inflammation of the gingiva (gums). It may lead to tooth loss, severe pain and foul-smelling breath.

Management

- Oral hygiene
- Antiseptic mouthwashes
- Antibiotics: Metronidazole 400 mg three times a day for 7 days
- Pain management – Paracetamol or paracetamol/codeine
- As this is a WHO clinical stage 3 condition, ensure that the patient is on effective ART.

Diarrhoea and Other Intestinal Parasites

Diarrhoea is defined by WHO as having three or more loose or liquid stools per day, or as having more stools than is normal for that person. There may be associated symptoms, particularly nausea, vomiting, fever and abdominal pain.

For children: An increase in stool frequency to twice the usual number per day in infants or three or more loose or watery stools per day in older children. Diarrhoea is defined as a change in consistency (liquid or watery stools) and frequency of stools, (occur >3 times a day). If there is associated visible blood in stools, it is termed as dysentery. In most cases, these acute episodes subside within 7 days. In 5%–15% cases, acute diarrhoea may persist beyond 2 weeks, which is then called **persistent diarrhoea. Chronic diarrhoea** is defined as an insidious onset diarrhoea of >2 weeks' duration in children. The term 'chronic diarrhoea' is not synonymous with persistent diarrhoea.

The two most important consequences of diarrhoea in children are malnutrition and dehydration. Malnutrition and diarrhoea form a vicious cycle since malnutrition increases the risk and severity of diarrhoea. Conversely, diarrhoea may aggravate the severity of malnutrition.

Diarrhoea can be categorized as inflammatory or non-inflammatory. All cause significant morbidity and

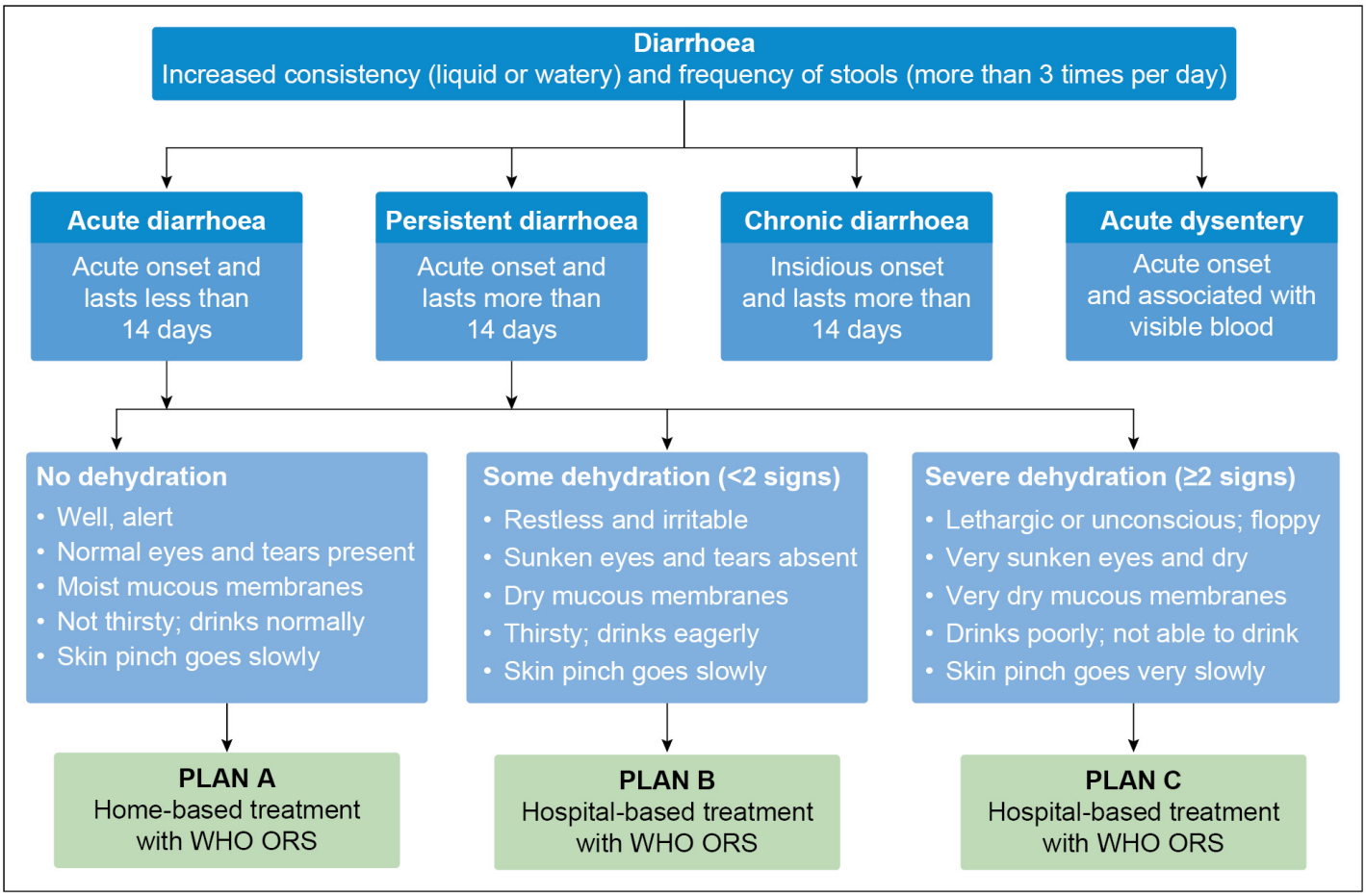
mortality.

- Inflammatory diarrhoea occurs when pathogens invade the wall of the large bowel, causing an immune response and mucosal bleeding.
- Non-inflammatory diarrhoea is a consequence of pathogens that superficially invade the epithelial layer of the small bowel and cause increased secretion of water and electrolytes into the lumen.

Causes of Diarrhoea

Diarrhoea can be caused by a full spectrum of infecting organisms and many non- infectious causes like drug induced. There are several factors that point the clinician in the direction of a possible cause: whether it is acute or chronic, inflammatory or non-inflammatory and the CD4 count.

Figure 4.4.6: Classification of diarrhoea in CLHIV



- Acute diarrhoea
- Acute inflammatory diarrhoea
- Acute non-inflammatory diarrhoea
- Chronic diarrhoea
- Chronic non-inflammatory diarrhoea

Table 4.4.1: Infections and parasitic infestations of diarrhoea

Acute diarrhoea	
Acute inflammatory diarrhoea	**Acute non-inflammatory diarrhoea**
Bacterial enteric infections • Shigella • Salmonella • Campylobacter • Escherichia coli • *Clostridium difficile*	**Viruses** • Rotavirus • Enteroviruses • Norovirus
Parasites ▪ Amoebiasis	**Parasites** ▪ Giardia lamblia
Viruses • **Cytomegalovirus disease**	
Chronic diarrhoea	
Chronic non-inflammatory diarrhoea (large volume, watery stools)	
• Coccidian parasites ▪ Cystoisospora (Isospora) ▪ Cryptosporidium ▪ Microspora ▪ Cyclosporidium • *Giardia lamblia* • *Strongyloides stercoralis*	
Persistent diarrhoea in CLHIV • Malnutrition • Pathogenic E. coli, especially the enteroaggregative and enteroadherent types • Prolongation of an acute diarrhoea may rarely be a manifestation of cow milk protein allergy • Antibiotic-associated diarrhoea due to bacterial overgrowth • Cryptosporidium infection	

Complications

- Dehydration often progressing to an acute kidney insult
- Electrolyte abnormalities
- Malnutrition
- Systemic sepsis resulting from bacterial causes

Bacterial Enteric Infections

Epidemiology

Rates of Gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population, but these rates decline when patients are treated with ART.[1] The risk of bacterial diarrhoea varies according to CD4 count and is greatest in individuals with clinical AIDS or <200 CD4 cells/mm^3.

The bacteria most frequently isolated by culture from HIV-infected adults are Salmonella (particularly

Salmonella enterica serotypes typhimurium and enteritidis), Shigella and Campylobacter.

Diarrhoeagenic E. coli, particularly enteroaggregative E. coli, may contribute to the burden of diarrhoeal disease, but their role is poorly understood because diagnosis remains a research-only test.

Clostridium difficile-associated infection (CDI) is common in HIV-infected patients; recent data suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to the traditional risk factors such as exposure in a healthcare facility or to antibiotics.

Other enteric infections that may cause diarrhoea include MAC. As with bacterial enteric infections in HIV-uninfected persons, the probable source for most enteric infections in HIV- infected patients is ingestion of contaminated food or water. Sexual activity with the potential for direct or indirect faecal-oral exposure also increases risk of infections, especially with *Shigella* and *Campylobacter.*

Clinical Manifestations

The following are the three major clinical syndromes of infection with Gram-negative enteric bacteria among PLHIV::

- Self-limited gastroenteritis
- More severe and prolonged diarrhoeal disease, potentially associated with fever, bloody diarrhoea and weight loss
- Bacteraemia associated with extra-intestinal involvement, with or without concurrent or preceding GI illness

In HIV-infected patients, the risk of more profound illness increases with the degree of immunosuppression. Relapses in infection with salmonella and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in PLHIV.

Diagnosis

Complete history including medication is an important part of evaluation of patients with diarrhoea. The diagnosis of Gram-negative bacterial enteric infection is established through **cultures of stool and blood.**

Blood cultures should be obtained from patients with **diarrhoea and fever, if possible**. Blood culture systems will typically grow other bacterias as well including campylobacters, but they are unlikely to be identified on routine stool cultures.

The diagnosis of CDI is usually complicated and needs careful selection of the correct testing and a correlation of clinical and laboratory findings.

Endoscopy with biopsy may be required for diagnosing aetiologies other than bacterial enteric infections including cryptosporidiosis, microsporidiosis, CMV or MAC gastroenteritis and non- infectious causes of GI symptoms.

If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, **diagnostic evaluation for STDs should be considered.**

Prevention and Management

The most common causes are ingestion of contaminated food or water and faecal-oral exposures. That needs to be prevented.

Antimicrobial prophylaxis to prevent bacterial enteric illness is usually not recommended, including for

travellers

Table 4.4.2: General issues in management

General Considerations

- Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhoea.
- Anti-motility agents should be avoided if there is concern about inflammatory diarrhoea, including Clostridium difficile infection (CDI).
- Diagnostic faecal specimens should be obtained prior to initiation of empiric antimicrobial therapy.
- If stool sample is obtained, antibiotic susceptibilities should be performed to confirm antibiotic choice given increased reports of antibiotic resistance.

Empiric Treatment of Bacterial Enteric Infections: For PLHIV with advanced HIV and clinically severe diarrhoea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills). For PLHIV with persistent diarrhoea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed.

Preferred Therapy	Alternative Therapy
Ciprofloxacin 500–750 mg Oral (or 400 mg IV) BD	• Ceftriaxone IV 1 g OD or • Cefotaxime IV 1 g TDS

Treatment of Salmonellosis

Preferred Therapy	Alternative Therapy
Ciprofloxacin 500–750 mg Oral (or 400 mg IV) BD	• Levofloxacin 750 mg (Oral or IV) OD or • Moxifloxacin 400 mg (Oral or IV) OD or • Trimethoprim 160 mg/sulfamethoxazole 800 mg (Oral or IV) BD or • Ceftriaxone IV 1 g OD, or • Cefotaxime IV 1 g TDS

Duration of Therapy for Gastroenteritis without Bacteraemia:

- If CD4 count >200 cells/mm^3: 7–14 days
- If CD4 count <200 cells/mm^3 particularly if primary illness was severe: 2–6 weeks

Duration of Therapy for Gastroenteritis with Bacteraemia:

- If CD4 count >200 cells/mm^3: 14 days; longer duration if bacteraemia persists or if the infection is complicated (e.g., metastatic foci of infection are present)
- If CD4 count <200 cells/mm^3: 2–6 weeks

Treatment of Shigellosis

Duration of Therapy:

- Gastroenteritis: 7–10 days (except azithromycin, treat for 5 days)
- Bacteraemia: ≥14 days
- Recurrent infections: up to 6 weeks

Preferred Therapy	Alternative Therapy (Depending on Susceptibility Results)
Ciprofloxacin 500–750 mg Oral (or 400 mg IV) BD if MIC<0.12 ug/m	Levofloxacin 750 mg (Oral or IV) OD or Moxifloxacin (Oral or IV) 400 mg OD or Trimethoprim 160 mg/sulfamethoxazole 800 mg Oral or IV BD or Azithromycin 500 mg Oral daily for 5 days

Treatment of Campylobacteriosis

- Gastroenteritis: 7–10 days [5 days if azithromycin is used]
- Bacteraemia: ≥14 days
- Recurrent bacteraemia disease: 2–6 weeks

Preferred Therapy:	Alternative Therapy (Depending on Susceptibility Results):
• Ciprofloxacin 500–750 mg Oral (or 400 mg IV) BD or • Azithromycin 500 mg Oral daily for 5 days	• Levofloxacin 750 mg Oral or IV OD or • Moxifloxacin 400 mg Oral or IV OD

Treatment of Clostridium difficile Infection

- Vancomycin 125 mg (Oral) 4 times per day for 10–14 days
  or
- Metronidazole 500 mg (Oral) 3 times per day for 10–14 days

Management of Diarrhoea in CLHIV

The objectives of assessment of children with diarrhoea are to (i) determine the type of diarrhoea, i.e., acute watery diarrhoea, dysentery or persistent diarrhoea; (ii) look for dehydration and other complications; (iii) assess for malnutrition; (iv) rule out non-diarrhoeal illness especially systemic infection; and (v) assess feeding, both pre-illness and during illness.

A detailed history should include information on (i) onset of diarrhoea; duration and number of stools per day; (ii) blood in stools; (iii) number of episodes of vomiting; (iv) presence of fever, cough or other significant symptoms (e.g. convulsions, recent measles); (v) type and amount of fluids (including breast milk) and food taken during the illness and pre-illness feeding practices; (vi) drugs or other local remedies taken (including opioids or anti-motility drugs like loperamide that may cause abdominal distention); and (vii) immunization history.

During examination, the most important assessment is for dehydration. The degree of dehydration is assessed as per Figure 4.4.6. One should look at the child's general condition, whether he/she is alert, restless, irritable, lethargic or unconscious. Look for the appearance of eyes (normal or sunken) and the ability to drink water or ORS solution, whether taken normally or refused, taken eagerly or an inability to drink due to lethargy or coma. Dehydration is also assessed by feeling for skin turgor; following pinching, the abdominal skin may flatten immediately, go back slowly or return very slowly (> 2 seconds). Based on the degree of dehydration after history and examination, the dehydration is classified as no dehydration (<50 ml/kg fluid loss), some dehydration (50–100 ml/kg fluid loss) or severe dehydration (>100 ml/kg fluid loss).

In addition, one should examine for features of malnutrition (anthropometry for weight and height; examination for wasting, oedema and signs of vitamin deficiency), systemic infection (presence of cough, high grade fever, fast breathing and/ or chest in-drawing suggests pneumonia; high-grade fever with splenomegaly suggests malaria) and fungal infections (oral thrush or perianal satellite lesions).

Most of acute diarrhoeal episodes can be managed effectively even in the absence of laboratory investigations. Stool microscopy is not helpful in management except in selected situations, such as cholera and giardiasis. Similarly, stool culture is of little value in routine management of acute diarrhoea. It is useful to decide on antibiotic therapy in patients with Shigella dysentery who do not respond to the initial empiric antibiotics. Tests for stool pH and reducing substances are not indicated in acute diarrhoea. Complete blood count, blood gas estimation, serum electrolytes or renal function tests are not indicated routinely and are performed only if the child has associated findings like pallor, tachypnoea, altered sensorium, seizures, paralytic ileus or oliguria, which suggest acid-base imbalance, dyselectrolytemia or renal failure.

The management of acute diarrhoea has four major components: (1) rehydration and maintaining hydration; (2) ensuring adequate feeding; (3) oral supplementation of zinc; and (4) early recognition of danger signs and treatment of complications.

Children with no dehydration should be treated with WHO ORS and home-available fluids to prevent dehydration. The mother should be given ORS and counselled about its preparation and method of use. The amount of ORS to be given to the child with no dehydration depends on age: age <24 months, 50–100 ml (maximum 500 ml/day); age 2–10 years, 100–200 ml (maximum 1000 ml/day); age >10 years, ad lib (max 2000 ml/day). The home-available fluids used should preferably contain salt, including ORS, salted drinks (e.g., salted rice water or salted yoghurt drink) or vegetable or chicken soup with salt. However, some unsalted fluids like plain water, water in which a cereal has been cooked (e.g., unsalted rice water), unsalted soup, yoghurt drinks without salt, green coconut water, weak unsweetened tea, unsweetened fresh fruit juice are also acceptable. Some fluids like commercial carbonated beverages, commercial fruit juices and sweetened tea are unsuitable for home-based rehydration therapy. Mothers of such children

should be counselled about dangers signs like continuing diarrhoea beyond 3 days, increased volume/ frequency of stools, repeated vomiting, increasing thirst, refusal to feed, fever or blood in stools and are advised to return to the healthcare facility.

Children with some dehydration should be treated at a hospital. The therapy with ORS should be promptly initiated and continued during transport. All children with severe dehydration should be promptly and urgently referred to a healthcare facility for rehydration with IV fluids.

Feeding should not be restricted in children with diarrhoea as this aggravates complications and increases morbidity and mortality. Early feeding during diarrhoea not only decreases the stool volume by facilitating sodium and water absorption along with the nutrients, but also facilitates early gut epithelial recovery and prevents malnutrition. Once the child's status starts improving, a higher than recommended intake is given to facilitate complete catch-up growth.

Zinc supplementation is recommended at a dose of 20 mg of elemental zinc per day for children older than 6 months of age for a period of 14 days. It is helpful in decreasing the severity and duration of diarrhoea and risk of persistent diarrhoea. For persistent vomiting, symptomatic treatment with a single dose of ondansetron (0.1–0.2 mg/kg/dose) should be given.

Antibiotics are not routinely indicated for the treatment of acute diarrhoea in children. However, antibiotics are indicated in bacillary dysentery, cholera, amoebiasis and giardiasis. When acute diarrhoea is a manifestation of systemic infection in a malnourished, prematurely born or young infant, age-appropriate systemic antibiotic is recommended. Anti-motility drugs and binding agents are not recommended and can be harmful to infants and children. Currently, there are insufficient data for the efficacy of anti-secretory agents like racecadotril and probiotics and hence not routinely recommended.

For children with acute dysentery, ORS, continued feeding, zinc supplementation and antibiotics are the components of therapy. IV ceftriaxone (50– 100 mg/kg/day for 3–5 days) should be the first line of treatment in a sick child. In a stable child, either ciprofloxacin (15 mg/kg/day in two divided doses for 3 days) or oral cefixime may be given, but the patient should be monitored for clinical improvement within 48 hours (decrease in fever, stool frequency and blood in stools). If no improvement is seen at 48 hours, antibiotics should be changed appropriately. Oral azithromycin (10 mg/kg/ day for 3 days) can be used for shigellosis, but the experience is limited. For children with amoebic dysentery, tinidazole or metronidazole is the drug of choice. Any young child presenting with blood in stools and persistent abdominal pain should be suspected to have intussusception and evaluated accordingly.

The principles of management of persistent diarrhoea are (i) correction of dehydration, electrolytes and hypoglycaemia; (ii) evaluation for infections using appropriate investigations (haemogram, blood culture and urine culture) and their management; and (iii) nutritional therapy. Children with persistent diarrhoea may be associated with secondary carbohydrate malabsorption. To ensure absorption and decrease stool output, diets with different degrees of carbohydrate exclusion in the form of diet A (lactose reduced), diet B (lactose free) and diet C (complex carbohydrate free) may be used. A systematic stepwise approach to evaluate a child with persistent diarrhoea and chronic diarrhoea is advised. Such children should be referred to a paediatrician for treatment that consists of dietary modification and appropriate antibiotics.

Cryptosporidiosis

Epidemiology

Intestinal parasitic infections are a major public health concern in PLHIV. A study done by Bangalore Medical College and Research Institute showed an overall prevalence of intestinal parasites of 27.2% among 209 study subjects and the most predominant parasite was Cryptosporidium and was reported in

51 (24.4%) out of 209 study subjects.[2] The study done by Nitya Vyas et al showed Cryptosporidium species was the most common enteric opportunistic parasite accounting for 37.93% of the total parasites, followed by Isospora belli, which accounted for 31.03%[3].

A study was undertaken at CMC, Vellore to determine the carriage rate of various enteric pathogens in southern Indian patients with HIV infection, both with and without diarrhoea.[4] Stool from 111 consecutive HIV-positive patients (50 without and 61 with diarrhoea) was examined by microscopy and culture. Jejunal biopsy and fluid examination were carried out if diarrhoea persisted, with negative stool examination. Enteric pathogens were detected from stool in 57.4% of diarrhoeal patients compared to 40% of those without diarrhoea (P >0.05). Jejunal biopsy and fluid examination provided 11 additional diagnoses. Protozoa accounted for 71.8% of all pathogens isolated. Isospora was significantly more common in patients with (11/61) than in those without (2/50) diarrhoea (P<0.05).[4]

In another study,[5] multiple stool samples from 200 patients in a cross-sectional study were subjected to microscopy and Cryptosporidium stool antigen ELISA. Parasites were identified in 18 samples (9%). Cystoisospora and Cryptosporidium spp. were seen in 9 cases (4.5%) and 5 cases (2.5%), respectively. Seven cases of Cystoisospora diarrhoea recovered after treatment with Cotrimoxazole.[5]

Clinical Manifestations

The most common presentation is acute or subacute onset of watery diarrhoea, which may be accompanied by nausea, vomiting and lower abdominal cramping. Disease severity can range from asymptomatic to profuse, cholera-like diarrhoea.

More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhoea alone is typical in patients with competent immune systems. Fever is present in approximately one third of patients, and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with Cryptosporidium, leading to sclerosing cholangitis and pancreatitis secondary to papillary stenosis, particularly among patients with prolonged disease and low CD4 counts.

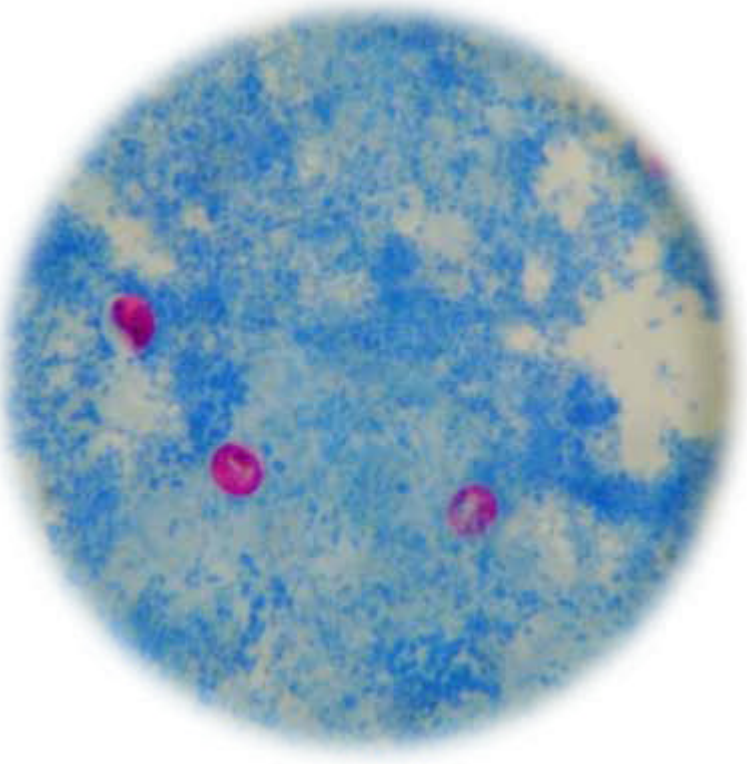
Diagnosis

Diagnosis is through microscopic identification of the oocysts in stool with acid-fast staining or direct immunofluorescence, which offers higher sensitivity.

Concentration methods (e.g., formalin ethyl acetate) may facilitate diagnosis of cryptosporidiosis. Antigen-detection by enzyme-linked immunosorbent assay or immunochromatographic tests also are useful. Cryptosporidium enteritis also can be diagnosed from small sections of tissue from intestinal biopsy..

A single stool specimen is usually adequate to diagnosis cryptosporidiosis in individuals with profuse diarrhoeal illness, whereas repeat stool sampling is recommended for those with milder disease.

Figure 4.4.7:. Cryptosporidium



(Image courtesy: CoE, GHTM, Tambaram, Chennai)

Prevention

Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease.

Treatment

- Aggressive oral and/or IV rehydration and replacement of electrolyte loss
- Rapid ART initiation
- Nitazoxanide 500 mg to 1,000 mg Oral twice daily with food for 14 days, or
- Paromomycin 500 mg Oral four times a day for 14 days–21 days

Cystoisosporiasis (Formerly Isosporiasis)

Clinical Manifestations

The most common manifestation is watery, non-bloody diarrhoea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting and low-grade fever. The diarrhoea can be profuse and prolonged, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalaemia, weight loss and malabsorption. Acalculous cholecystitis/cholangiopathy and reactive arthritis also have been reported.

Diagnosis

Infection is diagnosed by detecting Isospora oocysts in faecal specimens. Oocysts may be shed intermittently and at low levels, even by patients with profuse diarrhoea.

Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-

fast techniques, on which oocysts stain bright red, and UV fluorescence microscopy, under which they auto fluoresce. Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens

Prevention & Management

Prophylaxis

CPT prophylaxis has a protective role.

Management

Table 4.4.3: Treatment for Cystoisosporiasis

Acute management	
Preferred	**Alternatives**
• TMP–SMX (160 mg/800 mg) Oral (or IV) QDS for 10 days, or • TMP–SMX (160 mg/800 mg) Oral (or IV) BD for 7–10 days • One approach is to start with TMP–SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist • IV therapy for PLHIV with potential or documented malabsorption • For children: TMP–SMX 5 mg/kg per dose of the trimethoprim component, given twice daily for 10 days. If symptoms worsen or persist, the TMP–SMX dose may be increased to 5 mg/kg/dose of the trimethoprim component, 3–4 times daily for 10 days or the duration of treatment lengthened (up to 3–4 weeks)	For Patients with sulpha intolerance: • Pyrimethamine 50–75 mg Oral daily + leucovorin 10–25 mg Oral daily, or • Ciprofloxacin 500 mg Oral BD for 7 days
Chronic Maintenance Therapy (Secondary Prophylaxis)	
TMP–SMX (160 mg/800 mg) Oral 3 times weekly	• TMP–SMX (160 mg/800 mg) Oral daily, or • TMP-SMX (320 mg/1600 mg) Oral 3 times weekly, or • Pyrimethamine 25 mg Oral daily + leucovorin 5–10 mg Oral daily, or • Ciprofloxacin 500 mg Oral 3 times weekly as a second-line alternative

Other Causes of Diarrhea in PLHIV

Table 4.4.4: Other causes of diarrhoea in PLHIV

Infectious Causes	Diagnosis and Management Tips
Mycobacterium tuberculosis and Mycobacterium avium complex (MAC)	• Affects small or large bowel; terminal ileum is often affected. • Abdominal pain, distention or rectal bleeding may occur. • Clinical findings may include hepatomegaly, abdominal tenderness and ascites. Abdominal ultrasound may show lymph nodes and splenic micro abscesses. • May be evidence of disseminated TB
Cytomegalovirus disease (CMV)	• Causes ulceration of both small and large bowel • Colitis occurs in 5%–10% of patients with AIDS and CMV end-organ disease. The most frequent clinical manifestations are weight loss, anorexia, abdominal pain, debilitating diarrhoea and malaise. In the colon, especially in the caecum, CMV can produce perforation and present as an acute abdomen. If CMV colitis is present, computed tomography may show colonic thickening. Haemorrhage and perforation can be life-threatening complications. • Diagnosis is usually made when a patient with diarrhoea or rectal bleeding is found to have CMV retinopathy on funduscopy or in centres able to perform sigmoidoscopy and biopsy. • **Management: Preferred Therapy** • Ganciclovir 5 mg/kg IV BD, may switch to valganciclovir 900 mg Oral BD once the patient can absorb and tolerate Oral therapy (For more details on management, please refer **Chapter 4.2. Central Nervous System)**
Parasitic Infestations	
Strongyloides stercoralis infestation	• Larvae disseminate widely, autoinfection occurs, increasing the parasite burden. May be asymptomatic or cause epigastric pain, small bowel obstruction, chronic diarrhoea, recurrent urticaria and larva currens (rapidly elongating skin eruption). • If untreated, it can lead to hyperinfection syndrome in patients with advanced HIV, causing meningitis and multi-organ failure. • Treatment of choice is ivermectin, 200 µg/kg orally, as a single dose for 1–2 days. If ivermectin is unavailable, treat with albendazole 400 mg BD x 7 days. Ivermectin has a higher rate of parasite eradication. • If suspected or found incidentally, always treat.
Giardia lamblia	Metronidazole 2 g daily for 3 days or tinidazole 2 g single dose Children: Metronidazole 15 mg/kg/24 h divided TDS Oral for 5–10 days. Also, can use tinidazole for children ≥3 years of age: 50 mg/kg, maximum 2 g single oral dose
Non-infectious causes	
Lopinavir/ ritonavir associated	• GI tract (GIT) symptoms are common, particularly watery diarrhoea and abdominal pain. • If other causes are excluded, loperamide can be given. • Switch to Atazanavir/ritonavir if available; if also on TB treatment, Atazanavir/ ritonavir must be taken with rifabutin and not rifampicin.
Kaposi's sarcoma	• Affects small or large bowel • Around 80% of PLHIV with Kaposi's sarcoma have GI system involvement: undiagnosed KS is commonly seen at post-mortem. • Often, there are no specific symptoms of GIT involvement. Anaemia is common and in a PLHIV with KS, GIT involvement is likely. • Treatment: Urgent chemotherapy and effective ART

Anal lesions (Infective and Non-infective Lesions)

Non Infective anal lesions

- Peri-anal hematoma; Anal fissures; Thrombosed piles; Peri-anal abscess; Peri-anal fistula

Table 4.4.5: Anal lesions in PLHIV

Non-Infective	
Peri-anal haematoma	• Patient usually complains of piles or a painful lump, worsened when passing stools. Patient is quite often constipated. • Shows a painful purplish bump clearly visible in the anal skin, due to the rupture of a blood vessel under the surface of the anal skin. It is usually a bit painful due to the stretching of the skin. • Treatment: Leave it to absorb on its own and ideally soften the stool. Local anaesthetic applied regularly will help ease the pain from stretched skin.
Thrombosed piles	• Acute onset painful, swollen lump in the anus, often with bleeding. Red, tender, fleshy swelling emerging from the anus (not connected to the outside skin). • This is a surgical emergency and needs immediate referral.
Peri-anal abscess	• This is like any other abscess, tender, hot and often looks as if there is pus inside. Treatment is incision and drainage.
Peri-anal fistula	• Presents mostly with a painless anal discharge and itch. • Examination: On full opening of the anus the distal end of the fistula is often seen as a small site actively discharging pus. • Treatment: Chronic discharging perianal sinuses in PLHIV are very likely to be TB. Start TB treatment and ensure effective ART. Surgery has no role if cause is TB and can cause severe complications.

Infective anal lesions in PLHIV

- Herpes simplex
- Painful cluster of vesicles or shallow ulcers
- Treatment: Acyclovir 400 mg thrice daily for 5–7 days

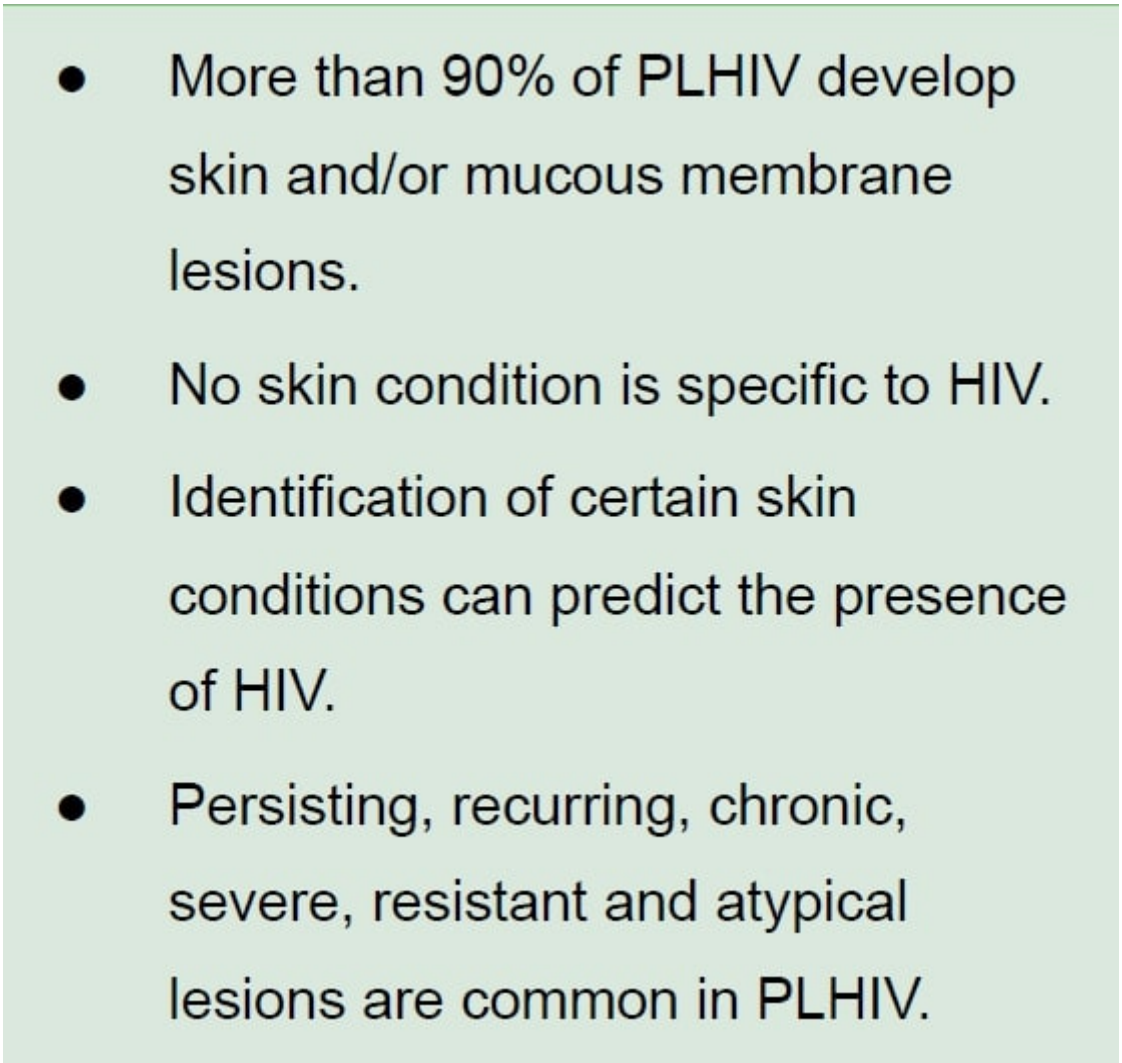
- Human papilloma virus lesions
- Present as warts, condylomata acuminata, with their typical cauliflower appearance; treat according to locally available preparations, usually podophyllin.
- Present as an anal ulcer or sore. This is a pre-malignant condition and needs to be referred for further management.

- Proctitis
- This presents with anal discharge/itch/pain in the rectum, ranging from mild to severe.

- Syphilis
- This can present with a primary chancre, the classic painless ulcer with raised edges, or as a wart looking like HPV warts but less raised.

4.5 Skin and Mucous Membranes

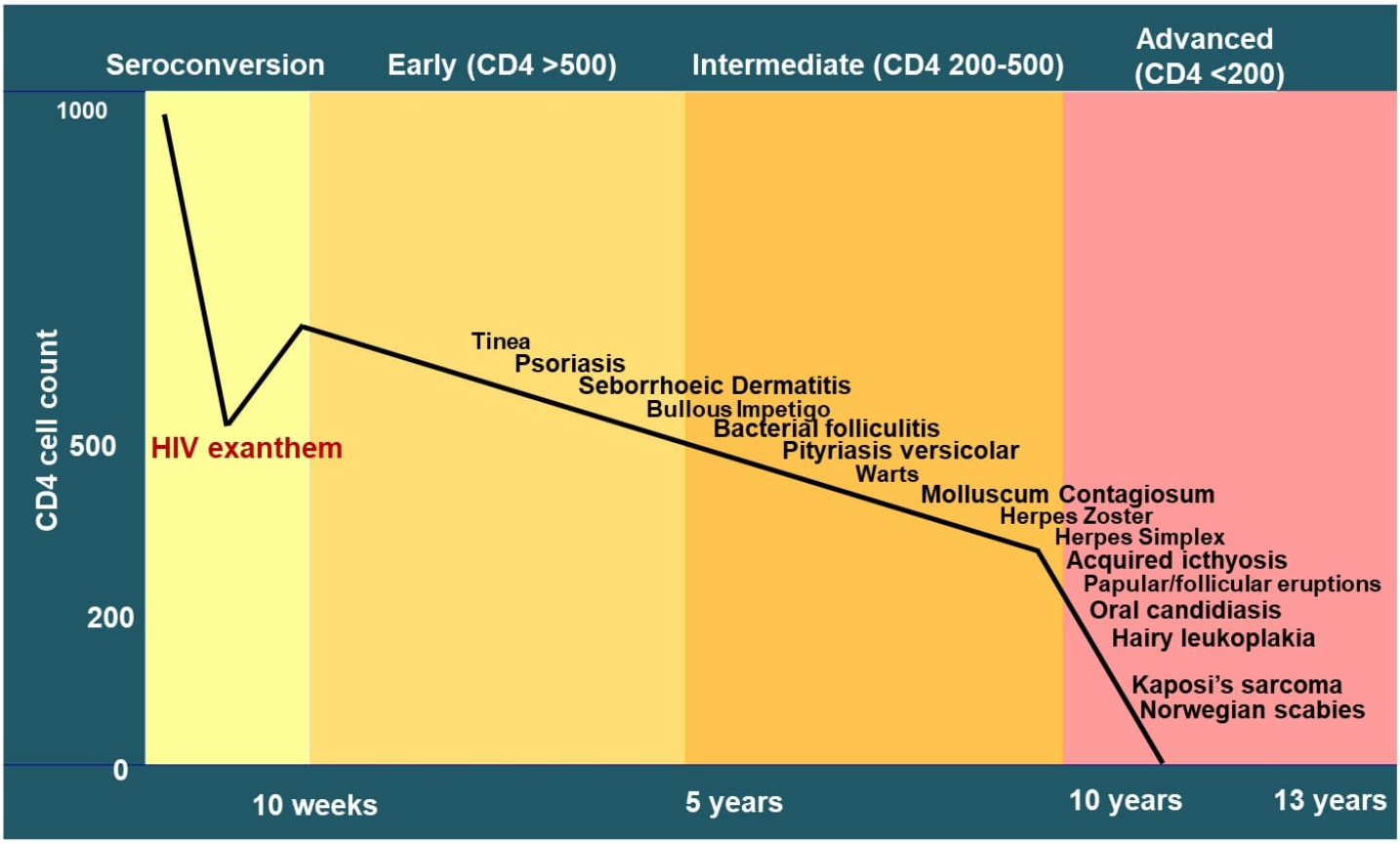
Dermatological diseases are common in the setting of HIV infection. Some dermatological conditions may be more severe, atypical in presentation or resistant to treatment in the context of HIV disease. The organisms causing infective dermatological diseases are diverse. Skin manifestations may be part of an underlying broader systemic infection.



Post-HIV disorders of the skin and mucous membranes occur throughout the course of HIV infection, affecting more than 90% of patients at some point of time. The prevalence of skin manifestations in CLHIV ranges from 36%–52%.[1]

Many infections are hospital acquired and may be due to a combination of organisms. Therapy often fails because of incorrect diagnosis, deeper and complex infection or rarely resistant organisms. Most PLHIV develop skin and/or mucous membrane lesions during the course of HIV infection.

Figure 4.5.1: Spectrum of dermatological manifestations in PLHIV



The skin diseases can be divided into four groups:

- Infective conditions: Bacterial, viral, fungal or parasitic
- Inflammatory conditions
- Cutaneous malignancies
- Miscellaneous

Table 4.5.1: Various cutaneous conditions in PLHIV

4.5.1.1 Infective conditions
Bacterial • Folliculitis, furuncle, ecthyma, abscess and impetigo • Bacillary angiomatosis • Syphilis • Cutaneous tuberculosis • Diseases caused by atypical mycobacteria
Fungal • Dermatophytosis • Candidiasis • Penicilliosis • Cryptococcosis • Histoplasmosis
Viral • Herpes Zoster • Herpes Simplex • Oral hairy leukoplakia • Molluscum contagiosum • Condyloma acuminata • Verruca vulgaris, V. Plana
Arthropod • Scabies, leishmaniasis • Demodex folliculitis
4.5.1.2 Inflammatory conditions
• Xerosis and ichthyosis • Psoriasis • Seborrheic dermatitis • Reiter’s syndrome i.e., reactive arthritis • Eosinophilic folliculitis • Atopic dermatitis
4.5.1.3 Cutaneous malignancies
• Kaposi’s sarcoma • Non-Hodgkin’s lymphoma
4.5.1.4 Miscellaneous
• Acute seroconversion illness • Drug reactions • Pruritic Papular Eruptions

Introduction

Skin Manifestations of Staphylococcus Aureus/ Streptococcal Infection

Staphylococcus aureus is the most common cutaneous bacterial infection in PLHIV. Infection with S. aureus may occur before any other signs or symptoms of HIV infection. Morphologic patterns that may occur include bullous impetigo, ecthyma, folliculitis, abscesses, cellulitis, hidradenitis suppurativa and pyomyositis.

Figure: 4.5.2: Cutaneous manifestations of Staphylococcus aureus



Folliculitis *Image courtesy: CoE, GHTM, Tambaram*



Ecthyma *Image courtesy: CoE, BJMC, Ahmedabad*



Non bullous impetigo

Table 4.5.2: Cutaneous manifestations of Staphylococcus aureus

Skin Manifestations of Staphylococcus aureus	Clinical Manifestations	Management
Bullous impetigo	Presenting as very **superficial blisters or erosions that may be polycyclic** on trunk and arms. Because the blisters are flaccid, they are short-lived; often only erosions or yellow crusts are present.	Gently clean the lesions with soap and water. In severe cases, give Aminopenicillins or Cephalosporins or cloxacillin or erythromycin 40 mg/kg/ day QDS for 5 days
Skin abscess or pyomyositis	Follicular lesions extend more deeply, forming abscesses making the affected area **fluctuant and warm**. Rarely, all follicles across several square centimetres are infected, forming a **large, violaceous plaque**. These plaques may mimic Kaposi's sarcoma (KS), but overlying pustules are quite unusual in KS. Rarely, abscess of the muscle (pyomyositis) may occur.	Surgical drainage and care of the lesion Antibiotics: Cephalosporins or Cloxacillin 500 mg Oral QDS for 10 days or cloxacillin 1–2 g IV QDS for 10 days. Vancomycin in case of severe sepsis
Furunculosis or folliculitis	Skin sepsis around hair follicles (trunk, groin, axilla or face). Carbuncles (clusters of furuncles) with multiple openings because of invasion and necrosis of the subcutis.	Local lesion care. Antibiotics: Cephalosporin, Cloxacillin 500 mg Oral QDS for 10 days

Bacillary Angiomatosis

Bacillary angiomatosis is caused by bacteria Bartonella *(B. henselae and B. quintana).* It clinically presents as reddish coloured papules that may look like KS. Cutaneous lesions start with small red papules that gradually expand into large papular, nodular, pedunculated lesions. Lesions have a vascular appearance, and the surface is friable and bleeds easily.

Systemic findings such as fever, night sweats, weight loss and anaemia are common in patients with bacillary angiomatosis. Visceral lesions may be as or more common than cutaneous lesions. Involvement of the liver and spleen with or without skin lesions is the most diagnosed form of visceral disease. These patients can present with abdominal pain, fever, elevated liver enzymes and hepatosplenomegaly.

Diagnosis: Diagnosis is confirmed by identifying the causative organism in affected tissue using special stain silver impregnation or by electron microscopy. The diagnosis of visceral disease is made based on biopsy of the affected organ and examination with silver stains or electron microscopy.

Treatment: Erythromycin 500 mg Oral QDS or doxycycline 100 mg Oral or IV for >3 months. Alternative:

Azithromycin 600 mg QDS.

Mycobacterial Diseases

MTB, Lupus Vulgaris, Scrofuloderma, Tuberculosis Verrucosa Cutis are common in India in patients with HIV disease. Mycobacterium avium-intracellulare can have cutaneous manifestations with unusual presentations. They commonly present as chronic sinuses over involved **lymph nodes (scrofula), chronic ulcerations, etc.**

Figure 4.5.3: Skin manifestations of mycobacterial diseases (scrofuloderma)



Scrofuloderma *Image Courtesy: GHTM-ITECH Fellowship programme*



Scrofuloderma *IImage Courtesy: CoE, BJMC, Ahmedabad*

M. haemophilum rarely can present with **cutaneous abscesses or ulcerations** and tenosynovitis or arthritis. We should suspect this organism if skin or joint lesions yield AFB on smears, yet standard mycobacterial cultures are negative.

Treatment: ATT according to national guidelines

Syphilis

Cutaneous presentations of primary and secondary syphilis in HIV-infected persons are usually like those in non-HIV-infected persons.

Primary: A painless, indurated genital ulcer (chancre), inguinal lymphadenopathy
Secondary: Rash, usually involves the palms and soles and is maculopapular.

Figure 4.5.4: Skin manifestations of syphilis



Primary Syphilis



Secondary Syphilis *Images' courtesy: CoE, BJMC, Ahmedabad*

Treatment: Benzathine penicillin 2.4 million units IM single dose. Follow-up RPR at 6 months,until negative

Fungal Infections

Dermatological manifestations of candidiasis

Candida (mainly *C. Albicans*) causes intertriginous infection and may involve the groin, axillary vault or inframammary areas. It presents as a **vivid red, slightly eroded and studded with tiny pustules at periphery.** A hallmark of this rash is satellite pustules extending out centrifugally from the eroded areas. In males, the scrotum is often involved. Patient complaints of a burning pain much more than pruritus.

Oral candidiasis: A white membrane covers the tongue that reveals the eroded surface on removal.

Candida can also infect nails. It affects the tissues around the fingernails, frequently presenting as paronychia, presenting as **tenderness, erythema and bogginess of the proximal nail fold.Pressure on the inflamed nail fold** may express purulent material. Infection tends to be chronic, in which case the cuticle is lost, and the nail plate may become ridged or dystrophic. Onycholysis (separation of the nail plate from the nail bed) may also occur.

Diagnosis: Diagnosis is by potassium hydroxide examination of scales taken from the active border or a satellite pustule

Treatment: Topical antifungal drug, such as clotrimazole 1% cream or ketoconazole 2% cream, fluconazole 100 mg or 3–6 mg/kg/day in children orally once for 10 days.

Tinea Infections:

The disease is caused by superficial fungal organisms belonging to various genera found in soil, animals and humans. Resulting manifestations are Tinea cruris, Tinea corporis, Tinea manuum, Tinea pedis, Tinea capitis, sycosis barbae and onychomycoses. In CLHIV, a higher incidence is observed in boys. Risk factors apart from HIV infection include overcrowding, large families and poor socioeconomic circumstances.

Tinea can also cause intertriginous infections like candida. T. cruris is usually pruritic. The scrotum is spared. The depth of the folds may be clear, and a well-demarcated, annular patch extends down the upper thigh. In more extensive cases, the lesions may extend onto the lower abdomen and buttocks. Extensive involvement covering many areas of the body can be seen in PLHIV. In CLHIV, T. capitis can present with broken hairs resulting in non-scarring alopecia, scaling and pustules. There may be associated cervical lymphadenopathy. Kerion is a variant that presents as a boggy plaque, pustules and a purulent discharge. This needs to be referred to a dermatologist as it may lead to permanent hair loss.

Other Fungal Infections

Three types are seen: *Pityrosporum ovale*, *P. orbiculare and Malassezia furf*

Colonization occurs in the scalp, flexures and upper trunk.

They cause pityriasis versicolor (**thick, scaly, hypopigmented or light-brown macules and patches** on the trunk), seborrheic dermatitis and folliculitis.

Diagnosis is clinical. It can be confirmed by histopathological examination of skin scrapings or by microscopic examination by potassium hydroxide examination of scales taken from the active border.

Treatment is with selenium sulphide shampoo. The shampoo is applied and left for 30 minutes and then washed off. Application is repeated daily for a week. A topical imidazole cream can be applied twice daily for 2 weeks. Oral itraconazole 200 mg daily for 1 week can be used for resistant, widespread involvement. The pigmentation takes months to return to normal. Folliculitis can be treated with ketoconazole shampoo, or a topical imidazole cream applied twice daily for 2 weeks.

Systemic/Deep Mycosis

Systemic infections reported in patients with symptomatic PLHIV disease include penicilliosis, cryptococcosis, histoplasmosis, sporotrichosis, aspergillosis, candidiasis, coccidioidomycosis and actinomycosis.

Talaromycosis (disseminated P. marneffei infection): Central-necrotic papules with umbilication appear on the face, trunk and extremities occurring in 40%–70% of patients. Cryptococcus **skin lesions** may show myriad different manifestations, including **umbilicated skin lesions mimicking Molluscum**

Contagiosum. Histoplasmosis rarely can also present with pustules, nodules, ulcers and papules.

Figure 4.5.5: Skin manifestations of talaromycosis, cryptococcal infection and histoplasmosis



Talaromycosis (Penicilliosis) *Courtesy: CoE, RIMS, Manipur, Imphal*



Cryptococcal *Pictures Courtesy: CoE, BJMC, Ahmedabad*



Histoplasmosis

Viral Infections

Human Herpes Virus-8 Disease

Epidemiology

Human herpesvirus-8 (HHV-8), also known as KS-associated herpes virus (KSHV). HHV-8 is etiologically associated with all forms of KS including classic, endemic, transplant-related and AIDS-related as well as rare neoplastic disorders (primary effusion lymphoma (PEL) and solid organ variants and the lymphoproliferative disorder like multi-centric Castleman's disease (MCD). Although the precise pathogenesis for these tumours remains unclear, infection with HHV-8 precedes their development. PLHIV who are HHV-8 seropositive and exhibit HHV-8 viremia are at increased risk (approximately nine-fold) for developing KS.

Clinical Manifestations

KS manifestations vary widely.

Skin lesions: Non-tender, hyperpigmented or violaceous macular or nodular skin lesions

Oral lesions: Approximately one third of patients have oral cavity lesions that are predictors of pulmonary involvement and less favourable treatment outcomes. Purplish fleshy swelling on the roof of the mouth or gums are also present. They may often bleed.

Lymphatic system: Localized lymphadenopathy is also common and may lead to debilitating lower extremity oedema.

Figure 4.5.6: Cutaneous Kaposi's sarcoma



Cutaneous Kaposi Sarcoma *Image Courtesy: CoE, JJ Hospital, Mumbai*



Image Courtesy: CoE, BJMC, Ahmedabad

Pulmonary: Pulmonary KS may have a similar presentation to PTB or PCP. Pleural effusion is common (and often blood-stained).

Internal viscera: Occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may be asymptomatic, or manifest with shortness of breath, painless rectal bleeding or melena, and other non-specific pulmonary and GI symptoms.

PEL characteristically presents with effusions isolated within the pleural, pericardial or abdominal cavities, but mass lesions and 'extra cavitary' disease within skin, hematopoietic organs and the GIT have been described.

MCD manifests with systemic symptoms like fever and night sweats, and findings on examination including generalized lymphadenopathy and hepatosplenomegaly. MCD may mimic other inflammatory conditions including sepsis, with hypotension, clinical evidence of systemic inflammatory response and progression to multi-organ failure.

Diagnosis:The diagnosis of KS depends on cytologic and immunologic cell markers, as well as histology. Clinical diagnosis alone is not sufficient for KS, and tissue examination is needed to confirm the diagnosis.

Prevention and Management

Early initiation of ART is likely to be the most effective measure for the prevention of KS.

Table 4.5.3: Management of Kaposi's sarcoma

Mild-to-moderate Kaposi's sarcoma (KS) (localized involvement of skin and/or lymph nodes)	Initiation or optimization of ART
Advanced KS (visceral and/or disseminated cutaneous disease)	• Chemotherapy (in consultation with specialist) + ART Liposomal doxorubicin is preferred first-line chemotherapy. • Avoid use of corticosteroids in patients with KS, including those with KS-IRIS, given the potential for exacerbation of life-threatening disease.
Primary effusion lymphoma (PEL)	• Chemotherapy (in consultation with a specialist) + ART • Oral valganciclovir or IV ganciclovir can be used as adjunctive therapy.
Multi-centric Castleman's disease (MCD)	All patients with MCD should receive ART in conjunction with IV ganciclovir (or oral valganciclovir) +/- high dose zidovudine or Rituximab +/- prednisone. For patients with concurrent KS and MCD, rituximab + liposomal doxorubicin should be used.

Herpes Simplex Virus Disease

Epidemiology

Infections with HSV-1 and HSV-2 are common. HSV-2 infection increases the risk of HIV acquisition two- to three-fold and in coinfected patients, HSV-2 reactivation results in increase in HIV RNA levels in blood and genital secretions.

Serological studies have found that >95% of homosexual men with AIDS have a history of HSV infection. Genital ulcerative disease due to HSV is also an important risk factor for the acquisition of HIV infection.

The course of herpesvirus infection can be divided into three phases:

- Primary infection: The host acquires infection for the first time; viral replication occurs leading to death of cells and is controlled by the host's immune system.
- Latent infection: The virus genome remains in the host's cells in an inactive form.
- Reactivation: The latent viral genome becomes active resulting in viral replication when the host's immune system is impaired. Most HSV infections among AIDS patients result from reactivation of latent virus.

Clinical Manifestations

Orolabial herpes (also known as cold sores or fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer and crust. The course of illness in untreated patients is 5 to 10 days. Lesions can be triggered by sunlight or physiologic stress.

Genital herpes is typically caused by HSV-2 and is the most common manifestation of HSV-2 infection. Increasingly, first-episode genital herpes is caused by HSV-1 and is indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV- 1 infection.

Typical genital mucosal or skin lesions evolve through stages of **papule, vesicle, ulcer and crust**. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on skin on or around the genitals (e.g., the penile shaft, mon pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. **Inguinal** lymphadenopathy is common with genital herpes, particularly in primary infection.

These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized. Regardless of the clinical severity of infection, viral shedding on mucosal surfaces occurs frequently and can result in transmission. HSV shedding occurs more frequently in persons with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 than in those with higher CD4 counts. An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but recurrences and viral shedding occur less often with genital HSV-1 infection.

HSV is a significant cause of proctitis in men with HIV infection who have sex with men and may not be associated with external anal ulcers. In profoundly immunocompromised patients, extensive, deep, non-healing ulcerations can occur. These lesions have been reported most often in those with CD4 counts <100 cells/mm^3 and may be associated with acyclovir-resistant HSV. In addition, atypical presentations such as hypertrophic genital HSV, which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

The manifestations of non-mucosal HSV infections (e.g., HSV keratitis, HSV encephalitis, HSV hepatitis, herpetic whitlow) are like those observed in HIV-seronegative individuals. Disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead to loss of vision rapidly.

Figure 4.5.7: Orolabial and genital herpes



Orolabial Herpes *Image Courtesy: CoE, RIMS, Imphal, Manipur*



Genital Herpes *Image Courtesy: NACO Training Module*

Diagnosis

Laboratory diagnosis of all suspected HSV mucosal infections should be pursued. PCR and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis.

Management

Orolabial Lesions (Duration: 5–10 Days)

- Acyclovir 400 mg orally three times a day and in children 20 mg/kg body weight (up to a maximum of 400 mg/dose) dose by mouth QID for 7–10 days, or
- Valacyclovir 1 g orally twice a day

Genital lesions

- Initial genital lesions (Duration: 7–10 days) or
- Recurrent genital lesions (Duration: 5–10 days)
- Acyclovir 400 mg orally three times a day, or
- Valacyclovir 1 g orally twice a day

Treatment of Severe Mucocutaneous HSV Infections

For initial therapy, Acyclovir 5 mg/kg IV every 8 hours and in children <12 years of age beyond neonatal period, 10 mg/kg body weight (up to 15 mg/kg body weight/dose) IV every 8 hours for 21 days.

- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Table 4.5.4: Acyclovir and Foscarnet doses in neonates and CLHIV

Drugs	Dosage	Adverse Effects	Remarks
Acyclovir	**Neonatal CNS disease** 20 mg/kg/dose IV TDS x 21 days **Neonatal skin, eye or oral disease** 20 mg/kg/dose IV TDS x 14 days **Outside neonatal period – CNS disease** 10 mg/kg/dose IV TDS x 14 days **Severe gingivostomatitis** 5–10 mg/kg/dose IV TDS x 14 days **Mild gingivostomatitis and genital herpes** 20 mg/kg/dose oral TDS x 7–14 days (Maximum: 400 mg/dose)	Phlebitis, renal toxicity, nausea, vomiting, rash, neutropenia	Drug of choice for Herpes simplex 1 and 2
Foscarnet	120 mg/kg/d IV in 2–3 divided doses till infection resolves	Renal toxicity, electrolyte abnormalities in calcium, phosphorus,	Renal toxicity, electrolyte abnormalities in calcium, phosphorus, magnesium, potassium, seizures, cardiac arrhythmias, elevated liver transaminases Used for Acyclovir-resistant HSV infection

Herpes Zoster

Epidemiology

Varicella zoster virus (VZV) or herpesvirus type 3 is also the causative agent of chicken pox. Zoster develops only if the person has been previously infected with chicken pox. The virus remains dormant in the posterior root ganglia of the spinal cord. Herpes zoster occurs in 5%–15% of HIV- infected individuals.[2] In most, it is a self-limited infection, although severe complications can arise with advanced HIV disease. Disseminated lesions of the lungs, liver or nervous system leading to pneumonitis, hepatitis, retinitis and encephalitis may occur. The course of herpes zoster is also more prolonged, with a higher risk of scarring and post-herpetic neuralgia in HIV-infected individuals.

Herpes zoster can occur in adults with HIV at any CD4 T lymphocyte (CD4) cell count, but the risk of disease is higher with CD4 counts <200 cells/mm^3. In addition, HIV viremia is associated with an increased risk for incidental herpes zoster.

Clinical Manifestations of Varicella

Rashes: These tend to have a central distribution with lesions first appearing on the head, then the trunk and finally the extremities, evolving through stages of **macules**, **papules**, vesicles, **pustules** and **crusts**. The rash is characterized by rapid evolution of lesions during the initial 8 to 12 hours after onset, by successive crops of new lesions, and by the presence of lesions in different stages of development. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise and anorexia. Primary varicella can cause substantial morbidity in adolescents and adults with HIV. Visceral dissemination, especially VZV pneumonitis, is well documented. In CLHIV with severe immunosuppression, vesicles may be large and extensive. New vesicles may also appear in crops over several days. Mucosal surfaces may also be involved. Systemic involvement in the form of pneumonia, hepatitis and encephalitis may be seen with immunosuppression.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40%–50% of cases), followed by cranial nerve (20%–25%), cervical (15%–20%), lumbar (15%) and sacral (5%) dermatomes.

Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain, which may be severe. New vesicle formation typically continues for 3 to 5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2 to 3 weeks.

About 20%–30% of patients with HIV have one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%. Approximately 10%–15% of patients with HIV report post-herpetic neuralgia as a complication following herpes zoster.

Figure 4.5.8: Herpes Zoster



Herpes Zoster *Courtesy: GHTM-I TECH Fellowship programme*



Herpes Zoster ophthalmicus *Courtesy: CoE, BJMC, Ahmedabad*

When herpes zoster involves the nasociliary branch of the trigeminal nerve, the eye can be affected (herpes zoster ophthalmicus [HZO]), resulting in **keratitis** (inflammation of the cornea) or anterior uveitis (inflammation of the iris and anterior ciliary body) or both.

Vesicles on the tip of the nose (**Hutchinson's sign**) are a clue that the nasociliary branch is involved. With corneal involvement, there may be an initial brief period during which the corneal epithelium is infected with VZV, but the major problem is inflammation of the corneal stroma, which can result in scarring, neovascularization or necrosis, with loss of vision.

Stromal keratitis can be chronic. Once it occurs, VZV-associated anterior uveitis also tends to be chronic and can result in increased intraocular pressure or glaucoma, scarring of intraocular tissues and cataract.

Stromal keratitis and anterior uveitis may not develop immediately after the appearance of skin vesicles on the forehead and scalp. Therefore, patients with normal eye examinations initially should receive **follow-up eye examinations**, even after the skin lesions heal. Necrotizing retinopathy is also a rare presenting feature.

Patients with HIV who have CD4 counts <200 cells/mm^3 are at highest risk for herpes zoster-related complications, including **disseminated herpes zoster**. The CNS is a target for herpes zoster dissemination in patients who also have HIV. Various VZV-related neurologic syndromes occur in patients with HIV, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies, focal brainstem lesions and aseptic meningitis.

Herpes zoster is rare in immunocompetent children, and if it occurs in a child, then HIV infection should be suspected. In HIV-infected children usually, vesicles occur in multiple dermatomes and can occur bilaterally. Patients may have associated retinitis, pneumonitis, hepatitis and even encephalitis.

Diagnosis

Clinical diagnosis is very distinct. When lesions are atypical or difficult to distinguish from those due to other potential aetiologies (including HSV), swabs of vesicular fluid from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing or PCR testing. Additionally, scabs may be adequate specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections.

Prophylaxis and Management

There is no recommended prophylaxis.

Treatment: **Duration: 7–10 days**

- Valacyclovir 1,000 mg Oral three times a day, or
- Famciclovir 500 mg Oral three times a day, or
- Acyclovir 800 mg Oral five times a day

Herpes zoster ophthalmicus: Late dendriform lesions of the corneal epithelium should be treated with systemic or topical anti-herpetic medications.

Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident.
- Switch to oral therapy (Valacyclovir 1 g three times a day, famciclovir 500 mg three times a day, or Acyclovir 800 mg orally five times a day to complete a 10–14-day course) when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving.

Management of Varicella in CLHIV

Moderate to severe disease

- Acyclovir - 10 mg/kg/dose IV every 8 hours for 7 days

Mild disease:

- Acyclovir - 20 mg/kg/dose orally every 6 hours for 7 days

Alternatively, Foscarnet 120 mg/kg/day IV in three divided doses for 7 days can be used in acyclovir-

resistant disease.
For herpes zoster in CLHIV, Acyclovir is the treatment of choice. IV Acyclovir (10 mg/kg/do IV TDS) for 7–14 days may be given in children with severe immunosuppression, trigeminal nerve involvement and multi-dermatomal zoster.

Oral Acyclovir (20 mg/kg/do orally TDS) for 7 days should be given for mild disease. Patients who fail to respond to acyclovir may be treated with Foscarnet (120 mg/kg/day IV in three divided doses).

Molluscum Contagiosum (MC)

Molluscum contagiosum (MC) is a superficial cutaneous viral infection. MC is caused by the molluscum contagiosum virus, a DNA pox virus. It spreads through skin-to-skin contact, especially during sexual activity that involves friction and skin irritation.

MC presents as one or more lesions on the skin that resemble warts or acne. They usually form clusters, notably on the thighs, buttocks, groin and lower abdomen, and may occasionally appear on the external genitalia and anal region, and on the face and eyelids. The clear pearl-like papules/ nodules are 2–10 mm in diameter with central umbilication.

MC looks like small flesh-coloured or pink dome-shaped bumps that are shiny in appearance. The lesions may be itchy or asymptomatic. Early in the infection, the lesions are usually mild and localized to the groin or face. Once CD4 counts fall below 200 cells/mm^3, lesions tend to proliferate. They often number greater than 100 and may involve the face, trunk and groin; there is a predilection for the eyelids. Extensive MC is a cutaneous marker of advanced HIV disease
(CD4 <50 cells/mm^3).

Figure 4.5.9: Molluscum Contagiosum



Molluscum Contagiosum *Images' courtesy: CoE, Bowring & Lady Curzon Hospital, Bengaluru*

Diagnosis is usually based on the clinical appearance. Giant confluent lesions may have a bizarre appearance and require biopsy.

Treatment

Cryotherapy using liquid nitrogen to freeze the lesions, curettage, extracting lesions and **electrocautery** can be used to remove the lesions.

Topical gels and creams such as podophyllum, trichloroacetic acid, cantharidin, tretinoin, tincture of iodine, silver nitrate or phenol can be applied directly to the lesions. Repeated application may be required until the lesions clear. The normal skin around may need to be protected with paraffin wax. Cimetidine can be used if the area becomes inflamed or itchy. If the lesions are extensive, ART needs to be initiated

Human Papillomavirus (Warts)

Superficial cutaneous infection with human papillomavirus (HPV), or warts, occurs with increased frequency in immunosuppressed patients. For more details, please refer **Chapter 5.4 (Management of Sexually Transmitted Infections/Reproductive Tract Infections in PLHIV).**

Oral Hairy Leukoplakia

Oral hairy leukoplakia is mucosal disease associated with EBV infection and almost exclusively occurring in people with immunosuppression. Although most people are infected with EBV, it causes disease mainly in immunocompromised individuals. More than 25% of HIV-positive people develop Oral Hairy Leucoplakia at some point. It is most common among HIV-positive men and smokers.

The presence of oral candidiasis and Oral Hairy Leucoplakia within the oral cavity not only suggests HIV infection but is also possibly **one of the first signs of development of AIDS** in the HIV-infected individual. It can occur at any level of T cell count but is more common at CD4 counts <200 cells/mm^3. It can also occur in people not infected with HIV.

It presents as white striations along the lateral margin of the tongue. They can be shaggy in appearance and may contain several ridges. **Oral Hairy Leucoplakia may resemble oral candidiasis**. However, candida patches usually come off when lightly scraped with a toothbrush, whereas those due to Oral Hairy Leucoplakia do not.

Oral Hairy Leucoplakia is asymptomatic and is usually discovered during a routine clinical examination. It does not cause discomfort or affect taste sensation. Rarely, mild pain, alterations in taste and heightened sensitivity to food temperature may be present.

Figure 4.5.10: Oral hairy leukoplakia



Oral Hairy Leucoplakia *Images Courtesy: CoE, GHTM, Tambara*

Diagnosis

The diagnosis is usually based on clinical inspection. A simple scrape test can be performed using a

tongue depressor or a toothbrush. If the patch appears to come off with scraping, it is probably not Oral Hairy Leucoplakia. A sample of the patch should be sent to the laboratory to confirm the diagnosis of EBV.

Diagnosis is ***confirmed*** if EBV is identified in the epithelial cells of an oral lesion by electron microscopy, in situ hybridization or immunocytochemistry.

Diagnosis is ***probable*** when there is a (a) white lesion (classically described as hairy, shaggy or furry) that cannot be scraped off with a tongue depressor blade, and (b) its location is limited to the lateral margin(s) of the tongue or the lesion extends beyond the lateral margin(s), but oral candidiasis has been excluded or the lesion persists after antifungal therapy and without anti-herpes therapy.

Treatment

Oral Hairy Leucoplakia usually does not require treatment. Tretinoin and podophyllin resin can be applied directly to the patches. Tretinoin is usually applied 2–3 times a day until the patches have disappeared. Podophyllin is applied 1–2 times over a 2–3-week period by a healthcare provider. Liquid nitrogen cryotherapy and surgery are other alternatives.

Inflammatory Conditions

Xerosis and Lchthyosis

PPLHIVs commonly complain of increasing dryness of the skin (xerosis). Typically, the xerosis is most prominent on the anterior lower legs, but it may be quite widespread. In winter, the xerosis is more severe and may be associated with dermatitis, manifesting as itching and dryness with areas of erythematous papules and fine scale on the posterior arms and lower legs.

Treatment: Patients should apply mainly moisturizers. A few may require mild topical steroid ointments (1.0%–2.5% hydrocortisone or 0.025% triamcinolone) for dermatitis three times a day and should cover all dry areas of the body with a moisturizing lotion or cream after bathing and at bedtime.

Dry and thickened skin, as is seen in acquired ichthyosis, is seen in patients with advanced HIV disease. Thickening of the palms and soles may be present as well. Acquired ichthyosis has been seen in association with a wasting syndrome. Treatment is the same as for xerosiss.

Seborrheic Dermatitis

Seborrheic dermatitis is a mild eruption, usually affecting the scalp and central areas of the face. Majority of PLHIV would have symptoms suggestive of seborrheic dermatitis during the illness. It is one of the most common inflammatory dermatoses observed in CLHIV, occurring with rates of up to 83% as compared to 1%–3% among immunocompetent non-HIV children.

It occurs predominantly on the scalp, usually with mild involvement of the face (particularly on the brows, around the eyelashes, nasolabial folds and in and around the ears). Occasionally, seborrheic dermatitis will affect the centre of the chest, particularly in individuals with a lot of chest hair, and the axillae and groin. The dermatitis usually manifests as poorly defined, faint pink patches, with mild-to-profuse fine, loose, waxy scales. The intertriginous lesions are clinically identical to those seen in Reiter's syndrome and psoriasis concurrent with HIV infection.

Rarely, it can take a severe form, which consists of typical severe seborrheic dermatitis of the **face and scalp**, plus extensive involvement of the intertriginous areas. **The axillae and groin are bright red and covered by a fine scale**. The eruption moves out from the intertriginous areas onto the trunk and neck

and may involve large areas of the body.

In CLHIV, seborrheic dermatitis may present as erythematous scaly patches with an overlying greasy scale on the scalp, eyebrows, peri-nasal, chest, back, axilla and groin. Blepharitis may be present. The clinical presentation is like that seen in immunocompetent children, but it may be more severe resulting in erythroderma. The severity of the disease correlates with the degree of immune suppression and the stage of HIV infection.

Lesions may be malodorous and weepy, signifying secondary bacterial infection.

Treatment: Mild topical steroids (e.g., 1% hydrocortisone), tar shampoos and often twice-daily application of topical imidazole cream (clotrimazole or ketoconazole).

There are other rare inflammatory conditions which are sometimes exacerbated in PLHIV like Reiter's Syndrome, Eosinophilic Folliculitis and Atopic Dermatitis.

Cutaneous Malignancies

Kaposi Sarcoma

Please refer Chapter 5.6 (Guidelines for the Management of HIV-associated Malignancies) for detailed discussion.

Non-Hodgkin’s Lymphoma

PLHIV are at increased risk of developing non-Hodgkin’s lymphoma (NHL) when compared to the general population with a prevalence up to 4.3% higher than that in the general population.[3] NHL appears to be the most common type of cancer reported in Indian PLHIV.

Based on a study done in Mumbai by Dhir A. et al, NHL constituted 38% of the cancers seen in male PLHIV and 16% in female PLHIV (because of the predominance of cervical cancers in females).[4] In HIV-positive men and women, increased risk was about 17 times and 10 times, respectively.

80% of cases of NHL present with advanced systemic disease and **high levels of lactate dehydrogenase.** NHL exhibits a highly variable clinical manifestation, which mainly depends on the sites involved. Compared to that in the general population, in PLHIV it has a highly invasive behaviour due to disease progression. Almost all patients have lymphadenopathy (primarily involving the neck) and frequently suffer from extra-nodal diseases at sites including the GIT, bone marrow, meninges and liver, as well as rare occurrences in the lung, heart, orbit, body cavity, kidney and adrenal gland.

Figure 4.5.11: Non-Hodgkin’s lymphoma



Cutaneous NHL *Images Courtesy: ART Plus Centre, Salem*

Treatment: Chemotherapy remains the mainstay of treatment modality for NHL. The CHOP treatment regimen containing Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine sulphate) and prednisone along with ART is the standard chemotherapy for NHL cases.

Miscellaneous

Drug Reactions

Cotrimoxazole is associated with adverse reactions. Most reactions occur in the second week of therapy and are typical maculopapular/morbilliform rash. They begin from any body part like trunk or face and pressure areas and quickly generalize.

The use of systemic corticosteroids in treating PCP has substantially reduced the rate of drug eruption from TMP–SMZ. In persons with HIV infection and PCP, the overall incidence of skin eruptions from TMP–SMZ is about 10 times that in a non–HIV-infected population. The reasons for this difference are unknown.

Figure 4.5.12: Different drug reactions



Macule



Papule



Vesicle

Pictures courtesy: CoE, School of Tropical Medicine, Kolkata

Other drug-induced hypersensitivity reactions in HIV-infected patients are urticarial reactions, exfoliative erythroderma, fixed-drug eruption, erythema multiforme and toxic epidermal necrolysis. These reactions are most often due to antibiotics, especially TMP–SMZ and the penicillin. These reactions may take up to 8 weeks to clear.

Pruritic Papular Eruptions

Pruritic papular eruptions are one of most common cutaneous manifestation of HIV disease, with a prevalence ranging from 11%–46%. Pruritic papular eruptions can be the first marker of HIV infection.

This is characterized by chronic **bilaterally symmetric pruritic papules and sterile pustules** on the trunk and extremities in an HIV-infected patient, with other definable causes of itching being ruled out.

The exact aetiology of pruritic papular eruptions is unknown. Most patients with pruritic papular eruptions have **folliculitis**. If possible, search for staphylococcal infection by abrading and culturing an unruptured pustule (if present).

Differential diagnoses for this are follicular (eosinophilic, Demodex, staphylococcal and pityrosporum folliculitis) and non-follicular pruritic eruptions, including scabies, insect bites, prurigo nodularis and eczematous eruptions.

Figure 4.5.13: Pruritic Papular Eruptions



Pruritic papular eruptions legs
Picture courtesy: PCoE, KSH, New Delhi



Pruritic papular eruptions hands and legs
Picture courtesy: CoE, Gandhi Hospital, Secunderabad

Treatment: Topical steroids, emollients and oral antihistamines form the first line of management. In case of suspicion of staphylococcal folliculitis, empiric treatment for staphylococcus is with a semi-synthetic penicillin (e.g., dicloxacillin) or a first-generation cephalosporin for 1 to 2 weeks. Some patients improve with this regimen, particularly those with positive cultures from the pustules.

Acute HIV Exanthem and Enanthem

The frequency of the rash in acute HIV infection may be as high as 50%. The rash may be exanthematous or pityriasis rosea-like, usually does not itch, is distributed over the upper trunk and proximal limbs and may involve palms and soles. Exanthem usually appears 2–3 days after the onset of glandular fever-like illness and lasts usually for a week. There are associated systematic features like fever, malaise myalgia,

arthralgia and pharyngitis, which last usually for a week. An associated **enanthem** of oral erythema or superficial erosions may be present. Dysphagia or retrosternal pain due to oral and oesophageal ulcerations may be the prominent complaint of patients. The exanthem and enanthem spontaneously resolve within 1 to 2 weeks.

Section 5

Comorbidities

5.1 Non-Communicable Diseases and Mental Health: Prevention, Screening, and Management among PLHIV

Introduction

The HIV/AIDS epidemic in India has changed drastically over the last decade, transforming the disease from a life-threatening condition to a manageable, chronic one. This can be attributed to increased ART coverage for PLHIV. PLHIV who are on ART and virally suppressed are living longer and require a comprehensive health and well-being approach that extends beyond HIV care.

While significant progress was made in the control of HIV/AIDS, the country was also undergoing a major epidemiological transition of communicable and non-communicable diseases (NCDs). Over the last 26 years, the country's disease patterns have shifted: mortality due to communicable, maternal, neonatal and nutritional diseases has declined substantially and NCDs are increasingly contributing to overall disease burden.

An NCD is a non-infectious health condition that cannot be spread from person to person. These diseases generally last for a long period of time and are chronic in nature. A combination of genetic, physiological, lifestyle and environmental factors can cause these diseases. Some of the major risk factors include unhealthy /unbalanced diets, lack of physical activity, smoking/tobacco use and excessive use of alcohol. Examples of common NCDs are given in Table 5.1.1.

Table 5.1.1: Common non-communicable diseases

Organ System	Examples of Non-communicable diseases
Cardiovascular	Hypertension Ischemic heart diseases Stroke Rheumatic heart disease
Respiratory	Asthma Chronic obstructive pulmonary disease (COPD) Occupational lung disease Cystic fibrosis Pulmonary hypertension
Endocrine	Diabetes (type 1/type 2/prediabetes, gestational)
Renal	Chronic renal disease
Central nervous system/ Psychiatric	Depression Anxiety Schizophrenia
Blood	Anaemia (Nutritional) Haemoglobinopathies
Cancers	Breast cancer Cervical cancer Lung cancer Oral cancer Prostate cancer Colon and stomach cancer Blood cancers (leukaemia, lymphoma)
Musculoskeletal	Arthritis

NCDs including hypertension, cardiovascular disease, renal disease, cancer, chronic respiratory disease, diabetes and mental health disorders account for 63% of global deaths. Among the leading NCDs, the largest disease burden or Disability-Adjusted Life Year (DALY) rate increased from 1990 to 2016 was observed for diabetes at 80%, and ischaemic heart disease at 34%.[1]

NCDs in PLHIV result from a mix of chronic immune activation, medication side effects, coinfections and the aging process itself. NCDs are now becoming one of the leading causes of non–AIDS-related morbidity and mortality in PLHIV.

The following five components are recommended for prevention and management of NCDs in PLHIV:

- Health promotion (primordial prevention)
- Screening for early detection
- Diagnosis
- Management (including lifestyle changes and pharmacologic therapy)
- Regular follow-up: Monitoring achievement of treatment goals and monitoring adherence,side effects and drug–drug interactions

Health Promotion

Health promotion is critical to promote a healthy lifestyle and reduce specific risk behaviours, e.g., unhealthy diets, physical inactivity, tobacco use, harmful drinking, etc. for prevention of NCDs. All PLHIV

shall be counselled on health behaviours and comprehensive healthy lifestyles (Table 5.1.2).

Table 5.1.2: Counselling messages related to health behaviour

Health Behaviour	Counselling Messages
Physical activity	• Active lifestyle with moderate levels of physical activity (for at least 150 minutes/ week) • Yoga and meditation
Weight Control	• Weight management to maintain a healthy BMI • All individuals who are overweight or obese should be encouraged to lose weight through a combination of a low-calorie diet and dynamic physical activity.
Diet	• Take balanced diet with whole grains, vegetables, fruits and pulses. • Diet shall be as per the locally available items. • Restrict salt to less than 5 grams (1 teaspoon) per day • Limit use of sugar, fatty meat, dairy fat and fried food
Tobacco cessation	• Tobacco cessation has multiple short-term and long-term benefits. • Encourage all non-smokers/tobacco chewers not to start smoking/tobacco chewing. • Strongly advise all smokers/tobacco chewers to quit tobacco and support them in their efforts.
Avoidance of alcohol	• Use of alcohol should be avoided by everyone as far as possible. • Counselling support for people with alcohol use disorder or drinking in excess of moderation
Adherence to treatment	• If the person is prescribed medication for NCDs ▪ Explain the dose and how many times a day to take the medication. ▪ Explain how to take with ARVs along with additional medications. ▪ Explain the importance of adherence to medicines for NCDs along with ART. ▪ Explain the need to take the medicines regularly as advised even if there are no symptoms. ▪ Counsel on the possible side effects and advise to report back immediately if any side effect/adverse drug reaction is experienced.

Recommendations for screening, diagnosis and initial management of hypertension, type 2 diabetes mellitus and dyslipidaemia are provided in Tables 5.1.3, 5.1.4 and 5.1.5.

Hypertension Screening, Diagnosis and Initial Management for Adult PLHIV

Table 5.1.3: Screening, diagnosis and initial management of hypertension in Adult PLHIV

For comprehensive and detailed guidance on prevention, diagnosis and management of hypertension, refer to Standard Treatment Guidelines – Hypertension, 2016, MoHFW, Government of India.[2]	
Screening	All PLHIV above the age of 18 years should undergo screening by healthcare providers, through blood pressure (BP) measurement at • Registration into HIV care or ART initiation • Every 6 months after ART initiation • or separately as a screening examination if requested by PLHIV or need felt by healthcare provider based on symptoms
Diagnosis	• The diagnosis of hypertension should be done by a physician, using a validated device, and following a standardized BP measurement procedure. • Diagnosis of hypertension should be based on at least two measurements taken on at least two visits, which are at least 1–4 weeks apart. • Except in the case of hypertensive urgencies, systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110 mm Hg with no evidence of acute target organ damage) and hypertensive emergencies (systolic blood pressure >180 mm Hg and/or diastolic blood pressure >110–120 mm Hg and associated with cardiovascular or cerebral or renal damage or Grade III–IV retinopathy) where hypertension is diagnosed during the first measurement itself • Hypertension should be diagnosed when BP is persistently above a systolic of 140 mm Hg and/or diastolic of 90 mm Hg
Additional investigations if available	**Essential (any PLHIV with hypertension)** • Fasting blood sugar: Assessment for diabetes • Urine analysis: Proteinuria may be an early indication of diabetic nephropathy and a marker for a higher risk of cardiovascular morbidity and mortality • Desirable for PLHIV with systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg • Lipid profile: Dyslipidaemia is a cardiovascular risk factor. • Serum creatinine, Na, K: Assessment for renal function • ECG: Evaluation for end-organ damage such as left ventricular hypertrophy
Management	**The target for BP control** • For patients below 80 years of age is systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg and • For patients 80 years or older is less than 150 mm Hg systolic and less than 90 mm Hg diastolic All patients require lifelong lifestyle modification including dietary change to heart-healthy diet, salt limited to 5–6 g/day, low-fat diet, regular exercise, weight maintenance with target BMI 18.5–22.9 kg/m2 and stop smoking Antihypertensive therapy for uncomplicated hypertension and irrespective of whether HIV status is either mono- or combination therapy with an: • angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril) • angiotensin receptor blocker (ARB) (e.g., losartan) • calcium channel blocker (CCB) (e.g., amlodipine) • thiazide diuretic (e.g., hydrochlorothiazide) • beta-blocker (e.g., Atenolol) Patients with Grade 1 hypertension (systolic blood pressure 140–159 mm Hg, diastolic blood pressure 90–99 mm Hg) may require only lifestyle modification, which should be tried for 3 months In patients with Grade 1 (Systolic blood pressure 140–159 mm Hg, diastolic blood pressure 90–99 mm Hg) not responding to lifestyle modification or Grade 2 hypertension (Systolic blood pressure 160–179 Hg, diastolic blood pressure 100–109 mm Hg), drug therapy can be initiated with one drug in combination with lifestyle modifications. In patients with Grade 3 hypertension (Systolic blood pressure ≥180 mm Hg, diastolic blood pressure ≥110 mm Hg), therapy should be initiated with two drugs in combination with lifestyle modifications. The dose of drugs can be increased, or a new drug added at approximately 2- to 4-week intervals. This frequency can be faster or slower depending on the clinical circumstances of the patient and the judgement of the treating physician. Patients with diabetes mellitus should be initiated on drug treatment when Systolic blood pressure is greater than 140 mm Hg, and the target for control should be a Systolic blood pressure of less than 140 mm Hg, and a diastolic BP of less than 90 mm Hg. ACE inhibitors are preferred as initial therapy and calcium channel blockers and diuretics may be used as add-on therapy.
Interactions	• Angiotensin converting enzyme (ACE) inhibitor and thiazide diuretic do not have any interaction with ARVs. • There are potential interactions between calcium channel blockers and beta blockers with ARVs:[3] ▪ Drug levels of calcium channel blockers and beta blockers are increased in the presence of protease inhibitors (PIs) and decreased in the presence of non-nucleoside reverse transcriptase inhibitors (NNRTIs). Dose adjustment of the antihypertensive agent may be required. ▪ Drug levels of ARVs are not affected by calcium channel blockers or beta blockers and no dose adjustment is required for ARV. ▪ Caution should be exercised when administering beta blockers and PIs due to the risk of QT prolongation. ECG monitoring is recommended.
Care provision and referrals	• Screening, diagnosis and treatment of uncomplicated hypertension can be provided by a trained medical officer. • Grade 3 hypertension and failure to achieve treatment goal following initiation and dose increase of two antihypertensives to maximum level shall be referred to physician experienced in management of hypertension. • Immediate referral to appropriate facility and provider shall be done in cases of hypertensive urgencies and hypertensive emergencies.

Diabetes Mellitus Screening, Diagnosis and Initial Management for Adult PLHIV

Table 5.1.4: Screening, diagnosis and initial management of diabetes mellitus in Adult PLHIV

For comprehensive and detailed guidance on prevention, diagnosis and management of diabetes mellitus, refer to ICMR Guidelines for Management of Type 2 Diabetes 2018.[4]	
Screening	All PLHIV should undergo screening, through random blood glucose test at • Registration into HIV care or ART Initiation • 1–2 months after ART initiation and then at every 6 months • At change of regimen (substitution or switch) • Or separately as a screening examination if requested by the person
Diagnosis	**Diagnostic criteria for diabetes:** • Symptoms of diabetes (mentioned below) plus casual or random plasma glucose ≥200 mg/dl (casual refers to without regard to time of last meal) • Fasting plasma glucose ≥126 mg/dl* • 2-hour post 75 g glucose ≥200 mg/dl (as part of oral glucose tolerance test)* • Glycated haemoglobin ≥6.5%* (It has been reported that HbA1c levels underestimate glycaemic levels by 10% to 15% in PLHIV.) *Diabetes diagnosed using any of these criteria should be confirmed with another test subsequently. **Symptoms of Diabetes** • Polyuria, polydipsia • Weight loss despite polyphagia • Tiredness, weakness • Generalized pruritus • Recurrent urogenital infections • Delayed healing of wounds
Monitoring	• Blood glucose: Fasting blood sugar (FBS) and 2-hr post-prandial blood sugar (PPBS) at least once a month and more often if values are not in the ideal target range • HbA1c at least every 6–12 months if available and more often (every 3 months) if values are not in the ideal target range • Clinical examination needs to be done during every visit, minimum every 3 months • Screening for long-term complications like retinopathy, nephropathy, neuropathy, peripheral vascular disease (PVD) and coronary artery disease at least once in 6 months, more often if needed • Optimizing weight, waist circumference, blood pressure, lipids • Routine examination of foot to be done during every visit and education regarding foot care to be given to patients at each visit • Discourage tobacco use and excess use of alcohol.
Additional Investigations if available	• Lipid profile • Serum creatinine • Urine analysis for proteinuria
Management	For patients with pre-diabetes (abnormal results but do not meet criteria above for diabetes), monitoring with FBS or HbA1C (if available) every 6 months and encouraging lifestyle modifications is recommended. Lifestyle modification as mentioned under health promotion is recommended for all PLHIV with diabetes for life. If target blood glucose is not achieved after lifestyle modification, within 3–6 months, oral hypoglycaemic shall be added. • Give metformin for type 2 diabetes. • Titrate metformin to target glucose value (FBS 126 mg/dl / A1c [if available]). • Sulfonylurea may be given to patients who have contraindications to metformin or if metformin does not improve glycaemic control. • Patients with Diabetes mellitus are at increased risk of developing TB.
Interactions[5]/ cautions	• Metformin should be used with caution in PLHIV with renal insufficiency, liver disease, active infection including TB, and those with wasting or congestive cardiac failure due to the risk of lactic acidosis induced by metformin. • Caution should be exercised when co-administering metformin with DTG as metformin levels are increased and dose reduction of metformin should be considered. • A dose adjustment of metformin should be considered when co-administering DTG with metformin in order to maintain glycaemic control. It is recommended to limit the total daily dose of metformin to 1,000 mg when co-administered with DTG.[5] • Monitoring renal function and blood glucose is recommended when metformin and DTG are co-administered. • NNRTIs and PIs may cause increase/decrease in level of sulfonylureas, which may require dose adjustment of the sulfonylurea. Dosage can be adjusted as needed based on blood glucose monitoring.
Care provision and referrals	• Screening, diagnosis and management through lifestyle modification can be provided by trained medical officer.[6] • Initiation of oral hypoglycaemic agents shall be done by physician. • Continuation of treatment can be provided by trained medical officer in PLHIV with controlled diabetes. • Management and follow-up by physician are recommended in patients with uncontrolled hyperglycaemia despite maximum doses of metformin and sulfonylurea, patients with foot ulcers and patients with vision impairment.

Cardiovascular disease risk factors: Screening, Assessment and Initial Management for Adult PLHIV

Table 5.1.4: Screening, diagnosis and initial management of cardiovascular disease risk factors in Adult PLHIV[7]

Cardiovascular diseases like ischemic heart disease, coronary heart disease and stroke are one of the major causes of mortality and morbidity among the general population. With changes in lifestyle, the incidence is increasing and PLHIV are also affected by these ailments.

While diagnosis and management of ischemic heart disease and stroke are best done at facilities with advanced interventions, it is important that assessment, prevention and management of known and preventable risk factors for cardiovascular disease is included in HIV care package.

Cardiovascular diseases risk Factors	• Hypertension • Diabetes mellitus • Dyslipidaemia (high fasting total cholesterol, LDL or triglycerides) • Obesity (BMI >30 kg/m^2) and increased waist circumference (men: 102 cm; women: 88 cm) • Physical inactivity • Tobacco use • Excessive alcohol consumption • Unhealthy diet and nutrition • Family history of cardiovascular disease
Assessment	Assessment shall be done at time of registration in HIV care or ART initiation, at 3 months and 6 months of ART and shall be repeated every 6 months thereafter. **Ask for history of** • Heart disease, stroke, diabetes or hypertension • Any angina, breathlessness on exertion and lying flat, numbness or weakness of limbs, loss of weight, increased thirst, polyuria, puffiness of face, swelling of feet, passing blood in urine • Any past/present treatment/medication • Current/past tobacco use and alcohol consumption • Lifestyle (sedentary or active) • Premature heart disease or stroke in first-degree relatives **Assess** • BMI and waist circumference • Measure blood pressure • Signs or symptoms of diabetes mellitus • Examine for signs such as pitting oedema, heart murmurs, basal crepitation in lung and tenderness in abdomen • Lipid profile (if available)
Management	All patients with history of angina, breathlessness on exertion and lying flat, numbness or weakness of limbs, loss of weight, increased thirst, polyuria, puffiness of face, swelling of feet, passing blood in urine, pitting oedema, heart murmurs, basal crepitation in lung and tenderness in abdomen need to be referred to a physician for further assessment and management.
Management	Follow lifestyle modification as mentioned under health promotion. Management of hypertension and/or diabetes as per Tables 5.1.2 and 5.1.3 Treatment with statins is recommended for all patients with established cardiovascular diseases and for patients with dyslipidaemia. For managing dyslipidaemia • In PLHIV on ARV with known impact on lipid metabolism (PIs and EFV), single drug substitution to lipid-friendly drug is recommended, if feasible. • If lipid profile does not improve with lifestyle modification, lipid-lowering drug like statin (Atorvastatin) may be added (starting dose of 10 mg OD (maximum dose 20 mg if patient is on a PI/r; maximum dose 80 mg once daily if not on a PI/r). • Simvastatin and lovastatin are contraindicated in the presence of PIs.

Mental Health Screening, Diagnosis and Management of Depression among PLHIV

PLHIV are prone to psychological ailments due to HIV per se as well as opinions and experiences regarding HIV in their surroundings. PLHIV may face multiple types of psychological issues like depression, anxiety, internalized stigma, etc. Any such issue can significantly hamper adherence and mental well-being.

Depression is a common mental disorder, which presents as persistent sadness or loss of interest or pleasure in daily living accompanied by disturbed sleep or appetite, feelings of guilt or low self-worth, tiredness, poor concentration, difficulty making decisions, agitation, hopelessness and suicidal and self-harm thoughts or acts.[8]

Depression is two to three times more prevalent in PLHIV than in the general population. It is a significant contributing factor to poor adherence to ART and poor HIV treatment outcomes including treatment failure. Mental health assessment and treatment (wherever required) shall be an essential part of the HIV care package.

Screening

All PLHIV should receive basic screening for depression before initiating ART and thereafter every 6 months using the following two questions:

- During the past two weeks, have you often been bothered by feeling down, depressed or hopeless?
- During the past two weeks, have you often been bothered by little interest or pleasure in doing things?

Any patient who answers ‘yes’ to either of the questions above, and all patients with a detectable viral load after 6 or more months on, should undergo a more thorough screening for depression using the PHQ-9 screening tool (Table 5.1.6) and scoring pattern (Table 5.1.7).

At the time of ART initiation, the patient shall also be screened for history of maniac symptoms (feeling very happy, elated or overjoyed, talking very quickly, feeling full of energy, being easily distracted, being easily irritated or agitated, being delusional, hallucinating and disturbed or illogical thinking), suicidal ideation or homicidal ideation. If any signs/symptoms suggestive of bipolar disorder/suicidal/homicidal tendencies are identified, the patient shall be referred to a psychiatrist.

Table 5.1.6: Patient health questionnaire-9

S. No.	Patient Health Questionnaire-9 (PHQ-9)				
	Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed or hopeless	0	1	2	3
3	Trouble falling or staying asleep or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself, or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite –being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Table 5.1.7: Patient health questionnaire: scores and related conditions

Total score	Patient Health Questionnaire: Scores and Conditions	
	Conditions	Recommendations
0-4	Depression unlikely	• Repeat screening as per schedule.
5-9	Mild depression	• Provide supportive counselling and continue to monitor. • If patient is on EFV, substitute with a different ARV after ruling out treatment failure.
10-14	Moderate depression	• Provide supportive counselling through trained counsellor. • If patient is on EFV, substitute with a different ARV after ruling out treatment failure; and • Referral to psychiatrist for further assessment and antidepressant medication
15-19	Moderate to severe depression	
20-27	Severe depression	

Supportive counselling for depression shall be provided by trained counsellor as detailed in Table 5.1.8.

Table 5.1.8: Key supportive counselling messages in PLHIV with depression

Component	Key message
Psycho-social support	• Explain about depression and assure that it can be managed. • Feeling of hopelessness, worthlessness, negative emotions are part of depression and will revert with proper counselling and treatment. • Inform on course of counselling and treatment. • Identify supportive family members and involve them as appropriate. • Involve peers and community support groups.
Self-management skills	• Continue ART as prescribed. • Identify activities that they used to find interesting and pleasurable: encourage participation in these activities. • Get regular and sufficient sleep (approx. 7 to 8 hours). • Physical activities to be increased. • Contact ARTC/ healthcare facility immediately if thoughts of self-harm.
Reduce stress	• Identify and try to reduce stress points. • Identify and discuss stress-increasing points such as health issues, family and relationship problems, gender-based or partner violence, finances, stigma and discrimination. • Identify and discuss problem-solving techniques. • Suggest stress management such as meditation and relaxation techniques.

The table content is being updated.

Medical management of depression

- Depression can be managed by a combination of medical and psychological interventions. Medications should not be considered as the only therapeutic strategy.
- Antidepressants should be prescribed by a psychiatrist.
- Antidepressant treatment is generally given for 6–9 months. Doses should start with the minimum recommended dose and increased gradually. It takes 2–4 weeks for maximum therapeutic benefit and improvement in symptoms to be achieved.
- Antidepressants should not be stopped abruptly. Dose should be tapered gradually.
- There are two main classes of antidepressants, tricyclic antidepressants, amitriptyline) and selective serotonin reuptake inhibitors (SSRI; fluoxetine).

Drug-drug interactions[5]

- There are no drug interactions between NRTIs, NNRTIs or integrase inhibitors and amitriptyline or fluoxetine.
- PIs increase drug levels of amitriptyline or fluoxetine, but no adjustment of dose of amitriptyline or fluoxetine is needed. Amitriptyline or fluoxetine do not affect ARV drug levels.
- Amitriptyline and PIs should be administered with caution as both prolong the cardiac QT interval and ECG monitoring is recommended.

Mental Health in Children and Adolescents Living with HIV

Childhood and adolescence are critical periods in development. Children and adolescents acquire cognitive and social-emotional skills that shape their future mental health and are important for assuming adult roles in society. The environment where children and adolescents grow up shapes their well-being and development. Early negative experiences at home, in school or with peers, such as exposure to violence, mental illness of a parent or other caregiver, bullying and poverty, increase the risk of mental illness.

Mental health disorders during childhood and adolescence are defined as delays or disruptions in developing age-appropriate thinking, behaviours, social skills or regulation of emotions. These problems are distressing to children and disrupt their ability to function well at home, in school or in other social situations.

Epidemiological and community-based studies in India have reported a prevalence of mental health conditions in children and adolescents between 6% and 12%. The recent National Mental Health Survey reported a prevalence of 7.3% in children and adolescents aged 13–17 years. Overall, 8%–13% of children are estimated to need mental health services.[9] Thus, there is a need to screen children and adolescents for mental health-related issues. This need is more urgent in children/adolescents with HIV.

Mental health issues in children and adolescents living with HIV

Various studies have shown that mental health issues and psychiatric illnesses are more common in children and adolescents living with HIV as compared to the general population. The proportion of ALHIV with psychiatric illness is reported to be higher in the older age group and in adolescents who know about their disease. This might be due to a better understanding of the disease and associated stigma attached to the disease in these children. Parental HIV status is also known to affect psychiatric illness among CLHIV. Hence, children whose either parent has positive HIV status and HIV orphans are more likely to suffer from them.

Warning signs of mental illness in children

Children can develop the same mental health conditions as adults, but their symptoms may be different. The symptoms of mental disorder may differ depending on a child's age, and children may not be able to explain how they feel or why they are behaving in a certain way.

Warning signs suggesting that the child or adolescent may have a mental health disorder are summarized in Table 5.1.9. The medical officer and the counsellor dealing with the child should look out for these. Children and adolescents who have one or more signs suggestive of a mental health condition needs an evaluation by a paediatrician and a clinical psychologist.

Table 5.1.9: Warning signs indicating presence of a mental health condition in children/adolescents

1. Persistent sadness — two or more weeks
2. Withdrawing from or avoiding social interactions
3. Hurting oneself or talking about hurting oneself
4. Talking about death or suicide
5. Outbursts or extreme irritability
6. Out-of-control behaviour that can be harmful
7. Drastic changes in mood, behaviour or personality
8. Changes in eating habits
9. Loss of weight
10. Difficulty sleeping
11. Frequent headaches or stomach aches
12. Difficulty concentrating
13. Changes in academic performance
14. Avoiding or missing school

Source: Mental illness in children: Know the signs; available at https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Normality-022.aspx

Screening for Common Cancers and Related Referral among PLHIV

Cancer is a group of diseases characterized by uncontrolled cell multiplication that can occur in any living tissue at any site in the human body. Cancer develops in several phases depending on the type of tissue affected. The three most commonly occurring cancers in India are those of the breast, uterine, cervix and oral cavity. Together, they account for approximately 34% of all cancers, and hence are public health priority in India.[6] Survival rates for all three cancers are good, provided they are detected and treated in the early stage; the prognosis for advanced stage on the other hand is poor.

As a comprehensive care package, screening for common cancers and its risk factors and appropriate referrals for diagnosis and management shall be included for all PLHIV.

Prevention of cancers among PLHIV

- Screen for tobacco use.
- Counsel on adverse effects of tobacco and encourage to quit tobacco use.
- Promote healthy dietary practices and physical activity.

Early detection of cancers

- Create awareness about the early warning signs of cancer like the following:
- Change in bowel or bladder habits
- Wound that does not heal

- Unusual bleeding or discharge
- Thickening or lump in the breast or elsewhere
- Indigestion or difficulty swallowing
- Obvious change in a wart or mole
- Nagging cough or hoarseness of voice

- Educate patients on self-examination and reporting for unusual signs/symptoms.
- Examine patients for warning signs and routine examination of oral cavity, breast and cervix, as detailed in Table 5.1.10.
- Refer any person with a suspicious lesion for accurate diagnosis and appropriate treatment.

Screening for Cervical Cancer among PLHIV

Table 5.1.10: Cervical cancer screening in PLHIV

PLHIV Group	All women and girls living with HIV who have initiated sexual activity
Screening frequency	• At ART initiation • Repeat screening within 3 years if the initial test is negative. • Women who have been treated should receive follow-up screening at 1 year. • Any other time if related signs/symptoms are reported
Method of screening	Visual inspection with Acetic Acid (VIA): 3%–5% acetic acid is generously applied to the mouth of the cervix (ectocervix) area and presence of any aceto-white lesion is noted.
Observations	• Normal squamous epithelium (of vagina) appears pink. • Columnar epithelium of uterus appears red. • In conditions like inflammation, benign and malignant growth, the epithelium contains a lot of cellular proteins because of increased nuclear activity, thereby giving a dramatic dense white patch (VIA positive).
Referrals	If screened positive, refer to a gynaecologist/lady medical officer wherever available or NCD Clinic at CHC/DH for confirmation and further management.

Screening for Breast Cancer among PLHIV

Table 5.1.11: Breast cancer screening in PLHIV

PLHIV Group	All women living with HIV above 30 years of age
Risk factors	• Reproductive and hormonal factors ▪ Older age at first pregnancy. ▪ Early menarche (before age 12), late menopause (after age 55) ▪ Never had children ▪ Women who take menopausal hormone therapy (oestrogen and progesterone) for 5 years or more after menopause
Risk factors	• Family history: Risk of breast cancer increases in women with a first-degree relative with breast cancer. • Other factors: ▪ Being obese after menopause ▪ Physical inactivity ▪ Alcohol intake
Breast awareness	Women should be counselled on breast awareness. The first person to detect any lump in the breast is the woman herself, which is by teaching the woman to be aware of any of the following signs at the earliest possible: • Change in size • Nipple that is pulled in or changed in position or shape • Rash on or around the nipple • Discharge from one or both nipples • Puckering or dimpling of skin • Lump or thickening in the breast • Constant pain in the breast or armpit
Screening	All women living with HIV of age >30 years should be screened using Clinical Breast Examination. Clinical Breast Examination is to be performed by a trained physician or a nurse. The screening shall be done • At ART initiation • Repeat screening within 3 years if the initial test is negative. • Any other time if related signs/symptoms are reported.
Method	Clinical Breast examination: Both breasts are visually inspected and palpated in different positions from all sides
Observations	Through Clinical Breast Examination (CBE), the following are noted **Inspection** • Any changes in symmetry in breast shape and size • Skin changes: dimpling, retraction, ulceration • The level of both nipples, retraction of nipple(s), inverted nipple **Palpation** • Any discharge from the nipple(s) • Colour of the discharge • Swelling, lumps, consistency of lumps • Swelling in the arm pit (axillary area), above the collar bone (supraclavicular area) and root of the neck (infraclavicular area)
Referrals	Clinical Breast Examination negative: If no signs/symptoms noticed, follow up as per routine screening schedule. Clinical Breast Examination positive: If any positive findings are noted during Clinical Breast Examination, referral to surgeon for further evaluation (USG, biopsy, etc.), diagnosis and management

Screening for Oral Cancer among PLHIV

Table 5.1.12: Oral cancer screening in PLHIV

PLHIV Group	All PLHIV
Risk factors	Tobacco chewing is the single most important risk factor for oral cancer. Other risk factors include alcohol use, betel nut chewing and chronic trauma to oral mucosa by sharp tooth or ill-fitting dentures.
Health promotion	Adequate emphasis shall be made for cessation of tobacco use.
Screening frequency	All PLHIV of age >30 years should be screened using oral visual examination. Screening shall be done • At ART initiation • Repeat screening within 3 years if the initial test is negative • Any other time if related signs/symptoms are reported.
Method of screening	Oral visual examination
Observations	Any abnormality shall be noted down. Specially mention pre-cancerous lesions, if any. Pre-cancerous lesions or conditions are local/generalized disturbances that predispose to malignancy in a particular site. • Leucoplakia • Erythroplakia • Palatal changes associated with reverse smoking or beedi smoking • Submucous fibrosis
Referrals	If any abnormality is noted during oral visual examination, PLHIV need to be referred to a surgeon/ENT specialist for further evaluation, diagnosis and management.

General guidance for PLHIV on treatment for cancer

PLHIV receiving radiotherapy or surgical intervention shall continue taking ART. In PLHIV receiving chemotherapy, treating physician and oncologist shall discuss and prepare individualized plan considering potential interactions and toxicity profile.

For more details on cancers in PLHIV and their management, please refer Chapter 5.6 (Guidelines for the Management of HIV-associated Malignancies).

5.2 HIV and Hepatitis Co-infection

Introduction

The National Viral Hepatitis Control Programme was launched in 2018 under the National Health Mission, Ministry of Health and Family Welfare. It delivers its services to all people with suspected or confirmed infection with hepatitis B and C through designated testing and treatment centres across the country.

Several of these are available in the same institute where ART centres are located. It is important to recognize the co-infection of hepatitis in HIV-infected individuals and ensure timely access to the management of the two diseases.

Hepatitis is the inflammation of the liver caused by viruses A, B, C, D or E, which can be differentiated based on the mode of transmission of the virus. Chronic HBV infection (defined as persistence of hepatitis B surface antigen [HBsAg] for more than 6 months) and chronic HCV infection (defined as HCV antibody–positive with viraemic HCV infection) are major global public health problems. An estimated 29,60,000 people in the world have chronic hepatitis B and another 580,000 chronic hepatitis C in 2019. Chronic hepatitis B and C claimed an estimated 820,000 and 290,000 deaths respectively in 2019.[1]

Globally, the estimated prevalence and burden of HCV co-infection among PLHIV are 6.2% (interquartile range 3.4%–11.9%) and 23,00,000 (interquartile range 13–14.4 lakhs), of which 13,00,000 are people who inject drugs. The numbers for HBV co-infection are 7.6% (interquartile range 5.6%–12.1%) and 27,00,000 (interquartile range 20–42 lakhs). HIV and HCV have common routes of transmission, and PLHIV, especially people who inject drugs and men who have sex with men, have an increased risk of HCV infection.

HBV, HIV and HCV share similar transmission routes. In general, concurrent or sequential infection with these viruses usually results in more severe and progressive liver disease, and a higher incidence of cirrhosis, hepatocellular carcinomas and mortality. Viral hepatitis is an increasing cause of morbidity and mortality among PLHIV, including those on ART. A comprehensive approach includes prevention, HBV and HCV testing, hepatitis B vaccination and treatment and care for PLHIV, who are coinfected with hepatitis B and/or hepatitis C.

HIV and Hepatitis B Co-infection

A recent factsheet published by National Programme on surveillance of viral hepatitis estimated a national seroprevalence of hepatitis B as 0.95 (0.89–1.01) among the National Family Health Survey (NFHS-4) samples that were tested.

The risk of developing chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20%–60% between the ages of 6 months and 5 years. Infection in adulthood leads to chronic hepatitis in less than 5% of cases in immunocompetent individuals. However, several studies have documented an increased risk of chronic infection in adults with immunocompromised state including HIV infection.

The term acute HBV infection refers to new onset hepatitis B infection that may or may not be icteric or symptomatic. Diagnosis is based on detection of HBsAg and IgM antibodies to hepatitis B core antigen (anti-HBc). Recovery is accompanied by clearance of HBsAg with seroconversion to anti-HBs (antibodies to hepatitis B surface antigen), usually within 3 months.

The term chronic HBV infection is defined as persistence of HBsAg for 6 months or more after acute infection with HBV.

Natural History among HIV–Hepatitis B Coinfected

The natural history of both diseases is affected when a person is coinfected with both HIV and hepatitis B, and this has implications on management of both diseases.

In the absence of treatment, HIV co-infection profoundly influences the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality and

decreased treatment response compared with people who do not have HIV. All people newly diagnosed with HIV should therefore be screened for HBsAg. Current evidence suggests that HIV infection has an adverse impact on HBV-related liver disease progression, with higher serum HBV DNA polymerase activity, lower rates of loss of serum hepatitis B e antigen, and increased risk of cirrhosis, liver-related mortality and hepatocellular carcinoma at lower CD4 T-cell counts. HBV infection is more likely to be chronic in those with HIV infection. In some cohorts, liver disease has emerged as a leading cause of death in HIV-infected persons coinfected with either hepatitis B or C, as mortality due to other HIV-related conditions has declined following the introduction of ART.

Similarly, HBV infection also negatively impacts the progression of HIV infection leading to faster immune deterioration and higher mortality. Other studies have suggested that HBV infection is associated with a rapidly progressive course of HIV infection. A retrospective analysis indicated that the risk of death in 64 individuals coinfected with HIV and HBV was approximately twofold higher than that in individuals with HIV mono infection. Prospective observational cohort among those with primary HIV infection showed that HBV co-infection is an independent predictor of immunologic deterioration in such a group of patients. In another large prospective multicentre cohort by Chun et al among 2352 (PLHIV) with seroconversion window of less than 3 years, coinfected persons with hepatitis B were associated with two times higher risk of AIDS/death, higher among HBV coinfected patients compared to HBV mono-infected patients.

The HIV–hepatitis coinfected people show faster CD4 decline, slower CD4 recovery following ART, increased incidence of AIDS and non-AIDS events, increased rate of ARV toxicity and increased chances of immune reconstitution hepatitis. In one of the large cohort studies of more than 5000 coinfected persons, the relative risk of liver-related deaths was found to be 17 times higher than those with HBV mono-infected patients.

Evaluation of HIV and Hepatitis B Coinfected People

The risk of HBV infection may be higher in HIV-infected adults, and therefore all people newly diagnosed with HIV should be screened for HBsAg. Those found positive for HBsAg should be evaluated further following the guidelines for evaluation of those with hepatitis B infection according to the technical guidelines for management of hepatitis B, National Viral Hepatitis Control Programme (NVHCP), MoHFW. Besides routine clinical evaluation, one should look for signs of cirrhosis and hepatic decompensation like jaundice, conjunctival haemorrhages, anaemia, spider angioma, palmar erythema, petechiae, clubbing, gynaecomastia, testicular atrophy, parotid enlargement, asterixis (liver flaps, flapping tremors), caput medusa, ascites, oedema, longitudinal veins alongside of abdomen, hepatomegaly, hepatic bruit, venous hum and splenomegaly.

Laboratory investigations, besides routine haemogram and chemistry, should specifically include LFT, prothrombin time, alpha-fetoprotein (AFP), ultrasound and upper GI endoscopy wherever indicated. The virological examination should include HBV DNA quantitative.

One important component in evaluation is the staging of cirrhosis. Earlier invasive techniques like liver biopsy were used and Metavir Score (F0–F4) was done. But now, newer techniques like liver elastography (FibroScan) are used to measure liver stiffness and determine the stage of liver cirrhosis. Non-invasive techniques like the AST to Platelet Ratio Index (APRI) and Fibrosis 4 (FIB- 4) score are recommended under the NVHCP. Also, it is important to do ‘Child Pugh Scoring’. All these investigations need the opinion of a trained physician or a gastroenterologist. Hence, appropriate referral should be made by the ART MO to the Model Treatment centre under NVHCP.

APRI: Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is a simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. A formula for calculating the APRI is given: APRI = * (AST/ULN) x 100)/platelet count (10^9/L). An online calculator can be found at http://www.hepatitisc. uw.edu/page/ clinical-calculators/apri.

FIB-4: A simple index for estimating hepatic fibrosis based on a calculation derived from AST, ALT and platelet concentrations and age. Formula for calculating FIB-4: FIB-4 = (Age (years) x AST (IU/L))/(Platelet count (109/L x [ALT (IU/L) x 1/2]). An online calculator can be found at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

Treatment of HIV and Hepatitis B Coinfected Patients

All HIV-positive patients with HBV co-infection should start dual anti-HIV and HBV therapy irrespective of CD4 count, HBV viral load or status of liver disease, e.g., ALT level or fibrosis stage. Hence, the patient should be linked to the designated treatment or Model treatment centre under the NVHCP for management of hepatitis B in the presence of HIV infection. While this will ensure the provision of drugs used for management of hepatitis (TDF or entecavir), it will also provide access to various investigations necessary for monitoring the response to treatment and monitoring for complications like cirrhosis of liver and hepatocellular carcinoma.
The recommended NRTI drugs for ART – TDF with 3TC or FTC – are also active against HBV. Fortunately, TDF, a drug widely included in ART regimens, is also the most effective drug for long-term treatment of HBV, leading to sustained HBV viral suppression, reversal of cirrhosis and fibrosis and reduction in HBV-related mortality. All people coinfected with HIV and HBV should therefore receive a TDF-based ART regimen in combination with 3TC (or FTC), as the NRTI backbone of an ART regimen, regardless of stage of disease or HBV DNA level. HIV treatment among people coinfected with HBV without using TDF in the regimen may lead rarely to flares of HBV because of ART-associated immune reconstitution. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs. Similarly, abrupt treatment discontinuation of TDF or 3TC may be associated with HBV reactivation, hepatic flares and, in rare cases, hepatic decompensation. Stopping Tenofovir based ART should be avoided in HIV + HBV co-infection for concern of severe hepatitis flare and decompensation following HBV reactivation.

The NACO guidelines on initiation of first-line ART and ART regimens in HIV and HBV coinfected patients are summarized in Table 5.2.1.

Table 5.2.1: ART guidelines for HIV and Hepatitis B coinfected people

When to start ART	All people diagnosed with HIV infection should be initiated on ART regardless of CD4 count or WHO clinical staging or age group or population sub-groups.
Choice of regimen	Nucleoside analogues with dual activity against both the viruses such as 3TC and TDF should be included in the first-line ART regimen for HIV-infected patients who are HBsAg positive. The choice of regimen, therefore, will align with the preferred regimen for any other treatment-naive PLHIV Tenofovir + Lamivudine + Dolutegravir
Preferred Regimen	TDF + 3TC + DTG (TDF may be replaced by ABC in case of TDF toxicity or contraindications). However, in such cases, entecavir is needed for managing hepatitis B (appropriate referrals are therefore recommended immediately to NVHCP on diagnosis of chronic hepatitis B in PLHIV).
Alternative Regimen	In case of renal toxicity, TDF must be replaced by ABC (ABC + 3TC + DTG) with dose adjustments for 3TC (as per guidelines; please refer to annexure 3). In these cases, management of hepatitis B must be ensured using other drugs under the NVHCP (entecavir).
Second-line regimen	3TC should be continued as part of the second-line ART following initial ART failure, even if it was used in the first-line regimen. TDF should be continued, if not contraindicated, to manage hepatitis B and to prevent any flares due to discontinuation.
HBV Resistance	Ideally, 3TC should be used either with TDF or not at all, because HBV resistance to 3TC develops quickly. HBV resistance to 3TC develops in 50% of patients after 2 years and in 90% after 4 years of treatment if 3TC is the only active anti-HBV drug in the ART regimen.
Hepatic Flares	HBV flares on ART start soon after the initiation of ART is a manifestation of IRIS.# Discontinuation of 3TC and TDF may also result in hepatic flares.
FTC vs 3TC	The rate of suppression of HBV and the safety profile and resistance pattern with FTC are like those with 3TC. FTC is not provided in the national ART programme.

#IRIS, immune reconstitution inflammatory syndrome

*Whenever TDF is substituted with AZT, the treating physician shall recognize the fact that Lamivudine is the only active anti-HBV drug in the ART regimen and another agent active against hepatitis needs to be considered according to the guidance provided under NVHCP; a timely referral, therefore, to model treatment centres under NVHCP at early stage of diagnosis will help ensure the continuity of appropriate management.

Notes: Hepatic flares typically present as an unexpected increase in ALT/AST levels and symptoms of clinical hepatitis (fatigue, nausea, abdominal pain and jaundice) within 6–12 weeks of commencing ART. The flares may be difficult to distinguish from ART-induced hepatic toxicity. Drugs active against HBV should preferably be continued during a suspected flare. If it is not possible to distinguish serious hepatitis B flare from grade 4 drug toxicity, ART should be stopped until the patient stabilizes.

This treatment strategy has achieved high rates of HBV DNA suppression (90 %), HBeAg loss (46%) and HBsAg loss (12%) in HBeAg-positive patients after 5 years of treatment, without evidence of resistance, and has reduced progression to cirrhosis with no significant differences in the response in those with or without HIV co-infection. Till date, no viral resistance to Tenofovir in vivo has been described, although resistant strains have been identified in vitro. Although the risk of developing cirrhosis is negligible in HBV/HIV-coinfected persons on long-term Tenofovir combined with lamivudine therapy, the risk of hepatocellular carcinomas persists, but is low.

If ARVs need to be changed because of HIV drug resistance or some drug toxicity, then Tenofovir and lamivudine should be continued together with the new ARV drugs unless TDF is specifically contraindicated due to its toxicity.

Prevention of Hepatitis B Infection

The risk of HBV infection may be higher in HIV-infected adults, and therefore all persons newly diagnosed with HIV should be screened for HBsAg and immunized if not infected. Those already infected with HBV (HBsAg positive) do not require HBV vaccine. PLHIV who have already suffered from HBV in the past and

have developed protective titre of anti-HBs antibody (>10 mIU/ml) also do not require HBV vaccine.

Those who are surface antigen negative need to be vaccinated against Hepatitis B besides following other precautions. Response to HBV vaccine is lower in persons with HIV or with a low CD4 count, and a meta-analysis has shown that a schedule of four double (40 µg) doses of the vaccine provide a higher protective anti-HBs titre than the regular three 20 µg dose schedule.

Besides this, all infants born to hepatitis B-positive women need to be immunized within 12 hours of birth (Dose - 0) followed by 1, 2 and 6 months (dose – 10 µg IM) and HBIG – 0.5 ml IM.

HIV and Hepatitis C Co-infection

Viral hepatitis C infection is associated with significant morbidity and mortality. Chronic HCV infection can cause a wide spectrum of liver disease, potentially leading to severe liver damage, including cirrhosis, organ failure and hepatocellular carcinoma. It accounts for nearly 12%–32% of all cases of liver cancer and 10%–20% cases of cirrhosis of liver, both of which have high treatment costs and poor outcomes.

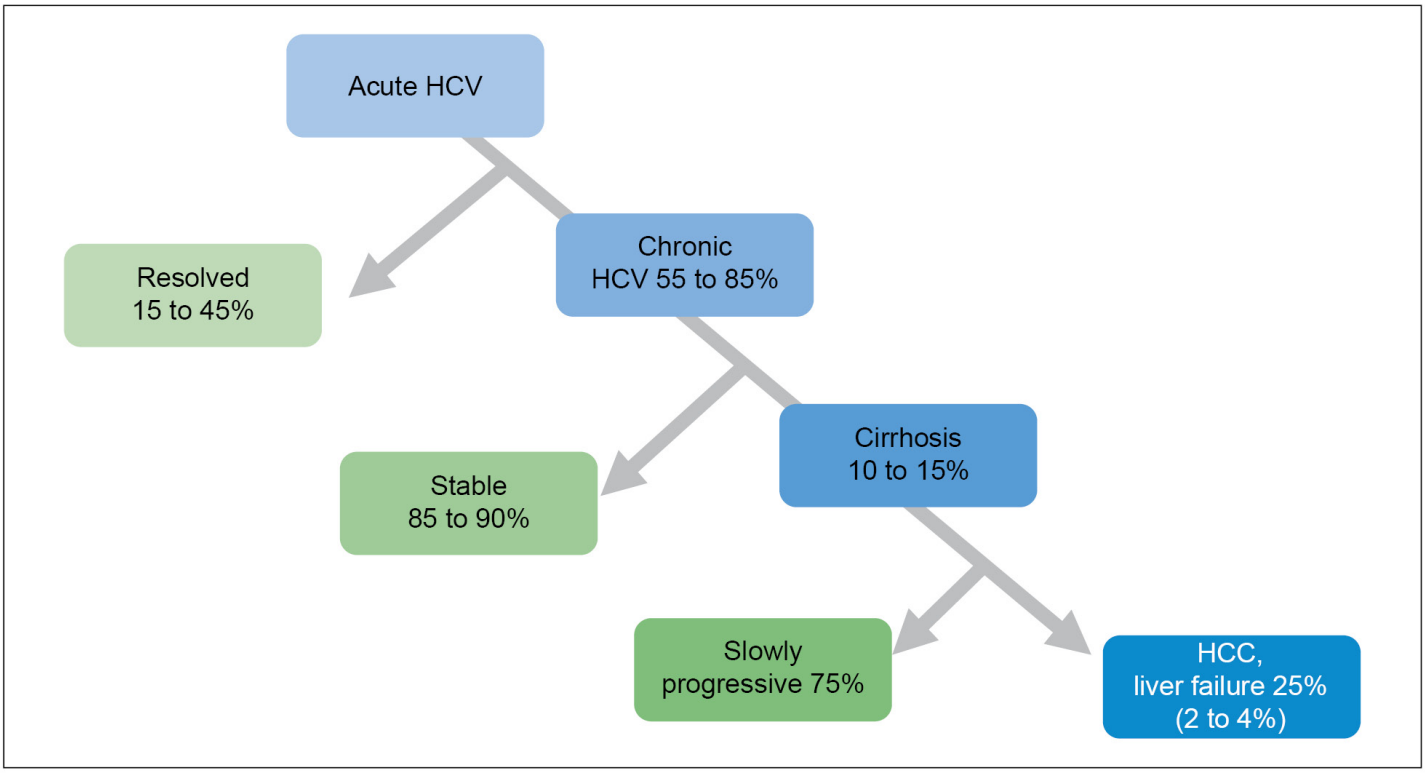
Globally, an estimated 580 lakh people may be chronically infected with hepatitis C and nearly 290,000 die each year from HCV-related causes. Around 23 lakh people may be coinfected globally. An analysis from Africa estimated that 5.7% of people with HIV were coinfected with HCV.

In a recent factsheet released by National Viral Hepatitis Surveillance Programme, it was estimated that based on NFHS 4 samples, National seroprevalence of hepatitis C was 0.32% (0.28–0.36). Currently, there are no country endorsed numbers for the disease burden. However, based on small studies and meta-analysis of HCV, it is estimated that a broad range of 52–130 lakh people may be infected with hepatitis C.

Because of shared routes of transmission, certain groups, in particular persons who inject drugs (PWID) have high rates of co-infection with HIV and HCV. Globally around 67% of PWID are infected with HCV. Other high-risk groups are those who have a high frequency of injections and a low level of infection control, transmission from HCV-infected mothers and people with HCV-infected sexual partners. People with HIV infection, in particular MSM, are at increased risk of HCV infection through unprotected sex. Tattoo recipients have higher prevalence of HCV compared with people without tattoos.

HCV causes both acute and chronic hepatitis. Infection with HCV is usually clinically silent and is only very rarely associated with life-threatening disease. Spontaneous clearance of acute HCV infection occurs within 6 months of infection in 15%–45% of infected individuals in the absence of treatment. Almost all the remaining 85%–55% of people (WHO website. https://www.who. int/news-room / fact-sheets / detail/hepatitis-c) will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection (Figure 5.2.1). Anti-HCV antibodies develop as part of acute infection and persist throughout life. In people who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of the virus, is needed to confirm the diagnosis of chronic HCV infection.

Figure 5.2.1: Natural history of HIV/HCV co-infection



Natural History of HIV/HCV Co-infection

The natural history of both diseases is affected when a person is coinfected with both HIV and hepatitis C; this has implications on the management of both diseases. Co-infection with HIV adversely affects the course of HCV infection, and coinfected people, particularly those with advanced immunodeficiency (CD4 count <200 cells/mm^3) have significantly accelerated progression of liver disease to cirrhosis, decompensated liver cirrhosis and Hepatocellular carcinoma than HCV mono-infected persons. Furthermore, even among patients in whom ART leads to successful control of HIV infection (i.e., undetectable HIV viral load), the risk of hepatic decompensation among coinfected patients is higher than among patients with HCV mono infection. In people with HIV infection, Hepatocellular carcinoma tends to occur at a younger age and within a shorter time. For these reasons, all people with HIV/HCV co-infection should be considered for HCV treatment.

The natural history of HIV is also affected by co-infection with HCV. Two large European cohorts have shown that after ART initiation, CD4 recovery was impaired in HIV/HCV coinfected persons when compared to those infected with HIV alone. HIV/HCV coinfected people also demonstrated more rapid HIV disease progression compared to those who were HIV infected alone and had impaired recovery of CD4 cells.

It is recommended to screen all PWID (IDUs), those with history of multiple blood/blood product transfusion, or those with raised liver enzymes (ALT) more than two times the ULN or based on strong clinical suspicion. There are additional risk groups identified under NVHCP that should be prioritized. The test used detects anti- HCV antibodies. However, since anti-HCV antibodies develop as part of acute infection, they persist throughout life. Among those infected, 40% may clear the virus but will still have persisting antibodies. Hence, in persons who have anti-HCV antibodies, a nucleic acid test (NAT) for HCV RNA, which detects the presence of the virus, is needed to confirm the diagnosis of chronic HCV infection.

Evaluation of HIV and HCV Coinfected People

The assessment of those with HCV HIV includes clinical evaluation: history, physical examination for jaundice, hepatosplenomegaly, ascites, cirrhosis/decompensation and laboratory tests including LFT, prothrombin time, complete haemogram, AFP, etc. Other tests required are abdominal ultrasound,

endoscopy, assessment of liver fibrosis (APRI/ FIB-4/FibroScan), described earlier in the chapter, and HCV RNA quantitative assay.

Treatment of HIV and Hepatitis C Co-infection

Treating HCV-infected people in the past with interferon and ribavirin combination therapy was very difficult, as many patients had to discontinue treatment due to side effects such as depression, weight loss, severe anaemia, thrombocytopenia and neutropenia. Furthermore, sustained virological response (SVR) rates in patients with co-infection were lower than among HCV mono-infected patients.

The advent of newer drugs, Directly Acting Antivirals (DAA), for HCV treatment has revolutionized the management of HCV. The results of treatment with DAAs in people with HIV co-infection are comparable to those with HCV mono-infection. Thus, DAA therapy has substantially simplified the treatment of persons with HIV and HCV co-infection. There are a fewer drug–drug interactions between DAAs and ARV medicines. SVR rates with DAA-based therapy among people with HIV co-infection are comparable to those without HIV infection.

The NVHCP provides free evaluation and treatment for all people infected with HCV, including PLHIV Hence, all PLHIV should be linked to the treatment/model treatment centres under NVHCP, many of which would be within the same institution as the ART centre.

The diagnostic algorithm for hepatitis under the NVHCP addresses the fact that hepatitis can present as acute or chronic. The diagnostic algorithms are given in Figures 5.2.2 and 5.2.3.

Figure 5.2.2: Testing algorithm for viral hepatitis in patients with jaundice

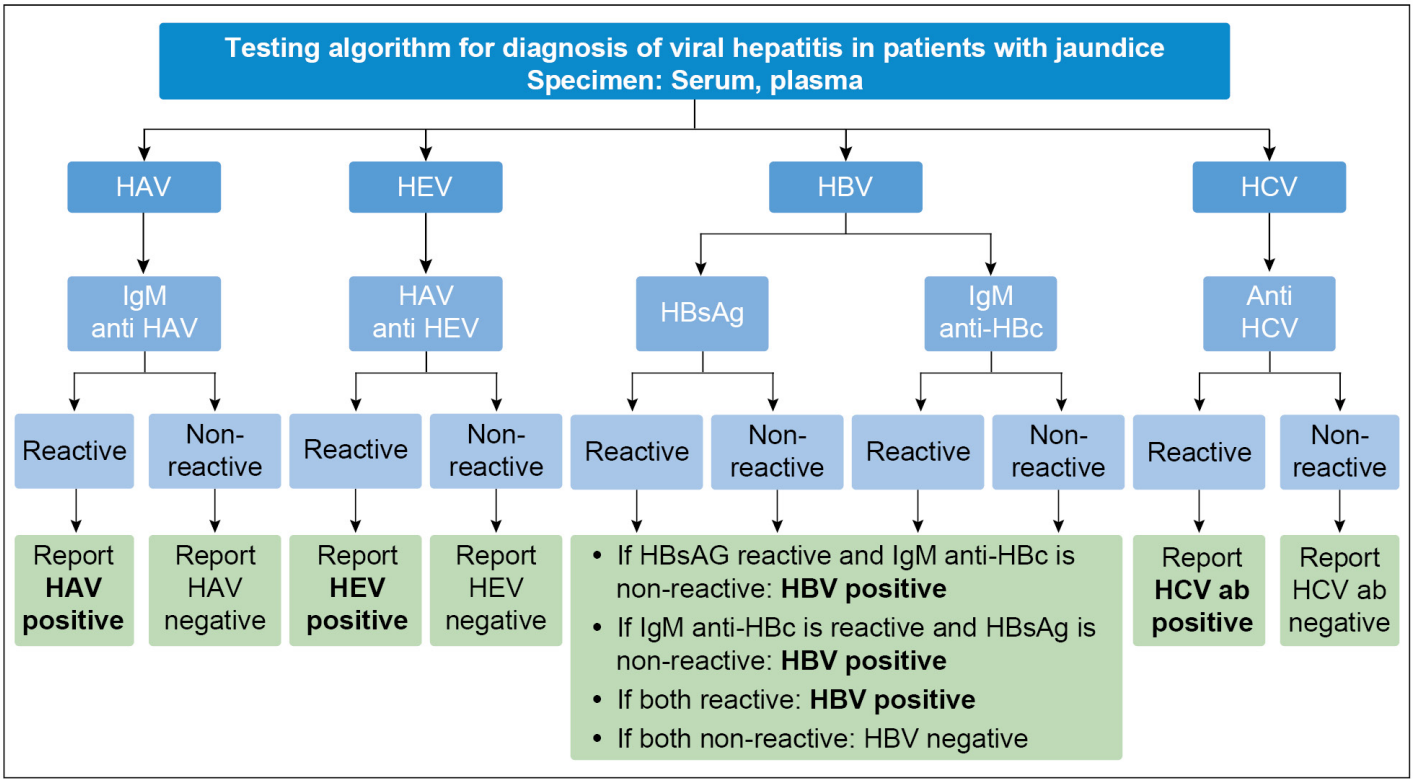
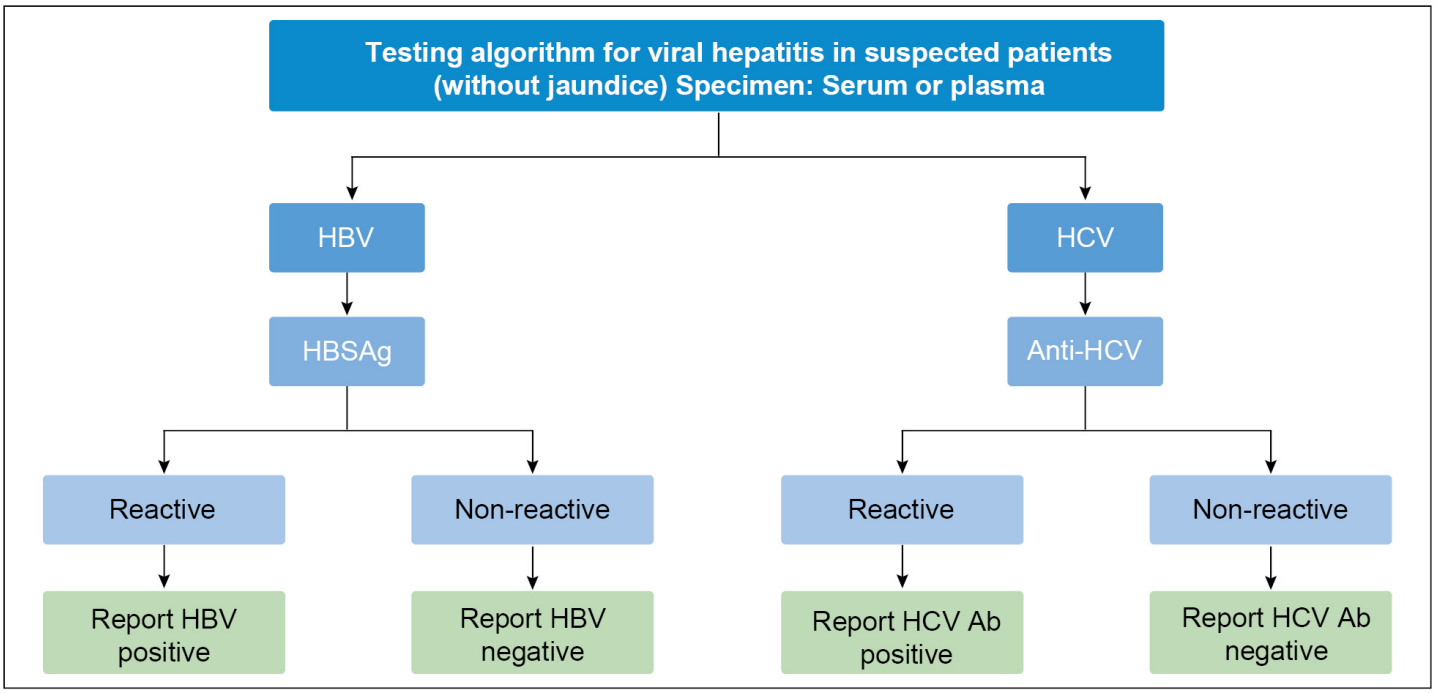


Figure 5.2.3: Testing algorithm for viral hepatitis in suspected patients without jaundice



The following drugs are currently available under the NVHCP for management of hepatitis C:

1. Sofosbuvir
2. Daclatasvir
3. Velpatasvir
4. Ribavirin

Treatment is currently recommended for individuals older than 18 years of age, and the place and choice of regimen is influenced by stage of disease (cirrhosis or no cirrhosis) and other comorbidities or complications.

All treatment-naive patients for hepatitis C, without cirrhosis and complications (these account for more than 80% cases) are managed at designated treatment centres under NVHCP while the complicated cases and re-treatment cases are managed at Model Treatment centres under the NVHCP.

The following algorithm provides guidance on selection of regimen and the duration in treatment- naive patients of hepatitis C under NVHCP.

Figure 5.2.4: Management approach in HIV-HCV co-infection

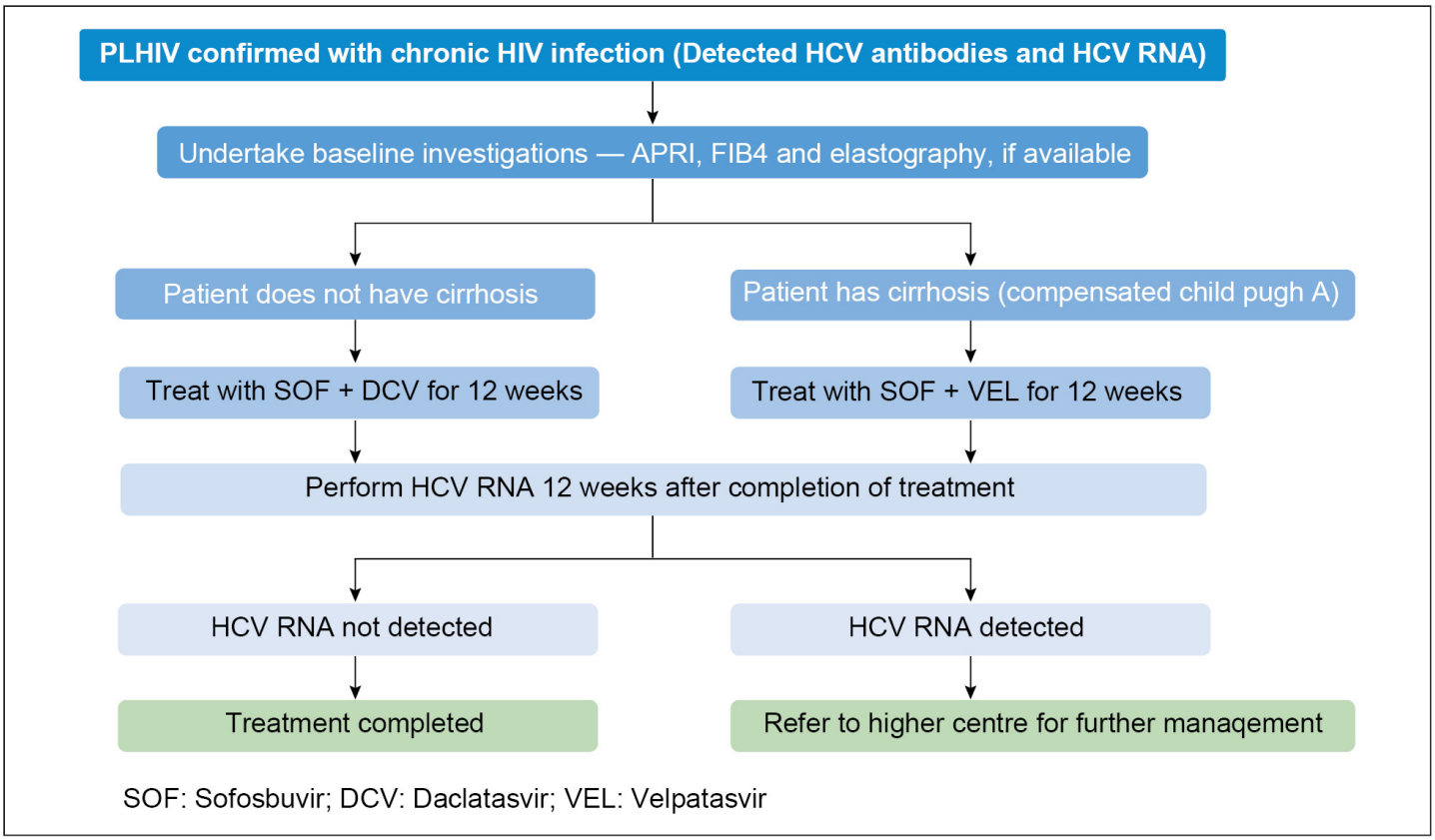


Table 5.2.2: Recommended regimens under NVHCP

Regimen Type	Category of Patients	Regimen Recommended	Duration of Treatment
I	Patient without cirrhosis (uncomplicated)	Sofosbuvir (400 mg) + Daclatasvir (60 mg) *	84 days (12 weeks)
II	Patient with cirrhosis compensated (Child-Pugh A)	Sofosbuvir (400 mg) + Velpatasvir (100 mg)	84 days (12 weeks)
III	Patient with cirrhosis decompensated (Child-Pugh B and C)**	Sofosbuvir (400 mg) + Velpatasvir (100 mg) & Ribavirin 600-1200 mg**)	84 days (12 weeks)
		In Ribavirin-intolerant patients Sofosbuvir (400 mg) + Velpatasvir (100 mg)	168 days (24 weeks)

*Dose adjustments may be required in PLHIV, renal inefficiency, etc.
**Refer to model treatment centre (MTC)

In general, clinical stabilization of HIV disease with ART is advisable before starting treatment for HCV, especially for people with advanced immunosuppression (CD4 count below 200 cells/mm^3).

While the DAA for treating hepatitis C infection have revolutionised treatment outcomes, it is important to bear in mind that there are important drug interactions between ARV drugs and DAA. These are summarized in Table 5.2.3.

Table 5.2.3: Drug Interactions

Selected HIV Drugs	Daclatasvir	Sofosbuvir	Ledipasvir/ Sofosbuvir	Sofosbuvir / Velpatasvir
3TC	√	√	√	√
ABC	√	√	√	√
FTC	√	√	√	√
TDF	√	√	√ Monitor for TDF toxicity	√ Monitor for TDF toxicity
Unboosted ATV	√	√	√	√
ATV/r or	√ Reduce DCV dose to 30 mg/day	√	√ If PI/r or PI/c used with TDF, increase concentration of TDF expected, Monitor TDF-associated toxicity	√ If PI/r or PI/c used with TDF, increase concentration of TDF expected, Monitor TDF-associated toxicity
DRV/r or	√	√		
LPV/r	√	√		
EFV	√ Increase DCV dose to 90 mg/day	√	√ If used with TDF, monitor for TDF toxicity	x
NFV	√ Increase DCV dose to 90 mg	√		x
RAL	√	√	√	√

√ ARV agents can be used concurrently; X ARV agents not recommended
Ref: National Guidelines for Diagnosis and Management of Viral Hepatitis, 2018, NVHCP, MoH & FW, India.

The decision to start ART among people coinfected with HCV should follow the same principles as for HIV mono infection. The ARV regimen for new initiation remains the same, Tenofovir, Lamivudine and Dolutegravir in single-pill FDC for adults and adolescents. Potential harmful effects of ARV drugs include their hepatotoxic effects. However, the highest rates of hepatotoxicity have been observed with ARV drugs that are no longer commonly used or recommended, including stavudine, didanosine, nevirapine or full-dose ritonavir (600 mg twice a day). For most HIV–HCV coinfected people, including those with cirrhosis, the benefits of ART outweigh the concerns regarding drug-induced liver injury.

Monitoring of Therapy in People with HIV–HCV co-infection

Regular monitoring of liver and renal functions is required when using DAA and ARV drugs together. Additional monitoring of liver function is recommended in people with cirrhosis, including albumin, bilirubin and coagulation tests. People with evidence of neutropenia, thrombocytopenia and anaemia require monitoring every 1-2 weeks.

Prevention of HCV Infection in HIV-positive People

There is no effective HCV vaccine and PPTCT (PMTCT) protocol for prevention of hepatitis C. The prevention of HCV infection among IDUs needs to be done by strict maintenance of disposal of needle, syringe, sharps etc. at healthcare settings and safe sexual behaviours.

For further details on technical information regarding Hepatitis B and C, and for detailed operational framework of NVHCP, one may refer to the following documents:

1. National Centre for Disease Control Directorate General of Health Services (Ministry of Health & Family Welfare) National Programme for Surveillance of Viral Hepatitis.Seroprevalence of Hepatitis B and Hepatitis C (Based on National Family Health Survey-4)-Fact sheet 2021
2. National Guidelines for diagnosis and management of Viral Hepatitis, 2018, NVHCP, MoH & FW, India.
3. Technical Guidelines for Diagnosis and Management of Hepatitis B, 2019, NVHCP, MoH & FW, India.
4. National laboratory guidelines for testing of viral hepatitis, 2018, NVHCP, MoH & FW, India..
5. National Action Plan: Combating Viral hepatitis in India, 2019, NVHCP, MoH & FW
6. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021.

5.3 HIV and Leishmaniasis Co-infection

Introduction

Leishmaniasis is a vector-borne neglected tropical disease caused by more than 20 species of the protozoan parasite Leishmania. It can present as a severe systemic form, Visceral leishmaniasis or Kala-azar, mucocutaneous leishmaniasis and cutaneous leishmaniasis

Epidemiology

An estimated 50,000 to 90,000 new cases of Visceral Leishmaniasis occur worldwide annually. In 2018, >95% of Visceral leishmaniasis new cases that were reported to WHO occurred in 10 countries: Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan. Annually 6–10 lakh new cases of cutaneous leishmaniasis (CL) occur worldwide. Over 90% of mucocutaneous leishmaniasis cases occur in Bolivia, Brazil, Ethiopia and Peru.

In India, the burden of disease is mainly due to Visceral Leishmaniasis and is endemic in 54 districts in the eastern states of India, namely, Bihar, Jharkhand, Uttar Pradesh and West Bengal with an estimated 1654 lakh population at risk in these four states. The state of Bihar majorly accounts for approximately 80% of cases. Cutaneous Leishmaniasis occurs in small pockets of Rajasthan, Himachal Pradesh and Kerala.

Leishmaniasis is transmitted by infected sand flies. The vectors are Phlebotomus in the Old World and *Lutzomyia* in the New World and the responsible protozoan parasite for Visceral leishmaniasis is *Leishmania donovani* complex. The parasite primarily infects reticuloendothelial system and may be found in abundance in bone marrow, spleen and liver. L. donovani is mainly present in the Indian subcontinent and Africa and L. *infantum* (chagasi) in Europe and New World.

Visceral Leishmaniasis

The core clinical features of Visceral Leishmaniasis are fever, anaemia, weakness, weight loss and splenomegaly. The lymph nodes are not very large, 1 to 2 cm maximum diameter, mainly in the groins or epitrochlear. Fever occurs in the late afternoon/evening, usually without rigors. There is often a soft cough. Watery diarrhoea is common. Many patients have a history of epistaxis. The spleen is soft at the start of the disease, later it can become quite hard. It is not tender unless a splenic infarct, bleed or abscess are complications (all very rare).

The incubation period is between10 days to over a year after infection, but more typically between 2 and 6 months. The patient with Kala-azar becomes debilitated due to anorexia, anaemia and protracted fever. The bone marrow and spleen involvement cause anaemia, leukopenia (neutropenia and lymphopenia) and thrombocytopenia (resulting in bleeding). The enlarged spleen (Figure 5.3.1) is not functional and causes further immune suppression. Hypoalbuminaemia results from malnutrition, and liver impairment (with jaundice) occurs in late-stage disease.

Figure 5.3.1: Visceral Leishmaniasis



Image courtesy: CoE, BHU, Varanasi

The skin becomes dry, thin and scaly and hair may be lost. Light-coloured people show greyish discolouration of the skin of hands, feet, abdomen and face, which gives the Indian name Kala-azar the meaning ‘black fever’ Anaemia with emaciation and gross splenomegaly produces a typical appearance of the patients.

Patients with Kala-azar are severely immunocompromised. Death occurs from opportunistic or concomitant infections such as pneumonia, dysentery, malaria, TB, viral influenza, measles and septicaemia; or from the effects of anaemia (heart failure) or bleeding (internally or externally). Without treatment, all or almost all Kala- azar patients die.

Post-Kala-azar dermal leishmaniasis (PKDL) is usually a sequel of Visceral Leishmaniasis that appears as macular, papular or nodular rash usually on face, upper arms, trunk and other parts of the body (Figure 5.3.2). It occurs mainly in East Africa and on the Indian subcontinent, where 5%–10% of patients with Kala-azar are reported to develop the condition. It usually appears 6 months to 1 or several years after Kala-azar has apparently been cured but can occur earlier. People with PKDL are considered a

potential source of Leishmania infection. It requires treatment and it is worth mentioning here that PKDL forms of Sudan heal spontaneously and rarely require treatment.

Figure 5.3.2: Nodular lesions (PKDL)



Image courtesy: CoE, BHU, Varanasi

HIV–Visceral leishmaniasis Co-infection

Leishmania amastigotes have evolved strategies to survive and multiply within macrophages, which are enhanced by HIV co-infection and accelerate progression of disease[1]. This also explains why the risk of developing Visceral leishmaniasis is estimated to be between 100 and 2300 times higher in HIV-infected individuals than in those who are HIV negative.[2] Data on the prevalence of HIV–Visceral leishmaniasis co-infection in India is scarce, although estimates range from 2–5.6%[3].

Coinfected patients with high parasite burden are a source of infection for sandfly vectors and they would also act as reservoirs; so it is very important to diagnose them early and start treatment.

Clinical manifestations of coinfected patients are similar to those of immunocompetent ones. However, as coinfected patients have some immunological characteristics, clinical manifestations of these patients may differ from those not infected with HIV, becoming a challenging diagnosis because of a similarity with other OIs. Clinical features are like what has been mentioned in the Visceral leishmaniasis part, but atypical presentations are also common in HIV–Visceral leishmaniasis owing to immune suppression. When coinfected patients present to clinical settings with amastigotes in unusual sites (GI and oral mucosa, skin, pleura, pericardium, lymph nodes, KS lesions and the respiratory tract), atypical manifestations are frequently observed. This fact contributes to misdiagnosis with other OIs or later diagnosis of Visceral leishmaniasis, culminating in poor outcomes for the coinfected.[4,5]

HIV-associated leishmaniasis has five major clinical characteristics:[6]

1. Parasitic dissemination, to the skin in diffuse Cutaneous Leishmaniasis, or throughout the reticuloendothelial system in visceral and visceralizing syndromes. It has been suggested that almost every organ containing phagocytic cells may eventually become infected by *L. donovani.*[7]
2. Atypical locations, as a consequence of this parasitic dissemination and a defect in cell-mediated immunity
3. A chronic and relapsing course,[8] with each patient typically experiencing two or three relapses despite proper treatment
4. Poor response to standard therapy[9]
5. Lack of anti-Leishmania antibodies, which is seen in many endemic areas.[10] The common

differential diagnoses in PLHIV are histoplasmosis, disseminated mycobacterial infections and lymphoma.

Diagnosis

Standard Kala-azar case definition:

- A 'suspect' case: history of fever of more than 2 weeks with splenomegaly and hepatomegaly not responding to antimalarial and antibiotics in a patient from an endemic area (domicile of North Bihar, Eastern Uttar Pradesh and Gangetic West Bengal) or
- A patient with above symptoms clinically examined by doctor and found positive on screening with rapid diagnostic test (RDT) or
- In cases with past history of Kala- azar or in those with high suspicion for Kala-azar with negative RDT result but found positive by examination of bone marrow/ spleen aspirate for Leishmania Donovani bodies at appropriate level (district hospital)
- Tissue specimens such as from skin sores (for Cutaneous Leishmaniasis) or from bone marrow/spleen (for Visceral Leishmaniasis): Leishmania Donovani bodies (as shown in Figure 5.3.3).

Figure 5.3.3: Splenic smear - Numerous Leishman-Donovan bodies inside a macrophage. In centre the round pink structure is the nucleus of the macrophage (Visceral leishmaniasis))

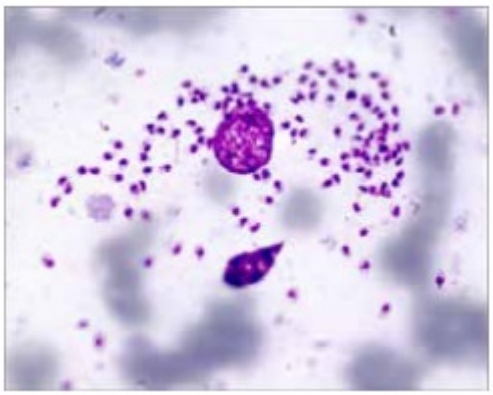


Image courtesy: CoE, BHU, Varanasi

Table 5.3.1: Management of visceral leishmaniasis

Recommended treatment regimens for visceral leishmaniasis	• Liposomal Amphotericin B: 10 mg/kg as a single dose by infusion • Combinations -10 days of intramuscular paromomycin11mg per kg body weight together with 10 days of oral Miltefosine. • Miltefosine after meals for 28 days ▪ For children aged 2–11 years, 2.5 mg/kg per day. ▪ For weight <25 kg –50mg/day. ▪ For 25–50 kg - 100 mg/day in two divided doses) ▪ For > 50 kg body weight, 150 mg/day; for 28 days or • Amphotericin B deoxycholate: 0.75–1.0 mg/kg per day by infusion, daily or on alternate days for 15 doses
HIV-VL Co-infection - Treatment	• Current guidelines—recommend liposomal amphotericin B (L-AmB) as preferred treatment in HIV-VL co infection. L-AmB - 4 mg/kg/day on days 1–5, 10, 17, 24, 31, and 38[11,12]
Post-kala-azar dermal leishmaniasis (PKDL)	• Miltefosine: ▪ Adults >25 Kg -50mg BD for 12 weeks ▪ Adults (>12 years) weighing (less than 25 kg): 50 mg OD for 12 weeks ▪ Children (2-11 years): 2.5 mg/kg once daily after meals for 12 weeks • L-AmB 5mg/kg/day, 2 times/week for 3 weeks – total dose 30 mg/kg • Amphotericin B – 1 mg/kg over 4 months, 60-80 doses
Cutaneous Leishmaniasis	Intralesional antimonial, azoles, cryotherapy

Cutaneous Leishmaniasis

Clinical Manifestations

Cutaneous Leishmaniasis mainly causes skin lesions, whichcan persist for months, sometimes years. The skin lesions usually develop within several weeks or months after the exposure but occasionally appear first years later (for example, in the context of trauma or immunosuppression). The lesions typically evolve from papules to nodular plaques to ulcerative lesions, with a raised border and central depression, which can be covered by scab or crust; some lesions persist as nodules. The lesions usually are painless but can be painful, especially if ulcerative lesions become infected with bacteria or if the lesions are near a joint. The healing process typically results in atrophic scarring.

Cutaneous involvement of Visceral leishmaniasis is a rare finding, but it is characteristic of HIV-related Visceral leishmaniasis. It is seen in 2%–12% of patients with HIV–Leishmania co-infection.[13]
Specimens from skin lesions should be obtained whenever there is a suspicion of leishmaniasis in HIV-infected patients. Unless otherwise demonstrated, any cutaneous specimen yielding Leishmania amastigotes in an HIV-infected patient should be considered, in the first place, as a disseminated form of Visceral leishmaniasis rather than a primary Cutaneous Leishmaniasis.[6,14]

Figure 5.3.4: Ulcerative lesion with raised borders and central depression (Cutaneous leishmaniasis)



Image courtesy: CoE, BHU, Varanasi

Mucocutaneous Leishmaniasis in HIV-positive Patients

Mucocutaneous Leishmaniasis appears in 2%–3% of all cases of HIV-Leishmania co-infection.[15] Practically all the leishmania species can be responsible for Mucocutaneous Leishmaniasis lesions. Although the nasal septum and the soft palate are usually affected by Mucocutaneous Leishmaniasis due to metastasis from a primary lesion, it can also appear as a primary lesion.[16] Nasal biopsy specimens are commonly needed to elucidate a definitive diagnosis of Mucocutaneous Leishmaniasis.

5.4 Management of Sexually Transmitted Infections / Reproductive Tract Infections in PLHIV

Introduction

Sexually Transmitted Infections/Reproductive Tract Infections (STI/RTI) are important public health problems in India. WHO tracks four curable STI: Syphilis, Gonorrhoea, Chlamydia and Trichomoniasis. A community-based STI/RTI prevalence study conducted by ICMR (of 2002–2003) for NACO suggests 5%–6% of the adults in India have one or more STI/RTI, which results in 300–350 lakh episodes of STI/RTI yearly among adults. Data from the STI/RTI Control and Prevention Programme suggests significant decline of bacterial STI (syphilis, gonorrhoea, chancroid) and increasing viral STI (herpes, genital warts, hepatitis B) and significant burden of lower RTI (bacterial vaginosis and candidiasis). Some of the STI/RTI increase the risk of acquiring/ transmitting HIV infection by three to many folds.

Transmission

- A person acquires STI from an STI-infected partner

  Infection can be transmitted through sores/discharge from penis, vagina, anus, rectum, mouth and lips
  Transmission occurs during unprotected sex (vaginal, anal, oral sex)
  From an infected parent to newborn

By using unsterilized medical equipment

- A person develops RTI mostly because of lack of hygiene

  Poor genital/menstrual/coital hygiene
  Medical procedures in and around the reproductive tract without precautions
  Physician intervention e.g., IUD insertion without proper infection control
  Illegal abortions

- RTI are not transmittable to partners whereas STI are, but both infections are mostly seen in and around the reproductive tract area. Hence all STI can be said to be RTI but not all RTI are STI.
- Asymptomatic clients can have STI and can transmit the same to their partners.
- STI are transferred more from men to women as women are receptive and have a larger surface area and longer contact period exposure with pathogens.

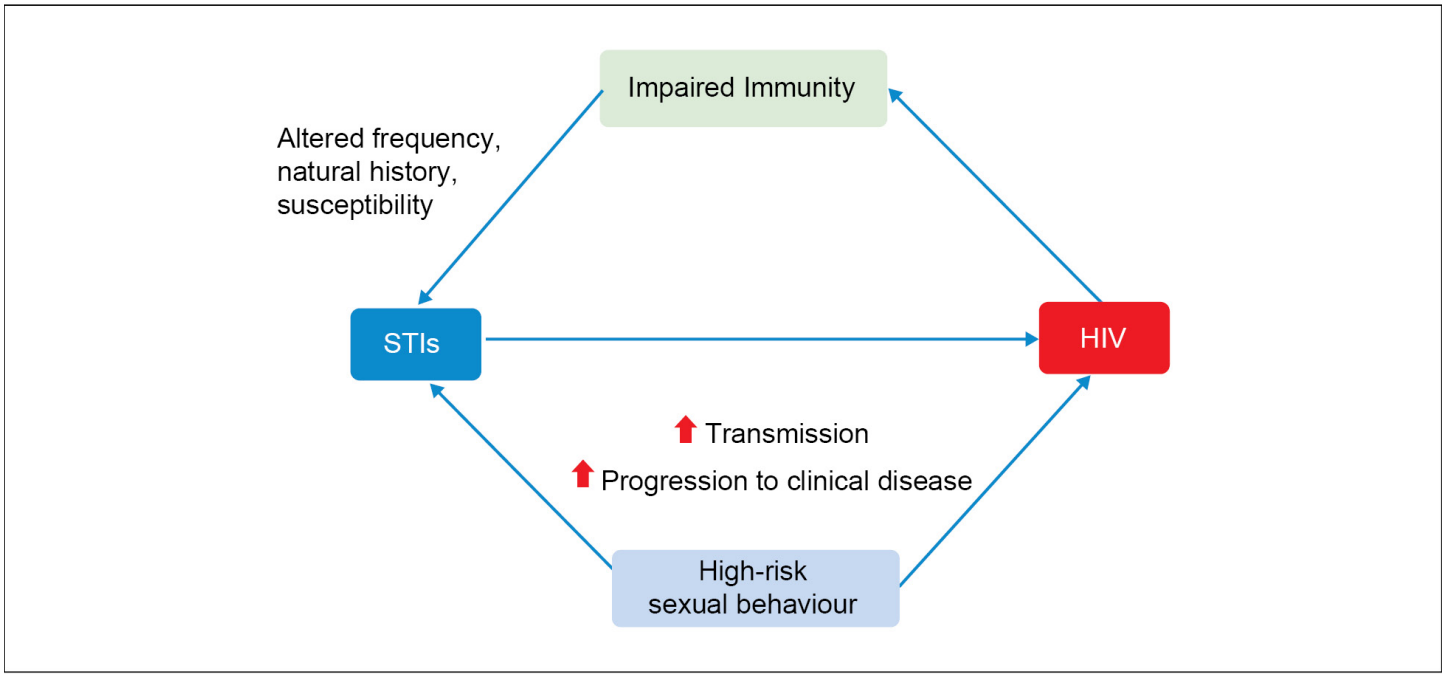
Relationship between STI/RTI and HIV (Cofactor Effects on HIV Acquisition/ Transmission)

- HIV infection is predominantly sexually transmitted in India (94%).
- Presence of STI/RTI increases risk of HIV acquisition/transmission due to

  Loss of epithelial integrity
  Recruitment and activation of inflammatory cells
  Immune dysregulation

- STI/RTI in HIV-positive people can increase viral load.
- A higher viral load increases efficiency of HIV transmission risk to others.

Figure 5.4.1: Interactions between STI and HIV



Impact of STI on HIV (Viral Load)

- Urethral HIV DNA more than doubled when there was also the presence of STI (e.g., gonorrhoea).
- However, treatment of gonorrhoea cuts the urethral HIV DNA in half, almost the same as those without STI, as shown in a study by G. Moss et al.[1]

Table 5.4.1: Impact of STI on HIV (viral load)

Sexually Transmitted Infections	Genital Viral Load
No gonorrhoea	19%
Gonorrhoea pre-treatment	44%
Gonorrhoea post-treatment	21%

Effect of sexually transmitted co-infections on HIV viral load among individuals on ART

Direct evidence about the effects of STI (RTI) co-infection on transmission from individuals on ART is very limited. Available data suggest that the average effect of STI co-infection on HIV viral load in individuals on ART is less than 1 log 10 difference, and thus unlikely to decrease the effectiveness of treatment as prevention.[2] However, there is not enough data to rule out the possibility that particular STI pose a larger threat.

Clinical Manifestations of STI/RTI

Common Symptoms/Signs of STI/RTI in Women

- Excessive/abnormal yellowish/greenish/foul-smelling vaginal discharge
- Itching/rash/sores/blisters/ulcers in genital/peri-anal/oropharynx area
- Swellings in the groin and vaginal area
- Lower abdominal pain
- Frequent urination
- Pain/burning while passing urine
- Pain while having sex (dyspareunia)
- Sore throat

Table 5.4.2: Most common STI/RTI syndromes in women

Symptoms	Syndrome	Common STI / RTI
Vaginal discharge	Vaginal discharge	Trichomoniasis, candidiasis, bacterial vaginosis
Cervical discharge	Cervical discharge	Gonorrhoea, chlamydia, trichomoniasis, herpes simplex
Lower abdominal pain	Lower abdominal pain	Gonorrhoea, chlamydia, mycoplasma, Gardnerella, anaerobic bacteria
Genital /anorectal ulcers	Genital ulcer syndrome	Syphilis, chancroid, genital herpes, (LGV, GV)
Anorectal discharge	Anorectal discharge	Gonorrhoea, chlamydia
Throat irritation	Gonococcal pharyngitis	Gonorrhoea, chlamydia
Genital skin conditions	Genital skin conditions	Genital warts, Molluscum contagiosum, pediculosis pubis, scabies – genital/Norwegian scabies

Common Symptoms of STI/RTI in Male

- Sores/ulcers/blisters in genital/anorectal/oropharynx area
- Swellings in groin and genital area
- Rashes around genital area/anal opening/mouth
- Frequency of urination
- Burning/pain while passing urine/motion
- Discharge from genital/anorectal area
- Inflammation or infection around anus/in rectum
- Sore throat

Table 5.4.3: Most common STI/RTI syndromes in men

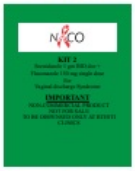
Symptoms	Syndrome	Common STI/RTI
Urethral discharge	Urethral discharge	Gonorrhoea, Chlamydia, Trichomoniasis
Genital ulcers	Genital ulcer	Chancroid, Syphilis, Genital Herpes
Inguinal bubo	Inguinal bubo syndrome	Lymphogranuloma Venerium, Chancroid
Scrotal swelling	Painful scrotal swelling	Gonorrhoea, Chlamydia
Anorectal discharge	Anorectal discharge	Gonorrhoea, Chlamydia
Throat irritation	Gonococcal pharyngitis	Gonorrhoea, Chlamydia
Genital skin conditions	Genital skin conditions	Genital warts, Molluscum contagiosum, Pediculosis pubis, genital scabies – Norwegian Scabies

Syndromic Approach to Treat Common STI/RTI Syndromes

In this section, each syndrome is analysed regarding causative agents, clinical manifestations and syndromic management for the following seven common syndromes associated with STI/RTI:

1. Urethral discharge/Burning micturition
2. Genital ulcer
3. Vaginal discharge
4. Scrotal swelling
5. Lower abdominal pain
6. Inguinal bubo
7. Oral and anal STI

Figure 5.4.2: STI/RTI Syndromic case management

Urethral discharge	Cervical discharge	Painful scrotal swelling	Vaginal discharge	Genital ulcer-non herpetic		Genital ulcer - herpetic	Lower abdominal pain (LAP)	Inguinal bubo (IB)
• Urethral discharge (Pus or muco-purulent) • Pain or burning while passing urine • Increased frequency of urination • Systemic symptoms like malaise, fever	• Nature and type of discharge (quantity, color and odor) • Burning while passing urine, increased frequency • Genital complaints by sexual partners • Low backache (Take menstrual history to rule out pregnancy)	• Swelling and pain in the scrotal region • Pain or burning while passing urine • Systemic symptoms like malaise, fever • History of urethral discharge	• Nature and type of discharge (quantity, color and odor) • Burning while passing urine, increased frequency • Genital complaints by sexual partners • Low backache (Take menstrual history to rule out pregnancy)	• Genital ulcer, single or multiple, painful or painless • Burning sensation in the genital area • Enlarged lymph nodes		• Genital ulcer or vesicles, single or multiple, painful recurrent • Burning sensation in the genital area	• Lower abdominal pain • Fever • Vaginal Discharge • Menstrual irregularities like heavy, irregular vaginal bleeding • Dysmenorrhoea, dysparenunia, dysuria, tenesmus • Lower backache • Cervical motion tenderness	• Swelling in inguinal region which may be painful • Preceding history of genital ulcer or discharge • Systemic symptoms like malaise, fever etc
Tab. Azithromycin 1 gm OD Stat + Tab, Cefixime 400 mg OD Stat	Tab. Azithromycin 1 gm OD Stat + Tab, Cefixime 400 mg OD Stat +	Tab. Azithromycin 1 gm OD Stat + Tab. Cefixime 400 mg OD Stat	Tab. Secnidazole 2 g OD Stat + Cap. Fluconazole 150 mg OD Stat	Inj. Benzathine penicillin (2.4 Ml-I) - 1 vial Tab. Azithromycin (1 gm) - Single dose	**If allergic to Inj. Penicillin:** Doxycycline 100 MG (Bid for 15 days) Azithromycin 1GM (Single dose)	Tab. Acyclovir 400 mg TDS for 7 days	Tab. Cefixime 400 mg OD stat + Tab. Metronidazole 400 mg BDX 14 days + Doxycycline 100 mg BD X 14 days	Tab. Azithromycin 1 gm OD Stat + Tab. Doxycycline 100 mg BD for 21 days
Kit 1/Grey	Kit 1/Grey	Kit 1/Grey	Kit 2/Green	Kit 3/White	Kit 4/Blue	Kit 5/Red	Kit 6/Yellow	Kit 7/Black
								
Treat all recent partners	Treat partners when symptomatic	Treat all recent partners	Treat partners when symptomatic	Treat all sexual partners for past 3 months		No partner treatment	Treat male partners with Kit 1	Treat all sexual partners for past 3 weeks

Important considerations for management of all STI/RTI

- Educate and counsel client and sexual partner/s regarding STI/RTI, safer sex practices and importance of taking complete treatment
- Treat partner/s
- Advise sexual abstinence or condom use during the course of treatment
- Provide condoms, educate about correct and consistent use
- Refer all patients to ICTC
- Follow up after 7 days for all STI, 3rd, 7th, and 14 day for LAP and 7th, 14th, and 21st day for IB
- If symptoms persist, assess whether it is due to re-infection and advise prompt referral
- Consider immunization against Hepatitis B

Syndromic Management[2]

Comprehensive Medical Treatment

- Comprehensive medical treatment
- Follow-up: Return in 3 to 21 days, more frequent if symptoms persist
- Partner treatment: STI need partner/s treatment while RTI does not require partner treatment unless partner is symptomatic
- Rule out presence of other STI (multiple studies in India suggest that about 7% are estimated to be having more than one STI at the time of clinical presentation)
- Voluntary HIV testing and counselling
- Counselling and education on
- Safer sexual practices
- Risk reduction strategies
- Behaviour modification
- Condom promotion and provision
- Proper documentation of STI/RTI
- Regular screening for syphilis, hepatitis B and C (wherever available)

Essential Steps of STI/RTI Syndromic Case Management

1. History taking
2. Clinical examination: Genital/oral and anorectal apart from general examination

3. Appropriate syndromic diagnosis as per syndromic flow charts
4. Minimal laboratory tests, wherever available
5. Early and effective treatment, preferably single dose and directly observed
6. Promotion and provision of condoms
7. Counselling for behaviour change and risk reduction
8. Referral for syphilis screening and HIV counselling and testing
9. Partner/s notification and management
10. Follow-up as per schedule
11. Documentation of case details and laboratory results

Syndromic Management Advantages

This method of management is

- Fast, the patient is diagnosed and treated in one visit
- Relatively inexpensive
- Without need for patient to wait for laboratory results
- All possible STI causing common symptoms and signs are treated
- Scientifically proven strategy in many parts of the world
- Easy to learn and practise by Healthcare Workers
- Can be implemented by Healthcare Providers at all levels of healthcare
- Facilitates standardization of treatment regimens

Limitations

- Not useful in asymptomatic individuals
- Over-treatment
- Cost of over-treatment and side effects
- Potential for antibiotic resistance development
- Poor sensitivity/specificity

Urethral Discharge

Usually, a young adult or adolescent male presents with history of unprotected sex a week before presenting with complaints of purulent urethral discharge. Since there is visible purulent discharge, treat for gonorrhoea and chlamydia as per syndromic flow treatment chart. As this syndrome has the shortest incubation period (ranging from 1 to 7 days), it is considered as a proxy for STI incidence and warrants epidemiological investigation to take site-specific intervention.

Urethral Discharge in PLHIV (in any population or geography) is a surrogate marker for incidence of STI and denotes the following:

Figure 5.4.3: Urethral discharge



- Changing sexual behaviour of PLHIV community
- Presence of an infectious case in community
- Non-use of condom: The patient starts believing that ART is taking care of all his ailments and there is no need to continue protected sexual practices.

Complications

- Epididymitis
- Periurethral abscess
- Urethral stricture
- Prostatitis
- Gonococcal arthritis
- Very rarely disseminated gonococcal infection involving many organs

Use Treatment KIT 1



Tablet Azithromycin 1 g, single dose plus

Tablet Cefixime 400 mg, single dose

Ideally, the medicines should be administered in the presence of healthcare personnel (DOTS) to ensure

compliance and adherence.

Follow-up schedule

3rd and 7th day

Partner Treatment

Contact tracing and treatment wherever possible. Abstinence or use condoms for a week.

Cervical Discharge Syndrome (Cervicitis)

Cervicitis is caused mostly by Neisseria gonorrhoeae and Chlamydia trachomatis while trichomonas, candida and bacterial vaginosis cause vaginitis. Clinical differentiation between the two is difficult. An assessment of the risk status and speculum examination will help in making a diagnosis.

Figure 5.4.4: Cervical discharge



Risk factors associated with cervical infection include the following

- Younger than 21 years of age
- Multiple (more than one) sex partners in the last 3 months
- A new casual sex partner in the last 3 months
- Current sex partner has a sexually transmitted infection
- Recent use of condoms by the partner

Clinical Manifestations

- Yellowish discharge with bad odour or marked
- Erythema of external os
- Nature and type of discharge: quantity, colour, odour
- Burning while passing urine, increased frequency

Use Treatment: KIT 1



- Tablet Azithromycin 1 g, single dose plus
- Tablet Cefixime 400 mg, single dose
- Ideally, the medicines should be administered in the presence of healthcare personnel (DOTS) to ensure compliance and adherence

- Follow-up schedule: 3rd, 7th and 14th day

Partner/s treatment

- Contact tracing and treatment of contacts wherever possible
- Abstinence or use condoms for a week

Painful Scrotal Swelling

A patient presents with pain and swelling in the scrotum, The possible aetiological agents would be gonorrhoea and chlamydia. Treat for both the infections.

The other differential diagnosis that can be thought of are the following:

- Infectious causes of scrotal swelling: TB, filariasis, coliforms, pseudomonas, mumps infection
- Non-infectious causes: Trauma, hernia, hydrocoele, testicular torsion and testicular tumours tumours.

Figure 5.4.5: Scrotal swelling



Clinical Manifestations

- Swelling and pain in the scrotum
- Pain or burning while passing urine
- Systemic symptoms like malaise, fever
- History of urethral discharge

Use Treatment KIT 1



- Tablet Azithromycin 1 g, single dose plus
- Tablet Cefixime 400 mg, single dose dose

Ideally, the medicines should be administered in the presence of healthcare personnel (DOTS), to ensure compliance and adherence

Follow-up schedule: 7th and 14th day

Partner/s treatment

Contact tracing and treatment of partners wherever possible Abstinence or use condoms till resolution of symptoms occurs

Vaginal Discharge Syndrome

Clinical Manifestations

- Vaginal discharge: Cheese white/greenish /frothy mixed
- Assess:
    - Quantity
    - Colour
    - Odour of discharge
- Itching around genitalia

Figure 5.4.6: Vaginal discharge



Use Treatment KIT 2



- Tablet Secnidazole 1 g, two tablets stat plus
- Tablet Fluconazole 150 mg, single dose Follow-up schedule: 7th day

Partner treatment

Only if partner/s is/are symptomatic

Contact tracing and treatment not required

Counselling and education on personal, genital and coital hygiene

Abstinence or use condoms for a week

Genital Ulcer: Non-Herpetic

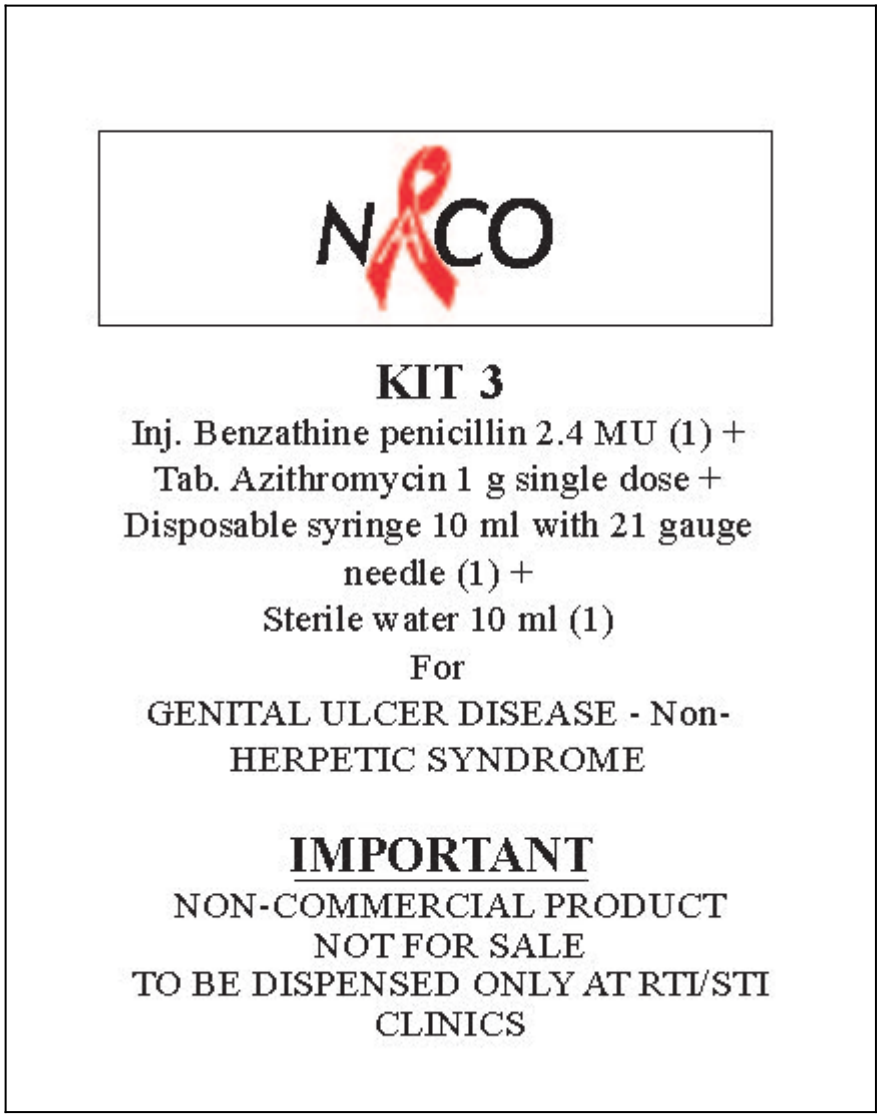
Causative Agents

- Genital ulcer is caused by Treponema pallidum (syphilis), herpes simplex (genital herpes), Haemophilus ducreyi (chancroid), Klebsiella granulomatis (granuloma inguinale) and C. trachomatis (Lymphogranuloma venerum).
- An assessment of the risk status will help in making a diagnosis.
- Syphilitic chancre is usually a single painless ulcer with induration though atypical presentations are common in HIV. Multiple chancres may be present. Onset of lesion is after a sexual exposure with an infected person.
- If there is no suspicion of herpes, then the treatment should cover for syphilis and chancroid.
- If herpes is suspected but not confirmed, then treat for both non-herpetic and herpetic causes.
- On review after a week, if the lesion persists, the patient should be referred.
- Herpetic ulcers are usually painful and multiple. The lesions are initially small vesicles, which break down to form erosions or ulcers.

Clinical Manifestations

- Genital ulcer; single or multiple; painful or painless
- Burning sensation in the genital area
- Burning sensation in the anogenital area
- Enlarged inguinal lymph nodes

Use Treatment KIT 3

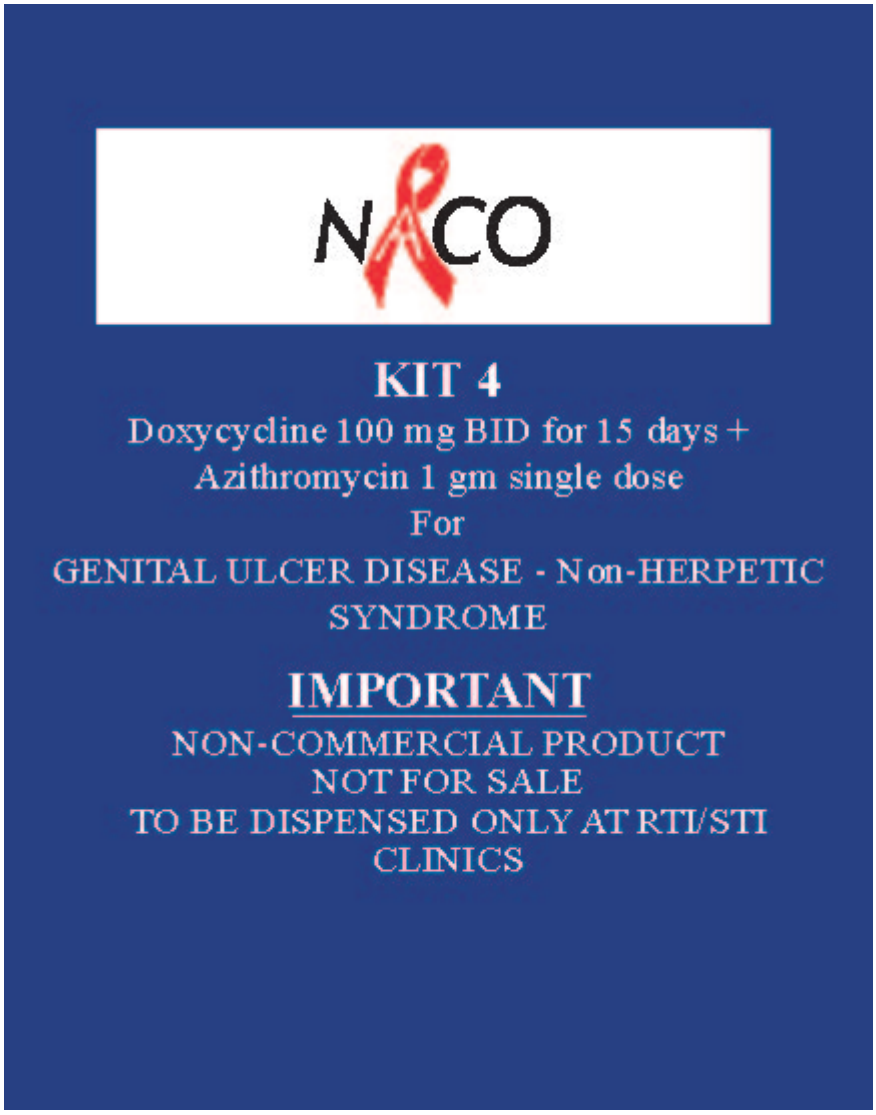


Injection Benzathine Penicillin 2.4 MU given
after sensitivity test plus
Tablet Azithromycin 1 g, single dose

Figure 5.4.7: Non-herpetic genital ulcer



Genital ulcer: non-Herpetic



If patient is allergic to Penicillin, use Treatment KIT 4.

Doxycycline 100 mg bid X 15 days plus
Tablet Azithromycin 1 g, single dose

Syphilis in PLHIV

Although syphilis is uncommon in PLHIV, unusual serologic responses have been observed among PLHIV, who have syphilis. Neurosyphilis should be considered in the differential diagnosis of PLHIV with neurological manifestations. PLHIV should be evaluated clinically and serologically for treatment failure at 6, 9, 12 and 24 months after therapy. CSF and re-treatment also should be considered for persons, in whom non-treponemal test titres do not decrease fourfold within 6–12 months of therapy

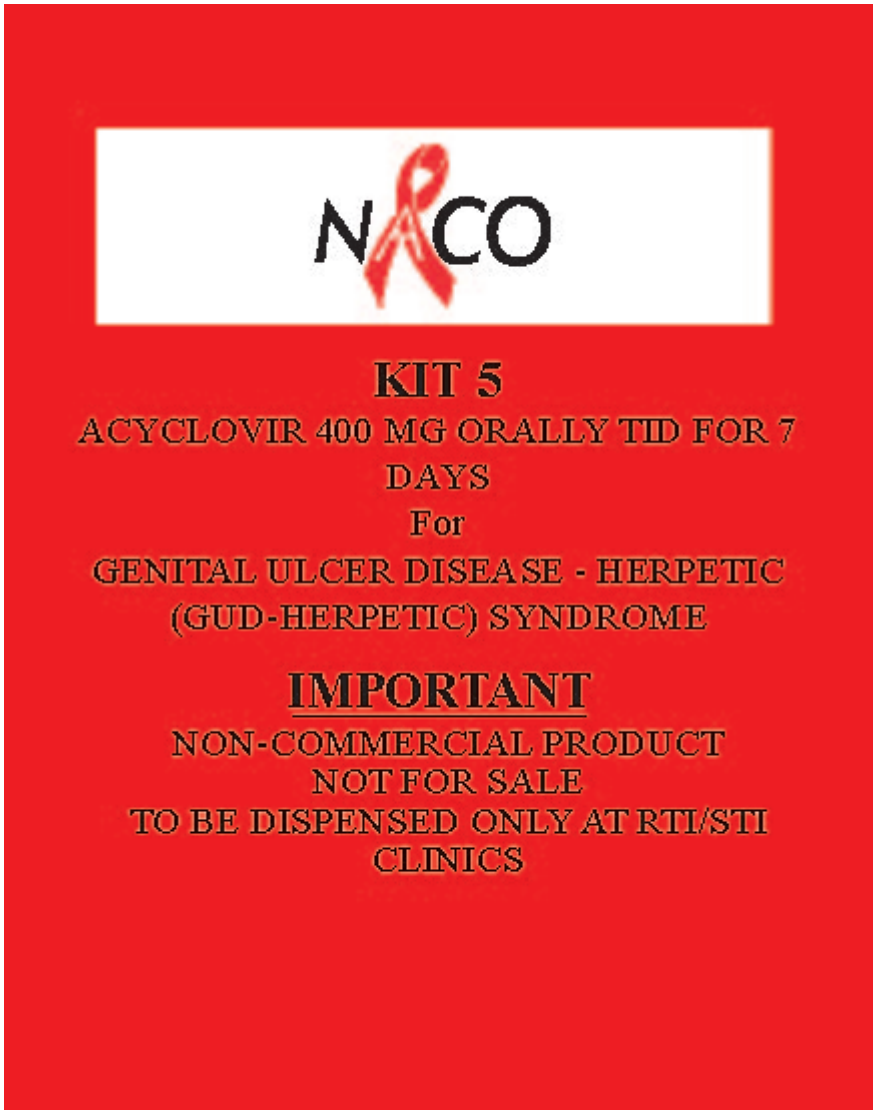
Genital Ulcer: Herpetic

- Herpetic ulcers are usually painful and multiple. The lesions present as small vesicles that break down to form erosions or ulcers. In a patient presenting with a genital ulcer, after confirming that the patient has an ulcer, look for evidence of present vesicles or those in the past. If vesicles are noted, then the patient should be treated for herpes for a week. Recurrence is common.
- Recurrence is common; erupted vesicles are multiple and painful; it can present as multiple genital ulcers with possibility of burning sensation in the genital area.

Figure 5.4.8: Herpetic genital ulcers



Treatment: KIT 5



Tablet Acyclovir 400 mg TDS x 7 days

Partner treatment should be given to those with genital ulcers other than herpes.

The partners of those with herpes should be examined and treated only if symptomatic.

RPR/VDRL test depending on what is available. All reactive samples should be tested for titres. Any

individual with positive titres of more than 1:8 should be followed for an extended treatment and possible treatment failure. High-titre syphilis is a marker of change in sexual behaviour of the community or geography from where the patient has come.

7th and 14th day with repeat serological study to assess the impact of treatment. Patients treated with non-penicillin regimen should be followed for longer period.

MSM and TG should not be treated with Kit 4. Avoid treating pregnant women with non-herpetic genital ulcers with Kit 4, as studies suggest that treatment with Kit 4 may not prevent onward transmission of syphilis from mother to newborn.

Partner treatment

- For herpes, only if partner/s is/are symptomatic.
- Contact tracing and treatment not required
- Counselling and education on safer sexual practices
- Abstinence or use condoms for 2 weeks

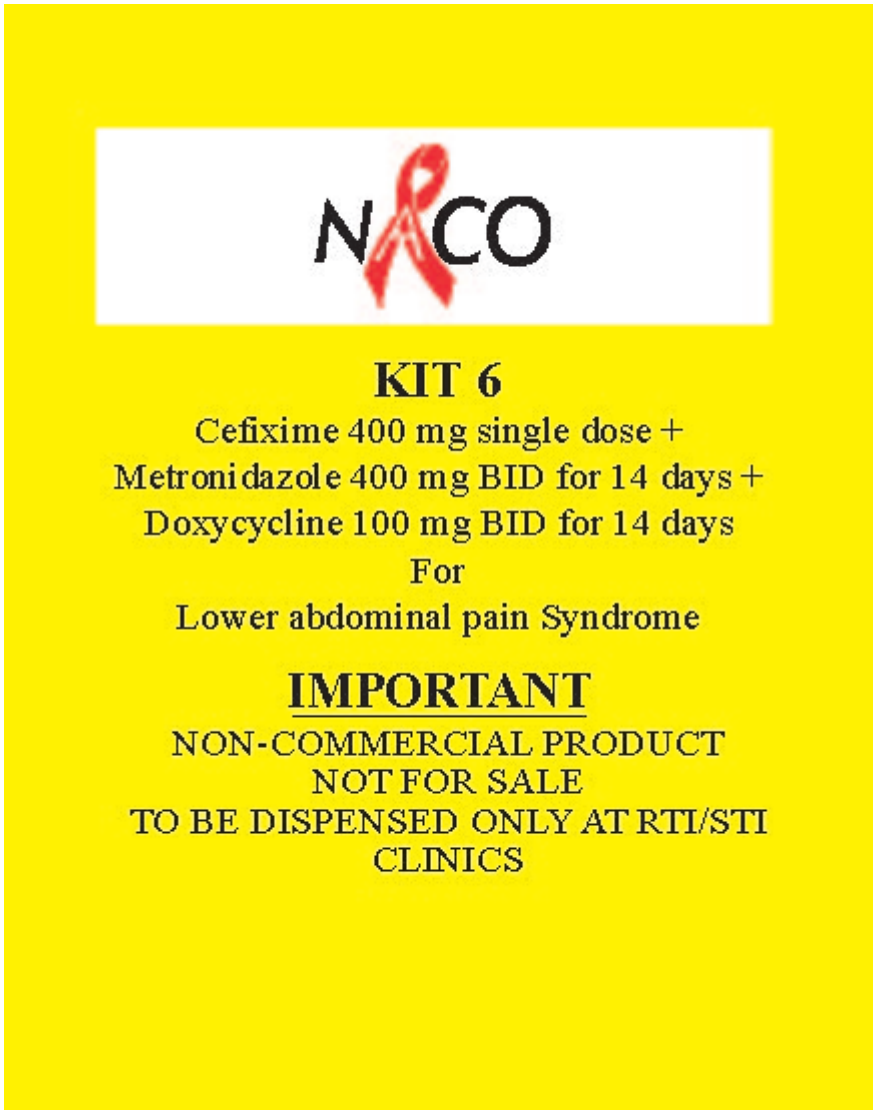
Lower Abdominal Pain

The common infections responsible for lower abdominal pain are gonorrhoea, chlamydia, mycoplasma, Gardnerella and anaerobic bacteria.

Common Symptoms/Signs of Lower Abdominal Pain

- Fever
- Vaginal discharge
- Menstrual irregularities like heavy, irregular vaginal bleeding
- Dysmenorrhoea, dyspareunia, dysuria, tenesmus
- Low backache
- Cervical motion tenderness

Treatment: KIT 6



Tablet Cefixime 400 mg single dose plus
Tablet Metronidazole 400 mg bid X 14 days plus
Tablet Doxycycline 100 mg bid X 14 days

Follow up schedule – 3rd, 7th, 14th and 21st day. If the pain and discomfort have not reduced or relieved at day 3, then the clinical diagnosis needs review.

Partner treatment

- For herpes only if partner/s are symptomatic
- Contact tracing and treatment not required
- Counselling and education on safer sexual practices
- Abstinence or use condoms for 3 weeks

Inguinal Bubo

The common infections responsible for inguinal bubo are lymphogranuloma venerium and chancroid.

- Swelling in inguinal region, which may be painful
- Preceding history of genital ulcer or discharge
- Systemic symptoms like malaise, fever

Figure 5.4.9: Inguinal bubo



Treatment: KIT-7



Tablet Doxycycline 100 mg BD x 21 daysplus
Tablet Azithromycin 1 g single dose
Follow up schedule - 7th, 14th and 21st day

Partner treatment:

- For herpes, only if partner/s is/are symptomatic
- Contact tracing and treatment not required
- Counselling and education on safer sexual practices
- Abstinence or use condoms for 3 weeks
- Aspiration if the bubo shows signs of rupture or break. Try to avoid formation of sinus

Complication of STI/RTI

Untreated or partially treated STI/RTI can cause the following

- **In Women**
- Miscarriage
- Ectopic pregnancy
- Increased risk of cervical cancer
- **In both men and women**
- Infertility
- Increased risk of HIV transmission (5–10 times)
- Late stages of syphilis can affect heart and brain and sometimes cause death
- Disseminated gonococcal infection – carditis/arthritis /synovitis
- **In Men**
- Epididymitis and rectal fistulas, urethral stricture, fistulae
- **In New-born**
- Neonatal syphilis
- Ophthalmia neonatorum

The lesions described under different syndromes depend on the sexual behaviour practices of patients. They may be seen in and around the oropharynx, anorectal or genital area or can be seen at all these sites. Hence a thorough history taking and general examination including physical and internal examination of oropharynx/anorectal/genital areas should be done.

Anogenital Wart

Figure 5.4.10: Anogenital warts



- **Causative Organism:** Human papilloma virus (HPV)
- **Clinical Manifestations:** Single or multiple soft, painless, pink in colour, 'cauliflower-like' growths that appear around the anus, vulvo-vaginal area, penis, urethra and perineum; warts could appear in other forms such as papules that may be keratinized.
- Most of the small warts disappear after initiation of ART, as the immunity improves.

Figure 5.4.11: Effect of ART on HPV lesions



Image courtesy: CoE, BJMC, Ahmedabad

Differential diagnoses

- **Condyloma lata of syphilis**
- **Molluscum contagiosum**

Diagnosis: Clinical diagnosis

ART; most small warts disappear spontaneously as the immunity improves.
Treatment of Large Warts:

Treatment of Large Warts

- Chemical cauterization with 20% Podophyllin in compound tincture of benzoin
- Cryotherapy with liquid nitrogen, solid carbon dioxide or cryoprobe
- Electrocautery
- Surgical excision

Key counselling messages to patients with HPV infection

- Genital HPV infection is very common.
- Many types of HPV are spread through genital contact, during vaginal and anal sexual contact. HPV can also be spread by oral sexual contact.
- Usually HPV infection clears spontaneously, some infections do progress to genital warts, pre-cancers and cancers.
- The types of HPV that cause genital warts are different from the types that can cause anogenital cancers.
- HPV vaccines are available, which offer protection against the HPV types that cause cervical cancer and genital warts.
- People with genital warts should refrain from sexual activity until the warts are gone or removed.

Molluscum Contagiosum

Figure 5.4.12: Cutaneous manifestations of Pox virus



Causative Organism: Pox virus. Facial molluscum and giant lesions are one of the HIV-defining criteria.

Clinical Features

Multiple, smooth, glistening, globular papules of varying size from a pinhead to a split pea can appear anywhere on the body.

- Sexually transmitted lesions on or around genitals can be seen.
- Lesions are not painful except when secondary infection sets in.
- When the lesions are squeezed, a cheesy material comes out.

Diagnosis: Clinical based on the above clinical features

Treatment

- Individual lesions usually regress without treatment in 9–12 months
- Needling followed by chemical cautery with 25% phenol solution or 30% trichloroacetic acid

Ectoparasitic Infections Pediculosis Pubis

Causative organism: Lice – Phthirus pubis

Clinical Features

- There may be small red papules with a tiny central clot caused by lice irritation; general or local urticaria with skin thickening may or may not be present; eczema and impetigo may be present.

Treatment: Recommended Regimen

- Permethrin 1% creme rinse applied to affected areas and washed off after 10 minutes.

Special Instructions

- Re-treatment is indicated after 7 days if lice are found, or eggs observed at the hair–skin junction.
- Clothing or bed linen that may have been contaminated by the client should be washed and well dried or dry cleaned.
- Sexual partner must also be treated along the same lines.

Scabies

Causative Organism: Mite – Sarcoptes Scabiei

Clinical Manifestations

- Severe pruritis (itching) is experienced by the client, which becomes worse at night. Other members of family are also affected.
- Sexual transmission to the partner, other members may get infected through contact with infected clothes, linen or towels.

Figure 5.4.13: Scabies



Complications

- Eczematization with or without secondary infection
- Urticaria

Treatment

- Permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8 to 14 hours
- Benzyl benzoate 25% lotion to be applied all over the body below the neck after a bath for two consecutive nights. Client should bathe in the morning and have a change of clothing.

Special instructions

- Clothing or bed linen that have been used by the client should be thoroughly washed and dried well in the sun.
- Family members and sexual partner must also be treated along the same lines at the same time.

Norwegian scabies

- Crusted scabies, also called Norwegian scabies, is an infestation characterized by thick crusts of skin that contain large numbers of scabies mites and eggs. It is a severe form of scabies that occurs in people who have a weakened immune system.

Treatment

- Treatment of crusted scabies can require oral medications along with multiple applications of a scabicide cream.
- Norwegian scabies is treated with topical permethrin cream and the oral medication ivermectin.
- Safety of Ivermectin in children weighing less than 15 kg and pregnant women is not established. Dose of Ivermectin: Oral drug 200 ug/kg single dose and repeat dose after 2 weeks.

STI Control and Prevention Objectives

- Interrupt the transmission of STI
- Early diagnosis and appropriate treatment
- Prevent complication and sequelae of STI
- Prevent parent to child transmission of HIV/Syphilis
- Reduce HIV infection risk
- Proven in the Mwanza trial[3]

Components of STI Control and Prevention

1. Creating awareness
2. Promoting early health-seeking behaviour
3. Treatment following syndromic case management protocols
4. Ensure compliance to treatment
5. Management of contact tracing and treatment of partner
6. Counselling for behaviour change and education on safer sexual practices
7. Condom promotion and provision
8. Clinical follow-up
9. Documentation and reporting

Condom Promotion Programme

Condom promotion is one of the key prevention strategies of NACP.

- Increase condom use as a barrier protection.

- Increase the number of condoms distributed by social marketing programmes.
- Increase the number of free condoms distributed through STI clinics//ICTC/PPTCT/ART/TI facilities.
- Increase access to condoms and lubricants, especially to MSM, TG.
- Increase the number of commercial condoms sold.
- Increase the number of outlets in strategically located hotspots of solicitation.

For further information on NACO's condom promotion programme, visit http://naco.gov.in/ condom-promotion-programme.

Role of Male Circumcision in Preventing HIV Transmission

- Male circumcision is an important way of reducing the spread of HIV infection.
- According to an important study in sub-Saharan Africa, male circumcision provides up to 60% protection against acquiring HIV infection (95% CI: 32%–76%)

Why is the foreskin more prone to HIV infection?

- Contains more accessible HIV-1 target cells (CD4+ T cells, macrophages and Langerhans cells)
- The Langerhans cells in the foreskin are closer to the epithelial surface, and are the first to be infected by HIV.
- Inner mucosal surface of the foreskin shows greater infectivity than that of cervical tissue, which is a known primary site of HIV-1 acquisition in women causing increased risk of genital ulcer diseases.[4]

5.5 Common Comorbidities in CLHIV

Introduction

At the time of HIV diagnosis, CLHIV may have a variety of clinical manifestations depending on their age and severity of immunodeficiency. These manifestations may involve one or more systems and influence the clinical staging of HIV, ART regimen, as well as the treatment for these conditions per se. This systemic involvement has a direct influence on the health status and mortality and an indirect influence on the ART adherence due to drug interactions and added pill burden. Practically, all the systems may be involved either directly by the HIV virus itself or secondarily to other OIs. Common comorbidities seen in CLHIV are summarized in Table 5.5.1. This section gives a brief description of these comorbidities; details of these are in the other relevant sections and in the manual on the management of OIs.

Table 5.5.1: Common comorbidities in CLHIV at time of diagnosis

System	Manifestations
Infections	TB, bacterial, fungal, viral infections: localized or disseminated (sepsis)
Nutrition	Wasting; Stunting; Vitamin deficiencies
Gastrointestinal system	Recurrent/persistent diarrhoea, oral/oesophageal candidiasis, recurrent/ persistent oral ulcers
Hepatobiliary system	Hepatitis B, hepatitis C, hepatitis due to other organisms
Haematological system	Anaemia, thrombocytopenia
Central nervous system	Delayed development, developmental regression, meningitis due to various bacterial/ viral agents including TB and cryptococcus, HIV encephalopathy
Respiratory system	Recurrent/persistent pneumonia, bronchiectasis, sinusitis, chronic otitis media, lymphoid interstitial pneumonitis (LIP)
Skin and soft tissue	Infections: bacterial/ fungal, nutritional dermatosis, scabies, molluscum contagiosum, herpes zoster, pruritic papular eruptions

Malnutrition

Malnutrition is extremely common in CLHIV. While infants and young children are more likely to present with wasting, older children who may have an intermediate disease progression, are more likely to present with stunting. Malnutrition is an important cause of mortality in CLHIV, especially in the developing world. Assessment of the nutritional status and management of children with malnutrition is detailed in Chapter 3.6 (Nutritional Care of HIV-infected Children). While children with mild/ moderate malnutrition may be managed on an out-patient basis, those with severe acute malnutrition will require admission and therapeutic feeding.

Anaemia and Thrombocytopenia

Anaemia

Anaemia is a condition in which the number of red blood cells is insufficient to meet the body's physiologic needs. The WHO defines anaemia in Table 5.5.2.

Table 5.5.2: Haemoglobin levels to diagnose anaemia

Age	Haemoglobin Level	Severe Anaemia
6–59 months	Hb <11.0 g/dl	Lower than 7.0 g/dl
5–11 years	Hb <11.5 g/dl	Lower than 8.0 g/dl
≥12 years	Hb <12.0 g/dl	Lower than 8.0 g/dl

Source: World Health Organization (2011): Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity; Available at https://www.who.int/vmnis/indicators/haemoglobin.pdf.

Anaemia is present in a large proportion of CLHIV at presentation. The important causes are anaemia of chronic disease and nutritional deficiencies. However, other contributory factors may be present. In a

patient on ART with rapid development of anaemia, Zidovudine-induced marrow suppression is a likely cause. Table 5.5.3 summarizes causes of anaemia in CLHIV.

Table 5.5.3: Causes of anaemia in CLHIV

Decreased production	Increased loss/destruction
• Deficiencies: Iron, B12, folate, erythropoietin • Infections: Malaria, Kala-azar, HIV, CMV, EBV, Parvovirus B19, TB, MAC, Histoplasma • Drugs: Zidovudine, Cotrimoxazole, Amphotericin B • Anaemia of chronic disease • Malignancies: Hodgkin's disease, NHL	• Haemolysis: Auto-immune haemolytic anaemia, pre-existing conditions like thalassemia • GI bleeding: Infections (CMV, candida, parasites), bowel lymphoma • Hypersplenism

Evaluation of CLHIV with Anaemia

History: History gives clues to the cause of anaemia and its severity.

The child usually presents with history of the following:

- Easy fatigability, irritability
- Anorexia, pica, looking pale
- Poor school performance
- Dyspnoea on exertion, palpitations, dizziness, headache

Further, history of the following need to be elicited:

- Blood loss: Epistaxis, melena, per-rectal bleeding due to anal fissure, menstrual losses in an adolescent girl
- Chronic diarrhoea, recurrent jaundice
- Drug intake: Anti-convulsant, zidovudine, Cotrimoxazole
- Repeated blood transfusions: Bleeding disorders, thalassaemia

Past History of chronic infections, liver and renal disease should be ascertained.

Family History of following should be taken:

- Severe anaemia in the family requiring frequent blood transfusions
- Bleeding disorders
- Recurrent jaundice or gall stones usually indicates haemolytic anaemia.

Dietary history is very important as the most common cause of anaemia in children is nutritional anaemia. History of the type of milk given after birth and age at which complementary foods were introduced should be taken as also of pica, which increases the risks of helminthic infection.

Examination: A general head-to-toe examination is essential to look for signs of anaemia, vitamin deficiencies, lymphadenopathy, splenomegaly and signs of congestive cardiac failure.

- Pallor can be assessed by comparing the child’s palm with your own to judge severity of anaemia.
- Presence of jaundice indicates possibility of haemolytic anaemia.

- Tachypnoea, tachycardia, hepatomegaly may indicate congestive heart failure that may accompany severe anaemia.
- Petechial rash, lymphadenopathy, organomegaly point to a lymphoreticular malignancy.
- Angular stomatitis, glossitis, koilonychia and signs of vitamin deficiency may also be present.

Investigations

- Complete blood count (CBC): Haemoglobin value confirms diagnosis of anaemia and its severity.
- Peripheral blood smear gives clues to the type of anaemia:

  Microcytic anaemia is usually due to iron deficiency, but thalassemia is an important differential diagnosis.
  Macrocytic anaemia is most likely to be due to B12 and folic acid deficiency.
  Normocytic normochromic anaemia: Anaemia of chronic infection and acute blood loss
  Pancytopenia: Aplastic anaemia and lymphoreticular malignancies
- Reticulocyte count: Helps in defining the aetiology of the anaemia

  Increased reticulocyte count: Ongoing haemolysis or non-chronic blood loss
  Low reticulocyte count: Bone marrow depression

Management

Evaluation for the type of anaemia and its correction using appropriate therapy are important components of nutritional rehabilitation of CLHIV. Patients with suspected nutritional anaemia/anaemia of chronic disease can be managed by the medical officer at the ART centre. The components of treatment include the following:

Deworming: All CLHIV need to be dewormed once in 6 months. This involves administration of tablet/syrup Albendazole 200 mg single dose for children up to 2 years of age. Children beyond 2 years of age are given a single dose of 400 mg.

Iron/folic acid therapy: Supplement with oral iron at a dose of 3–6 mg/kg/day of elemental iron.

Ferrous sulphate, containing 20% elemental iron, is the most effective and economical oral formulation available as both tablet and syrup. Iron absorption is best when taken on an empty stomach or in between meals. Anaemia usually gets corrected over 2–3 months of treatment; oral iron should however be continued for another 2–3 months to replenish iron stores. Folic acid is usually combined with iron since most formulations of iron contain folic acid as well. Folic acid at a dose of 100–200 g/day is adequate to treat associated folic acid deficiency.

Nutritional Counselling: Mother needs to be counselled to give the child iron-rich food items such as green vegetables, peanuts, jaggery, eggs, chicken etc. Milk and milk products are poor sources of iron.

The following children with anaemia need to be referred to a paediatrician for evaluation:

- Those with severe anaemia with/without congestive heart failure
- Those with megaloblastic anaemia or pancytopenia on haemogram
- Those with clinical features suggestive of haemolytic anaemia or lymphoreticular malignancy
- Those not responding to haematinics

Thrombocytopenia (Platelet count <100,000/mm^3)

Thrombocytopenia is also commonly encountered in CLHIV and may be an initial manifestation of HIV infection.

Aetiologies include the following:

- Immune-mediated platelet destruction
- Thrombotic thrombocytopenic purpura
- Impaired haematopoiesis

Bone marrow studies are needed for evaluation of cause and the child should be referred to a paediatrician for the same. Management is usually the same as in HIV non-infected children. Once causes like malignancy and aplastic anaemia are ruled out, most CLHIV with mild thrombocytopenia will respond to ART itself.

All children with thrombocytopaenia need to be referred to a paediatrician for evaluation.

Hepatic Dysfunction in CLHIV

Hepatomegaly and mildly elevated liver enzymes are common in CLHIV, though chronic/ progressive liver disease is unusual. The causes are as follows:

- Co-infection with viruses (hepatitis A–E, CMV, EBV)
- Co-infection with MAC, cryptosporidium
- Fatty liver
- Drug toxicity

Clinical Manifestations

History: Jaundice, anorexia, nausea/vomiting, fever, right hypochondriac pain, pruritus and pale-coloured stools

Examination: Icterus, hepatomegaly or decreasing span of liver size

Additional features indicating hepatic failure include altered sensorium, irritability, altered sleep patterns, poor feeding, ascites and bleeding manifestations.

The investigations indicated in evaluation of a child with hepatitis are as follows:

1. Liver function tests: (Total/direct serum bilirubin, serum ALT/AST)
2. Enzymes: ALT and AST are usually elevated. Decreasing levels of enzymes, when associated with rising bilirubin, may be an ominous sign indicating severe hepatic damage and the need for urgent and thorough clinical management. Peripheral blood smear for malaria
3. Peripheral blood smear for malaria
4. HBsAg, HCV, HAV testing
5. Blood glucose
6. Prothrombin time

7. Electrolytes (Na, K)

The presence of jaundice (recently onset) is indicative of an acute hepatitis. It is essential to gauge the severity of the dysfunction, i.e., is there hepatic encephalopathy and coagulopathy?

The treatment is mainly supportive and involves the following:

- Remove the potentially offending medication(s) as per the ARV adverse event guidelines.
- If the child is on ATT, institution of modified the anti-tubercular regimen
- Supportive care (monitor, nutrition, rest)
- For hepatic failure, monitor intestinal decontamination, lactulose and neomycin, low protein intake, vitamin K, fresh frozen plasma, antibiotics, correction of dyselectrolytemia, antacids/ H2 blockers, oxygen/ventilation

Presence of hepatitis and its severity and aetiology influence the initiation of ART as well as the drug regimens; many ARV drugs especially Nevirapine and PIs have associated hepatotoxicity.

Chronic Respiratory Morbidities in CLHIV

Chronic sinusitis and chronic otitis media are common and a source of recurrent morbidity in CLHIV. HIV-associated chronic lung diseases include bronchiectasis, lymphoid interstitial pneumonitis and chronic infections. Underlying cardiac disease like cardiomyopathy may also present as respiratory disease.

Bronchiectasis

Bronchiectasis is a disease characterized by irreversible abnormal dilatation of the bronchial tree and represents a common end stage of a number of non-specific and unrelated antecedent events, especially recurrent/persistent pneumonia due to bacterial, mycobacterial, fungal, viral or mixed infections. Bronchiectasis is classified as WHO stage 3 disease. Persistent cough and fever with productive purulent sputum or haemoptysis should arouse suspicion for bronchiectasis. Clubbing is usually present. Chest examination reveals localized signs, which do not easily resolve with the usual antibiotic treatment. CXR may show cystic spaces, occasionally with air-fluid levels and honeycombing. However, these findings are seen in more severe forms. Milder cases will show loss of bronchovascular markings, crowding of bronchi and loss of lung volume.

Bronchiectasis needs careful management. Acute exacerbations need to be treated with adequate antibiotic therapy (2–4 weeks) and postural drainage of sputum. Antibiotics should be carefully chosen to cover a broad spectrum of micro-organisms, including gram-negative bacteria. Attempt should be made to isolate the organism by sputum culture or induced sputum, or secretions obtained through bronchoscopy. TB and LIP may be frequently underlying and need to be looked for. The treatment involves administration of antibiotics during acute exacerbations and bronchodilators. Surgical treatment may be necessary if the symptoms are severe or refractory to medical management and the disease is limited to one segment or a lobe.

Lymphocytic Interstitial Pneumonia

Lymphocytic interstitial pneumonia (LIP), a stage 3 clinical condition is a lymphoproliferative and non-infectious pulmonary disorder that is characterized by diffuse infiltration of CD4 lymphocytes, plasma cells and histiocytes in the alveolar septa and along the lymphatics. It is most common in children infected with HIV, especially those aged >2–3 years. The disease usually has an insidious onset of mild but

persistent cough, with or without exertional dyspnoea, and breathing difficulty. The patients also have associated clubbing. LIP should be suspected if a child does not respond, or if CXR findings persist or worsen despite appropriate antibacterial and anti-tuberculosis treatments. Treatment of LIP includes bronchodilators and corticosteroids (short course for mild intermittent symptoms and long course with slow taper in chronic cases).

While evaluating a HIV-infected child with respiratory symptoms, it should be remembered that the patient may be having more than one clinical entity responsible for his/her symptoms. It is not infrequent for a patient to have TB and bronchiectasis or TB and LIP or LIP and bronchiectasis.

Neurological Morbidities in CLHIV

Neurological involvement in CLHIV is three times more than that in adults with HIV, especially in younger children and infants. Primary involvement of nervous system is seen in 50%–90% of perinatally acquired HIV infection in developing countries. Neurological disease is the first manifestation of HIV infection in approximately 10%–20% of children.

Pathogenesis of Neurological Illness in HIV

HIV enters the brain through infected monocytes and T-lymphocytes that cross the blood–brain barrier. Direct invasion of nerves by the virus causes inflammation, degeneration, disruption of neurotransmission, vasculopathy and demyelination. In children, all these changes occur in an immature brain and hence morbidity is more severe as compared to adults.

Risk Factors for Neurological Involvement in HIV in Children

- Route of transmission: Higher risk of neurological morbidities in children with perinatal transmission
- Severe immunosuppression in child: Results in a high plasma viral load in blood and CSF
- Age of the child: Highest incidence of HIV-related CNS manifestations occurs in the first 2 years of life, with incidence rates of 9.9% in the first year of life, 4.2% in the second and less than 1% in the third year of life and thereafter.
- Presence of other comorbidities: Prematurity, low birth weight, poor nutritional status

Spectrum of Primary Neurological Manifestations:

- HIV-associated encephalopathy (HIVE)
- HIV-associated neurocognitive disorder, which can vary in severity from asymptomatic neurocognitive impairment to severe dementia
- Stroke syndromes

General Principles for Management of Neurological Morbidity

- CNS involvement in CLHIV can be subtle. Assess neurodevelopment and look for red alerts in HIV-infected children, especially infants and toddlers.
- Follow a syndromic approach to identify aetiology. (CNS involvement is diffuse or focal.)
- Neuroimaging can be very useful.
- Early detection of HIV infection through systematic follow-up and evaluation of HIV-exposed infants and timely ART initiation is the key to mitigate CNS insult.
- Effective ART can prevent and to some extent reverse neurological signs and symptoms.

HIV Encephalopathy

HIV encephalopathy is the most common CNS manifestation of paediatric AIDS. It can occur in the first few months of life and may precede signs of immune deficiency and other systemic manifestation of HIV disease.

Table 5.5.4: Neurological manifestations in CLHIV

Younger Children (less than 5 years)	Older Children (5–15 years)

• Global delay in achieving milestones (motor and cognitive)
• Static or regression of milestones
• Acquired microcephaly
• Progressive spastic paralysis
• Pyramidal tract signs
  ▪ Basal ganglia dysfunction (rare)
  ▪ Ataxia
  ▪ Seizures
	• Slow progression or regression of learning milestones
	• Attention difficulties
	• Impaired cognitive functions:
	  ▪ Conversation
	  ▪ Comprehension
	  ▪ Perception and motor activity

HIV encephalopathy is diagnosed if CLHIV have any one of the following signs for 2 months in the absence of demonstrable causative organisms:

First is failure to attain or loss of developmental milestones or loss of intellectual ability. Second is progressive impaired brain growth demonstrated by stagnation of head circumference and the third is acquired symmetric motor deficit manifested by any two of following signs: paresis, exaggerated reflexes, ataxia or gait disturbances.

CT scan of the brain may show cortical atrophy and bilateral basal ganglia calcifications.

MRI films in HIV encephalopathy may show presence of cerebral atrophy, cerebellar atrophy, calcification in the basal ganglia and signs of attenuation of white matter. **Neurocognitive Delays in CLHIV** (Ref: Adolescents living with HIV-UNICEF 2017) HIV encephalopathy, even when arrested by ART, leaves residual cognitive and motor deficits with significant impact on independent mobility and daily living. Even in children without overt HIVE, increased rates of expressive language delay and behavioural difficulties are reported in pre-school children and subtler educational difficulties become more apparent in secondary school-aged children. Frequent association with lack of nurturing, a poor social environment and parental sickness contribute towards overall poor development of these children. Thus, poor school performance and dropping out of school is common.

Management

All HIV-exposed and infected children must undergo routine development assessment at presentation and during follow-up visits. This has been discussed in **Chapter 3.2 (Management of Newly Diagnosed HIV-infection in Children Including ART Initiation)**. A detailed evaluation is needed for children with developmental delay, poor scholastic performance or behavioural issues. They will need a referral to a paediatrician and a psychologist as appropriate. Counselling and support for neurodevelopmental disorders has been covered in **Chapter 3.7 (Counselling for Children and Adolescents Living with HIV).**

Other Comorbidities

Cardiomyopathy

Follow-up of HIV-infected children has shown that all components of the cardiovascular system might be affected during the course of the disease. The reported incidence of cardiac involvement in HIV-infected children varies from 0.9%–14%. It is likely that HIV-related cardiac disease has a multifactorial origin due to HIV, secondary infections, other concurrent disease states, side effects of therapy, nutritional deficiencies or yet-unknown mechanisms.

Dilated cardiomyopathy is the most common cardiac complication of HIV infection in children and is an adverse prognostic indicator in patients with HIV infection. The 5-year cumulative incidence of dilated cardiomyopathy is reported to be as high as 28% in vertically HIV-infected children. Zidovudine has been implicated in the aetiology of cardiomyopathy in these children though its role has not been firmly established. Nonetheless, CLHIV on zidovudine-based ART should be monitored clinically for evidence of cardiac disease.

Early atherosclerosis may be a new emerging disease in HIV-infected children.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a serious disease of the pulmonary arteries characterized by an increase in pulmonary vascular resistance and pulmonary arterial pressure.

Pulmonary arterial hypertension is defined as resting mean pulmonary arterial pressure greater than 25 mm Hg or mean pulmonary artery pressure following exercise that exceeds 30 mm Hg.

The child usually presents with exertional breathlessness due to the inability of the right ventricle to raise cardiac output with exercise. Other symptoms are haemoptysis, chest pain, congestive heart failure, dizziness or syncope and arrhythmias. Chest X-rays may show cardiomegaly and pulmonary artery enlargement. ECG is usually diagnostic with right axis deviation and right ventricular hypertrophy with right axis deviation.

HIV-associated PAH is confirmed only after all other possible causes of PAH have been excluded. Hence all children with signs suggestive of PAH need an urgent referral to a paediatrician.

5.6 Guidelines for the Management of HIV associated Malignancies

Introduction

HIV is associated with an increased risk for many malignancies. While Kaposi Sarcoma, high-grade B-cell Non-Hodgkin Lymphoma and invasive cervical cancer have been designated as AIDS defining malignancies, several other cancers have been found to occur with increased frequency and often with accentuated aggressiveness in PLHIV. Cancers account for approximately one third of all deaths in HIV patients. In fact, HIV patients have a higher risk to die from a tumour than from an AIDS-related infection, with aggressive Non-Hodgkin's Lymphoma as the most frequent event. This guideline aims to summarize the screening and management strategies of the malignancies associated with HIV infection.

Kaposi Sarcoma

Kaposi sarcoma is caused by the Kaposi sarcoma herpes virus (KSHV). Lesions appear most often on the lower extremities, face (especially the nose) and genitalia, with hues including pink, red, purple and brown.

Figure 5.6.1: Kaposi sarcoma



Image courtesy: CoE, RIMS, Imphal, Manipur *CoE, JJ Hospital, Mumbai*

The diagnosis is usually based on the characteristic clinical appearance of cutaneous or mucosal lesions, but histological confirmation is essential. Histopathological grading classifies KS lesions into patch, plaque or nodule. Risk stratification is based on tumour stage (T0/T1), immune status (I0/I1) and systemic illness (S0/S1) (Table 5.6.1). Extra-cutaneous spread is seen in one third, with oral cavity (15%), GI tract (40%) and pulmonary and lymph node involvement. Occult blood in stool is an excellent screening modality and a cherry red nodule on bronchoscopy is strongly suggestive of the diagnosis. Staging of KS includes a complete inspection including oral and genital mucous membranes, an abdominal ultrasound and a chest radiography (exclusion of a pulmonary KS). Gastroduodenoscopy and colonoscopy should be considered when mucous membranes are involved.

Table 5.6.1: Modified AIDS clinical trials group staging of Kaposi's sarcoma

	Good Risk (All of the following)	Poor Risk (Any of the following)
Tumour	**T0 (Good risk): Localized tumour** KS is only in the skin and/or the lymph nodes (bean-sized collections of immune cells throughout the body), and/or there is only a small amount of disease on the palate (roof of the mouth). The KS lesions in the mouth are flat rather than raised.	**T1 (Poor risk):** The KS lesions are widespread. One or more of the following is present: • Oedema (swelling) or ulceration (breaks in the skin) due to the tumour • Extensive oral KS: lesions that are nodular (raised) and/or lesions in areas of the mouth besides the palate (roof of the mouth) • Lesions of KS are in organs other than lymph nodes (such as the lungs, the intestine, the liver, etc.). KS in the lungs can sometimes mean a worse prognosis (outcome).
Immune status	**I0 (Good risk)** CD4 cell count >150 cells/mm^3	**I1 (Poor risk)** CD4 cell count <150 cells/mm^3
Systemic illness	S0 (Good risk): No systemic illness present; all of the following are true: • No history of opportunistic infections (infections that rarely cause problems in healthy people but affect people with suppressed immune systems) or thrush (a fungal infection in the mouth) • No B symptoms lasting more than 2 weeks. B symptoms include unexplained fever, night sweats (severe enough to soak the bed clothes), weight loss of more than 10% without dieting • Karnofsky performance status (KPS) score of 70 or higher. Patient is up and about most of the time and able to take care of himself/herself.	S1 (Poor risk): Systemic illness present; one or more of the following is true • History of opportunistic infections or thrush • One or more B symptoms is present • KPS score is under 70. • Other HIV-related illness is present.

The major treatment goals for KS are palliation of symptoms; shrinkage of tumour to alleviate oedema, organ compromise and psychological stress; prevention of disease progression and perhaps cure. ART has been associated with a significant decrease in the incidence of KS worldwide.

Local Therapy

Although KS is a systemic multifocal disease, local therapies may be most useful for localized bulky KS lesions or for cosmesis but does not affect the development of new lesions in untreated areas. Alitretinoin gel 0.1% (9-cisretinoic acid, a naturally occurring retinoid that binds both to retinoic acid receptors and to retinoid X receptors) is the only topical, self-administered therapy approved for the treatment of KS. Patients require 4 to 8 weeks for clinical benefit and dermal irritation appears to be a common adverse effect. Dark-skinned patients may on occasion have undesirable skin lightening after the use of

Alitretinoin gel 0.1%. Alternative local treatments include intralesional chemotherapy, radiation therapy, laser therapy and cryotherapy. Vinblastine is recommended as the only alternative local therapy, with an excellent response rate of 70%.

Systemic Therapy

The two currently approved liposomal anthracyclines, liposomal doxorubicin and liposomal daunorubicin, are recommended as the first-line chemotherapeutic treatments for patients with disseminated, symptomatic KS. The recommended dosage of liposomal doxorubicin is 20 mg/ m2 every 3 weeks, and that of liposomal daunorubicin is 40 mg/m2 every 2 weeks. Paclitaxel, at a dose of 100 mg/m2 every 2 weeks, is the newest systemic chemotherapeutic agent approved for KS, and is recommended to be used in anthracycline-resistant disease. It is not recommended to use Interferon therapy for KS in view of poor tumour response and drug-related toxicity.

Figure 5.6.2: Kaposi's sarcoma – response to treatment



Recommendations

- Local radiotherapy or intralesional vinblastine for symptomatic or cosmetic improvement in early stage T0 KS
- Chemotherapy along with ART for T1 advanced stage KS
- Liposomal anthracyclines are first-line chemotherapy for T1 advanced KS
- Paclitaxel for second-line treatment of anthracycline-refractory KS

Systemic AIDS-related Non-Hodgkin's Lymphoma

PLHIV have an increased risk of developing Non-Hodgkin Lymphoma (NHL) (Table 5.6.2). The two most common subtypes are diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma/ leukaemia (BL), which are considered AIDS-defining illnesses (ADI). Despite the decrease in incidence of AIDS-related lymphomas (ARLs) with increasing ART use, ARLs have increased as a percentage of first ADI. The development of ARL has been shown to be related to older age, low CD4 cell count and no prior treatment with ART and is characterized by advanced clinical stage, B symptoms and extra-nodal involvement, including bone marrow.

Figure 5.6.3: Non-Hodgkin's lymphoma



Multiple, bilateral, freely mobile, non-tender and firm 1-3 cm lymph nodes, with normal skin over the swelling in the cervical area



X-ray chest: Mediastinal widening due to multiple enlarged mediastinal lymph nodes

CT abdomen report: Multiple nodes in left para-aortic and aorta-caval region; small rounded hypodense lesions in anterior aspect of upper pole of right and mid-pole of left kidney; lymphomatous deposits with minimal left pleural effusion

Case and pictures courtesy: CoE, GHTM, Tambaram, Chennai

Table 5.6.2: Lymphomas associated with HIV infection

Lymphomas also occurring in immunocompetent patients
• Burkitt's lymphoma • Diffuse large B-cell lymphoma (DLBCL) • Hodgkin's lymphoma • Other lymphomas (MALT lymphoma; peripheral T-cell and NK-cell lymphoma)
Lymphoma occurring more specifically in HIV+ patients
• Primary effusion lymphoma (PEL) • Plasmablastic lymphoma (PBL) • Lymphoma arising in HHV8-associated multicentric Castleman's disease (MCD) • Lymphomas occurring in other immunodeficient states • Polymorphic lymphoid proliferations resembling post-transplant lymphoproliferative disorder (PTLD)

Apart from usual blood tests, the evaluation and clinical staging of ARL requires CT scans, bone marrow aspiration and bone marrow trephine biopsy. 18F-FDG PET scanning at diagnosis improves staging accuracy. CSF examination is recommended if there are clinical signs of CNS involvement, or paranasal sinus, breast, epidural or testicular involvement. Virological testing is advised (Table 5.6.3).

Table 5.6.3: HIV-associated lymphomas and associated viruses

HIV-associated Lymphomas	Associated Oncogenic Virus
Diffuse large B-cell lymphoma	Immunoblastic EBV 90%, centroblastic EBV 30%
Burkitt's lymphoma	EBV 25–40%
Primary effusion lymphoma	EBV 80–100%, HHV8 100%
Primary CNS lymphoma	EBV 80–100%
Plasmablastic lymphoma	EBV 90–100%
Hodgkin's lymphoma	EBV 90–100%
Multicentric Castleman's disease	HHV-8 100%

Diffuse Large B-cell Lymphoma

DLBCL, the most frequent ARL, often presents at an advanced stage and with B symptoms and extra-nodal tissue is frequently involved, mainly in severely immune-suppressed patients. Prognosis is determined by patient-, lymphoma- and HIV-specific factors. The International Prognostic Index (IPI) has been extensively validated and remains a reliable predictor of outcomes. Low CD4 counts have been reported to be predictors of poor survival in several studies.

First-line Chemotherapy for DLBCL in HIV-infected Individuals

ART has led to better immune reconstitution and hematopoietic growth factors (G-CSF) have allowed the use of conventional myelotoxic chemotherapy. Accordingly, the R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone plus Rituximab) and the DA-R-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and hydroxydaunorubicin plus Rituximab) are both recommended as first-line options. Dose adjustment to the neutrophil nadir minimizes haematological toxicity.

Localized disease

Localized DLBCL usually refers to patients with stage I disease and should be treated with combined-modality treatment with three cycles of chemotherapy followed by radiotherapy or 4–8 cycles of chemotherapy alone.

Disseminated Disease

Either R-CHOP or DA-R-EPOCH are advocated first-line regimens for disseminated DLBCL. It is recommended that a minimum of six cycles are given or two cycles beyond documentation of a complete response (CR) (i.e., a maximum of eight cycles). Despite concerns for the use of Rituximab at CD4 <50 cells/mm3, the addition of Rituximab to chemotherapy is now routinely recommended for DLBCL with appropriate antimicrobial prophylaxis and pre-emptive G-CSF.

Relapsed/Refractory disease

Response to treatment has been well described (Table 5.6.4). Treatment options for relapsed/ refractory (R/R) disease have been poorly investigated. High-dose salvage regimens such as ICE (ifosfamide, cisplatin and etoposide), DHAP (dexamethasone, high-dose cytarabine and cisplatin), ESHAP (etoposide, methylprednisolone (Solu-Medrol), high-dose cytarabine (ara-C) and cisplatin), GDP (gemcitabine, dexamethasone and cisplatin) with Rituximab appear to have similar efficacy, and patients with chemo-

sensitive disease who are eligible for transplant should proceed to Autologous Stem Cell Transplant.

Recommendations

- R-CHOP or DA-R-EPOCH are first-line options for DLBCL.
- Chemotherapy should be combined with ART.
- Closer surveillance is mandated for those with CD4 <50 cells/mm^3.
- Patients with Relapse / refractory disease should proceed to ASCT, after high-dose therapy.
- 18F-FDG PET scan should be performed at the end and after 4–6 weeks of therapy.

Table 5.6.4: Response assessment in patients with DLBCL

Response	Definition
Complete response (CR)	Complete clinical and radiological disappearance of disease PET negative
Partial response (PR)	≥50% decrease in diameter of up to 6 of the largest dominant masses PET positivity in a previously involved site
Stable disease (SD)	Failure to attain CR/PR
Relapsed or RD	Any new lesion or increase by ≥50% of a previously involved site

Burkitt's Lymphoma

BL, the second most common subtype of ARL, occurs in individuals with relatively preserved CD4 counts. Patients typically present with poor performance status and high lactate dehydrogenase level. Extra-nodal involvement is common, and the incidence of CNS involvement ranges from 8%–28%. The risk stratification system is used to decide on therapy (Table 5.6.5).

Table 5.6.5: Risk stratification for treatment of Burkitt's lymphoma

Low-risk disease Must have at least three of these factors	• Normal LDH • Stage I or II disease • WHO performance score 0–1 • Number of extra-nodal sites ≤1
High-risk disease Two or more of these factors	• Raised LDH • Stage III or IV disease • WHO performance score 2–4 • Number of extra-nodal sites >1

The most widely used regimen for BL is CODOX-M/IVAC. The CODOX-M/IVAC (Cyclophosphamide, Vincristine, Doxorubicin, High-dose Methotrexate/Ifosfamide, Etoposide, High-dose Cytarabine) regimen consists of four cycles, each cycle lasting until blood counts recover (absolute neutrophil count >1000/mm^3; platelets> 100,000/mm^3). Cycles 1 and 3 involve CODOX-M, and cycles 2 and 4 involve IVAC. Three cycles of CODOX-M are usually enough for low-risk patients, whereas high-risk patients receive 4 total cycles (2 cycles of CODOX-M, alternating with 2 cycles of IVAC). The reported treatment-related death rate is around 8–14% and mucositis is common. To overcome concerns of treatment toxicity in HIV-associated BL, the DA-EPOCH regimen plus Rituximab may be considered.

Recommendations

- CODOXM/IVAC and DA-R-EPOCH are first-line options for BL.
- Chemotherapy regimens should be combined with ART.

Prevention of Secondary CNS Lymphoma

CNS involvement by systemic NHL has been reported up to 25% in HIV-positive patients, and the use of intrathecal (i.t.) prophylaxis with MTX and/or ARA-C has been long considered a mandatory part of the systemic treatment of all HIV-infected patients with aggressive NHL. Advanced stage, elevated serum LDH, extra-nodal disease and involvement of testes, paranasal sinuses, paraspinal location, breast, renal, epidural space and bone predict a higher likelihood of CNS relapse. However, with effective ART, the incidence of CNS involvement has decreased, and CNS prophylaxis should be reserved for those who need it based on sites of involvement, stage and histological subtype.

Recommendations

- All patients with DLBCL should receive CNS prophylaxis (IT or IV MTX).
- All patients with Burkitt lymphoma (BL) should receive CNS prophylaxis (IT or IV MTX).

Tumour Lysis Syndrome

Patients thought to be at high risk for developing Tumour Lysis Syndrome (TLS) include those with DLBCL, elevated LDH, bulky disease and those with BL with stage III/IV disease. These patients should receive aggressive treatment to prevent TLS, including adequate intravenous hydration and Rasburicase. The first dose of Rasburicase should be administered 4 to 24 hours before starting chemotherapy. Rasburicase is given as an intravenous infusion over 30 minutes and should not be given as a bolus infusion. A repeated dose should be used if the serum uric acid level is above 7 mg/dl during the 96 hours after receiving the first dose of Rasburicase. Those who do not meet the criteria for high-risk disease should also be adequately hydrated, although oral hydration and Allopurinol may suffice.

Relapsed/refractory AIDS-related Lymphoma (R/R ARL)

In the absence of any standard second-line chemotherapy regimen, various aggressive regimens, mostly containing platinum, have been tried. Commonly used regimens include DHAP (Dexamethasone, High-dose Cytarabine and Cisplatin) and ICE (Ifosfamide, Cisplatin and Etoposide). This is usually combined with Rituximab, although the value of Rituximab in those who relapse early after, or are refractory to, upfront treatment with rituximab is less clear. For those who respond, studies have shown that consolidation with High-Dose Therapy and Autologous Stem Cell Transplantation is the optimal therapy for relapsed NHL

Recommendations

- Those who are fit for intensive chemotherapy should receive a second-line regimen, which may contain platinum.
- Those who achieve CR or PR with second-line chemotherapy should be considered for high- dose therapy with ASCT.

Primary Central Nervous System Lymphoma

PCNSL is defined as a subtype of DLBCL with a post-germinal centre phenotype, confined to the craniospinal axis without systemic involvement. It can affect any part of the brain, leptomeninges, cranial nerves, eyes or spinal cord. Clinical presentation varies from subacute focal neurological features in 50% to neuropsychiatric signs, increased intracranial pressure, and ocular symptoms. Investigations including serum LDH and CSF analysis should be done only when lumbar puncture can be safely performed. Radiology (MRI brain, CT CAP) will help support the diagnosis of PCNSL. Although stereotactic brain biopsy is essential for a definitive diagnosis, the combination of detectable EBV in CSF and consistent radiological findings in severely immune- suppressed HIV-positive patients may be sufficient. MRI is the most sensitive imaging modality and shows single (65%) or multiple lesions on non-enhanced T1-weighted images, hyperintense tumour and oedema on T2 or FLAIR images, and densely enhancing masses after administration of gadolinium. 50% or more of the lesions are in contact with the meninges, and meningeal enhancement appears in 10%–20%. The diagnostic algorithm for the management of cerebral mass lesions in HIV patients includes a 2-week trial of anti-toxoplasmosis therapy (sulfadiazine 1 gm QID and pyrimethamine 75 mg OD).

HIV-positive patients with PCNSL usually have advanced immune suppression and CD4 count <50 cells/mm^3, making impossible the administration of high-dose (HD) methotrexate (MTX) and cytosine arabinoside. HD MTX and Rituximab appear to be a valid alternative. If induction treatment is well tolerated and a response is documented, consolidation with high-dose therapy and ASCT could be considered in selected patients.

Recommendations

- High dose Methotrexate (HD-MTX)-containing chemotherapy regimen
- Combination with ART
- Whole brain radiotherapy is a useful palliative treatment modality for control of symptoms or should be considered as an alternative first-line treatment modality in those patients where the risks of toxicity from High-dose intravenous agents are considered unacceptable.

Primary Effusion Lymphoma

PEL is a rare B cell lymphoma characterized by effusions involving the pleura, pericardium and/or peritoneum, without identifiable tumour masses or lymphadenopathy. Severe immune suppression with low CD4 cell counts is common. Most PELs have lymphocyte activation markers (CD30 and CD38) without normal B cell markers (CD19, CD20, CD79a) and T cell markers (CD3, CD4, CD8). HHV-8 has a pathogenetic role and is present in almost 100% of cases. Other HHV-8- related complications such as KS or MCD may precede or occur concurrently with PEL.

Patients commonly present with dyspnoea because of pleural or pericardial involvement or abdominal distension from peritoneal involvement. Cytological analysis of the involved effusion fluid reveals tumour cells that are large, have round-to-irregular nuclei and conspicuous nucleoli, and may have the appearance of immunoblasts, plasmablasts and/or anaplastic forms. Detection of evidence of viral infection is a sine qua non to make the diagnosis, and immunohistochemical staining for latency-associated nuclear antigen-1 (LANA-1) expression is the standard for detecting HHV-8 in tumour samples. LANA-1 is a gene product that functions to tether the viral genome to the infected host cell’s genome and promotes cell survival. The most used CT regimen is CHOP that allows achieving CR rate of 40%–50%, with median survival around 6 months.

Recommendations

- In the absence of any standard treatment, PEL in HIV should be treated with CHOP regimen.
- Such treatment should be included as part of a clinical trial if possible.
- ART should be administered concurrently with such treatment.

Plasmablastic Lymphoma

Plasmablastic lymphoma is a rare variant of DLBCL, with plasmacytoid appearance, affecting primarily mucosal sites of the oropharynx in males with HIV. The three histological subtypes include monomorphic plasmablasts with minimal plasmacytic differentiation predominantly affecting the oral cavity, those with more plasmacytic differentiation involving extra-oral sites and plasmablastic lymphoma involving nodes or spleen associated with Castleman's disease. IHC positivity for plasma cell markers VS38c, CD38, multiple myeloma oncogene-1 (mum-1) and CD138 (syndecan-1), the constant presence of EBV and the absent expression of leukocyte common antigen (CD45) or the B cell markers CD20, CD79a and PAX5, serve to distinguish Plasmablastic lymphoma from immunoblastic variant of DLBCL, body and extra-cavity variants of PEL, BL with plasmacytoid differentiation and extramedullary plasmablastic secondary multiple myeloma.

CHOP-like treatments have been the standardofcare but due to the disappointing long-term survival rates, more intensive regimens have been suggested, such as hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) or CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine). CHOP-14 (shortening the time between cycles from 21 days to 14 days) has been found to be more effective in recent years. Plasmablastic lymphoma should be treated with intensive chemotherapy (CHOP-14 as an option) followed by RT, at least in a localized stage. Early consolidation with ASCT might be an option for advanced-stage patients and ART should be concurrently used.

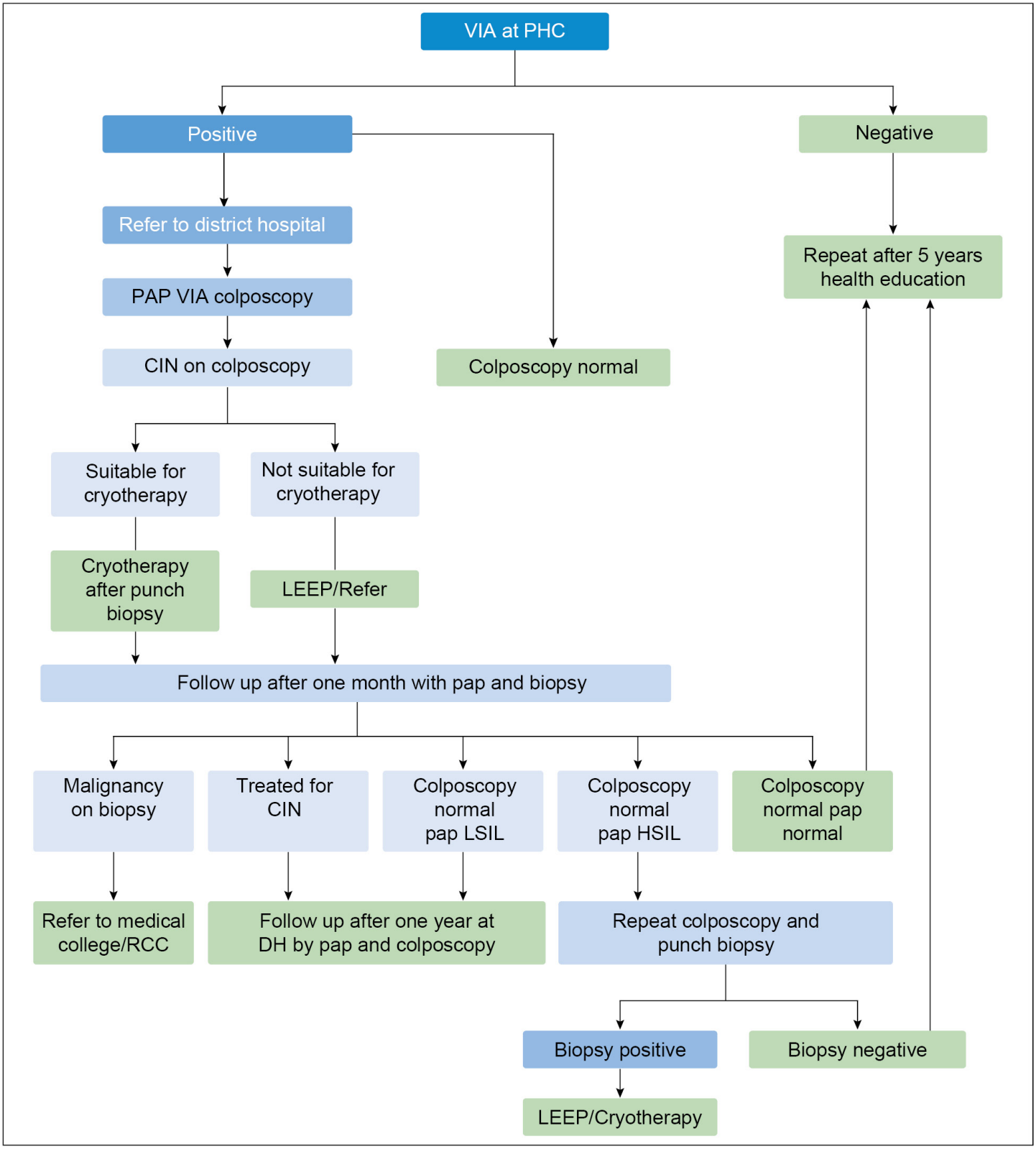
Recommendations

- Plasmablastic lymphoma should be treated with CHOP-14 or other intensive chemotherapy.
- Follow-up radiotherapy may be used for localized disease.
- Early consolidation with ASCT for more advanced disease
- Concurrent ART

Cervical Intraepithelial Neoplasia (CIN) and Cervical Cancer

Cervical cancer is common in HIV patients with an earlier age of diagnosis, aggressive course and poor treatment outcome. Cervicovaginal HPV infection has also been reported to be higher in HIV-positive women (60%–65%) than in their HIV-negative counterparts (25%–30%). Despite the increased risk of false negative cytology, studies have shown that 2-yearly testing for cervical smear is sufficiently sensitive for cervical surveillance in PLHIV. ART has had minimal effect on the incidence of invasive cervical cancer but has effectively brought down the incidence of CIN in women with HIV.

Figure 5.6.4: Diagnostic algorithm of cervical cancer screening in India at the PHC



Foot note: VIA: Visual Inspection with Acetic Acid, Pap: Papanicolaou staining, CIN: Cervical Intraepithelial Neoplasia, LEEP: Loop electrosurgical excision procedure, LSIL Low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesion.

HPV-16 and HPV-18 encode for three oncoproteins (E5, E6 and E7) that stimulate growth and have transforming properties. The integration of HPV DNA within the host genome results in chromosomal instability and favours the progression from CIN to invasive carcinoma. HIV- mediated immune suppression prevents the clearance of HPV, leading to a gradual loss of control over HPV replication. There are now three major alternatives for cervical cancer screening: cytology, HPV testing and cytology-HPV co-testing. Co-testing is currently recommended as the best screening option in the USA.

Treatment of cervical cancer includes surgery, radiotherapy and chemotherapy. Surgery, including radical hysterectomy and lymphadenectomy, plays an important role in the management of early stage cervical cancer. Treatment of locally advanced cervical cancer includes RT (external RT and brachytherapy) and chemotherapy.

Recommendations

- Screening cytology for HIV-positive women is recommended at the time of HIV diagnosis, and annually thereafter. If three annual PAP smears are negative, it should be repeated every 3 years.
- Colposcopy should be performed if abnormalities are seen on PAP screening.
- The treatment of CIN or invasive cervical cancer should follow the same guidelines as those advocated for the HIV-negative population (Figure 5.6.4)

Anal Cancer

The incidence of anal cancer in PLHIV is up to 40 times higher compared with that in the general population, occurring at a much younger age, with the highest risk in men who have sex with men. Anal cancer can present with rectal bleeding and anal pain, or incontinence if anal sphincter is affected. The pathogenesis resembles that of cervical cancer with HPV infection leading to anal intraepithelial neoplasia (AIN) and ensuing progression from low-to-high-grade dysplasia and subsequently, invasive cancer (Tables 5.6.6 and 5.6.7).

Table 5.6.6: Histopathological grading of anal intraepithelial neoplasia (AIN)

AIN grade	Area of dysplastic cells in the epithelium	Cytological grade
Grade 1	Lower third	LSIL
Grade 2	Lower two-thirds	HSIL
Grade 3	Entire epithelium	HSIL

LSIL = Low-grade squamous intraepithelial lesion HSIL = High-grade squamous intraepithelial lesion

Table 5.6.7: Classification of anal cytology according to the Bethesda system

N	Normal
ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells, cannot exclude HSIL
LSIL	Low-grade squamous intraepithelial lesion
HSIL	High-grade squamous intraepithelial lesion
CA	Squamous cell carcinoma

Since abdominoperineal resection of anal cancer yielded 5-year overall survival (OS) rates of no more than 40%–70%, primary surgery has nowadays been replaced by concomitant chemoradiotherapy (CRT), whereas primary tumour resection is restricted to small tumours of the anal margin. CRT achieves local control and sphincter preservation.

Concomitant chemoradiotherapy (CRT) in HIV patients should be performed according to current guidelines for non-infected individuals. Intensity-modulated radiation therapy (IMRT) or Volumetric modulated arc therapy (VMAT) with a stage-adapted dose of 50.5–59.4 Gy, is combined with chemotherapy in the first and fifth week (usually consisting of 5×1,000 mg/m2 5-FU combined with 1×10

mg/m2 Mitomycin C (MMC) on days 1 and 29), provided the number of CD4 cells is no less than 100–200/mm^3 and the performance status is adequate. Because of the nephrotoxic potential of MMC, tenofovir should be used with caution, and zidovudine should be avoided in view of possible bone marrow toxicity.

Response to CRT should be assessed at 6–8 weeks after completion of CRT with clinical evaluation, MRI imaging of the pelvis and examination under anaesthesia. Clinical evaluation and review should continue every 3–6 months for 2 years and every 6–12 months up to 5 years.

Residual primary disease or local recurrence after CRT demands salvage surgery, involving abdominal perineal resection (APR) of rectum and anal canal. Patients with metastatic disease or local relapse following salvage surgery may be considered for palliative chemotherapy. The results of palliation are suboptimal, and best supportive care may be more appropriate.

Recommendations

- All suspected cases of anal cancer should have examination under anaesthesia (EUA) and biopsy.
- CT and MRI should be performed to assess regional nodes and tumour extension.
- High-resolution anoscopy services should be available for surveillance.
- CRT with 5-fluorouracil and MMC is the first-line treatment, along with ART and OI prophylaxis.
- Salvage surgery should be advised for loco-regional disease persistence or relapse.
- Best supportive care should be advised for metastatic disease or local relapse following salvage surgery.

Hodgkin’s Lymphoma

Hodgkin’s lymphoma (HL) is one of the commonest tumours among the non–AIDS-defining cancers with a 10- to 20-fold increased incidence in HIV patients in comparison with the HIV- negative population. HL occurs most commonly at CD4 cell counts <200 cells/mm^3. However, the risk of developing HL remains while on ART, and HL incidence rates are higher in the first few months after starting ART. Viral load has not been shown to relate to incidence rates.

HL in HIV patients is characterized by advanced stage at diagnosis, more extra-nodal involvement, especially bone marrow infiltration, higher frequency of B symptoms and poor performance status. A predominance of the mixed cellularity (MC) and lymphocyte depleted (LD) subtypes, as opposed to nodular sclerosis (NS) histology and a higher percentage of EBV positivity is seen in HIV-associated HL.

The diagnosis of HL mandates tissue sample biopsy. The Ann Arbor classification/Cotswolds modification requires blood tests, whole body FDG-PET/CT scan and unilateral bone marrow biopsy (in view of the higher chance of bone marrow involvement) (Table 5.6.8).

Table 5.6.8: Ann Arbor classification/ Cotswolds modification for staging HIV-associated HL

Stage I	Involvement of a single lymph node group or lymphoid structure
Stage II	Involvement of two or more lymph node groups on the same side of the diaphragm
Stage III	Involvement of lymph node groups on both sides of the diaphragm
Stage IV	Involvement of extra-nodal site(s) beyond those designated 'E'
X	Bulky disease: >10 cm or >1/3 widening of the mediastinum at T5–6
E	Extra-nodal extension contiguous or proximal to known nodal site of disease or single isolated site of extra-nodal disease
A / B	Absence/presence of B symptoms (weight loss >10%, fever, drenching night sweats)

The most used initial systemic therapy for HL is the combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). The German Hodgkin Study Group (GHSG) demonstrated that ABVD x 2 + 20 Gy involved field radiotherapy (IF-RT) results in a comparable freedom from treatment failure (FFTF) and overall survival to ABVD x 4 + 30 Gy and with less toxicity. The BEACOPP (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone) regimen has been reported to result in a superior freedom from progression than ABVD but this did not translate into a superior OS (7-year OS: 89% vs. 84%) as patients who failed ABVD could be rescued with second-line chemotherapy followed by high-dose chemotherapy with autologous stem cell rescue (HDT-ASCR).

Management of HD in HIV may be summarized as follows

- For early favourable HL: ABVD x 2-4 + IFRT 20–30 Gy
- For early unfavourable HL: ABVD x 4 + IFRT 30 Gy
- For advanced-stage HL: ABVD x 6-8 +/- RT

Recommendations

- ABVD is the first-line chemotherapy for HL, to be administered in conjunction with IFRT.
- Good-performance patients with relapsed/refractory HL should receive salvage chemotherapy, and if the disease proves to be chemosensitive, the treatment should be consolidated with High-Dose Therapy or Autologous Stem Cell Rescue (HDT/ASCR).
- ART should be co-administered during chemotherapy and PI-based regimen should be avoided to minimize additive toxicities like vinblastine-mediated neurotoxicity and neutropenia.
- PCP, MAC and fungal infection prophylaxis during and after chemotherapy
- Assessment of response after treatment should be performed by FDG-PET scan and BM biopsy.
- Follow-up should be performed every 2–4 months during the first 2 years and every 3–6 months for 3 further years.

Multicentric Castleman's Disease

Castleman's disease (CD) describes a group of at least four disorders that share a spectrum of characteristic histopathological features but have a wide range of aetiologies, presentations, treatments and outcomes. CD includes unicentric CD (UCD) and multicentric CD (MCD), the latter of which is divided into idiopathic MCD (iMCD), human herpes virus-8 (HHV8)-associated MCD (HHV8-MCD) and polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes (POEMS)-associated MCD (POEMS-MCD).iMCD can be further sub-classified into iMCD–thrombocytopenia, ascites, reticulin fibrosis, renal dysfunction, organomegaly (iMCD-TAFRO) or iMCD–not otherwise specified (iMCD-NOS). MCD is a relatively rare lymphoproliferative disorder that classically presents with fevers,

anaemia and multifocal lymphadenopathy and is now most diagnosed in individuals infected with HIV-1.

MCD presents with generalized malaise, night sweats, rigors, fever, anorexia and weight loss. Clinical examination reveals widespread lymphadenopathy, often with hepatosplenomegaly, ascites, oedema and pulmonary and pericardial effusions. Laboratory investigations may reveal thrombocytopenia, anaemia, hypoalbuminemia and hypergammaglobulinemia.

The diagnosis of MCD can only be established definitively by lymph node biopsy. The characteristic features of HIV-associated MCD are a characteristic ‘onion skin’ appearance and interfollicular plasmablasts that express the HHV-8 latent nuclear antigen (LANA). These plasmablasts also express high levels of λ light-chain restricted immunoglobulin M (IgM) but are polyclonal and do not contain somatic mutations in their IgV genes, suggesting that they arise from naive B lymphocytes. Occasionally, these plasmablasts join together to form clusters or ‘micro lymphomas’ and may progress to monoclonal Plasmablastic Lymphoma.

It is suggested that histological confirmation with immunocytochemical staining for HHV-8, and IgM lambda is essential for the diagnosis of MCD. Elevated serum levels of HHV-8 support the diagnosis of MCD.

Unlike other lymphoproliferative disorders, ART had no impact on the incidence or outcome of MCD in HIV. HIV-infected patients with HHV8-MCD are estimated to have a 15-fold increased frequency of lymphoma compared with an HIV-infected population without MCD.

Rituximab-based therapy has dramatically improved 5-year OS for HHV8-MCD from 33% to 90%. Rituximab is used as a single agent weekly for 4 weeks in patients with adequate performance status and with absence of hemophagocytic syndrome, haemolytic anaemia or end-organ damage. The combination of rituximab and liposomal doxorubicin every 3 weeks appears to attenuate Kaposi sarcoma exacerbation. Rituximab with or without etoposide appears to be effective in HHV8-MCD, regardless of HIV status.

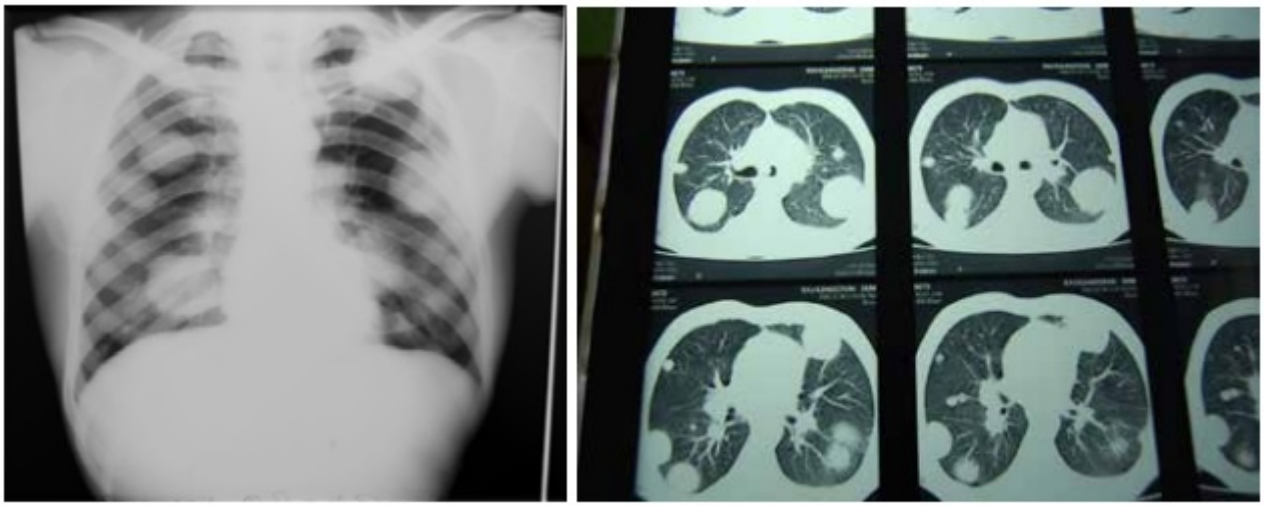
Recommendations

- Histological confirmation of MCD requires immunocytochemical staining for HHV-8 and IgM lambda.
- Monitoring for lymphoma is important as the risk of lymphoma is high in patients diagnosed with MCD.
- Rituximab is the first-line chemotherapy agent and aggressive disease needs to be treated with other agents in addition to Rituximab.
- Re-treatment with Rituximab-based therapy for relapsed MCD
- Plasma HHV-8 levels can predict relapse and clinical monitoring for patients in remission should include measurement of blood HHV-8 levels.

Testicular Germ Cell Tumours

Seminoma, and not non-seminoma, germ cell tumours (GCTs), occur more frequently in HIV infection. Irrespective of HIV serostatus, a testicular mass must be treated with the utmost suspicion and an ultrasound scan (or MRI) and tumour markers (AFP, HCG) should follow. The differential diagnosis for a testicular mass in this setting includes orchitis and lymphoma. A CT scan of the chest, abdomen and pelvis should be performed for full staging.

Figure 5.6.5: Secondaries of seminoma testis



Multiple Pulmonary Secondaries

Images courtesy: I-TECH-GHTM, Tambaram Fellowship Programme

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) described a prognostic staging system for metastatic testis tumour based on histology, location of the primary tumour, location of metastases and pre-chemotherapy marker levels to categorize patients into ‘good’, ‘intermediate’ or ‘poor’ prognosis categories (Table 5.6.9).

Table 5.6.9: Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)

Good-prognosis group	
Non-seminoma (56% of cases) 5-year PFS 89% 5-year survival 92%	**All of the following criteria:** • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP <1,000 ng/ml • hCG <5,000 IU/L (1,000 ng/ml) • LDH <1.5 x ULN
Seminoma (90% of cases) 5-year PFS 82% 5-year survival 86%	**All of the following criteria:** • Any primary site • No non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Intermediate-prognosis group	
Non-seminoma (28% of cases) 5-year PFS 75% 5-year survival 80%	**All the following criteria** • Testis/retroperitoneal primary • No non-pulmonary visceral metastases • AFP >1,000 and <10,000 ng/ml or • hCG >5,000 and <50,000 IU/L or • LDH >1.5 and <10 x ULN
Seminoma (10% of cases) 5-year PFS 67% 5-year survival 72%	**Any of the following criteria:** • Any primary site • Non-pulmonary visceral metastases • Normal AFP • Any hCG • Any LDH
Poor-prognosis group	
Non-seminoma (16% of cases) 5-year PFS 41% 5-year survival 48%	**Any of the following criteria:** • Mediastinal primary • Non-pulmonary visceral metastases • AFP >10,000 ng/ml or • hCG >50,000 IU/L (10,000 ng/ml) or • LDH >10 x ULN
Seminoma	No patients classified as poor prognosis

Patients with stage I disease (seminomas or NSGCT) can be safely treated with surveillance alone. For metastatic disease, good-risk patients should be offered three cycles of standard 5-day BEP (bleomycin, etoposide and cisplatin) with concurrent ART, and prophylactic antifungals should be considered. Patients with intermediate- and poor-risk disease should be offered four cycles of standard 5-day BEP chemotherapy. Those with extensive pulmonary limitation from previous infection can alternatively have four cycles of EP or VIP chemotherapy, the latter being more myelosuppressive in HIV-negative patients. Those with relapsed disease after two or more treatment regimens should be offered high-dose

chemotherapy followed by autologous peripheral blood stem cell transplant as in HIV-negative patients. Guidelines advocate avoiding Bleomycin in situations where pulmonary involvement appears likely.

Recommendations

- Surveillance may be considered for seminoma of testis in PLHIV.
- Concomitant ART and infection prophylaxis is advocated during chemotherapy for testicular GCT.
- GCT of the testis should be treated in an identical manner regardless of HIV status.
- Bleomycin may be avoided in the management of testicular GCT in PLHIV.

Non-small Cell Lung Cancer

Non-small cell lung cancer (NSCLC) appears to occur at a higher frequency at a younger age and present with more advanced disease in HIV-infected patients. Despite the wide spectrum of infectious differentials of a lung mass in HIV, the possibility of NSCLC in HIV should be borne in mind. In addition to a tissue diagnosis, a CT of the chest and abdomen, with special attention to the adrenals, along with a bone scan is advocated. Interpretation of FDG-PET should be done keeping in mind the HIV viral load, the CD4 cell count and the consequent possibility of OIs.

Operable lung cancer in HIV deserves curative surgery, although a higher risk of complications and recurrence are noted in HIV patients, especially if the CD4 count is low. Locally advanced disease merits chemoradiation according to HIV-negative guidelines, although grade III/IV treatment-related toxicities are more common in HIV. Patients must be on ART and appropriate OI prophylaxis before anti-cancer therapy is administered. Metastatic disease must be treated with chemotherapy alone. The presence of activating mutations within the epidermal growth factor receptor (EGFR) gene of lung cancer cells has made these tumours highly sensitive to EGFR-targeting tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib. Use of EGFR TKIs requires caution due to potential interaction with ART through induction of cytochrome P450 isoenzyme CYP3A4. While anti-smoking advocacy remains important, there appears to be no role for lung cancer screening in HIV as of now.

Recommendations

- Elderly PLHIV, especially smokers, have a higher risk of NSCLC.
- Routine screening for NSCLC is not advocated in PLHIV.
- Standard treatment of NSCLC is advisable in PLHIV.

Hepatocellular Cancer

There is debate as to whether there is an increased incidence of Hepatocellular carcinoma in HIV primarily because of the confounding influence of HBV and HCV. In Western countries approximately 30% of people with HIV are coinfected with HCV, rising to approximately 75% in IV drug users. Regional variation for HIV–HBV co-infection ranges from 10%–90%. Indian studies have documented HBV and HCV to coinfect 11% and 13% of PLHIV, in contrast to 2% and 3% of the non-HIV population, respectively. HCV, and to a lesser extent HBV, augment the pathogenesis of Hepatocellular carcinoma in PLHIV.

Hepatocellular carcinoma patients with HIV tend to be younger, are more often HCV coinfected, more likely to present with cirrhosis, more likely to be only moderately immune-suppressed (due to pre-existing ART) and likely to have similar Barcelona Clinic Liver Cancer (BCLC) stage at presentation, as compared to non–HIV-infected individuals. USG and AFP levels suffice as diagnostic tools. A CT scan of the chest,

abdomen and pelvis is required to exclude metastatic disease. The degree of immune suppression does not appear to correlate with the BLCC stage. However, patients with CD4 >200 cells/mm3, undetectable HIV viral load and lower AFP levels are more likely to achieve a better median survival. Accordingly, effective ART is important.

Solitary or a small number of Hepatocellular carcinoma lesions are resectable and complete resection should be attempted if the Child-Pugh score is A. Liver transplantation appears to be superior to resection alone in HIV-negative patients, and HIV seropositivity does not appear to be a negative prognostic factor for transplantation (Table 5.6.10). It is wise to remember that PIs may inhibit the cytochrome P450 enzyme and interact with immunosuppressive agents like Tacrolimus, which are routinely used following liver transplantation.

Table 5.6.10: Immunological and virological criteria necessary for considering liver transplant in HIV-related patients

Immunological criteria	• No AIDS-defined opportunistic infections within the previous year • CD4 cell count >200 cells/mm^3 or >100 cells/µL in cases of therapy intolerance
Virological criteria	• Undetectable HIV viral load (<50 copies/ml) in the last 12 months or effective therapeutic options for HIV infection during the post-transplant period

Sorafenib, an oral multi-TKI targeting the Raf cascade as well as vascular endothelial growth factor/platelet-derived growth factor receptors on tumour cells, has been well established for Hepatocellular carcinoma in HIV-negative subjects and appears to be equally effective in PLHIV on ART.

In contrast to 6-monthly USG, AFP estimation appears to be logistically feasible in resource limited settings. Accordingly, all HBV or HCV coinfected PLHIV should be advised 6-monthly AFP estimation, even in the absence of cirrhosis.

Recommendations

- AFP screening every 6 months should be offered to all cirrhotic PLHIV and non-cirrhotic PLHIV with HBV or HCV co-infection.
- Hepatocellular carcinoma screening with liver USG should be offered to all PLHIV with cirrhosis or decompensated liver disease.
- Hepatocellular carcinoma should be treated in the same manner irrespective of HIV status.
- Hepatocellular carcinoma in PLHIV may be treated with liver transplantation if feasible.
- Sorafenib may be used as a treatment option in inoperable cases of Hepatocellular carcinoma.

Skin Cancer

Among PLHIV, primary skin malignancies are the most frequent non-AIDS-defining malignancies (NADMs). The risk is higher for developing a non-melanoma skin cancer and the ratio of squamous cell carcinoma to basal cell carcinoma in HIV-infected individuals is 1:7. Atypical features of HIV- associated squamous cell cancers are presentation at a younger age, at unusual sun-unexposed sites including the mouth, genitalia and perineum, multifocal, aggressive and higher potential for recurrence and metastasis. Routine clinical skin examination and self-surveillance of skin in older PLHIV are warranted in those with a history of skin cancer.

Basal cell carcinoma may be multiple and is commonly of the superficial type. Melanoma is probably two to three times more common. Although conventional treatment protocols are acceptable for HIV-

associated skin cancers, special attention to local excisional margin control, more extensive investigations for dissemination of disease and more intensive follow-up are mandated. An MDT sensitized to the enhanced malignancy potential and higher recurrence rates must be involved in the care of these patients.

Basal cell carcinoma and squamous cell carcinoma have been reported to remit with ART. Topical imiquimod has been used for treatment of basal cell carcinoma in HIV and is useful for the common scenario of multifocal superficial basal cell carcinomas.

Recommendations

- Behavioural counselling to PLHIV with fair skin to minimize ultraviolet radiation exposure and reduce skin cancer risks
- Counselling on frequent photoprotective behaviour and sunscreen use
- Regular self-examination of skin and clinical skin examination
- Early treatment of pre-malignant lesions is important to reduce skin cancer risk.

Penis Pre-cancer and Cancer

Despite ART, penis cancer is five to six times more common in HIV. Uncircumcised state, poor hygiene, smoking, lichen sclerosis and HPV are the principal risk factors. Uncircumcised men with HIV should be counselled and questioned at diagnosis and during management about genital health and smoking, have their genitalia examined at follow-up and preputial ill-health should evoke a low threshold for circumcision. Penile intraepithelial neoplasia (PeIN) and established penile cancer should be treated as per standard guidelines with preventive and curative tissue conservation and sentinel node biopsy occupying central roles.

Recommendations

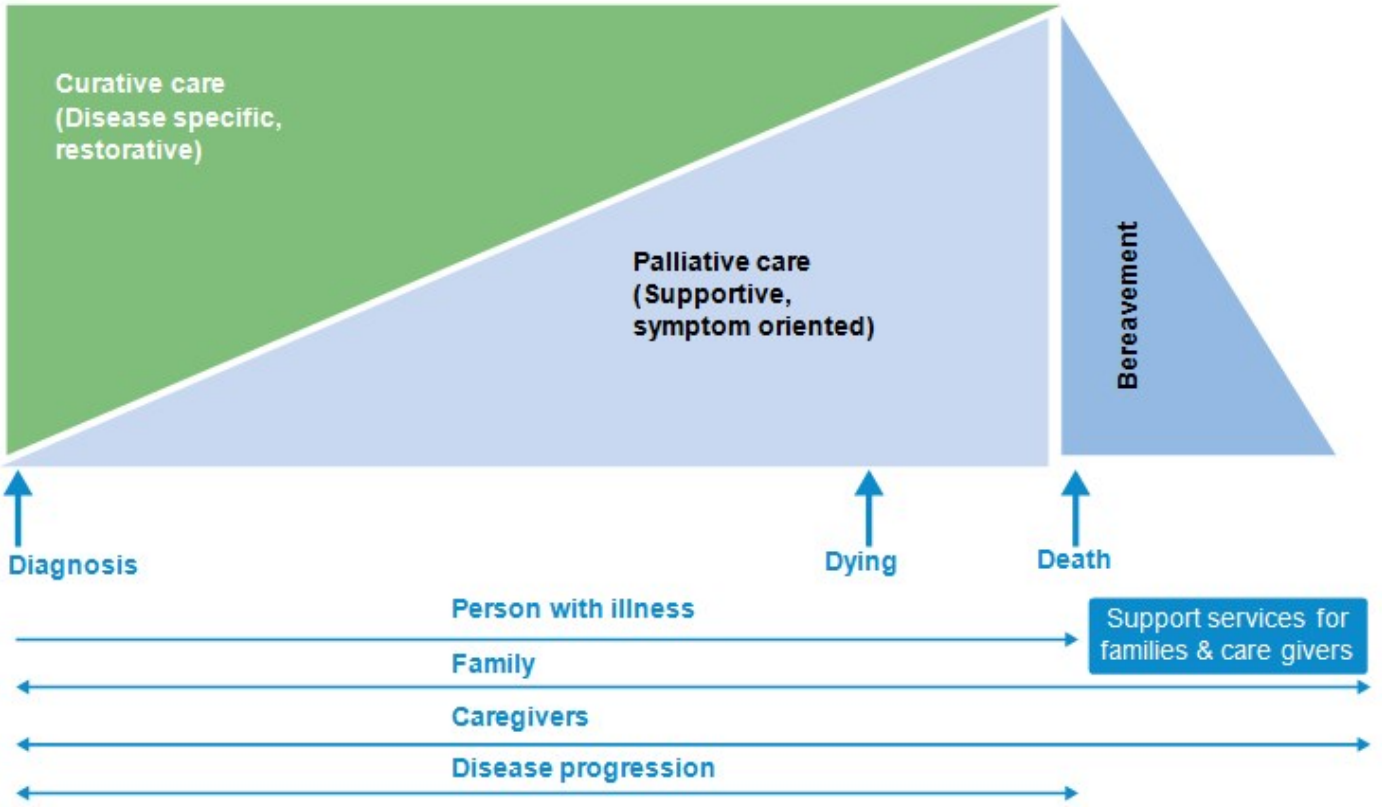
- Counselling about genital hygiene and health is important to prevent penile cancers.
- Routine circumcision is not advocated for the prevention of penile cancers.
- However, examination of genitalia and circumcision should have a low threshold.

5.7 Palliative Care for Adults and Children with HIV

Introduction

The Government of India has adopted WHO's definition of palliative care, which is the "active total care of patients whose disease is not responsive to curative treatment" (Manual on Palliative Care, MOHFW, November 2005). Palliative care is an "approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (WHO. 2002.
http://www.who.int/cancer/palliative/definition/en).
Palliative care extends, if necessary, to support in bereavement.

Figure 5.7.1: "Continuum of care" HIV/AIDS



Source: Strategies for Palliative Care in India (Expert group report). 2012. Directorate General of Health Services, Ministry of Health & Family Welfare, Govt. of India.

Palliative Care in HIV

- Should be family and patient centred
- Optimizes the quality of life by active participation, prevention and treatment of suffering
- Involves an inter-disciplinary team approach throughout the continuum of illness, placing critical importance on the building of respectful and trusting relationships
- Addresses physical, intellectual, emotional, social and spiritual needs

The availability of ART and palliative care has made HIV a chronic, manageable disease for many. Apart from regular pain management, nutritional support and OI management, palliative care includes giving support for drug failure and severe toxicities due to ART.

Severe oral and oesophageal candidiasis leading to severe pain and weight loss; Cryptococcal meningitis and Toxoplasma encephalitis.

Special attention needs to be given to the following HIV-related conditions, which may present as terminal illness. These conditions can be managed with proper medical care and support.

Components of Palliative Care

The main components include the following

1. Pain management

2. Symptomatic management
3. Nutritional support
4. Psychosocial support
5. Spiritual support
6. End-of-life care
7. Bereavement counselling

Management of Pain

Step 1: Assess the patient for pain.

- Determine the severity, site and nature of the pain (bone pain, mouth pain, shooting nerve pain, colicky pain, severe muscle spasms).
- If there is infection, prompt management of infection is the main step in controlling the pain (e.g., treating severe oral and oesophageal candidiasis with fluconazole relieves the pain).
- The severity of the pain can be graded with the help of the tools below. GO BY WHAT THE PATIENT SAYS IS HURTING: Do not disregard the patient's complaint of pain just because there is no apparent physical cause.

Pain can be assessed by using the PQRST characteristics given in Table 5.7.1.

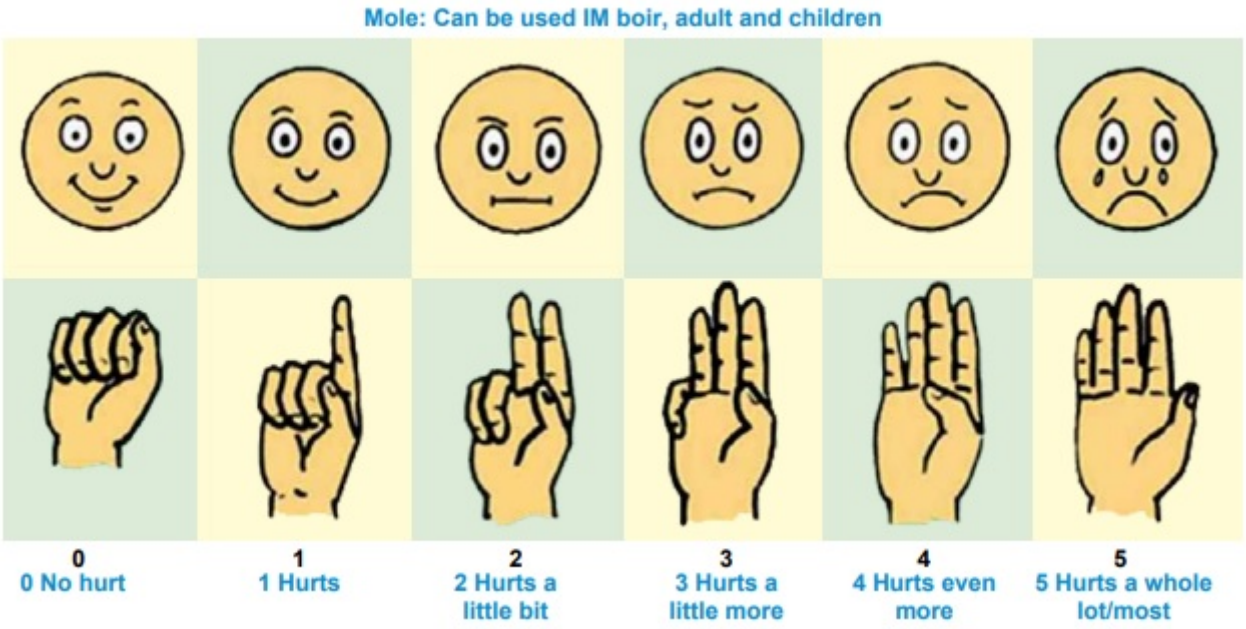
Table 5.7.1: PQRST characteristics in pain assessment

Factors for Assessment	Answer-Eliciting Questionnaire
P- Palliative factors **Provocative factors**	"What makes it better?" "What makes it worse?"
Q- Quality	"What exactly is it like?"
R- Radiation	"Does it spread anywhere?"
S- Severity	"How severe is it?" "How much does it affect your life?"
T- Temporal factors	"Is it there all the time or does it come and go?" "Is it worse at any particular time of the day or night?"

Table 5.7.2: Various scales for pain assessment

Various scales for pain assessment	
• Descriptive scale • Numeric scale • Visual analogue scale	• Percentage scale • Coin scale • Face ccale
The following format may be used for assessing pain in any given patient	

Figure: 5.7.2: Pain/Emotion scale: Visual analogue scale



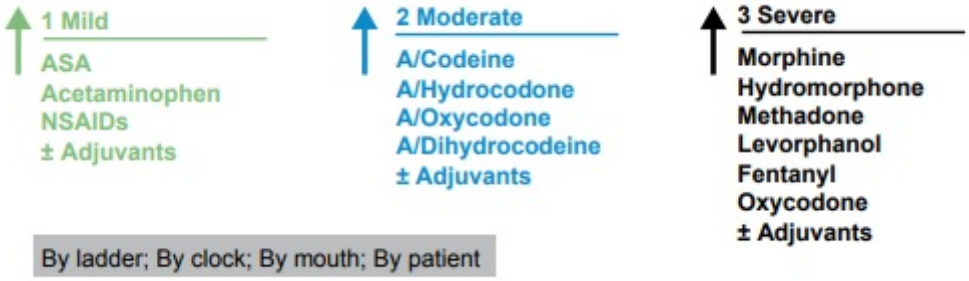
Source: WHO, India

Step 2: Decide the treatment strategies for pain.

Table 5.7.3: Strategies for treatment of pain

By Mouth	By the Clock
If possible, administer painkiller by mouth • Rectal administration is an alternative. • Avoid intramuscular route.	1. Give painkillers at fixed time intervals (by clock, radio or sun) 2. Start with a small dose, then titrate the dose against the patient's pain until the patient is comfortable. 3. The next dose should be given before the effects of the previous one wears off. 4. For breakthrough pain, give an extra 'rescue' dose in addition to the regular schedule

Figure 5.7.3: WHO 3-Step pain relief analgesic ladder



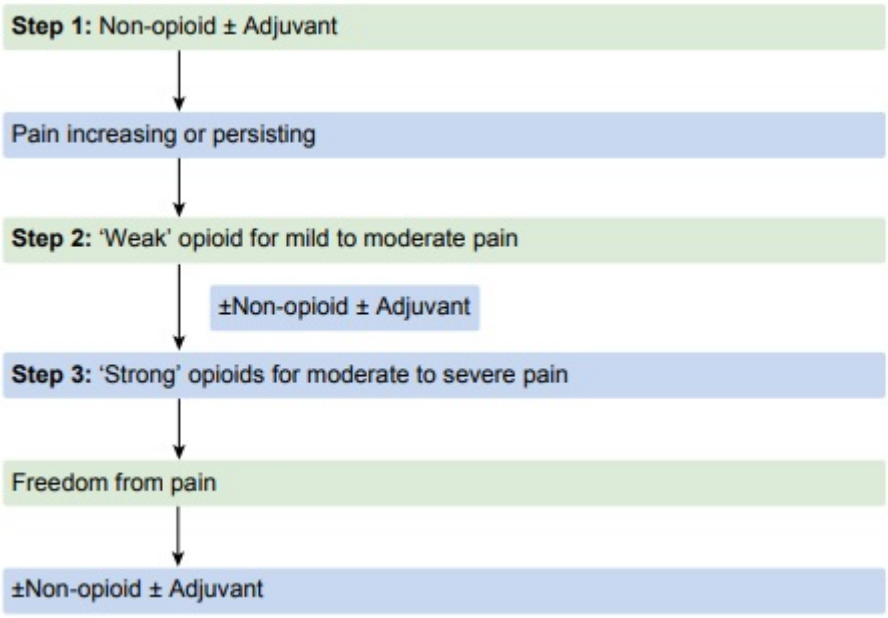
Step 3: Prescribe analgesics: use of opioid and non-opioid analgesics.

Give only one drug from the opioid and non-opioid groups at a time. The exception is if codeine cannot be given, use aspirin every 4 hours combined with paracetamol every 4 hours: overlap so one is given every 2 hours.

After adequate pain assessment and evaluation on parameters described above, pharmacotherapy must be individualized to maximize pain relief and minimize adverse effects. WHO has devised a model paradigm

for pain management approach (Figure 3).

Figure 5.7.4: WHO analgesic ladder



The WHO approach advises clinicians to match the patient's reported pain intensity with the potency of analgesic to be prescribed. For mild pain, one should use a non-opioid drug like acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) (Table 5.7.4). For **moderate pain** not controlled by NSAID alone, a 'weak' opioid like codeine phosphate or hydrocodone bitartrate should be used in combination with aspirin, another NSAID or acetaminophen (Table B). For **severe pain**, a 'strong' opioid such as morphine, hydromorphone, methadone or fentanyl should be used (Table 5.7.5). The various pain management scales described earlier should be used to assess the outcome of pain management.

Table 5.7.4: Partial list of acetaminophen and non-steroidal anti-inflammatory drugs used for cancer pain

Drug	Dosage Schedule
Acetaminophen	650 mg q4h p.o.
Aspirin	650 mg q4h p.o.
Ibuprofen	200–800 mg q6h p.o.
Diclofenac sodium	50–75 mg q8–12h p.o.
Flurbiprofen	200–300 mg q4–8h p.o.
Naproxen	250–750 mg q12h p.o.
Piroxicam	10–20 mg q daily p.o
Ketoprofen	50 mg q6h p.o.
Ketorolac tromethamine	10 mg q4–6h p.o.
Ketorolac tromethamine	30 mg IM or IV x 1 then 15 mg IM or IV q6h

Table 5.7.5: Commonly used opioids for cancer pain

World Health Organization step I/II Opioids	Usual starting dose
Codeine phosphate	60 mg q3–4h p.o.
Hydrocodone bitartrate	10 mg q3–4h p.o.
Oxycodone hydrochloride	10 mg q3–4h p.o.
Tramadol hydrochloride	50 mg four times daily p.o.
World Health Organization Step II/III Opioids	**Usual Starting Dose**
Morphine sulfate immediate release	30 mg q3–4h p.o.
Morphine sulfate controlled release	10 mg q3–4h iv.
Morphine sulfate sustained release	30 mg q12h p.o.
Morphine sulfate suppository	As advised
Oxycodone hydrochloride immediate release	10 mg q4h p.o.
Oxycodone hydrochloride controlled release	20 mg q12th p.o.
Hydromorphone	6 mg q12h p.o.
Fentanyl: Duragesic (transdermal)	50 mg/h q72h
Fentanyl: Sublimize	50 mg/h via continuous infusion
Methadone hydrochloride	20 mg q6–8h p.o.
Levorphanol tartrate	4 mg q6–8h p.o.

NSAIDs act by inhibiting cyclo-oxygenase, thereby inhibiting prostaglandin synthesis, which are important mediators of inflammatory process. Recent introductions in NSAID therapy include two isoforms of enzyme cyclo-oxygenase, COX-I and COX-2. Ketorolac tromethamine is available as oral, intramuscular and IV formulations. Various NSAIDs differ in their cost, dosing interval, analgesic ceiling and safety. The choice of NSAIDs must be individualized to patient's need. The common adverse effects of NSAIDs include GI toxicity, ulceration and bleeding. NSAIDs and opioids have different mechanisms of action and logically would have additive analgesia.

The opioids form an essential component of pharmacotherapy of pain and can be classified as **weak** or **strong** depending on their relative efficacy in releasing pain. Morphine sulfate is the prototype opioid agonist and is designated by WHO, as **'drug of choice'** for treatment of severe pain associated with cancer. The half-life of morphine is approximately 2 hours, and it is available both as an **oral immediate release** preparation and **slow-release preparations** that permit once- or twice-daily drug regimens. Oral administration of opioids is convenient, well tolerated, inexpensive and effective therapy. Moreover, these can also be used in epidural and intrathecal space in selected cases.

The **most common adverse effect** of opiates is **constipation** that may be the result of reduced gastric, biliary, pancreatic and intestinal secretions and a decrease in propulsive motility of stomach and intestines. The other effects include nausea and vomiting caused by direct stimulation of chemoreceptor trigger zone for emesis in the medulla. Transient sedation is common when opioid therapy is initiated but it wears off with prolonged usage.

The adjuvant drugs used include certain anticonvulsants such as gabapentin, carbamazepine and clonazepam; oral local anaesthetics, topical therapies, alpha 2 adrenergic receptors like Clonidine and Tizanidine; N-methyl-D-aspartate receptor antagonists like Ketamine, dextromethorphan and amantadine.

Certain neuroleptics like fluphenazine and haloperidol are also being used increasingly for various neuropathic pains.

Some commonly used **non-pharmacological therapies** finding increasing acceptance in pain management are quick distraction and imagery, hypnosis, **music therapy**, specialized cognitive-behavioural interventions, massage, thermal modalities, electrical stimulation etc. Certain **future neurosurgical interventions** that may be helpful in pain management include medullary or pontine tractotomy, medullary trigeminal tractotomy, mesencephalotomy, thalamotomy, myelotomy and anterolateral cordotomy.

Give medications to control special pain problems.

There are nerve injury pains and pains from special conditions that can be relieved by specific medications. Provide specific treatment in combination with drugs from the analgesic ladder.

Table 5.7.6: Medications for special pain problems

Special Pain Problems	Medication – Adolescent/Adult
For burning pains, abnormal sensation pains, severe, shooting pains with relatively little pain in between, pins and needles	Pregabalin 75 mg twice a day or low-dose amitriptyline (25 mg at night or 12.5 mg twice daily; some start at 12.5 mg daily); wait 2 weeks for response, then increase gradually to 50 mg at night or 25 mg twice daily
For muscle spasms in end-of-life care or paralyzed patient	Diazepam 5 mg orally or rectally 2–3 times per day
Herpes zoster (or shooting pain following it): refer patients with ophthalmic zoster	Low-dose amitriptyline Early eruption: acyclovir if available; apply gentian violet if ruptured vesicles
Gastrointestinal pain from colic only after intestinal obstruction has been excluded (i.e., vomiting, no stool and gas passing, visible bowel movements)	Codeine 30 mg every 4 hours or Hyoscine 10 mg three times daily (can increase up to 40 mg three times daily)
Bone pain or renal colic or dysmenorrhoea	Ibuprofen (or other NSAID)
If Pain from: • Swelling around tumour • Severe oesophageal ulceration and cannot swallow • Nerve or spinal cord compression • Persistent severe headache (likely from increased intracranial pressure)	When giving end-of-life care and referral not desired, can consider use of steroids under careful clinical supervision

Additional methods for pain control

Combine these with pain medications if patient agrees and it helps

- Emotional support

- Physical methods:

    1. Touch (stroking, massage, rocking, vibration)
    2. Ice or heat
    3. Deep breathing

- Cognitive methods: Distraction such as radio, music, imagining a pleasant scene
- Prayer (with respect to patient’s practice)

    1. Traditional practices that are helpful and not harmful—get to know what can help in the local setting.

Symptom Management

Table 5.7.7: Management of symptoms with medications and home care

Symptoms	Medications to Give	Home Care
Nausea and Vomiting	Give anti-emetic: Ondansetron 24 mg tid/ Domperidone up to 20 mg tid/ metoclopramide (10 mg every 8 hours). Give only for a day at a time or haloperidol (1–2 mg 4–6 hourly) or chlorpromazine (25–50 mg every 6–12 hours). Injectable anti-emetics may be needed in several cases	• Eat small, frequent meals. • Avoid an empty stomach as this makes the nausea worse. • Eat bland foods. • Avoid foods with strong or unpleasant odour. • Drink plenty of liquids. • Rest and relax after and between meals. • Avoid lying down immediately after eating. • Avoid coffee and alcohol. • Assess for any signs of dehydration and consult the healthcare provider if there is dehydration.
Painful mouth ulcers or pain on swallowing	• If Candida, give fluconazole, nystatin or miconazole orally. Topical anaesthetics can provide some relief. Pain medication may be required according to analgesic ladder • For aphthous ulcers, crush one 5 mg prednisone tablet and apply a few grains. • Smelly mouth/breath (halitosis) from oral cancer or other lesion: metronidazole 400 mg bid or chlorhexidine gluconate 1% 10 ml qid mouthwash or hexetidine 0.1% 10 ml qid or Benzydamine 0.5 mouthwash or sodium bicarbonate mouthwash (1 tsp in 1 pint warm water) • For herpes simplex: 3 ml nystatin solution (500,000 U) + 2 tablets metronidazole + 1 capsule acyclovir (if available): paint on lesions	• Remove bits of food stuck in the mouth with cotton wool, gauze or soft cloth soaked in salt water. • Rinse the mouth with diluted salt water (a finger pinch of salt or ½ teaspoon sodium bicarbonate in a glass of water) after eating and at bedtime. • Mix 2 tablets of aspirin in water and rinse the mouth up to 4 times a day. • Soft diet to decrease discomfort such as rice porridge, oat meals, depending on what the sick person feels is helpful. • More textured foods and fluids may be swallowed more easily than fluids. • Avoid extremely hot or cold or spicy foods.

The **commonly administered anti-emetic** agents are all 5-HT3 antagonists. Even metoclopramide that acts through a dopamine receptor (O23) probably works via 5-HT3 pathway at higher doses.

Use of the newer anti-emetic agents has decreased the incidence and severity of nausea and vomiting induced by chemotherapy (Table 5.7.8). However, these agents have not totally solved the problem. Adequate control of nausea and vomiting is a must to ensure patient compliance and follow-up ultimately leading to a better quality of life.

Table 5.7.8: Commonly administered anti-emetics: Classes, drugs and dosage schedules

Anti-emetics		
Class	**Drug**	**Dosage Schedule**
Serotonin receptor antagonists	Ondansetron	8 mg IV x 1, 24 mg p.o. x 1
	Granisetron	10 µg/kg iv. x 1, 2 mg p.o. x 1
	Dolasetron	1.8 mg/kg IV x 1, 200 mg p.o. x 1
	Tropisetron	5 mg IV x 1
Substituted benzamide	Metoclopramide	1–3 mg/kg IV x every 3 h
Phenothiazine	Prochlorperazine	10–20 mg IV x 1 over 5 min.
Butyrophenone	Haloperidol	1–3 mg IV q4–6h 1–2 mg p.o. q4–6h
Corticosteroid	Dexamethasone	10–20 mg IV x 1 over 5 min
Cannabinoid	Dronabinol	2.5–5.0 mg p.o. q3–6h
Benzodiazepine	Lorazepam	0.5–2.0 mg IV q4–6h 0.5–1.0 mg p.o. q4–6h

Table 5.7.9: Handling of PLHIV with hiccups and bedsores

Hiccups	• First try to manoeuvre to control. If oral thrush, treat • If no response or recurrent, metoclopramide (10 mg tablet, 1–2 tablets three or four times daily) OR • haloperidol (5 mg tablet: ¼ to ½ tablet 1–3 times daily) • If patient has brain tumour, consider anti-epileptic medication	• Manoeuvre to stop hiccups. • Stimulate the throat. • Quickly eat 2 heaped teaspoons sugar or • Drink cold water or eat crushed ice, or rub with a clean cloth inside the top of the mouth (feel towards the back where the top of the mouth is soft). • Interrupt the normal breathing by holding breath or breathe into paper bag: stop when you feel uncomfortable. • Pull knees to chest and lean forward (compress the chest).
Bedsores	• All patients need skin care to avoid pressure problems. • Check for signs of infection. • For smelly tumours or ulcers, sprinkle metronidazole powder – enough to cover the area and keep dry.	• For small sores, clean gently with salt water and allow to dry. • Apply honey to bedsores that are not deep and leave the wound open to the air. • If painful, give painkillers such as paracetamol or aspirin regularly. • For deep or large sores, every day clean gently with diluted salt water, fill the bedsore area with pure honey and cover with a clean light dressing to encourage healing.

End-of-life Care

“How people die lives in the memory of those left behind.”

The terminal phase is defined as the period when day-to-day deterioration, particularly of strength, appetite and awareness is occurring. Is it difficult to predict when death will occur, and is it better not to do so? The aim of care at this stage should be to ensure the patient’s comfort holistically, and a peaceful and dignified death.

Provide psychosocial and spiritual support to the patient:

- Other patients’ active listening, counselling and social/emotional support
- Spiritual support is very important.
- Be prepared to discuss all matters if patient would like to.
- Learn to listen with empathy.
- Understand reactions to the losses in their life (the different stages of grief).
- Be prepared to ‘absorb’ some reactions, e.g., anger projected onto the healthcare provider.
- Do not impose your own views.
- Share religious beliefs with the appropriate person (e.g., religious leader, spiritual counsellor) as required.
- Empower the family to provide care: see Table 5.7.10.
- Help the family to come to terms with the fact that the patient is leaving them soon: let family members be around to see and talk to the patient.
- Deal with their anxieties and fears gently.
- Give information and skills.

Table 5.7.10: Management of end-of-life care issues

Steps	Actions
Preparing for death	• Encourage communication within family. • Discuss worrying issues such as custody of children, family support, future school fees, old quarrels, funeral costs. • Tell the patient that he/she is loved and will be remembered. • Talk about death if the patient wishes to (keep in mind cultural taboos if not in a close relationship). • Make sure the patient gets help with feelings of guilt or regret. • Connect with spiritual counsellor or pastoral care as patient wishes.
Presence	Approach, be present with compassion. • Outreach visit regularly with home-based care • Someone needs to hold hand, listen and converse with the patient and family. This could be a volunteer, NGO worker, outreach worker, counsellor, etc
Caring	• Provide comfort and physical contact by light touch, holding hands (if appropriate).
Comfort measures near the end of life	• Moisten lips, mouth, eyes. • Keep the patient clean and dry and prepare for incontinence of bowel and bladder. • Only give essential medications: pain relief, anti-diarrhoeal drugs, treat fever and pain (e.g., paracetamol round-the-clock) etc. • Control symptoms with medical treatment as needed to relieve suffering (including antibiotics and antifungal drugs). • Eating less is okay; ensure hydration. • Skin care: Turn every 2 hours or more frequently to prevent bedsores. • Make sure pain is controlled.
Signs of imminent death	• Decreased social interaction: sleeps more, acts confused, coma • Decreased food and fluid intake: no hunger or thirst • Changes in elimination: reduced urine and bowel movements, incontinence • Respiratory changes: irregular breathing, 'death rattle' • Circulatory changes: cold and greyish or purple extremities, decreased heart rate and blood pressure
Signs of death	• Breathing stops completely. • Heartbeat and pulse stop. • Totally unresponsive to shaking, shouting • Eyes fixed in one direction, pupils dilated, eyelids open or closed • Changes in skin tone: white to grey

For more details on end-of-life care, those interested can read Mathura Declaration on EOLC 2017 (available on Google).

Palliative care in Children

Paediatric palliative care (PPC) is a specialized comprehensive care approach for children living with life-limiting and life-threatening illness. The focus is providing relief from the symptoms and the stress of the illness. The goal is to improve quality of life for both child and the family.

WHO's definition of palliative care appropriate for children and their families is as follows; the principles apply to other paediatric chronic disorders:

- It is the active total care of the child's body, mind, and spirit, and involves giving support to the family.
- It begins when illness is diagnosed and continues regardless of whether a child receives treatment directed at the disease.
- Health providers must evaluate and alleviate a child's physical, psychological, and social distress.
- Effective palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited.
- An integrated palliative care consists of out-patient, in-patient, hospice, and home care to maintain continuum of services

Palliative Care in Children with HIV

The physical needs of children infected with HIV may vary greatly. There is evidence that physical pain in children with HIV/AIDS has historically been underestimated and undertreated. The prevalence of pain in children with HIV/AIDS continues to be high, understudied and associated with poor quality of life and increased mortality. There is a significant need to recognize and manage pain in children, as well as other physical needs.

Palliative care in HIV-infected children may be needed from infancy and for many years for some children, while others may not need it until they are much older and for a shorter duration. Also, transition between aggressive treatment to prolonging quality of life and palliative care may not be clear.

Care and support as indicated below is integral to palliative care in children:

- Establishing a mutual trusting relationship between the child and family with the clinical team is very essential (counsellor/paediatrician/physiotherapist/nurse/ NGO/volunteer, etc.) and depends on factors unique to children.
- Child development: Physical, emotional and cognitive development influences all aspects of care from understanding of the disease, drug dosages to communication skills and death.
- Care at home: Most children are cared for at home. If the parent (if still alive) is present, the family unit needs to be given support and be taught appropriate skills.
- Assessing symptoms in children: Healthcare providers must provide an environment where children

    1. Do not fear repercussions from their honest expressions (especially if there is an authority figure like doctors/parents);
    2. Understand that there is a possibility to reduce pain if present;
    3. Learn to trust the healthcare providers and express future feeling and symptoms.

- The palliative care team should provide support during emergencies and health crises and help in the challenges of day-to-day living.
- Relief of symptoms and the management of pain need to continue, even when the option to stop ART may have to be considered.
- Prevention of opportunistic infections (Cotrimoxazole prophylaxis).

Essential components of palliative care for children

Pain Management

It is important to note that pain is often not adequately treated in children because of the following reasons:

- Some children are unable to express their pain due to their age, lack of verbal skills or disability.

- Few healthcare professionals are trained and skilled at evaluating children's pain and suffering, and therefore pain is left unrecognised, ignored and untreated.
- Majority of health professionals lack competence in prescribing opioids in children.
- There is fear of using opioids for pain management due to common belief that it will lead to addiction.
- Acknowledgement and support for spiritual pain and conflict, and the impact of culture and language is mostly ignored in children.

Successful pain management in HIV-infected children begins with efforts to diagnose and treat the underlying conditions causing pain.

Non-pharmacological measures: Various cognitive methods help relieve pain.

- Age-appropriate active distraction
- Older children can be encouraged to concentrate on a game, a conversation or special story.
- Swaddling or carrying an infant, providing warmth, breastfeeding, or feeding, stroking, rocking, massaging
- Relaxation techniques and behaviour modifications
- Environmental management, including play opportunities, music, scheduled (rather than random) medical and nursing interventions and structured opportunities for sleep and rest
- Nutritional support, adequate hydration and electrolyte replacement
- Pharmacological measures: Correct use of analgesic medicines will relieve pain in most children.

Although there are a limited number of analgesic medicines that can be safely used in children, it is still possible to provide adequate analgesia according to the child's level of pain severity: for children assessed as having mild pain, paracetamol and ibuprofen should be considered as first options and in children assessed as being in moderate to severe pain, the administration of an opioid should be considered.

Symptom management

HIV infection is associated with a variety of symptoms due to the infection itself, OIs and treatment side effects. Common symptoms include fever, cough, diarrhoea, anorexia, sore mouth, nausea, vomiting and shortness of breath. These are major causes of discomfort and poor quality of life during HIV infection in infants and children.

Many of these symptoms can be prevented, treated or controlled with basic medications and therapies. Non-pharmacological methods are important adjuvants to symptom management. Alleviating symptoms enables the children to function, freeing them from the restrictions of the disease as much as possible.

Psychosocial and Spiritual Support

In addition to coping with a life-threatening disease and debilitating symptoms, HIV-infected children and their infected/uninfected families may have to manage changing family dynamics, stigma in the community, loss of their own physical functions, depression and hopelessness. In this context, psychosocial support can significantly improve their quality of life.
This may need an inter-disciplinary team including doctors, social workers, psychotherapists and counsellors who are trained to provide counselling and to address mental health issues. They may help them in dealing with the emotional effects of their illness, as well as the social environment in which they function.

Home-Based Care

Home-based care means any form of care given to sick people in their own homes instead of in a hospital setting. Home-based care covers physical, emotional, spiritual and social aspects, including self-care, care provided by family members, peer counsellors, outreach workers (ORW), link workers or ASHA.

Home-based Care Components

The following components are an integral part of managing PLHIV in their homes by the caregivers:

- Symptom and pain management
- Clinic/hospital referral for routine visits and acute care
- Treatment support for adherence and side effect management
- Nutritional support
- Emotional support, spiritual support (links with religious organizations as appropriate)
- Social services (income generation, child support, food support)
- Future planning for self/family preparing will, identifying guardian for child
- End-of-life care (pain management, funeral, grieving support for family)

Caregivers to Know

The caregivers should be educated or given information on basic knowledge of HIV/AIDS, personal and environmental hygiene, prevention of infections and injuries to themselves and others, management of infections at home and necessary information on essential nutritional needs and additional energy requirements. In addition, they should be equipped with information about medicines to be taken by the patient and their possible side effects and on whom to call for help whenever necessary.

Symptom Management at Home

The caregivers, with the information and knowledge provided, will be able to address and manage symptoms like cough, fever, hiccups, weight loss, nausea and vomiting, mouth ulcers, pain on swallowing, dry mouth, constipation and incontinence of stool and urine. They should be able to alleviate anxiety and trouble sleeping, which might be bothering the patient on various issues. The caregivers should be in touch with the ART centres to seek advice on the suspected side effects of ARV drugs.

Interventions in Home-based Care

It would be more beneficial for the patients if the caregivers were oriented with certain skills on prevention of bedsores, prevention of pain, stiffness and contractures in joints, bathing and handling the bedridden. For managing PLHIV in their homes, there should be necessary materials made available as the part of ‘home healthcare kit’.

Table 5.7.11: Home healthcare kit

Items	Quantity (minimum)
Sterile gauze pads	20
1-, 2-, 3-inch gauze rolls	2 each
Clean cotton	1 small package
Soap	1 bar
Scissors	1 pair
Calamine lotion	1 bottle
Bleaching powder	500 g
Petroleum jelly or Vaseline	1 jar
Gentian violet crystals or solution	1 small packet or bottle
Potassium permanganate crystals	1 small packet
Betadine ointment	1 small bottle
Rubber gloves or plastic bags	1 pack each
Towels or clean cotton cloth	Sufficient quantity

Challenges Faced by Caregivers

Over a period, caregivers are subjected to physical and emotional stress, burden of providing care and also taking care of household work, especially women, lack of income if the head of the family is sick and this will be more intense if there is only one caregiver and that too as and when he/she also falls ill.

Caregiver stress
Symptoms of caregiver stress: Stress in the caregivers can be identified by surfacing emotional symptoms like crying, worry or anxiety, irritability, anger, feeling exhausted and/or lack of interest in their activities.

Approach to caregiver stress

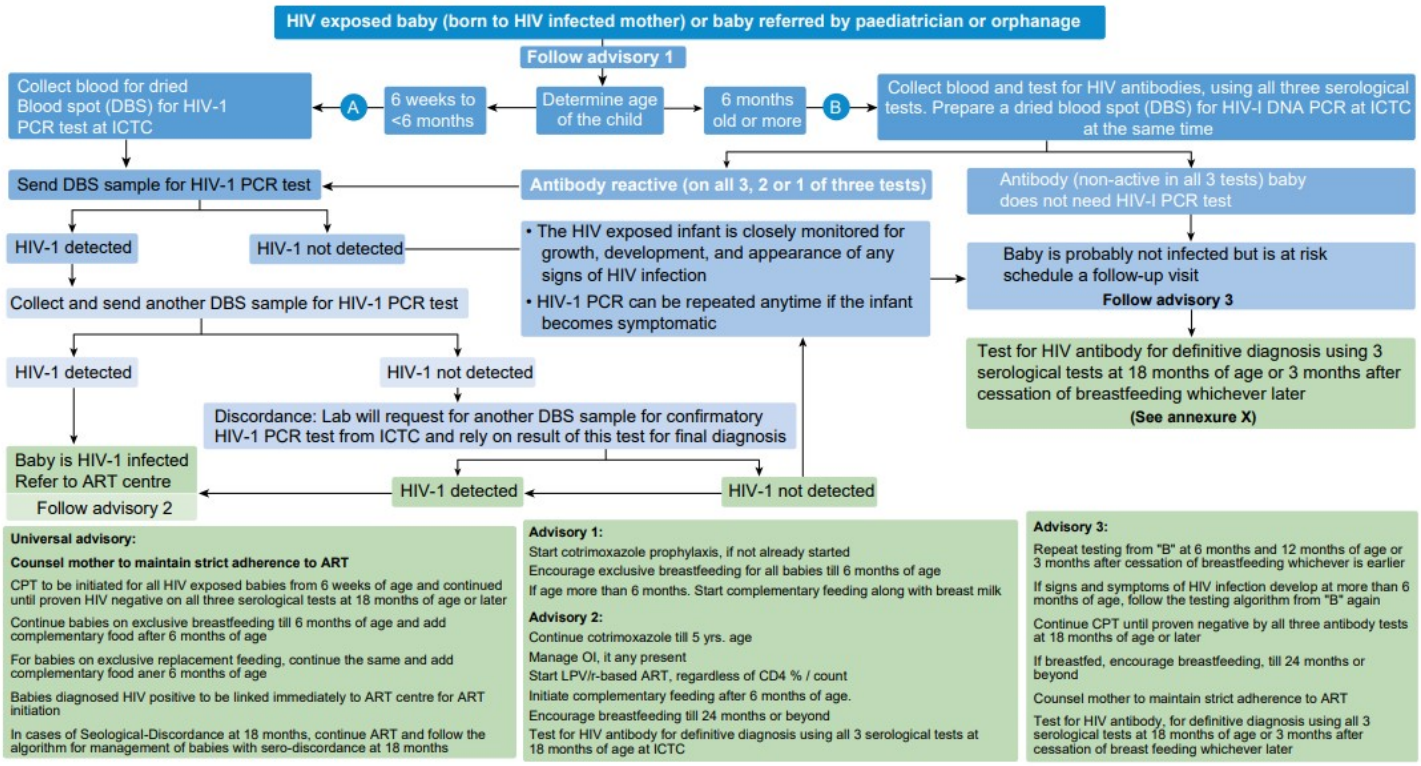
- Encourage them to talk to friends and relatives whom they trust, participate in activities outside home, support groups and hobbies, make them eat well and take care of their own health, train them to become peer educators with positive attitude and approach.
- Train more family members: Apart from the caregivers, other family members also should be educated on providing adequate and appropriate nutrition, nursing the patient according to his/her prevailing conditions, preventing complications, preventing transmission of infections like TB, linking with the community Home Based care provider for support and referrals, alleviating pain as much as possible, seeing that patient seeks medical care for any trivial infection, supporting the patient in order to avoid risky situations and providing emotional support and spiritual care. This helps identify additional caregivers within the family and provides needed relief and rest for the overburdened caregivers.

Section 6

Annexures

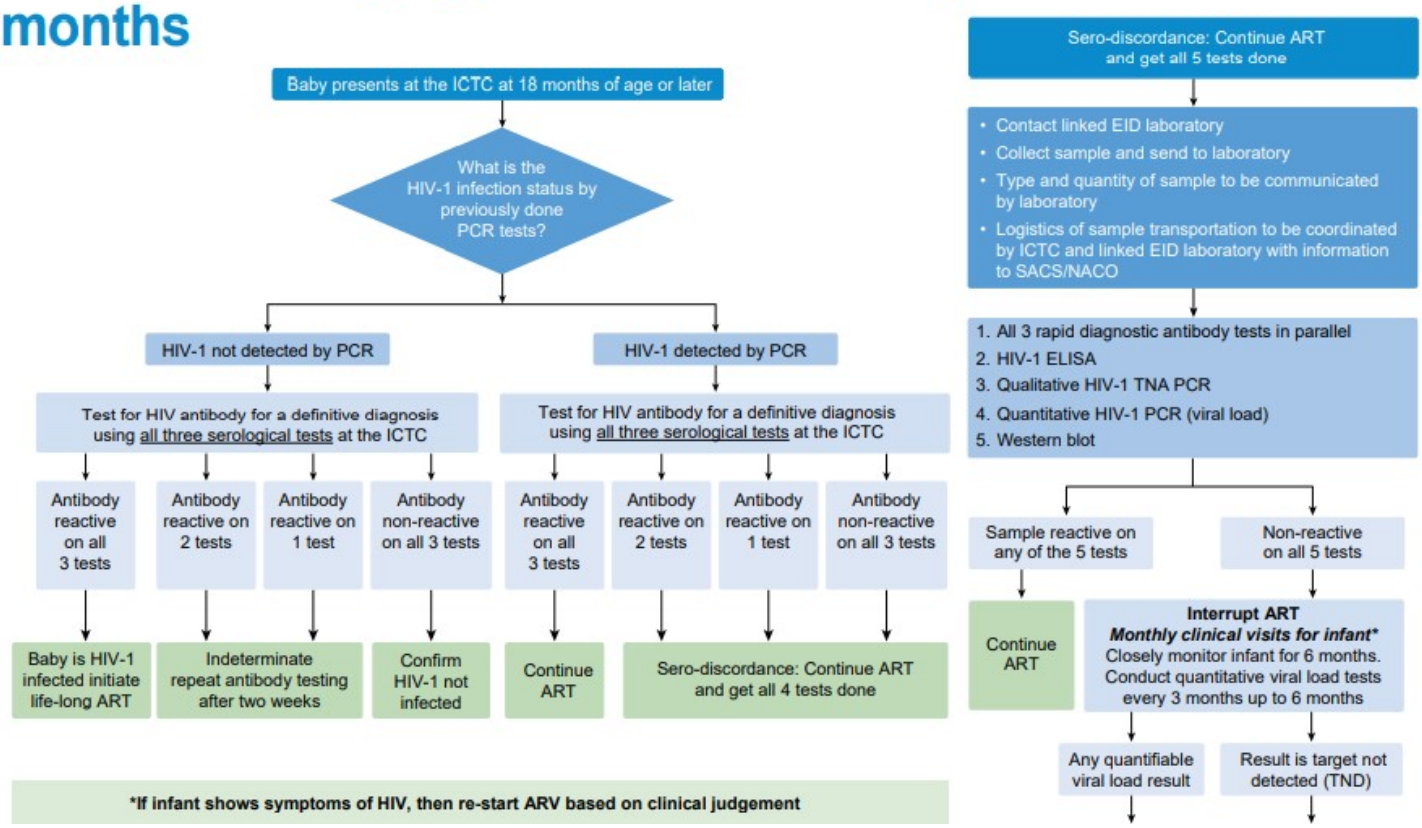
Annexure 1 National testing algorithm for HIV-1 exposed infants and children

National testing algorithm for HIV-1 exposed infants and children <18 months



Annexure 1x National testing algorithm for HIV-1 exposed children >18 months

National testing algorithm for HIV-1 exposed children >18 months



Annexure 2 ≫ Paediatric ARV dosage schedule

Paediatric ARV dosage schedule

FDC dosing table: (*rows highlighted (in yellow) indicate new FDC formulations devised as per WHO policy brief 2020)

Drug formulations	Body Weight in Kg & doses as Morning (M) / Night (N)															
	3–5.9		6–9.9		10–13.9		14–19.9		20–24.9		25–29.9		30–39.9		>40	
	M	N	M	N	M	N	M	N	M	N	M	N	M	N	M	N
ABC/3TC 120/60 mg scored dispersible tablet$	1	–	1.5	–	2	–	2.5	–	3	–						
ABC/3TC 600/300 mg tablet											1	–	1	–	1	–
ABC/3TC 60/30mg tablet	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
AZT/3TC 60/30 mg tablet	1	1	1.5	1.5	2	2	2.5	2.5	3	3						
AZT/3TC 300/150 mg tablet											1	1	1	1	1	1
LPV/r 40/10 mg pellets	2	2	3	3	4	4	5	5								
LPV/r 80/20 mg/ml syrup	1 ml	1 ml	1.5 ml	1.5 ml	2.0 ml	2.0 ml										
LPV/r 100/25 mg tablet					2	1	2	2	3	2	3	3				
LPV/r 200/50 mg tablet$													2	2	2	2
RTV 100 mg tablet for super boosting#@			1	1	1	1	2	1	2	1	2	2	2 (till 35 kg)	2 (till 35 kg)		
EFV 200 mg tablet$					–	1	–	1.5	–	1.5	–	2.0				
EFV 400 mg tablet$											–	1	–	1	–	1
DTG 5 mg dispersible tablets$	1	–	3	–	4	–	5	–								
DTG 10 mg scored dispersible tablet$	0.5	–	1.5	–	2	–	2.5	–								
DTG 50 mg tablet									1	–	1	–	1	–	1	–
TDF/3TC/DTG 300/300/50 mg tablet													1	–	1	–
DRV 100 mg/ml syrup$					2.5 ml	2.5 ml	3 ml till 15 kg	3 ml till 15 kg								
DRV 75 mg tablet#$							5 for ≥15 kg	5 for ≥15 kg	5	5						
DRV 400 mg tablet#$											1	1	1 (till 35 kg)	1 (till 35 kg)		
DRV 600 mg tablet#$													1 (≥ 35 kg)	1 (≥ 35 kg)	1	1
DRV/r 600/100 mg tablet#@													1 (≥ 35 kg)	1 (≥ 35 kg)	1	1
DRV/r 400/50 mg tablet$							1	1	1	1	1	1	1 (till 35 kg)	1 (till 35 kg)		
DRV/r 800/100 mg tablet$															1	–
RTV 80 mg/ml syrup$					0.5 ml	0.5 ml	0.6 ml	0.6 ml								
RTV 25 mg tablet#@$									2	2	2	2				
RTV 50 mg tablet#@$									1	1	1	1				
RTV 100 mg tablet#@													1	1	1	1
ATV/r 300/100 mg tablet#@													1 (for >35 kg)	–	1	
TDF/3TC/EFV (TLE) 300/300/400 mg tablet$													–	1	–	1

*Rows highlighted (in yellow) indicate new FDC formulations devised as per WHO policy brief 2020.

#All protease inhibitors (PIs) including Ritonavir should not be broken, crushed or powdered, as efficacy will be compromised.

@Dose of Ritonavir for boosting will vary with the PI used; the doses mentioned are when used with LPV/r

$Drugs/ FDC are not available under the National AIDS Control Programme

All PIs including Ritonavir should not be broken, crushed or powdered, as efficacy will be compromised.

LPV/r Pellets to be restricted to only those small children who cannot swallow the whole LPV/r paediatric tablet; Transitioning from pellets to tablets should be encouraged as soon as feasible, for better compliance as the child grows.

Dosage Chart for Ritonavir in Super Boosting of Lopinavir (LPV/r+r) in HIV–TB co-infection

Weight (kg)	Morning/ Night	Dosage of ABC/LMV+ LPV/r		Dose of Additional Ritonavir Tablet 100 mg
3 – 5.9	Morning	ABC/ 3TC (60/30) Syp LPV/r (80/20)	1 tab 1 ml	Add Tab Ritonavir 50 mg 1 tablet$
	Night	ABC/ 3TC (60/30) Syp LPV/r (80/20)	1 tab 1 ml	Add Tab Ritonavir 50mg 1 tablet$
6 – 9.9	Morning	ABC/ 3TC (60/30) Syp LPV/r (80/20)	1 tab 1.5 ml	Add Tab Ritonavir 100 mg 1 tablet
	Night	ABC/ 3TC (60/30) Syp LPV/r (80/20)	1.5 tabs 1.5 ml	Add Tab Ritonavir 100 mg 1 tablet
10 – 13.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	2 tabs 2 tabs	Add Tab Ritonavir 100 mg 2 tablets
	Night	ABC/ 3TC (60/30) LPV/r (100/25)	2 tabs 1 tab	Add Tab Ritonavir 100 mg 1 tablet
14 – 19.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	2.5 tabs 2 tabs	Add Tab Ritonavir 100 mg 2 tablets
	Night	ABC/ 3TC (60/30) LPV/r (100/25)	2.5 tabs 2 tabs	Add Tab Ritonavir 100 mg 1 tablet
20 – 24.9	Morning	ABC/ 3TC (60/30) LPV/r (100/25)	3 tabs 3 tabs	Add Tab Ritonavir 100 mg 2 tablets
	Night	ABC/ 3TC (60/30) LPV/r (100/25)	3 tabs 2 tabs	Add Tab Ritonavir 100 mg 1 tablet
25 – 29.9	Morning	ABC/ 3TC (600/300) adult dose LPV/r (100/25)	1 tab 3 tabs	Add Tab Ritonavir 100 mg 2 tablets
	Night	LPV/r (100/25)	3 tabs	Add Tab Ritonavir 100 mg 2 tablets
30 – 34.9	Morning	ABC/ 3TC (600/300) adult dose LPV/r (200/50) adult dose	1 tab 2 tabs	Add Tab Ritonavir 100 mg 2 tablets
	Night	LPV/r (200/50) adult dose	2 tabs	Add Tab Ritonavir 100 mg 2 tablets

Raltegravir Oral Suspension dosing table for full-term neonates from birth to age 4 weeks [https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/raltegravir]

Neonates Aged ≥ 37 Weeks and Weighing ≥ 2 kg[a]	
Birth to 1 Week of Age: Once-daily dosing	**Approximately 1.5 mg/kg per dose**
2 kg to <3 kg	0.4 ml (4 mg) once daily
3 kg to <4 kg	0.5 ml (5 mg) once daily
4 kg to <5 kg	0.7 ml (7 mg) once daily
1–4 weeks of age: Twice-daily dosing	**Approximately 3 mg/kg per dose**
2 kg to <3 kg	0.8 ml (8 mg) twice daily
3 kg to <4 kg	1 ml (10 mg) twice daily
4 kg to <5 kg	1.5 ml (15 mg) twice daily

[a]Raltegravir is metabolized by uridine diphosphate glucuronyl transferase (UGT1A1), and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4–6 weeks of life.

Note: If the mother has taken Raltegravir 2–24 hours prior to delivery, the neonate's first dose should be delayed until 24–48 hours after birth.

Infant >4 Weeks of Age and Child (Weighing ≥3 kg to <20 kg) dose for children weighing 3–20 kg, either oral suspension or chewable tablets can be used.

Raltegravir Oral Suspension Dosing Table for CLHIV aged >4 weeks[$]

Weight	Dose
3 kg to <4 kg	2.5 mL (25 mg) twice daily
4 kg to <6 kg	3 mL (30 mg) twice daily
6 kg to <8 kg	4 mL (40 mg) twice daily
8 kg to <10 kg	6 mL (60 mg) twice daily
10 kg to <14 kg	8 mL (80 mg) twice daily
14 kg to <20 kg	10 mL (100 mg) twice daily

[$]The weight-based dose recommendation for the oral suspension is based on a dose of approximately Raltegravir 6 mg/kg per dose twice daily.

Note: The maximum dose of oral suspension is 10 ml (RAL 100 mg twice daily).

References

1. WHO policy brief, 1 July 2020-Considerations for introducing new antiretroviral drug formulations for children, Available at: https://apps.who.int/iris/rest/bitstreams/1285186/retrieve

2. Update of recommendations on first- and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019 (WHO/CDS/HIV/19.15). Available at https://apps.who.int/iris/ handle/10665/325892

3. WHO July 2021-Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring, Available at: https://www.who.int/publications-detail-redirect/9789240031593

Annexure 3 Additional guidance on Tenofovir related renal toxicity

Additional Guidance on Tenofovir- Related Renal Toxicity

Tenofovir disoproxil fumarate (TDF)–containing regimen is the preferred first-line ART for all patients in the national programme. It has a good overall safety profile, with fewer metabolic side effects and mitochondrial toxicities. TDF has a relatively long half-life, allowing once-daily dosing and making compliance easier for patients. The major side effects of TDF are (i) renal toxicity and (ii) decrease in bone mineral density. However out of these, the most significant is TDF-related renal toxicity, though overall incidence may be only 3%–5%. The renal proximal tubule (PT) is the main target of TDF toxicity; although the pathogenesis is incompletely elucidated, mitochondria appear to be a major target.

Effect on Glomerular Function

In a pooled analysis comparing TDF with Zidovudine, a modest but significant decline in estimated glomerular filtration rate (eGFR) was observed in the TDF-exposed patients. A meta-analysis that included data from 17 studies concluded that TDF exposure is associated with a mean difference in estimated creatinine clearance (CrCl) of −3.9 ml/min over the course of treatment. However, this meta-analysis also found a high degree of statistical heterogeneity in the published data, due to variability in parameters such as follow-up time, previous ART exposure and concomitant usage of protease inhibitors (PIs).

Effect on Tubular Function

Serum creatinine and eGFR are predominantly measurements of glomerular function; however, the main target of TDF nephrotoxicity is the proximal tubule (PT) and in severe cases leading to a breakdown of solute transport in this nephron segment (renal Fanconi's syndrome [FS]) or acute kidney injury (AKI). Fanconi's syndrome includes aminoaciduria, glycosuria, tubular proteinuria, uricosuria and also bone demineralization due to phosphate wasting. This may lead to acute renal failure and this renal toxicity can usually present after 20 weeks or more of Tenofovir therapy; resolution typically takes place within 10 weeks after the discontinuation of the therapy.

Numerous case reports and case series have described FS or AKI in PLHIV taking TDF. The exact incidence of TDF-induced FS is unknown and attempts at accurate estimates are hampered by under-reporting and a lack of clear diagnostic criteria, but based on the available data it is estimated to be <1%. Renal biopsy specimens from patients with TDF toxicity typically show acute tubular damage, with misshapen and swollen mitochondria in the PT on electron microscopy. While cases of FS and AKI are relatively infrequent in patients taking TDF, these represent the most severe end of the PT toxicity spectrum. Studies have majorly demonstrated mild or subclinical PT dysfunction in patients on TDF. The reported prevalence varies among studies, partly because of a lack of standardized definitions. It is currently unknown whether mild PT toxicity will lead to progressive chronic kidney disease (CKD) over time in these patients, but one credible concern is that chronic phosphate wasting might cause a decrease in bone mineral density.

Effect on Tubular Secretion of Creatinine

Serum creatinine is widely used to calculate CrCl/eGFR; however, in addition to glomerular filtration, about 10%–40% of creatinine clearance occurs by secretion across the PT epithelium. Decline in CrCl/eGFR within the first 2–3 months of commencing therapy, with very little further change over time, has been seen in many studies. Therefore, given the pattern of CrCl/eGFR changes reported in patients taking TDF, it is plausible that they might be due to impaired PT creatinine secretion rather than alterations in actual GFR. To explore this hypothesis, a small study of 19 HIV-infected patients, either remaining on Zidovudine therapy or switching to TDF, looked in detail at changes over time in actual GFR, calculated CrCl and urine excretion of tubular protein. In the patients switching to TDF, mean CrCl was significantly decreased, while urine excretion of tubular protein was significantly increased after 48 weeks; however, there was no corresponding change in actual GFR and no changes in any of the three parameters were observed in the Zidovudine group, which helps to conclude that decrease in CrCl in the TDF patients was more likely to be due to impaired PT creatinine secretion rather than a change in glomerular function.

Guidance for Treatment

The main target of TDF toxicity is the proximal tubule and hence for the suspicion of renal toxicity, the presence of tubular proteinuria is thought to be the most sensitive test for proximal tubule dysfunction. For monitoring the renal tubular dysfunction that often results in Fanconi Syndrome, urine routine showing pH as acidic along with glycosuria and albuminuria will be sufficient for the diagnosis though a 24-hour urine sample for phosphate (hypophosphatemia and hypokalaemia), protein and calcium are confirmatory. If feasible, the creatinine clearance may also be calculated and any adverse raise in the level of serum creatinine should raise suspicion for early signs of renal damage.

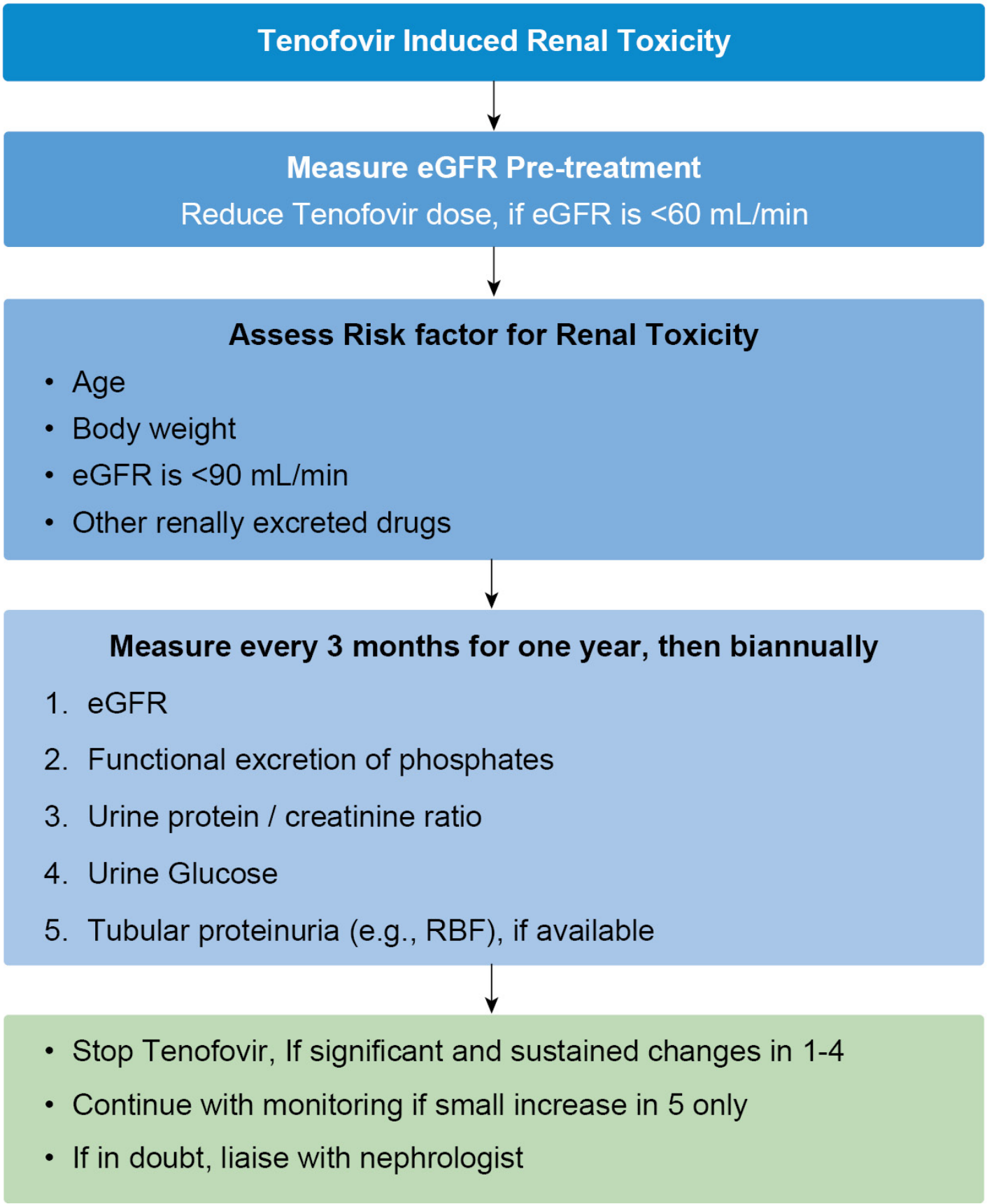
For initiating on TDF-containing regimens, creatinine clearance calculation is recommended, if feasible,

before initiation and every 6 months. Especially in patients in high-risk situations like underlying renal disease, age >40 years, BMI <18.5 (or body weight <50 kg), diabetes mellitus, hypertension, concomitant use of nephrotoxic drugs, doing a creatinine clearance is strongly recommended before opting for TDF. The inability to perform creatinine clearance is not a barrier to TDF use. Hence in a resource-limited setting, TDF can even be started without a creatinine clearance level; however, the above-mentioned risk factors should be assessed. TDF dose should be reduced in patients with pre-existing decreased kidney function.

Cockcroft-Gault formula: eGFR = (140 – age) X (Weight in kg) X 0.85 (if female) / (72 X Cr in mg%)

Do not continue TDF when the estimated glomerular filtration rate is <50 ml/min. In patients suspected with Fanconi syndrome, treatment should be stopped, and resolution typically occurs within 10 weeks after discontinuation of the therapy. Patients receiving TDF and meeting any one of the four below mentioned criteria should have kidney function (eGFR) and serum phosphate measured every 6 months and be analysed for proteinuria and glycosuria.

1. GFR <90 ml/min
2. Use of other medications eliminated through renal secretion (e.g., adefovir, acyclovir, ganciclovir or cidofovir)
3. Other comorbid diseases (e.g., diabetes or hypertension)
4. Following a ritonavir-boosted protease inhibitor regimen


Tenofovir Induced Renal Toxicity
Measure eGFR Pre-treatment
Reduce Tenofovir dose, if eGFR is <60 mL/min
Assess Risk factor for Renal Toxicity
• Age
• Body weight
• eGFR is <90 mL/min
• Other renally excreted drugs
Measure every 3 months for one year, then biannually
1. eGFR
2. Functional excretion of phosphates
3. Urine protein / creatinine ratio
4. Urine Glucose
5. Tubular proteinuria (e.g., RBF), if available
• Stop Tenofovir, If significant and sustained changes in 1-4
• Continue with monitoring if small increase in 5 only
• If in doubt, liaise with nephrologist

Tenofovir and Lamivudine Dosage** Adjustment in Relation to Creatinine Clearance Values			
Creatinine Clearance	**Tenofovir Dose**	**Creatinine Clearance**	**Lamivudine Dose**
30–49	300 mg q48h	30–49	150 mg QD
10–29	300 mg twice a week	15–29	150 mg first dose and then 100 mg QD
<10*	Not recommended	5–14	150 mg first dose and then 50 mg QD
Haemodialysis (HD)	Every 7 days, after dialysis	Less than 5 or on haemodialysis	50 mg first dose and then 25 mg QD

*Note: The pharmacokinetics of Tenofovir have not been evaluated in non-HD patients with CrCl <10 mL/min; therefore, no dosing recommendation is available for those patients.

**Considering the non -availability of Lamivudine single tablet, following steps are recommended:

- For patients with creatinine clearance ≥ 30 ml/min, full dosage of Abacavir 600 + Lamivudine 300 (AL) can be given
- For patients with creatinine clearance < 30 ml/min, if Lamivudine single tablet of 100mg is not available, full dose of AL may be given with close monitoring of renal function test, till creatinine clearance improves and to be stopped if it worsens.

Annexure 4 Grading of selected clinical and laboratory toxicities

Grading of selected clinical and laboratory toxicities

Estimating severity of grade	Mild Grade 1	Moderate Grade 2	Severe Grade 3	Potentially life-threatening Grade 4
Clinical adverse events NOT identified elsewhere in the table	Symptoms causing minimal or no interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care OR medical or operative intervention indicated to prevent permanent impairment, permanent disability or death
Haemoglobin	8.0 – 9.4 g/dl	7.0 – 7.9 g/dl	6.5 – 6.9 g/dl	<6.5 g/dl
Absolute neutrophil count	1000 – 1500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
Platelets	75000 – 99000/mm^3	50000 – 74999/mm^3	20000 – 49999/mm^3	<20000/mm^3
Hyper bilirubinaemia	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.5 – 5 X ULN	>5 X ULN
Glucose (Fasting)	110 – 125 mg/dl	126 – 250 mg/dl	251 – 500 mg/dl	>500 mg/dl
Hypoglycaemia	55 – 64 mg/dl	40 – 54 mg/dl	30 – 39 mg/dl	<30 mg/dl
Hyperglycaemia (non-fasting no prior diabetes)	116 – 160 mg/dl	161 – 250 mg/dl	251 – 500 mg/dl	>500 mg/dl
Triglycerides	-	400 - 750 mg/dl	750 - 1200 mg/dl	> 1200 mg/dl
Creatinine	>1.0 – 1.5 X ULN	>1.5 – 3.0 X ULN	>3.0 – 6.0 X ULN	>6.0 X ULN
AST (SGOT)	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
ALT (SGPT)	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
GGT	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
Alkaline Phosphatase	1.25 – 2.5 X ULN	>2.25 – 5.0 X ULN	>5.0 – 10.0 X ULN	>10.0 X ULN
Bilirubin	1.1 – 1.5 X ULN	1.6 – 2.5 X ULN	2.6 – 5.0 X ULN	>5.0 X ULN
Amylase	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.0 – 5.0 X ULN	>5.0 X ULN
Pancreatic amylase	>1.0 – 1.5 X ULN	>1.5 – 2.5 X ULN	>2.0 – 5.0 X ULN	>5.0 X ULN
Lactate	<2.0 x ULN without acidosis	>2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life threatening consequences	Increased lactate with pH <7.3 with life threatening consequences
Gastrointestinal	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Nausea	Mild OR transient; reasonable intake maintained	Moderate discomfort OR intake decreased for <3 days	Severe discomfort OR minimal intake for ≥3 days	Hospitalization required
Vomiting	Mild OR transient; 2-3 episodes per day OR mild vomiting lasting <1 week	Moderate OR persistent; 4-5 episodes per day OR vomiting lasting ≥1 week	Severe vomiting of all foods/fluids in 24 hours OR orthostatic hypotension OR intravenous treatment required	Hypertensive shock OR hospitalization for intravenous treatment required
Diarrhoea	Mild OR transient; 3-4 loose stools per day OR mild diarrhoea lasting <1 week	Moderate OR persistent; 5-7 loose stools per day OR diarrhoea lasting ≥1 week	Bloody diarrhoea OR orthostatic hypotension OR >7 loose stools per day OR intravenous treatment required	Hypertensive shock OR hospitalization required
Respiratory	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Dyspnoea	Dyspnoea on exertion	Dyspnoea with normal activity	Dyspnoea at rest	Dyspnoea requiring Oxygen therapy
Urine analysis	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Spot urine	1+	2+ or 3+	4+	Nephrotic syndrome
24 hours urine	200 mg to 1 g loss/ day OR <0.3% OR <3 g/L	1-2 g loss/day OR 0.3% to 1% OR 3-10 g/L	2-3.5 g loss/day OR >1% OR >10 g/L	Nephrotic syndrome OR >3.5 g loss/day
Gross haematuria	Microscopic only	Gross, no clots	Gross plus clots	Obstructive
Miscellaneous	**Mild Grade 1**	**Moderate Grade 2**	**Severe Grade 3**	**Potentially life-threatening**
Fever (Oral, >12 hours)	37.7-38.5^{0}C OR 100.0-101.5^{0}F	38.6-39.5^{0}C OR 101.6-102.9^{0}F	39.6-40.5^{0}C OR 103-105^{0}F	>40.5^{0}C OR >105^{0}F for ≥12 continuous hours
Headache	Mild; no treatment required	Moderate OR non-narcotic analgesia treatment	Severe OR responds to initial narcotic treatment	Intractable
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria, angioedema	Anaphylaxis
Rash hypersensitivity	Erythema, pruritus	Diffuse maculopapular rash OR dry desquamation	Vesiculation OR moist desquamation OR ulceration	ANY ONE OF: Mucous membrane involvement, suspected Stevens-Johnson's syndrome, toxic epidermal necrolysis (TEN), erythema multiforme, exfoliative dermatitis
Fatigue	Normal activity reduced by <25%	Normal activity reduced by 25%-50%	Normal activity reduced by >50%; cannot work	Unable to care for self

Note: This clarification includes addition of Grade 5 toxicity, which is death

Annexure 5 Atazanavir-induced unconjugated hyperbilirubinemia

Atazanavir-induced unconjugated hyperbilirubinemia

Background

The recommended prescribed dose of Atazanavir (ATV) is ATV 300 mg + Ritonavir (RTV) 100mg once daily. No dosage adjustment is required for patients with renal dysfunction unless they are on haemodialysis. Considering the widespread use of ATV, clinicians caring for HIVinfected patients should have familiarity with the entity of protease inhibitor-associated hyper bilirubinaemia.

Isolated unconjugated hyper bilirubinaemia is the most common laboratory abnormality associated with the use of ATV and this is not associated with hepatocellular injury. Although not considered a serious adverse effect, the higher levels of unconjugated hyper bilirubinaemia associated with this drug can manifest as jaundice with a high coloured urine. The onset of ATV associated hyper bilirubinaemia typically occurs within several months, and bilirubin levels generally peak within 4 months (range 1 to 8 months); the subsequent natural history on therapy is notable for a non-progressive course, with bilirubin levels remaining generally stable in patients on further **follow-up**. Routine monitoring of bilirubin is acceptable.

An isolated elevation in total bilirubin should be confirmed as predominantly unconjugated by testing the indirect fraction of bilirubin. The presence of elevated conjugated bilirubin or changes in serum hepatic aminotransferases or alkaline phosphatase warrant further investigation for other causes of hyper bilirubinaemia, such as other drug hepatotoxicity, viral hepatitis, alcoholic hepatitis or cholestasis. It is important to recognize that patients who are on ATV but with acute haemolysis will also develop increased indirect bilirubin levels.

Management

For patients who develop clinically evident jaundice, the decision of whether to discontinue the offending

protease inhibitor (ATV) usually depends on how severe and noticeable the jaundice is, and whether the patient is willing to tolerate it. Additional work-up is not required if liver enzymes are not raised and consistent with baseline values. The patient requires proper counselling on the development of yellowish discolouration of eye that is not associated with liver damage and it should be reemphasized that this is physiological and not alarming.

Dose reduction of ATV is not recommended in this setting. In most cases, a change to an alternative regimen is necessary only for patients who develop an unacceptable level of jaundice with Grade 3 (5-10 times ULN) and 4 (>10 times ULN) elevation of serum ALT and AST.

In case of hepatic insufficiency, dosage adjustment is recommended. Child-Pugh score is utilized to assess the severity and prognosis of chronic liver disease and to identify patients who require liver transplantation. This score is to be used only in those HIV infected subjects who have concomitant chronic liver disease e.g. chronic hepatitis B and C, alcoholic liver disease, NASH and other chronic liver diseases.

ATV/r (300/100 mg) can only be used in patients with chronic liver disease in Child Pugh Class A. It should not be used on second line patients with Child Pugh Class B or C. Please refer the following tables for the scores and classifications.

Component	Child-Pugh Score		
	Point 1	Points 2	Points 3
Encephalopathy	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretic
Albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Total bilirubin or	<2 mg/dl (<34 µmol/l)	2–3 mg/dl (34 µmol/l to 50 µmol/l)	>3 mg/dl (>50 µmol/l)
Modified total bilirubin (for patients of Gilbert's disease and patients on Atazanavir and Indinavir)	<4 mg/dl	4–7 mg/dl	>7 mg/dl
Prothrombin time (Seconds prolonged)	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

Encephalopathy Grades

- **Grade 1:** Mild confusion, anxiety, restlessness, fine tremor, slowed coordination
- **Grade 2:** Drowsiness, disorientation, asterixis
- **Grade 3:** Somnolent but arousable, marked confusion, incomprehensible speech, incontinence, and hyperventilation
- **Grade 4:** Coma, decerebrate posturing, flaccidity

Child-Pugh Classification

Child-Pugh Classification	Total Score
Class A	5-6 points
Class B	7-9 points
Class C	>9 points

Annexure 6 National TB elimination programme: Anti-TB drugs – Adverse effects and drug interactions

National TB elimination programme:Anti-TB drugs – Adverse effects and drug interactions

1. **Anti-TB drugs: Adverse drug reactions**

Symptoms and causative anti-TB drugs

Symptoms	Drug responsible
Upper abdominal pain – Frequent	All oral anti-tubercular drugs
Nausea, vomiting	All oral anti-tubercular drugs
Nausea, vomiting with yellowness of skin and dark colour urine; indication of Jaundice	Mainly by Pyrazinamide, Rifampicin. and Isoniazid
Loose stools frequency >4 times, liquid stools	Poor hygiene and mainly by Isoniazid and Rifampicin
Itching / Rashes	Mainly by Ethambutol, Rifampicin and Streptomycin
Rashes (Steven-Johnson's syndrome / TEN)	Mainly by Ethambutol, Rifampicin and Streptomycin
Anaemia: Tiredness, lethargy, headache, pale look, palpitations	Mainly Isoniazid, Rifampicin, Pyrazinamide
Ear toxicity: Ringing in the ears, loss of hearing, dizziness and loss of balance leading to recurrent fall	Mainly Streptomycin and other amino glycosides
Kidney toxicity: Swelling of face or legs, less or no urine	Mainly Streptomycin and other amino glycosides
Giddiness, feeling abnormal	Mainly Streptomycin and Isoniazid
Tingling / burning / numbness in the hands and feet	Mainly Isoniazid
Seizure: Convulsion	Isoniazid
Psychiatric disturbances: Seeing abnormal things, change of thoughts, suicidal thoughts	Isoniazid

TEN, Toxic epidermal necrolysis.

Anti-TB drugs – side effects and interactions

Drug	Side effects	Potential drug interactions	Notes
Rifampicin	Gut upset, rash, fever, orange urine / tears / saliva, light sensitivity, liver problems, acute renal failure	PIs, NNRTIs, '-azole' anti-fungal drugs, oral contraceptives, methadone, dapsone	Do not use with PIs or Nevirapine
Rifabutin	Gut upset, rash, eye inflammation, blood cell changes, joint pain, orange urine / tears / saliva, liver function changes, fever	PIs, NNRTIs, fluconazole, oral contraceptives, steroids, methadone	Avoid wearing soft contact lenses as they can become discoloured. Avoid Nevirapine

NNRTI, Non-nucleoside reverse transcriptase inhibitors; PI, Protease Inhibitor.

Anti-TB drugs with different antiretroviral drugs used in adults

ARV	Rifampicin	Rifabutin	Notes
NRTIs (Zidovudine, Tenofovir, Lamivudine, Stavudine)	Use as per weight band	Use in adult patients only; 150 mg once daily	No interactions
Efavirenz	Use as per weight band		Efavirenz usual dose (600mg daily)
Nevirapine	Drug interaction Do not use	Do not use	High risk of liver toxicity
Boosted PIs	Drug interaction Do not use	Use in adults (150 mg daily)	Rifabutin does not interact with PIs Rifabutin: 150 mg daily
Dolutegravir	Use as per weight band	Use in adults (50 mg daily)	Rifampicin interacts with Dolutegravir In the presence of Rifampicin, Dolutegravir dosage must be 50 mg twice daily
			When Rifabutin is used in place of Rifampicin, dosage of Dolutegravir must be 50 mg once daily
Raltegravir	Use as per weight band	Use in adults (150 mg daily)	Rifampicin interacts with Raltegravir In the presence of Rifampicin, Raltegravir dosage must be 800 mg twice daily
			When Rifabutin is used in place of Rifampicin, dosage of Raltegravir must be 400 mg twice daily

PI, Protease Inhibitor.

2. Management of drug-induced hepatitis

- Features that indicate the need to stop medication

  Transient, asymptomatic increases in serum liver transaminases occur during the early weeks of treatment.

  There is no need to interrupt or change treatment unless there is anorexia, malaise, vomiting or clinically evident jaundice.

  Clinical features of concern include protracted vomiting, mental changes, and signs of bleeding, all of which suggest impending acute liver failure and require immediate discontinuation of anti-tuberculosis medications.

- Management of jaundice and other severe features

  If jaundice or any of the clinical features suggestive of acute liver failure develop, all drugs must be stopped until the jaundice or hepatic symptoms have resolved, and the liver enzymes have returned to baseline levels .

  Other causes of hepatitis must be sought

    It is advisable to wait 2 weeks after the jaundice has disappeared before starting anti-TB treatment.

3. Anti-TB drugs: Dosage adjustment in renal impairment

- Dose modification for anti-TB drugs:

- Severity of renal impairment is defined by CrCl and renal impairment is considered as follows:

  Mild (1.5–2 mg/dl serum creatinine)

  Moderate (2–3 mg/dl serum creatinine)

  Severe (>3 mg/dl serum creatinine)

  Creatinine clearance calculation by Cockcroft–Gault formula

- Required details:

  Patient’s age in years

Patient’s weight in kg

Patient’s serum creatinine in mg/dl

- Calculating CrCl: Cockcroft–Gault formula

CrCl (ml/min) =

(140 – age in years) x weight in kg

72x serum creatinine in mg/dl

In female patients, the whole product needs to be multiplied by 0.85.

Algorithm for reintroduction of ATT

Adverse drug reaction	Advice on reintroduction
Hepatotoxicity	Can be given after liver enzyme returns to 2x ULN
Ocular toxicity	• The main suspect drug is Ethambutol • Reintroduction of Ethambutol is not recommended
Immune mediated nephritis	• The main suspect drug is Rifampicin • Reintroduction with Rifampicin is not recommended
Non-serious cutaneous ADRs - no mucous membrane involvement or less than 10% of BSA	After withholding all drugs, reintroduce the drugs one at a time
Serious cutaneous adverse drug reactions - mucous membrane involvement or more than 10% of BSA	Reintroduction is not recommended (applies for all anti-tubercular drugs)
Immune thrombocytopenia	• The main suspect drug is Rifampicin • Reintroduction with Rifampicin is not recommended
Aplastic anaemia	• The main suspect drug is Isoniazid • Reintroduction with Isoniazid is not recommended
Nephrotoxicity	• The main suspect drugs are Amino Glycosides (AGs) • Reintroduction at low doses of AGs can be given after the renal function returns to normal
Ototoxicity	• The main suspect drugs are AGs • Reintroduction of AGs is not recommended
Diarrhoea	• Reintroduction is recommended with one drug at a time every fourth day, once the diarrhoea is resolved

For key drugs, Isoniazid, Rifampicin, Ethambutol, detailed desensitisation protocol with very small dose and method of dosage preparation is given below:

Stepwise increase in the dosage for reintroduction

Drug	Day 1	Day 2	Day 3
Isoniazid	50 mg	Full dose	Full dose
Rifampicin	75 mg	300 mg	Full dose
Pyrazinamide	250 mg	1000 mg	Full dose
Ethambutol	100 mg	500 mg	Full dose

If the test dose of any drug causes a reaction, discontinue the drug unless it is deemed essential to the regimen. If that is the case, desensitization can be considered. If rash is particularly severe, dose increment should still be slower.

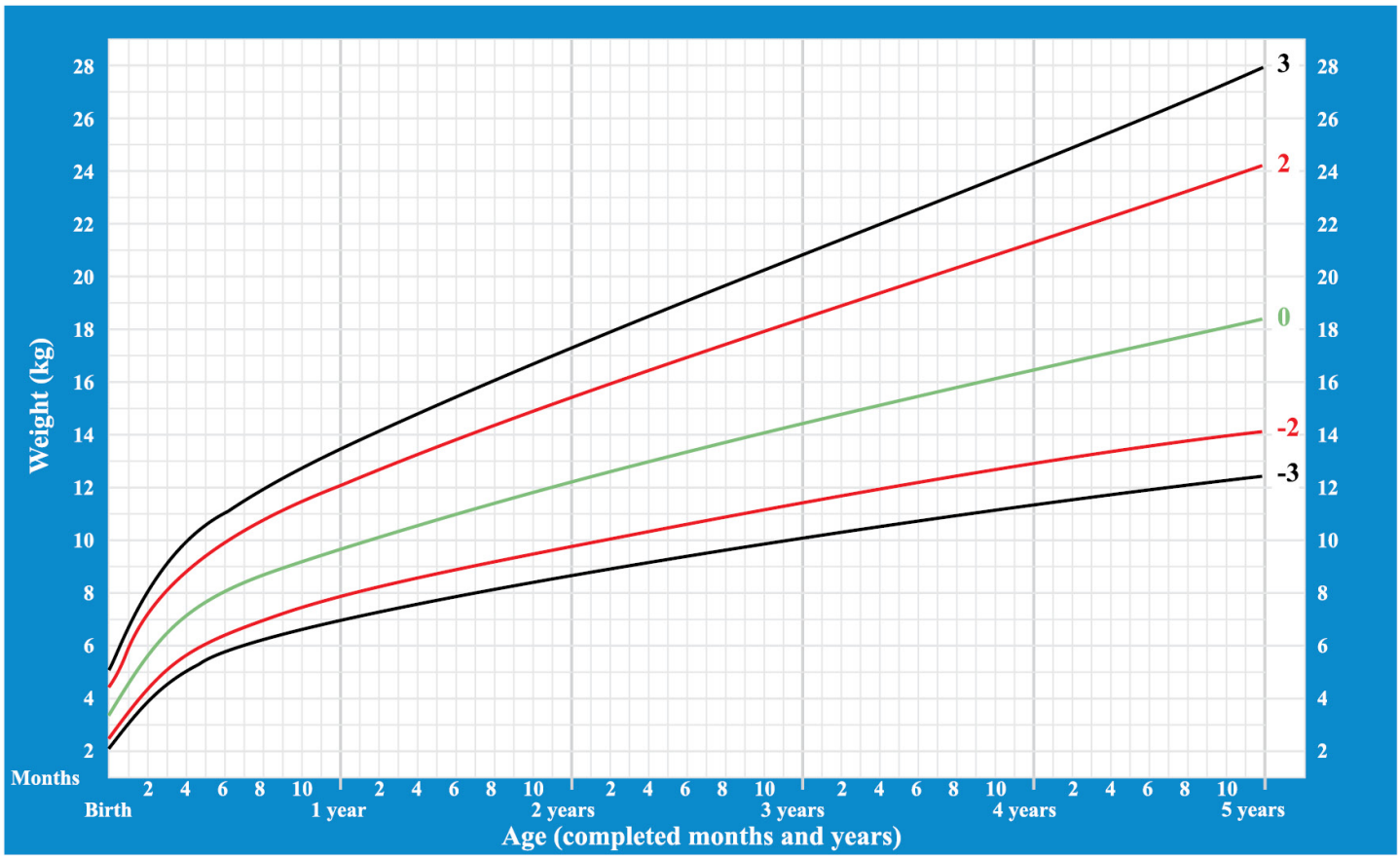
Annexure 7 ≫ WHO weight-for-age chart (Birth to 5 years of age)

WHO weight-for-age chart (Birth to 5 years of age)

Weight-for-age BOYS

Birth to 5 years (z-scores)

World Health Organization

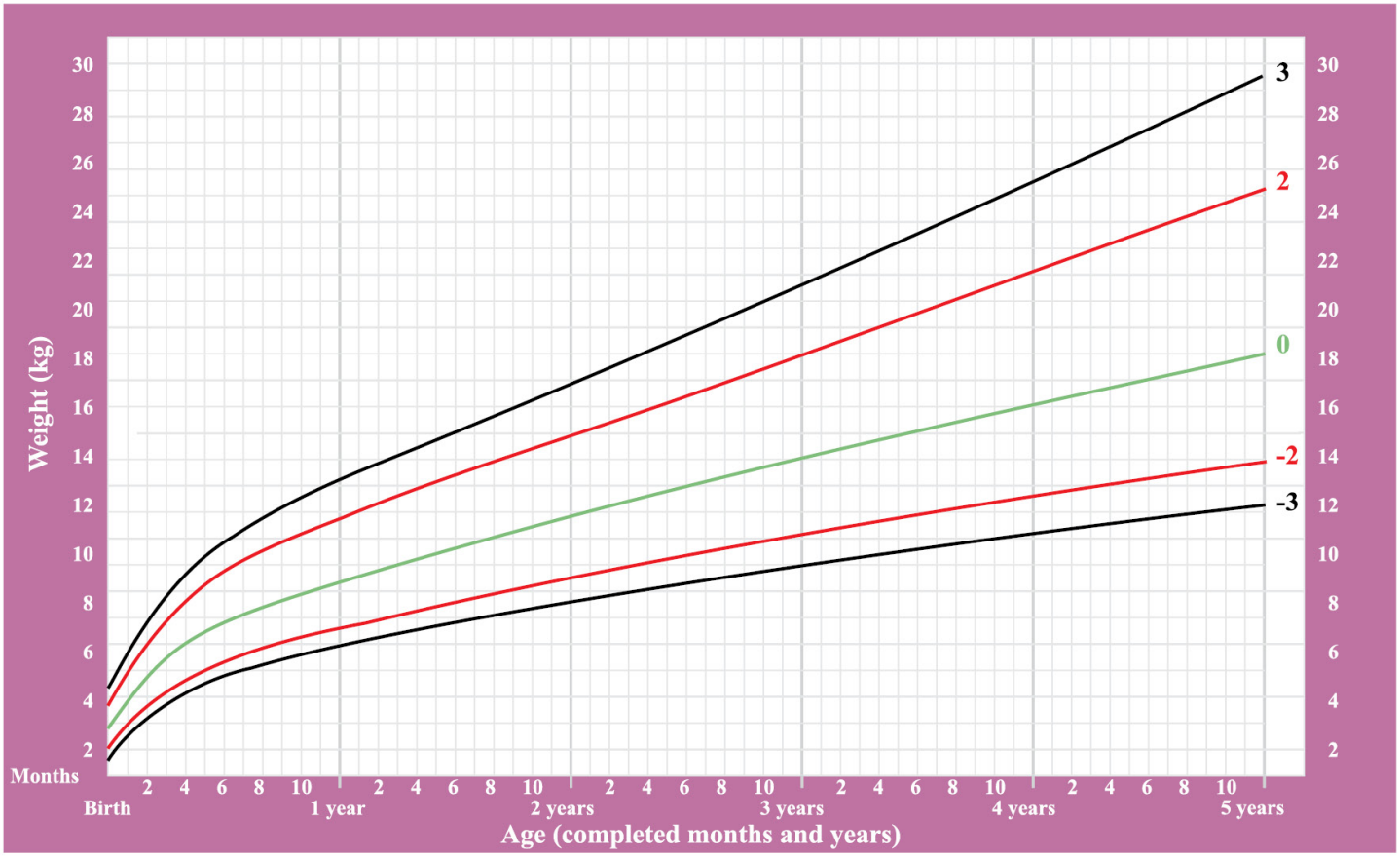


WHO Child Growth Standards

Weight-for-age GIRLS

Birth to 5 years (z-scores)

World Health Organization

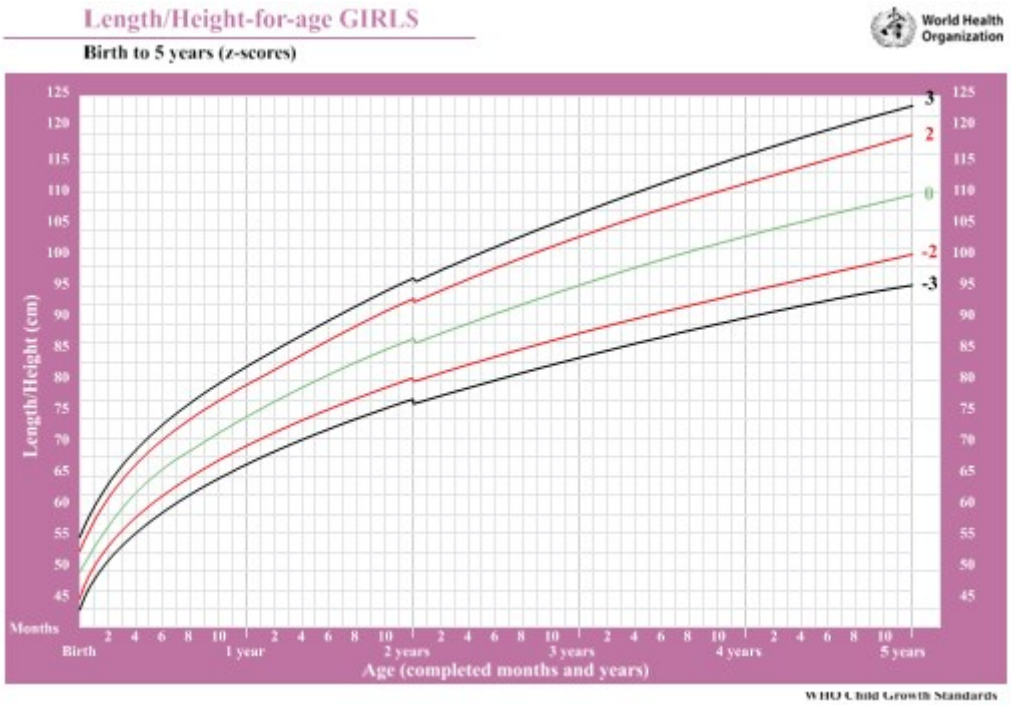


WHO Child Growth Standards

Annexure 8 ≫ WHO length/height-for-age chart (Birth to 5 years of age)

WHO length/height-for-age chart (Birth to 5 years of age)



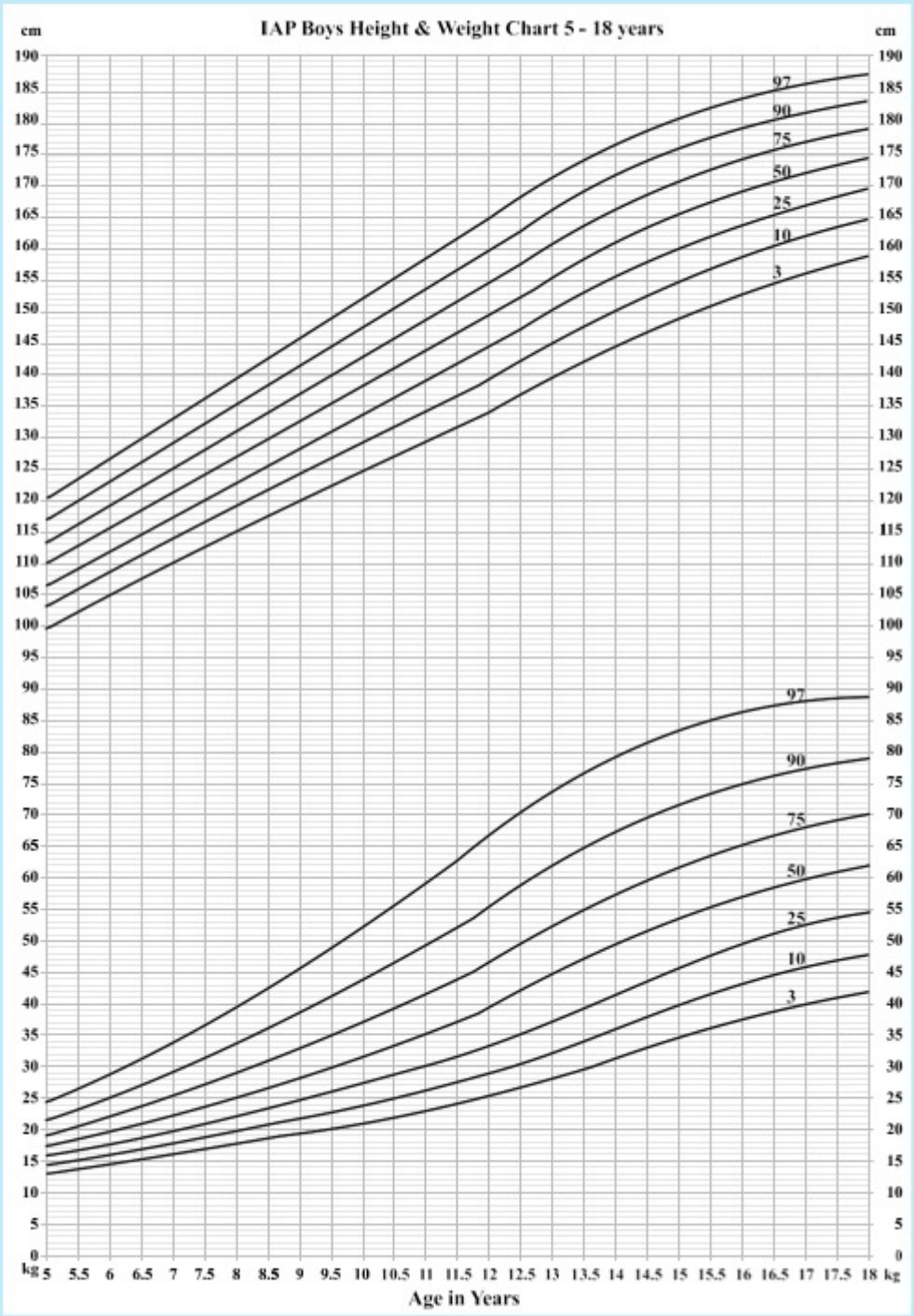


Annexure 9 ≫ IAP boys height and weight chart: 5-18 years

IAP boys height and weight chart: 5-18 years

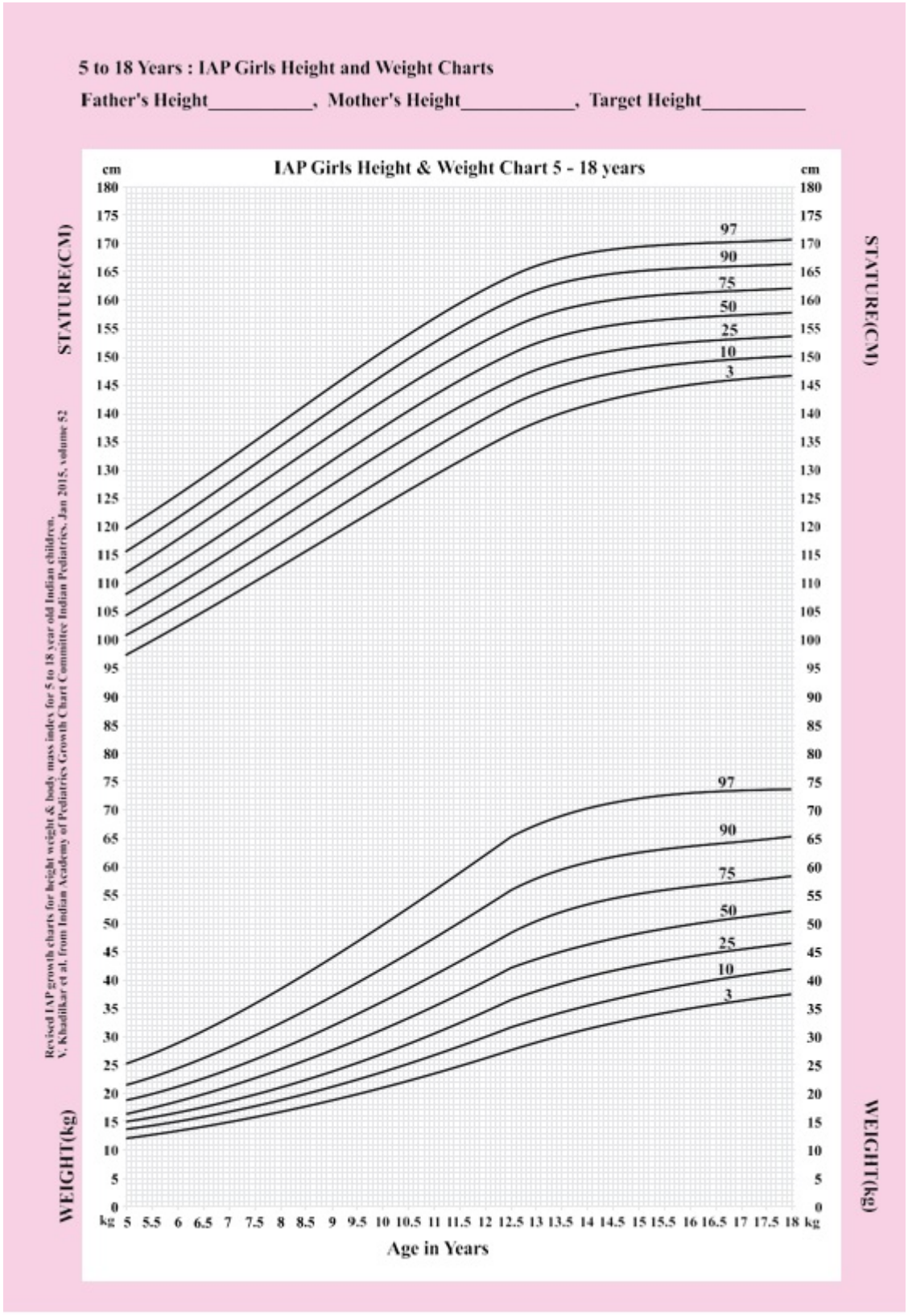
5 to 18 Years : IAP Boys Height and Weight Charts

Father's Height_____, Mother's Height_____, Target Height_____



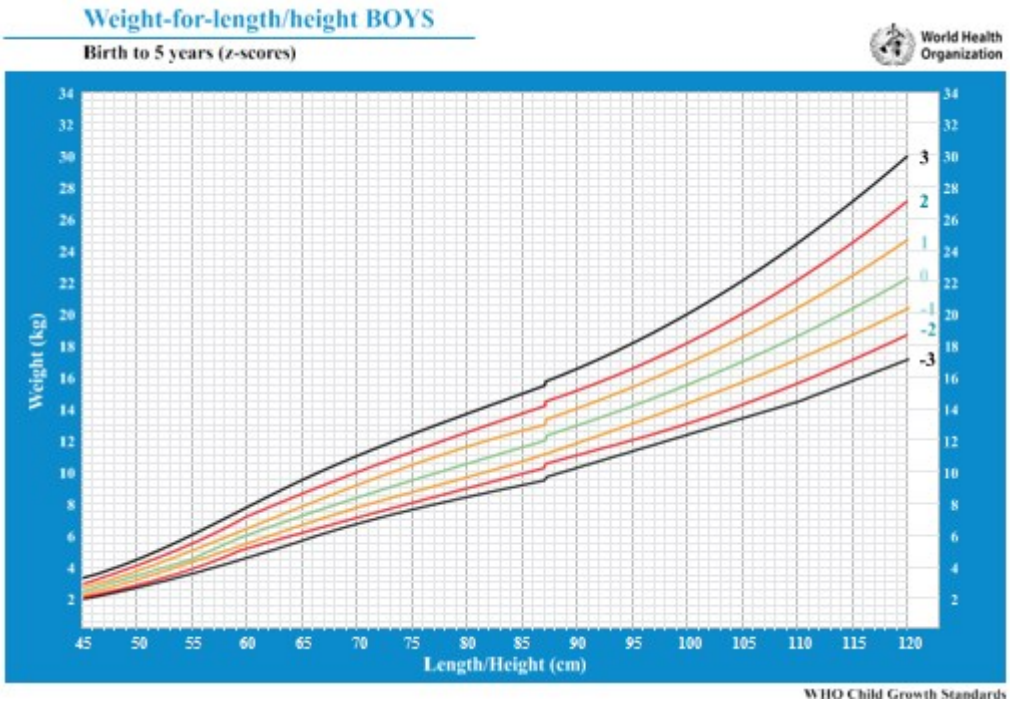
Annexure 10 » IAP girls height and weight chart: 5-18 years

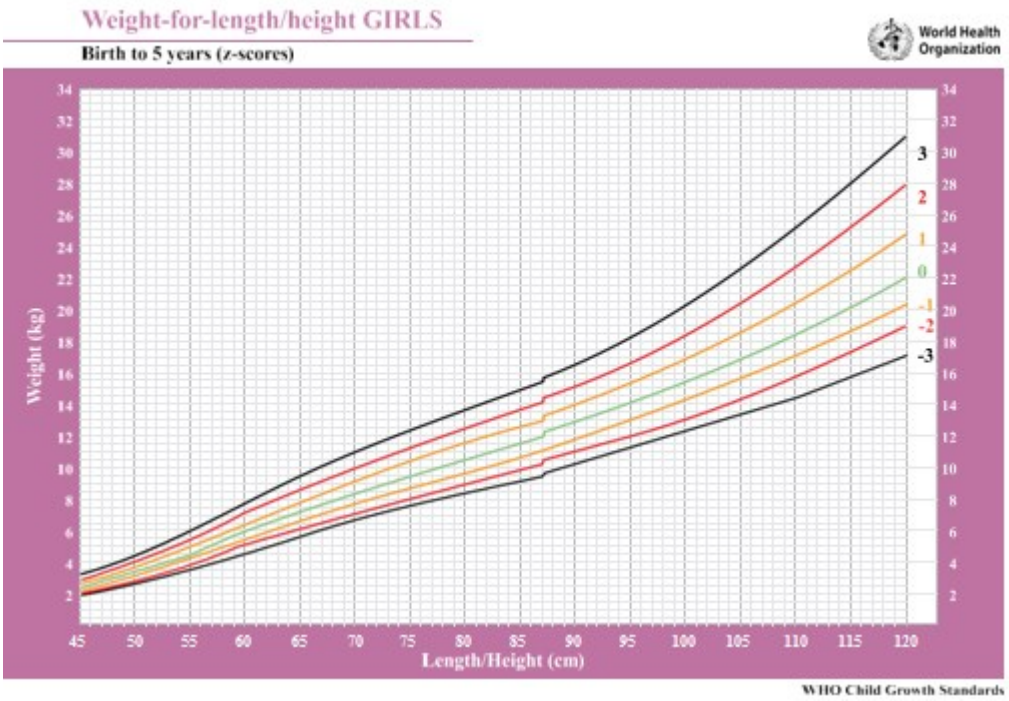
IAP girls height and weight chart: 5-18 years



Annexure 11 ≫ WHO weight for length/height chart: 0-5 years

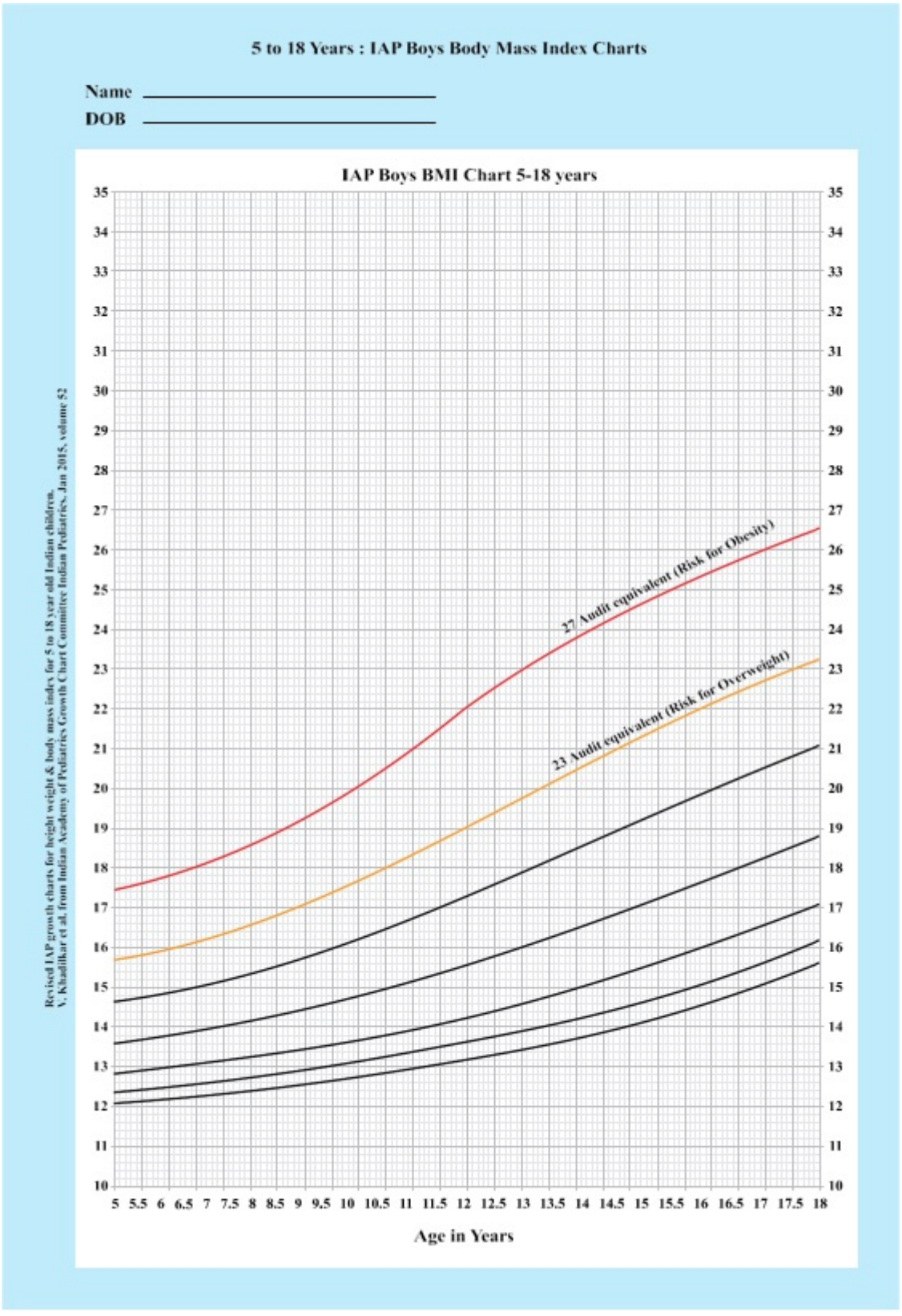
WHO weight for length/height chart: 0-5 years





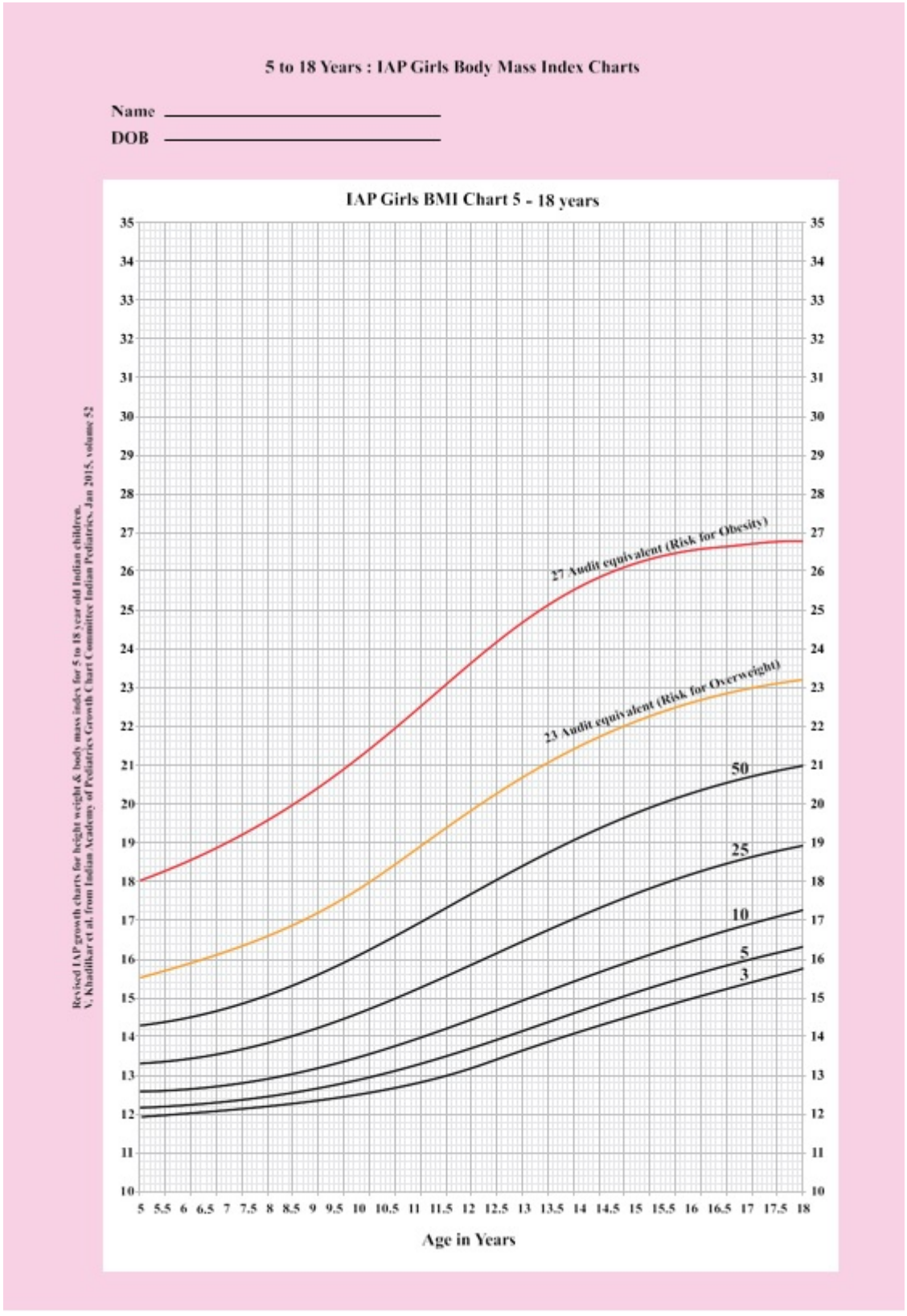
Annexure 12 ≫ IAP boys BMI chart 5-18 years

IAP boys BMI chart 5-18 years



Annexure 13 ≫ IAP girls BMI chart 5-18 years

IAP girls BMI chart 5-18 years



Annexure 14 Safe preparation of formula/ animal milk and the amount of milk the child will need at different ages

Safe preparation of formula/animal milk and the amount of milk the child will need at different ages

- Wash your hands with soap and water before preparing a feed.
- Use clean utensils for preparation of feed.
- Use suitable infant formula reconstituted as per manufacturer's recommendations / undiluted animal milk with a cup (katori or katori and spoon). Remember cup or spoon feeding is safer than bottle-feeding. (Evidence suggests formula feed is nutritionally more suitable)
- Wash the utensils with soap and water

Safe preparation of formula/animal milk

Animal milk feed	Formula feed
• To prepare milk feed, mix 1 level teaspoon of sugar in 1 cup boiled whole cow's milk. Give plain water (preferably boiled and cooled) to the infant between feeds.	• Always use the marked cup or glass to measure water and the scoop to measure the formula powder as per manufacturer's recommendation. • Measure the exact amount of powder that you will need for one feed. • Boil enough water vigorously for 1 or 2 seconds. • Add the hot water to the powdered formula. The water should be added while it is still hot and not after it has cooled down. Stir well. • Only make enough formula for one feed at a time. Do not keep milk in a thermos flask because it will become contaminated quickly. • Demonstrate and let the mother show mixing of correct amounts of water and formula powder.

Amount of milk the child will need at different ages

Age	Approximate amount of milk in 24 hours	Approximate number of feeds
0 to 4 weeks	200-500 ml	8 x 60 ml
1 up to 2 months	650 ml	7 x 90 ml
2 up to 3 months	750 ml	6 x 120 ml
3 up to 4 months	750 ml	6 x 120 ml
4 up to 5 months	900 ml	6 x 150 ml
5 up to 6 months	900 ml	6 x 150 ml

Annexure 15 IMNCI Guidelines on Feeding Recommendations for Children

IMNCI Guidelines on Feeding Recommendations for Children

Up to 6 months	6 to 12 months	12 months to 2 years	2 years & older
Breast feed as often as the child wants, day and night, at least 8 times in 24 hours Do not give any other foods or fluids, not even water.	Breast feed as often as the child wants Give at least one katori serving* at a time of: Mashed roti/rice/ bread/biscuit mixed in sweetened undiluted milk OR Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR Mashed boiled/fried potatoes *3 times per day if breast fed; 5 times per day if not breast fed.	Breast feed as often as the child wants Offer food from the family pot Give at least 1½ katori serving* at a time of: Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR Mashed roti/rice/bread/biscuit mixed in sweetened undiluted milk OR Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR Mashed boiled/fried potatoes Also give nutritious food between meals, such as: banana/ biscuit/ chiku/mango/papaya as snacks *5 times per day.	Give family foods at 3 meals each day. Also, twice daily, give nutritious food between meals, such as: banana/ biscuit chiku/mango /papaya as snacks.
Remember Continue breastfeeding if the child is sick.	**Remember** Hold the child on your lap and feed with your own hands. Wash your own and child's hands with soap and water every time before feeding.	**Remember** Ensure that the child finishes the serving. Wash your child's hands with soap and water every time before feeding.	**Remember** Ensure that the child finishes the serving Teach your child to wash his/her hands with soap and water every time before feeding.

Annexure 16 » Age-related food intake standards for children

Age-related food intake standards for children

Age	Milk Toned (ml)	Food Cooked	Approximate Calories
6 – 11 Months	If BF, then frequently or on demand If not BF, then 500 ml milk	If BF, give ½ K cereals 3 times/day If not BF, give½ K cereals 5 times/day +½ K vegetable +½ K dal + ½ egg*	645 Kcal (if not BF)
12 – 23 Months	500 ml	1 K cereals 3 – 4 times/day +3/4 K vegetable + 3/4 K dal + 1 egg*	925 – 1000 Kcal
2 – 5 Years	500 – 750 ml	6 – 8 cereal exchanges/day +1 K vegetable +1 K dal + 1 egg*	1100 – 1250 Kcal
5 – 9 Years	500 – 750 ml	8 – 10 cereal exchanges / day +2 K vegetable +2 K dal + 1 egg*	1350 – 1650 Kcal
10 – 14 Years	500 – 750 ml	12–14 cereal exchanges / day +3 K vegetable +2 K dal + 2 eggs*	2000 – 2200 Kcal

BF: Breastfeeding

1 K = 1 medium size katori = 150 ml;

1 Egg = 2 pcs (30g) non-vegetarian or 3O g paneer or 100 g curd

Cereal exchange list	
Exchange of cereal	1 Chapatti (20gm), 1 bread slice, ½ K khichri, ½ K suji kheer ½ K rice, ½ K upma, ½ K poha, ½ K dalia, ½ K vermicelli 1 medium idli, 8 ml oil, 100 g fruit, ½ small potato 2 sweet biscuits, 3 salty biscuits

*If vegetarian then substitute egg with milk product

Annexure 17

Five keys to safer food (Ref: Nutrition guidelines for HIV-exposed and infected children [0-14 years of age])

Five keys to safer food

(Ref: Nutrition guidelines for HIV-exposed and infected children [0-14 years of age])

1. Keep clean

- Wash your hands before handling food and often during food preparation.
- Wash your hands after going to the toilet, changing the baby or being in contact with animals.
- Wash/clean all surfaces and equipment used for food preparation or serving.
- Protect kitchen areas and food from insects, pests, and other animals.

2. Separate raw and cooked foods

- Separate raw meat, poultry, fish, and seafood from other foods.
- Use separate equipment and utensils, such as knives and cutting boards for handling raw foods.
- Store foods in covered containers to avoid contact between raw and cooked foods.

3. Cook thoroughly

- Cook food thoroughly, especially meat, poultry, eggs, fish, and seafood. For meat and poultry, make sure juices are clear, not pink.
- Bring foods like soups and stews to boiling point.
- Reheat cooked food thoroughly. Bring to the boil or heat until too hot to touch. Stir while re-heating.

4. Keep food at safe temperatures

- Do not leave cooked food at room temperature for more than 2 hours.
- Do not store food too long, even in a refrigerator.
- Do not thaw frozen food at room temperature.
- Food for infants, young children and other people with low immune systems should ideally be freshly prepared and not stored at all after cooking.

5. Use safe water and foods

- Use safe water or treat it to make it safe.
- Choose fresh and wholesome foods.
- Do not use food beyond its expiry date.
- Use pasteurized milk or boil milk before use.
- Wash fruits and vegetables in safe water, especially if eaten raw.

Annexure 18 » Feeding recommendations during sickness and health

Feeding recommendations during sickness and health

Counsel the mother

Feeding recommendations during sickness and health

 Up to 6 months of age	 6 months up to 12 months	 12 months up to 2 years	 2 years and older
• Breastfeed as often as the child wants, day and night, at least 8 times in 24 hours. • Do not give other foods or fluids.	• Breastfeed as often as the child wants. • Give at least one katori serving* at a time of: ▪ Mashed roti/rice/bread/ biscuit mixed in sweetened undiluted milk OR ▪ Mashed roti/rice/bread/ biscut mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR ▪ Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR ▪ Mashed boiled/fried potatoes ▪ Offer banana/biscut/cheeko/ mango/papaya	• Breastfeed as often as the child wants. • Offer food from the family pot ▪ Give at least 1½ Katori serving* at a time of: ▪ Mashed roti/rice/bread mixed in thick dal with added ghee/oil or khichri with added oil/ghee. Add cooked vegetables also in the servings OR ▪ Mashed roti/rice/bread/ biscuit mixed in sweetended undiluted milk OR ▪ Sevian/dalia/halwa/kheer prepared in milk or any cereal porridge cooked in milk OR ▪ Mashed boiled/fried potatoes ▪ Offer banana/biscuit/cheeko/ mango papaya	• Give family foods at 3 meals each day. • Also, twice daily, give nutritious food between meals, such as: banana/biscuit/cheeko/ mango papaya as snacks
Remember Countinue breastfeeding if the child is sick	*3 times per day if breastfed plus snacks 5 times per day if not breastfed. **Remember** • Keep the child in your lap and feed with your own hands • Wash your own and child's hands with soap and water every time before feeding	*5 times per day if not breastfed. **Remember** • Sit by the side of child and help him to finish the serving • Wash your child's hands with soap and water every time before feeding	**Remember** • Ensure that the child finishes the serving • Teach your child wash his hands with soap and water every time before feeding

Feeding recommendations for a child who has persistent diarrhoea

- If still breastfeeding, give more frequent, longer breastfeeds, day and night
- If taking other milk:
- Repalce with increased breastfeeding OR
- Repalce with fermented milk product, such as yoghurt OR replace half the milk with nutrient-rich semisoild food.
- Add cereals to milk (rice, wheat, semolina)
- For other foods, follow feeding recommendations for the child's age

Annexure 19 ≫ Amphotericin B, Fluconazole and Flucytosine in renal impairment (Creatinine clearance <50 ml/min)

Amphotericin B, Fluconazole and Flucytosine in renal impairment (Creatinine clearance <50 ml/min)

If there is renal impairment at the time of diagnosis of cryptococcal meningitis with a calculated creatinine clearance of 30 to 50 ml/min, the recommended dose adjustment to be done is as per the table below.

Induction doses of Amphotericin B, Fluconazole and Flucytosine according to estimated glomerular filtration rates for adults

Antifungal agent	eGFR >50	eGFR 10–50	eGFR <10	Haemodialysis
Amphotericin B deoxycholate	1 mg/kg	1 mg/kg	1 mg/kg	1 mg/kg (can administer during dialysis)
Fluconazole	1200 mg daily	600 mg daily	600 mg daily	600 mg daily; dose after dialysis
Flucytosine	25 mg/kg 6 hourly	25 mg/kg 12 hourly	25 mg/kg daily	25 mg/kg daily; dose after dialysis
Note: Multiply by 0.85 for women.				

Source: The Sanford guide to antimicrobial therapy 2019/Editors, David N. Gilbert, M.D., George M. Eliopoulos, M.D., Henry F. Chambers, M.D., Michael S. Saag, M.D., Andrew T. Pavia, M.D. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]

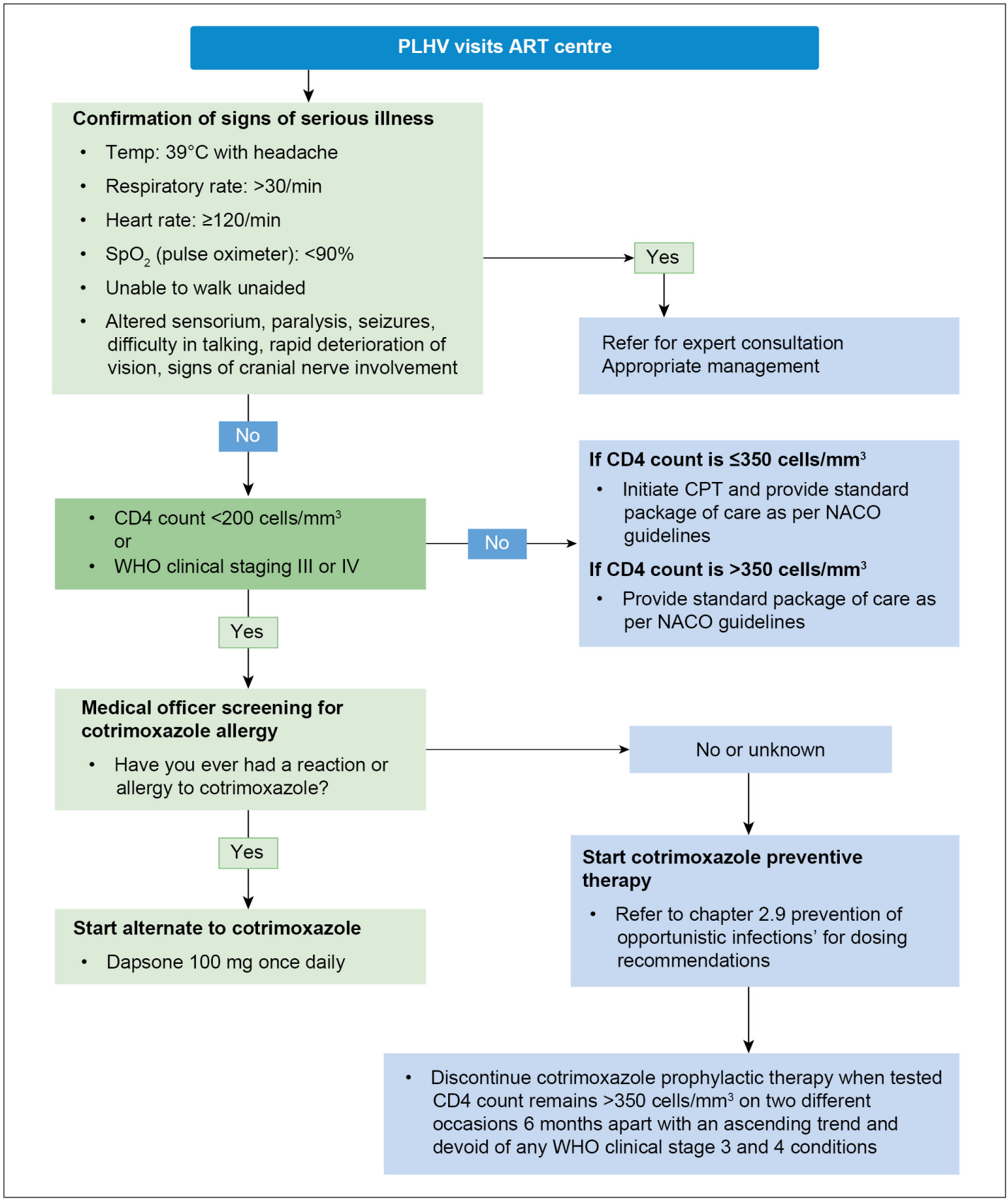
Intravenous fluids should be administered to all patients. Tenofovir and Amphotericin B Deoxycholate can be used together provided the patient's renal function is normal and serum creatinine does not double on treatment. Among patients with renal impairment, ART regimens containing tenofovir should be adjusted, switching to an alternative antiretroviral agent such as abacavir. If the patient's initial reason for a reduced creatinine clearance was dehydration and this has been corrected with fluid administration, the patient can be switched back to amphotericin B deoxycholate at normal doses.

Flucytosine has a short plasma half-life and is cleared unchanged via the kidneys. Flucytosine requires dose adjustment if there is renal impairment; where patients are dialysed, it should be given after dialysis.

Fluconazole monotherapy is not recommended except as a last resort. When used as monotherapy during induction, the fluconazole dose is 1200 mg daily with normal renal function. With a creatinine clearance of <50 ml/min, the induction dose of fluconazole should be reduced by 50% to 600 mg daily.

Annexure 20 Evaluation of Cotrimoxazole preventive therapy in advanced disease management

Evaluation of Cotrimoxazole preventive therapy in advanced disease management


PLHV visits ART centre
Confirmation of signs of serious illness
• Temp: 39°C with headache
• Respiratory rate: >30/min
• Heart rate: ≥120/min
• SpO_2 (pulse oximeter): <90%
• Unable to walk unaided
• Altered sensorium, paralysis, seizures, difficulty in talking, rapid deterioration of vision, signs of cranial nerve involvement
Yes
Refer for expert consultation
Appropriate management
No
• CD4 count <200 cells/mm³
or
• WHO clinical staging III or IV
No
If CD4 count is ≤350 cells/mm³
• Initiate CPT and provide standard package of care as per NACO guidelines
If CD4 count is >350 cells/mm³
• Provide standard package of care as per NACO guidelines
Yes
Medical officer screening for cotrimoxazole allergy
• Have you ever had a reaction or allergy to cotrimoxazole?
No or unknown
Yes
Start alternate to cotrimoxazole
• Dapsone 100 mg once daily
Start cotrimoxazole preventive therapy
• Refer to chapter 2.9 prevention of opportunistic infections' for dosing recommendations
• Discontinue cotrimoxazole prophylactic therapy when tested CD4 count remains >350 cells/mm³ on two different occasions 6 months apart with an ascending trend and devoid of any WHO clinical stage 3 and 4 conditions