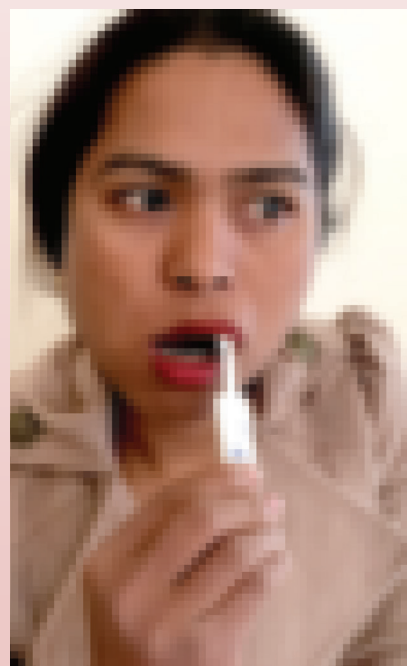


2022



NATIONAL HIV TESTING AND TREATMENT GUIDELINES

AUGUST 2022



Government of Nepal
Ministry of Health and Population
National Centre for AIDS and STD Control
Teku, Kathmandu

2022

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National HIV Testing and Treatment Guidelines 2022

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FOREWORD

The Government of Nepal (GoN), Ministry of Health and Population (MoHP) started response to HIV/AIDS endemic in 1995 with release of National policy on AIDS and STI Control with commitment to provide free effective treatment for HIV/AIDS.

Today we have controlled the HIV epidemic and we have the lowest incidence of HIV since the first case of HIV was detected in Nepal. The epidemic is now concentrated in key populations such as sex workers, injecting drug users (IDUs), men who have sex with men (MSM), transgender (TG), prison inmates and labor migrants. The HIV response in Nepal is the best example of how the government, partners, donor, civil societies and communities work together to achieve better results and make measurable impact.

I want to congratulate the Department of Health Services (DoHS) and National Center for AIDS and STD Control (NCASC) for their effective leadership to update the standard National HIV Testing & Treatment guidelines which provide quality service in line with the new global guidance and recommendation.

Government of Nepal, MoHP is committed to invest in National HIV response and accelerate progress towards achieving the 95-95-95 target by 2026 and ending HIV by 2030. In addition, MoHP is committed to providing social financial net to the people living with HIV with increasing access to health insurance schemes, social securities, and developing skills to live a healthy and productive life.

I want to thank all the technical experts, partner organization, communities, citizens, and donor agencies for their active contribution to HIV response in Nepal.

Dr Roshan Pokhrel
Secretary
Ministry of Health and Population



Ref No.:

Foreword

HIV/AIDS is a priority public health program of Ministry of Health and Population (MoHP). The program is designed inline with SDG and National Strategic Plan 2021-2026 achievements.

This guideline has covered the main areas of HIV testing and treatment especially HIV Testing Services, HIV Treatment in Adults and Adolescents, Monitoring of People on ART, Antiretroviral drugs for HIV prevention, Management of HIV in Children, Adherence and Retention, Management of Advanced HIV Diseases, Comorbidities and Elimination of Vertical Transmission of HIV. The key populations at risk of HIV/AIDS are mostly the vulnerable and the marginalized group with low access to the health services. The National Center for AIDS & STD Control (NCASC) in guidance of Department of Health Services (DoHS) is working closely with community members, civil societies, development partners and organization to achieve better results and make measurable impact in HIV/AIDS response. I believe that this guideline will play a vital role to enhance the quality services provided to PLHIV.

I thank Dr Sudha Devkota and her team for updating the National HIV Testing and Treatment guidelines 2022 based on global standards.

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Foreword

Anti-retroviral treatment (ART) program was started in 2004, since then early diagnosis, effective drugs and quality health services has been the key to success HIV program in Nepal.

The National Public Health Laboratory (NPHL) has been an integral part of National HIV response in Nepal. NPHL has supported in the expansion for HIV testing initiatives during the “test and treat policy”, community-based testing using lay providers and HIV self-testing initiation. At the same time, strengthening viral load testing services for disease monitoring is also important for improving the coverage and quality of the HIV care.

National Guideline on HIV testing and treatment 2022 introduces new standards for viral load testing and viral load suppression. The guidelines also stress on community-based care of PLHIV with differentiated care approach which means less hospital visits for healthy PLHIV and more time to provide for critical patients. I am confident that this guideline will support the national program and guide the front-line health workers to provide the best care to the PLHIV in the country.

The successful implementation of this guideline is possible on the degree of cooperation and collaboration between NCASC and NPHL. I do admire the NCASC for establishing enabling environment while updating this guideline. I encourage all partners, health workers and laboratory personnel working in the field of HIV in Nepal to use these guidelines appropriately for effective testing and treatment and monitoring for patient care and achieving 95-95-95 target by 2026.

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Foreword

In 2020, the National HIV program introduced dolutegravir (DTG) as the first line ARVs in Nepal. Currently more than 95% of the patient on ARVs are on DTG based regimen which is highly efficient, few side effects, provides rapid viral load suppression and with high barrier to the development of resistance mutations.

The 2022 update in the National HIV testing and treatment guidelines incorporates new recommendation on viral load suppression, PrEP monitoring, management of advanced diseases with focus on TB and prioritization of elimination of vertical transmission of HIV and syphilis from pregnant women to newborn. Adoption of these new technical and strategic changes will be key to achieve the new targets: 95-95-95 by 2026 in line with the National HIV Strategic Plan 2021-2026. I am confident that this guideline will support the national program, the front-line health workers to provide the best care to the PLHIV in the country.

I am very thankful to the members of the Technical Working Group on HIV, the UN organization, Save the Children, USAID, FHI 360, AHF and extend my special appreciation to civil society networks and community activists for their persistent advocacy and support during the COVID-19 pandemic which was important in ensuring essential HIV services to the PLHIV and the community. I would especially thank the WHO, Nepal for providing technical support for developing this guideline.

I hope this new updated guideline will be useful for all the health workers and program manager working in the field of HIV in Nepal.

Dr Sudha Devkota
 Director

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DEFINITIONS OF KEY TERMS

Acute infection: the period in which an individual becomes HIV-infected and before HIV antibodies can be detected by a serological assay.

Adherence is the extent to which a person's behaviour – taking medication, following a diet and/or changing lifestyle – corresponds with agreed recommendations from a health worker.

Age groups and populations

An **adult** is a person older than 18 years of age.

An **adolescent** is a person 10–18 years of age, inclusive.

A **child** is a person 1 to younger than 10 years of age.

An **infant** is a child younger than 1 year of age.

Assay, test for HIV infection: a complete procedure for detecting the presence or concentration of an analyte, including all the components of the test kit used to identify the HIV p24 antigen or HIV-1/2 antibodies.

Assay or test for recent HIV infection: a laboratory test that is used to classify a case of HIV infection as recent or not.

Antiretroviral (ARV) drugs refer to the medicines used to treat HIV.

Antiretroviral therapy (ART) refers to the use of a combination of three or more ARV drugs to treat HIV infection.

Combination prevention refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

Community health workers are health workers who have received standardized and nationally endorsed training outside the nursing, midwifery or medical curricula.

Concentrated epidemic: a situation where HIV has spread rapidly in a defined subpopulation (such as men who have sex with men, sex workers, transgender people, people who use drugs, or people in prison or closed settings) but is not well established in the general population.

Continuum of HIV services refers to a comprehensive package of HIV testing, prevention, treatment and care services provided for people at risk of acquiring HIV and people living with HIV (PLHIV) and their families.

Cryptococcal antigen positivity: serum, plasma or cerebrospinal fluid positive for cryptococcal antigen. A positive cerebrospinal fluid antigen test indicates cryptococcal meningitis.

Cryptococcal-persistent symptoms: symptoms consistent with cryptococcal disease that fail to resolve after two weeks of initial antifungal induction treatment.

Cryptococcal-recurrent symptoms: symptoms consistent with cryptococcal disease that reappear after full resolution following treatment for the initial episode of cryptococcal meningitis.

Cryptococcal-suboptimal treatment: treatment with an inadequate drug regimen, dose or duration of induction, consolidation or maintenance therapy; may also result from drug interactions or drug resistance.

Cryptococcal-sustained clinical response: resolution of clinical symptoms and signs of cryptococcal disease for at least two continuous weeks.

Cryptococcal-treatment failure or microbiological relapse: lack of clinical or mycological response in a person in whom raised intracranial pressure or cryptococcal immune reconstitution inflammatory syndrome is not the only cause; includes people who received suboptimal treatment or who received optimal treatment but failed to clinically respond or who were poorly adherent.

Differentiated service delivery is an approach that simplifies and adapts HIV services to better serve the needs of PLHIV and reduce unnecessary burden on the health system. For example, under a differentiated service delivery approach, people who are stable on treatment would have a reduced frequency of clinical visits and medication prescribing, allowing health service resources to focus on care for patients who are ill and need intensive clinical follow up.

Early infant diagnosis: testing of infants to determine their HIV status, given that HIV can be acquired in utero (during pregnancy), peripartum (during delivery), postpartum (through breastfeeding) or via parenteral exposure.

Eclipse period: the period between HIV infection and detection of virological markers, such as HIV RNA/DNA or HIV p24 antigen.

Elimination of vertical transmission refers to the use of ARV drugs to prevent the transmission of HIV from the mother to the infant during pregnancy and breastfeeding.

External quality assessment (EQA): interlaboratory comparison to determine if the HIV testing service can provide correct test results and diagnosis.

HIV status: a collection of results from one or more in vitro diagnostic tests. It refers to reports of a person being HIV positive, HIV negative or HIV inconclusive.

HIV test result: the result from a single test on a given assay.

Index testing: index testing is a focused HIV testing approach in which providers work with individuals living with HIV (index clients) to elicit their sexual or injecting partners, their biological children, or biological parents (if a child is the index client) for HIV testing and counselling.

Integrase inhibitor: an ARV drug that binds to and blocks integrase, an HIV enzyme. ARV drugs from this class include dolutegravir and raltegravir.

Integration: the co-location and sharing of services and resources across different disease areas. In the context of HIV, this may include the provision of HIV testing, prevention, care and treatment services alongside other health services, such as tuberculosis (TB), sexually transmitted infection (STI) or viral hepatitis services, antenatal care, contraceptive and other family planning services, and screening and care for other conditions, including noncommunicable diseases.

In vitro diagnostic (IVD): a medical device, used alone or in combination, intended by the manufacturer for the examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. For example, IVDs can be used for the following test purposes: diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status. Examples of IVDs include reagents, calibrators, control materials and specimen receptacles.

Key populations are groups that have a high risk and disproportionate burden of HIV in all epidemic settings. Key populations include men who have sex with men, people who inject drugs, sex workers, transgender people, migrant workers and prison inmates.

Lay provider: any person who performs functions related to health-care delivery and has been trained to deliver specific services but has not received a formal professional or paraprofessional certificate or tertiary education degree.

Linkage is defined as a process of actions and activities that support people testing for HIV and people diagnosed with HIV in engaging with prevention, treatment and care services, as appropriate for their HIV status. For people with HIV, it refers to the period beginning with an HIV diagnosis and ending with enrolment in care or treatment.

Non-nucleoside reverse transcriptase inhibitor (NRTI): an ARV drug that binds to and blocks reverse transcriptase, an HIV enzyme. ARV drugs from this class include nevirapine and efavirenz.

Non-reactive test result: a test result that does not show a reaction indicating the presence of analyte.

Nucleic acid testing (NAT): also referred to as molecular technology, for example, polymerase chain reaction (PCR) or nucleic acid sequence-based amplification (NASBA). This type of testing can detect very small quantities of viral nucleic acid, that is RNA, DNA or TNA, qualitatively and quantitatively.

Nucleoside reverse transcriptase inhibitor (NNRTI): an ARV drug that binds to and blocks reverse transcriptase, an HIV enzyme. ARV drugs from this class include abacavir, emtricitabine, lamivudine, tenofovir and zidovudine.

Post-exposure prophylaxis (PEP) of HIV is the use of ARV drugs by people who are not infected with HIV but who may have been exposed to HIV to block HIV infection.

Pre-exposure prophylaxis (PrEP): oral PrEP for HIV is the use of ARV drugs by people who are not infected with HIV to block the acquisition of HIV.

Pre-test information: a dialogue and the provision of accurate information by a trained lay provider or health worker before an HIV test is performed.

Protease inhibitor: an ARV drug that blocks protease, an HIV enzyme. ARV drugs from this class include atazanavir, darunavir and lopinavir.

Point-of-care testing is conducted at or near the site at which care is being provided. The test results are usually returned rapidly so that clinical decisions can be made in a timely and cost-effective manner.

Prophylaxis aims to avoid either the first occurrence of infections (primary prophylaxis) or their recurrence (secondary prophylaxis or maintenance).

Quality assurance (QA): a systematic and planned approach to assessing, monitoring and improving the quality of health services on a continuous basis within available resources.

Quality control (QC): an assessment of product compliance with stated requirements.

Reactive test result: a test result that shows a reaction to indicate the presence of analyte.

Repeat testing: refers to a situation where additional testing is performed for an individual immediately following initially discrepant test results; within the same testing visit, using the same assays and, where possible, the same specimen.

Retention in HIV care means a person living with HIV and is enrolled in HIV care who routinely attends HIV services in accordance with the need. This excludes people who have died or who were lost to follow up.

Retesting: there are certain situations in which individuals should be re-tested after a defined period of time: (1) HIV-negative people with recent or ongoing risk of exposure; (2) those with an HIV-inconclusive status; and (3) HIV-positive people before they enrol in care or initiate treatment. Reasons for retesting before initiation of care or treatment include ruling out laboratory or transcription error and either ruling in or ruling out seroconversion.

Rapid diagnostic test (RDT): in vitro diagnostic of immunochromatographic or immunofiltration format for, in the case of HIV diagnosis, the detection of HIV-1/2 antibodies and/or HIV p24 antigen.

Self-testing (HIV-ST): a process in which an individual who wants to know his or her HIV status collects a specimen, performs a test and interprets the result by himself or herself, often in private. Reactive test results must be followed by additional HIV testing services.

Sensitivity denotes the probability that an HIV assay or a testing algorithm will correctly identify all specimens that contain HIV-1/2 antibodies and/or HIV p24 antigen.

Sentinel surveillance: a type of surveillance that is conducted through selected sites among populations of particular interest or that may provide approximations of prevalence for a larger population, for example, antenatal clinics.

Seroconversion: when an individual produces a quantity of HIV antibodies sufficient to be detectable on a given HIV serological assay.

Serodiscordant couples are couples in which one partner is living with HIV and the other is HIV negative. A couple refers to two people in an ongoing sexual relationship; each of these people is referred to as a partner in the relationship. Couples should not be limited to men–women couples, but also include non-heteronormative couples/partners (men–men or men–transgender persons [TG] or TG–TG).

Serological assay: an assay that detects the presence of antibodies in human specimens, typically serum or plasma but also capillary/venous whole blood and oral fluid. RDTs, immunoassays (including enzyme immunoassays [EIAs], chemiluminescence immunoassay [CLIAs], enhanced chemiluminescence [ECLs]) and certain supplemental HIV assays are examples of serological assays.

Specificity: denotes the probability that the assay or a testing algorithm will correctly detect specimens that do not contain HIV-1/2 antibodies and/or HIV-1 p24 antigen.

Supplemental assay: an assay that provides additional information for specimens that a first-line assay has found to be reactive but may not be able to definitively confirm that reactivity.

Task-shifting and task-sharing are the rational redistribution of tasks between cadres of health workers with longer training and other cadres with shorter training, such as lay providers.

Universal access to ART is defined broadly as a high level of treatment coverage (80% or more of the eligible population) that is accessible and affordable. It does not necessarily mean 100% coverage.

Viral load, low-level viraemia is one or more viral load results that are detectable (more than 50 copies/mL) but equal to or less than 1000 copies/mL.

Viral load, undetectable refers to a viral load below the detection threshold (less than 50 copies/mL) using viral assays.

Viral load suppression: refers to a viral load below the 50 copies/mL after at least six months of starting a new ART regimen.

Virological/Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/mL in a two consecutive viral load measurements within a three-month interval with adherence support between measurements after at least six months of starting a new ART regimen.

Vulnerable populations are groups of people that are vulnerable to HIV in certain situations or contexts, such as adolescents (especially adolescent girls in sub-Saharan Africa), orphans, people with disabilities, and migrant and mobile workers.

ABBREVIATIONS AND ACRONYMS

| | |
|----------|---|
| 3TC | lamivudine |
| ABC | abacavir |
| aDR | adverse drug reaction |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| ANC | antenatal care |
| ANM | auxiliary nurse midwife |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATT | antituberculosis treatment |
| ATV | atazanavir |
| AZT | zidovudine |
| CB-ART | community-based ART site |
| CBO | community-based organization |
| CBT | community-based testing |
| CD4 | cluster of differentiation 4 |
| CLT | community-led testing |
| CM | cryptococcal meningitis |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| COC | combined oral contraceptive |
| CPT | co-trimoxazole preventive therapy |
| CrAg LFA | cryptococcal antigen lateral flow assay |
| CSF | cerebrospinal fluid |
| DAA | direct-acting antiviral |
| DBS | dried blood spot |
| DDA | Department of Drug Administration |
| DMPA | depot medroxyprogesterone acetate |
| DNA | deoxyribonucleic acid |
| DOT | directly observed therapy |

| | |
|-------|---|
| DR | drug resistance |
| DRV | darunavir |
| DTG | dolutegravir |
| EFV | efavirenz |
| eGFR | estimated glomerular filtration rate |
| EID | early infant diagnosis |
| ELISA | enzyme-linked immunosorbent assay |
| EMTCT | elimination of mother-to-child transmission |
| EPOA | enhanced peer outreach approach |
| EQA | external quality assurance |
| EQAS | external quality assessment scheme |
| ETG | etonogestrel |
| eVT | eliminate vertical transmission |
| FDC | fixed-dose combination |
| FTC | emtricitabine |
| FWD | Family Welfare Division |
| Hb | haemoglobin |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| HIVDR | HIV drug resistance |
| HIVST | HIV self-testing |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| iHMIS | integrated health management information system |
| HTS | HIV testing services |
| HPV | human papillomavirus |
| IgG | immunoglobulin G |
| IGRA | interferon gamma release assay |
| INSTI | integrase strand transfer inhibitor |
| IRIS | immune reconstitution inflammatory syndrome |
| IUD | intrauterine device |

| | |
|------------|--|
| KP | key population |
| LNG | levonorgestrel |
| LPV | lopinavir |
| LTBI | latent TB infection |
| MAC | <i>Mycobacterium avium complex</i> |
| MNCH | maternal, neonatal and child health |
| MSM | men who have sex with men |
| MTCT | mother-to-child transmission |
| NAAT (NAT) | nucleic acid amplification testing |
| NCASC | National Centre for AIDS and STI Control |
| NCD | noncommunicable disease |
| NET-EN | norethisterone enanthate |
| NGO | nongovernmental organization |
| NNRTI | non-nucleoside reverse-transcriptase inhibitor |
| NPHL | National Public Health Laboratory |
| NRTI | nucleoside reverse-transcriptase inhibitor |
| NSP | needle and syringe programme |
| NVP | nevirapine |
| OI | opportunistic infection |
| OST | opioid substitution therapy |
| PCP | <i>Pneumocystis jiroveci</i> pneumonia |
| PCR | polymerase chain reaction |
| PEP | post-exposure prophylaxis |
| PI | protease inhibitor |
| PITC | provider-initiated testing and counselling |
| PLHIV | people living with HIV |
| PM | peer mobilizer |
| PMTCT | prevention of mother-to-child transmission |
| POP | progestogen-only pill |
| PrEP | pre-exposure prophylaxis |
| QA | quality assurance |
| r or RTV | ritonavir |

| | |
|------|--------------------------------------|
| RAL | raltegravir |
| RDS | respondent-driven sampling |
| RDT | rapid diagnostic test |
| RITA | recent infection testing algorithm |
| RNA | ribonucleic acid |
| SGPT | serum glutamic pyruvate transaminase |
| SMX | sulfamethoxazole |
| SOP | standard operating procedure |
| STI | sexually transmitted infection |
| TAF | tenofovir alafenamide |
| TB | tuberculosis |
| TDF | tenofovir disoproxil fumarate |
| TE | toxoplasmic encephalitis |
| TG | transgender person |
| TLD | tenofovir, lamivudine, dolutegravir |
| TMP | trimethoprim |
| TPT | TB preventive treatment |
| TST | tuberculin skin test |
| VCT | voluntary counselling and testing |
| VL | viral load |
| VMMC | voluntary medical male circumcision |
| WHO | World Health Organization |

1

HIV TESTING SERVICES

1.1 HIV testing services

The term “HIV testing services” embraces the full range of services that should be provided together with HIV testing. This includes counselling (brief pre-test information and post-test counselling); linkage to appropriate HIV prevention, care and treatment services and other clinical and support services; and coordination with laboratory services to support quality assurance.

- **Consent.** The age of consent for HIV testing in the country is 16 years. Clients must provide informed consent for getting tested and counselled. They should be informed of the process, and of their right to decline testing. Mandatory testing is never appropriate, whether coercion comes from a health-care provider, or from a partner or a family member. Verbal consent is usually adequate, but all individuals should have a private opportunity to refuse testing.
- **Confidentiality.** All the information collected should be kept confidential and should not be shared with anyone without the consent of the client. Although confidentiality always needs to be respected, it should never reinforce secrecy, fear, shame or prejudice. Shared confidentiality with a partner or family member, or trusted others is often highly beneficial.
- **Counselling.** Services must be accompanied by appropriate and good-quality pre-test information and post-test counselling. All people should have the opportunity to ask questions in a private setting if they request it. All HIV testing must be accompanied by appropriate and high-quality post-test counselling, based on the specific HIV test result and HIV status reported.
- **Correct test results.** Quality assurance mechanisms, supportive supervision and a mentoring system should ensure that people receive a correct diagnosis. All these services need to be in place to ensure the provision of high-quality testing and counselling.
- **Connection.** All HIV services should have linkage to prevention, care and treatment services. All positive clients should be linked to treatment and care without delay. Partner notification and testing services should be offered to all HIV-positive clients. Those with negative results should also be connected to prevention services – PrEP, opioid substitution therapy (OST), needle syringe program, behaviour change counselling, and access to condoms and condom-compatible lubricants.

The goal of HIV testing services (HTS) is “to identify people living with HIV as early as possible and to link them appropriately, in a timely manner, to treatment and care services”. Similarly, it also links those who test “not HIV-infected” to appropriate services to prevent HIV infection, such as HIV pre-exposure prophylaxis (PrEP), harm reduction services, behaviour change interventions and access to condoms and condom-compatible lubricants.

HTS in Nepal follows the standard guiding principles and adheres to the five C’s: consent, confidentiality, counselling, correct test results and immediate connection to services for HIV prevention, treatment and care.

1.1.1 Model of HTS

Diverse models of differentiated HTS delivery approaches are available in Nepal to increase access to HIV diagnosis, including testing services in health-care facilities, stand-alone sites, and through a range of community-based approaches. The different HIV testing service delivery approaches provided are discussed below.

i. Facility-based HIV testing services

Facility-based HIV testing services refers to HTS provided in a health facility or in a stand-alone laboratory setting. Facility-based services are provided by the government, community-based organizations (CBOs)/nongovernmental organizations (NGOs). Facility-based HTS are provided using two approaches:

■ Voluntary counselling and testing

Voluntary counselling and testing (VCT) is an earlier model for delivering HTS in dedicated stand-alone facilities. Clients voluntarily report to the health facility for testing for HIV. It is now recognized that HIV testing in clinical sites may be more effective when it is offered as part of general medical care. Therefore, in many settings, HTS has been integrated with other health services so that it can be either offered routinely to all those attending services or in particular clinical settings to those with indicator conditions. However, despite limitations due to higher costs and the need for the client to initiate the process of testing, stand-alone HTS may still be a way to reach people in some high-burden settings, as it complements other approaches.

■ Provider-initiated testing and counselling

Provider-initiated testing and counselling (PITC) denotes HTS that is routinely offered in a health facility. Although it involves the routine offering of HTS, PITC should not develop into mandatory testing or testing people without receiving the informed consent first and informing them that they can decline.

It is recommended for clients who visit a health facility for general health services with signs and symptoms or medical conditions that indicate possible HIV infection, including presumed and confirmed tuberculosis (TB) cases. PITC should be considered in malnutrition clinics; sexually transmitted infection (STI), hepatitis and TB services; antenatal care (ANC) settings and health services for key populations (KPs).

PITC should be offered to the following categories of people:

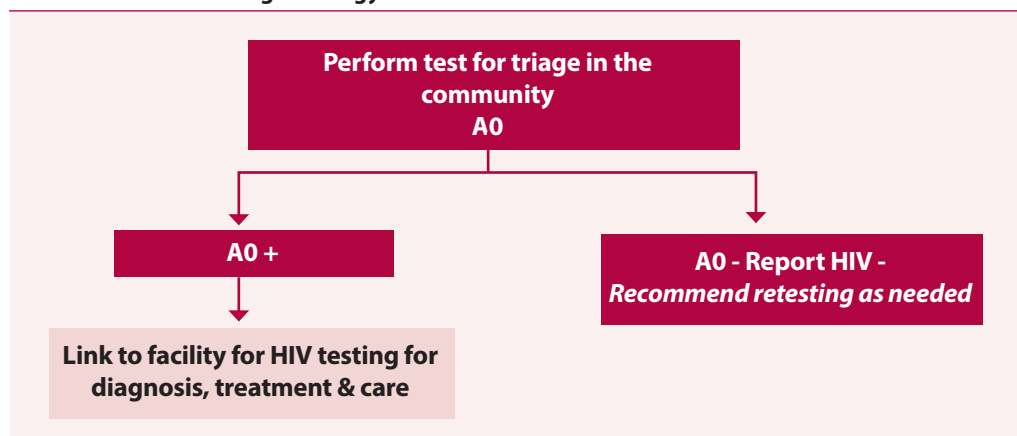
- all the clients with presumptive and diagnosed TB;
- people with STIs, hepatitis B and C;
- all pregnant women attending ANC settings;
- KPs and their partners - notably men who have sex with men (MSM), transgender persons (TG), sex workers, people who use drugs with a history or current injecting practices;
- people enrolled in OST;
- migrant workers and their spouses with a history of possible unsafe exposure;
- people in prison; and all others deemed at high risk of HIV.

ii. Community-based testing services

Community-based testing services are provided to at-risk populations by health workers and trained lay providers at a workplace, entertainment sites, hot spots and cruising sites of KPs, border check points, educational facilities or at home.

Community-led testing (CLT) is recommended as part of community-based testing (CBT) and “test for triage” strategy in which at-risk populations are offered HTS by trained lay providers (Fig. 1.1). It can be performed in both facility and community settings. Lay providers can conduct screening tests either with blood or oral fluid.

FIGURE 1.1: Test for triage strategy



Procedure

- Lay providers conduct a single HIV rapid diagnostic test (RDT) referred as A0 (assay 0) which can be done with blood-based or oral-fluid-based testing kits.
- Clients with reactive test results (A0+) should be referred and accompanied to health facilities where confirmatory testing is performed by trained laboratory personnel according to the national algorithm. Confirmatory tests can be conducted in the community following the full national algorithm.
- Clients with non-reactive test results (A0-) should be recommended for re-testing based on the risk factors identified and referred to prevention services.
- All sites providing community testing services (CBT/CLT) should participate in quality assurance (QA) mechanism conducted by the National Public Health Laboratory (NPHL).

iii. HIV self-testing

HIVST is a process in which a person collects his/her own specimen (oral fluid or blood) and then performs an HIV test and interprets the result, often in a private setting, either alone or with someone he/she trusts. As HIVST reduces the number of visits to a facility and eliminates travel and time to access HIV testing, HIVST may be more convenient for users.

Procedure

HIVST can be delivered through two approaches, i.e. supervised and unsupervised.

- Supervised HIVST means receiving in-person assistance from a trained provider or peer before or during HIVST with instructions on how to perform a self-test and how to interpret the self-test result.
- Unsupervised HIVST means that an individual obtains a kit for HIVST and performs the HIVST himself/herself following the instructions in the package insert.

Oral fluid-based test kits are used for HIVST in Nepal. *Oraquick*[®] is currently registered in Nepal. Oral fluid-based HIVST is not recommended for people taking antiretroviral (ARV) drugs as this may cause a false non-reactive result. This test should not be performed immediately after using a mouthwash or eating or drinking.

All persons identified as HIV test reactive (A0+) using HIVST or by test for triage should be re-tested using the national testing algorithm to confirm their HIV status.

1.1.2 Innovative approaches to HIV testing

i. Index testing

Index testing is a focused HIV testing approach in which providers work with individuals living with HIV (index clients) to elicit voluntary HTS to their sexual or injecting partners, their biological children or biological parents (if a child is the index client) for HIV. The index testing approach has the highest HIV case-finding yield. All HIV-positive clients should be offered index testing and it is recommended as part of a comprehensive package of testing and care. When an index case is identified, mutual disclosure needs to be encouraged. Service providers must be aware of potential intimate partner-based aggression and violence, and the need to support individuals who do not want to test with their partners, and/or do not agree to mutual disclosure. Screening for violence and referral is an essential component of index testing.

Index testing can be conducted through:

- provider-assisted referral, in which a trained provider directly assists people who have tested HIV-positive by contacting their partners (s) and offering them HTS. People with HIV should be provided with options on how their partners can be contacted, and given time to consider the best options, based on their needs. People who do not want their partners to be contacted or need time to consider should be supported in their decision;
- patient referral, in which a trained provider encourages the client to disclose their HIV status to their partners.

ii. Recency testing

HIV infection occurring within the past six months is considered a recent infection. As HIV transmission is higher from people who have early HIV infection, targeting effective prevention and behavioral interventions to populations presenting with recent infections could have a large impact on overall levels of transmission.

HIV recency testing is a serological laboratory-based assay or an RDT at the point of care that classifies an HIV infection as a recent or established infection. The estimated time since detection of infection depends on the assay but is generally within 12 months. Recent infection testing algorithm (RITA) includes the recency test, supplementary laboratory and clinical information to classify an HIV infection as recent or not.

The Global HIV Strategic Information Working Group recommends the use of these assays for epidemiological and surveillance purposes. Recency testing may be considered in national programmes if sufficient evidence and resources are available.

iii. Risk network referral

This extends beyond index testing. Providers offer people living with HIV (PLHIV) additional, self-guided options to informally extend links to HIV testing and other services to a broader set of social- and risk-network members who have an elevated risk of HIV infection. This broader set of social and risk network members can include other friends and acquaintances who live and work within the same area or have similar risk behaviours. It does not require PLHIV to name — or even know the names of — these contacts to make referrals. They can make confidential or anonymous referrals. Referral can also be made online or using referral coupons.

iv. Online and social media referral

This approach helps to reach virtually active and hidden/hard-to-reach KPs and other people at risk of HIV.

- An online risk assessment and reservation through a web application provides the most convenient means of assessing HIV, STI related risk, and locating services at a convenient date and time.
- The link of the web application can be shared with high-risk individuals and peers/partners/spouses of PLHIV through SMS or mobile applications (messenger, Viber, Imo, etc).
- Those reached online can be linked to offline programmes for HIV testing.
- Individuals reached online can also be linked to various testing strategies such as HIVST and test for triage.

Social media platforms such as Facebook and Twitter can also be used for demand generation, education and counselling for testing through one-on-one chat.

v. Enhanced peer outreach approach (EPOA)

- The primary actors of the EPOA are community-based workers. These lay providers identify and recruit peer mobilizers (PMs) within their network in the community as seeds.
- Like the respondent-driven sampling (RDS) method used in research and surveillance and now used in outreach, PMs recruit peers exclusively from their hidden/hard-to-reach social networks.
- PLHIV are also offered and recruited as PMs/seeds to reach out to their partners/spouses, and within their peer networks.
- Once a PM has exhausted the potential recruits in his social network, he will be replaced with a new PM, and in this manner, the EPOA continually refreshes the pool from which clients are drawn.

1.2 Pre-test information and post-test counselling

Pre-test information can be provided in groups or individually if the client requests. Clients' consent should be taken individually, and they should be provided with opportunities to ask questions in private. Pre-test counselling is not recommended as a part of HIV testing services. Concise information and messages that offer and encourage testing, including peer-led and digital platforms, as well as short pre-recorded videos can be used to encourage HTS uptake.

Pre-test information should include the following:

- the benefits of HIV testing;
- the meaning of an HIV-positive and HIV-negative diagnosis;
- the services available for those with an HIV-positive diagnosis, including where antiretroviral therapy (ART) is provided;
- a description of prevention options and encouragement for partner testing;
- the right to confidentiality of information, status and right to refuse or decline the test without any further consequences related to the client's access to HIV-related services or general medical care;
- the possible results – HIV negative or HIV positive;
- what needs to be done after each type of result;
- encouragement to screen for STIs, hepatitis B and C;
- special precautions related to the use of test kits, such as HIV self-test kit, e.g. not to clean or brush the teeth or eat and drink 30 minutes before the test;
- provide an opportunity to ask questions.

Post-test counselling should be provided on an individual basis. The counsellor should review the result and verify it against the name or identification number of the client before providing it to the client.

Post-test counselling for those with an HIV-negative result include the following:

- meaning of the test result and reported HIV status;
- methods to prevent HIV acquisition and provision of male and female condoms, lubricant and guidance on their use; post-exposure prophylaxis (PEP) and PrEP;
- the importance of disclosing the status of sexual partner(s) and information on and availability of partner and couples testing services;
- referral and linkage to relevant HIV prevention services: OST, NSP, PEP, PrEP, safe conception and family planning, promotion of condoms and lubricants;
- recommendation on retesting based on client's level of recent exposure and/or ongoing risk of exposure.

Post-test counselling for those with a reactive screening test

The test is a screening test only; it does not confirm an HIV-positive status. A confirmatory HIV test using the full national algorithm is needed to confirm the HIV test result. The client needs to get a confirmatory test either in a facility or by trained laboratory personnel in the community.

Post-test counselling for those with an HIV-positive result

- These people need to be told the meaning of the test results and diagnosis.
- They should be supported to cope with the emotions arising from the diagnosis of HIV infection.
- Immediate concerns should be discussed with the client and they should be helped to decide who in their social network may be available to provide immediate support.
- The risk of suicide, depression and other mental health consequences of a diagnosis of HIV infection should be discussed.
- Substance use, such as alcohol use should be assessed and linked to rehabilitation centers
- Clear information should be provided on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to obtain ART.
- The provision of accompanied referral to ART centres should be explained or support available in community if applicable.
- Information should be provided on how to prevent transmission of HIV, including information of the reduced transmission risk when virally suppressed on ART.
- Male or female condoms and lubricants should be provided along with guidance on their use.
- HIV testing for sex partners, children and other family members of the client should be encouraged and provided. This can be done individually, through couples testing, index testing or partner notification.
- Disclosure of HIV status should be promoted.
- Additional referrals should be provided for prevention, counselling, support and services as appropriate (TB diagnosis and treatment, prophylaxis for opportunistic infections [OIs], STI screening and treatment, contraception, ANC, OST, access to sterile needles and syringes, and sexual health counselling).

1.3 Laboratory diagnosis of HIV infection

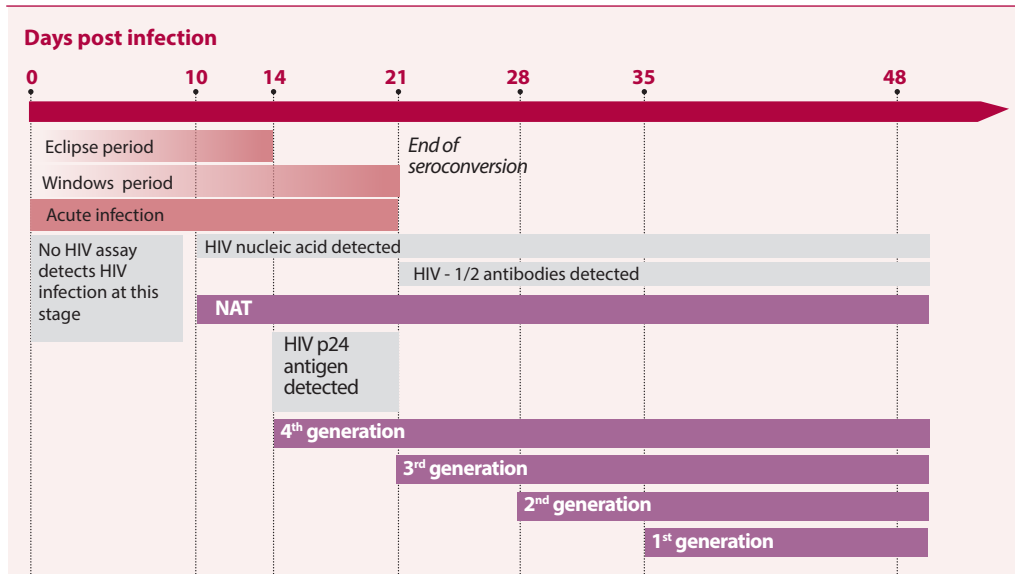
HIV is a member of the genus Lentivirus, which belongs to family Retroviridae. HIV has two major types: HIV type 1 (HIV-1) and HIV type 2 (HIV-2). HIV-1 is the most common and pathogenic strain of the virus. HIV-1 can be divided into groups: M, N, O and P. The epidemic is dominated by group M, which is composed of subtypes A–K.

HIV-1, subtype C is found to be dominant in Nepal. HIV-2 is most often found in West Central Africa, parts of Europe and India, although a few cases have been confirmed in Nepal. Some assays can differentiate between HIV-1 and HIV-2 antibodies, but differentiation between dual infection and mono-infection remains challenging for HIV testing. To determine the virus type or diagnose coinfection, appropriate supplemental testing should be performed, including immunological assays specific to HIV-1 and HIV-2 and molecular technologies. If there is any suspicion of HIV-2 infection, the laboratory (test site) should contact the NPHL for further investigations.

The detection of HIV infection depends on the presence of antibodies and virus component, which depends on the days since initial infection (Fig. 1.2).

- **Eclipse period.** This period refers to the period of about 7–10 days following HIV infection, during which currently available assays cannot detect any marker of HIV infection. The end of the eclipse period is marked by the appearance of HIV RNA or DNA, detectable by nucleic acid testing (NAT) and then HIV p24 antigen, detectable by immunoassay. After a week of detection of HIV antigen in the blood, HIV antibodies appear in the blood and antibody-based assays can detect HIV infection.
- **Acute HIV infection.** Acute HIV-1 infection is the phase of HIV-1 disease immediately after infection, which is characterized by an initial burst of viraemia; HIV-1 RNA or p24 antigen is present.
- **Window period.** The period between HIV infection and the detection of HIV-1/2 antibodies using immunological assays is the window period. This signals the end of the seroconversion period. With third-generation HIV antibody tests, antibody can be detected after 21 days, the period of the first 21 days can be considered window period.
- **Recent infection.** Any infection detected within six months of infection is considered recent infection.

FIGURE 1.2: Detecting HIV infection with various formats and generations of in vitro diagnostics over the natural history of infection



Source: Rosenberg et al. 2015

1.4 Early infant diagnosis

Diagnosis of HIV infection in babies born to HIV-infected mothers cannot be confirmed by conventional antibody tests. The presence of anti-HIV antibody in the new-born may not necessarily indicate primary infection. It may be due to the presence of passively transmitted anti-HIV antibodies from the mother to the uninfected baby, which may remain in the blood of the baby for up to 18 months. Hence, virological testing or HIV nucleic acid amplification testing (NAAT) is used for early infant diagnosis. Point-of-care nucleic acid testing can also be used to diagnose HIV among infants and children younger than 18 months of age.

The following are the guiding principles of the national early infant diagnosis (EID) programme:

- Perform HIV NAT of all HIV-exposed infants at birth.
- Repeat the test of the child at 4–6 weeks of age (if the first test was negative).
- Repeat the test of the child at 9 months of age (if the HIV-exposed child tested negative in the first two tests – at birth and 4–6 weeks of age).
- Repeat HIV testing of the HIV-exposed child after 3 months of cessation of breastfeeding.
- Ensure that confirmatory testing is undertaken following any positive result.

- Ensure that indeterminate test results are repeat tested immediately and given priority.
- Ensure regular follow up for all HIV-exposed infants until a final diagnosis is made, including providing co-trimoxazole prophylaxis, and clinical and nutritional assessment.

Diagnostic algorithm for EID

- i. Samples from HIV-exposed infants will be collected within 48 hours (at the earliest after birth) in the form of dried blood spot (DBS).
- ii. All infants with non-reactive HIV NAT at birth will be retested at 4–6 weeks (as mentioned in the algorithm) (Fig. 1.3).
- iii. Infants with a first reactive sample will be initiated on ART and a confirmatory test (HIV NAT) done to confirm the status. Two consecutive HIV NAT will be considered as a positive HIV status.

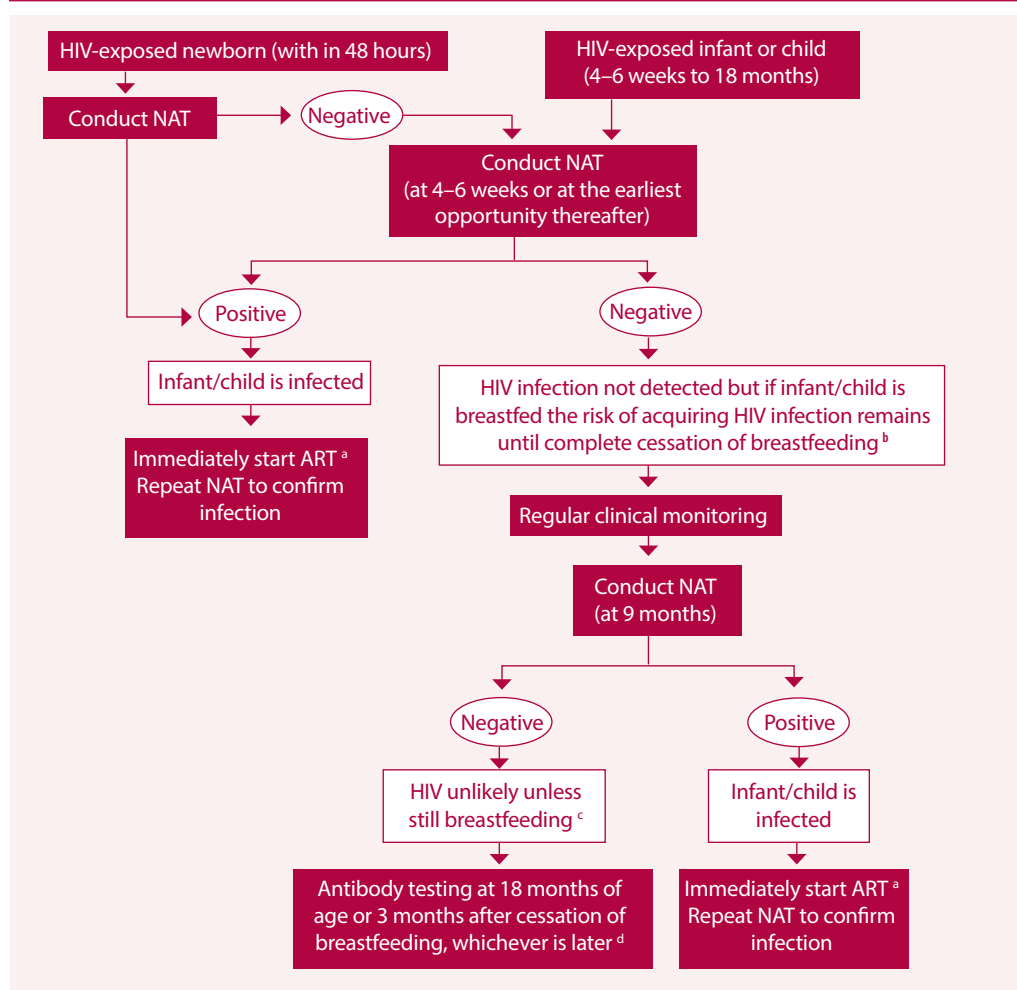
1.4.1 Interpreting HIV test results for infants and children younger than 18 months

Positive HIV NAT. A child with a positive NAT at any age is presumed to be HIV-infected. Repeat the test to confirm infection status, but ART should be started immediately without waiting for confirmation of the second test. If the second test is negative, a third NAT should be performed before interrupting ART.

Negative HIV NAT. The interpretation of a negative test is dependent upon whether the child is breastfeeding.

- **Children who have never breastfed.** Additional testing at 9 months is needed following a negative NAT at 4–6 weeks.
- **Children weaned away more than 3 months prior to the test at 9 months.** A single negative NAT is likely to exclude HIV infection.
- **Children weaned away less than 3 months prior to the test at 9 months.** Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be done.
- **Children on breastfeeding at the time of the test.** Confirmatory testing should be done more than 3 months after breastfeeding has stopped.

FIGURE 1.3: Diagnostic algorithm for EID



- a. Start ART, without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and mother-to-child transmission rates decrease, false-positive results are expected to increase; retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.
- b. For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.
- c. The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.
- d. If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can be assessed only at the end of breastfeeding. If breastfeeding ends before 18 months, a final diagnosis of HIV status with antibody testing can be assessed only at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age, NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the child is uninfected; positive antibody testing confirms that the infant is infected.

Indeterminate result. Early infant diagnostic assays measure the presence of virus using real-time nucleic acid-based technologies. These often report cycle thresholds that are inversely correlated with the amount of virus in a sample. The indeterminate range detection threshold will be 32–35 cycles by Roche® COBAS® Ampliprep/COBAS® Taqman qualitative test v2.0 assay.

All indeterminate tests should be repeat tested on the same specimen, if available. Most indeterminate test results are expected to be resolved with a repeat test on the same specimen, which would avoid the need for and delay incurred in requesting a new specimen from the infant. If the same specimen cannot be repeat tested, then a new specimen should be requested and tested as quickly as possible.

For a repeat indeterminate result, a task team of laboratories and clinicians should review the results along with clinical information. Do not report as positive or initiate ART but maintain prophylaxis in accordance with current guidance. Infants should be actively tracked to ensure follow up and retention.

Approaches are needed to increase EID and timely referral of infants diagnosed as HIV-positive to care and treatment. Both are key to improving health outcomes and child survival. The time taken for sample transport and turnaround time from the laboratory needs to be reduced using email/SMS for communicating the results.

1.5 HIV testing algorithm for all above 18 months

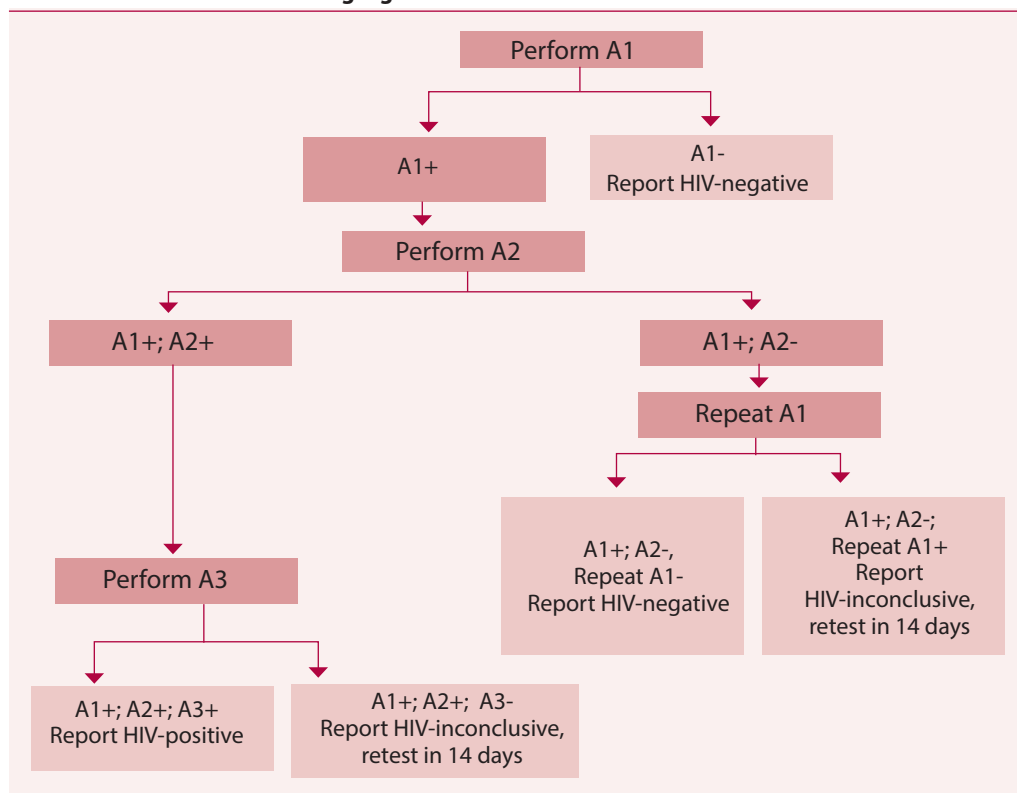
An HIV testing algorithm describes the combination and sequence of specific assays used for the diagnosis of HIV. A three-test HIV testing algorithm is adopted for Nepal. Test kit selection for different line assays will be based on the WHO prequalification list, diagnostic sensitivity and specificity, antigens used and performance characteristics. The first assay (A1) should be the most sensitive, and the second and third tests should have higher specificity. Assay 1 (A1), Assay 2 (A2) and Assay 3 (A3) should be three different immunological assays that do not share the same false reactivity. The first test used in a serial HIV testing algorithm should be highly sensitive so that all positive samples are identified as positive.

TABLE 1.1: Test/diagnostic kits used in the national algorithm

| Assay 1 (A1) | Assay 2 (A2) | Assay 3 (A3) |
|--------------------|--------------|------------------|
| Determine HIV- 1/2 | Uni-Gold HIV | HIV 1/2 Stat-Pak |

The testing algorithm shown in Fig. 1.4 will be used for HIV testing by the national programme.

FIGURE 1.4: National HIV testing algorithm



- All individuals are tested on Assay 1 (A1). Anyone with a non-reactive test result (A1-) is reported as HIV negative.
- Individuals who are reactive on Assay 1 (A1+) should then be tested on a separate and distinct Assay 2 (A2).
- Individuals who are reactive on both Assay 1 and Assay 2 (A1+; A2+) should then be tested on a separate and distinct Assay 3 (A3).
 - Report as HIV positive if Assay 3 is reactive (A1+; A2+; A3+).
 - Report as HIV inconclusive if Assay 3 is non-reactive (A1+; A2+; A3-). The individual should be asked to return in 14 days for additional testing.
- Individuals who are reactive on Assay 1 but non-reactive on Assay 2 (A1+; A2-) should be repeat tested on Assay 1.
 - If repeat Assay 1 is non-reactive (A1+; A2-; repeat A1-), the status should be reported as HIV negative;
 - If repeat Assay 1 is reactive (A1+; A2-; repeat A1+), the status should be reported as HIV inconclusive, and the individual asked to return in 14 days for additional testing.

Clients with an HIV-inconclusive status

Receiving an HIV-inconclusive status may be confusing and stressful for the individual or couple and may be difficult for the provider to explain. Clients with an HIV-inconclusive status should be told that a definitive diagnosis cannot be provided that day and that immediate referral to HIV care or ART initiation is not appropriate. A clear plan for follow up should be developed and explained.

On identification of the client with an inconclusive report, send DBS sample for HIV NAT. The client should be followed up and retested using the national HIV testing algorithm in 14 days. If the results are still inconclusive, collect the blood sample and send for HIV NAT. The result of the NAT will be final and confirmatory.

Clients with unconfirmed results

Unconfirmed results occur when clients who have an initially reactive HIV test result do not receive additional testing in the same visit to confirm their HIV diagnosis. This may occur in community settings where only one assay is performed, an approach known as test for triage. Providers and counsellors should explain that this initial result is not an HIV diagnosis and needs confirmation, and refer clients with a reactive test result to a site where they can receive an HIV diagnosis. In particular, every effort is needed to reduce loss to follow up between a reactive test and additional testing for an HIV diagnosis.

Retesting of individuals who test HIV negative

The primary goal of retesting should be to enable those who have previously tested HIV negative to stay HIV negative and to identify those who have become HIV positive as early as possible so that they can start treatment.

The majority of individuals do not require retesting in the absence of any ongoing risk. In general, certain individuals as listed below who test HIV negative should be retested every **6 months** (or earlier if they have any signs symptoms suggestive of HIV):

- Key populations and their partners;
- people with a known HIV-positive partner;
- individuals presenting with a diagnosis of or receiving treatment for STIs or viral hepatitis;
- individuals with a confirmed or presumptive TB diagnosis;
- outpatients with clinical conditions indicative of HIV infection;
- individuals with recent HIV risk exposure.

Retest pregnant women in the third trimester ANC visit

- pregnant women with unknown or HIV-negative status who are in serodiscordant relationships or have other known ongoing HIV risk in late pregnancy;
- pregnant women from KPs.
- If either the first test or retest is missed or delayed, “catch-up” testing should be done during the postpartum period.

Repeat testing to verify an HIV-positive diagnosis prior to initiation of ART

To ensure that individuals are not needlessly placed on lifelong ART with potential side-effects, there is no wastage of resources, or psychological impact of misdiagnosis; retesting should be done only if an HIV diagnosis is made at a different centre and there is evidence to suggest that the diagnosis was not made as per the standard national algorithm.

1.6 Laboratory quality assurance in HIV testing

National Public Health Laboratory (NPHL) is the National Reference Laboratory for HIV related laboratory services and will be responsible for the selection and validation of HIV tests, quality control, monitoring, and supervision of HIV laboratories in coordination with NCASC. Standard operational guidelines developed by NPHL for HIV related laboratory services will be followed at all level of laboratory and health facility.

The QA system is a part of overall quality management that aims to ensure consistency, reproducibility, traceability, reliability and efficiency of products or services. Laboratories that conduct HIV testing should have functioning internal quality control and participate in an HIV external quality assessment scheme (EQAS).

- Internal quality control includes procedures undertaken by laboratory staff at the institution to ensure quality from the collection of specimens, performance of the test up to analytical results, and the procedure being planned, ordered and followed up by the staff itself.
- External quality assurance (EQA) is the assessment of the quality of laboratory by a reference laboratory, higher authorities or independent agency. EQA leads to correction and improvement of laboratory quality. EQA can be done through proficiency panel testing, retesting or on-site monitoring.

1.7 Linking people diagnosed with HIV to treatment

Linkage is the process of undertaking actions and activities that support people testing for HIV and those diagnosed with HIV in engaging with appropriate care and treatment services for their HIV status. Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. ART initiation should be offered on the same day to people who are ready to start.

2 HIV TREATMENT IN ADULTS AND ADOLESCENTS

2.1 Antiretroviral drugs

Drugs are agents that act on various stages of the life cycle of HIV in the body. These drugs work by interrupting the process of replication of the virus and hence reducing the destruction of CD4 cells, which prevents the progression of HIV infection to acquired immune deficiency syndrome (AIDS). ARVs are categorized according to their mechanism of action. The most commonly used drugs are listed in Annex 2.

In 2018, WHO published interim guidelines recommending dolutegravir (DTG)-containing regimens as the preferred first- and second-line ART regimens for PLHIV.

An updated systematic review conducted in 2019 to support the guidelines reaffirmed that a first-line regimen of DTG combined with two nucleoside reverse-transcriptase inhibitors (NRTIs) leads to higher viral suppression and lower risk of discontinuing treatment and developing HIV drug resistance compared with efavirenz (EFV)-based regimens among treatment-naïve adults. DTG has other advantages over EFV, including lower potential for drug–drug interactions, more rapid viral suppression and a higher genetic barrier to developing HIV drug resistance (HIVDR). DTG is also active against HIV-2 infection, which is naturally resistant to EFV.

This recommendation comes at a time when pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTI) is increasing in low- and middle-income countries, creating a demand for access to alternative non-NNRTI ARV drugs. A pretreatment HIVDR study (2016) in Nepal also showed >10% resistance to NNRTIs (nevirapine [NVP] and EFV).

2.2 ART initiation

ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count.

The National Centre for AIDS and STI Control (NCASC) has adopted the WHO “TREAT ALL” policy since the revision of the national HIV testing and treatment guidelines in 2017. All persons diagnosed with HIV should be linked to care as soon as possible. All efforts should be made to reduce the time between HIV diagnosis and ART initiation.

Rapid initiation is defined as **initiation of ART within seven days** from the day of HIV diagnosis. Rapid ART initiation should be offered to all PLHIV following a confirmed HIV diagnosis and clinical assessment, preferably **within the same day** to people who are ready to start. All efforts should be made to reduce the time between HIV diagnosis and ART initiation based on an assessment of the person’s readiness.

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation. Rapid ART start is especially important for people with a very low CD4 cell count, for whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART.

Health-care providers should hold detailed discussions with all clients about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects, and the required follow-up and monitoring visits. Adequate preparedness counselling must be ensured while initiating ART.

For children with HIV, this conversation should directly involve their caregivers and include discussion of disclosing their HIV status. Initiation of ART should always consider nutritional status, any comorbidities and potentially interacting medications for possible contraindications or dose adjustment.

Clinical assessment when initiating ART

A comprehensive clinical assessment should be done as baseline status and to rule out OIs. A physical examination checklist (Annex 4) can guide in assessment and help in the following ways:

- to identify current HIV-related illnesses (TB, cryptococcal meningitis) that may require treatment;

- to determine the need for OI prophylaxis;
- to carry out the required baseline investigations as per the national protocol;
- to identify coexisting medical conditions such as diabetes, hepatitis, etc. and treatment that may influence the choice of ARV drugs;
- to determine the nutritional status and needs;
- to identify a history of past illnesses (especially STI, hepatitis);
- to assess the need for psychosocial support.

Baseline investigations recommended by the national programme for monitoring of PLHIV at ART centres are summarized below (Table 2.1). ART initiation should not be delayed while waiting for the baseline results.

TABLE 2.1: Baseline investigations

| Indications | Baseline tests |
|--|---|
| All HIV patients | <ol style="list-style-type: none"> 1. Conduct TB screening questionnaire, chest X-ray (CXR) 2. If either symptomatic or CXR abnormal: order sputum for acid-fast bacilli (AFB) tested by GeneXpert (preferred) or microscopy 3. Do a Venereal Disease Research Laboratory (VDRL) test for syphilis 4. Test for hepatitis B 5. Test for hepatitis C 6. Do a complete blood count (CBC) 7. Do a CD4 count 8. Conduct a pregnancy test |
| If planning to start a regimen with TDF | Blood urea, serum creatinine |
| Regimen with DTG or EFV | Alanine aminotransferase (ALT)/serum glutamic pyruvate transaminase (SGPT) |

Note: Additional tests may be done at baseline as per the physician's decision, depending on the clinical presentation.

ART MUST BE STARTED EVEN IF LAB REPORTS ARE AWAITED

2.3 What to start: choice of antiretroviral regimen

The basic principle of ART is to use a triple drug fixed-dose combination (FDC) from two different classes of ARVs. Using simplified, less toxic and more convenient regimens as FDCs is recommended for first-line ART. In line with the WHO recommendation to use DTG and the findings from the national HIV pre-treatment drug resistance (PDR) conducted in 2016 showing more than 10% resistance to NNRTIs, Nepal decided to transition to a DTG-containing regimen as first-line ART.

DTG in first-line ART

DTG combined with two NRTIs is the preferred first-line regimen (Table 2.2). Randomized controlled trials have shown that DTG-based regimens have a faster rate of viral suppression (28 days vs 84 days compared with EFV-based regimens), higher viral suppression (88% vs 81% with EFV), higher gains in CD4 count (267 cells vs 208 cells) at 48 weeks after ART initiation, fewer adverse events, lower risk of discontinuing treatment, fewer drug interactions and less chances of developing HIVDR compared with EFV-based regimens among treatment-naive adults.

Neural tube defects associated with the use of DTG at conception have been reported in the Tsepamo study. Although low, the prevalence is higher than other ARV drug exposure groups (3 per 1000 deliveries vs 1 per 1000 deliveries). However, risk-benefit models suggest that the benefits of DTG for women of childbearing potential newly initiating ART, which include greater maternal viral suppression, fewer maternal deaths, fewer sexual transmissions and fewer mother-to-child transmissions, are likely to outweigh the risks, such as adult morbidity resulting from DTG-associated weight gain and neonatal deaths among the infants of pregnant women with DTG-associated weight gain. DTG is also predicted to be more cost effective, resulting in more disability-adjusted life years averted at a lower cost than EFV.

Therefore, women of childbearing potential or any pregnant or breastfeeding woman should receive full information about the risks and benefits of ART and medical guidance that is appropriate to her situation. She should be supported in making voluntary choices around medical therapy initiation with DTG or other ART, continuation and adherence or retention in care. Health workers must help women to appropriately address their health-care needs and those of their children.

TABLE 2.2: First-line ART regimen for adults, adolescents, pregnant or breastfeeding women

| First-line ART | Preferred first-line regimens | Alternative first-line regimens |
|--|-------------------------------|---|
| Adults/adolescents, pregnant ^a or breastfeeding women | TDF +3TC + DTG ^a | ABC + 3TC + DTG AZT + 3TC + DTG TDF +3TC + EFV ^a |

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; TDF: tenofovir disoproxil fumarate

^a See table below

DTG in second-line ART

DTG is generally safer and more effective than protease inhibitor (PI)-based second-line regimens. For those taking a first-line regimen containing DTG that has failed, a boosted PI-containing regimen should be used (Table 2.3).

TABLE 2.3: Second-line ART regimen for adults, adolescents, pregnant and breastfeeding women

| Population | Failing first-line | Preferred second-line | Alternative second-line |
|---|---|------------------------------|--------------------------------------|
| Adults/ adolescents, pregnant ^a and breastfeeding women | TDF + 3TC + EFV | AZT +3TC + DTG ^a | AZT +3TC + ATV/r (or LPV/r or DRV/r) |
| | TDF + 3TC + DTG ^a ABC + 3TC + DTG | AZT + 3TC + ATV/r (or LPV/r) | AZT + 3TC + DRV/r |
| | AZT +3TC + DTG | TDF + 3TC + ATV/r or LPV/r | TDF + 3TC + DRV/r |

3TC: lamivudine; ABC: abacavir; ATV: atazanavir; AZT: zidovudine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; LPV: lopinavir; r: ritonavir; TDF: tenofovir disoproxil fumarate

^a. Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.

2.3.1 Transition to DTG in the national HIV programme

In Nepal, 6182 children and adults are on NVP and 10952 are on EFV-based regimens. The transition to a DTG-based regimen is being planned as per the tenofovir, lamivudine, dolutegravir (TLD) transition plan (Table 2.4). An important consideration is how to transition people who are stable on ART to a DTG-based regimen. Routine viral load (VL) monitoring should be encouraged but VL testing should not be a requirement for transitioning to optimal regimens. In stable patients, if the VL report is more than 12 months old, VL testing should be done prior to a change in regimen.

TABLE 2.4: Consideration for transition to TDF + 3TC + DTG among adults and adolescents

| Treatment transition scenario | Preferred approach | Comments |
|---|--|---|
| DTG for people living with HIV initiating ART | | |
| Adults and adolescents ^a | Initiate TDF + 3TC + DTG | Potential risk of neural tube defects among infants exposed to DTG during the conception period. Women not using or accessing contraception or who want to become pregnant can use DTG or EFV based on an informed choice of the risks and benefits of each regimen. |
| Pregnant and breastfeeding women ^b Initiate TDF + 3TC + DTG | Initiate TDF + 3TC + DTG | Possibility of conception during breastfeeding remains. |
| TB coinfection | Initiate TDF + 3TC + DTG (DTG dose adjustment needed) | DTG 50 mg twice daily if rifampicin is being used as the anti-TB regimen. |
| DTG for people living with HIV already using a ART regimen | | |
| Clinical or immune failure or viral load not suppressed (on 2NRTI + NNRTI; TDF/3TC/EFV regimen) | ^c Switch to 2NRTIs + DTG or PI/r | Provide adherence support. |
| Viral load suppressed | Substitution to TDF + 3TC+ DTG, according to national recommendations | Substitution should be considered in the context of a TLD transition plan. DTG regimens may be more durable in the long term. |
| Clinically well and viral load unknown | Give priority to viral load testing Substitution to TDF + 3TC + DTG | Provide adherence support. |
| Stable ^d on suboptimal first-line ART regimens | Substitute to TDF + 3TC + DTG | Substitution may confer new side-effects. Provide adherence support. |

3TC: lamivudine; AZT: zidovudine; DTG: dolutegravir; PI: protease inhibitor; r: ritonavir; TDF: tenofovir disoproxil fumarate; TLD: tenofovir, lamivudine, dolutegravir

- a Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester).
- b If women identify as pregnant after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.
- c At least two drugs should be changed at a time, 3TC remains same as a backbone. Other NRTIs are substituted with one another (TDF can be substituted with AZT and vice versa; if ABC was used TDF or AZT can be used).
- d Defined as stable based on national guidelines.

2.4 Service delivery model

The National HIV program encourages the community-led responses as a key element of effective health system. Health services delivery in HIV program advocates a client centered approach that consciously adopts the perspectives of individuals, families and communities, and sees them as participants as well as beneficiaries of trusted health systems that supports in making informed decision and play an active role in their own care.

The HIV clinical services are currently provided from following outlets:

i. ART centres

These are the traditional ART centres attached to a public health facility or hospital. These centres should have facilities to manage adverse events, life-threatening OIs with additional clinical and diagnostic services either at the same facility or through referral. They should have provision for providing hospitalized care or have formal linkage with facilities that can provide hospitalization. The centre should provide routine investigations for monitoring of OIs and the effectiveness of ARVs.

ii. Community-based ART sites

Community-based ART sites (CB-ART) are stand-alone ART sites, mostly run by CBOs, NGOs staffed with trained medical doctors and health workers to provide ART services to specific KPs and at-risk populations. They provide HIV testing and counselling services, ART initiation, medicine refills and adherence support, and support for PrEP and PEP. HIV services and human resources required are arranged in line with the National Standard Service Package of 2020. These sites should provide linkage with ART centres for managing advanced disease and for routine investigations to monitor treatment of OIs.

iii. ART dispensing sites

ART dispensing sites provide ARV refills through trained health workers. ART dispensing sites are in government-managed health posts, sites approved by the NCASC and in line with national standard operating procedures (SOPs).

2.5 General care for people living with HIV

General care includes basic HIV prevention, promoting the health of PLHIV, and screening, prophylaxis and management of HIV-related coinfections and comorbidities. Apart from these, PLHIV require different kinds of care without which a good quality of life for a long period may not be possible. WHO has produced summary guidelines on general care and prevention interventions and recommends a package of 13

prevention interventions for adults and adolescents living with HIV in resource-limited settings. These are as follows:

1. Psychosocial counselling and support;
2. Disclosure and partner notification;
3. Co-trimoxazole (CTX) prophylaxis;
4. TB counselling, screening and preventive therapy;
5. Prevention of common fungal infections;
6. Treatment of STIs and support for reproductive health needs, including prevention and screening for cervical cancer;
7. Preventing malaria (CTX, bed nets and particularly preventing malaria among pregnant women);
8. The use of vaccines for the prevention of COVID-19, pneumococcal disease, influenza, hepatitis B and yellow fever;
9. Provision of adequate nutrition;
10. Family planning services;
11. Elimination of vertical transmission;
12. Harm reduction program for people who inject drugs; and
13. Water, sanitation and hygiene.

2.5.1 Nutritional care and support

Low energy intake combined with increased energy demand because of HIV and related infections may lead to weight loss and wasting. In addition, altered metabolism, reduced appetite and higher incidence of diarrhoea may lower the nutrient intake and absorption, and also lead to nutrient losses. These effects may all be compounded in low-income, food-insecure contexts. Low body mass index (BMI) in adults (BMI less than 18.5 kg/m²), weight loss and wasting in children are all independent risk factors for progression of HIV disease and mortality. Nutritional assessment (anthropometry, clinical and dietary assessment), counselling and support need to be integral components of HIV care and should be conducted at enrolment in care and monitored during all HIV care and treatment. Malnourished people with HIV, especially in food-insecure contexts, may require food supplements, in addition to ART, to ensure that appropriate food is consumed to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection or ART should trigger further assessment and appropriate interventions.

2.5.2 Palliative care: symptom management and end-of-life care

Throughout all stages of HIV disease, and when receiving treatment, PLHIV may experience various forms of pain and other discomfort. Caregivers should identify and treat the underlying cause, whenever possible, while controlling the pain. Pain should be managed in line with the WHO pain management guidelines.

3 MONITORING OF PEOPLE ON ART

Monitoring people with HIV on ART is crucial for the success of any ART programme, as well as its outcome for an individual. Monitoring ART is important for timely and early recognition of drug toxicities, treatment failure and drug resistance, so that necessary action can be taken to switch to second-line drugs (Table 3.2).

Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART. However, opportunistic infections and/or immune reconstitution inflammatory syndrome (IRIS), as well as early adverse drug reactions (ADR), such as drug hypersensitivity, may develop, especially in the first three months of treatment.

In most adults and children, CD4 cell counts rise when ART is initiated, and immune recovery starts. Generally, this increase occurs during the first year of treatment, plateaus, 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 when initiating ART. However, as long as the VL remains below the level of detection, there is no need to be concerned even with decreases in the number of CD4 T cells.

3.1 Recommended follow-up visit

Individuals who have recently initiated ART will have to pay more frequent visits to the ART centre till they are stabilized, after which the frequency of visits can be reduced. All clients diagnosed with HIV can be classified into four key groups which specific needs and should be managed accordingly.

1. Individuals presenting or returning to care when clinically well; may be **newly initiated on ART** or have returned after interrupted treatment.
2. Individuals who are **stable on ART**: defined as those who have received ART for at least one year and have no ADR that require regular monitoring, no current illnesses or pregnancy, are not currently breastfeeding and have good understanding of lifelong adherence and evidence of treatment success (i.e. two consecutive VL measurements below 1000 copies/mL). Less frequent clinic visits and medication pick-up are required. Rapidly growing children (0–5 years of age) and adolescents will need to

be monitored more frequently for treatment dosing/weight changes and adherence support. Follow up for ARV drugs can be at ART dispensing centres, CB-ART or ART centres, with drugs provided for up to a 6-month supply of ARVs. All clients should be monitored in the community for adherence every 3 months by trained community workers (community home-based care [CHBC] workers, peer navigators).

3. **People with advanced disease** are defined as those presenting to care with a CD4 count below 200 cells/mm³ or WHO disease stages 3 and 4 (refer to Chapter 7).
4. **Treatment failure** (individual receiving an ART regimen that is failing): defined as persistently detectable VL exceeding 1000 copies/mL in two consecutive VL measurements within a 3-month interval with adherence support between measurements after 6 months of starting a new ART regimen. Treatment failure monitoring and classification are described in Fig. 3.1 and Table 3.3.

Follow up and laboratory investigation

All new and stable clients on ART should be followed at the health facility for ARV drug refills as per Table 3.1. This follow up visits should be used to provide counselling support for adherence and also to monitor drug specific laboratory investigation as mentioned in Table 3.2.

TABLE 3.1: Follow-up visits for ARV drug refills

| | 2 weeks | 1 month and every month until 6 months | 12 months | Every 6 months after first year |
|--------|---------|--|-----------|---------------------------------|
| New | ✓ | ✓ | ✓ | |
| Stable | | | | ✓ |

TABLE 3.2: Drug-specific laboratory investigation for monitoring people on ART

| Specific ARV drugs | 2-week visit | 1 month visit | 3 months visit | Every 6 months visits |
|---------------------|--------------------|--------------------|--|----------------------------|
| TDF | | | Blood urea, creatinine | Blood urea, creatinine |
| AZT | Hb | Hb | Haemoglobin (Hb), complete blood count (CBC) | Hb, CBC |
| EFV | SGPT/ALT | SGPT/ALT | SGPT/ALT | SGPT/ALT |
| ATV/r | SGPT, S. bilirubin | SGPT, S. bilirubin | SGPT, S. bilirubin | LFT, RBS and lipid profile |
| LPV/r, DRV/r | | | | RBS and lipid profile |
| DTG | | SGPT/ALT | SGPT/ALT | SGPT/ALT |

AZT: zidovudine; ATV: atazanavir; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; LFT: liver function tests; r: ritonavir; RBS: random blood sugar; SGPT/ALT: serum glutamic pyruvate transaminase/alanine aminotransferase; TDF: tenofovir

The national programme recommends VL testing routinely as the preferred ARV drug monitoring tool. The national programme recommends VL testing and CD4 count at 6 months and 12 months and only VL for stable patients after 12 months. If there are no sign of treatment failure, CD4 test is stopped.

- New clients: conduct VL, CD4 6 in months and 12 months.
- Stable clients with viral load <50 copies/mL (undetectable/viral load suppression): conduct VL every 12 months.
- Stable clients with viral load >50 and <1000 copies/mL (low level viremia): Repeat VL in three months and reassess.

The target of the ARV treatment is to achieve Viral Load equal or less than 50 copies/mL. In individuals with viral load > 50 to < 1000 copies/mL, maintain ARV regimen, enhance adherence counselling and repeat viral load testing after three months. Consider switch after second viral load > 50 to < 1000 copies/mL if people are on NNRTI-based ART.

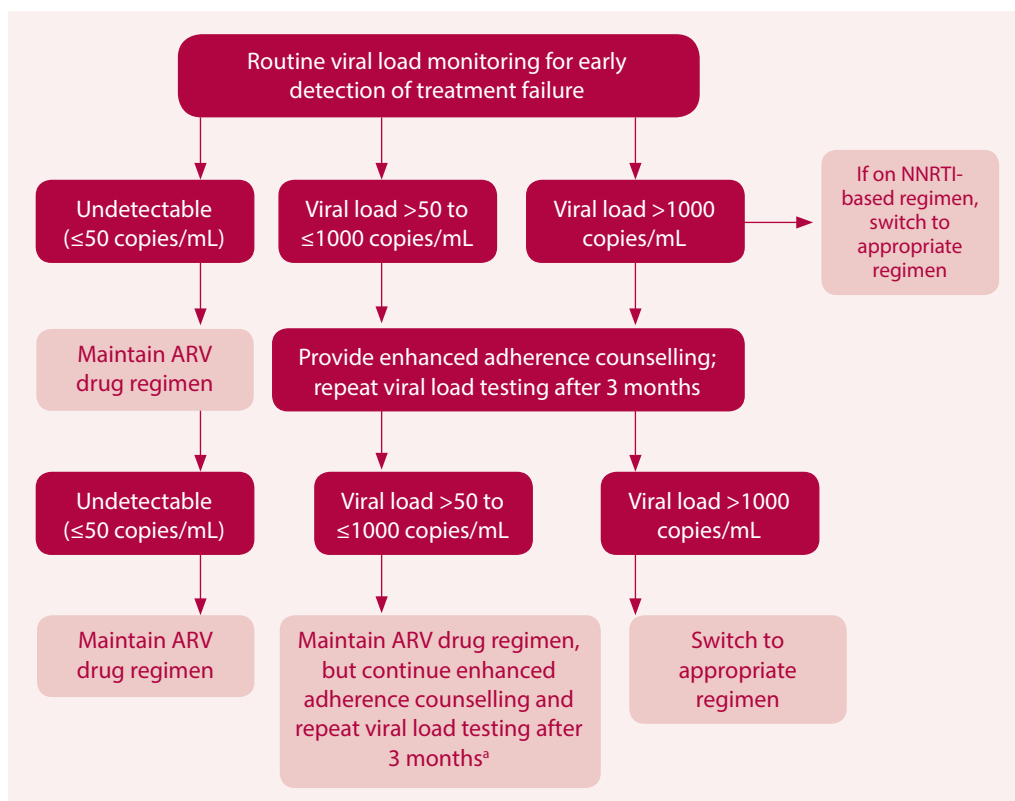
A treatment failure threshold must not be considered synonymous with being undetectable or suppressed. All people living with HIV should be supported with adherence counselling to achieve viral suppression (undetectable). However, treatment failure should be considered for those with a repeat viral load result >1000 copies/mL, three months after a first viral load result >1000 copies/mL. Those with low-level viraemia (50–1000 copies/mL) need to be provided with enhanced adherence counselling and additional viral load testing to promote viral suppression.

The algorithm in Fig. 3.1 is to support clinicians in deciding whether the raised VL or treatment failure is caused by drug resistance or poor adherence. VL is conducted as a routine test and can also be done as part of a physician's assessment in suspected clinical or immunological failure.

Determining treatment failure in the absence of viral load monitoring

In the absence of VL monitoring, use CD4 cell count and clinical assessment to identify those at the highest risk of disease progression and mortality. Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. However, a single CD4 count at or below 250 cells/mm³ following clinical failure is an indicator of immunological failure, although it has low sensitivity and positive predictive value for identifying individuals with virological failure.

FIGURE 3.1: Monitoring treatment failure



a. Consider switching ART for those receiving NNRTI-based regimens based on clinical considerations and address any adherence concerns.

CD4 count monitoring

Long-term CD4 cell count monitoring adds little value in people who are stable on ART, so the national programme does not recommend CD4 count for stable patients. However, CD4 count is important for assessing the baseline risk of disease progression, particularly for individuals presenting with advanced disease, and decisions regarding starting and stopping prophylaxis for OIs. CD4 cell count measurement may also be important for people who are failing ART and for unstable patients.

Viral load for assessing transmission risk

VL testing provides additional value for assessing transmission risk to children, especially from pregnant women not on ART. For babies born to women with a high VL during delivery, enhanced infant prophylaxis, using AZT and NVP together, instead of AZT or NVP, is required to reduce transmission in high-risk infants.

TABLE 3.3: WHO definition of clinical, immunological and virological failure for the decision to switch ART regimens

| Failure | Definition | Comments |
|------------------------------|---|---|
| Clinical failure | <p>Adults and adolescents New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) ^a after 6 months of effective treatment.</p> <p>Children New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stages 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment.</p> | <p>The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiation of ART.</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure. ^a</p> |
| Immunological failure | <p>Adults and adolescents CD4 count at or below 250 cells/mm³ following clinical failure ^b or Persistent CD4 levels below 100 cells/mm³</p> <p>Children <i>Younger than 5 years</i> Persistent CD4 levels below 200 cells/mm³ <i>Older than 5 years</i> Persistent CD4 levels below 100 cells/mm³</p> | <p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count, current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure.</p> <p>There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure.</p> |
| Virological failure | Viral load above 1000 copies/mL based on two consecutive viral load measurements in 3 months, with adherence support following the first viral load test | An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed. |

- a. See the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in Annex 1.
- b. Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at or below 250 cells/mm³ following clinical failure is based on an analysis of data from Uganda and Zimbabwe.

Undetectable viral load is defined as viral load equal to or less than 50 copies/mL. Evidence shows that achieving undetectable viral load with successful ARV treatment prevents HIV transmission to sexual partners and has led to an increasing consensus that people who have achieved and maintained undetectable VL cannot transmit HIV sexually to their partners.

3.2 Monitoring ARV drug toxicities

The availability of laboratory monitoring is not required for initiating ART. For those receiving ART, symptom-directed laboratory monitoring for safety and toxicity can be used. In general, in the event of severe and life-threatening toxicity or hypersensitivity, ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated.

■ Evaluation of ARV drug toxicity

- It is important to differentiate between complications of HIV disease and ARV toxicities as these may present similar signs and symptoms.
- Intercurrent illnesses like hepatitis A and malaria must be kept in mind as they may also lead to symptoms similar to the toxicities of ARV drugs.
- Toxicities due to other drugs used concurrently such as co-trimoxazole, anti-TB drugs and other antibiotics must be ruled out before the toxicities are thought to be due to ARV drugs.
- Delaying substitutions or switches when there are severe adverse drug effects may cause harm and may affect adherence, leading to drug resistance and treatment failure.
- When drug interruptions are required, such as for severe and life-threatening adverse events related to toxicity, it is important to consider the various half-lives of ARV drugs.
- Drug regimen or single-agent substitutions may be required in the case of drug toxicity and to avoid drug interactions. Annex 3 lists the key types of toxicity and associated risk factors for the major ARV drugs.

3.2.1 Monitoring TDF toxicity

The renal toxicity of TDF is characterized by proximal tubular cell dysfunction, which may be associated with acute kidney injury or chronic kidney disease, as well as with bone mineral density loss. However, the incidence of clinically significant renal toxicity with TDF is very low. The best parameter for TDF-related renal toxicity monitoring needs to be evaluated. Laboratory monitoring using a creatinine test is

not compulsory for starting treatment with TDF. People with an impaired estimated glomerular filtration rate (eGFR) at baseline (<60 mL/min) should not initiate TDF.

A serum creatinine test to detect and limit further progression of renal impairment is recommended in patient with the following major risk factors:

- age above 50 years
- underlying renal disease
- low body weight (<50 kg), notably in women
- long-term diabetes
- uncontrolled hypertension
- concomitant use of nephrotoxic drugs, nonsteroidal anti-inflammatory drugs, boosted PIs and ledipasvir (worse if TDF is given in combination with atazanavir (ATV)/r compared to a combination of lopinavir [LPV]/r).

Careful growth monitoring is recommended for children receiving treatment with TDF because of TDF-related decreases in bone mineral density.

Clinical considerations

- Routine blood pressure monitoring should be done to assess for hypertension.
- Urine dipsticks may be used to detect glycosuria or severe TDF nephrotoxicity in individuals without diabetes using TDF-containing regimens.
- If the creatinine clearance test is routinely available, use the eGFR at baseline before initiating a TDF regimen.
- TDF should not be initiated when the eGFR is <60 mL/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Growth should be monitored in children using TDF.

3.2.2 Toxicity monitoring for other ARV drugs

DTG

An increase of 3–5 kg in body weight in individuals receiving DTG-based regimens at 48 weeks is noted, greatest with the tenofovir alafenamide (TAF)+emtricitabine (FTC)+DTG regimen. Therefore, the patient should be counselled on the importance of a healthy diet, avoidance of tobacco and regular exercise to manage weight.

DTG should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin or mineral supplements because of the risk of chelation. If needed, DTG should be administered 2 hours before or 6 hours after taking medication containing polyvalent cations.

ABC

Abacavir (ABC) increases the risk of a hypersensitivity reaction and myocardial infarction in adults. A hypersensitivity reaction is associated with the presence of the HLA-B *57:01 allele.

AZT

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin is recommended before initiating ART mainly for adults and children with low body weight, low CD4 count and advanced HIV disease. AZT should be avoided as first-line therapy in people with HIV with severe anaemia (haemoglobin <6.5 g/dL) at baseline.

NVP

Although measurement of liver enzymes has very low predictive value for NVP-containing regimens, monitoring hepatic enzymes is recommended, especially for women with HIV who have CD4 cell counts >250 cells/mm³ and individuals with HIV who are coinfecting with hepatitis B virus (HBV) or hepatitis C virus (HCV).

EFV

The main type of toxicity of EFV is central nervous system (CNS) side-effects, which typically resolve after a few weeks. However, in some cases, they can persist for months or not resolve at all. Recent data have shown that there is no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARVs; thus, it can be used safely.

3.2.3 Key ARV drug interactions

It is important to be aware of all the drugs that the patient with HIV is taking while initiating ART and adding new drugs in the regimen. Pharmacological interactions can reduce the efficacy of ART and/or increase ART-related toxicities. Major interactions with commonly used drugs are discussed in Table 3.4.

Antituberculosis drugs

Rifampicin is known to significantly lower plasma concentrations of DTG and increasing the dose to 50 mg twice-daily is recommended. The extra dose of DTG is well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared to EFV. When people infected with both TB and HIV are receiving a boosted PI, the dose of the boosted PI should be doubled.

Drugs for hepatitis C

Simeprevir and the combination of ombitasvir + paritaprevir + ritonavir plus dasabuvir should not be co-administered with any PI or NNRTI. Daclatasvir is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative direct-acting antivirals (DAAs). Ledipasvir and sofosbuvir have shown reduced potential for drug interactions with ARV drugs. Ribavirin and pegylated interferon alpha-2a with AZT have been associated with an increased risk of anaemia and hepatic decompensation. People coinfecting with HCV and HIV who are using AZT may need to be switched to TDF. A complete list of drug–drug interactions is available at www.hep-druginteractions.org.

Antifungal agents

NVP may decrease the concentrations of itraconazole and ketoconazole to subtherapeutic levels when they are used together; so, when treating fungal infections, fluconazole or flucytosine can be used to ensure adequate treatment.

Opioid substitution therapy

EFV decreases methadone concentration, leading to withdrawal symptoms and increasing the risk of relapse to opioid use. Hence, dose adjustment is required.

Hormonal contraceptives

ARVs, especially some NNRTIs and RTV-boosted PIs, may alter the effectiveness of mainly estrogen-containing hormonal contraceptives. In such cases, consistent use of condoms or other contraceptive methods is recommended.

Antihistamines

Concomitant use of boosted PIs and NNRTIs with antihistamines (e.g. astemizole and terfenadine) is associated with severe and life-threatening reactions such as cardiac arrhythmias. Alternative agents like loratadine and cetirizine are preferred.

Statins

Boosted PIs may lead to increased concentrations of lovastatin and simvastatin, which may increase the risk of developing serious adverse events such as myopathy, including rhabdomyolysis. Alternative dyslipidaemia agents should be used to prevent severe toxicity among PLHIV.

The interactions of key ARVs with common drugs for treating other conditions and the suggested management are given in Table 3.4.

TABLE 3.4: ARV drug interactions and suggested management

| ARV drug | Key interactions | Suggested management |
|---|---|--|
| Boosted PIs (ATV/r, DRV/r and LPV/r) | Rifampicin | Adjust the dose of LPV/r or substitute with three NRTIs (for children) |
| | Halofantrine | Use an alternative antimalarial agent |
| | Lovastatin and simvastatin | Use an alternative statin (such as pravastatin) |
| | Hormonal contraceptives | Use alternative or additional contraceptive methods |
| | Metformin | Adjust methadone and buprenorphine doses as appropriate |
| | Astemizole and terfenadine | Use an alternative antihistamine agent |
| | TDF | Monitor renal function |
| | Simeprevir | Use an alternative direct-acting antiviral agent |
| | Ombitasvir + paritaprevir/ritonavir + dasabuvir | Use an alternative direct-acting antiviral agent |
| DTG | Dofetilide | Use an alternative antiarrhythmic agent |
| | Rifampicin | Adjust the dose of DTG |
| | Carbamazepine, phenobarbital and phenytoin | Use an alternative anticonvulsant agent (such as valproic acid or gabapentin) |
| | Polyvalent cation products containing Mg, Al, Fe, Ca and Zn | Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to the following products: multivitamin supplements containing Fe, Ca, Mg or Zn; mineral supplements, cation-containing laxatives and antacids containing Al, Ca or Mg. Monitor for efficacy in suppressing viral load. |

| ARV drug | Key interactions | Suggested management |
|----------|----------------------------------|--|
| EFV | Amodiaquine | Use an alternative antimalarial agent. |
| | Cisapride | Use an alternative gastrointestinal agent. |
| | Methadone | Adjust the methadone dose as appropriate. |
| | Hormonal contraceptives | Use alternative or additional contraceptive methods. |
| | Astemizole and terfenadine | Use an alternative antihistamine agent. |
| | Ergotamine and dihydroergotamine | Use an alternative antimigraine agent. |
| | Simeprevir | Use an alternative direct-acting antiviral agent. |
| | Midazolam and triazolam | Use an alternative anxiolytic agent. |

This table was developed by WHO using the University of Liverpool's drug interaction charts, which can be found online at www.hiv-druginteractions.org and www.hepdruginteractions.org.

3.2.4 Immune reconstitution inflammatory syndrome (IRIS)

This is a condition that can occur shortly after a person starts HIV therapy for the first time. 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, *Mycobacterium avium* complex (MAC) or cytomegalovirus (CMV). In general, people with more severely damaged immune systems before starting HIV therapy are most at risk for IRIS. It occurs in 10–30% of patients initiating ART, usually within the first 4–8 weeks but can occur up to six months. The degree of viral suppression is crucial: the lower the VL, the more pronounced the effect of IRIS.

The possible risk factors for IRIS are shown below:

- people with CD4 counts below 100 cells/mm³ before starting therapy;
- people with greater fall in HIV VL due to therapy;
- people with a diagnosis of another infection before starting therapy; the closer the appearance or diagnosis is to starting therapy, the higher the risk;
- severity of TB disease, especially a high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatment.

After a patient starts ART, IRIS may manifest as a worsening of previously diagnosed disease, termed paradoxical IRIS, or as the appearance of a previously undiagnosed disease, termed unmasking IRIS.

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:

- active OIs,
- treatment failure,
- side-effects of ARVs,
- ARV resistance.

The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi sarcoma and herpes zoster. BCG vaccine-associated IRIS (localized and systemic) may occur in infants infected with HIV in settings where BCG immunization is routine.

Management of IRIS

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

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 or poor adherence to ART.

If not severe, symptomatic treatment, e.g. NSAIDs, is required. Decrease the immune response by:

- giving immunosuppressive agents, e.g. corticosteroids 1–2 mg/kg usually for 1–2 weeks, sometimes for up to 12 weeks;
- continuing ART and OI therapy + steroids;
- treating OIs for the standard period or longer.

If OI treatment has already been stopped, reintroduction of OI treatment may help to decrease the antigen load.

3.3 Identification and management of adverse drug reaction of ARV drugs

The WHO definition of an adverse event is, "Any untoward medical occurrence that may appear during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with the treatment."

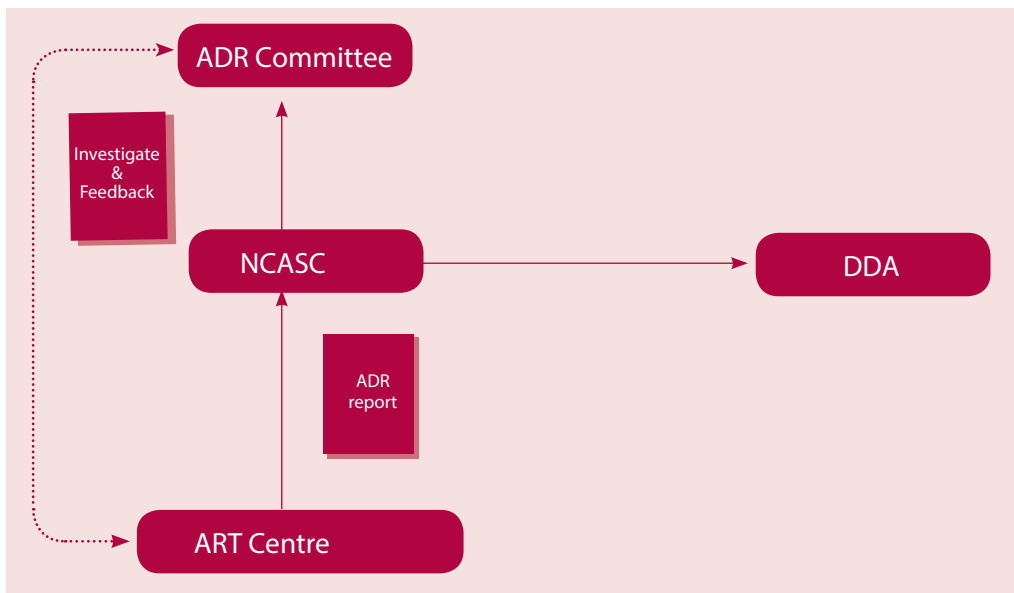
As of 2020, around 19 000 people are on ART in Nepal. Although the safety profile of the new ARVs has significantly improved, ARVs are associated with significant safety concerns, including serious ADR to medicines, with both short- and long-term effects. These reactions may damage confidence in any national ARV programme and affect patient adherence leading to problems for themselves and the national programme. Poor adherence is known to lead to failure of therapy in the patient (he or she will not get well and may die) and development of resistance by the virus leads to reduced efficacy of these life-prolonging medicines.

A pharmacovigilance system can help achieve comprehensive, safe and effective health care for all patients on ART. Timely identification and management of ADR is very important for patient management and ensuring adherence to treatment. Detection of ADR is primarily dependent upon reporting from patients, nurses, doctors, counsellors, among others. At every encounter with patients, health workers should ask the patient about clinical symptoms of common ADR such as nausea, vomiting, itching, headache, abdominal pain, dizziness, insomnia, etc.

Management includes measures taken to alleviate the signs and symptoms of ADR with careful individual case review and referrals to higher centres for further management in case of serious adverse events.

If any adverse reactions are noted, an adverse event recording and reporting form should be completed by the health-care provider using the Annex 16 form. All the ADR (Annex 16) should be sent to the NCASC every month. However, serious adverse events requiring hospitalization, deaths and adverse fetal outcomes (eg. neural tube defects, congenital infections, etc.) for pregnant women should be reported immediately within 24 hours. The ADR committee formed by the NCASC will review, investigate and advise within 72 hours. The NCASC will coordinate with the Department of Drug Administration (DDA) to establish a reporting channel for all the ADR (Fig. 3.2).

FIGURE 3.2: Adverse drug reactions (ADR) reporting pathway for ARV drugs in the HIV programme



4 ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

4.1 Oral pre-exposure prophylaxis

Oral pre-exposure prophylaxis (PrEP) is the use of ARV drugs by people who are not infected with HIV in order to prevent the acquisition of HIV. The national HIV programme recommends daily oral PrEP as a combined HIV prevention approach among at-risk and key populations.

WHO recommends offering PrEP to people at substantial risk of acquiring HIV infection. Substantial risk of HIV infection is provisionally defined as an HIV incidence of around 3 per 100 person-years or higher in the absence of PrEP.

Indications for PrEP (by history over the past 6 month)

HIV-negative individuals AND

sexual partner with HIV, OR

Sexually active in a high-risk group AND any of the following:

- vaginal or anal sexual intercourse without condoms with more than one partner, OR
- a sexual partner with one or more HIV risk factors, OR
- a history of an STI by lab testing or self-report or received syndromic STI treatment, OR
- use of PEP, OR
- request for PrEP.

Contraindications to PrEP

- HIV-positive persons
- Estimated creatinine clearance <60 mL/min
- Allergy or contraindication to any medication in the PrEP regimen.

Counselling points before starting PrEP

- PrEP is provided as an additional prevention choice as part of a comprehensive prevention package of services, which includes HIV testing, counselling, ART for partners with HIV infection, condoms and lubricants, harm reduction and access to NSP.
- PrEP is offered as a choice, free of coercion, and with access to other prevention strategies that may be preferred by individuals at substantial risk.
- PrEP can be discontinued if a person taking PrEP is no longer at risk and when such a situation is likely to be sustained.
- Take one tablet each day. It may be easiest to remember if you take the tablet at the same time each day (see Tables 4.1 and 4.2).
- PrEP is highly effective in preventing HIV infection, but it does not protect against other STIs or prevent pregnancy. (Advice about condoms and contraception can be shared where appropriate.)
- PrEP provides high levels of protection in people who take PrEP medicines regularly. As time is needed to build up protective levels of the medicine in the blood and other tissues, additional HIV prevention should be taken for the first 7 days of PrEP use. PrEP begins to work only after taking seven doses.
- PrEP can be stopped 28 days after the last possible exposure to HIV.

TABLE 4.1: Recommended regimen for pre-exposure prophylaxis

| Generic name | |
|---|-----------|
| Tenofovir disoproxil fumarate 300 mg (TDF)/emtricitabine 200 mg (FTC) | Preferred |
| Tenofovir disoproxil fumarate 300 mg (TDF)/lamivudine 300 mg (3TC) | Alternate |

TABLE 4.2: Monitoring clients on pre-exposure prophylaxis

| Baseline tests | Monitoring frequency |
|--|--|
| HIV test | <ul style="list-style-type: none"> • HIV testing at month after initiation and repeat every three months during PrEP use. |
| Creatinine | <ul style="list-style-type: none"> • Not indicated for clients <30 years old with no any co-morbid conditions*. • At baseline/initiation for clients 30-50 years old with no any co-morbidities*. • At baseline/initiation and every six months for clients above 50 years old or any one with co-morbid conditions*. |
| HBsAg | <ul style="list-style-type: none"> • If HBsAg is negative: consider vaccination. • If positive, suggest further testing and assessment for hepatitis B treatment. Not everyone with HBsAg requires treatment. Oral PrEP containing TDF can benefit people with HBV infection who need treatment. HBV flares can be expected on discontinuation of PrEP in such client. |
| Anti-HCV (HCV antibodies) | <ul style="list-style-type: none"> • Test annually during PrEP use. |
| Syphilis (VDRL) | <ul style="list-style-type: none"> • Test every three to six months during PrEP use to check for active syphilis infection and to evaluate the response to treatment. |
| Look for signs of STIs and treat syndromically | <ul style="list-style-type: none"> • Routine visits (every 3 months). |

* diabetes, hypertension and previous creatinine clearance <90ml/min

Management of a rise in serum creatinine

Approximately one in every 200 PrEP users will have a raised serum creatinine during PrEP use. Around 80% of these are self-limiting (without stopping PrEP) and resolve when a separate specimen, collected on a different day, is tested. Such transient increases in creatinine are often due to dehydration, exercise or diet, or they could reflect a false-positive result. If the creatinine clearance is less than 60 mL/min, the clinician can consider discontinuation of PrEP, recheck in 1–3 months and continue if the creatinine clearance is more than 60 mL/min.

The provider can calculate the estimated creatinine clearance based on measured serum creatinine, the client's sex at birth, age and estimated lean body weight.

Creatinine clearance = Sex × {(140–Age)/ (Serum creatinine)} × (Weight/72)

- For "sex", use 1 for a male, 0.85 for a female (for TG, the sex at birth is used).
- Give "age" in years.
- Provide "serum creatinine" value in mg/dL.
- Give "weight" in kg.

4.2 Post-exposure prophylaxis

Post-exposure prophylaxis (PEP) is the short-term use of ARV drugs to help prevent HIV transmission. The rationale is that ARVs given immediately after exposure can stop the virus from disseminating in the body and establishing infection. The risk of HIV transmission following skin punctures from a needle or other sharp objects that are contaminated with blood from a person with laboratory-confirmed HIV infection is about 0.3%. The risk of HIV transmission is less with injuries sustained with solid-bore (e.g. suture) needles than with hollow-bore (e.g. blood drawing) needles. Similarly, the smaller the size of hollow-bore needles, the lesser the risk of HIV transmission. The risk of HIV infection by exposure of mucous membranes (of the eyes, nose or mouth) or abraded (broken) skin to HIV-infected material is estimated to be about 0.09%.

Everyone possibly exposed to HIV should be assessed by a trained health-care worker. Essential components of the clinical examination include assessing the mechanism of exposure and assessing eligibility for post-exposure prophylaxis, examination of any wound and initial first-aid treatment needed (Table 4.3).

TABLE 4.3: First aid measures for post-exposure prophylaxis

| Type of exposure | First aid measures |
|--|---|
| If the skin is broken following an injury with a used needle or sharp instrument | <ul style="list-style-type: none"> Do not squeeze or rub the injury site. Wash the site immediately using soap or a mild disinfectant solution that will not irritate the skin. Do not use strong solutions, such as bleach or iodine, to clean the site as these may irritate the wound and make the injury worse. |
| After a splash of blood or body fluids on broken skin | <ul style="list-style-type: none"> Follow the same steps as for broken skin. |
| After a splash or contact with the eye | <ul style="list-style-type: none"> Irrigate the exposed eye immediately with water or normal saline. Sit in a chair, tilt the head back and have a colleague gently pour water or normal saline over the eye, pulling the eyelids up and down to make sure the eye is cleaned thoroughly. If contact lenses are worn, leave these in place while irrigating the eye. Once the eye has been cleaned, remove the contact lenses and clean them in the usual manner. Do not use soap or disinfectant in the eye. |
| After a splash or contact with the mouth | <ul style="list-style-type: none"> Spit the 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. |

Indications for PEP

1. The exposed person is HIV negative.
2. The source person is HIV positive, or at high risk of recent infection and thus likely to be in the window period.
3. The exposure to the following poses a risk of transmission:
 - a. Parenteral or mucous membrane exposure (sexual exposure and splashes to the eye, nose or oral cavity)
 - b. Bodily fluids may pose a risk of HIV infection: blood, blood-stained saliva, breast-milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleural fluids.*
 - c. sexual assault;
 - d. exposure of non-intact skin or mucous membranes to potentially infectious body fluids.

**The list is not exhaustive and all cases should be assessed clinically and decisions made by the health-care workers as to whether exposure constitutes significant risk.*

PEP is not indicated

- if the exposed individual is HIV positive;
- if the source is established to be HIV negative; and
- if exposed to body fluids posing an insignificant risk of transmission, such as tears, non-blood-stained saliva, urine and sweat.

Recommendations for PEP

- Start as soon as possible, preferably within 2 hours and maximum within 72 hours of exposure. The duration of treatment is 28 days.
- Get a baseline HIV antibody test and monitor for seroconversion at 6 weeks, 3 months and 6 months after exposure.
- Test for hepatitis B and C.
- Counsel the exposed person and take informed consent for initiating PEP.

Counselling for PEP must include the following:

- the risk of acquiring HIV infection from a specific exposure;
- risk and benefits of HIV PEP;
- the importance of having an initial baseline HIV test;
- Link to treatment for those who are HIV positive;
- Enhanced adherence counselling to take the medicine daily for its effectiveness;

- common side-effects that may be experienced while taking PEP;
- PEP is safe during pregnancy and breastfeeding;
- Specific support in case of sexual assault;
- For non-occupational exposure, provide HIV prevention counselling.

4.2.1 Drug regimens for post-exposure prophylaxis

The choice of PEP drugs should be based on the country's first-line ART regimen to treat HIV infection (Table 4.4).

TABLE 4.4: Drugs for PEP

| Adults and adolescents (>10 years) | |
|------------------------------------|-------------------------------------|
| Preferred regimen | TDF + 3TC + DTG |
| Alternative regimen | TDF+3TC +LPV/r or ATV/r |
| Children (≤10 years) | |
| Preferred regimen | AZT+3TC+LPV/r |
| Alternative regimen | ABC+3TC with ATV/r OR RAL or DTG |

3TC: lamivudine; ABC: abacavir; ATV: atazanavir; AZT: zidovudine; DTG: dolutegravir; LPV: lopinavir; r: ritonavir; RAL: raltegravir

Clinical considerations

People with established chronic HBV infection should be monitored for hepatic flare after PEP is discontinued or assessed for the need of ongoing HBV therapy after discontinuing PEP.

4.3 Combination HIV prevention

The approach to HIV prevention needs to be changed over the course of a lifetime, and a combination approach helps people to access the types of activities that best suit their needs at different times. Combining approaches may also result in synergies that have a greater impact than single activities and strategies. Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of the following.

- **Male condoms** reduce heterosexual transmission by at least 80% and offer 64% protection during anal sex among gay men and other MSM, if used consistently and correctly. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect.

- **Needle and syringe programmes (NSP)** are highly associated with reduction in HIV transmission through injecting drug use.
- **Opioid substitution therapy (OST) with methadone or buprenorphine** is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviours and transmission through injecting drug use. OST also provides adherence support to people on ART.
- **Voluntary medical male circumcision (VMMC)** reduces acquisition of infection and the risk of acquisition in men by up to 66% and offers significant lifelong protection.
- **Behavioural strategies** reduce the frequency of potential transmission events and include the following:
 - Targeted information and education programmes that use various communication approaches, for example, school-based sex education, peer counselling and community-level and interpersonal counselling, to disseminate behavioural messages designed to encourage people to reduce behaviours that increase the risk of HIV, and increase behaviours that are protective (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, using male and female condoms correctly and consistently, and knowing your and your partner's HIV status).
 - Structural and supportive strategies affect access to, uptake of and adherence to behavioural and biomedical initiatives. These need to address the critical social, legal, political and environmental enablers that contribute to HIV transmission. These include legal and policy reforms, measures to reduce prejudice and discrimination, promotion of gender justice and prevention of gender violence, economic empowerment, access to schooling and supportive strategies designed to enhance identification, outreach, testing, treatment and retention of persons at higher risk for HIV.

5 MANAGEMENT OF HIV IN CHILDREN

5.1 Introduction

Most children acquire HIV infection in utero, during delivery or through breastfeeding. Paediatric HIV disease progression can be rapid or slow. Rapidly progressing disease results in high mortality during the first few years of life. “Slow progressors” will develop immunosuppression (AIDS) several years after initial infection.

ARV drugs should be used properly to avoid the development of drug resistance and restore or maintain the immune status. It is recommended that potent first-line ARV regimens be started, convenient once-daily dosing and FDCs be chosen, whenever possible.

Adherence to treatment is dependent on the counselling provided to the caregiver and to the child and, to some extent, the commitment of the caregiver. Children have special counselling needs; older children, especially adolescents, need to understand their diagnosis if they are to adhere to ART. Disclosure of HIV status to a child needs to be handled with care and should take place only with the involvement of the family or guardian.

The review of evidence, together with operational considerations, has led to revised recommendations for simplifying and expanding treatment for children, including initiating ART in all children.

5.2 Clinical features in children

The immunosuppressive effects of HIV are additive to the poor response of the immature immune system at birth, predisposing to an increased frequency of invasive bacterial infections and OIs. Common childhood infections and conditions are more frequent in HIV-infected children and have a higher case fatality rate compared to uninfected children.

The common clinical manifestations are as follows:

1. Failure to thrive. It may manifest as early as 4–6 months of age in perinatally infected infants and is also commonly seen in most children with HIV.
2. Lymphadenopathy. The causes of lymphadenopathy include infiltration of the lymph nodes by HIV and may present as persistent generalized lymphadenopathy or it could be because of infections such as TB, disseminated atypical mycobacterial infections, viral infections such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), and malignancies such as lymphoma and lymphosarcoma.
3. Respiratory manifestations. Pneumonia is the commonest bacterial infection among HIV-infected children. *Pneumocystis jiroveci* pneumonia (PCP) is the most common OI associated with HIV in children. It predominantly occurs between 3 and 6 months of age. Recurrent otitis media and sinusitis are also common. Chronic HIV-associated lung diseases include TB, lymphoid interstitial pneumonitis and bronchiectasis.
4. Gastrointestinal and hepatobiliary conditions:
 - Diarrhoea is one of the commonest clinical manifestations in children with HIV. Diarrhoea tends to be prolonged and is usually complicated by dehydration and malnutrition in HIV-infected children. Chronic or recurrent diarrhoea with malabsorption, abdominal pain, dysphagia, and failure to thrive are also common. Persistent diarrhoea is associated with a high risk of death in HIV-infected children.
 - Hepatomegaly is a common gastrointestinal manifestation of paediatric HIV infection. Development of hepatomegaly within 3 months of age is associated with rapid progression of the disease.
 - Parotitis tends to be recurrent or chronic and painless and may manifest as unilateral or bilateral parotid swelling.
 - Oral manifestations include thrush (candidiasis), periodontitis, ulcerative gingivitis, oral hairy leukoplakia and oral or oesophageal ulcerations.
5. Skin manifestations are common in children and may be of the following types:
 - infectious (bacterial: impetigo, scabies; viral: herpes simplex, herpes zoster, molluscum contagiosum, warts; fungal: candidiasis, tinea, onychomycosis)
 - non-infectious (seborrheic dermatitis, atopic dermatitis, generalized dermatitis, nutritional deficiency, eczema, psoriasis, drug eruptions, vasculitis, alopecia).
6. Haematological manifestations such as anaemia occur in 20–70% of HIV-infected children. Leukopenia occurs in almost 30% of untreated HIV-infected children, and neutropenia is common. Thrombocytopenia is reported in 10–20% of patients.

7. Neurological manifestations are seen in about 40–70% of HIV-infected children. They develop symptomatic neurological disturbances, and the brain is most commonly affected. Manifestations may range from subtle developmental delay to progressive encephalopathy with loss or plateauing of developmental milestones, cognitive deterioration, impaired brain growth resulting in acquired microcephaly, and symmetrical motor dysfunction. Encephalopathy may be the initial manifestation of the disease or may present much later when severe immune suppression occurs.
8. Malignancies are less frequent in children. The most common malignancies include non-Hodgkin lymphoma, CNS lymphoma, leiomyoma, EBV-associated leiomyosarcoma and leukaemia.

Differences between paediatric and adult HIV infection

- Overall progression of disease is more rapid in children.
- The immune system is more immature than in adults, even in those with a high CD4 count.
- Recurrent invasive bacterial infections are more common in children.
- Disseminated CMV, candidiasis, herpes simplex and varicella zoster are more common.
- Lymphocytic interstitial pneumonia occurs almost exclusively in children.
- CNS infections are common. Peripheral neuropathy, myopathy and Kaposi sarcoma are rare in children.

5.3 Preparation of children for ART

Prior to initiating ART, it is important to adequately prepare the child and their caregivers.

- Baseline investigations: the following tests should be carried out to assess haematological, liver and kidney functions, as well as immune status:
 - haemoglobin (Hb), total and differential leukocyte counts (TLC, DLC), platelet count, erythrocyte sedimentation rate (ESR)
 - liver function tests (alanine aminotransferase)
 - renal function tests (blood urea and creatinine)
 - random blood sugar (RBS)
 - CD4% or count
 - chest X-ray.

- All children enrolled in care or those being assessed for ART should be screened for TB. This should take into account the history of TB in the child's immediate family.
 - treat any intercurrent illnesses.
 - initiate co-trimoxazole prophylaxis in all children.
- Counselling, education and support

Counsel the parent/guardian on the following:

 - goals of ART;
 - lifelong nature of therapy;
 - importance of adherence to ART;
 - importance of monitoring and the need to attend clinic regularly as required, as well as for intercurrent conditions;
 - when and how to store and administer the drugs;
 - possible adverse effects of ARV drugs intended for use, how to recognize them and what to do should they arise;
 - caregivers should be encouraged to bring a child on treatment back to the clinic if they have concerns or the child becomes ill;
 - nutritional counselling should be done;
 - children have to be weighed and their height measured regularly at each clinic visit, and the dose adjusted as children grow and gain weight;
 - the specific need for counselling for adolescents who are becoming sexually mature and highlighting adherence issues.

5.3.1 Disclosure

- Many children living with HIV survive into adolescence as a result of increased access to ART. With children and adolescents living longer with HIV on ART, the focus turns from survival to improving the quality of life, treatment adherence, retention in care and treatment, viral suppression, and sustaining physical and mental well-being.
- Disclosure of HIV status among paediatric and/or adolescent patients and their families and support structures is a critically important component of the care and treatment cascade.
- The process of disclosure is complex, both emotionally and socially.
- Disclosure of HIV status is not a one-time event, but rather a process, involving ongoing discussions about the disease as the child or adolescent matures cognitively, socially, emotionally and sexually.

- Discussion with caregivers should begin early with age-appropriate information, and with the aim of full disclosure by the age of 12–14 years.
- Other factors that may influence the decision to disclose include: caregivers wanting their child to improve or maintain a certain level of adherence, the caregiver’s level of knowledge of HIV disclosure, and the child or adolescent’s status on ART.

5.4 ART for infants and children

The advent of potent ART has dramatically reduced the rates of mortality and morbidity and has improved the quality of life of infants and children living with HIV. As a result, HIV is now perceived as a manageable chronic illness. **Important information on pediatric drug formulations, dosages and schedule are listed in the Annex 8-13.**

When to start ART in children:

- ART should be started in all children infected with HIV below 18 years of age regardless of WHO clinical staging or CD4 count.

First-line ART regimen for infants and children

- For infants and children >1 month to less than 10 years of age, the NRTI backbone for an ART regimen should be ABC + 3TC.
- DTG is approved for use among children older than 6 years and weighing more than 20 kg who can take the 50 mg film-coated adult tablets.
- Among children for whom approved dosing of DTG is not available, raltegravir (RAL) is considered an effective option and is approved for use from birth. RAL successfully reduces VL among highly viraemic infants and is safe and well tolerated among neonates and infants at high risk of infection.
- RAL can be considered as an alternative only if LPV/r solid formulations are not available for children weighing less than 20 kg.
- LPV/r syrup or granules can be used for neonates after 2 weeks of age.

Based on current recommendations and available drugs and formulations, the first-line ART regimen for infants and children is given in Table 5.1.

TABLE 5.1: First-line ART for infants and children

| Age category | Preferred regimen | Alternative regimen |
|--|------------------------------|---|
| For neonates up to 1 month | AZT+3TC+ NVP | AZT + 3TC + LPV/r ^a |
| Infants 1 month to 6 years | ABC+3TC+LPV/r | ABC + 3TC + RAL ^b AZT + 3TC + RAL AZT + 3TC + LPV/r ABC + 3TC + NVP |
| Children >6 years up to 10 years (wt 20–30 kg) | ABC + 3TC + DTG ^c | ABC + 3TC + LPV/r ABC+3TC+RAL |
| Children >10 years and above (wt 30 kg or more) | TDF + 3TC + DTG ^c | TDF + 3TC + LPV/r |

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir

^a LPV/r syrup or granules can be used after 2 weeks of age.

^b RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.

^c For age and weight groups with approved DTG dosing.

Second-line ART for children

Recommendations

- After failure of a first-line NNRTI-based regimen, children 6 years or less should be switched to a RAL-based second-line regimen and to a DTG-based regimen if more than 6 years of age and weighing more than 20 kg. If a suitable RAL formulation is not available then a boosted PI should be used (LPV/r).
- After failure of a first-line LPV/r-based regimen, children 6 years or less should be switched to a RAL-based second-line regimen and to a DTG-based regimen if more than 6 years and weighing more than 20 kg.
- After failure of a first-line regimen of ABC + 3TC, the preferred NRTI for second-line ART is AZT + 3TC.
- After failure of a first-line regimen of AZT + 3TC, the preferred NRTI for second-line ART is ABC + 3TC.
- After failure of a first-line regimen of AZT or ABC+ 3TC, the preferred NRTI for second-line ART is TDF + 3TC in adolescent children more than 10 years and weighing more than 30 kg (Table 5.2).

TABLE 5.2: Preferred second-line ART regimens

| Failing first-line in neonates, infants and children | Preferred second-line regimen | Alternate second-line regimen |
|--|--|--|
| ABC (or AZT) +3TC+NVP | AZT (or ABC) +3TC+ RAL (if <6 years) | AZT (or ABC) +3TC+ LPV/r if RAL formulation is not available |
| | AZT (or ABC) +3TC + DTG (if >6 years & wt >20 kg) | - |
| ABC (or AZT) + 3TC + LPV/r | AZT (or ABC) + 3TC + RAL (if <6 years) | AZT (or ABC) + 3TC + LPV/r if RAL formulation is not available |
| | AZT (or ABC) +3TC+DTG (if >6 years & wt >20 kg) | - |
| ABC (or AZT) + 3TC + RAL/ DTG | AZT (or ABC) +3TC + LPV/r or ATV/r | AZT (or ABC) + 3TC + DVR/r ^a |
| AZT (or ABC) +3TC+ EFV | ABC (or AZT) + 3TC + DTG (if >6 years and wt >20 kg) TDF+3TC+DTG (if >10 years and wt >30 kg) | ABC (ABC or AZT) + 3TC + LPV/r (or ATV/r ^b) |

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TDF: tenofovir disoproxil fumarate

a. DRV should not be used for children younger than 3 years and should be combined with appropriate dosing of ritonavir.

b. ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than 6 years, the lack of a fixed-dose formulation and the need for separate administration of the ritonavir booster should be considered when choosing this regimen.

5.5 Vaccination for children living with HIV

- HIV infection, because of the immunocompromised state it causes, is a risk factor for morbidity and mortality caused by a number of infections that can usually be prevented by immunization.
- Although vaccine efficacy is usually compromised in advanced disease, adequate responses can be achieved when vaccines are administered early after HIV infection or after virological suppression and immune reconstitution with ART.
- Vaccines usually have better safety and efficacy among people with HIV who are receiving ART and those without significant immunosuppression, notably when the CD4 count is above 200 cells/mm³.
- HIV-exposed and -infected infants and children with HIV should receive all vaccines under routine vaccination according to the recommended national immunization schedules. However, live vaccines should be avoided in children in advanced clinical stages and with severe immunosuppression.
- An extra dose of measles vaccination at 6 months of age is recommended and vaccine against chickenpox is also recommended.

TABLE 5.3: Considerations for transition to optimal ART regimens for children who are considered stable on ART based on national guidelines

| Current regimen | Weight | Optimal regimen for transition | Consideration |
|--|----------|---|--|
| AZT + 3TC + NVP ^a | <20 kg | ABC + 3TC + LPV/r | If stable, children can be transitioned to DTG when they reach 20 kg. |
| AZT + 3TC + EFV ^a | 20–30 kg | ABC + 3TC + DTG | If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg. |
| ABC + 3TC + NVP | >30 kg | TDF + 3TC + DTG | |
| ABC + 3TC + EFV | <20 kg | ABC + 3TC + LPV/r | Transition to optimal regimens for these children is of value once they reach 20 kg and DTG can be used maintaining once daily administration. |
| | 20–30 kg | ABC + 3TC + DTG | If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg. |
| | >30 kg | TDF + 3TC + DTG | |
| ABC + 3TC + LPV/r AZT + 3TC + LPV/r | <20 kg | No change until they reach 20 kg unless treatment failure occurs. | Ensure the use of tablets as soon as possible to reduce pill burden. Transition from AZT + 3TC + LPV/r to ABC + 3TC + LPV/r can be considered to reduce the pill burden and preserve the antiviral advantage of NRTI's sequencing. |
| | 20–30 kg | ABC + 3TC + DTG | If stable, children can be transitioned to TDF + 3TC + DTG when they reach 30 kg wt. |
| | >30 kg | TDF + 3TC + DTG | |

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir/ritonavir; NVP: nevirapine; PI/r: protease inhibitor boosted with ritonavir; RAL: raltegravir; TDF: tenofovir disoproxil fumarate

^a The HIV PDR survey showed 10% resistance to NNRTI, so the use of NVP/EFV is discontinued.

5.6 Nutritional care and support of HIV-infected children

- HIV infection can impair the nutritional status of infected children early in life. Growth faltering and reduction in length and height often occur even before OIs or other symptoms appear in almost all infected children.
- Early nutritional advice and active support are recommended to ensure adequate energy, protein and micronutrient intake at all stages of HIV infection, prevent growth failure and loss of weight. Malnutrition itself results in decreased immune function and greater susceptibility to infections, accelerating disease progression.

- Breastfeeding should be promoted and supported for optimal growth and development of infants. Infants should be exclusively breastfed for the first 6 months of life and appropriate complementary foods introduced thereafter, and breastfeeding continued at least for 12 months and continued up to 24 months. The risk of transmitting HIV to infants through breastfeeding is low when the mother is receiving ART and the infant is on ARV prophylaxis.

Targets for energy and micronutrient intake

Children who are growing well and are asymptomatic or with mild symptoms only (may include children on ART >6 months following recovery of weight):

- The energy needs of these children are increased by about 10% (based on actual weight rather than expected weight for age).
- These children need appropriate energy intake according to their age and weight.
- The additional energy helps to maintain normal growth, development, activity and body functions. The additional energy is best given through additional household foods provided as part of a balanced and varied diet.

Children with conditions with increased energy need, e.g. chronic lung disease or chronic infections, such as TB or persistent diarrhoea):

- These children with chronic illnesses require an extra 20–30% of energy each day based on actual weight rather than expected weight for age.

Children with severe malnutrition, i.e. signs of visible wasting, bilateral edema or severely impaired growth:

- These children need 50–100% extra energy each day (based on actual weight rather than expected weight for age) for a limited period until they recover the lost weight.
- These children should be treated with therapeutic feeding, which should continue until nutritional recovery is achieved (average 6–10 weeks).

Deficiency of vitamins and minerals, such as vitamins A, B complex, C, E, and selenium and zinc, which are needed by the immune system to fight infection, are common in children living with HIV. Vitamin A, multivitamins, folate, and adequate amounts of zinc and copper are given at the recommended doses. Iron should not be started initially but should be given once the appetite returns and the child is gaining weight.

6 ADHERENCE AND RETENTION

Adherence to ART is the primary determinant of viral suppression and the risk of transmission, disease progression and death. Suboptimal adherence is a major challenge and is associated with a diversity of individual- and programme-related causes. A high degree of adherence to ARV drugs is necessary for optimal virological suppression. Studies indicate that >95% of the doses should be taken for optimal suppression. A lesser degree of adherence is more often associated with virological failure. Adherence is equally important for other approaches where ARVs are used such as PEP and PrEP for HIV. With the commencement of ART irrespective of CD4 count, people will be on ART for a longer time, and many may be feeling well and may not always see the rationale for a high level of adherence. Therefore, the role of increased education, counselling and support to people on ART is critical.

6.1 Optimize adherence to ART

Clients diagnostic with HIV are motivated to continue their ART by desire to live longer and remain healthy for a longer period. Tangible and emotional support delivered in culture-specific ways can help to foster adherence, such as beliefs and perceptions of the positive results of ART. Health-care workers should continuously offer information and counselling: (a) to prevent individual from stopping treatment; and (b) to make intake of medication a daily priority.

Health-care workers play an important role in supporting and encouraging clients to adhere to their medication. Good relationships with care providers and trust in them improve adherence. Health-care providers who spend time explaining things to clients have a positive influence on them. Service providers should promote optimal adherence by giving clear instructions, providing adequate medical follow ups that address possible side-effects and how to handle these in order to reinforce adherence. Family support increases the likelihood of clients maintaining optimal adherence. Particularly for women and children, the family acts as a facilitator for adherence.

A local study conducted in Nepal identified five major facilitators of adherence to ART:

- trusting the health workers;
- positive beliefs about ART;
- ART as a part of daily life;
- responsibilities for children; and
- family and mechanical support.

6.2 Adherence counselling

Routine adherence assessments and counselling strategies, client education and counselling are essential strategies to optimize retention and adherence. Adherence counselling is essential both before and after ART initiation as it helps client gain a better understanding of their disease and builds a more supportive environment. Adherence counselling should be provided by the ART counsellor at ART centres in multiple settings (at least three counselling sessions are recommended) before the initiation of ART to prepare clients for it. Preparedness for ART varies from person to person and some clients may well be prepared in two visits while others may require more visits. The counsellor has to assess this on an individual basis, but a minimum of two counselling sessions are advisable for good adherence. The information may have to be tailored as per the client's understanding. Suggested contents of ART adherence counselling in each visit include the following:

First visit

- Conducting clinical assessment;
- Exploring the client's knowledge and understanding of HIV and their health status;
- Introducing the concept of ART and other treatments to the client;
- Explaining the consequences of non-adherence;
- Exploring potential barriers to adherence;
- Explaining the transmission of resistance and reviewing the client's personal plans for reducing transmission risk;
- Discussing the concept of having a "treatment buddy" selected by the client or a trained volunteer appointed to assist with the client's permission.

Second visit

- Providing feedback by the care provider to the client on the medical assessments conducted during the previous visit;

- Reviewing the client’s understanding of the information provided in the previous visit and assessing the client’s understanding of the feedback provided by the doctor;
- Reviewing the potential barriers that the client expected in the previous visit and offering strategies for addressing these barriers;
- Reviewing the treatment plan with the client (the correct dose in the correct way at the correct time).

Third visit

- Reviewing the client’s understanding of the information provided in the previous two sessions; reinforcing the fact that there is much to remember and it is easy, if focused;
- Reviewing the client’s problem-solving strategies and familiarizing the client with the counselling treatment reminder cue cards and adherence recording tools, if any;
- Reviewing the treatment plan again, as in the second visit;
- Assessing the client’s readiness by simply asking the client to answer questions about the regimen and what they propose to do when there are problems;
- Providing feedback on the client’s readiness to the medical team;
- Meeting the client’s “treatment buddy” to review their role and to make follow-up arrangements with the client. A start date for “buddy support” should be established.

6.2.1 Follow-up counselling

The clients should have follow-up adherence counselling at their scheduled visits and attempts should be made to understand potential barriers to adherence which may differ by clients. The intervention should be tailored accordingly. Adherence barriers can change over time and individual clients will need different levels of support as their life circumstances change and they become accustomed to their treatment. Ongoing adherence counselling and continuing interactive communication are keys to providing effective adherence support to the client on ART.

A follow-up counselling session involves:

- reviewing the treatment experience of the client;
- assessing the need for referral back to the doctor, usually related to side-effects;
- monitoring adherence over a defined period;
- reviewing and finding solutions to barriers to adherence;
- reviewing adherence to measures that reduce the risk of transmission; and
- conducting a psychosocial assessment.

6.3 Monitoring adherence to ART in clinical care settings

Monitoring of the client for drug adherence can be reflected by clinical outcomes, which can be monitored by VL monitoring. Other approaches are monitoring the drug consumption pattern, which can be self-reported or verified from the register. The following approaches to monitoring adherence are recommended:

a. Viral load monitoring

VL monitoring is considered the gold standard for monitoring adherence and confirming treatment response. Although treatment failure is often caused by lapses in adherence to ART, it may also result from other factors, including drug resistance, malabsorption, drug–drug interactions and other drug-associated effects. VL monitoring also has a high potential to motivate adherence. Based on the VL monitoring (Fig 3.1), the clients can be classified as stable (VL <50 copies/ml) and treatment failure (VL >1000 copies/ml).

After a high VL test (>50 copies/ml), counselling should include the following points:

- Ensure that the client understand that the ART taken by the client is not controlling the virus as the VL is not controlled. Non-adherence to treatment could be a cause.
- Review the barriers of the client to taking ART.
- Prepare strategies to address the barriers and reach consensus with the client on the strategies.
- Help the client prepare action points based on strategies, and set a date for follow-up action points.
- Organize follow-up sessions to help the client adhere to the action points and review the progress.
- At the end of 3 months, refer the clients for a repeat VL test. If the client receives a VL test result of >50 copies/ml, refer the client to the ART clinician for evaluation.

b. ARV dispensing records

Review of the ARV dispensing records (patient cards, prescriptions) provide information on when PLHIV pick up their ARV drugs. Receiving ARVs at irregular intervals may indicate non-adherence to ART; however, in some cases, receiving the supply of ARVs at a regular interval only may not indicate proper adherence to ART. So, this approach should be combined with other methods of measuring adherence (self-report and pill counts).

c. Self-reporting

Self-reporting includes reporting by the client to their caregivers on how many doses of ARVs they missed or forgot to take since the last visit or within a specific period in the past. Counselling on the importance of remembering ART doses and an environment that promotes and enables honest reporting of non-adherence are critical components of monitoring adherence to ART in routine care settings.

d. Pill counts

Counting the remaining pills in the container and comparing them with the number of pills dispensed to the client in the most recent visit provides the estimated number of pills taken by the client. Each client should be asked to bring the container with the remaining pills to the ART centre while collecting the supply for the next period. Community-based workers can also count the pills on their visit and assess the adherence. The adherence percentage can be calculated on the basis of the pill count as follows:

$$\text{Adherence percentage} = \frac{\text{Number of pills taken during the specific period (1 month)}}{\text{Number of pills to be taken during that specific period (1 month)}} \times 100$$

The expected optimal adherence percentage is more than 95% for any period.

6.3.1 Advice for missed ARV dose

Patients should be counselled on each visit that they should not miss even one dose as this may not be good for their long-term outcomes. All doses should be taken exactly as per the instructions of the treating doctor and at the same time every day. However, it is likely that clients forget to take their regular doses. The following are the recommendations in such situations:

1. Take the pill immediately after the patient notices that the dose is missed.
2. For the next dose:
 - **If the patient is taking a twice-daily dose (every 12 hours):**
 - If the patient is scheduled to take their next dose in less than 4 hours, it is not recommended that they take that dose. They must wait for 4 hours (from the time they have taken the missed dose) to take the next dose. Thereafter, the patient can follow the regular dosing schedule.

- **If the patient is taking a once-daily dose (every 24 hours)**
 - If the patient is scheduled to take their next dose in less than 12 hours, it is not recommended that they take that dose. They must wait for 12 hours (from the time they have taken the missed dose) to take the next dose. Thereafter, the patient can follow the regular dosing schedule.
 - If the scheduled time is more than 12 hours from the time the patient has taken the missed dose, they can take the regular dose at the scheduled time.
 - If the patient remembers to take the missed dose at the next scheduled time, it is recommended that they take the scheduled dose only. It is strictly not recommended to take two doses at a time.

7

MANAGEMENT OF ADVANCED HIV DISEASE, COINFECTIONS AND COMORBIDITIES

7.1 Advanced HIV disease

For adults and adolescents, and children older than 5 years, advanced HIV disease is defined as a CD4 cell count <200 cells/mm³ or WHO stage 3 or 4 event. All children younger than 5 years of age with HIV are considered as having advanced HIV disease.

The proportion of people presenting with advanced HIV disease has remained largely unchanged during the past 5 years although the number of people receiving ART in low- and middle-income settings has more than doubled over this period. Recent estimates suggest that about 30–40% of people living with HIV and starting ART in low- and middle-income settings have a CD4 cell count of less than 200 cells/mm³, and 20% have a CD4 cell count of less than 100 cells/mm³.

Leading causes of mortality among adults with advanced HIV disease globally include TB, 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.

7.1.1 Package of care

WHO recommends a package of interventions, including screening, treatment and/or prophylaxis for major OIs, rapid ART initiation and intensified adherence support. These interventions should be offered to everyone presenting with advanced HIV disease. The algorithm in Table 7.1 and Fig. 7.1 summarize the steps to be considered in managing a person with HIV who might have advanced disease.

TABLE 7.1: Package of care for advanced HIV disease






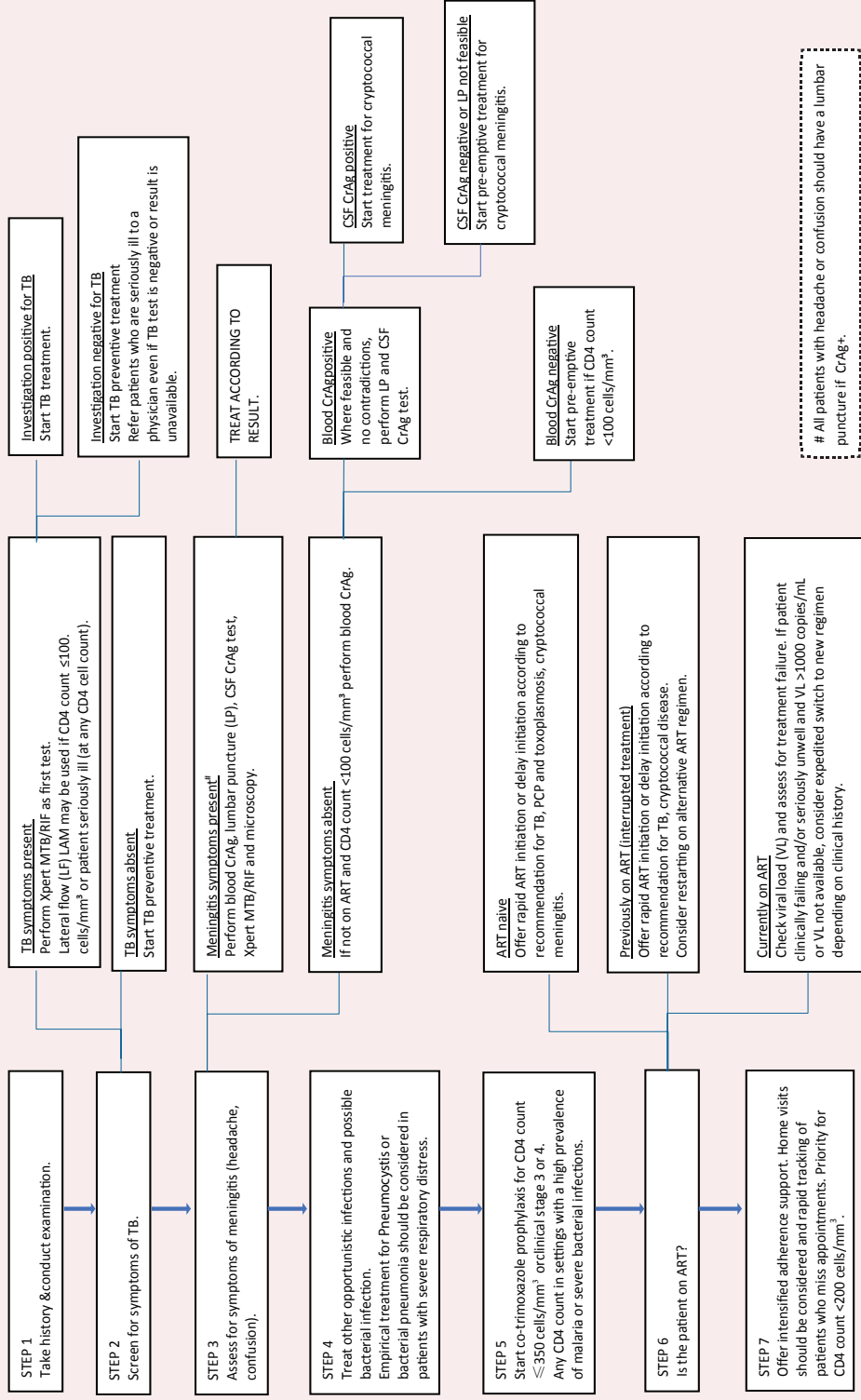
| | |
|---|---|
|  | <p>Screen for severe opportunistic infections:</p> <ul style="list-style-type: none"> - symptoms of TB; - cryptococcal meningitis using cryptococcal antigen lateral flow assay (CrAg LFA). |
|  | <p>Give preventive therapy:</p> <ul style="list-style-type: none"> - TB preventive therapy; - co-trimoxazole to prevent severe bacterial infections and PCP; and - fluconazole primary prophylaxis to prevent the development of cryptococcal meningitis (CD4 count \leq 100 cells/mm³). |
|  | <p>Test those with symptoms of severe infections (or who are seriously ill).</p> |
|  | <p>Start ART as soon as possible.</p> |
|  | <p>Give tailored counselling to people with advanced HIV disease to support their care.</p> |

FIGURE 7.1: Algorithm on package of care for advanced HIV disease



7.2 Screening and prevention of tuberculosis in people living with HIV

Tuberculosis is the most frequent life-threatening OI and a leading cause of death among PLHIV accounting for about a third of all mortality. PLHIV are around 20 times more likely to develop TB disease than those without HIV infection and should be prioritized for systematic evaluation and TB preventive treatment (TPT) in all settings. ART should be provided to all PLHIV with active TB disease along with TB treatment. Preventing and managing TB among HIV-infected individuals is one of the major responsibilities of the ART clinician.

TB preventive treatment (TPT) is an important intervention for preventing and reducing active TB among PLHIV. TPT is also one of the key interventions recommended by WHO in 1998 to reduce the burden of TB in PLHIV. Screening for active TB should be performed for all newly HIV-infected clients at their first visit using a TB screening questionnaire, a full initial history and physical examination. Symptom screening should be continued at each visit (each time the PLHIV visits the health facility for care, treatment or ART refill).

Active TB must be excluded before beginning TB preventive treatment. All PLHIV with the clinical symptoms of TB should be further screened (Fig 7.2).

Symptoms suggestive of TB in adults, adolescents and children living with HIV:

1. current cough, or
2. fever, or
3. unexplained weight loss in adults and adolescents and poor weight gain in children (<10 years of age), or
4. night sweats.

Clinical screening becomes difficult to apply in younger children. Ask for a history of contact with a TB case, particularly a bacteriologically confirmed case. This is usually a requirement for giving TPT in infants (<1 year) living with HIV.

Absence of all four of these signs and symptoms is usually a reliable way of excluding active TB in adults and adolescents (>10 years of age or more) living with HIV. Use of chest radiography is not routinely required in this age group to exclude active disease.

A tuberculin skin test (TST/interferon gamma release assay (IGRA) is not a requirement for initiating TPT in PLHIV. PLHIV who have a positive TST/IGRA benefit more from TPT; TST or IGRA can be used where feasible/available to identify such individuals.

How should screening be done?

The questions in the box below should be asked to all HIV-positive clients. Adults, adolescents and children living with HIV who respond “NO” to all the screening questions below are unlikely to have active TB and should be offered TPT. Any “YES” response to screening questions should be investigated as described in Fig. 7.2.

TB screening questions for adults and adolescents and children living with HIV

1. Is the client currently coughing? Yes/No
2. Has the client been having fever? Yes/No
3. Has the client been experiencing unexplained weight loss in adults and adolescents and poor weight gain in children (<10 years of age*)? Yes/No
4. Has the client been having night sweats? Yes/No

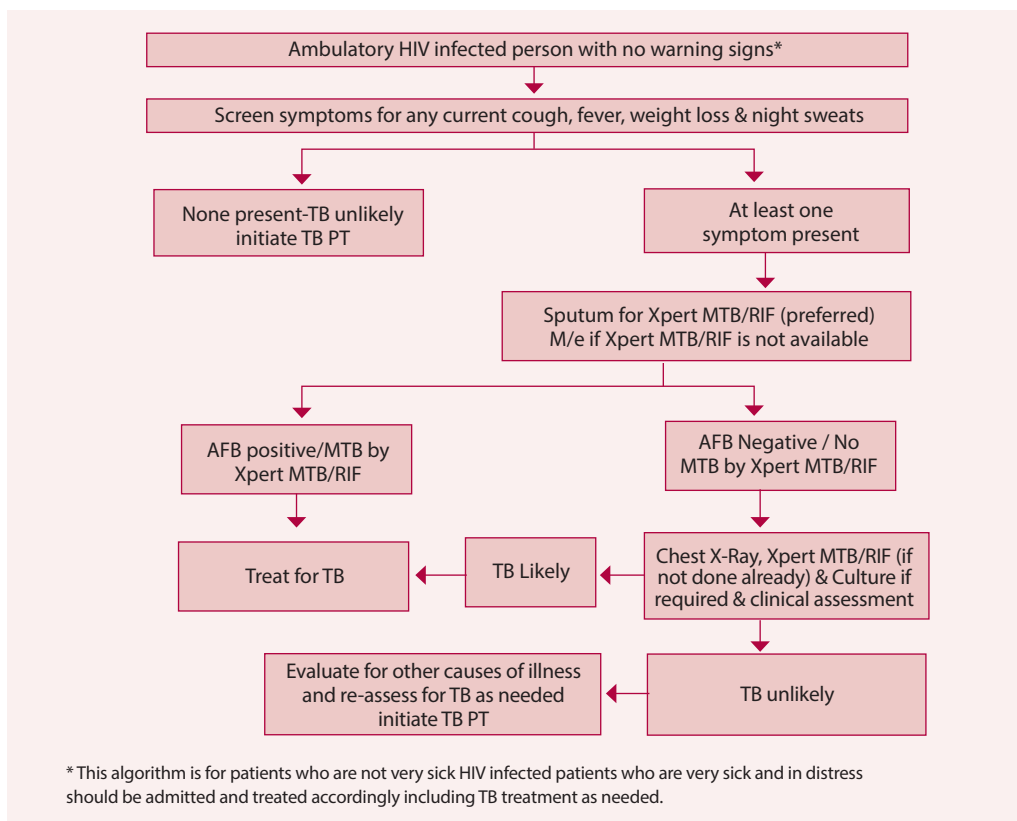
** For children <10 years of age, ask for a contact history with TB patients, particularly bacteriologically confirmed cases.*

Who should receive TB preventive treatment?

- Adults and adolescents living with HIV who are unlikely to have active TB should receive TPT as part of a comprehensive package of HIV care. Treatment should also be given to those on ART, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if latent TB infection (LTBI) testing is unavailable.
- 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 TPT.
- Children aged ≥ 12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TPT as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with a person with TB.
- All children living with HIV who have successfully completed treatment for TB disease may receive TPT. TPT may be started immediately after the last dose of TB curative treatment or later among adults and children living with HIV following clinical judgement.
- Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered TPT, regardless of their ART status.

- Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB (Fig. 7.2). If TB disease is excluded after an appropriate clinical evaluation and according to national guidelines, they should be offered TPT.
- Infants and children living with HIV (CLHIV) who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.
- In CLHIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive TPT if the evaluation shows no TB disease.
- Chest radiography may be offered to PLHIV on ART, and TPT can be given to those with no abnormal radiographic findings.

FIGURE 7.2: Algorithm for TB screening for ambulatory people infected with HIV



TB preventive treatment

The 2020 update of WHO guidelines on TPT makes 9H, 6H, 4R, 3HP, 3HR, 1HP (*box below*) as options for use across all disease burden settings and target populations including the PLHIV. The choice will depend on availability of appropriate formulations and considerations for age, safety, drug–drug interactions, pill burden and adherence.

| | |
|----------|---|
| (6H, 9H) | 6 or 9 months of daily isoniazid monotherapy |
| (4R) | Four months of daily rifampicin |
| (3HR) | Three months of daily rifampicin plus isoniazid |
| (3HP) | Three months of rifapentine plus high dose isoniazid weekly: 12 doses |
| (1HP) | One month of rifapentine plus isoniazid daily: 28 doses |

The national HIV programme currently recommends the 6-month isoniazid (6H) regimen for TPT.

Adults

Isoniazid is given as daily, self-administered therapy for 6 months at a dose of 5 mg/kg body weight for people aged 10 years or more to a maximum of 300 mg/day. These individuals should be seen monthly and given a one-month supply of medication at each visit. Adherence may be improved by giving an additional 2 weeks emergency buffer supply to be used if the individual must defer the monthly review.

Children

The isoniazid dose for children (<10 years) living with HIV is 10 mg/kg (7–15 mg/kg body weight) daily for 6 months.

Pyridoxine (vitamin B6) supplementation

The standard dose of pyridoxine when used prophylactically for prevention of neuropathy among patients taking isoniazid is 25 mg/day for adults as well as for children and should be provided to all on TPT. However, lack of pyridoxine should not become a barrier to starting TPT.

Follow-up visits while on TB preventive treatment

Adherence to TPT is important for the individual and poor adherence will limit the impact of TPT. Hence, follow up of patients on TPT is essential.

- A client must be seen every month to check for adherence, side-effects and ensure TPT medication refill.
- Check for adverse reactions. Manage any ADR identified or refer if needed.
- Reinforce understanding of the patient with regard to the TB disease process, rationale for preventive treatment and importance of completing the course.
- If an encounter at the person's home or at the facility is not possible, contact via phone may be helpful to encourage adherence, answer questions, check for ADR or indications of active disease (including in other household contacts) and whether the individual has sufficient stock of medicines for TPT.
- Record the visit, drug intake and all findings from the evaluation on the case files or forms prescribed by national programme.
- The patient must be asked about symptoms of breakthrough TB during each visit. If any symptom occurs, evaluate for active TB.
- For any interruption of TPT, Table 7.2 should be followed for further management.

TABLE 7.2: Management for interruption of TPT

| Duration of treatment interruption | How to manage |
|------------------------------------|---|
| Less than 2 weeks | <ul style="list-style-type: none"> ■ Resume preventive treatment immediately on return and add number of days of missed doses to the total treatment duration. ■ Don't change scheduled date of the next follow-up visit but the last follow-up visit will be postponed by the number of extra days to compensate for the missed doses |
| More than 2 weeks | <ul style="list-style-type: none"> ■ If more than 80% of the doses expected in the regimen have already been taken no action is required. Continue and complete the remaining treatment as per the original plan. ■ If less than 80% of doses expected in the regimen have been taken, consider restarting the full course of preventive treatment. |

7.3 TB management in PLHIV

- All HIV-infected people with diagnosed active TB should be put on TB treatment immediately.
- Antituberculosis treatment (ATT) should be initiated first, followed by ART as soon as possible within the first 2 weeks of treatment and within the first 8 weeks of treatment for drug resistance TB, irrespective of the CD4 count.
- In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for elimination of vertical transmission of HIV.
- IRIS may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS.
- Treatment support, which can include directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected people with active TB disease.

ARV drug adjustment for TB coinfection

- DTG 50 mg BID (instead of 50 mg once daily) should be used for patients using rifampicin-based TB drugs.
- In case a patient on a PI-based regimen needs to start ATT, the dose of PI should be doubled.
- In patients already receiving ART when they develop TB, the ART regimen should be adjusted to be compatible with the TB treatment. Following completion of TB treatment, the ART regimen can be continued or changed, depending upon the clinical and immunological status of the patient.

Please refer to the National TB Management Guidelines for detailed case management.

TB coinfection in children

HIV increases the risk of activation of TB in children with latent infection (10–30 times risk). HIV increases the susceptibility to the primary infection (more common in children) as well as to reactivation of TB (more in adults) due to suppressed immunity. Extrapulmonary, disseminated TB and drug-resistant TB are seen more frequently in those with HIV.

Up to 25% of TB in children is extrapulmonary. The most common sites are the lymph nodes, pleura, pericardium, meninges and miliary TB. Children with advanced HIV disease are at high risk of extrapulmonary TB. The principles for

the treatment of TB in HIV-infected children are the same as in HIV-uninfected children. A trial of treatment with anti-TB drugs is not recommended as a method of confirming a presumptive diagnosis of TB in children.

Interactions between rifampicin and LPV/r mean that co-treatment in children under 3 years is challenging. If the child is on a PI or an integrase strand transfer inhibitor (INSTI) regimen, the dose of ARV requires to be doubled during the course of ATT.

7.4 Cryptococcal meningitis

Cryptococcal disease is caused by *Cryptococcus neoformans*, a yeast-like fungus. It is a relatively common life-threatening infection in severely immunocompromised PLHIV and a major contributor to high mortality before and after ART is initiated. *Cryptococcus* grows readily in soils contaminated with bird droppings, particularly those of pigeons. Initial cryptococcal infection most likely occurs via inhalation of the fungus, leading to colonization of the airways. The incidence of cryptococcal meningitis increases as the CD4 count falls below 100 cells/mm³ and most cases occur when the CD4 count falls below 50 cells/mm³ (Annex 5).

Cryptococcal disease in PLHIV most commonly presents as a cryptococcal meningitis or meningo-encephalitis. However, other organs such as the lungs, prostate, skin, etc. can be involved.

Cryptococcal meningitis can present with:

- fever
- malaise
- headache
- neck stiffness and photophobia (i.e. meningeal symptoms in 25–30%)
- altered mental status, personality changes, memory loss (encephalopathic symptoms), impaired consciousness and coma
- cranial nerve palsies.

7.4.1 Laboratory diagnosis of cryptococcal meningitis

For adults, adolescents and children living with HIV and presenting with symptoms of suspected cryptococcal meningitis, perform:

- a prompt lumbar puncture with measurement of the cerebrospinal fluid (CSF) opening pressure;

- a rapid CSF CrAg assay, which is the preferred diagnostic approach;
 - blood CrAg.
- A. In settings with ready access to and no contraindication to lumbar puncture:
- If access to a CrAg assay (either LFA or latex agglutination assay) and rapid results (less than 24 hours) are available, lumbar puncture with rapid CSF CrAg assay is the preferred diagnostic approach.
 - If access to a CrAg assay is not available and/or rapid results are not available, lumbar puncture with CSF India ink test examination is the preferred diagnostic approach. (Note: CrAg LFA is positive in >95% of the cases. India ink is less sensitive and positive in 60–80% of patients).
- B. In settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated:
- If both access to a CrAg assay and rapid results (less than 24 hours) are available, rapid serum, plasma or whole-blood CrAg assays are the preferred diagnostic approaches.
 - If a CrAg assay is not available and/or rapid access to results is not ensured; prompt referral should be made for further investigation and treatment as appropriate (Table 7.3).

TABLE 7.3: Diagnostic approach to cryptococcal meningitis

| | Lumbar puncture available | No lumbar puncture available or contraindicated |
|--|--|---|
| Rapid cryptococcal antigen test available | CSF cryptococcal antigen (preferably lateral flow assay) | Serum, plasma or whole blood cryptococcal antigen (preferably lateral flow assay or latex agglutination assay), treat immediately and refer for further investigation |
| No rapid cryptococcal antigen test available | CSF India ink | Prompt referral for further investigation |

CSF findings: mild increase in protein, low-normal glucose, pleocytosis with lymphocytes, although some patients have no cells, which could be associated with more severe disease.

7.4.2 Screening for and preventing cryptococcal disease

Adults and adolescents living with HIV who have no symptoms of meningitis and with CD4 cell count < 100 cells/mm³ (Annex 5):

Screening for blood CrAg: Provide pre-emptive antifungal therapy among those who are CrAg positive to prevent the development of invasive cryptococcal disease. This is recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm³.

When CrAg screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm³.

Screening and primary prophylaxis are not recommended for children, given the low incidence of cryptococcal meningitis in this age group.

Pre-emptive antifungal therapy: fluconazole 800 mg/day for adults, 12 mg/kg/day for adolescents for 2 weeks; followed by consolidation and maintenance fluconazole therapy, as per treatment.

Fluconazole primary prophylaxis: fluconazole 100 mg PO daily for at least 12 months. Test for CD4 count at 6 months and 12 months. Discontinue once CD4 count >200 cells/mm³ for more than 6 months and 12 months (two readings).

Adults and adolescents living with HIV who show symptoms of meningitis:

Conduct full laboratory diagnosis for cryptococcal meningitis or confirmation tests.

7.4.3 Treatment for cryptococcal meningitis

Untreated cryptococcal disease is fatal. Even with treatment mortality rates are high. Treatment of cryptococcal meningitis and disseminated non-meningeal infection in adults, adolescents and children includes the induction, consolidation and maintenance phases with antifungal agents.

i. Induction phase

The following is recommended as the preferred induction regimen:

- For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg/day) and flucytosine (100 mg/kg/day, divided into four doses per day), followed by 1 week of fluconazole (1200 mg/day for adults, 12 mg/kg/day for children and adolescents, up to a maximum dose of 800 mg daily), is the preferred option for treating cryptococcal meningitis among PLHIV.

Alternative option for induction:

The following induction regimens are recommended as alternative options depending on drug availability:

- two weeks of fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents) + flucytosine (100 mg/kg/day, divided into four doses per day)
- two weeks of amphotericin B deoxycholate (1.0 mg/kg/day) + fluconazole (1200 mg daily for adults, 12 mg/kg/day for children and adolescents up to a maximum of 800 mg daily).

ii. 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) is recommended for the consolidation phase (for 8 weeks following the induction phase).

iii. Maintenance phase (or secondary prophylaxis)

Fluconazole (200 mg daily for adults, 6 mg/kg/day for adolescents and children) is recommended for the maintenance phase for at least 1 year.

Discontinuing maintenance treatment (secondary prophylaxis)

Among adults, adolescents and children older than 5 years living with HIV who have been successfully treated for cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal maintenance treatment is advised based on the following criteria:

- If HIV VL monitoring is available:
 - the person is stable on and adherent to ART and has received antifungal maintenance treatment for at least 1 year and has a CD4 cell count ≥ 100 cells/mm³ and a fully suppressed VL
- If HIV VL monitoring is not available:
 - the person is stable on and adherent to ART and has received antifungal maintenance treatment for at least 1 year and has a CD4 cell count ≥ 200 cells/mm³.

For children living with HIV who are 2–5 years old and have successfully been treated for cryptococcal disease (meningeal and non-meningeal), discontinuing antifungal maintenance treatment is recommended if the child is stable on and adherent to ART and antifungal maintenance treatment for at least 1 year and has a CD4 cell count percentage greater than 25% or an absolute count >750 cells/mm³. Maintenance treatment for cryptococcal disease should not be discontinued for children younger than 2 years.

Secondary prophylaxis for cryptococcal disease should be restarted if the CD4 count drops to <100 cells/mm³ or less for adults, adolescents and children older than 5 years living with HIV (or CD4 cell count $\leq 25\%$ or ≤ 750 cells/mm³ for children 2–5 years old) or if a WHO stage 4 clinical event occurs, regardless of age. Although CD4 cell count monitoring is no longer recommended for monitoring the response to ART in settings in which VL is available, it remains important in guiding decisions about when to discontinue fluconazole maintenance therapy.

Treatment for pregnant women

Amphotericin B therapy can be given to pregnant women with meningeal and non-meningeal disease. Exposure to flucytosine and fluconazole during pregnancy has been associated with an increased risk of birth defects in animal studies and some uncontrolled human studies. The use of flucytosine and fluconazole for treating cryptococcal disease in pregnant women should be evaluated on an individual basis, considering the benefits and potential harm.

Adjunctive corticosteroid therapy

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended for treating HIV-associated cryptococcal meningitis among adults, adolescents and children.

Managing raised intracranial pressure

Initial measurement of intracranial pressure and management of raised intracranial pressure is an essential part of the management of cryptococcal meningitis to prevent death and serious nervous system complications. Raised intracranial pressure is a frequent and potentially life-threatening complication, occurring in up to 80% of people with HIV-associated cryptococcal meningitis. Intracranial pressure may be raised even in the absence of symptoms. The limitations of using clinical symptoms or signs to identify people suspected of having raised intracranial pressure requiring repeat therapeutic lumbar puncture has been recognized.

The following steps are advised for managing raised intracranial pressure:

- Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to <20 cm H₂O or halving the baseline pressure if extremely high.
- The persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of raised intracranial pressure, repeat daily

therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days.

There are no data on the maximum volume of CSF that can be safely drained at one lumbar puncture. CSF opening pressure can be rechecked after every 10 mL removed. Usually 20–25 mL is enough to reduce the opening pressure sufficiently.

Using drugs (mannitol, acetazolamide, furosemide or steroids) for managing raised intracranial pressure is not recommended because there is no evidence to indicate that using these drugs improves outcomes in managing cryptococcal meningitis-associated raised intracranial pressure, and some evidence indicates that using them may be harmful.

Monitoring treatment response

- Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy.
- Among people with evidence of a sustained clinical response, routine follow-up lumbar puncture after completing induction treatment to assess the response to antifungal treatment (CSF fungal culture and CSF CrAg) or serum or plasma CrAg is not advised in low- and middle-income countries.

Diagnostic approach to patients with persistent or recurrent symptoms

Many people with cryptococcal meningitis experience persistent (failing to resolve after 2 weeks of antifungal treatment) or recurrent symptoms (reappearing after initial resolution following treatment for an episode of cryptococcal meningitis). Among people receiving optimal induction therapy, the most common causes of recurrence of symptoms are raised intracranial pressure, non-adherence to fluconazole and IRIS.

The following diagnostic approach should be used for people with persistent or recurrent symptoms to establish potential underlying causes:

- i. Review the patient's history for evidence that suggests underlying treatment failure from an inadequate drug regimen, dose and duration, poor adherence to consolidation and maintenance treatment with fluconazole or underlying fluconazole drug resistance among people with previous prolonged fluconazole therapy.

- ii. Perform a lumbar puncture with measurement of the opening pressure to establish the presence or absence of raised intracranial pressure and do a CSF examination with other relevant investigations to exclude concomitant illnesses.
- iii. Consider paradoxical cryptococcal IRIS after excluding other causes of recurrent symptoms among people who have started ART.
- iv. Send or resend CSF for prolonged fungal culture (two weeks of incubation).

Managing relapse

In case of persistent or recurrent symptoms resulting from treatment failure or relapse, induction therapy should be restarted according to the recommendations for treatment of cryptococcal meningitis. Particular attention should be paid to reinforcing adherence to therapy. Where possible, fluconazole susceptibility testing should be performed at a national reference laboratory when clinically suspected (culture-positive relapse despite fluconazole adherence). For people who present with relapse of cryptococcal meningitis, the following steps are advised:

- Start or restart induction treatment.
- Manage raised intracranial pressure with therapeutic lumbar puncture.
- Reinforce adherence.
- If ART has not already been started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended.

ART initiation in patients with 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. ART initiation should be deferred for 4 weeks following an amphotericin B-based induction regimen or 4–6 weeks following a fluconazole + flucytosine induction regimen (based on a slower rate and longer time to achieve CSF fungal clearance with fluconazole versus amphotericin B).

Managing cryptococcal immune reconstitution inflammatory syndrome

Paradoxical cryptococcal IRIS occurs among 10–50% of people with cryptococcal disease who initiate ART and is associated with a high mortality in some studies. The median time to onset in reported cohort studies ranges from 1 to 10 months but is typically 3–12 weeks after initiating ART. The following steps are advised for managing cryptococcal IRIS:

1. Continue ART.
2. Promptly manage raised intracranial pressure.

3. Optimize antifungal therapy and consider restarting induction therapy according to the recommendations for treatment of cryptococcal meningitis.
4. Short-course oral steroid^a therapy may be considered if there is continued deterioration and/or the development of life-threatening complications (such as intracranial space-occupying lesion with mass effect or extracranial disease impinging on vital structures), despite the above measures.

^a Prednisolone 1 mg/kg/day or dexamethasone at equivalent doses for at least 1 week or until clinical improvement, with tapering over 2–6 weeks. Longer treatment may be required depending on the symptom response.

7.5 Co-trimoxazole preventive therapy

Co-trimoxazole preventive therapy (CPT) should be implemented as an integral component of a package of HIV-related services. PLHIV should be evaluated for the possible need of prophylaxis at the time of preparing for ART or even in areas without ART accessibility (Table 7.4).

Co-trimoxazole prophylaxis is a cost-effective intervention, effective against the following infections in HIV-positive patients:

- common bacterial infections, including bacterial pneumonia, septicaemia
- diarrhoea, including that caused by *Isospora belli*
- malaria
- toxoplasmosis (primary or recurrent)
- *Pneumocystis pneumonia* (PCP; primary or recurrent).

7.5.1 Co-trimoxazole prophylaxis for adult

- Co-trimoxazole prophylaxis for adults (including pregnant women) should be started for:
 - HIV-infected persons with a CD4 count <350 cells/mm³; or
 - all adults with severe and advanced HIV disease (WHO stage 3 or 4; please refer to Annex 1).
- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.
- Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV who are clinically stable on ART with evidence of immune recovery and viral suppression.
- Routine co-trimoxazole prophylaxis should be given to all HIV-infected patients with active TB disease regardless of CD4 cell count.

The prophylactic regimen is:

- one double-strength (DS) tablet (160 trimethoprim [TMP]/800 sulfamethoxazole [SMX]) every day; or
- Two single-strength (SS) tablets (80 TMP/400 SMX) every day.

7.5.2 Co-trimoxazole prophylaxis for infants, children and adolescents

- HIV-exposed infants 4–6 weeks of age should be continued on co-trimoxazole prophylaxis until HIV infection has been excluded by an age-appropriate HIV test to establish a final diagnosis after complete cessation of breastfeeding;
- HIV-infected infants, irrespective of clinical and immune conditions;
- HIV-infected children younger than 5 years of age, regardless of CD4 cell count;
- HIV-infected children more than 5 years of age with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a CD4 count ≤ 350 cells/mm³.

TABLE 7.4: Criteria for initiation and discontinuation of co-trimoxazole

| Population | Recommendation | |
|--|---|---|
| | Criteria for initiation of co-trimoxazole prophylaxis | Criteria for discontinuation of co-trimoxazole prophylaxis |
| Adults (including pregnant women) with HIV | <ul style="list-style-type: none"> Initiate in all with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤ 350 cells/mm³ ^a In settings with a high prevalence of malaria and/or severe bacterial infections^b: initiate in all regardless of WHO clinical stage or CD4 cell count | <ul style="list-style-type: none"> May be discontinued in those who are clinically stable^c, with evidence of immune recovery and/or viral suppression on ART^{d, e} In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued |
| Children and adolescents with HIV | <ul style="list-style-type: none"> Initiate in all regardless of WHO clinical stage or CD4 cell count As a priority: (1) initiate in all less than 5 years of age, regardless of WHO clinical stage or CD4 cell count; (2) initiate in all older than 5 years of age and with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count ≤ 350 cells/mm³ | <ul style="list-style-type: none"> In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued until adulthood In settings with a low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than 5 years of age who are clinically stable, with evidence of immune recovery^f and/or viral suppression on ART |
| HIV-exposed uninfected infants | <ul style="list-style-type: none"> Initiate in all starting at 4–6 weeks after birth | <ul style="list-style-type: none"> Until the risk of HIV transmission ends or HIV infection is excluded^g |
| People living with HIV and TB ^h | <ul style="list-style-type: none"> Initiate in all with active TB regardless of CD4 cell count | <ul style="list-style-type: none"> Until criteria for discontinuation in adults or children are met |

- This group is also prioritized for ART initiation (as recommended for ART in the 2013 WHO *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*).
- Settings where malaria and/or severe bacterial infections are highly prevalent include low- and middle-income countries with high rates of mortality among children less than 5 years (http://www.who.int/gho/child_health/mortality/mortality_under_five/en).
- Clinically stable adults are defined as those individuals on ART for at least 1 year without any new WHO clinical stage 2, 3 or 4 events.
- CD4 count >350 cells/mm³, with viral load suppression, is considered indicative of immune recovery (some countries may adopt a threshold of CD4 count >500 cells/mm³).
- WHO recognizes that in settings with a low prevalence of malaria and severe bacterial infections where co-trimoxazole is used primarily as prophylaxis for some AIDS-associated OIs (PCP and toxoplasmosis), guidelines exist for discontinuing co-trimoxazole in adults with HIV infection when there is evidence of viral suppression and immune recovery at CD4 cell counts >200 cells/mm³ and being on ART for at least 1 year.
- Parameter for immune recovery in children when >5 years of age: CD4 cell count >350 cells/mm³, with viral load suppression.
- In settings with a high malaria transmission, consideration may be given to extend co-trimoxazole prophylaxis in HIV-exposed uninfected infants up to 2 years of age.
- Recommendation maintained from: *WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders*. Geneva: WHO; 2012.

7.5.3 Adverse reaction to co-trimoxazole

Adults and adolescents with a history of severe adverse reaction to co-trimoxazole or other sulfa drugs should not be prescribed co-trimoxazole prophylaxis. In situations where co-trimoxazole cannot be continued or should not be initiated, dapsone 100 mg per day can be used as an alternative. Dapsone is less effective than co-trimoxazole in preventing PCP and lacks the broad antimicrobial activity of co-trimoxazole. It is therefore desirable to attempt desensitization (Table 7.5) to co-trimoxazole, if feasible in the clinical setting, among individuals with a previous non-severe reaction, before substituting dapsone. However, co-trimoxazole desensitization should not be attempted among individuals with a previous severe reaction to co-trimoxazole or other sulfa-containing drugs.

Co-trimoxazole must be discontinued in the following situations:

- severe cutaneous reactions, such as Stevens–Johnson syndrome, renal and/or hepatic failure, and severe haematological toxicity.

For intolerance, consider the following alternatives:

- dapsone 100 mg once daily is the first choice, or
- in case of non-life-threatening adverse reactions, stop treatment for 2 weeks; then re-challenge the client with TMP/SMX in a gradually increasing dose of an oral suspension of TMP/SMX. After desensitization under surveillance, up to 70% of clients may again tolerate TMP/SMX.

TABLE 7.5: Protocol for co-trimoxazole desensitization among adults and adolescents

| | |
|----------------------|--|
| Day 1 | 80 mg sulfamethoxazole + 16 mg trimethoprim (2 mL of oral suspension) |
| Day 2 | 160 mg sulfamethoxazole + 32 mg trimethoprim (4 mL of oral suspension) |
| Day 3 | 240 mg sulfamethoxazole + 48 mg trimethoprim (6 mL of oral suspension) |
| Day 4 | 320 mg sulfamethoxazole + 64 mg trimethoprim (8 mL of oral suspension) |
| Day 5 | One single-strength sulfamethoxazole–trimethoprim tablet (400 mg sulfamethoxazole + 80 mg trimethoprim) |
| Day 6 onwards | Two single-strength sulfamethoxazole–trimethoprim tablets or one double strength tablet (800 mg sulfamethoxazole + 160 mg trimethoprim). Co-trimoxazole oral suspension contains 40 mg trimethoprim + 200 mg sulfamethoxazole per 5 mL |

Follow up of clients on co-trimoxazole prophylaxis should be done every month during the initial stage. Once the person is stable on prophylaxis:

- monitor for toxicity, clinical events and adherence;
- do laboratory tests for haemoglobin and white blood counts only as indicated.

Adherence counselling on co-trimoxazole can be useful to help prepare clients for ART in the future and solve barriers to medication adherence. Use an alternative antibiotic for treating breakthrough bacterial infections among PLHIV receiving co-trimoxazole prophylaxis, while continuing co-trimoxazole.

For toxoplasmosis and PCP infections, prophylaxis should be suspended and full active treatment initiated. Co-trimoxazole prophylaxis should be started after the treatment course (secondary prophylaxis).

7.6 HIV/HCV coinfection

Coinfection with HIV and HCV poses a challenge because of the large number of persons affected, the negative impact of HIV on the natural history of HCV infection, and the therapeutic challenges of dealing with interactions between the drugs used for treating HIV and HCV infection.

Both ART and treatment for HCV infection may slow the progression of HCV-related liver disease; therefore, treating both infections is a priority for persons with HIV/HCV coinfection.

In HIV/HCV-coinfected persons, there is more rapid progression of HCV-related liver disease, and treatment for HCV may slow the progression of hepatic fibrosis and/or delay the onset of the clinical consequences of decompensated cirrhosis.

Therefore, treatment of HCV is a priority for persons with HIV/HCV coinfection. The decision to initiate treatment for HCV is more complex than in those with HCV mono-infection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV. In general, clinical stabilization of HIV disease with ART is advisable prior to starting treatment for HCV, especially in persons with advanced immunosuppression (CD4 count <200 cells/mm³). The decision to start ART among HCV-coinfected persons should follow the same principle as in those with mono-infected HIV.

HCV infection among persons with HIV coinfection can be treated with DAA combinations of sofosbuvir plus velpatasvir and sofosbuvir plus daclatasvir as pangenotypic regimens for adults 18 years old and more (refer to the *National hepatitis C guidelines* for detailed case management). Genotypic assay and a genotype-based regimen is needed currently for adolescents 12–18 years of age. Efavirenz and velpatasvir co-administration is contraindicated and drug modification is needed among patients using an EFV-based regimen. The dose of daclatasvir should be increased to 90 mg/day and decreased to 30 mg/day if the patient is using an EFV- and ATV/r-based regimen, respectively. Current first-line ARV drugs using a DTG-based regimen do not need any drug modifications.

The potential harmful effects of ARV drugs include their hepatotoxic effects. Several studies have shown that hepatotoxicity as a result of ART may be worsened in the presence of concomitant HCV infection. For most HIV/HCV-coinfected persons, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

Raised liver enzymes may be the result of ART-induced drug toxicity and/or OIs, making interpretation of liver enzyme elevations more problematic than for patients with HCV infection alone. ALT and aspartate aminotransferase (AST) should be monitored at 1 month after ART initiation and then every 3–6 months. A significant rise in AST/ALT may prompt careful evaluation for other causes of liver impairment (e.g. alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation.

7.7 HIV/HBV coinfection

People who are coinfecting with HBV and HIV progress to cirrhosis and hepatocellular carcinoma, liver-associated mortality and decreased treatment response compared with people who do not have HIV.

Adults, adolescents and children with chronic hepatitis B and clinical evidence of cirrhosis (or cirrhosis based on a score >2 in adults on the non-invasive AST-to-platelet ratio index [APRI] test) should be treated regardless of ALT, hepatitis B e antigen (HBeAg) status or HBV DNA level. The recommended drugs that are active against HBV are TDF with 3TC or FTC.

TDF should be recommended for use in hepatitis-coinfected patients; otherwise, hepatitis B flares can occur. Similarly, discontinuation of 3TC can lead to HBV flares; so

TDF and 3TC should be continued even in clients failing the regimen while adding new drugs. All HIV-infected clients should be screened for hepatitis B surface antigen (HBsAg) and, if negative, should be vaccinated against hepatitis B.

7.8 CMV retinitis

This is the most common clinical manifestation of CMV end-organ disease in people living with HIV. It occurs as a unilateral disease in two thirds of patients at presentation, but the disease ultimately is bilateral in most patients in the absence of therapy or immune recovery. If untreated, retinitis invariably progresses, usually within 10–21 days after presentation. Colitis occurs in 5–10% of patients, who present with weight loss, anorexia, abdominal pain, debilitating diarrhoea and malaise. Oesophagitis occurs among a small percentage of cases and presents with odynophagia, nausea, and occasionally mid epigastric or retrosternal discomfort. Colitis and oesophagitis may cause fever. CMV pneumonitis is extremely uncommon. CMV neurological disease includes dementia, ventriculoencephalitis and polyradiculomyelopathies.

Viraemia can be detected by PCR, antigen assays or culture. The presence of serum antibodies to CMV is not diagnostically useful, although a negative immunoglobulin G antibody level indicates that CMV is unlikely to be the cause of the disease process. CMV retinitis is usually diagnosed based on recognition of the characteristic retinal changes observed through ophthalmoscopy. CMV colitis and oesophagitis are diagnosed by demonstrating mucosal ulcerations on endoscopic examination, combined with histopathological demonstration of the characteristic intranuclear and intracytoplasmic inclusions.

Treatment of CMV retinitis

Intravitreal injections of 1–4 doses of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) over a period of 7–10 days, plus

Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily

Or

Intravitreal injections as listed above plus one of the following systemic therapies:

Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily, or

Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily.

Administer one of the systemic antiviral therapies listed above for the first 3–6 months until there is ART-induced immune recovery.

Stopping chronic maintenance therapy for CMV retinitis

CMV treatment should be continued for at least 3–6 months; the lesions are inactive, and CD4 count is >100 cells/mm³ for 3–6 months in response to ART.

Treatment of CMV oesophagitis or colitis

The doses are the same as for CMV retinitis. The duration of treatment is 21–42 days or until the signs and symptoms have resolved. Maintenance therapy is usually not necessary, but should be considered after a relapse.

7.9 Malaria

People with HIV with immunosuppression living in malaria-endemic areas are at high risk of the complications of malaria, and all infants and children under 5 years of age and pregnant women are at particular risk of severe malaria and its complications. PLHIV who develop malaria should receive prompt, effective antimalarial treatment regimens. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or an RDT.

The drugs used to treat malaria and ARV drugs may share toxicities (particularly sulfa-based drugs) and may have clinically important pharmacokinetic interactions (especially the artemesinins, lumefantrine, NNRTIs and PIs). For this reason, people receiving treatment for both HIV and malaria should be monitored closely for aDRs, and people with HIV receiving AZT or EFV should, if possible, avoid amodiaquine-containing artemisinin-based combination regimens because of the increased risk of neutropenia in combination with AZT, and hepatotoxicity in combination with EFV.

Malaria is not a major problem in Nepal.

7.10 Histoplasmosis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. A CD4 T lymphocyte count <150 cells/mm³ is associated with an increased risk of symptomatic illness in people with HIV.

Clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss and hepatosplenomegaly. Cough, chest pain and dyspnoea occur in approximately 50% of patients. CNS, gastrointestinal and cutaneous manifestations occur in a smaller percentage of patients. Approximately 10% of patients experience shock and multiorgan failure.

Detection of *Histoplasma* antigen in the 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.

Patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (preferred) at 3 mg/kg daily or amphotericin B lipid complex at 5 mg/kg IV daily for ≥ 2 weeks or until clinically improved, then on maintenance therapy with oral itraconazole 200 mg three times a day for 3 days, and then 200 mg twice a day given for ≥ 12 months.

Long term suppressive therapy for severe disseminated or CNS infection after completing ≥ 12 months of treatment, and relapse despite appropriate initial therapy with itraconazole 200 mg PO once daily should be given for at least 12 months.

7.11 *Toxoplasma gondii* encephalitis

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. The disease appears to occur almost exclusively because of reactivation of latent tissue cysts. Primary infection is occasionally associated with acute cerebral or disseminated disease. Cerebral toxoplasmosis is the most frequent cause of expansive brain lesions among adults living with HIV not receiving co-trimoxazole. People with latent toxoplasmosis infection are at risk of developing cerebral toxoplasmosis when their CD4 count falls below 200 cells/mm³. The cause of death in about 15% of hospitalized HIV-infected adults dying from AIDS-related illnesses is cerebral toxoplasmosis.

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 edema. HIV-infected patients

with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies. The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma IgM antibodies are usually absent.

TMP–SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID is the available treatment for *Toxoplasma gondii* encephalitis. Treatment should be given for at least 6 weeks (induction duration). A longer duration is needed if clinical or radiological disease is extensive or the response is incomplete at 6 weeks.

TMP–SMX DS 1 tablet BID should be used for chronic maintenance therapy for *Toxoplasma gondii* encephalitis. Discontinuation of maintenance therapy can be done after successful completion of initial therapy, the patient remaining asymptomatic, and CD4 count >200 cells/mm³ for >6 months in response to ART.

Adjunctive corticosteroids (e.g. dexamethasone) should be administered only when clinically indicated to treat a mass effect associated with focal lesions or associated edema; discontinue as soon as clinically feasible.

Start ART at 6 weeks after the initiation of treatment for cerebral toxoplasmosis.

7.12 *Pneumocystis pneumonia*

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a ubiquitous fungus. The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; the incidence at present among patients with AIDS in Western Europe and the United States is <1 case per 100 person-years. Most cases of PCP now occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV and in those with advanced immunosuppression (i.e. CD4 count <100 cells/mm³).

In patients with HIV, the most common manifestations of PCP are subacute onset of progressive dyspnoea, fever, non-productive cough and chest discomfort that worsens within days to weeks. TMP–SMX is the treatment of choice for PCP. Patients who have PCP despite TMP–SMX prophylaxis can usually be treated effectively with standard doses of TMP–SMX (Table 7.6). Secondary PCP prophylaxis with TMP–SMX should be initiated immediately upon successful completion of PCP therapy and maintained until immune reconstitution occurs as a result of ART.

Start ART after 6 weeks of initiation of PCP treatment.

TABLE 7.6: Recommendation for treatment of PCP

| PCP treatment |
|---|
| <p>TMP–SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV/PO given every 6 or 8 hours. May switch to PO formulations after clinical improvement if on IV.</p> <p>Total duration of treatment is 21 days (induction duration).</p> |
| <p>Adjunctive corticosteroids for moderate to severe PCP</p> <p>Prednisone doses (beginning as soon as possible and within 72 hours of PCP therapy)</p> <ul style="list-style-type: none"> Days 1–5: 40 mg PO twice daily Days 6–10: 40 mg PO daily Days 11–21: 20 mg PO daily <p>IV methylprednisolone can be given as 75% of the prednisone dose.</p> |

7.13 Sexually transmitted infections

HIV and sexually transmitted infections (STIs) of the reproductive tract frequently coexist. Most of these infections are asymptomatic, especially among women. However, even asymptomatic STI can cause complications, be transmitted to sex partners and enhance HIV transmission.

HIV infection alters the natural history of STI. The objectives of diagnosing and managing STI include identifying the infection and providing appropriate treatment and preventing transmission. Screening, diagnosis and treatment of STI should be offered routinely as part of comprehensive HIV care among adults and adolescents.

(Refer Annexes 6 and 7 for STI management)

7.14 Cervical cancer

It is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of precancerous lesions and invasive cervical cancer. The risk and persistence of human papillomavirus (HPV) infection increases with a decreasing CD4 count and increasing HIV VL.

Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women living with HIV should be followed closely for evidence of precancerous changes in the cervix, regardless of ART status or CD4 count and VL. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions, which

would prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management should be provided of precancerous and cancerous lesions. WHO guidance covers HPV vaccination and prevention, screening, and treatment and palliative care of cervical cancer.

To date, concerns about safety or reduced efficacy among women who may be infected with HIV should not defer the initiation of large-scale HPV immunization. HIV testing should not be a prerequisite before routine HPV immunization.

7.15 Noncommunicable diseases

PLHIV are at increased risk of developing a range of noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, hypertension, dyslipidaemia (hypercholesterolaemia, raised low-density lipoprotein, hypertriglyceridemia, low high-density lipoprotein), overweight and obesity, depression, chronic lung disease and HIV-associated cancer. Regular screening for these conditions should be done among adults and geriatric HIV-infected populations.

Integrating interventions such as nutrition assessment, dietary counselling and support, smoking cessation, promoting exercise, monitoring blood pressure and, where available, cholesterol as part of HIV care provide opportunities for reducing the risks of NCDs among PLHIV.

With effective ART, PLHIV are also living longer and experiencing NCDs associated with ageing. Both HIV and NCDs require health systems that can deliver effective acute and chronic care, and support adherence to treatment. Chronic HIV care provides an opportunity for screening, monitoring and managing NCDs, especially through primary care.

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to national protocols recommended for the general populations.

For reference: <http://edcd.gov.np/resources/download/pen-training-trainees-manual>

7.16 Mental health

PLHIV and their caregivers may have a wide range of mental health needs. The most common mental health comorbidities among PLHIV include depression, anxiety, dementia and other cognitive disorders, and substance use disorders. HIV care settings provide an opportunity for ensuring the detection and management of mental disorders among PLHIV. Treatment, or lack of treatment, of these conditions can affect adherence to ARV drugs, retention in care and may involve potential side-effects and drug interactions. Recommendations related to general mental health can be relevant for PLHIV. Screening for depression can be undertaken at a clinic with a clear referral pathway to a counsellor or a psychiatrist.

8

ELIMINATION OF VERTICAL TRANSMISSION OF HIV

8.1 Introduction

Vertical transmission of HIV is the most frequent source of HIV infection in children in Nepal, as in other countries. Prevention of mother-to-child transmission (PMTCT) was started in 2005 in Nepal as the earliest public health intervention, where single doses of NVP were given to the mother and infant. With the scaling up of the national HIV programme, and an important shift in WHO guidelines, Nepal adopted Option B in 2011 and Option B+ in 2014. Lifelong ART was rolled out in all women regardless of CD4 count and WHO clinical staging.

Since 2009, the PMTCT service in Nepal has been integrated into maternal and neonatal health services in the districts. All health-care providers at birthing centres of the country are trained on PMTCT, and HIV test kits are available to screen all pregnant women. The National HIV Strategic Plan 2016–2021 has articulated its commitment to eliminate vertical transmission (eVT) in children and keeping mothers alive and well by 2021.

The programme has been integrated and delivered through maternal health services (integrated with ANC services), in order to maximize the coverage, benefit and synergy. The HIV screening test is done at these health facilities during ANC and those with a confirmed diagnosis of HIV are linked with ART services in the district.

The Government of Nepal has been scaling up eVT services in hospitals, primary health care centres (PHC) and health posts with defined roles and responsibilities of the institutions, follow-up mechanism for babies born to HIV-positive mothers and supporting agencies such as community care providers working with PLHIV.

A comprehensive and integrated four-pronged approach for preventing HIV infection in women, infants and young children is as follows:

- Prevent HIV infection among women of childbearing age.
- Prevent unintended pregnancies among women living with HIV.

- Prevent vertical HIV transmission from infected mothers to their children:
 - ART for mother and infant prophylaxis
 - safer delivery practices
 - safer infant-feeding choices.
- Provide appropriate treatment, care and support to women living with HIV and their children and families.

Elimination of mother-to-child transmission (EMTCT) of HIV and syphilis is a global health priority. It is estimated that there are 1.4 million new maternal HIV infections and 988 000 new maternal syphilis infections every year. Globally, there has been marked progress toward EMTCT of HIV, with a 41% reduction in new paediatric HIV cases between 2010 and 2018. However, syphilis remains the second most common cause of stillbirth globally.

In 2019, 431 912 pregnant women were tested for HIV during ANC in Nepal and 73 new cases were identified and linked to care. Though syphilis screening is conducted for pregnant women, the coverage in the public sector remains low. The types of interventions required to prevent mother-to-child transmission (MTCT) of HIV are similar to those needed for preventing vertical transmission of syphilis, which makes an integrated approach to dual EMTCT highly feasible.

HIV testing services are the gateway for HIV treatment, care and prevention. To provide early diagnosis, pregnant women should be tested as early as possible. WHO recommends dual HIV/syphilis RDTs as the first test in HIV testing strategies at ANC settings to achieve EMTCT of HIV and syphilis. The national programme will work in coordination with the Family Welfare Division (FWD) to develop a comprehensive ANC package of care for syphilis.

For successful implementation of eVT programmes, the following elements should be included as part of ANC:

- health information and interpersonal communication on safer sex practices and HIV infection;
- HIV testing and counselling, including partner HIV testing;
- linkage with the “Aama” programme and free newborn care programme;
- linkage of HIV-positive pregnant women with ART services;
- counselling on infant feeding;
- discussion of family planning choices following delivery;
- diagnosis and treatment of STI;
- counselling and testing for TB and malaria.

8.1.1 Elimination of vertical transmission

Elimination of mother-to-child transmission (EMTCT) of HIV, syphilis and HBV is a global health priority. All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible. Syphilis testing and treatment coverage among pregnant women are typically lower than antenatal HIV testing and treatment coverage and use of dual HIV/syphilis RDT among pregnant women is cost-saving and can immediately close the gap between HIV and syphilis testing, with the goal of eliminating adverse birth outcomes due to syphilis.

All the reactive for syphilis results should be referred for treatment and further testing accordingly to the National STI guidelines.

- Provider-initiated testing and counselling (PITC) for a pregnant woman in ANC is a key component of eVT.
- Pregnant women who were not screened during ANC, HIV testing should be done during delivery and even the breastfeeding period.
- Retest pregnant women in the third trimester visit if:
 - they have an unknown or HIV-negative status and are in serodiscordant relationships or have other known ongoing HIV risk in late pregnancy;
 - they are from key populations;
 - either the first test or retest have been missed or delayed, “catch-up” testing should be done during the postpartum period.

8.2 Providing treatment and care

ART should be initiated urgently in all pregnant and breastfeeding women, even if they are identified late in pregnancy or postpartum because the most effective way to eliminate vertical HIV transmission is to reduce maternal VL. Whenever possible, all efforts should be made to identify HIV-infected pregnant women early enough to avoid the need for high-risk prophylaxis.

Nepal has started providing lifelong ART to all pregnant and breastfeeding mothers with HIV since March 2014 based on the recommendations of the WHO Consolidated guidelines, June 2013. The following four elements of eVT should be considered for women identified as HIV positive during labour and the postpartum period:

- provide ART to the mother and the baby following delivery;
- implement safer delivery practices;
- provide ongoing counselling and support for safer infant feeding;
- provide counselling and support for EID at birth and at 6 weeks (follow the EID protocol).

These interventions can be offered before conception, during the antenatal period, during labour, following delivery and throughout the reproductive life.

8.2.1 First-line ART for pregnant and breastfeeding women

Providing an optimized, FDC first-line ART regimen of TDF + 3TC + DTG in a single pill is the recommended first-line regimen for all pregnant women (body weight >30 kg) (Table 8.1). Those who have crossed the first trimester of pregnancy can benefit from DTG due to its high potency, rapid VL suppression, low drug–drug interaction and high genetic barrier for HIVDR. If the woman is diagnosed with HIV during the planning of pregnancy or early stage of pregnancy, she should be given the right to make her own choices, and whether she takes ART and/or contraception.

TABLE 8.1: First-line ART regimen for treating pregnant women

| Timing | ARVs |
|---|---------------------------------------|
| Pregnant women diagnosed after the first trimester (or 28 days) | TDF + 3TC+ DTG |
| Women diagnosed while planning for pregnancy | TDF + 3TC +DTG* or TDF + 3TC + EFV |

*The neural tube closes by 28 days. So DTG can be given to pregnant women diagnosed with HIV after 28 days. For women who are planning to become pregnant, clear information on the risks/benefits of DTG and alternative options should be provided.

Women do raise concerns of ARV drug toxicity for themselves and their infants, but generally value the health benefits and ability to protect their children from HIV. There are challenges of lifelong treatment, including disclosure to partners, prejudice, lack of support, and costs and time off work associated with clinic visits and drug pick-ups. Still, the uptake of ART among those diagnosed is very good.

Viral load monitoring of pregnant and breastfeeding women on ART

Although treatment monitoring using VL is important for all people on ART, it may be especially valuable for pregnant women (before getting pregnant or at 36 weeks of pregnancy) and breastfeeding women for whom there is added

benefit in terms of eVT. It would guide health-care providers in providing ARV prophylaxis to the HIV-exposed baby. A maternal VL above 1000 copies/mL during the last few weeks before delivery will increase transmission risk.

8.2.2 Maternal prophylaxis and treatment of opportunistic infections

Maternal prophylaxis and treatment of OIs should be given antenatally, during labour and delivery, and postpartum (Table 8.2).

Women who fulfil the following criteria for co-trimoxazole (TMP–SMX) prophylaxis for PCP and toxoplasmosis should start and remain on TMP–SMX throughout their pregnancy:

- WHO stage 3 or 4 disease, irrespective of CD4 cell count, or
- WHO stage 1 disease with CD4 count $<350/\text{mm}^3$.

The dose is one DS tablet (800/160 mg) daily.

Although trimethoprim is hypothetically teratogenic to the baby during the first trimester of pregnancy, co-trimoxazole prophylaxis should commence irrespective of the gestational age. This is because the benefits of the protective effects of TMP–SMX against OIs in the mother far outweigh the very small risk of adverse effects on the fetus.

Sulfonamides can displace bilirubin from plasma albumin and are associated with an increased risk of jaundice and kernicterus in the newborn baby. Careful monitoring of the baby should be undertaken, but TMP–SMX should not be discontinued prior to delivery, if required for maternal health.

TABLE 8.2: Prophylaxis for and treatment of OIs in pregnant women

| | |
|--|--|
| <i>Pneumocystis pneumonia</i> (PCP) | <ul style="list-style-type: none"> ▪ TMP–SMX prophylaxis should be implemented according to standard criteria for non-pregnant PLHIV. ▪ Dapsone and aerosolized pentamidine are also considered safe in pregnancy. |
| Fungal infection | <ul style="list-style-type: none"> ▪ Fluconazole has been associated with fetal deaths and fetal abnormalities in animal studies, but the potential benefits outweigh the risks from treatment. ▪ Itraconazole shows embryotoxicity and teratogenicity in pregnant animals. ▪ Amphotericin B is preferred when therapy is needed for fungal infection. |
| Hepatitis B | <ul style="list-style-type: none"> ▪ Hepatitis B immunoglobulin should be given to a susceptible pregnant woman after exposure. |
| Herpes simplex | <ul style="list-style-type: none"> ▪ Use of acyclovir is controversial but experience has shown that it is safe. |
| Influenza vaccine | <ul style="list-style-type: none"> ▪ It is safe in pregnancy. |
| <i>Mycobacterium avium</i> complex (MAC) | <ul style="list-style-type: none"> ▪ Clarithromycin is teratogenic in animals and must be used with caution in pregnancy. ▪ There has been limited experience with rifabutin in pregnancy. ▪ For secondary MAC prophylaxis – use azithromycin and ethambutol. |
| Toxoplasmosis | <ul style="list-style-type: none"> ▪ Delay primary prophylaxis with pyrimethamine-containing regimens (the risk cannot be excluded but the potential benefits may outweigh the risk) owing to the risk associated with this drug and low probability of toxoplasmosis. ▪ Secondary prophylaxis – most could continue pyrimethamine because of a high rate of relapse when the drug is stopped. |
| Tuberculosis | <ul style="list-style-type: none"> ▪ GeneXpert should be used to diagnose TB if it is suspected. ▪ Chest X-ray should be done where GeneXpert is not available and with the appropriate lead aprons for pelvic protection. ▪ Diagnosed cases should be treated according to the national TB programme following directly observed treatment (DOT) protocols. |
| Varicella zoster | <ul style="list-style-type: none"> ▪ Zoster immune globulin is not contraindicated in pregnancy and should be given to a susceptible pregnant woman after exposure. ▪ Acyclovir is considered safe in pregnancy for severe or disseminated herpes zoster. |

8.3 Neonatal/infant prophylaxis

- 1. Low-risk HIV-exposed children:** pregnant mothers are on ART and the maternal VL is suppressed. The neonate should receive 6 weeks of infant prophylaxis with daily NVP or AZT. Since resistance to the NNRTIs among those with HIV pre-treatment drug resistance is more than 10% in Nepal, syrup AZT is preferred. In case there is a contraindication to AZT, syrup NVP should be provided.
- 2. High-risk HIV-exposed children:** pregnant mothers have received ART for less than 8 weeks, VL is more than 1000 copies/mL; or the mother is diagnosed as HIV positive during labour and delivery and even breastfeeding: the neonate should receive dual prophylaxis with NVP and AZT for 12 weeks (Table 8.3).

Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum. Ensure that NVP and AZT are available through the health worker or community home-based care worker if delivery occurs at home or a health facility with no eVT services.

TABLE 8.3: ARV dosages for infant prophylaxis

| ARV | Infant age | Daily dose |
|-----|---|--|
| NVP | Birth ^a to 6 weeks • Birth weight 2000–2499 g • Birth weight >2500 g | 10 mg once daily 15 mg once daily First dose should be started as soon as possible and continued |
| | ^b 6 weeks–12 weeks | 20 mg once daily |
| AZT | Birth ^a to 6 weeks • Birth weight 2000–2499 g • Birth weight >2500 g | 10 mg twice daily 15 mg twice daily |
| | ^b 6–12 weeks | 60 mg twice daily |

^a. Infants weighing <2000 g should receive mg/kg dosing; the suggested starting dose is 2 mg/kg once daily.

^b. Continue ARV prophylaxis for 12 weeks for high-risk infants.

8.4 Immediate new-born care

- Maintain universal precautions throughout care and treatment:
 - wear gloves when giving injections;
 - clean injection sites;
 - dispose of all needles according to the injection safety protocol.
- During cord clamping after birth
 - avoid “milking” the cord towards the baby;
 - cover the cord with a gloved hand or gauze before cutting.
- Use suction only when meconium-stained liquid is present; use mechanical suction at less than 100 mmHg pressure.
- Wipe the infant dry with a towel, wrap with warm cloth, and give the baby to the mother for skin-to-skin contact.
- Determine the mother’s infant feeding choice, encourage breastfeeding according to the national breastfeeding protocol.
- Administer vitamin K, and bacillus Calmette–Guérin (BCG; TB) vaccine according to the national guidelines.
- Administer the first dose of ARV prophylaxis within 6–12 hours of delivery.
- Regardless of the mother’s HIV status, all infants should be kept warm after birth and handled with gloves until maternal blood and secretions have been washed off.

8.4.1 Postpartum care of women who are HIV infected

Immediate postpartum care: community-based service providers should ensure that women who are infected with HIV and have given birth at a health facility return for postpartum appointments or are visited at home on the first, third and seventh day after delivery.

As a minimum, women should be evaluated in the first week after the birth and again at the sixth week. More frequent monitoring at home will assist in adherence to neonatal ARV prophylaxis and maternal ART and/or co-trimoxazole for the mother, if prescribed. Extra support for infant-feeding choice is essential during the first week of life.

Health-care workers should include the following during postnatal visits:

- Check perineal or caesarean section wound healing.
- Monitor for uterine involution.
- Monitor for signs of puerperal infection.
- Monitor for lochia and any signs of secondary postpartum haemorrhage.
- Check for any signs of infection.

Infant-feeding support:

- Assess progress with and adherence to exclusive breastfeeding.
- Assist the mother to safely breastfeed.
- Assess family support for breastfeeding.
- Identify any risk factors for mixed feeding, and counsel and manage as appropriate.
- Ensure women take good care of their breasts to prevent abscesses, nipple fissures and mastitis; if there is fever or other signs of breast infection or inflammation, advise or refer them promptly for treatment.

The postpartum period is essential to link the woman who is HIV infected to comprehensive care that will support her health, prevent complications and improve her ability to live with HIV, if she has not already been linked. The majority will have initiated comprehensive HIV care before delivery.

The range of services that should be provided, either directly or by referral, includes:

- prevention and treatment of OIs;
- ART;
- management of symptoms and palliative care;
- management of HIV- or ART-related symptoms (including nausea, vomiting, fatigue and skin problems) to ease discomfort;
- nutritional counselling, care and support;
- personal and environmental hygiene;
- social and psychosocial support.

PLHIV face prejudice and discrimination and, therefore, are reluctant to disclose their status to partners, family or friends. Therefore, the following support services should be offered, either directly or by referral:

- counselling and support to help the woman come to terms with her diagnosis and consider her options for disclosure, including assisted partner notification;
- specific psychosocial support and education for the mother whose infant has been exposed to HIV but whose HIV status is uncertain, or when a positive diagnosis is made;
- community support, including referrals to programmes run by community- and faith-based organizations;
- peer group counselling and support from health facilities or NGOs;
- support and counselling to assist women who are HIV infected and their partners with disclosure issues;

Community service providers are close to the community and they will be able to care for PLHIV throughout the continuum of HIV infection and can assist in diagnosis, during times of illness, around the start or continuation of ART, in follow up from hospitalization or during the terminal stages of the disease.

8.4.2 Recommendations on breastfeeding and infant feeding

Breastfeeding should be promoted and supported for optimal growth and development of infants. Infants should be exclusively breastfed for the first 6 months of life and appropriate complementary foods introduced thereafter. Breastfeeding can be continued up to 24 months and beyond with ART adherence. The risk of transmitting HIV to the infant through breastfeeding is low when the mother is receiving ART and the infant is on ARV prophylaxis.

All pregnant women with HIV who are on ART are recommended to continue breastfeeding as per the national breastfeeding protocol; however, during breast infection, especially mastitis and cracked or bloody nipples, there is an additional risk of HIV transmission; and the sores or oral thrush (candidiasis) in the infant's mouth may aggravate infection occurring during breastfeeding. It is suggested that breastfeeding be avoided until the mother is completely cured or expressed breast milk be given.

8.4.3 Establishing and managing linkages

Eliminating viral transmission needs multidisciplinary and multisectoral initiatives. Linkages with various agencies are very important for ensuring that adequate resources – human, financial and material – are available and allocated to care and support services. Related sectors such as education, health, women, children and social welfare should all be involved in HIV awareness and prevention, care and support services. In addition, NGO and private sector partners can supplement and complement the expansion of eVT services. At the same time, involvement of local partners and community workers is crucial to track pregnant HIV-infected women and ensure that they adhere to treatment, have a safe delivery, receive NVP and co-trimoxazole prophylaxis for the baby and do EID testing at birth and 6 weeks of age. It is crucial to ensure that the mother–baby pair are followed up regularly for EID, and timely ART initiated for children found to be positive. Immunization and nutritional counselling should be done.

Linkages between maternal, neonatal and child health (MNCH) and clinical HIV services

- MNCH services are an important entry point for accessing eVT interventions; mainstreaming of eVT services in MNCH commences in a phase-wise manner.
- ANMs and paramedics can be supported to conduct clinical follow up,

supervision and provision of adherence support to any prescribed treatment (e.g. prophylaxis against OIs). They can also provide information on health promotion and disease prevention.

- Specialists in HIV who provide clinical ART for adults and children are aware of the need for community-level support for clinical supervision and ART.

Linkages with other health programmes for special needs

- Linkage is needed with programmes providing specific health needs, such as family planning, treatment of STIs, or assistance with substance abuse.
- Linkage is also needed with disease-specific programmes, such as those for people with TB.
- Linkage with nutritional support programmes for mothers and children are especially important for PLHIV.

Linkages with CBOs

- Linkages to CBOs can provide resources to help women who are HIV infected and their families to cope with the isolation, social prejudice, and the emotional pressures that often accompany a diagnosis of HIV.
- NGOs often provide HIV-related and non-HIV care and support services for KPs and are a valuable resource for mothers who are HIV infected and their families.

8.5 Family planning services for women with HIV

Many PLHIV experience strong pressure from their family, community and health providers to give up the idea of having children either because of the risk of HIV transmission to the baby or out of concern for the welfare of the children if their parents struggle to care for and support them in later childhood.

Some PLHIV may prefer to prevent pregnancy, either to delay their childbearing until they are clear about quality-of-life issues and access to ART or to avoid childbearing due to complexities in their lives. Optimally, these interventions work best when the mother's HIV status is known before conception so that the pregnancy can be carefully planned.

Reproductive decision-making

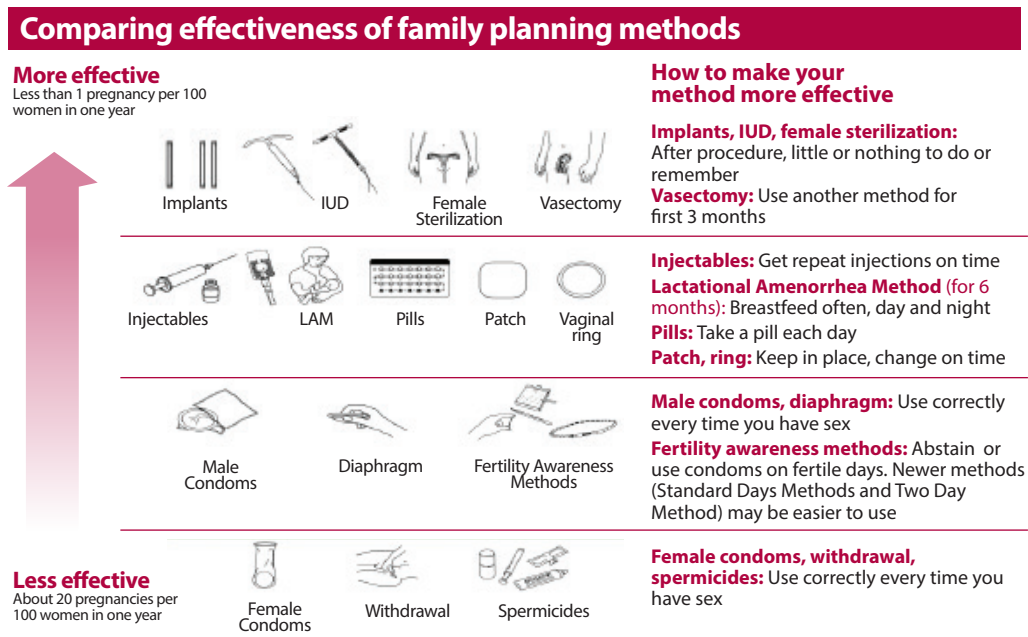
To avoid unintended and unplanned pregnancies among HIV-positive women, careful reproductive health and family planning counselling is essential for all PLHIV. HIV-positive couples should be able to make informed choices, free of coercion and to have access to quality services to implement these choices.

- Family planning counselling for PLHIV should:
 - assess the fertility intentions and desired family size;
 - balance the desire for pregnancy against the risks, consequences and choices related to an unplanned, unintended pregnancy;
 - consider the woman's and couple's previous and current contraceptive practices; and,
 - recommend dual method use – an effective contraceptive method for pregnancy prevention combined with a barrier method for STI and HIV transmission prevention – a “Condom PLUS” approach.
- Women and adolescent girls who want a pregnancy: Pregnancy planning, preconception care and safe conception are the right of all women and improve health outcomes for mothers and babies. Contraception can be used to plan and delay conception until the VL is low or undetectable, so that fully informed ART decisions can be made (use of a DTG-based regimen versus EFV-based regimen to avoid DTG exposure at conception and during the first 8 weeks of pregnancy). Preconception counselling (detailed below) should be provided to all couples where one or both partners are HIV positive. This helps couples to conceive when both of them are in good health, have a good nutritional status and the risk of HIV transmission is minimized.
 - If on ART, advise to achieve viral suppression with complete adherence to ART for over 6 months for those on ART before attempting conception. PrEP can be used for the partner, along with viral suppression in the PLHIV partner with early ART.
 - Discuss the chance of transmitting HIV to the child during pregnancy, birth or breastfeeding.
 - Counsel on the need to test the newborn baby immediately after birth.
 - Counsel on need to provide ARV prophylaxis to the new-born baby to reduce HIV transmission.
 - Counsel on the need to have good general health and nutritional status during conception.
 - Discuss the impact on the family of having another child.

8.5.1 Contraceptive services

Women and adolescent girls living with HIV should be given comprehensive information about the full range of contraceptive options available to make their decisions about the method they would prefer (Fig. 8.1). They should also be informed that the long-acting reversible methods (intrauterine contraception and implants) are the most effective reversible methods. No contraceptive method is

FIGURE 8.1: Comparing the effectiveness of contraceptive methods



Source: Family planning: a global handbook for providers. Baltimore and Geneva: Center for Communication Programs and World Health Organization; 2018

contraindicated because of having HIV or using ART, although interactions with some ARV drugs may reduce the effectiveness of some hormonal contraceptives. A “condom plus” approach is encouraged: consistently using male/female condoms in addition to using another contraceptive method to prevent pregnancy and also prevent the transmission of HIV and other STIs. Emergency contraception can prevent unintended pregnancy, and all women and adolescent girls should have access to emergency contraception when needed.

8.5.2 Specific contraceptives and potential interactions with ARV drugs

Non-hormonal methods of contraception

ARV drug interactions do not affect the effectiveness of the copper-intrauterine device (Cu-IUD), the permanent methods of contraception (female sterilization and male vasectomy) and male and female condoms.

Levonorgestrel – IUD

Given the localized delivery and action of the levonorgestrel (LNG) hormone released from IUDs, it is unlikely that drug interaction with ARV drugs reduces the effectiveness of the hormonal IUD (LNG-IUD), although data are limited.

Implant: levonorgestrel (LNG) and etonogestrel (ETG)

Concurrent use of LNG and ETG contraceptive implants and the NNRTI EFV can reduce the effectiveness of LNG and ETG implants and could put users at risk of unintended pregnancy. Pharmacokinetic studies of women using LNG and ETG implants found significantly lower LNG or ETG levels among women taking EFV-based ART compared with women taking no ART, and pregnancy rates among implant users who take EFV range from 5.5% to 15%. Despite the decreased contraceptive effectiveness among women using EFV-based ART and an implant, the rate of unintended pregnancy remains much lower for these women than for women not using contraception and is also lower than for women using methods that require regular adherence for effective use, such as injectables and pills. The NNRTI NVP, NRTIs and PIs do not reduce implant effectiveness. No direct evidence indicates whether the integrase inhibitor DTG affects the contraceptive effectiveness of implants.

Progestogen-only injectables (DMPA and NET-EN)

ARV drugs do not reduce the effectiveness of the progestogen-only intramuscular injectable DMPA. Studies of intramuscular DMPA users who take NNRTIs (both EFV and NVP) found that pregnancy rates were comparable to those among intramuscular DMPA users who are not receiving ART. NRTIs and PIs do not reduce the effectiveness of intramuscular DMPA. There are no data for injectable norethisterone enanthate (NET-EN) and subcutaneous DMPA. No evidence indicates whether the integrase inhibitor DTG affects the contraceptive effectiveness of DMPA, although this is unlikely because significant drug–drug interactions with these agents and hormonal contraceptives are not expected. Progestogen-only injectable contraceptives are unlikely to be affected by interactions with ARV drugs.

Oral contraceptive pills (combined oral contraceptive and progestogen-only pill)

Pharmacokinetic studies have shown that EFV could reduce the effectiveness of combined oral contraceptive pills (COC), progestogen-only pill (POP) and progestogen-only emergency contraception by reducing the levels of hormonal

contraceptive (progestogen) exposure. Robust data on pregnancy rates are lacking. For oral contraceptive pills, because contraceptive effectiveness relies on user adherence and consistent use, any potential additional reductions in effectiveness from drug–drug interactions are a matter of concern. The NNRTI - NVP, NRTIs, PIs and the integrase inhibitor DTG do not seem to reduce the effectiveness of COC and POP.

8.5.3 TB treatment and hormonal contraception

Rifampicin, rifapentine and rifabutin therapy interacts with some hormonal contraceptive methods and emergency contraceptive pill formulations. Women and adolescent girls using TB regimens containing rifampicin, rifapentine or rifabutin should be advised against using COC or other combined hormonal methods. There are theoretical concerns of lowered effectiveness for LNG and ETG implants, NET-EN injectable, and POP. These TB medications are not considered to reduce the effectiveness of the DMPA progestogen-only injectable.

Annexes

ANNEXES

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ANNEX 1

WHO clinical staging of HIV disease in adults, adolescents and children

| Adults and adolescents ^a | Children |
|--|--|
| Clinical stage 1 | |
| <ul style="list-style-type: none"> ■ Asymptomatic ■ Persistent generalized lymphadenopathy | <ul style="list-style-type: none"> ■ Asymptomatic ■ Persistent generalized lymphadenopathy |
| Clinical stage 2 | |
| <ul style="list-style-type: none"> ■ 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 | <ul style="list-style-type: none"> ■ 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 | |
| <ul style="list-style-type: none"> ■ Unexplained severe weight loss (>10% of presumed or measured body weight) ■ Unexplained chronic diarrhoea for longer than 1 month ■ Unexplained persistent fever (intermittent or constant for longer than 1 month) ■ Persistent oral candidiasis ■ Oral hairy leukoplakia ■ 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), neutropaenia (<0.5 × 10⁹/L) and/or chronic thrombocytopenia (<50 × 10⁹/L) | <ul style="list-style-type: none"> ■ Unexplained moderate malnutrition^b 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 one month) ■ Persistent oral candidiasis (after first six weeks of life) ■ Oral hairy leukoplakia ■ Lymph node tuberculosis; pulmonary tuberculosis ■ Severe recurrent bacterial pneumonia ■ Acute necrotizing ulcerative gingivitis or periodontitis ■ Unexplained anaemia (<8 g/dL), neutropaenia (<0.5 × 10⁹/L) or chronic thrombocytopenia (<50 × 10⁹/L) ■ Symptomatic lymphoid interstitial pneumonitis ■ Chronic HIV-associated lung disease, including bronchiectasis |

| Adults and adolescents ^a | Children |
|---|---|
| <p>Clinical stage 4^c</p> <ul style="list-style-type: none"> ■ HIV wasting syndrome ■ <i>Pneumocystis (jirovecii)</i> pneumonia ■ Recurrent severe bacterial pneumonia ■ Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month in duration or visceral at any site) ■ Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) ■ Extrapulmonary tuberculosis ■ Kaposi sarcoma ■ Cytomegalovirus infection (retinitis or infection of other organs) ■ Central nervous system toxoplasmosis ■ HIV encephalopathy ■ Extrapulmonary cryptococcosis, including meningitis ■ Disseminated nontuberculous mycobacterial infection ■ Progressive multifocal leukoencephalopathy ■ Chronic cryptosporidiosis ■ Chronic isosporiasis ■ Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) ■ Lymphoma (cerebral or B-cell non-Hodgkin) ■ Symptomatic HIV-associated nephropathy or cardiomyopathy ■ Recurrent septicaemia (including nontyphoidal <i>salmonella</i>) ■ Invasive cervical carcinoma ■ Atypical disseminated leishmaniasis | <ul style="list-style-type: none"> ■ Unexplained severe wasting, stunting or severe malnutrition^d not responding to standard therapy ■ <i>Pneumocystis (jirovecii)</i> 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's duration or visceral at any site) ■ Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) ■ Extrapulmonary tuberculosis ■ Kaposi sarcoma ■ Cytomegalovirus infection (retinitis or infection of other organs with onset at age older than one month) ■ Central nervous system toxoplasmosis (after the neonatal period) ■ HIV encephalopathy ■ Extrapulmonary cryptococcosis, including meningitis ■ Disseminated nontuberculous mycobacterial infection ■ Progressive multifocal leukoencephalopathy ■ Chronic cryptosporidiosis (with diarrhoea) ■ Chronic isosporiasis ■ Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis) ■ Cerebral or B-cell non-Hodgkin lymphoma ■ HIV-associated nephropathy or cardiomyopathy |

^a In the development of this table, adolescents were defined as 15 years or older. For those younger 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 five 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.

Source: Adapted from: WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, World Health Organization, 2007 (www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf).

ANNEX 2

Dosages of antiretroviral drugs for adults and adolescents

| Generic name | Dose |
|---|--|
| Nucleoside reverse-transcriptase inhibitors (NRTIs) | |
| Abacavir (ABC) | 300 mg twice daily or 600 mg once daily |
| Emtricitabine (FTC) | 200 mg once daily |
| Lamivudine (3TC) | 150 mg twice daily or 300 mg once daily |
| Zidovudine (AZT) | 300 mg twice daily |
| Nucleotide reverse-transcriptase inhibitors (NtRTIs) | |
| Tenofovir disoproxil fumarate (TDF) | 300 mg once daily |
| Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) | |
| Efavirenz (EFV) | 600 mg once daily |
| Proteases inhibitors (PIs) | |
| Atazanavir/ritonavir (ATV/r) | 300 mg/100 mg once daily (FDC) |
| Darunavir + ritonavir (DRV/r) | 600 mg + 100 mg twice daily (separate pill) |
| Lopinavir/ritonavir (LPV/r) | 400 mg/100 mg twice daily (FDC) |
| | Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of LPV/r: (“Double dose” LPV 800 mg/ + ritonavir 200 mg twice daily or “super boosted” with LPV 400 mg/ + ritonavir 100 mg twice daily plus additional doses of ritonavir 300mg twice daily). |
| Integrase strand transfer inhibitors (INSTIs) | |
| Dolutegravir (DTG) | 50 mg once daily ^a |
| Raltegravir (RAL) | 400 mg twice daily |
| | Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of DTG (50 mg twice daily) and RAL (800 mg twice daily), with close monitoring. |

^a. DTG 50 mg and TLD (Tenofovir 300 mg, lamivudine 300 mg, Dolutegravir 50 mg fixed dose combination) can be used once daily in adolescents living with HIV weighing at least 30 kg.

ANNEX 3

Types of toxicity associated with ARV drugs

| ARV drug | Major types of toxicity | Risk factors | Suggested management |
|----------|---|--|---|
| ABC | Hypersensitivity reaction | Presence of <i>HLA-B*5701</i> gene | Do not use ABC in presence of the <i>HLA-B*5701</i> gene. Substitute with AZT or TDF. |
| ATV/r | Electrocardiographic abnormalities (PR and QRS interval prolongation) | People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome | Use with caution in people with pre-existing conduction disease or who are taking concomitant drugs that may prolong the PR or QRS intervals. |
| | Indirect hyperbilirubinaemia (clinical jaundice) | Presence of UDP-glucuronosyltransferase 1-1 enzyme (<i>UGT1A1*28</i> gene) | This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised. |
| | Nephrolithiasis | History of nephrolithiasis | Substitute with LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting with integrase inhibitors. |
| AZT | Severe anaemia neutropaenia | Baseline anaemia or neutropaenia CD4 cell count of ≤ 200 cells/mm ³ | Substitute with TDF or ABC. Consider using low-dose zidovudine. |
| | Lactic acidosis or severe hepatomegaly with steatosis, lipoatrophy, lipodystrophy, myopathy | BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs | Substitute with TDF or ABC. |
| DTG | Hepatotoxicity Hypersensitivity reactions | Coinfection with hepatitis B or C Liver disease | Substitute with another therapeutic class: EFV or boosted PIs. |
| | Insomnia | Older than 60 years Female | Consider morning dose or substitute with EFV, boosted PI or RAL. |
| DRV/r | Hepatotoxicity | Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs | Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available. For hypersensitivity reactions, substitute with another therapeutic class. |
| | Severe skin and hypersensitivity reactions | Sulfonamide allergy | |

| ARV drug | Major types of toxicity | Risk factors | Suggested management |
|--------------|--|--|--|
| EFV | Persistent central nervous system toxicity (such as dizziness, insomnia and abnormal dreams) or mental symptoms (anxiety, depression and mental confusion) | Depression or other mental disorder (previous or at baseline) Daytime dosing | For CNS symptoms, dosing at bedtime. Consider using EFV at a lower dose (400 mg/day or an integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. |
| | Convulsions | History of seizure | |
| | Hepatotoxicity | Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs | For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs). |
| | Severe skin and hypersensitivity reactions | Risk factors unknown | |
| | Gynaecomastia | Risk factors unknown | Substitute with another therapeutic class (integrase inhibitors or boosted PIs). |
| LPV/r | Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes) | 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 | Use with caution for people with pre-existing conduction disease or taking concomitant drugs that may prolong the PR or QRS intervals. |
| | Hepatotoxicity | Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs | If LPV/r is used in first-line ART for children, substitute with RAL or DTG if younger or older than 6 years respectively. If integrase inhibitors are not available, boosted ATV can be used. If LPV/r is used in second-line ART for adults and the person has treatment failure with NNRTIs in first-line ART, consider integrase inhibitors. |
| | Pancreatitis | Advanced HIV disease, alcohol | Substitute with another therapeutic class (integrase inhibitors). |

| ARV drug | Major types of toxicity | Risk factors | Suggested management |
|------------|---|--|---|
| | Dyslipidaemia | Cardiovascular risk factors such as obesity and diabetes | Substitute with another therapeutic class (integrase inhibitors). |
| | Diarrhoea | Risk factors unknown | Substitute with atazanavir/r, darunavir/r or integrase inhibitors. |
| RAL | Rhabdomyolysis, myopathy and myalgia | Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins | Stop ART. When symptoms are resolved, substitute with another therapeutic class (etravirine, boosted PIs). |
| | Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction | Risk factor(s) unknown | |
| TDF | Chronic kidney disease Acute kidney injury and Fanconi syndrome | Underlying renal disease Older than 50 years old BMI <18.5 or low body weight (<50 kg), notably in females Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI | Substitute with AZT or ABC. Do not initiate TDF at an estimated glomerular filtration rate of <60 mL/min, uncontrolled hypertension, untreated diabetes or kidney failure. |
| | Decreases in bone mineral density | History of osteomalacia (adults) and rickets (children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency | |
| | Lactic acidosis or severe hepatomegaly with steatosis | Prolonged exposure to nucleoside analogues Obesity Liver disease | |

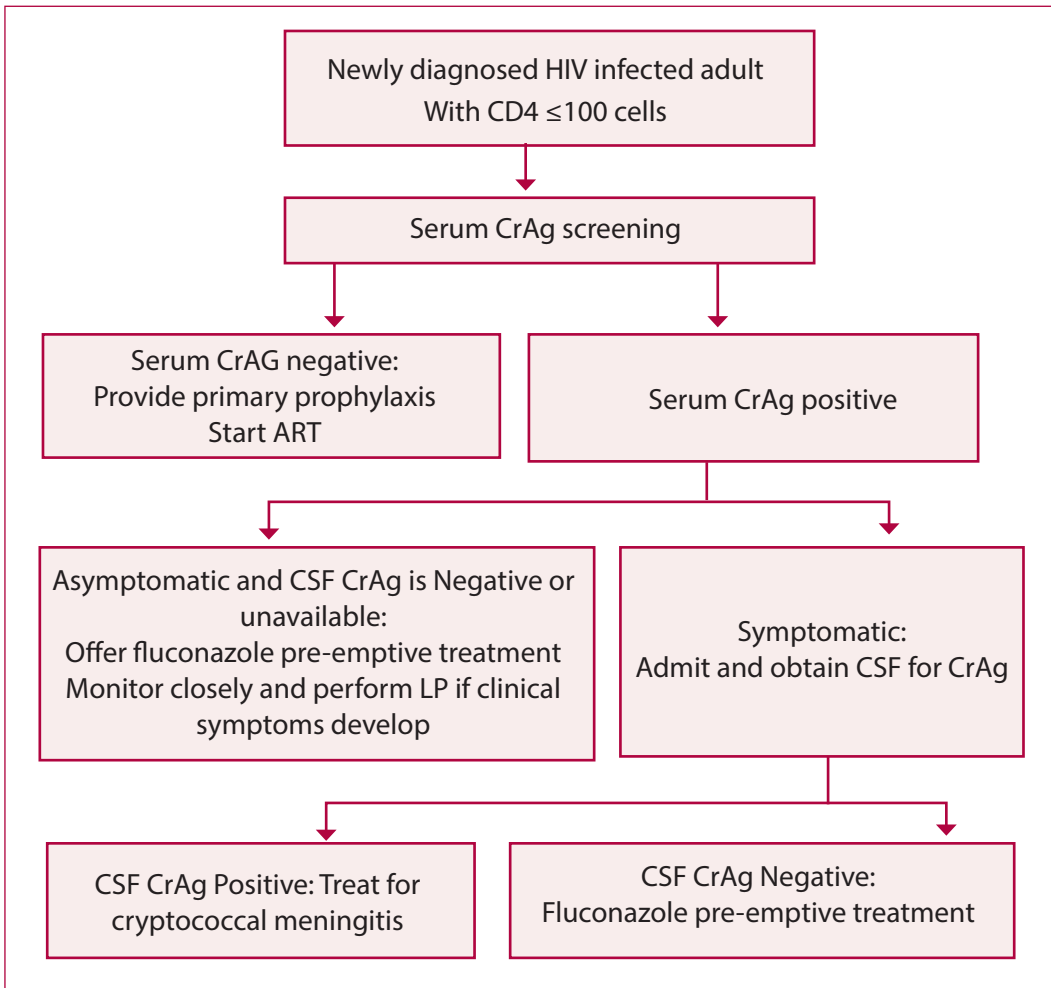
ANNEX 4

Adult physical examination checklist

| | |
|---|--|
| Appearance | <ul style="list-style-type: none"> ■ Unexplained moderate or severe weight loss, HIV wasting. ■ Rapid weight loss is suggestive of active OI, 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 which are common among IDUs. |
| Consider conditions other than HIV | <ul style="list-style-type: none"> ■ Malaria, tuberculosis, syphilis, gastrointestinal infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis other than HIV. |
| Skin | <ul style="list-style-type: none"> ■ Look for signs of HIV-related and other skin problems. These include diffuse dry skin, typical lesions of PPE, especially on the legs, seborrheic dermatitis on face and scalp. ■ Look for herpes simplex and herpes zoster or scarring of previous herpes zoster (especially multi-dermatome). |
| Lymph nodes | <ul style="list-style-type: none"> ■ Start with posterior cervical nodes. ■ PGL (persistent glandular lymphadenopathy) that 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 | <ul style="list-style-type: none"> ■ Look for signs suggestive of HIV infection including white plaques on tongue, cheeks and roof of mouth (oral candida), white stripped lesions on the side of the tongue and cracking at the corners of the mouth (angular cheilitis). ■ Difficulty in swallowing is commonly caused by oesophageal candida. |
| Chest | <ul style="list-style-type: none"> ■ The most common problems will be PCP and TB. ■ Signs and symptoms are cough, shortness of breath, haemoptysis, weight loss, fever, congestion or consolidation. ■ Perform a chest X-ray, if symptomatic. |
| Abdomen | <ul style="list-style-type: none"> ■ Hepatosplenomegaly, masses and local tenderness. ■ Jaundice may be indicative of viral hepatitis. |
| Neurological | <ul style="list-style-type: none"> ■ Focus on visual fields and the signs of neuropathy (bilateral peripheral examination or localized mono-neuropathies). ■ Assess focal neurological deficit. |
| Ano-genital | <ul style="list-style-type: none"> ■ Herpes simplex and other genital sores/lesions, vaginal or penile discharge. ■ Perform PAP smear, if possible. |

ANNEX 5

Routine screening for cryptococcal meningitis for HIV-infected adults



ANNEX 6

Simplified dosing of child-friendly fixed-dose solid formulations for twice daily dosing among children 4 weeks of age and older^a

| Drug | Strength of paediatric tablets (mg) | Number of tablets by weight band morning and evening | | | | | | | | | | Strength of adult tablet (mg) | Number of tablets by weight band |
|------------------------------|---|--|----------|------------|------------|------------|------------|-----|----|----|----------------|-------------------------------|----------------------------------|
| | | 3–5.9 kg | 6–9.9 kg | 10–13.9 kg | 14–19.9 kg | 20–24.9 kg | 25–34.9 kg | AM | PM | AM | PM | | |
| AZT/3TC | Tablet (dispersible) 60 mg/30 mg | 1 | 1 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300/150 mg | 1 | 1 |
| AZT/3TC/ NVP ^b | Tablet (dispersible) 60 mg/30 mg/50 mg | 1 | 1 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300/150/200 mg | 1 | 1 |

a. For infants younger than 4 weeks of age refer to ANNEX 11 for more accurate dosing which is reduced due to the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the appropriate dosing of ARVs in preterm and low birth weight infants.

b. Please note that this regimen and formulation is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

c. This formulation will be phased out of use over time and programs should transition to use of the 120 mg/60 mg dispersible scored tablet.

ANNEX 7

Simplified dosing of child-friendly solid formulations for once-daily dosing in children 4 weeks of age and older^a

| Drug | Strength of tablets (mg) | Number of tablets by weight band morning and evening | | | | | Strength of adult tablet (mg) | Number of tablets by weight band |
|------------------|-------------------------------|--|----------|------------|------------|------------|-------------------------------|----------------------------------|
| | | 3–5.9 kg | 6–9.9 kg | 10–13.9 kg | 14–19.9 kg | 20–24.9 kg | | |
| | | | | | | | | |
| EFV ^b | Tablet (scored) 200mg | - | - | 1 | 1.5 | 1.5 | - | 2 |
| | Tablet (double scored) 600mg | - | - | One third | One half | Two thirds | 600 | 2/3 |
| ABC/3TC | Tablet (dispersible) 60/30mg | 2 | 3 | 4 | 5 | 6 | 600 mg/300 mg | 1 |
| ABC/3TC | Tablet (dispersible) 120/60mg | 1 | 1.5 | 2 | 2.5 | 3 | | |
| ATV ^c | Capsules 100 mg | - | - | 2 | 2 | 2 | 300 mg | 1 ^d |
| | Capsules 100 mg | - | - | 1 | 1 | 1 | | |
| DRV ^e | Tablet 600 mg | - | - | - | 1 | 1 | 600 mg | 1 |
| | Tablet 150 mg | - | - | - | 4 | 4 | | |
| RTV ^f | Tablet 25 mg | - | - | - | 4 | 4 | 100 mg | 1 |
| | Tablet 50 mg | - | - | - | 2 | 2 | | |
| DTG ^g | Film-coated tablet 50 mg | | | | | 1 | 50 mg | 1 |

a. See ANNEX 11 for dosing recommendations for infants younger than 4 weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the appropriate dosing of ARVs in preterm and low birth weight infants.

b. EFV is not recommended for children younger than 3 years and weighing less than 10 kg.

c. ATV is only approved for use in children 3 months and older. ATV single strength capsules should be administered with RTV 100 mg for all weight bands 10 kg and above. ATV powder formulation has limited availability in LMIC but enables administration of ATV to infants and children as young as 3 months. Infants and children 5-15 kg should be administered 200 mg of ATV powder (4 packets, 50 mg/ packet) with 80 mg of RTV oral solution (1 ml). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042.2_06352s007tbl.pdf

d. A 300 mg dose for 25-29.9 kg is recommended on the basis of findings from the PRINCE-2 study.

e. DRV in combination with RTV should be used, in children older than 3 years, once daily when this is used without previous exposure to PI. While approved dosing for 30-35kg is 675 mg, preliminary data from adult studies suggest that even lower DRV doses may be effective, therefore use of 600 mg dose was extended to the entire 25-35 kg weight band.

f. RTV should only be use as a boosting agent in combination with ATV or DRV or to “super boost” LPV/r when given with concomitant rifampicin for TB.

g. All children over 20 kg receiving 50 mg FCT will continue to be followed up in ODYSSEY and toxicity data collected. For adolescents living with HIV weighing more than 30 Kg a fixed dose formulation of TDF 300mg/3TC 300mg/DTG 50mg (TLD) can be used and is preferred.

ANNEX 8

Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing in children 4 weeks of age and older^a

| Drug | Strength of tablets (mg) or oral liquid (mg/ml) | Number of tablets by weight band morning (AM) and evening (PM) | | | | | | | | | | Strength of adult tablet (mg) | | Number of tablets by weight band | | | |
|---------------------------|---|--|----|----------|-----|------------|----|------------|-----|------------|-----|-------------------------------|-----|----------------------------------|--------|---|---|
| | | 3–5.9 kg | | 6–9.9 kg | | 10–13.9 kg | | 14–19.9 kg | | 20–24.9 kg | | 25–34.9 kg | | AM | PM | | |
| | | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | | | | | | |
| Solid Formulations | | | | | | | | | | | | | | | | | |
| AZT | Tablet (dispersible) 60mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 3 | 300 | 1 | 1 |
| ABC | Tablet (dispersible) 60mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 3 | 300 | 1 | 1 |
| NVP ^b | Tablet (dispersible) 50mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 3 | 200 | 1 | 1 |
| LVP/r ^c | Tablet (heat stable) 100 mg/25mg | - | - | - | - | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 100/25 | 3 | 3 |
| | Pellets 40 mg/10 mg | 2 | 2 | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | - | 3 | 3 |
| | Granules 40 mg/10 mg sachet | 2 | 2 | 3 | 3 | 4 | 4 | 4 | 5 | 5 | 5 | 6 | 6 | 6 | - | 3 | 3 |
| DRV ^d | Tablet 75 mg | - | - | - | - | - | - | - | 5 | 5 | 5 | 5 | 5 | 5 | 400 mg | 1 | 1 |
| RTV ^e | Tablet 25 mg | - | - | - | - | - | - | - | 2 | 2 | 2 | 2 | 2 | 2 | 100 mg | 1 | 1 |
| | Tablet 50 mg | - | - | - | - | - | - | - | 1 | 1 | 1 | 1 | 1 | 1 | | | |
| RAL ^f | Chewable tablet 25 mg | 1 | 1 | 2 | 2 | 3 | 3 | 3 | 4 | 4 | 4 | 6 | 6 | 6 | 400 mg | 1 | 1 |
| | Chewable tablet 100 mg | - | - | - | - | - | - | - | 1 | 1 | 1 | 1.5 | 1.5 | 1.5 | | | |

| Drug | Strength of tablets (mg) or oral liquid (mg/ml) | | Number of tablets by weight band morning (AM) and evening (PM) | | | | | | | | | | | | Strength of adult tablet (mg) | | Number of tablets by weight band | |
|----------------------------|--|------|--|--------|----------|--------|------------|--------|------------|--------|------------|--------|--------|------|-------------------------------|------|----------------------------------|---|
| | | | 3–5.9 kg | | 6–9.9 kg | | 10–13.9 kg | | 14–19.9 kg | | 20–24.9 kg | | AM | PM | | | | |
| | | | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | | | | | | |
| Liquid Formulations | | | | | | | | | | | | | | | | | | |
| AZT | 10 mg/ml | 6 ml | 6 ml | 9 ml | 9 ml | 12 ml | 12 ml | 12 ml | 12 ml | - | - | - | - | - | - | - | - | - |
| ABC | 20 mg/ml | 3 ml | 3 ml | 4 ml | 4 ml | 6 ml | 6 ml | 6 ml | 6 ml | - | - | - | - | - | - | - | - | - |
| 3TC | 10 mg/ml | 3 ml | 3 ml | 4 ml | 4 ml | 6 ml | 6 ml | 6 ml | 6 ml | - | - | - | - | - | - | - | - | - |
| NVP ^b | 10 mg/ml | 5 ml | 5 ml | 8 ml | 8 ml | 10 ml | 10 ml | 10 ml | 10 ml | - | - | - | - | - | - | - | - | - |
| LPV/r ^c | 80/20 mg/ml | 1 ml | 1 ml | 1.5 ml | 1.5 ml | 2 ml | 2 ml | 2 ml | 2 ml | 2 ml | 2.5 ml | 2.5 ml | 2.5 ml | 3 ml | 3 ml | 3 ml | - | - |
| DRV ^d | 100 mg/ml | - | - | - | - | 2.5 ml | 2.5 ml | 2.5 ml | 2.5 ml | 3.5 ml | 3.5 ml | 3.5 ml | 3.5 ml | - | - | - | - | - |
| RTV(r) | 80 mg/ml | - | - | - | - | 0.5 ml | 0.5 ml | 0.5 ml | 0.5 ml | 0.6 ml | 0.6 ml | 0.6 ml | 0.6 ml | - | - | - | - | - |
| RAL ^f | 10 mg/ml (oral granules for suspension: 100 mg/sachet) | 3 ml | 3 ml | 5 ml | 5 ml | 8 ml | 8 ml | 8 ml | 8 ml | 10 ml | 10 ml | 10 ml | 10 ml | - | - | - | - | - |

- a. See ANNEX 11 for dosing recommendations for infants younger than 4 weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern but uncertainty still exists on the dosing of ARVs in preterm and low birth weight infants.
- b. NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS) – 1 trial suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose. Please note that this regimen is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

- c. LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 tablet could be used for patients 14–24.9 kg (1 tab am and 1 tab pm) and for patients 25–34.9 kg (2 tab am and 1 tab pm). LPVr pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPV/r pellets can be found at <https://www.who.int/hiv/pub/toolkits/jatt-factsheet-lopinavir-ritonavir/en/>. This dosing schedule applies to equivalent solid dosage forms such as LPVr granules which can be used from 2 weeks of age. Since supply is currently constrained both pellets and granules should be discouraged for children above 14 kg who should receive LPV/r 100/25 mg tablets instead. Info on LPV/r formulations for children available at: <https://www.arvprocurementworkinggroup.org/lpv-r-supply>
- d. DRV to be used in children older than 3 years, must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if less than 15 kg and with RTV 50 mg (using 25 mg or 50 mg solid formulation) in children 15 to 30 kg. RTV 100 mg tablets can be used as booster if lower-strength RTV tablets are not available. This is based on limited experience suggesting good acceptability and tolerability. But no efficacy data.
- e. RTV should only be used at this dose as a boosting agent in combination with ATV or DRV.
- f. RAL granules are approved from birth. Feasibility and acceptability of such formulations has not been widely investigated and concerns have been raised regarding administration in resource limited settings. Due to the administration challenges presented by the granule formulation the use of the 25 mg chewable tablets as dispersible has been endorsed by the PAWG for infants and children older than 4 weeks and weighting at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules as well as considering the limited availability of adequate alternatives for this age group. However, findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administration of RAL granules in rural settings is feasible as long as supported with adequate training and counselling.

ANNEX 9

Drug dosing of liquid formulations in infants less than 4 weeks of age^a

| Drugs | Strength of oral liquid | 2 – 3 kg | | 3 – 4 kg | | 4 – 5 kg | |
|--------------------|---|----------|--------|----------------------------------|--------|----------------------------------|--------|
| | | AM | PM | AM | PM | AM | PM |
| AZT | 10 mg/mL | 1 mL | 1 mL | 1.5 ml | 1.5 ml | 2 mL | 2 mL |
| NVP | 10 mg/mL | 1.5 mL | 1.5 mL | 2 mL | 2 mL | 3 mL | 3 mL |
| 3TC | 10 mg/mL | 0.5 mL | 0.5 mL | 0.8 mL | 0.8 mL | 1 ml | 1 mL |
| LPV/r ^b | 80/20 mg/mL | 0.6 mL | 0.6 mL | 0.8 mL | 0.8 mL | 1 ml | 1 mL |
| | Granules 40 mg/10 mg sachet | - | - | 2 | 2 | 2 | 2 |
| RAL | 10 mg/mL (Oral granules for suspension: 100 mg/sachet) ^c | < 1 week | | 0.4 ml (once daily) ^c | | 0.7 ml (once daily) ^c | |
| | | > 1 week | | 0.8 ml | | 1 mL | |
| | | | | 1 mL | 1 mL | 1.5 mL | 1.5 mL |

- a. PK data in preterm infants are available only for AZT; there is considerable uncertainty of appropriate dosing for NVP, RAL and 3TC in preterm and low birth weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects that may occur in this population. This guidance will be updated when more evidence is available from ongoing trials.
- b. Do not use LPV/r solution in infants aged <2 weeks of age. LPV/r pellets should not be used in infants younger than 3 months. More details on the administration of LPV/r pellets can be found at <http://www.emtct-iaatt.org/wp-content/uploads/2015/09/IATT-LPV-Factsheet-Final-30-September-2015.pdf>
- c. RAL granules for oral suspension should use in neonates of at least 2 kg and be administered in once a day during the first week of life and twice a day afterwards (http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf).

ANNEX 10

Simplified dosing of isoniazid (INH) and cotrimoxazole (CTX) prophylaxis for infant and children who are at least 4 weeks of age^a

| Drug | Strength of tablets oral liquid (mg or mg/5 ml) | Number of tablets or mL by weight band once daily | | | | | Strength of adult tablet (mg) | Number of tablets by weight band |
|-------------------------|---|---|----------|------------|------------|------------|-------------------------------|----------------------------------|
| | | 20–24.9 kg | | | | | | |
| | | 3–5.9 kg | 6–9.9 kg | 10–13.9 kg | 14–19.9 kg | 20–24.9 kg | | |
| INH | 100 mg | 0.5 | 1 | 1.5 | 2 | 2.5 | 300 mg | 1 |
| CTX (SMX/TMP) | Suspension 200/40 mg per 5 ml | 2.5 ml | 5 ml | 5 ml | 10 ml | 10 ml | - | - |
| | Tablets (dispersible) 100/20 mg | 1 | 2 | 2 | 4 | 4 | - | - |
| | Tablets (scored) 400/80 mg | - | One half | One half | 1 | 1 | 400/80 mg | 2 |
| INH/CTX/B6 ^a | Tablets (scored) 800/160 mg | - | - | - | One half | One half | 800/160 mg | 1 |
| | Tablets (scored) 300 mg/ (800mg/160mg)/25 mg | - | - | - | One half | One half | 300 mg/ (800mg/160mg)/25 mg | 1 |

^a A scored tablet (150mg/(400mg/80mg)/12.5 mg) is under development.

ANNEX 11

Dosing for RTV super-boosting of LPV/r for children receiving rifampicin-containing TB treatment^a

| Drug | Strength of paediatric tablets or oral liquid | Number of tablets by weight-band morning (AM) and evening (PM) | | | | | | | | | | Strength of adult tablet | | Number of tablets by weight band | | |
|---|---|--|--------|----------|--------|------------|--------|------------|--------|------------|--------|--------------------------|---|----------------------------------|----|---|
| | | 3-5.9 kg | | 6-9.9 kg | | 10-13.9 kg | | 14-19.9 kg | | 20-24.9 kg | | 25-34.9 kg | | AM | PM | |
| | | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | | | | | |
| For children able to swallow tablets | | | | | | | | | | | | | | | | |
| LPV/r ^b | Tablet 100/25 mg | - | - | - | - | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 |
| RTV | Tablet 100 mg | - | - | - | - | 1 | 1 | 1 | 2 | 1 | 2 | 100 mg | 2 | 2 | | |
| | Tablet 50 mg | - | - | - | - | 2 | 2 | 3 | 3 | 3 | 3 | | | | | |
| | Tablet 25 mg | - | - | - | - | 4 | 4 | 6 | 6 | 6 | 6 | | | | | |
| For children unable to swallow tablets | | | | | | | | | | | | | | | | |
| LPV/r | Oral solution ^c 80/20 mg/ml | 1 ml | 1 ml | 1.5 ml | 1.5 ml | 2 ml | 2 ml | 2.5 ml | 2.5 ml | 3 ml | 3 ml | - | - | - | - | - |
| | Pellets ^d 40 mg/10 mg | 2 | 2 | 3 | 3 | 4 | 4 | 5 | 5 | 6 | 6 | - | - | - | - | - |
| RTV ^e | Oral solution 80 mg/ml | 0.8 ml | 0.8 ml | 1.2 ml | 1.2 ml | 1.5 ml | 1.5 ml | 2 ml | 2 ml | 2.3 ml | 2.3 ml | - | - | - | - | - |
| RTV | Powder 100 mg/packet | - | - | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | - | - | - | - | - |

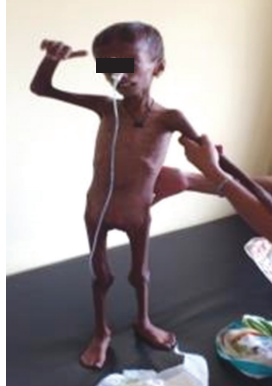
a. Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study which explored this approach in young children receiving LPV/r.
 b. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 tablet could be used for patients 14-24.9kg (1 tab AM and 1 tab PM) and for patients 25-34.9 kg (2 tab AM and 1 tab PM).
 c. RTV liquid requires a cold chain during transport and storage.
 d. LPV/r pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPV/r pellets can be found at <http://www.emctct-ia.ttc.org/wp-content/uploads/2015/09/IATT-LPV-r-Factsheet-Final-30-September-2015.pdf>. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPV/r granules.
 e. RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super boosting.

ANNEX 12

Pictures of opportunistic infections



Pic. 1 Children with severe malnutrition



Pic. 2. Cervical lymphadenopathy



Pic. 3. Child with pneumonia with distress



Pic 4. Chest X-ray showing consolidation of right upper and mid-zone



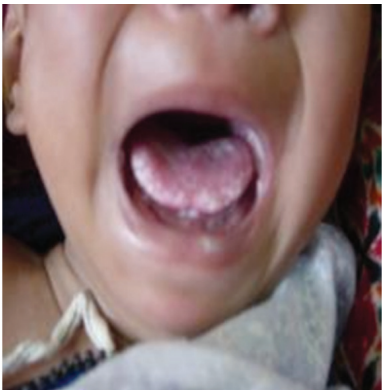
Pic. 5. Chest X-ray showing right and left bronchiectatic changes lower zones



Pic. 6. Hepatosplenomegaly



Pic. 7. Parotid gland Swelling



Pic. 8. Oral Candidiasis



Pic. 9. Pyoderma



Pic. 10. Tenia coporis



Pic. 11. Moluscum contagiosum



Pic. 12. Herpes Zoster



Pic. 13. Varicella zoster



Pic. 14. Severe anaemia in tongue



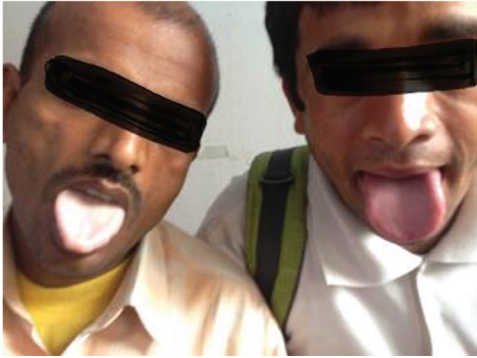
Pic. 15. Severe anaemia in palm



Pic. 16. Ecchymotic

ANNEX 13

Adverse reactions to the ARVs



Pic. 1. Anaemia caused by AZT



Pic. 2. Gynaecomastia caused by EFV



Pic. 3. Lipodystrophy caused by d4T



Pic. 4. Maculopapular rash caused by NVP

ANNEX 14



Government of Nepal
Ministry of Health
Department of Drug Administration

Adverse Event Reporting Form for ARV Medicines

| PATIENT DETAILS | | |
|--|-------------------|--------------|
| Patient ID No: | Patient Name: | Sex: F/ M /O |
| Age: _____ years _____ months | Weight(kg): _____ | |
| Patient residential/contact information: | | |

| Type of Treatment: <input type="checkbox"/> HAART <input type="checkbox"/> PMTCT <input type="checkbox"/> PEP <input type="checkbox"/> PrEP | | | | |
|---|--|--------------|--------------|------------------------------------|
| Drug Details (dosage and frequency) | Brand, generic name, manufacturer, batch No. | Date started | Date stopped | Remarks/reason for discontinuation |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |

| DETAILS OF ADVERSE EVENT | |
|--|----------------------------------|
| Date event started: __ / __ / __ | Date event stopped: __ / __ / __ |
| Adverse reaction observed (please tick all that apply) <input type="checkbox"/> Vomiting <input type="checkbox"/> Nausea <input type="checkbox"/> Itching <input type="checkbox"/> Skin rashes <input type="checkbox"/> Diarrhoea <input type="checkbox"/> Dizziness <input type="checkbox"/> Headache <input type="checkbox"/> Mouth sores <input type="checkbox"/> Abdominal pain <input type="checkbox"/> Insomnia <input type="checkbox"/> Dark coloured urine <input type="checkbox"/> Clinical jaundice <input type="checkbox"/> Weight gain <input type="checkbox"/> Others (pls specify) | |
| Description of event (continue on back page if necessary): | |
| Treatment or action taken (continue on back page if necessary): | |
| Seriousness (please tick all that apply) <input type="checkbox"/> Not Serious <input type="checkbox"/> Life threatening <input type="checkbox"/> Caused hospital admission <input type="checkbox"/> Death <input type="checkbox"/> Other outcome (please specify): | |
| Outcome (please tick all that apply) <input type="checkbox"/> Recovered <input type="checkbox"/> Recovering <input type="checkbox"/> Ongoing <input type="checkbox"/> Change of therapy <input type="checkbox"/> Died <input type="checkbox"/> Unknown <input type="checkbox"/> Other outcome (please specify): | |
| REPORTER DETAILS | |
| Name: | Position: |
| Signature: | Hospital: |
| Date: | Contact No: |

Please return this form to the focal person at the NCASC via email/fax
Email: data@ncasc.gov.np Fax: +977- 1- 4261406

ANNEX 15

List of viral load and CD4 reagent

| Name of Product | | Unit | Pack Size |
|--|--|-------------------|-----------|
| VL reagents (Roche -Automatic) | | | |
| 1 | Cobas AmpliPrep/Taqman HIV-1 Test v2.0 | Kits | 48 |
| 2 | Cobas AmpliPrep/Cobas Taqman wash reagent 5.1 L | 5.1 L bottle | 1 |
| 3 | Cobas AmpliPrep sample processing unit (SPU) | Pcs | 288 |
| 4 | Cobas AmpliPrep sample input tube (S-tube) | Pcs | 288 |
| 5 | Cobas AmpliPrep -Tube rack | Pcs | 1152 |
| 6 | Cobas AmpliPrep K-tip 1.2mm | Pcs | 432 |
| 7 | Vacutainer (K3E 7.5 % 0.072 ml) 5 ml | Tube | 100 |
| VL reagents (Roche - Automatic for EID) | | | |
| 1 | Cobas AmpliPrepCobas Tagman HIV-1 Qual Test V2.0*** | Kits | 48 |
| 2 | Cobas Specimen Pre-extraction reagent 78ml V2.0*** | 5 bottle/box/78ml | 5 |
| 3 | Cobas AmpliPrep/Cobas Taqman wash reagent 5.1 L | 5.1 L bottle | 1 |
| 4 | Cobas AmpliPrep sample processing unit (SPU) | Pcs | 288 |
| 5 | Cobas AmpliPrep sample input tube (S-tube) | Pcs | 288 |
| 6 | Cobas AmpliPrep K-Tube rack | Pcs | 1152 |
| 7 | Cobas AmpliPrep K-tip 1.2mm | Pcs | 432 |
| 8 | Vacutainer (K3E 7.5 % 0.072 ml) 5 ml | Tube | 100 |
| Qiagen Automatic (Viral Load) | | | |
| 1 | Arts HIV-1 RG RT-PCR kit, a pack of 72, QIAGEN | Kit | 72 |
| 2 | DSP Virus/Pathogen Midi Kit (96) | Kit | 96 |
| 3 | Conical tube 2 ml | Pcs | 500 |
| 4 | Microtube Plastic 0.7 ml/EMTR Plate | Pcs | 2304 |
| 5 | Filter Tips 1500 (1024) | Pcs | 1024 |
| 6 | Filter Tips 200 (1024) | Pcs | 1024 |
| 7 | Filter Tips 50 (1024) | Pcs | 1024 |
| 8 | PCR Tubes 4- strip w cap 0.1 ml | Pcs | 1000 |
| 9 | 8-Rod Cover QIASymphony (144) | Pcs | 144 |
| 10 | Preparation cartridge 8 well for QIASymphony (336) | Pcs | 336 |
| VL reagents (Corbett, Qiagen - Manual) | | | |
| 1 | Artus HIV-1 RG RT-PCR kit, a pack of 24, QIAGEN | Kit | 24 |
| 2 | DSP Virus/Pathogen Midi Kit (50) | Kit | 50 |
| 3 | Rotor Adapter | Pcs | 240 |
| 4 | Filter Tips 1000 ul (1024) | Pcs | 1024 |
| 5 | Sample tube 2ml | Pcs | 1000 |
| CD4 reagents PIMA | | | |
| 1 | Cartridges for PIMA POC CD4 machine | Tests | 100 |
| 2 | Finger Stick Sample | Pes | 100 |
| 3 | Pima Bead Standards (shelf life will be 6 months from date of opening) | Test | 100 |
| 4 | Thermal Paper for PIMA POC | Rolls | 5 |
| CD4 reagents BD FACSPresto | | | |
| 1 | BD FACSPresto Cartridge (REF-655495) | Test | 100 |
| 2 | Thermal Paper for Presto | Rolls | 5 |

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