

# National HIV Testing and Treatment Guidelines 2017

**NEPAL**



# **National HIV Testing and Treatment Guidelines 2017**



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

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**Edited by: Dr. Rajya Shree Nyachhyon Kunwar  
Dr. Subhash Lakhe**

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Ref. No. :

Government of Nepal  
Ministry of Health  
National Centre for AIDS & STD Control



4261653  
4262753  
4258219

Fax: 4261406

Email: [ncasc@ncasc.gov.np](mailto:ncasc@ncasc.gov.np)  
Website: [www.ncasc.gov.np](http://www.ncasc.gov.np)  
Taku, Kathmandu, Nepal

Date: .....

## Foreword

Based on the WHO "Consolidated guidelines on HIV testing services" that recommend training lay providers in using rapid diagnostic tests, independently to conduct safe and effective HIV testing services, innovative service delivery approaches in "Nepal HIVision 2020" include intensified testing to reach key populations through facility-based outreach and community-led in-reach; linking testing to treatment.

Since the inception of Nepal's anti-retroviral treatment (ART) programme in 2004, under the leadership of the Ministry of Health, National Centre for AIDS and STD Control, the country has taken many measures to scale up ART with the objective of reaching everyone who needs treatment. Development of these "National HIV Testing and Treatment Guidelines 2017" is another milestone.

Following the directives of the National HIV Strategic Plan 2016-2021, these Guidelines support the Test, Treat and Retain continuum, based on the "WHO Consolidated Guidelines on the use of Antiretroviral Drugs for treating and preventing HIV infection", published in 2016. 'Test-and Treat' keeps infected people healthy and living longer, and dramatically reduces the risk of HIV transmission to others.

I am very thankful to the members of the Guidelines Development Group and members of the Technical Working Group on HIV Testing, Counselling, Treatment, Care and eVT. I would like to especially thank the WHO Country Office in Nepal and UNAIDS for providing technical support for developing these Guidelines.

I extend my special appreciation to civil society networks and community activists for their persistent evidence-informed advocacy that has resulted in community-led HIV testing to be an important strategy in our Guidelines. I thank you for inspiring and stimulating us.

I encourage all partners working in the field of HIV in Nepal to use these Guidelines appropriately, and together Fast-Track towards ending the AIDS HIV epidemic in Nepal, by 2030.

Dr Tarun Poudel  
Director  
National Centre for AIDS and STD Control





Government of Nepal  
Ministry of Health

Department of Health Services

**National Public Health Laboratory**

Teku, Kathmandu

Tel : 4252421

Fax : 4252375

Email: [nphl@wlink.com.np](mailto:nphl@wlink.com.np)

## COMMITMENT

With these 'National HIV Testing and Treatment Guidelines - 2017,' our traditional facility-based HIV testing, in clinical settings, such as standalone HIV testing services and antiretroviral therapy sites, mobile facilities, antenatal care and labour rooms, opioid substitution therapy sites, TB care sites and private clinics, have been expanded. This include innovative public-private partnerships, applying 'test-for-triage,' such as community-led HIV testing among key populations, using mobile units, entertainment sites, and hotspots for sex work and injecting drug use - also focusing on remote birthing sites and areas with higher numbers of male labour migrants and their partners.

Our Guidelines describe both HIV testing and counselling recommended by a health-care provider in a clinical setting, and client-initiated testing, where a person takes the initiative to seek information on their HIV status. Testing for diagnostic purposes is recommended for all adults, adolescents and children who present to health facilities with signs or symptoms that could indicate HIV infection. HIV testing is also recommended as part of the clinical evaluation of people with sexually transmitted infections, tuberculosis and during pregnancy in order to identify the need for antiretroviral therapy or prophylaxis, as part of the 'Elimination of Vertical Transmission of HIV' program. Regardless of the type of testing or location, all HIV testing must always be carried out under conditions respecting Quality, Confidentiality, Consent and Counselling.

The primary function of the National Public Health Laboratory (NPHL) is to support the diagnosis of infectious as well as non infectious disease, as referral center in country and also support outbreak investigation following health improvement goals of Government of Nepal. Our services are directed to networking, Licensing, monitoring, supervision, capacity strengthening and conducting research activities and National EQAS of the laboratories. Currently, NPHL has facility of biosafety level (BSL) II lab and real time PCR (RT-PCR) facilities for HIV viral load testing. Our mandate is to protect the public from the spread of infectious diseases, to identify disease conditions early for appropriate treatment to prevent spread, and to identify populations at increased risk.

The National Public Health Laboratory is, therefore, a critical institution in the HIV prevention-treatment continuum, linking people who test positive for HIV to treatment through right diagnosis and monitoring. This highlights NPHL's responsibility and our commitment for optimal training of both laboratory scientists and lay providers from the key populations, and quality assurance, as part of our key role to ensure reliable case finding in the "Identify, Reach, Recommend, Test, Treat and Retain" approach of Nepal.

Dr. Raj Kumar Mahto

Director

National Public Health Laboratory

Department of Health Services, MoH

Nepal



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# LIST OF TECHNICAL WORKING GROUP AND WRITING COMMITTEE MEMBERS

- 1 Dr Tarun Paudel, Director, National Centre for AIDS and STD Control (NCASC), Teku, Kathmandu, Nepal
- 2 Dr Bikash Lamichane, Director, National Tuberculosis Centre, Thimi, Bhaktapur, Nepal
- 3 Dr Purusotam Raj Shedain, Senior Integrated Medical Officer, NCASC, Teku, Kathmandu, Nepal
- 4 Dr Sushil Kumar Shakya, Consultant General Practice Specialist, HIV Physician, Registrar Emergency Department, ART Unit Chief, NAMS, BIR Hospital, Kathmandu, Nepal
- 5 Dr Laxman Shrestha, Professor of Paediatrics, Chief of Neonatal Division, Department of Paediatrics, Tribhuvan University Teaching Hospital (TUTH), Maharajgunj, Medical Campus, Institute of Medicine (IOM), Kathmandu, Nepal
- 6 Dr Prem Khadga, Professor, Head of Department Gastroenterology, Sub-Coordinator–HIV Committee, TUTH, Maharajgunj Medical Campus, IOM, Kathmandu, Nepal
- 7 Dr Indira Upadhyaya, Consultant Obstetrician/Gynaecologist, Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu, Nepal
- 8 Dr Dinesh Binod Pokharel, Professor and former Head of Dept., Dept. of Dermatology, TUTH, Maharajgunj Medical Campus, IOM, Kathmandu, Nepal
- 9 Dr Sashi Sharma, Professor, Department of Medicine, Faculty of Gastroenterology, Chief, HIV/AIDS Committee, TUTH, Maharajgunj Medical Campus, IOM, Kathmandu, Nepal
- 10 Dr Geeta Shakya, Director, National Public Health Laboratory (NPHL), Teku, Kathmandu
- 11 Dr Raj Kumar Mahato, Consultant Pathologist, HIV Unit In-charge, NPHL, Teku, Kathmandu
- 12 Dr Anup Bastola, Consultant Dermatologist/Tropical Medicine and Hygiene, Sukraraj Tropical and Infectious Disease Hospital, Teku, Nepal
- 13 Dr Rajya Shree Nyachhyon Kunwar, HIV Technical Specialist, NCASC, Kathmandu, Nepal
- 14 Dr Saroj Dhakal, Program Coordinator-Treatment, Care and Support, NCASC, Kathmandu, Nepal

- 15 Dr Subhash Lakhe, National Professional Officer, Communicable Disease Control, WHO Country Office, Nepal
- 16 Birendra Pradhan, HIV Specialist, UNICEF, Kathmandu, Nepal
- 17 Dr Durga Prasad Bhandari, Technical Advisor, LINKAGES Nepal, FHI360
- 18 Khagendra Prakash KC, Laboratory Specialist, LINKAGES Nepal, FHI360
- 19 Dr Ruben F del Prado, Country Director and Representative, UNAIDS
20. Bina Pokharel, Community Mobilization and Networking Adviser, UNAIDS
21. Komal Badal, Strategic Information Associate, UNAIDS
22. Neichu Mayer, Partnership Coordinator, UNAIDS

### **Technical Specialist**

Dr B. B. Rewari, World Health Organization (WHO) SEARO

# ABBREVIATIONS AND ACRONYMS

<b>3TC</b>	Lamivudine
<b>ABC</b>	Abacavir
<b>AIDS</b>	Acquired Immunodeficiency Syndrome
<b>ALT</b>	Alanine Aminotransferase
<b>ANC</b>	Antenatal Clinic
<b>ART</b>	Antiretroviral Therapy
<b>ARV</b>	Antiretroviral
<b>AST</b>	Aspartate Aminotransferase
<b>ATV</b>	Atazanavir
<b>AZT</b>	Zidovudine (Also known as ZDV)
<b>CBT</b>	Community-based Testing
<b>CD4</b>	Cluster of Differentiation 4
<b>CHW</b>	Community Health Workers
<b>CITC</b>	Client-initiated Testing and Counselling
<b>CLIA</b>	Chemiluminescence Immunoassay
<b>CMV</b>	Cytomegalovirus
<b>CNS</b>	Central Nervous System
<b>CPT</b>	Cotrimoxazole Preventive Therapy
<b>CXR</b>	Chest X-Ray
<b>DAA</b>	Direct Acting Antiviral Drug
<b>DBS</b>	Dried Blood Spot
<b>DNA</b>	Deoxyribonucleic Acid
<b>DOT</b>	Directly Observed Therapy
<b>DRV</b>	Darunavir
<b>DTG</b>	Dolutegravir
<b>ECL</b>	Electrochemiluminescence Immunoassay
<b>ECP</b>	Emergency Contraceptive Pills
<b>EFV</b>	Efavirenz
<b>EIA</b>	Enzyme Immunoassay

<b>EID</b>	Early Infant Diagnosis
<b>EPTB</b>	Extrapulmonary Tuberculosis
<b>EQA</b>	External Quality Assessment
<b>eVT</b>	elimination of Vertical Transmission
<b>FBC</b>	Full Blood Count
<b>FBT</b>	Facility-based Testing
<b>FDC</b>	Fixed-Dose Combination
<b>FSW</b>	Female Sex Worker(s)
<b>FTC</b>	Emtricitabine
<b>GI</b>	Gastrointestinal
<b>Hb</b>	Haemoglobin
<b>HBV</b>	Hepatitis B Virus
<b>HCV</b>	Hepatitis C Virus
<b>HIV</b>	Human Immunodeficiency Virus
<b>HIVDR</b>	HIV Drug Resistance
<b>HIVRNA</b>	Human Immunodeficiency Virus Ribonucleic Acid
<b>HIVST</b>	HIV self-testing
<b>HSV</b>	Herpes Simplex Virus
<b>HTS</b>	HIV testing services
<b>IDV</b>	Indinavir
<b>INH</b>	Isoniazid
<b>IPT</b>	Isoniazid Preventive Therapy
<b>IRIS</b>	Immune Reconstitution Inflammatory Syndrome
<b>IVD</b>	In Vitro Diagnostic
<b>KP</b>	Key Populations
<b>LPV</b>	Lopinavir
<b>LPV/r</b>	Lopinavir/Ritonavir
<b>LTC</b>	linkage to care
<b>M&amp;E</b>	Monitoring and Evaluation
<b>MCH</b>	Maternal and Child Health
<b>MSM</b>	Men Who Have Sex With Men
<b>MSW</b>	Male Sex Worker

<b>MTCT</b>	<b>Mother–To–Child Transmission (Of HIV)</b>
<b>NAT</b>	<b>Nucleic Acid Testing</b>
<b>NCASC</b>	<b>National Centre for AIDS and STI Control</b>
<b>NNRTI</b>	<b>Non-Nucleoside Reverse Transcriptase Inhibitor</b>
<b>NPHL</b>	<b>National Public Health Laboratory</b>
<b>NRTI</b>	<b>Nucleoside Reverse Transcriptase Inhibitor</b>
<b>NSAIDS</b>	<b>Non-Steroid Anti-Inflammatory Drugs</b>
<b>NSEP</b>	<b>Needle and Syringe Exchange Programme</b>
<b>NVP</b>	<b>Nevirapine</b>
<b>OCP</b>	<b>Oral Contraceptive Pills</b>
<b>OI</b>	<b>Opportunistic Infections</b>
<b>OST</b>	<b>Opioid Substitution Therapy</b>
<b>PCP</b>	<b>Pneumocystis Jiroveci Pneumonia</b>
<b>PCR</b>	<b>Polymerase Chain Reaction</b>
<b>PEP</b>	<b>Post-Exposure Prophylaxis</b>
<b>PGL</b>	<b>Persistent Generalized Lymphadenopathy</b>
<b>PHC</b>	<b>Primary Health Care</b>
<b>PI</b>	<b>Protease Inhibitor</b>
<b>PITC</b>	<b>Provider-Initiated Testing and Counselling</b>
<b>PLHIV</b>	<b>People Living With HIV</b>
<b>PMTCT</b>	<b>Prevention of Mother–To–Child Transmission (see eVT)</b>
<b>PoC</b>	<b>Point-of-Care</b>
<b>PQ</b>	<b>Pre-qualification</b>
<b>PrEP</b>	<b>Pre-Exposure Prophylaxis</b>
<b>PWID</b>	<b>People Who Inject Drugs</b>
<b>QA</b>	<b>Quality Assurance</b>
<b>QC</b>	<b>Quality Control</b>
<b>QI</b>	<b>Quality Improvement</b>
<b>r</b>	<b>Low-Dose Ritonavir</b>
<b>RAL</b>	<b>Raltegravir</b>
<b>RBV</b>	<b>Ribavirin</b>
<b>RDT</b>	<b>Rapid Diagnostic Test</b>

<b>RNA</b>	Ribonucleic Acid
<b>RT</b>	Reverse Transcriptase
<b>RTI</b>	Reverse Transcriptase Inhibitor
<b>RTV</b>	Ritonavir
<b>SJS</b>	Stevens-Johnson Syndrome
<b>SoP</b>	Standard Operating Procedure
<b>SQV</b>	Saquinavir
<b>STI</b>	Sexually Transmitted Infections
<b>TB</b>	Tuberculosis
<b>TDF</b>	Tenofovir Disoproxil Fumarate
<b>TEN</b>	Toxic Epidermal Necrolysis
<b>TG</b>	Transgender
<b>TI</b>	Targeted Intervention
<b>TLC</b>	Total Lymphocyte Count
<b>TWG</b>	Technical Working Group
<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>VL</b>	Viral Load
<b>VMMC</b>	Voluntary Medical Male Circumcision
<b>WAB</b>	Working Ambulatory Bedridden
<b>WB</b>	Western blot
<b>WHO</b>	World Health Organization



## 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.

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

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

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

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

**ART** (antiretroviral therapy) refers to the use of a combination of three or more ARV drugs for treating 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:** 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 care** 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. Examples of these services include combination HIV prevention, including PrEP; HIV testing and linkage to care; managing OIs and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care.

**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 during pregnancy and breastfeeding.

**External quality assessment (EQA):** inter-laboratory 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 diagnostics. An HIV status is similar to HIV diagnosis. It refers to reports of HIV positive, HIV negative or HIV inconclusive, whereas HIV diagnosis generally refers to HIV positive diagnoses and in some cases HIV negative diagnoses.

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

**Index testing:** a focused approach in which the household and family members (including children) of people diagnosed with HIV are offered HIV testing services; also referred to as index case HIV testing.

**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 TB, 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 (1) men who have sex with men, (2) people who inject drugs, (3) sex workers and transgender people.

**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 supports 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 HIV diagnosis and ending with enrolment in care or treatment.

**Negative predictive value:** the probability that a person with a negative test result is not infected with HIV, that is “true negative”.

**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.

**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 of 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.

**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.

**Positive predictive value:** the probability that a person with a positive test result is infected with HIV, that is “true positive”.

**Public health approach:** A public health approach addresses the health needs of a population or the collective health status of the people, rather than focusing primarily on managing individual cases. This approach aims to ensure the widest possible access to high quality services and medicines at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings.

**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.

**Quality improvement (QI):** an approach to the study and improvement of the processes of providing health-care services to meet clients’ needs.

**Quality management system:** a systematic, process-oriented approach to meeting quality objectives.

**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 who is enrolled in HIV care routinely attends these 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) 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 (HIVST):** 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. How individuals define their relationships will vary according to their cultural and social contexts. Serodiscordant couples should not limit to men–women couples, but also include non-heteronormative couples/partners (men-men or men-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 EIAs, CLIAs, 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.

**Use of ARV drugs for HIV prevention** refers to the HIV prevention benefits of ARV drugs and includes ARV drugs for the elimination of vertical transmission of HIV, ARV drugs to reduce the transmission of HIV to serodiscordant sex partners and ARV drugs to prevent the acquisition of HIV when a person is exposed (PEP and PrEP).

**Viral suppression** refers to a viral load below the detection threshold using viral assays.

**Viral failure** refers to the inability to achieve or maintain viral suppression below a certain threshold. Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of using ART.

**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.

# EXECUTIVE SUMMARY

## Background

In Nepal an HIV case was first detected in 1988. The prevalence of HIV in adults is 0.17 percent in 2016. The National Centre for AIDS and STD Control (NCASC) has taken the lead role in lowering the rate of HIV infections throughout Nepal. HIV prevalence has reduced significantly during the last decade due to effective targeted interventions among key populations and greater enrolment in treatment. The NCASC, with technical assistance of key stakeholders, has been able to follow the “test and treat approach” to reach the global target (90-90-90).

## Objectives

1. To provide comprehensive evidence-based recommendations for HIV Testing Services (HTS), including community-based testing by lay providers, with a view to moving towards the first 90 of 90-90-90 in the country;
2. To revise the National HIV testing algorithms and provide guidance on a mix of HTS approaches;
3. To provide evidence-based recommendations following a public health approach (in view of the revised WHO Consolidated Guidelines on Antiretroviral Therapy [ART], July 2016) for the delivery of ART and monitoring patients on ART in general population and specific population groups like pregnant women, children, HIV-TB coinfecting patients, People Who Inject Drugs (PWID), Female Sex Workers (FSW), Men Who Have Sex With Men (MSM), Male Sex Workers (MSW), Transgender (TG) people, migrants, etc;
4. To provide guidance on the use of potent less toxic, more efficacious first-line, second-line and third-line ART regimens and managing HIV in special situations;
5. To provide guidance on use of Pre-Exposure Prophylaxis (PrEP) as an additional prevention choice for people at substantial risk of acquiring HIV; and
6. To provide guidance on various operational issues like retention in care, adherence, differentiated care model and cascade monitoring with a view to achieving 90-90-90 by 2020.

## Rationale for Revising the Guidelines

In order to achieve optimal treatment outcomes, it is necessary to follow standardized treatment protocols and ensure highest levels of adherence to treatment (> 95%) and to periodically update them based on emerging evidence.

Since the formulation of the first ART guideline in the country in 2006, a number of new

developments have occurred in the field of HIV. The 2013 WHO Consolidated Guidelines on the Use of ART for Preventing and Treating HIV Infection followed a public health approach. The aims of the guideline are to ensure universal access to ART, use of fixed drug combinations, strategic and rational use of medicines, and to optimize existing health care systems to ensure long-term sustainability of HIV treatment activities. The guidelines clearly state that “implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost-effectiveness issues.” The national ART guidelines for the country were revised in March 2014 in line with the 2013 WHO guidelines. Based on evidence from recent studies (African Temprano and START and other large observational studies), WHO revised the consolidated guidelines on “The Use of ARV Drugs for Treating and Preventing HIV Infection, Recommendation for a Public Health Approach” in 2016. The current revision of the 2014 national guidelines is based on evidence in the 2016 WHO guidelines and recommendations of the Technical Working Group (TWG) meetings, held in September 2016, and the National Workshop on Revision of Guidelines, held in December 2016.

## Target Audience for the Guidelines

The target audiences for the guidelines are the national AIDS programme managers, partners involved in HIV care and treatment services, and organizations providing technical and financial support to HIV care and treatment programmes in Nepal. This document will also be of immense help to clinicians who take care of HIV patients, whether in public, private or NGO sector. The document will also guide the national HIV programme managers and other senior policymakers who are involved at the policy planning level for necessary logistic, infrastructure, human resources (HR) and funding-related issues.

## Process of Guidelines Development

An HIV TWG meeting was held in September 2016 and a core committee was formed for reviewing and revising the National Consolidated Guideline for Treating and Preventing HIV in Nepal 2014. After finalizing the revised guidelines, a clinical symposium was organized with district- and national-level experts and WHO experts in HIV to come up with a consensus on the content of the guidelines.

# SUMMARY OF KEY RECOMMENDATIONS

## On HIV Testing Services (HTS)

1. Follow the 5Cs (consent, confidentiality, counselling, correct test results, and immediate connection to services) in all settings, facility-based as well as community-based.
2. Verbal consent is sufficient; provide pre-test information and detailed post-test counselling for positives and those at high risk; age of consent is 16 years.
3. Use Rapid Diagnostic Test (RDT) kits at all HTS sites.
4. Implement HIV self-testing, finalize QA mechanism and obtain regulatory approvals.
5. Phase in community-led testing, done by lay providers, in different regions and roll them out.
6. Adopt Nucleic Acid Testing (NAT) at birth in addition to 6-week testing and carry out re-tests at 6 weeks for negatives. Initiate ART after the first reactive polymerase chain reaction (PCR) and confirm it with a second PCR.
7. Follow the 3-test strategy by a national algorithm.
8. Carry out re-testing before ART initiation.
9. Establish linkage to appropriate care and treatment or preventive service to be part of HTS.



## On ART

### When to start ART

Issue	Situation criteria/definitions
<b>When to start ART</b>	
Adults and adolescents (10–19 years)	Any HIV positive individuals, irrespective of CD4 count or clinical stage, as soon as found positive
Pregnant and breastfeeding women	All pregnant and breastfeeding women with any CD4 count, irrespective of duration of pregnancy and continued lifelong (option B+)
Infants and children (< 10 years)	All HIV-infected children, irrespective of CD4 count
<b>Monitoring ART</b>	
Baseline tests	Hb, Alanine Aminotransferase (ALT), Urea, Hbs Ag, Anti-HCV, X-ray chest, CD4 count, gene expert, where required
Clinical monitoring	On every visit, weight, clinical stage, Working Ambulatory Bedridden (WAB) scoring and adherence monitoring
Laboratory monitoring	During ART, viral load every 6 months and 12 months after ART initiation and thereafter every 12 months. CD4 count every 6 months, urine for albuminuria and creatinine for TDF, Hb for Zidovudine (AZT), ALT for NVP
<b>Detecting treatment failure</b>	
Failure of ART	New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) <sup>a</sup> after six months of effective treatment Virological failure: Plasma viral load above 1000 copies/ml
Switching ART	No drug should be changed or added to a failing regimen. The new regimen should have minimum of three active drugs, one of them drawn from at least one new class. The Protease Inhibitor (PI) class is reserved for the second-line treatment and ritonavir-boosted protease inhibitors (RTV-PIs) are to be preferred

*a Refer to Annex 1*

# HIV TESTING SERVICES, INCLUDING LABORATORY DIAGNOSIS



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# 1. HIV TESTING SERVICES, INCLUDING LABORATORY DIAGNOSIS

## 1.1 Introduction

The 'Identify, Reach, Recommend, Test, Treat and Retain' (IRRTTR) strategy is central to Nepal's National HIV Strategic Plan (NHSP) 2016–2021. 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.' Those who are not tested HIV-infected will be linked to appropriate services to prevent HIV infection and those who use drugs to harm reduction services and encouraged to take retesting at a later time. HTS in Nepal follows the standard guiding principles (see Box 1.1)

### Box 1.1 HIV Testing Services in Nepal: Guiding Principles

HIV Testing Services are an essential part of the case finding/case management continuum of "Identify, Reach, Recommend, Test, Treat and Retain" (IRRTTR). Services have to adhere to five Cs: consent, confidentiality, counselling, correct test results and immediate connection to services for HIV prevention, treatment and care:

**Consent:** 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. Exception is blood or organ donation. Verbal consent is usually adequate, but all individuals should have a private opportunity to refuse testing. Mandatory testing is never warranted.

**Confidentiality:** All collected information 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 others trusted, is often highly beneficial.

**Counselling:** Services must be accompanied by appropriate and good quality pre-test information and post-test counselling. All people should be given 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. People who test HIV negative will usually need only brief health information about their HIV status report, how to prevent acquisition of HIV in the future and where and how to link to HIV prevention services, as appropriate. People with significant ongoing risk may need more active support and linkage to HIV prevention services. Everyone who is diagnosed HIV positive, including couples where one or both are diagnosed HIV positive, should receive post-test counselling.

**Correct:** QA mechanisms (both internal and external measures) should ensure that people receive a correct diagnosis. Quality assurance mechanisms and supportive supervision and mentoring systems need to be in place to ensure the provision of high-quality testing and counselling. People whose test results are not yet confirmed or whose HIV status is reported as inconclusive need follow-up services to ensure that they receive a correct HIV diagnosis.

**Connection:** All HIV services should have linkage to prevention, care and treatment services. All HIV positive clients should be linked to treatment and care without delay. Those with negative result should also be connected to prevention services-OST, needle syringe exchange, behaviour change counselling, etc.

## 1.2 Models of HIV Testing Services (HTS)

Diverse models of HTS are available in Nepal to increase access to HIV diagnosis, including testing services in healthcare facilities and at stand-alone sites, as well as through a range of community-based approaches. The national programme plans to follow a mix of facility-based testing (FBT) and community-based testing (CBT) approaches for greater reach and detection of maximum number of persons with HIV and at the earliest stage of infection. This approach will help reduce the travel and waiting time, as well as the expenses incurred in reaching the FBT. The FBT takes place in a health facility, whereas the CBT is available in the community. Community-based HTS includes a number of approaches: door-to-door/home-based testing, mobile outreach to parks, bars and testing at the workplace. Testing at targeted intervention (TI) drop-in centre is considered facility-based HTS.

**The age of consent for HIV testing in the country is 16 years**

### 1.2.1 Facility-based HIV testing services

Facility-based HTS are available either at general health service sites or at stand-alone sites for HIV testing. These health facilities follow two approaches: client-initiated testing and counselling (CITC) and provider-initiated testing and counselling (PITC). Both approaches are voluntary, where the client gives verbal consent for HIV testing. Facility-based services are provided by the government and NGOs.

CITC is recommended for clients who voluntarily report to the health facility for testing for HIV.

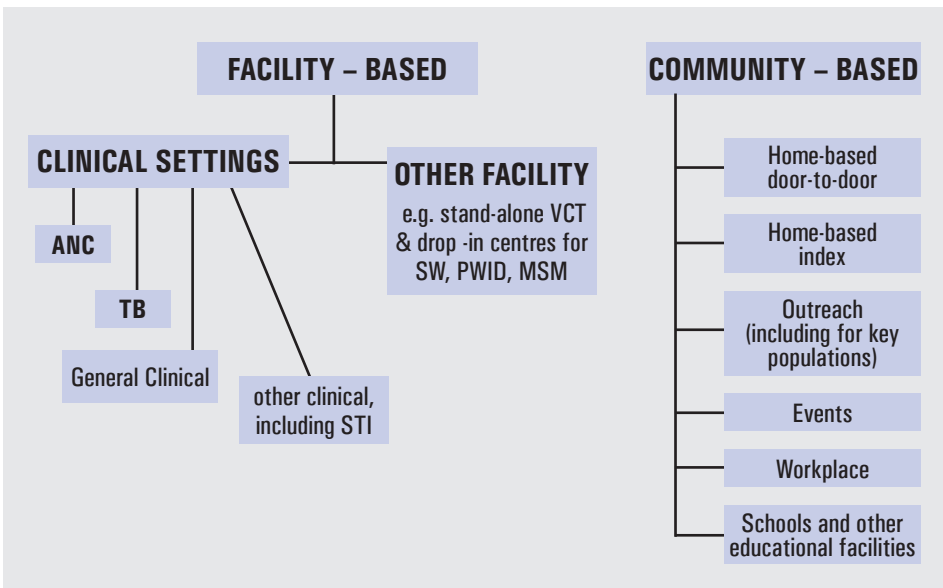


Figure 1.1. Comparison between facility-based and community-based HIV testing services

PITC is recommended for adults, adolescents and children with signs and symptoms or medical conditions that indicate possible HIV infection, including TB; HIV-exposed children and symptomatic infants and children, including malnourished children; people with sexually transmitted infections (STI), people with hepatitis; all pregnant women attending antenatal care settings; key populations (KP), notably men who have sex with men (MSM), transgender (TG), sex workers, people who use drugs with a history or current injecting practices; people enrolled in Opioid Substitution Therapy (OST); migrant workers and their spouses with history of possible unsafe exposures; people in prison; and all others deemed at high risk of HIV. For PITC, the informed consent of client is mandatory for performing the HIV test. However, mandatory HIV testing is not recommended.

At FBT centres, the national algorithm shall be followed by trained personnel.

## **Guidelines on providing pre-test information and post-test counselling as part of HTS**

### **Pre-test information**

Pre-test information can be provided in group and without individual risk assessment. If the client requests, individual counselling should be offered. Client's consent should be taken individually and he/she should be provided with opportunities to ask questions in private.

Pre-test information should include the following:

- Benefits of HIV testing;
- Meaning of HIV positive and HIV negative diagnosis;
- Services available for HIV positive diagnosis, including where Antiretroviral Therapy (ART) is provided;
- Brief description of prevention options and encouragement of partner testing;
- The fact that the test result and any information shared by the client are kept confidential;
- The fact that the client has the right to refuse to be tested and that declining the test will not affect her/his access to HIV-related services or general medical care;
- Potential risks of testing in settings where there are legal implications for those who test positive and/or for those whose sexual and/or other behaviour is prejudiced;
- Opportunity to ask the provider questions;
- Special considerations for pregnant women; and
- HIV TB linkages-intensified case finding.

## Post-test counselling

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

### Post-test counselling for those with HIV negative result

Post-test counselling should be provided as follows:

- Explanation of the test result and reported HIV status;
- Education on methods to prevent HIV acquisition and provision of male and female condoms, lubricant and guidance on their use;
- Emphasis on the importance of knowing the status of sexual partner(s) and information about the availability of partner and couples testing services;
- Referral and linkage to relevant HIV prevention services, OST, needle and syringe exchange services, Post- Exposure Prophylaxis (PEP), Pre-Exposure Prophylaxis (PrEP) for people at substantial ongoing HIV risk, including those in serodiscordant relationships and men who have sex with men, safe conception and family planning;
- Recommendation on re-testing based on client's level of recent exposure and/or ongoing risk of exposure.

### Post-test counselling for those with HIV positive results

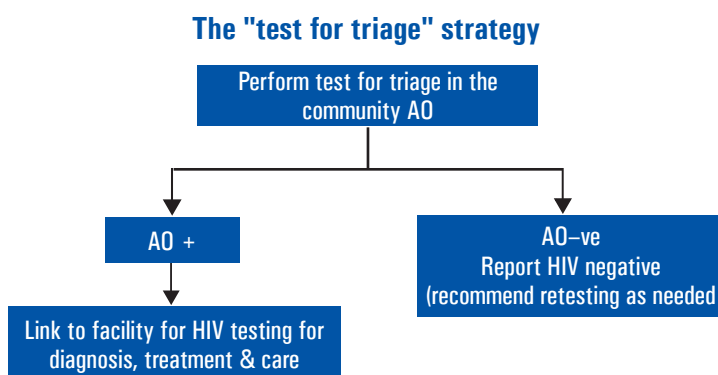
Post-test counselling should be provided as follows:

- Explanation of the test results and diagnosis;
- Giving the client time to consider the results and helping her/him to cope with the emotions arising from the diagnosis of HIV infection;
- Discussion of immediate concerns with the client and helping her/him decide who in her/his social network may be available to provide immediate support;
- Assessment of the risk of suicide, depression, and other mental health consequences of diagnosis of HIV infection;
- Providing clear information on ART and its benefits for maintaining health and reducing the risk of HIV transmission, as well as where and how to obtain ART;
- Providing information on how to prevent transmission of HIV, including information of the reduced transmission risk when virally suppressed on ART;
- Providing male or female condoms and lubricants and guidance on their use;
- Encouraging and offering HIV testing for sex partners, children and other family members of the client. This can be done individually, through couples testing, index testing or partner notification.

- Providing additional referrals for prevention, counselling, support and other services as appropriate (for example TB diagnosis and treatment, prophylaxis for Opportunistic Infections (OIs), STI screening and treatment, contraception, antenatal care, OST, access to sterile needles and syringes, and brief sexuality counselling).

## 1.2.2 Community-Led HIV Testing Services (CL-HTS)

The NHSP 2016–2021 has endorsed, community-led HIV testing (CL-HTS) as part of the CBT following the 'test for triage' strategy for screening and referral approach. Nepal will phase in 'test for triage' as it has been found to be highly successful in many countries and settings, and has been associated with higher HIV testing among KP for early detection, through in-reach by members of KP themselves.



*Figure 1.2. The Test for Triage strategy*

The objective of CL-HTS is to contribute to national targets for HIV testing by involving communities through 'in-reach'. In CL-HTS, the organizing and managing of community testing sites, conducting of pre- and post-test services, and rapid diagnostic testing are performed by trained members of the KP.

At least three observational studies have shown that the lay provider results and laboratory staff test results were concordant in nearly all cases. In two observational studies comparing lay provider and laboratory staff test results, sensitivity was calculated as 98.0% (95% CI: 96.3–98.9%) and 99.6%, and specificity was calculated as 99.6% (95% CI: 99.4–99.7%) and 100.0%.

Lay providers conduct a single HIV rapid diagnostic test (RDT) referred as AO (Assay O) in the Test for Triage strategy. According to the Test for Triage algorithm, clients with reactive test results, through this HIV screening, will be referred and accompanied to health facilities, where confirmatory testing will be performed by trained laboratory personnel, according to the national algorithm. CL-HTS can be performed in both facility and community settings.

Recording and reporting of such screening will be done as per the national standards

and guidelines. All community testing services sites will participate in external quality assurance mechanism conducted by the National Public Health Laboratory (NPHL). National Centre for AIDS and STD Control (NCASC) will develop a training package and protocol for community-led testing.

### 1.2.3 Other innovative testing approaches for HIV testing

#### Self-testing for HIV (HIVST)

**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 some he/she trusts.

HIV self-testing is an empowering and innovative way to reach more people with HIV and help achieve the first of the United Nations' 90–90–90 targets—for 90% of all people with HIV to know their status by 2020. Expanded use of HIVST can contribute to these global targets by reaching the first-time testers, people with undiagnosed HIV or those at ongoing risk who need frequent retesting. HIVST reduces the number of visits to facilities for frequent testers, and eliminating travel distances or wait in long queue to access HIV testing, HIVST may be more convenient for users.

The result of a single RDT is not sufficient for HIV positive diagnosis. HIVST requires self-testers with a reactive (positive) result to receive further testing from a trained provider using a validated national testing algorithm. All self-testers with a non-reactive test result should re-test for exposure to HIV in the preceding six weeks or if they are at high HIV risk. HIVST is not recommended for people taking antiretroviral drugs as this may cause a false non-reactive result. The following requirements are needed for implementing HIVST:

- **Quality assured products.** Any HIV RDT for self-testing, either oral or blood, which is procured or used for HIVST, should be approved by a relevant regulatory authority or an international regulatory review.
- **Policy and regulatory frameworks.** Adapt, develop and harmonize existing national policies on HIV testing to incorporate HIVST, such as:
  - Laws permitting the sale, distribution, advertisement and use of quality assured RDTs for HIVST;
  - Age of consent for self-test;
  - Human rights laws, policies and regulations to protect individuals and address misuse of HIVST, if and when it occurs;
  - Quality assurance and post-market surveillance systems for RDTs.

The national programme will work further to develop these guidelines and get regulatory approvals at the earliest. The country will also test other innovative approaches to increase HIV testing, which includes the use of mobile technologies, using standard computer applications, etc.



## 1.3 HIV Testing Services in Specific Populations and Settings

### 1.3.1 Couple/Partner

Couple/partner testing and counselling can identify seroconcordant couples who can be linked to services for HIV prevention and treatment. Such HTS need to be offered to married and cohabiting couples, premarital couples and other sex partners. When found positive, mutual disclosure needs to be encouraged. Service providers must be aware of potential intimate partner-based aggression and violence and need to support individuals who do not want to test with their partners and/or do not agree to mutual disclosure. Such clients can be encouraged and HIV testing offered for sex partners, children and other family members, which can be done individually, through couple testing, index case testing, family testing or partner notification, intimate partner notification by provider, with permission, if feasible.

### 1.3.2 Pregnant and postpartum women

Provider-initiated testing and counselling for pregnant women needs to be offered in every antenatal care setting, both public and private, as part of the eVT programme to eliminate vertical transmission of HIV and to keep mothers alive and well. Linkages to services to prevent HIV and offer care and support are essential. At antenatal care settings, group pre-test counselling can be offered, while post-test counselling should be individual. Antenatal screening of HIV should be coupled with testing for other STI such as syphilis and Hepatitis B. If any postpartum woman was not screened for HIV during her antenatal period, immediate postpartum screening for HIV needs to be performed. Partner testing is highly recommended when a pregnant or postpartum woman is found positive. If applicable, screening of other children within the family for HIV should be conducted.

### 1.3.3 Infants and children

A summary of recommended testing approaches for early infant diagnosis (EID) is provided in Table 1.1. Polymerase Chain Reaction (PCR) testing is recommended for all HIV-exposed children at birth, at 6th week, and later with antibody testing. Older children who are malnourished, are suffering from TB, or have other signs or symptoms of OIs should also be offered testing as part of PITC.

Adolescent children need to be informed of their HIV positive status and their parents' or caregivers' status, if appropriate. Younger children should be told about their status incrementally to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure.

RDTs for HIV serology can be used to assess HIV exposure only in infants less than 4 months of age. HIV exposure status in infants 4–18 months can be done by serological

testing in the mother. RDT for HIV serology can be used at 9th month to rule out HIV infection in asymptomatic HIV-exposed infants. RDT for HIV serology can be used to diagnose HIV infection in children older than 18 months.

**Table 1.1. Summary of recommended testing approaches for infants**

Category	Test required	Purpose	Action to be taken
<b>Well, HIV-exposed infant</b>	Virological testing at birth and then at 6 weeks of age	To diagnose HIV	Start ART if HIV-infected
<b>Infant–unknown HIV exposure (4–18 months of age)</b>	Maternal HIV serological test or infant HIV serological test	To identify or confirm HIV exposure	Need virological test if HIV-exposed
<b>Well, HIV-exposed infant at 9 months</b>	HIV serological test	To identify infants who have persisting HIV antibodies or have sero-reverted	Those HIV seropositive need virological test and continued follow up; those HIV negative, assume uninfected, repeat testing required if still breastfeeding
<b>Infant or child with signs and symptoms suggestive of HIV infection</b>	HIV serological test	To confirm exposure	Perform virological test if < 18 months of age; presumptive treatment of HIV can be considered.
<b>Well or sick child seropositive &gt; 9 months and &lt; 18 months</b>	Virological testing	To diagnose HIV	PCR positive – start HIV care and ART
<b>HIV-exposed children more than 18 months of age</b>	HIV serological test	To diagnose HIV if breastfeeding has been stopped	If HIV positive start ART at earliest
<b>Infant or child who has completely discontinued breastfeeding</b>	Repeat testing six weeks or more after breastfeeding cessation – usually initial HIV serological testing followed by virological testing for HIV positive child and < 18 months of age	To exclude HIV infection after exposure ceases	Infected infants and children < 5 years of age, start ART at earliest

### 1.3.4 Adolescents

Adolescents—those who are between 10 and 19 years of age—are considered as a vulnerable group in Nepal. They can acquire HIV infection through vertical or horizontal transmission. As with adults, horizontal HIV transmission can occur through sexual and through parenteral transmission, such as by injecting drugs. Adolescents living with HIV who have not been diagnosed and thus are not on treatment, can be long-term surviving slow progressers of vertical transmission. HTS for adolescents offers many important benefits. Adolescents who learn that they have been diagnosed with HIV are more likely to obtain emotional support and practise preventive behaviours to reduce the risk of transmitting HIV to others, and are more likely to receive HIV treatment and care. Access

to HTS is also important for those adolescents who are not HIV positive, to reinforce prevention messages, and facilitate access to services and commodities to prevent HIV.

Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV status and be empowered and supported to determine if, when, how, and to whom to disclose. It is important to emphasize how to address the adolescent issues to healthcare workers during their training in HTS. Facilitating access to HTS and linkages to care for the following is critical: orphans and vulnerable adolescents, including those living on the street; adolescents in child-headed households, and particularly vulnerable adolescents from KP; girls and boys engaged in sex with older men and in multiple or concurrent sex partnerships; and adolescents affected by sexual exploitation.

In Nepal, adolescents above 16 years of age can give consent for HIV testing without parental permission. For adolescents younger than 16, parents or guardians or related institutions, and especially for adolescents from KP, older peers can give consent to receive HTS.

### 1.3.5 Specific populations

Recommendations for HIV testing services for KP and others who are vulnerable and at higher risk of HIV emphasize consent and confidentiality, as well as ensuring that HTS is part of the comprehensive prevention–treatment–care continuum of 'Identify, Reach, Recommend, Test, Treat and Retain', including their partner(s) counselling and testing.

**Table 1.2. HIV testing and counselling recommendations**

Who to test	When to test	Where to test
<b>People with signs or symptoms of HIV infection, including TB, Hepatitis patients, patients</b>	Integrate in healthcare encounter–provider-initiated HIV testing and counselling in health facilities, including through community in-reach	HTS centres, STI clinics, TB clinics, hospitals, Primary Health Care (PHC), health posts, other clinics, stand-alone clinics, OST sites and community settings
<b>Partners of people with HIV</b>	As soon as possible after partner diagnosis. For the negative person in Serodiscordant couples, offer re-testing every 6–12 months	HTS centres, TB clinics, STI clinics, hospitals, PHC, health posts, community-led HTS
<b>Families of index cases</b>	As soon as possible after the family member is diagnosed	HTS centres, community-led, including home-based, hospitals, PHC, health posts testing services
<b>KP: people who inject drugs, gay men and other men who have sex with men, transgender people and sex workers</b>	Every 3 months	HTS centres, STI clinics, community-led services for KP and harm-reduction services, hospitals, PHC, health posts
<b>Pregnant women</b>	At the first antenatal care visit–provider-initiated HIV testing and counselling	ANC settings, hospitals, PHC, health posts
<b>Migrant workers</b>	On their return to place of origin and before departure to destination. If any signs and symptoms of HIV infection	HTS centres, STI clinics, community-led services for KP

### 1.3.6 Blood donors

Primarily, donated blood units are screened for HIV according to national algorithms. Under specific emergency life-or-death conditions, mainly where fresh blood transfusion is required, blood donors are screened for HIV using a rapid HIV test. All blood donors are required to complete a donor screening questionnaire prior to donating blood. When the donated blood unit is found positive for HIV, it is discarded and the donor is referred for conducting confirmatory test and further management.

## 1.4 Laboratory Diagnosis of HIV Infection

### 1.4.1 Background

#### Introduction to Human Immunodeficiency Virus (HIV)

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).

- 1 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. Based on available data from ongoing study, HIV-1, subtype C is found dominant in Nepal.
- 2 HIV-2 is most often found in West Central Africa, parts of Europe and India. Few cases have been confirmed in Nepal. In case of suspicion of HIV-2, the laboratory (test site) should contact the NPHL for further investigations.

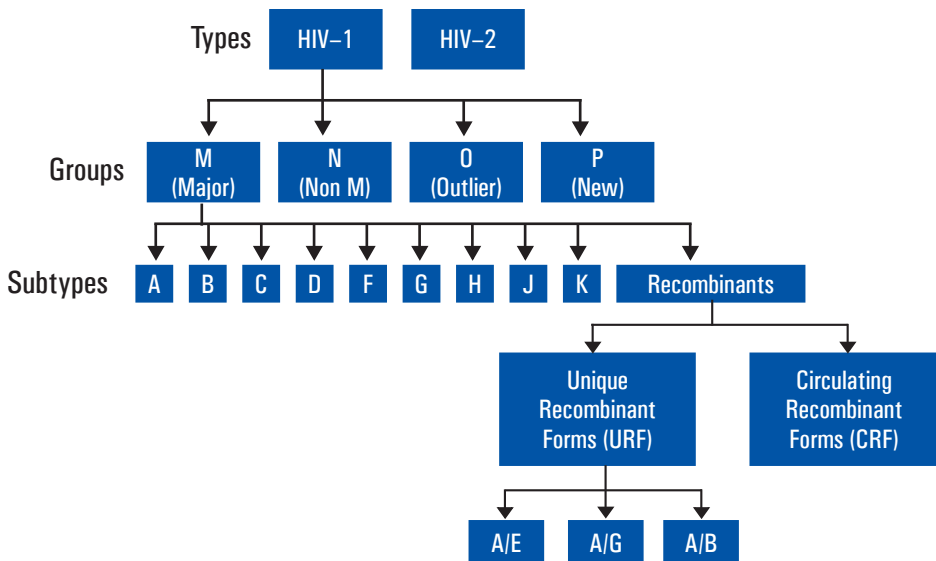


Figure 1.3. Types of Human Immunodeficiency Virus with groups and subtypes

The presence of HIV-1/2 infections in individuals can be ascertained only through the use of laboratory tests on body fluids such as blood, plasma, serum, oral fluid, vaginal fluid, etc. The laboratory confirmation of HIV infection is needed at different settings to ensure HIV status.

- Blood and blood products safety,
- Screening of donor's sperms, organs and tissues,
- Diagnosis of HIV infection in clinically suspected cases,
- HIV testing and counselling,
- HIV studies, research and surveys, and
- Antenatal care.

### 1.4.2 Overview of HIV diagnosis

For people over 18 months of age, HIV is typically diagnosed through detection of HIV antibodies (a serological marker) and/or HIV p24 antigen, rather than direct detection of the components of the virus itself (virological markers). For children below 18 months, direct detection of virus components, including antigen or nucleic acid, is needed.

- **Eclipse period:** The period refers to the period of about 10 days following HIV infection where no currently available serological or virological assay can detect any marker of HIV infection.
- **Window period:** The period between HIV infection and detection of HIV-1/2 antibodies using serological assays. This signals the end of the seroconversion period. The duration of the window period depends on three main factors: (1) the genetics of the virus, (2) the genetics and immunocompetence of the host, and (3) what exactly the assay detects (antigen, antibodies).
- **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 viremia. Although anti-HIV-1 antibodies are undetectable, HIV-1 RNA or p24 antigen is present.
- 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 (IA). After a week of detection of HIV antigen in blood, HIV antibodies appear in blood and antibody-based assay can detect HIV infection.
- Among RDTs, those using oral fluid specimens exhibit the longest window period, irrespective of their generation, may be because the concentration of HIV-1/2 antibodies is lower in oral fluid than in other specimen types.

## Days post infection

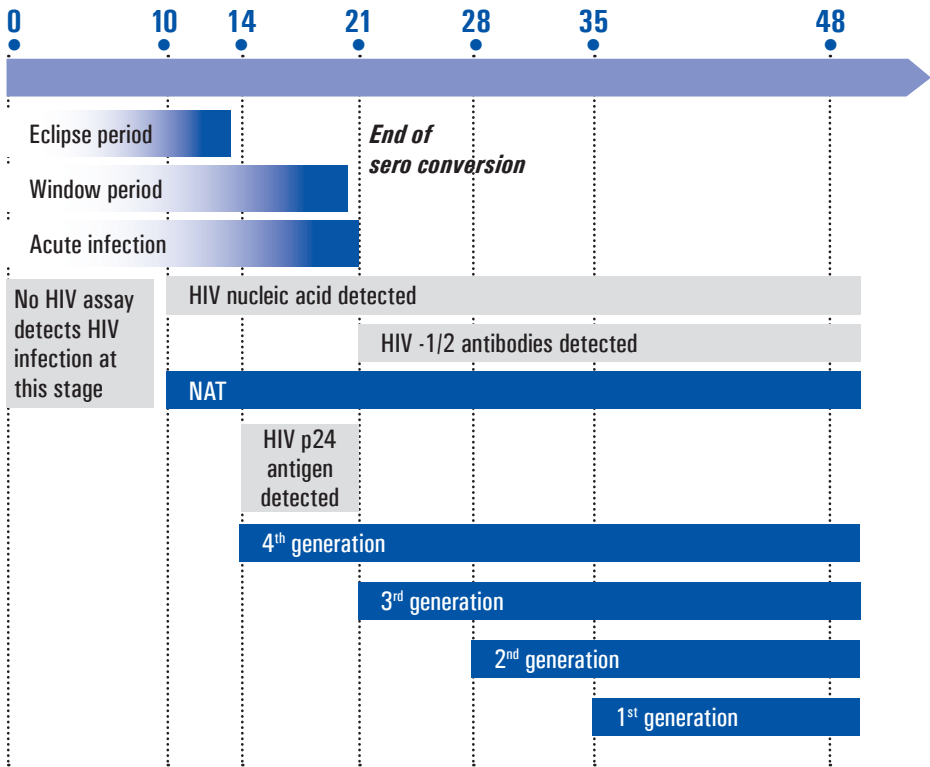


Figure 1.4. Detecting HIV-infection with various formats and generations of *in vitro* diagnostics over the natural history of infection

### 1.4.3 Types of HIV assays

Diagnosis of HIV infection can be carried out by detecting any of the following:

- Antibodies or antigen detection (rapid test, ELISA, Chemiluminescence Immunoassay (CLIA) and Western Blot),
- HIV nucleic acid detection (DNA/RNA PCR), and
- Fourth generation HIV assays.

**Table 1.3. Types of HIV assays**

Detection type	Assay type	Properties
Antibodies or antigen for HIV detection	Rapid HIV Tests	Rapid diagnostic tests (RDTs) are so called as they produce a test result quickly, usually in less than 30 minutes. RDTs are suited for use in both community- and facility-based settings, including sites with limited infrastructure that process low numbers of specimens daily.
	Simple assays	This type of HIV assay typically requires 30 minutes to 2 hours to produce results. These types of assays are more suited to laboratory- or facility-based testing than in the community, as cold chain storage of test kits and the use of precision pipettes are usually required.
	Immunoassays, including EIA, CLIA, ECLIA	Enzyme immunoassays (EIA), chemiluminescence immunoassays (CLIA) and electrochemiluminescence immunoassays (ECLIA) for HIV are laboratory-based techniques for detecting the presence of HIV-1/2 antibodies and/or HIV-1 p24 antigen. Generally, these assays are the most cost-effective to perform in laboratory settings with high specimen throughput (> 40 per day).
	Western Blot (WB)	Western blotting uses a blotting immunoassay technique to detect HIV-1 antibodies. It is based on capturing different antibodies present in the blood in a single test.
	HIV Antigen detection-p24 Antigen test	The antigen test detects the presence of the p24 protein of HIV in blood, the capsid protein of the virus.
HIV Nucleic acid detection HIV DNA PCR test	Nucleic acid testing (NAT)	Nucleic acid testing (NAT) utilizes molecular techniques that may be used qualitatively to assist the diagnosis of HIV infection and quantitatively to monitor the progression of HIV infection and the response to ART. They include NAT technologies that detect the presence of HIV viral nucleic acid (RNA, DNA) via techniques based on amplification of viral nucleic acids, such as polymerase chain reaction (PCR) and nucleic acid sequence-based amplification (NASBA), or on amplification of the bound probe signal, as in branched-DNA (bDNA) assays.
HIV antigen and antibody detection combo test	Fourth generation-based test	The fourth generation serological assays (RDTs, EIAs, CLIAs, ECLIAs) that detect both HIV p24 antigen and HIV-1/2 antibodies have the potential to identify infected individuals earlier in the course of disease. In other words, these assays greatly shorten the diagnostic window period (two weeks).

### 1.4.4 Testing algorithm for adults and adolescents (above 18 months of age)

An HIV testing algorithm describes the combination and sequence of specific assays used in a given HIV testing strategy. Testing strategy generically describes a testing sequence for a specific objective, taking into consideration the presumed HIV prevalence in the population being tested.

Nepal being an HIV low prevalence country, three-test HIV testing algorithm is adopted. Test kits selection for different line assay will be based on the WHO pre-qualification list, diagnostic sensitivity and specificity, antigens used and performance characters. However, kits included in the algorithm will be validated at NPHL.

The first assay will be the most sensitive and all HTC's shall use RDT only for all three tests. However, at some selected high load sites and at NPHL, the first test can be ELISA due to large number of samples. For the first test there are four options of RDTs and ELISA-based test kits. The second- and third-line assays will have only one choice as mentioned in the algorithm. The fourth generation test, western blot test and/or NAT can be used as supplemental test, if needed.

The first test used in a serial HIV testing algorithm should be highly sensitive so that all positive samples are identified as positive. The second and third tests should have higher specificity. The antigenic characters will be different in all third-line assays.

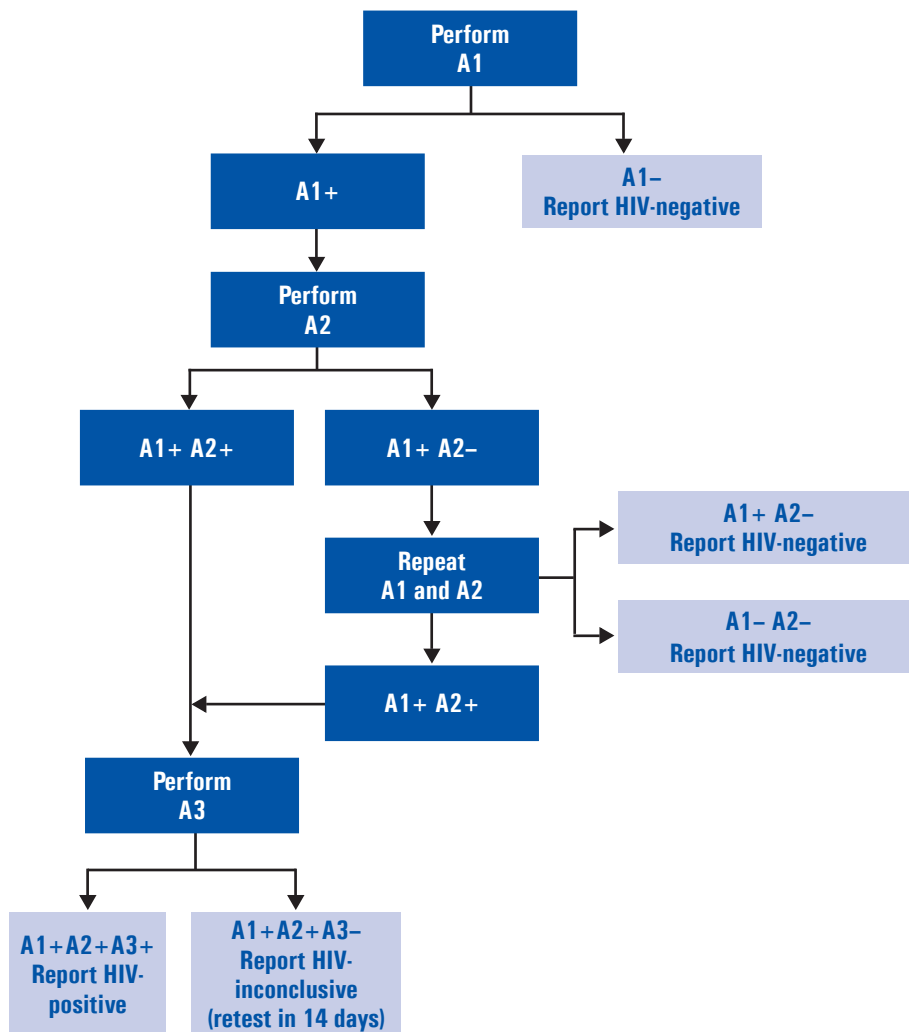
**Table 1.4. Test kits used in national algorithm**

Assay 1 (A1)	Assay 2 (A2)	Assay 3 (A3)
Determine HIV ½	Uni-Gold HIV ½	Stat pak HIV-1/2
SD Bioline HIV 1 and 2		
ABON HIV ½		
ELISA 1		
ELISA 2		

*Note: The above-mentioned RDTs and ELISA will be evaluated by NPHL for internal and external QA for test kits, as well as for test procedures, including post-marketing.*



The testing algorithm, shown in Figure 1.5, will be used for HIV testing by the national programme. The figure describes the sequence of assays and the number of tests to be performed. Assay 1 (A1), Assay 2 (A2) and Assay 3 (A3) should be three different serological assays that do not share the same false reactivity.



**Figure 1.5. National HIV testing algorithm (Three-test algorithm)**

- All specimens shall be first tested with A1, and specimens that are non-reactive (A1-) are considered HIV negative and reported as such. **A1 shall be the most sensitive assay available, taking into account diagnostic sensitivity, seroconversion sensitivity and analytical sensitivity.**
- Any specimens that are reactive on the first-line assay (A1+) shall be retested, using a separate and distinct second assay (A2) comprising a different antigen

preparation to avoid false cross-reactivity with A1. Specimens that are reactive on the first-line assay but nonreactive on the second-line assay (A1 +; A2 –) shall be repeated, using the same specimen with the same two assays.

- A specimen that remains reactive following repeat testing with the first assay but non-reactive on the second assay (A1 +; A2 –) is considered HIV negative and reported as HIV negative status.
- For specimens that are reactive on the first and second assays (A1 +; A2 +), a third separate and distinct assay (A3) shall be used to confirm the results and issue HIV positive diagnosis. If the third test result is also reactive (A1 +; A2 +; A3 +), the status is reported as HIV positive.

***Retesting to verify the HIV diagnosis should be performed prior to initiation of ART using same testing algorithm.***

- If the result of the third assay is non-reactive (A1 +; A2 +; A3 –), then the test result is discrepant and inconclusive HIV status should be reported. The client should be asked to return in 14 days for additional HIV testing.
- At sites where HIV diagnosis is done using ELISA test kits, the sensitivity and specificity of the kits should be similar to the rapid test kits used in the national HIV testing algorithm. The reactive sample from the first ELISA test should be confirmed, using the second and third assay test kits of the algorithm.

**Table 1.5. National HIV testing algorithm**

HIV Test	Assay 1 (A1)	Assay2 (A2)	Assay3 (A3)	HIV Status	Remarks
1	Non-reactive	No test needed	No test needed	Negative	
2	Reactive	<i>Non-reactive</i>	<i>No test needed</i>		<i>Repeat Assay 1 and Assay 2</i>
	Non-Reactive	Non-reactive	<i>No test needed</i>	Negative	
	Reactive	Non-reactive	<i>No test needed</i>	Negative	
3	Reactive	Reactive	Non-reactive	Inconclusive	<i>Repeat the test after 14 days</i>
4	Reactive	Reactive	Reactive	Positive	

### 1.4.5 Retesting to verify HIV status

“Retesting” refers to using the same testing algorithm on a second specimen from the same individual. “Supplemental testing” refers to further testing of the same specimens with additional assay(s) to obtain more information.

### 1.4.5.1 Retesting of individuals who test HIV negative

A vast majority of individuals do not require retesting to verify HIV negative status, particularly in the absence of any ongoing risk. However, it is important to accurately identify individuals who test HIV negative and may require retesting in certain circumstances.

Certain individuals who test HIV negative warrant retesting:

- people from key populations,
- people with a known HIV positive partner,
- people with known recent HIV exposure,
- people seen for diagnosis or treatment of STI,
- TB patients with a possible recent HIV exposure or who are at higher risk of HIV exposure,
- Outpatients with clinical conditions indicative of HIV infection, and
- Individuals taking PEP or PrEP.

### 1.4.5.2 Retesting clients with HIV inconclusive status

The clients with HIV inconclusive status should be retested in 14 days in order to:

- rule out seroconversion, if HIV reactivity evolves to concordant between A1 and A2, that is A1 +; A2+;
- rule out seroconversion, if HIV reactivity remains unchanged, with likely non-specific false-positive reaction for A1 and A3 (the negative predictive value for A2 will be very high);
- rule out specimen mix-up, particularly if a unique client identifier and consecutive specimen identifiers are not assigned; or
- rule out random error, either user/operator error or test device error;
- if the HIV status is the same upon retesting, then the individual or the specimen should be tested using nucleic acid-based molecular test (RNA/DNA PCR) to confirm the HIV status at a higher-level facility.

### 1.4.5.3. Retesting to verify HIV positive diagnosis prior to initiation of ART

To ensure that individuals are not needlessly placed on lifelong ART (with potential side-effects, waste of resources, psychological impact of misdiagnosis), WHO recommends that all individuals be retested to verify their HIV status prior to starting ART. Misdiagnosis, irrespective of its scale, is of critical importance. Any incorrect diagnosis, whether false positive or false negative, has deleterious personal and public health consequences, often with severe repercussions.

The “retesting” will be testing of a new specimen for each newly diagnosed individual, conducted by a different provider using the same testing algorithm, prior to initiation of ART.

The national programme, while accepting this recommendation, agrees that retesting will be done at an ART centre, and not at the HTC site.

### 1.4.6 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 antibodies in the newborn may not necessarily indicate primary infection. It may be due to the presence of passively transmitted anti-HIV antibodies from the mother to uninfected babies. These maternal antibodies may persist in the infant for as long as 18 months. Hence, virological assays such as HIV DNA–PCR or total nucleic acid-based assays represent the gold standard for diagnosing of HIV infection in children younger than 18 months. Some DNA assays support the use of Dried Blood Spot (DBS) samples, which have considerable advantage in settings where sample transportation and storage are problematic.

The following are the guiding principles of the National EID programme:

- Routine virological test of all HIV-exposed infants at birth and again at six weeks of age;
- Virological test prior to six weeks of age in any HIV-exposed infant with signs and symptoms suggestive of HIV infection or referred by ART clinician;
- Routine virological test of all HIV-exposed infants entering care at six weeks to nine months of age at their first health contact;
- Repeat virological test for the following situations:
- Any HIV-antibody-positive infant aged less than 18 months who develops signs and symptoms consistent with HIV infection;
- Children aged less than nine months who initially tested HIV negative by HIV DNA PCR testing while breastfeeding or within 3 months of last breastfeeding who have now stopped breastfeeding for more than 3 months;
- Children between 9 and 18 months of age who have completely stopped breastfeeding for more than 3 months and whose HIV antibody test is positive, using a rapid antibody assay; and
- To confirm any positive initial virological test.

#### 1.4.6.1 Diagnostic Algorithms for EID

- a. **Diagnosis at birth:** Samples from HIV-exposed infants will be collected within 48 hours (at the earliest after birth) in DBS. All infants with non-reactive DNA

PCR at birth will be retested at six weeks (as mentioned in the algorithm). Infants with the first reactive sample will be put on ART and another DNA PCR done to confirm the status.

- b. **Diagnosis of HIV in infants 6 weeks to 9 months of age:** When an HIV-exposed infant from 6 weeks to 9 months of age is brought to the health facility, a whole blood specimen or DBS is collected and sent for HIV DNA PCR at the NPHL. (Fig. 1.6)
- c. **Diagnosing HIV infection in babies 9–18 month of age:** When a baby 9–18 month of age is brought for HIV testing, collect blood for a rapid test and a DNA PCR test. Perform a rapid test first. If the rapid test is positive, then send the DBS specimen or the whole blood for a DNA PCR test. He/she may have maternal antibodies or may be HIV-infected. (Fig. 1.7)
- d. **Diagnosing HIV infection in breastfeeding infants:** If an infant is breastfeeding, it remains at risk of acquiring infection throughout the breastfeeding period, and, therefore, a negative virological test in an infant who is continuing to breastfeed does not rule out infection. Diagnostic testing in these situations should be conducted at least 3 months after complete cessation of breastfeeding.

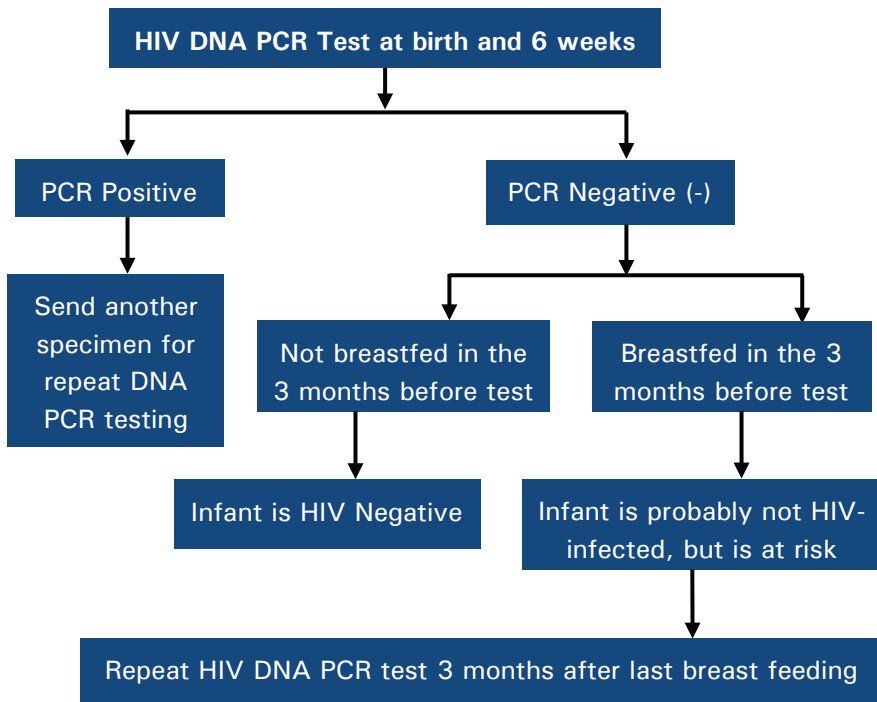


Figure 1.6, Algorithm for diagnosis of HIV exposed infants at birth and 6 weeks (6 weeks to < 9 months)

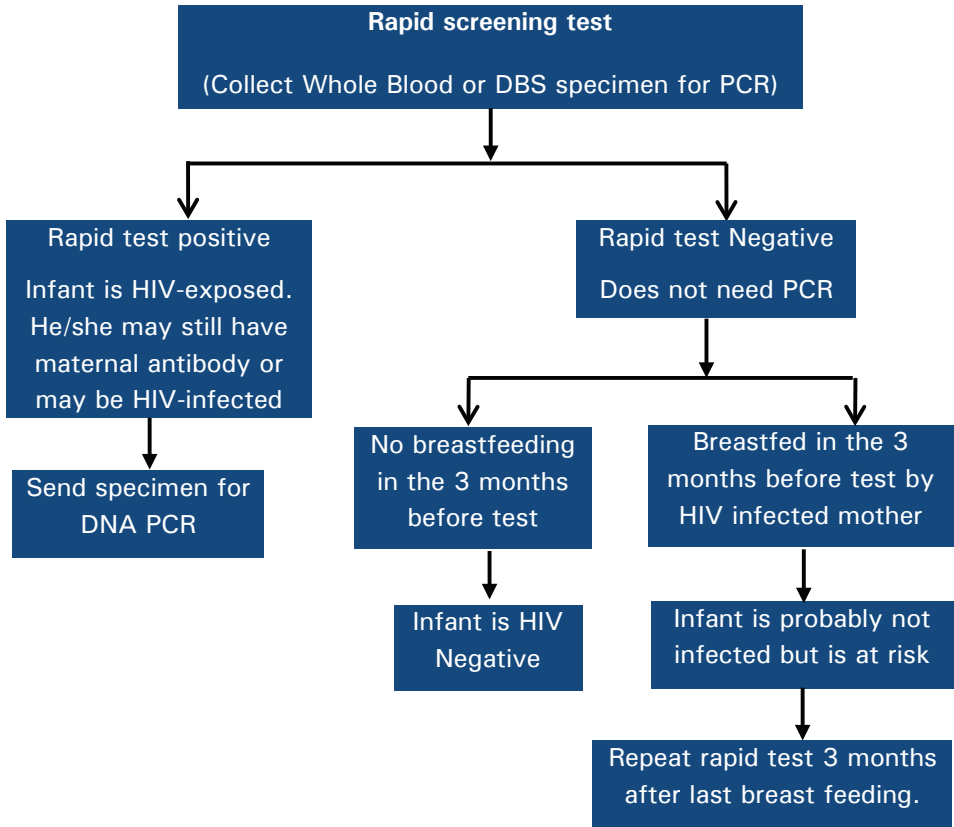


Figure 1.7. Diagnosing HIV infection in babies 9–18 month of age

If the initial DNA PCR test is positive, repeat the DNA PCR for confirmatory testing. All PCR positive children should have an antibody test at 18 months of age to confirm HIV positive status.

#### 1.4.6.2 Interpreting HIV test results for infants and children

##### a) Virological test (HIV DNA PCR)

- **Positive HIV DNA PCR:** A child with a positive virological test 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 the confirmation of the second test.
- **Negative HIV DNA PCR:** The interpretation of a negative virological test is dependent upon whether or not the child is breastfeeding:
  - **In a child who has never breastfed:** A single negative PCR test is likely to exclude HIV infection. An antibody test at 18 months is done to confirm that the child is not infected.

- **In a child who was weaned more than 3 months prior to virological test:** A single negative PCR test is likely to exclude HIV infection. An antibody test at 18 months is done to confirm that the child is not infected.
- **In a child who is breastfeeding at the time of virological test:** A negative HIV DNA PCR test demonstrates that the child is not infected at the time of testing. However, ongoing exposure to HIV through breastfeeding continues to put the child at risk of infection. Confirmatory testing should be done more than three months after breastfeeding is stopped.

After an initial positive, if the second test returns negative, a third sample must be collected and sent for analysis. Direct communication with the laboratory staff responsible for the EID programme is needed to arrive at the correct diagnosis. Consultation with an expert HIV clinician is recommended in all cases of discordant results.

## b) HIV antibody

### Children below 18 months:

A positive HIV antibody test indicates HIV exposure, not HIV infection. If the child was born to an HIV-infected woman, a positive test does not confirm HIV infection in this age group.

A negative HIV antibody test means that the child is not HIV-infected, except if it is currently breastfeeding or has recently stopped breastfeeding but has become infected close to the time of weaning. It can take three months to detect HIV antibody. In this case, antibody testing should be repeated after three months after complete cessation of breastfeeding to confirm the child's HIV negative status.

### Children 18 months of age and above:

- A positive HIV antibody test indicates HIV infection.
- A negative HIV antibody test means that the child is not HIV-infected, unless it was breastfed within the last three months.

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 laboratory need to be reduced using email/SMS for communicating the results.

## 1.4.7 HIV-2 diagnosis

There are only two cases of HIV-2 identified so far. If there is any suspicion of HIV 2 infection, inform the NPHL, which will investigate and confirm the status.

### 1.4.8 HIV testing for survey and research

For conducting HIV testing for survey and research purposes, ethical clearance must be obtained from the Nepal Health Research Council (NHRC). The national algorithm for HIV testing needs to be followed with tests similar to those that have been approved for diagnostic testing in Nepal. Whenever test results are returned to participants, the standards of confirmation and quality assurance appropriate for diagnostic testing must be applied. The diagnostic testing process needs to include high quality counselling and referral to follow-up services, as with all other diagnostic HIV testing.

### 1.4.9 Linking people diagnosed with HIV to care and treatment

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

Special efforts should be made to link people who have a reactive test result in a community setting to facility-based services for additional testing and HIV diagnosis. For those diagnosed HIV positive, linkage to retesting to verify diagnosis is critical before care or treatment is started.

HTS must be accompanied by assured linkages to prevention, treatment, care, and support services, including services for ART, TB, STI, eVT, and family planning services. This will enable early enrolment in treatment, as well as access to services to prevent further transmission of HIV, prevent other OIs and comorbidities. This is especially important to prevent that the client is lost to follow-up. Making these linkages is the responsibility of HTS providers. This may include assisting with transportation of the client; involving community in-reach workers; identifying and finding people lost to follow-up; ensuring support from peers or experienced patients; and using new technologies such as social, medical, and mobile phone reminder text messaging.

#### 1.4.9.1 Expanding diagnostic services to point-of-care (PoC) settings

Point-of-care (PoC) technologies are the diagnostic tests done at the time and place of patient care with same day result. These are simple tests and can be operated with minimal training. As HIV-infected individuals require testing for initial diagnosis, staging and ongoing monitoring throughout treatment, implementation and expansion of POC technologies in resource-limited setting will be helpful in providing HIV services to needy people in time.

Advances in PoC testing for HIV diagnosis, EID, CD4, and viral load (VL) are likely to bring about significant changes in access to quality health care, particularly in resource-limited settings. Improvements in access is likely to be achieved through a combination of sophisticated, high volume, low unit cost laboratories in high density areas, and lower volume, simpler, PoC platforms in less densely populated regions or remote areas.



## Advantages of PoC technologies include:

- Reducing the turnaround time for test;
- Reducing the likelihood that clients is lost to follow-up;
- Preventing delays in starting treatment; and
- Increasing the rate of treatment initiation.

Many PoC technologies for HIV diagnosis, EID, viral load, and CD4 count are available in the market.

### 1.4.10. Laboratory Quality Assurance in HIV Test

Quality system is part of overall quality management that aims to ensure consistency, reproducibility, traceability, reliability, and efficiency of product or service. Organizational management and structure, Quality standards, Documentation, Training, and Assessment are the major components of the quality system. Laboratories that conduct HIV tests should have functioning internal quality control and participate in HIV External Quality Assessment Scheme (EQAS) programmes.

**Internal Quality Control:** Internal quality control is a set of procedures undertaken by laboratory staff to ensure quality ranging from the collection of specimens to performance of test to analytical results, and the procedure being planned, ordered and followed up by the staff itself. Each laboratory conducting HIV test should routinely monitor and assess quality in the pre-analytical, analytical, and post-analytical phases of the testing process.

**External Quality Assurance:** External Quality Assurance (EQA) is the assessment of 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.

- a) **EQAS for retesting for HIV:** All positive and 10% of total negative tested samples in DBS papers from testing sites are sent to a reference laboratory (currently NPHL) for retesting as part of EQAS. The samples in DBS paper are received at the NPHL on monthly basis, tested on-site following the same algorithms, and reports from NPHL, along with feedback and result summary, are dispatched to sites on quarterly basis.
- b) **Proficiency panel testing--CD4 T-lymphocyte count and viral load:** Blinded samples for CD4 T-lymphocyte count and viral load test are received from external sources as part of EQA for CD4 count, EID test and viral load. The results are sent to respective external agencies and a summary report with feedback is received by the NPHL. This helps to assess the testing performance of laboratories.

Similarly, the NPHL is implementing the proficiency panel test for HTS sites which do not participate in HIV DBS EQAS.

- c) **On-site coaching and supportive supervision:** There should be regular supportive supervision and on-site coaching at HTS, CD4 count and viral load testing sites.

### 1.4.11. Universal Precautions and Safe Health Care Waste Management (HCWM)

Healthcare waste is generated during laboratory activities at the HTC. Waste can be classified as non-hazardous or general, healthcare waste, comparable to domestic waste, or as hazardous waste, which has the potential to pose a variety of health risks. Hazardous healthcare waste may also include infectious waste, pathological waste, sharps, pharmaceutical waste, genotoxic waste, chemical waste, waste with high heavy metal content, pressurized containers, and radioactive waste.

Safe healthcare waste management (HCWM) practices and follow-up of standard universal precautions are key to reducing harm among healthcare workers, clients, communities, and in the environment. The waste produced during the clinical and non-clinical services needs proper segregation following the guidelines and standard operating procedures (SoPs), and special attention and treatment are needed to address the hazardous waste generated in the course of clinical service.

The HIV testing site or clinic should adopt safe healthcare waste management practices and strictly adopt standard universal precautions following the national guidelines and SoPs. Waste minimization, waste segregation based on colour code, safe storage/transportation, treatment of waste based on type and safe disposal practices based on waste type should be in place to address safe HCWM practices. Staff should be aware of the use of personal protective equipment (PPE), Post-Exposure Prophylaxis (PEP), SoP or safe healthcare waste management practices.



# ARV DRUGS FOR HIV PREVENTION AND TREATMENT IN ADULTS AND ADOLESCENTS

## 2

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## 2. ARV DRUGS FOR HIV PREVENTION AND TREATMENT IN ADULTS AND ADOLESCENTS

### 2.1 Background

The prevalence of HIV in Nepal is around 0.17% among the age group 15–49 years in 2016 and has been decreasing over the years. As per spectrum estimates, there are 32,853 people living with HIV (PLHIV) in the country in 2016. So far, 18,130 are living and know their HIV status and among them 13,069 are on ART at 67 ART sites in the country (2016). Currently, there are 12,446 PLHIV on ART at 65 ART sites in the country (July 2016). Nepal has recently formulated its NHSP for the period 2016–2021, and it is committed to working on the 90-90-90 strategy and achieving the targets of reducing new infections by 75% and eliminating vertical transmission of HIV by 2020 so as to work towards ending AIDS by 2030.

### 2.2 Antiretroviral Drugs

Antiretroviral drugs are the agents which act on the various stages of lifecycle of HIV in the body. These drugs work by interrupting the process of replication of virus and hence reducing the destruction of CD4 cells, which leads to delay in progression of HIV infection to AIDS.

To understand the mechanism of action of ARV, one needs to understand the basic steps of viral replication, in other words the lifecycle of HIV virus. Virus enters the CD4 (host) cell involving glycoproteins of the virus and receptors of host cells. The process is called fusion. ARVs interfering with the fusion are called fusion inhibitors. This is the new class of ARV and includes drugs like T20 (Enfuvirtide), CCR5 entry inhibitors (Maraviroc) and CXCR4 antagonist.

After the fusion with the host cell membrane, viral particles, including the viral RNA and enzymes (reverse transcriptase, integrase and protease) enter the cytoplasm of the host cell. The first process inside the host cell is the reverse transcription in which viral DNA is synthesized from viral RNA. The process involves the reverse transcriptase enzyme. The ARVs interfering with this process are called nucleoside and nucleotide reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). Nucleoside analogue reverse transcriptase inhibitors inhibit the production of proviral DNA by competing with normal nucleotide. Thus, in place of normal nucleotide, defective nucleotide analogues are placed in the DNA fragment, thus producing a

defective DNA, which cannot serve the purpose of proviral DNA in the subsequent stages of HIV replication. In this way, the replication of HIV is blocked. Non-nucleosides analogue inhibitor acts by destroying the active site of reverse transcriptase.

The viral DNA synthesized in cytoplasm travels to the nucleus of the host cell, where it integrates with the DNA of the host cell with the help of integrase. Integrase inhibitors are the ARVs that block the process of integration. After integration, the DNA of the infected cell converts itself into the viral DNA and starts to produce copies of viral RNA. For the production of viral particles, the RNA copies thus produced need to be cut into particles of exact size with the help of protease.

The viral RNA, after the action of protease, converts into viral particles. These particles assemble with the enzymes to form capsules, which eventually leave the infected cell by a process called budding. After budding, the viruses develop into mature viruses. There are some ARVs, called maturation inhibitors, which inhibit the process of maturation.

Newer classes of antiretroviral drugs like Fusion Inhibitors (FI), Integrase Strand Transfer Inhibitors (INSTI), CCR5 Antagonists act by preventing fusion and entry of the virus into the target cell (CD4), preventing integration of the HIV proviral DNA into the human DNA and blocking co-receptors needed for the virus to enter the cell.

Although not all antiretroviral drugs mentioned in the guidelines are currently available in Nepal, some of them may become available soon in the future. Hence, the list of drugs needs to be expanded so that clinicians and programme managers can utilize these drugs.

## 2.3 Classes of Antiretroviral Drugs

Depending on the mechanism of action, the ARVs are categorized into the following classes:

1. Nucleoside and nucleotide analogues:
  - a. Nucleoside reverse transcriptase inhibitors (NRTI)
  - b. Nucleotide reverse transcriptase inhibitors (NtRTI)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Protease inhibitors (PIs)
4. Integrase Strand Transfer Inhibitors (INSTI)
5. Fusion Inhibitors
6. Cellular Chemokine Receptor (CCR5) Antagonist

The first two groups of drugs are used in the first-line ART, while PIs are used for the second-line ART.

The mechanism of the action of different ARVs is shown graphically below in Figure 2.1.

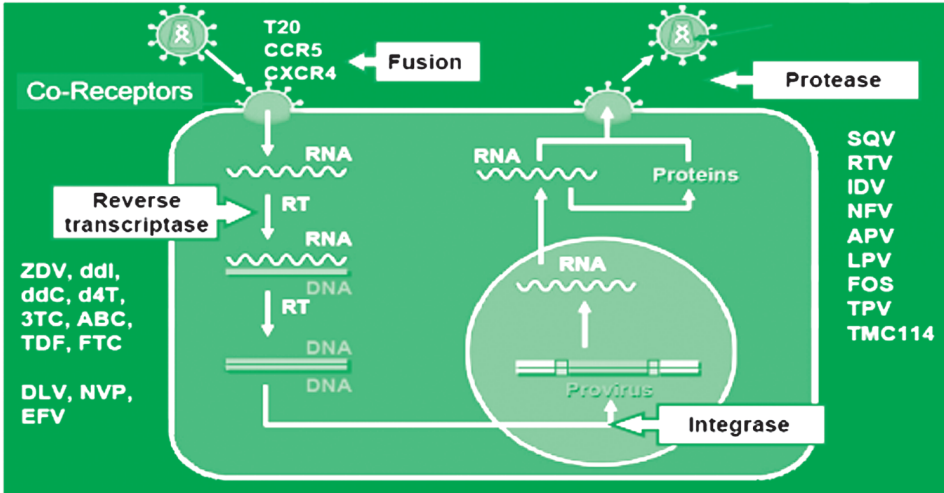


Figure 2.1. Targets of antiretroviral drugs

Currently available antiretroviral drugs globally are shown in Table 2.1.

### Table 2.1. Classes of ARV drugs available

Nucleoside reverse Transcriptase inhibitors (NRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)	Fusion inhibitors (FI)
Zidovudine (AZT/ZDV)	Nevirapine (NVP)	Saquinavir (SQV)**	Enfuvirtide (T-20)**
*Stavudine (d4T)	Efavirenz (EFV)	Ritonavir (RTV)	<b>Integrase Inhibitors</b>
Lamivudine (3TC)	Etravirine**	Nelfinavir (NFV)**	Raltegravir (RAL) Dolutegravir (DTG)**
*Didanosine (ddl)	*Delveridine	Atazanavir (ATV)	<b>CCR5 Entry Inhibitors</b>
Zalcitabine (ddC)		*Indinavir (INV)	Maraviroc (MVC)**
Abacavir (ABC)		Lopinavir/Ritonavir (LPV)**	
Emtricitabine (FTC)		Foseamprenavir (FPV)**	
<b>(NtRTI)</b>			
Tenofovir (TDF)		Tipranavir (TPV)**	

\* These drugs are no longer used in clinical practices.

\*\* These drugs are currently not available in the national programme.

## 2.4 Clinical Pharmacology of Commonly Used ARV Drugs

### Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI)

The first effective class of antiretroviral drugs was the **Nucleoside analogues**, which act by incorporating themselves into the DNA of the virus, thereby stopping the building process. The resulting DNA is incomplete and cannot create new virus. **Nucleotide analogues** work in the same way as nucleosides, but they have a non-peptidic chemical structure. All nucleoside analogues have been associated with lactic acidosis and hepatic steatosis as their common side-effects. The details of individual ARV of this class are shown in Table 2.2.

**Table 2.2 Commonly used NRTIs**

Generic Name	Dose	Adverse effects
Zidovudine (ZDV, AZT)	300mg twice daily	Anaemia, neutropenia, bone marrow suppression, gastrointestinal intolerance, headache, insomnia, myopathy, lactic acidosis <sup>1</sup> , skin and nail hyperpigmentation
Tenofovir (TDF)	300mg once daily	Renal toxicity, Bone demineralization
Lamivudine(3TC)	150mg twice daily Or 300mg once daily	Minimal toxicity, rash though very rare
Emtricitabine (FTC)	200mg once daily	Unusual, mild to moderate diarrhoea, headache, nausea, and rash. Some patients may experience hepatotoxicity or lactic acidosis.
Abacavir (ABC)	300mg twice daily or 600mgOD	Hypersensitivity reaction in 3 to 5% (can be fatal), fever, rash, fatigue, nausea, vomiting, anorexia, respiratory symptoms (sore throat, cough, shortness of breath) Re-challenging after reaction can be fatal.

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs stop HIV production by binding onto reverse transcriptase and preventing conversion of RNA into DNA. These drugs are called "non-nucleoside" inhibitors because even though they work at the same stage as nucleoside analogues, they are not nucleoside analogues. The details of individual ARV of this class are shown in Table 2.3.



**Table 2.3. Commonly used NNRTIs**

Generic Name	Dose	Food-related Advice	Adverse Effects
Efavirenz (EFV)	600mg once daily (bed time administration is suggested to decrease CNS side-effects)	Avoid taking after high fat meals	CNS symptoms (dizziness, somnolence, insomnia, confusion, hallucinations, agitation), and personality change. Rash occurs, but less common than NVP. Avoid taking EFV after heavy fatty meals.
Nevirapine (NVP)	200mg once daily for 14 days, followed by 200mg twice daily	Take without regard to meals	Hepatitis (usually within 12 weeks), sometime life-threatening hepatic toxicity. Skin rash occasionally progressing to severe conditions, including Stevens Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Patients who develop severe hepatic toxicity or grade 4 skin rashes while treated with Nevirapine should not be re-challenged.

### Protease Inhibitors (PIs)

PIs work at the last stage of the viral reproduction cycle. They prevent HIV from being successfully assembled and released from the infected CD4 cell. All PIs can produce increased bleeding in haemophilia, GI intolerance, altered taste, increased liver function test, and bone disorder, and all have been associated with metabolic abnormalities, such as hyperglycemias, insulin resistance, and increase in triglycerides, cholesterol and body fat distribution (lip dystrophy). The details of individual ARV of this class are shown in Table 2.4.

**Table 2.4. Commonly used PIs**

Generic Name	Dose	Adverse Effects
Atazanavir/ ritonavir (ATV/r)	300mg Atazanavir + 100mg ritonavir once daily	Hyperbilirubinemia. Less lipid problems than LPV/r Hyperglycaemia, Fat maldistribution, Nephrolithiasis  Interaction with acid blocking agents. Do not co administer with H2 receptor antagonist. Give 12 hours gap when using proton pump inhibitors
Lopinavir /ritonavir (LPV/r) Heat stable tablets	200mg Lopinavir/50mg Ritonavir  Fixed dose tablet 2 tablets twice daily	Diarrhoea, nausea, vomiting, abnormal lipid profiles, glucose intolerance. Any PI should not be prescribed with Simvastatin as they significantly increase the level of Simvastatin leading rhabdomyolysis, resulting in severe kidney failure
Darunavir (DRV) and Ritonavir (r)	600 mg and 100mg One tablet twice daily	Hepatotoxicity and Allergic reactions, Fat maldistribution

## 2.5 Goals of Antiretroviral Therapy (ART)

The currently ARV drugs cannot eradicate HIV from the human body because a pool of latently infected CD4 cells is established during the earliest stages of acute HIV infection and persist within the organs/cells and fluids (eg liver and lymphoid tissue) even with prolonged suppression of plasma viraemia to  $< 50$  copies/ml by antiretroviral therapy (ART). The goals of therapy are shown in Box 2.1.

### Box 2.1. Goals of ARV therapy

- **Clinical goals:** Prolongation of life and improvement in quality of life
- **Virological goals:** Greatest possible sustained reduction in viral load
- **Immunological goals:** Immune reconstitution that is both quantitative and qualitative
- **Therapeutic goals:** Rational sequencing of drugs in a manner that achieves clinical, virological and immunological goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence
- **Prevention goals:** Reduction of HIV transmission due to suppression of viral load

These goals are achieved by suppressing viral replication for as long as possible, using well-tolerated and sustainable treatment. With prolonged viral suppression, CD4 lymphocyte count usually increases, which is accompanied by partial restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality.

The programmatic goals of ART are:

- To provide lifelong ART to all eligible patients;
- To attain individual drug adherence rate of 95% or more;
- To ensure retention in care and provide necessary care and support services; and
- To monitor and report treatment outcomes on the cascade.

## 2.6 Provision of ART for Adults and Adolescents

After discussion at Technical Working Group and consultation with all stakeholders, the NCASC decided to adopt the **TREAT ALL** policy enunciated in the WHO 2016 Guidelines. ART shall now be provided to all adults and adolescents living with HIV regardless of the WHO clinical stage and CD4 count.

All persons diagnosed with HIV at HTC should be registered in HIV care as soon as possible. All efforts should be made to reduce the time between HIV diagnosis and ART initiation based on assessment of person's readiness.

Simultaneously, it is important to expand the HTS using a mix of facility- and community-based testing so as to detect people earlier and at higher CD counts for better treatment outcomes. This has already been discussed in Chapter 1.

Before a person is put on ART, it is important to confirm the HIV diagnosis according to the national testing algorithm. It is recommended that all positive people are retested prior to initiating ART, when they are enrolled in HIV care at ART in order to ensure correct diagnosis of HIV infection.

Healthcare providers should hold detailed discussions with all clients about their willingness and readiness to initiate ART, ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects, and the required follow-up and monitoring visits. For children with HIV, this conversation should directly involve 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 contra-indications or dose adjustment. All efforts should be made to ensure initiation of ART at the earliest possible.

## 2.7 Assessment of Adults and Adolescents with HIV Infection

### Clinical Assessment and Laboratory Tests

A comprehensive clinical assessment should be done as baseline status and to rule out OIs. This helps to:

- Identify current HIV-related illnesses that may require treatment;
- Determine the need for OI prophylaxis;
- Carry out required baseline investigations as per national protocol;
- Identify co-existing medical conditions like diabetes, hepatitis, etc and treatment that may influence the choice of ARV drugs;
- Determine nutritional status and needs;
- Identify history of past illnesses (especially TB, STI, Hepatitis); and
- Assess the need for psychosocial support.

It is important to elicit those risk factors which may influence the type of counselling requirement as well as drugs to be used for ART. One has to look for history for:

- use of injecting drugs;
- sexual contact without use of condom;
- sexually transmitted infection (STI);
- TB;
- recipient of blood or blood products;
- key populations such as MSM, MSW, TG, FSW, PWID, etc as this may require special counselling and ART delivery mechanisms; and
- injections, tattoos, ear piercing or body piercing using non-sterile instruments.

**Table 2.5. Medical History Checklist**

HIV Testing	HIV risks (can have multiple factors)
<ul style="list-style-type: none"> <li>• Ever tested for HIV in the past</li> <li>• Date and place of first HIV test</li> <li>• Reason for the test</li> <li>• Documentation of result</li> <li>• Previous CD4 cell counts (if available)</li> <li>• Previous viral load (if available)</li> </ul>	<ul style="list-style-type: none"> <li>• Unprotected sexual contact</li> <li>• Injecting drug use</li> <li>• Men having sex with men</li> <li>• Perinatal transmission</li> <li>• Recipient of blood products</li> <li>• Unknown partner's HIV status being positive</li> </ul>
System Review	Past history of HIV-related illnesses
<ul style="list-style-type: none"> <li>• Unexplained weight loss</li> <li>• Swollen lymph nodes</li> <li>• Night sweats and fever</li> <li>• Unusual headaches or poor concentration</li> <li>• Changes in appetite</li> <li>• Skin rashes</li> <li>• Sores or white spots in mouth</li> <li>• Painful swallowing</li> <li>• Chest pain, cough or shortness of breath</li> <li>• Stomach pain, vomiting or diarrhoea</li> <li>• Numbness or tingling in hand or feet</li> <li>• Muscular weakness and changes in vision</li> </ul>	<ul style="list-style-type: none"> <li>• Oral candidiasis or candida esophagitis</li> <li>• Persistent diarrhoea</li> <li>• Tuberculosis</li> <li>• Varicella zoster (Shingles)</li> <li>• Oral hairy leukoplakia</li> <li>• Pneumococcal STI jirovecipneumonia (PCP)</li> <li>• Recurrent bacterial pneumonia</li> <li>• Cryptococcal meningitis</li> <li>• Toxoplasmosis</li> <li>• Kaposi sarcoma</li> <li>• Disseminated Mycobacterium avium complex</li> <li>• Cytomegalovirus (CMV) infection</li> <li>• Invasive cervical cancer</li> </ul>
Tuberculosis history	ART history
<ul style="list-style-type: none"> <li>• Last chest X-ray</li> <li>• History of past TB</li> <li>• Treatment given (drugs and duration)</li> <li>• History of exposure to TB in the family/close contacts</li> <li>• Ask the four TB screening questions (any cough, fever or weight loss and night sweat).</li> </ul>	<ul style="list-style-type: none"> <li>• Current and past exposure to ARVs</li> <li>• ARV use during pregnancy of PMTCT</li> <li>• Use of PEP in the past</li> <li>• ARV drugs taken and for how long</li> <li>• Understanding of and readiness to commence ART</li> <li>• Partner's ART history (if HIV positive)</li> </ul>
Sexually transmitted infections (STI)	Substance use
<ul style="list-style-type: none"> <li>• Genital ulcer or other lesion</li> <li>• Genital discharge (abnormal vaginal discharge in women and urethral discharge in men)</li> <li>• Lower abdominal pain</li> </ul>	<ul style="list-style-type: none"> <li>• Alcohol, stimulant, opiate and other drug use</li> <li>• Smoking history</li> </ul>

<p style="text-align: center;"><b>General medical history</b></p> <ul style="list-style-type: none"> <li>Any other past medical condition such as diabetes, hypertension, coronary artery disease, hepatitis B, hepatitis C, hyperlipidemia</li> <li>Mental health issues, eg depression</li> </ul>	<p style="text-align: center;"><b>Allergies</b></p> <ul style="list-style-type: none"> <li>Known allergies to drugs or other substances or materials</li> </ul>
<p style="text-align: center;"><b>Medication</b></p> <ul style="list-style-type: none"> <li>Past use of drugs and reasons for taking those drugs Current use of drugs and reasons</li> <li>Current use of traditional/herbal remedies Opioid substitution therapy (OST)</li> </ul>	<p style="text-align: center;"><b>Vaccination history</b></p> <ul style="list-style-type: none"> <li>BCG</li> <li>Hepatitis A vaccine</li> <li>Hepatitis B vaccine</li> </ul>
<p style="text-align: center;"><b>Psychosocial history</b></p> <ul style="list-style-type: none"> <li>Family history, eg other immediate family members with known HIV infection</li> <li>Social history, eg marital status, education, occupation, source of income</li> </ul>	<p style="text-align: center;"><b>Social history</b></p> <ul style="list-style-type: none"> <li>Financial and family support status</li> <li>Disclosure status, readiness to disclose</li> <li>Availability of care and treatment supported supporter</li> <li>Able to work, go to school, do housework</li> <li>Ambulatory but not able to work</li> <li>Bed-ridden</li> <li>Amount of day-to-day care needed</li> </ul>
<p style="text-align: center;"><b>Gynaecological history</b></p> <ul style="list-style-type: none"> <li>Last PAP smear</li> <li>Menstrual irregularities</li> <li>Pelvic pain or discharge</li> </ul>	<p style="text-align: center;"><b>Pregnancy and contraception history</b></p> <ul style="list-style-type: none"> <li>Previous pregnancies and MTP (years)</li> <li>Children and HIV status of children (living and dead)</li> <li>Exposure to ARVs during pregnancy</li> <li>Drugs and duration of ART</li> <li>Contraception used</li> <li>Last menstrual period</li> </ul>

## Physical Examination

It is essential to carry out a thorough physical examination for clinical staging and screening. Table 2.6 details the specific physical signs related to HIV/AIDS which should be screened.

**Table 2.6. Physical examination checklist**

<b>Record vital signs, body weight, height and body mass index (BMI), temperature, blood pressure, pulse rate, respiratory rate</b>	
<b>Appearance</b>	<ul style="list-style-type: none"> <li>• Unexplained moderate or severe weight loss, HIV wasting</li> <li>• Rapid weight loss is suggestive of active OI, especially if associated with fever</li> <li>• Gradual weight loss (not caused by malnutrition or other obvious illness) is suggestive of HIV infection</li> <li>• "Track marks" and soft tissue infections which are common among IDUs</li> </ul>
<b>Consider conditions other than HIV</b>	<ul style="list-style-type: none"> <li>• Malaria, tuberculosis, syphilis, gastrointestinal infections, bacterial pneumonia, pelvic inflammatory disease, viral hepatitis other than HIV</li> </ul>
<b>Skin</b>	<ul style="list-style-type: none"> <li>• 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</li> <li>• Look for herpes simplex and herpes zoster or scarring of previous herpes zoster (especially multi-dermatome)</li> </ul>
<b>Lymph nodes</b>	<ul style="list-style-type: none"> <li>• Start with posterior cervical nodes</li> <li>• PGL (persistent glandular lymphadenopathy) that typically presents as multiple bilateral, soft, non-tender, mobile cervical nodes, other than axillary or inguinal nodes</li> <li>• Tuberculous lymph nodes typically present with constitutional symptoms such as fever, night sweats and weight loss</li> </ul>
<b>Mouth</b>	<ul style="list-style-type: none"> <li>• 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 (OHL) and cracking at the corners of the mouth (angular cheilitis)</li> <li>• Difficulty in swallowing is commonly caused by oesophageal candida</li> </ul>
<b>Chest</b>	<ul style="list-style-type: none"> <li>• The most common problems will be PCP and TB</li> <li>• Signs and symptoms are cough, shortness of breath, haemoptysis, weight loss, fever, congestion or consolidation</li> <li>• Perform a chest X-ray, if symptomatic</li> </ul>
<b>Abdomen</b>	<ul style="list-style-type: none"> <li>• Hepatosplenomegaly, masses and local tenderness</li> <li>• Jaundice may be indicative of viral hepatitis</li> </ul>
<b>Neurological</b>	<ul style="list-style-type: none"> <li>• Focus on visual fields and the signs of neuropathy (bilateral peripheral examination or localized mono-neuropathies)</li> <li>• Assess focal neurological deficit</li> </ul>
<b>Ano-genital</b>	<ul style="list-style-type: none"> <li>• Herpes simplex and other genital sores/lesions, vaginal or penile discharge</li> <li>• Perform PAP smear, if possible</li> </ul>
<i>Note: During each consultation, patient is to be clinically screened for TB (history and physical examination)</i>	

## Comprehensive Laboratory Evaluation in HIV/AIDS

The purpose of the baseline laboratory evaluation is to:

- (i) Rule out other concomitant infections, OIs and
- (ii) Determine baseline safety parameters.

The investigations recommended by the national programme for monitoring of PLHIV at ART centres are summarized in Table 2.7.

## Table 2.7. Laboratory monitoring for patients on ART

### Baseline Tests: Essential tests for all patients registering in HIV care

- TC, DC, ESR, Hb Platelets
- ALT/SGPT - If needed LFT (Liver function test)
- Blood Urea, Serum creatinine, If needed, kidney function test (Electrolytes – sodium, potassium)
- Blood sugar level
- VDRL
- Hepatitis B and Hepatitis C
- Urine analysis to assess for proteinuria
- Urine pregnancy test as indicated in female
- Sputum for AFB tested by Gene Xpert, Microscopy, Chest X ray,
- CD4 cell count not for initiation of ART. Necessary, however, to know baseline and future prognostic value and diagnosis of treatment success or failure
- For women, cervical pap smear or other method of cervical cancer screening, if available.

### Additional tests at baseline as per the physician's decision depending on clinical presentation

- USG abdomen,
- CSF analysis, etc.
- Any other test required to rule out OIs
- Fundus examination in those with low CD count

### NON-AVAILABILITY OF ANY OF THESE TESTS SHOULD NOT DELAY THE INITIATION OF ART

### Tests for monitoring patients on ART (follow-up tests)

For all patients on ART: do CD4, Hb, TLC, DLC, ALT (SGPT)

For those on TDF-based regimen: Creatinine/creatinine clearance, at baseline, 4 weeks, 6 weeks and every 6 months or earlier if required.

For those on AZT-based regimen: Hb at 15 days, then every month for initial 3 months, 6 months and then every 6 months as and when indicated.

For those on NVP-based regimen: ALT (SGPT) at 15 days, 1 month and then every 6 months. For those on EFV-based regimen: lipid profile should also be done yearly, if available.

For those on ATV-based regimen: LFT to be done at 15 days, 1 month, 3 month, 6 months and then every 6 months. Blood sugar and Lipid profile every 6 months for patients on PI-based regimen.

Any other can be done earlier based on clinician's assessment/discretion and as per availability.

It is preferable/desirable to monitor patients with viral load at 6 and 12 months after initiation of ART and then at every 12 months. For stable patients with virological suppression, frequency of CD4 can be reduced. Till the time viral load facility is available for all patients, CD4 count every six months should be done. For ART centres without CD4 machine, efforts should be made to transport the samples and not send patients to sites with CD4 facility. CD4 test is required for Cotrimoxazole Preventive Therapy (CPT) initiation/stopping CPT and for primary and secondary prophylaxis for some OIs.

**Table 2.8. Assessment and initial management after HIV diagnosis is confirmed**

Visit 1	Initiation of ART
	<ul style="list-style-type: none"> <li>• Medical history</li> <li>• Symptom checklist</li> <li>• Screen for TB</li> <li>• Physical examination</li> <li>• Chest X-ray if chest symptoms present</li> <li>• Behavioural/psychosocial assessment:</li> <li>• Social support, family/household structure</li> <li>• Disclosure status, readiness to disclose</li> <li>• Understanding of HIV/AIDS, transmission, risk reduction, treatment options</li> <li>• Nutritional assessment</li> <li>• Investigation: baseline Blood profile, CD4 count, other test as necessary</li> </ul>
Visit 2	within 2-3 days after first visit
	<ul style="list-style-type: none"> <li>• History (new problems)</li> <li>• Symptom check-list</li> <li>• Screen for TB</li> <li>• Physical examination</li> <li>• Cotrimoxazole prophylaxis</li> <li>• Psychosocial support</li> <li>• Adherence counselling on at least two occasions and assessment clients preparedness to initiate ART. Initiate ART if the counsellor feels that the patient is adequately prepared.</li> </ul>
Subsequent visits	every month until stable
	<ul style="list-style-type: none"> <li>• History (new problems)</li> <li>• Symptom check-list</li> <li>• Screen for TB</li> <li>• Clinical examination</li> <li>• Adherence assessment/support</li> <li>• Looking for side-effects, if any</li> <li>• Investigations as per ART monitoring guidelines</li> </ul>



## 2.8 Initiation of ART

As per revised guidelines, all PLHIV should be put on ART as soon as they are found positive.

The broad recommendation is to treat all PLHIV regardless of CD4 count or clinical stage for all age groups and all populations. This includes all pregnant women irrespective of stage of pregnancy.

The following principles need to be kept in mind:

- Treatment should be started based on a person's informed decision and preparedness to initiate ART.
- Interventions to remove barriers to ART initiation once an individual is diagnosed HIV positive need to be implemented. A caregiver should be identified for each person to provide adequate support.
- HIV programme needs to promote treatment literacy among all people with HIV, including information on the benefits of early treatment, the lifelong commitment required, the risks of delaying treatment and available adherence support.
- Caregivers must be trained to support treatment adherence, follow-up visits and shared decision-making.
- Although ART initiation is rarely urgent, it may need to be expedited in certain circumstances, such as serious ill health and for pregnant women in labour whose HIV test results are positive.

As a principle, ART should not be initiated in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. Mycobacterium Avium Complex (MAC) and progressive multifocal leukoencephalopathy (PML) are exceptions, in which commencing ART may be the preferred treatment, especially when specific MAC therapy is not available.

All patients with CD4 less than 350 need to be put on CPT. All patients need to be screened for TB using the 4-symptom (fever, current cough, night sweats, weight loss) tool and those who do not have TB need to be put on Isoniazid Preventive Therapy (IPT).

The guidelines on CPT and IPT are described in detail in Chapter 6.

## 2.9 When to start ART in Adults, including Pregnant, Breastfeeding Mothers and Adolescents

### Recommendations

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

- As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count  $\leq 350$  cells/mm<sup>3</sup>.

## 2.10 What to Start: Choice of Antiretroviral Regimen

The basic principle is to use a triple drug fixed dose combination from two different classes of ARVs. Using simplified, less toxic and more convenient regimens as fixed-dose combinations (FDCs) is recommended for the first-line ART.

The WHO 2013 Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection recommend tenofovir (TDF) + lamivudine (3TC) (or emtricitabine [FTC]) + efavirenz (EFV) as the preferred first-line regimen for initiation of treatment of ART-naïve adults, preferably as an FDC. This approach has clinical, operational and programmatic benefits. This once daily combination is less frequently associated with severe adverse events and has a better virological and treatment response when compared with other once- or twice-daily NNRTI- or PI-containing regimens. TDF + 3TC or FTC is the preferred NRTI backbone for people infected with both HIV and HBV and can be used for people coinfecting with TB as well as for pregnant women. EFV is also the preferred NNRTI for people with HIV and TB due to pharmacological compatibility with TB drugs and for people with HIV and HBV. EFV, on the other hand, showed no increased risk of birth defects in the first trimester of pregnancy, confirming its safety for pregnant women.

Based on evidence supporting better efficacy and fewer side-effects, it is now recommended to use:

**TENOFOVIR (TDF) + LAMIVUDINE (3TC) (OR EMTRICITABINE-FTC) + EFAVIRENZ (EFV) AS FIXED DOSE COMBINATION (FDC) IN A SINGLE PILL.**

### Special Conditions

- In cases where non-Thymidine NRTI or EFV are contra-indicated or have adverse events, the other combinations of AZT and NVP can be used as alternative first-line.
- ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.
- Safety and efficacy data on the use of DTG in pregnant women, people with HIV/TB coinfection and adolescents younger than 12 years of age are not yet available.
- Conditional recommendation, moderate quality evidence.

3TC lamivudine, ABC abacavir, AZT zidovudine, DRV darunavir, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NVP nevirapine, r ritonavir, TDF tenofovir.

The recommended regimens are shown in Table 2.9.

**Table 2.9. Choice of first-line ART regimen for adults, pregnant or breastfeeding women and adolescents**

First-line ART	Preferred first-line regimens	Alternative first-line regimens a, b
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG* TDF + 3TC (or FTC) + NVP ABC + 3TC + NVP (or EFV)
Pregnant or breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF(orABC)+3TC(orFTC)+DTG* TDF (or ABC) + 3TC (or FTC) + NVP

\*DTG (not available yet) to be implemented later when good evidence of efficacy is available

**Table 2.10. First-line ART regimen for adults**

Preferred regimen	FDC of TDF + 3TC (or FTC) + EFV
Alternative regimens	AZT + 3TC + EFV (or NVP)
	TDF + 3TC (or FTC) + DTG <sup>a</sup>
	TDF + 3TC (or FTC) + NVP
Special circumstances <sup>b</sup>	Regimens containing ABC and boosted PIs

- Safety and efficacy data on DTG for pregnant and breastfeeding women and TB coinfection are still pending. DTG is not available in Nepal.
- Special circumstances may include situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug–drug interactions, drug procurement and supply management issues, or other reasons.

3TC lamivudine, ABC abacavir, AZT zidovudine, DTG dolutegravir, EFV efavirenz, FTC emtricitabine, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

The WHO 2016 Guidelines recommends DTG and EFV 400mg/day as new alternative options in the first-line regimens.

The analysis showed moderate quality evidence that two NRTIs + INSTI was a generally more effective regimen (with higher viral suppression and CD4 cell recovery rates and

lower risk of treatment discontinuation) than two NRTIs + EFV at the standard dose of 600mg/day in ART-naive adults and that DTG has a comparable effect to that of RAL but better than that of EVG + cobicistat in terms of viral suppression and treatment discontinuation. There was a non-statistically significant tendency towards increased viral suppression with DTG when compared with EFV at a lower dose of 400mg/day.

In the same systematic review, there was moderate quality evidence showing that EFV 400mg/day was comparable to EFV 600mg/day in terms of viral suppression but better in terms of CD4 cell count recovery and protection in terms of treatment discontinuation due to adverse events.

DTG also has other clinical and programmatic advantages when compared with EFV 600mg, including lower potential for drug interactions, a shorter median time to viral suppression and a higher genetic resistance barrier when compared with EFV and other ARV drugs. Its long half-life, low cost and low dose mean that it is feasible to include this drug in a small once-daily FDC. DTG has documented in vitro and clinical activity against HIV-2 infection, which is naturally resistant to EFV. When compared with the standard dose of EFV, EFV 400mg/day is also associated with lower toxicity, lower cost and smaller pill size.

Single formulations and FDCs containing these two new options are expected to be available in 2017 and 2018 respectively with forecasting projections, suggesting good potential for price reduction as a result of generic competition in the future.

The clinical and potential programmatic benefits of DTG and EFV 400mg/day for the majority of patients warrant their inclusion as new alternative options in the first-line ART. However, further research is needed to establish their suitability for use during pregnancy and concurrent Rifampicin-based TB treatment.

At present, this information is intended for knowledge of caregivers and will be updated once these drugs are available in the market.

## 2.10.1 First-line ART for adolescents

### First-line recommendations

First-line ART for adolescents should consist of two NRTIs plus an NNRTI or an INSTI:

- TDF + 3TC (or FTC) + EFV as an FDC is recommended as the preferred option to initiate ART
- TDF + 3TC (or FTC) + DTG\* may be used as an alternative option to initiate ART

If preferred regimens are contra-indicated or not available, one of the following alternative options is recommended (strong recommendation, moderate quality evidence):

ABC + 3TC + EFV

ABC + 3TC + NVP

AZT + 3TC + EFV

AZT + 3TC + NVP

TDF + 3TC (or FTC) + NVP

*\* Currently not available in Nepal*

There is a relative merit of ABC versus TDF versus AZT. There is no definitive evidence for deciding which one is superior and preferred. Each drug should be judged in respect of its risks and benefits.

TDF has got the advantages of once-daily dosing. TDF-containing FDCs are currently only available in adult, unscored tablets for once-daily use. At or above 35kg, the dose of TDF in adult dual and triple FDCs and the dose of EFV in adult triple FDCs are acceptable for use in adolescents.

ABC or boosted PIs can be used in special circumstances. ABC can be used once daily as FDCs with 3TC for different age groups and it harmonizes with TDF from resistance perspective.

AZT has been commonly used and is available in both dual and triple FDCs with NVP but is dosed twice daily and can cause severe anaemia.

## 2.11 What to Expect in the First Six Months of ART

Although taking ART is a lifelong commitment, the first six months of therapy are especially important. Clinical and immunological improvement and viral suppression are expected when individuals adhere to ART, but OIs and/or immune reconstitution inflammatory syndrome (IRIS), as well as early adverse drug reactions, such as drug hypersensitivity, may develop, especially in the first three months of treatment. ART significantly decreases overall mortality, but death rates are also the highest in the first three months of ART. These complications are the most common when people starting ART already have advanced HIV disease with severe immunodeficiency and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index and very low CD4 counts or are severely malnourished. Poor adherence in this period is also associated with the risk of early treatment failure and rapid development of drug resistance.

### 2.11.1 CD4 recovery

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. Failure to achieve some CD4 recovery should alert the health caregiver to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for OIs such as cotrimoxazole preventive therapy (CPT) and isoniazid preventive therapy (IPT). As long as the viral load remains below the level of detection, there is no need to be concerned even with decreases in CD4 T cells.

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

- Concurrent infections, specifically hepatitis;
- Leucopenia of varying etiology, especially caused by ARV itself and steroids or other immunosuppressive therapies;
- Pregnancy can also lead to lower values;
- Diurnal variation may occur: CD4 T cells are the lowest at noon and the highest in the evening (around 8 pm);
- Psychological stress seems to play a negligible role, even though patients often assume the contrary.

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

### 2.11.2 Viral Load

Within the first few weeks of therapy, the viral load should start decreasing and a viral load test should be done after six months to evaluate the response to ARVs. Viral load testing should be done at the 6<sup>th</sup> month after initiation of ART, again at the 12<sup>th</sup> month and, once suppressed, every 12 months.

### 2.11.3 Early ARV toxicity

The first-line drug toxicities fall into two categories. Early toxicity usually presents in the first few weeks to months of ART. Early and potentially severe toxicities such as hypersensitivity to NNRTIs (EFV and NVP) normally occur within the first few weeks of therapy and AZT-related anaemia and neutropenia typically present themselves in the first few months of therapy. *(These are discussed later in the guidelines.)*

### 2.11.4 Mortality on ART

While ART significantly decreases mortality, the risk of death is higher in the first six months than during the subsequent period of therapy, particularly when the patient starts ART with clinical stage 4 events, severe immunosuppression and very low CD4 counts.

## 2.12 Immune Reconstitution Inflammatory Syndrome (IRIS)

This is a condition that can occur shortly after a person starts HIV therapy for the first time. It is a spectrum of clinical signs and symptoms resulting from the body's ability to mount an inflammatory response associated with immune recovery. The suppression of CD4 T cells by HIV causes a decrease in the body's normal response to certain infections. ART partially restores the immune defects caused by chronic HIV infection, including restoration of protective pathogen-specific immune responses. If 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, eg TB, MAC or 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 first 4–8 weeks but can occur up to six months. The possible risk factors for IRIS are as shown below:

- People with CD4 counts below 100 before starting therapy;
- People with greater drops in HIV viral load due to therapy;
- People with diagnosis of another infection before starting therapy, the closer the appearance or diagnosis is to starting therapy, the higher the risk;
- Severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatment.

IRIS may present itself in three ways:

**Unmasking IRIS** refers to the initial clinical expression of active TB occurring soon after ARV agents are started. **Paradoxical IRIS** refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment.

IRIS should be considered only when the **presentation cannot be explained** by a new infection, expected course of a known infection or drug toxicity. IRIS should be diagnosed by excluding:

- Active OIs
- treatment failure
- Side-effects of ARV
- Highly active antiretroviral therapy (HAART) treatment failure (resistance)

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumours and non-infectious conditions. The most serious and life-threatening forms of paradoxical IRIS are for TB, cryptococcosis, Kaposi's 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. A low CD4+ cell count ( $< 50$  cells/mm<sup>3</sup>) at ART initiation, disseminated OIs or tumours, a shorter duration of therapy for OIs before ART starts, increasing CD4, and decreasing viral load very rapidly after ART are the main risk factors.

The most important steps to reducing the development of IRIS include: earlier HIV diagnosis and initiation of ART before a decline of CD4 below 200 cells/mm<sup>3</sup>; improved screening for OIs before ART, especially TB, Cryptococcus and CMV; and optimal management of OIs before initiating ART. Timing of ART in people with OIs requires balancing a greater risk of IRIS after early initiation against continuing high mortality, if ART is delayed.

## IRIS treatment

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, eg non-steroid anti-inflammatory drugs (NSAIDs), is required.

Decrease immune response by:

- Immunosuppressive agents, eg corticosteroids 1-2 mg/kg usually for 1 to 2 weeks, sometimes up to 12 weeks.
- Continuing HAART and OI therapy + steroids
- Treat OI for standard period or longer.

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

The monitoring of patients on ART, response to ART, ARV toxicities, substitution, diagnosis of treatment failure, switching to second-and third-line drugs and monitoring HIV drug resistance are described in Chapter 4.

## 2.13 General Care for PLHIV

Apart from treatment with ARV drugs and proper treatment of different OIs, comorbidities and some malignancies, PLHIV require different kinds of care, without which good quality of life for long period may not be possible. For that purpose, the following care should be provided adequately.



## 2.13.1 Nutritional care and support

Low energy intake, combined with increased energy demands because of HIV and related infections, may lead to HIV-related weight loss and wasting. In addition, an 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 in adults (BMI less than 18.5kg/m<sup>2</sup>), weight loss and wasting in children are all independent risk factors for HIV disease progression 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 HIV patients, 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.

## 2.13.2 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 and appropriate medication used in line with the Pain Ladder (for details, see [http://www.southwesthealthline.ca/healthlibrary\\_docs/B.5.3.WHOPainLadder.pdf](http://www.southwesthealthline.ca/healthlibrary_docs/B.5.3.WHOPainLadder.pdf)). Furthermore, effectively managing the side-effects of ART is important to support adherence.

## 2.14 HIV Prevention based on ARV Drugs

### 2.14.1 Pre-exposure prophylaxis (PrEP)

Oral PrEP is the use of antiretroviral (ARV) drugs before HIV exposure by people who are not infected with HIV in order to block the acquisition of HIV. The national HIV programme agrees to implement PrEP as a combined HIV prevention approach among key populations.

Twelve trials on the effectiveness of oral PrEP conducted on Serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women have shown high levels of efficacy, showing the value of this intervention as part of combination prevention approaches.

In 2012, WHO recommended PrEP for use among serodiscordant couples, men who have sex with men and transgender people in demonstration projects. It was strongly

recommended for men who have sex with men. Furthermore, it recommended offering PrEP to people at substantial risk of acquiring HIV rather than limiting the recommendation to specific populations. Substantial risk of HIV infection is provisionally defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP.

Before providing PrEP, the following information should be discussed:

- PrEP to be provided as a comprehensive prevention approach with condoms and lubricant, harm reduction, including access to sterile or new injection materials.
- Access to accurate knowledge and information about PrEP also needs to be ensured.
- 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.
- HIV testing, HbsAg and serum creatinine levels will be done at baseline.
- PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained.
- PrEP users should be provided information that ARV drugs will begin to work only after 7 doses.

PrEP will be implemented with TDF+FTC (3TC)-based regimen and has to be taken once daily. During PrEP HIV and creatinine level tests will be done every three months for the first 12 months. While HIV testing is done every three months, the creatinine levels can be done every six months thereafter. The frequent HIV testing during PrEP use also ideally becomes an opportunity for STI screening and management.

The national guideline now recommends making available oral PrEP to the affected key populations with substantial risk of HIV. The PrEP, in combination with other HIV prevention approaches, shall be implemented in phased manner and will be supported by adherence counselling support and repeat HIV testing and will be guided by specific standard operating guidelines. Detailed operational guidelines will be developed soon.

### 2.14.2 Post-Exposure Prophylaxis (PEP) for occupational and non-occupational exposure to HIV

PEP is one of the major ways to reduce the risk of HIV infection in persons exposed to the virus either occupationally or through non-occupational means. It is a short-term use of antiretroviral 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. PEP should be provided to health personnel as part of a comprehensive package of universal precautions that reduce the risk of acquiring disease through exposure to infectious hazards at work. The majority of occupational exposures

do not lead to HIV 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 infections is about 0.3%. The risk of HIV transmission is less with injuries sustained with solid bore (eg suture) needles than with hollow bore (eg 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 membrane (of eyes, nose or mouth) or abraded (broken) skin to HIV-infected material is estimated to be about 0.09%.

Following an exposure, first aid measures should be taken immediately to reduce contact time with the source person's blood, body fluids or tissues, and to clean and decontaminate the site of exposure.

If the skin is broken following an injury with a used needle or sharp instrument, the following is recommended:

- Do not squeeze or rub the injury site.
- Wash the site immediately using soap or a mild disinfectant solution that does not irritate the skin.
- If running water is not available, clean the site with a gel or other hand-cleaning solution, whatever is customarily available.
- 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, the following is recommended:**

- Wash the area immediately.
- If running water is not available, clean the area with a gel or other hand- rub solution, whatever is customarily available.
- Do not use strong disinfectants.

### **After a splash contacts the eye, do the following:**

- 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, as they form a barrier over the eye and will help protect it. Once the eye has been cleaned, remove the contact lenses and clean them in a normal manner. This will make them safe for wearing again.
- Do not use soap or disinfectant on the eye.

## After a splash contacts the mouth, do the following:

- 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 poses a risk of transmission, that is:
  - a. Percutaneous exposure to potentially infectious body fluids (infectious body fluids [viz. semen, cervico-vaginal secretions, and blood] and non-infectious body fluids [faeces, saliva, urine and sweat]).
  - b. Sexual intercourse without an intact condom
  - c. Sexual assault
  - d. Exposure to non-intact skin or mucus membranes to potentially infectious body fluids
- 4 The exposure occurred less than 72 hours ago.
- 5 The exposure is not part of chronic exposure (prevention support needed instead).

## Initiating PEP

- Start as soon as possible, preferably within 2 hours.
- The current recommended duration of PEP for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure.
- HIV antibody testing (rapid or ELISA) should be used for monitoring for sero-conversion, and the test should be performed at baseline, 6 weeks, 3 months and 6 months after exposure.
- Testing for other blood-borne diseases, such as hepatitis B and C, is also important, depending on the nature of risk and the local prevalence, if testing is available.
- In the process of seeking informed consent for HIV PEP, people who have been exposed to HIV must be made fully aware of the following:
  - The risk of acquiring HIV infection from specific exposure;
  - What is known and not known about the efficacy of PEP;
  - The importance of having an HIV test and of receiving appropriate post-test counselling (although test may be delayed, if necessary);

- The possibility that they might already be infected with HIV will need to be assessed if they have not already had an HIV test;
- PLHIV should be referred for treatment of their infection and, if they have already started PEP, the medicine should be stopped when the diagnosis is confirmed;
- If PEP regimen comprised Zidovudine, a baseline haemoglobin test should be performed on the exposed person. NVP should not be used for PEP due to the risk of hepatotoxicity.
- The importance of adhering to medicine is essential during counselling (Refer to ART adherence section for management of missing dose and/or if vomiting occurs after taking ARV.)
- Common side-effects may be experienced while taking PEP medicine.
- They can stop taking PEP medicine at any time, but if they do so, they will probably not get the full benefit of PEP if the source to which they were exposed was HIV positive.
- PEP medicine can be taken during pregnancy and may protect the infant from getting HIV infection after exposure.
- It is safe to breastfeed while taking PEP, although if women get infected by HIV while breastfeeding, the risk of transmitting HIV through breastfeeding is higher at the early stage of infection in the absence of ARVs.
- PEP for rape victims should be provided based on risk assessment.
- For non-occupational exposure other than rape, clinicians will decide whether PEP should be provided or not on a case-by-case basis.
- A pack of 7-day drugs for PEP should be made available at all health facilities so that treatment can be immediately initiated as these drugs are usually not available in the open market.

Exposures that do not require HIV PEP include the following:

- when the exposed individual is already HIV positive;
- when the source is established to be HIV negative; and
- when exposures to bodily fluids, ie tears, non-blood-stained saliva, urine and sweat, do not pose a significant risk.

In cases that do not require PEP, the exposed person should be counselled about limiting future exposure risk. Although HIV testing is not required, it may be provided if desired by the exposed person.

## Drug regimens for PEP

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

**Table 2.11 Drug regimens for PEP**

Adults and adolescents (> 10 years)	
Preferred regimen	TDF + 3TC + LPV/r (or ATV/r)
Alternative regimen	TDF + 3TC* + EFV (or RAL or DRV/r)
Children (≤ 10 years)	
Preferred regimen	AZT + 3TC + LPV/r
Alternative regimen	TDF + 3TC or ABC + 3TC with NVP (or ATV/r, RAL for < 3 years) and EFV (or DRV/r for > 3 years)

\* AZT + 3TC in case of intolerance/contra-indication to TDF

### Clinical considerations

The concern about the potential risk of hepatic flares among people with chronic HBV once TDF-, 3TC- or FTC-based PEP is stopped should be considered by clinicians. HBsAg test is not a precondition for starting TDF-, 3TC- or FTC-based PEP, but people with established chronic HBV infection should be monitored for hepatic flare after PEP is discontinued or the need for ongoing HBV therapy after discontinuing PEP should be considered.

NVP should not be used for PEP for adults, adolescents and older children because of the risk of life-threatening serious adverse events associated with HIV negative adults using this drug.

EFV is widely available as a third agent as this drug is used as part of the preferred first-line ART regimen. EFV is well-tolerated for treatment but has limited acceptability for use as PEP as there are concerns about giving a drug associated with early neuropsychiatric adverse events to HIV negative people who may have anxiety related to HIV exposure.

### 2.14.3 Combination of HIV prevention

People's HIV prevention approach needs change during their lifetime, and a combination approach helps people to access the types of activities that prevent HIV that best suit their needs at different times. Combining approaches may also result in synergies that have 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 men who have sex with men, 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 exchange programmes (NSEP)** 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. Opioid substitution therapy also provides adherence support to people on ART.
- **Voluntary medical male circumcision (VMMC)** reduces acquisition of infection and the risk of acquisition for men by up to 66% and offers significant lifelong protection.
- **Behavioural strategies** reduce the frequency of potential transmission events, including 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 the behaviour that increases the risk of HIV and increases the behaviour that is 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, including 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 identifying, reaching, recommending, testing, treatment and retaining persons at higher risk for HIV.

# ARV DRUGS FOR TREATMENT OF INFANTS AND CHILDREN

## 3

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## 3. ARV DRUGS FOR TREATMENT OF INFANTS AND CHILDREN

### 3.1 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.

Antiretroviral drugs should be used properly so as to avoid development of drug resistance and restore or maintain the immune status. It is recommended that the potent first-line antiretroviral regimens be started and 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 to simplify and expand treatment in children, including initiating ART in all children.

### 3.2 Diagnosis of HIV Infection

Early diagnosis for infants is critical, and new evidence supports diagnosis at or within 6 weeks of birth itself. The programme has agreed for birth NAT testing in addition to 6 weeks testing so as to reduce loss to follow-up on HIV-exposed infants. The laboratory diagnosis of infants and children is presented in Chapter 1, HIV Testing Services and Laboratory Diagnosis. WHO has prequalified the Gene XPert platform for EID and this technology is also available in Nepal. For infants and children aged less than 18 months, if access to laboratory testing using PCR is not available, but a child has symptoms that are suggestive of HIV infection, a presumptive clinical diagnosis of HIV infection may need to be made as follows:

- Infant is confirmed HIV-antibody positive; and
  - diagnosis of AIDS-indicator condition(s) can be made or <sup>1</sup>
- the infant is symptomatic with two or more of the following:
  - oral thrush<sup>2</sup>
  - severe pneumonia
  - severe sepsis
- Other factors that support the diagnosis of severe HIV disease in an HIV seropositive infant include:
  - recent HIV-related maternal death or advanced HIV disease in the mother;
  - CD4 < 20%.
- Confirmation of the diagnosis of HIV infection should be sought as soon as possible.

### 3.3 Staging of HIV Infection and 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 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.

Differences in paediatric and adult HIV infection:

- Overall progression of disease is more rapid in children.
- Immune system is more immature with higher CD4 count.
- Recurrent invasive bacterial infections are more common in children.
- Disseminated CMV, Candida, herpes simplex and varicella zoster are more common.
- Lymphocytic Interstitial Pneumonia (LIP) occurs almost exclusively in children.
- CNS infections are common.
- Peripheral neuropathy, myopathy and Kaposi sarcoma are rare in children.

1 AIDS indicator conditions include some but not all HIV paediatric clinical stage 4 such as Pneumocystis pneumonia, cryptococcal meningitis, severe wasting or severe malnutrition, Kaposi sarcoma, extrapulmonary tuberculosis.

2 As per IMCI definition:

- Creamy white to yellow soft small plaques on red or normally coloured mucosa which can often be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender. Not responding to topical antifungal treatment.
- Cough or difficult breathing in a child with chest in drawing, stridor or any of the IMCI general danger signs; ie lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to antibiotics.
- Fever or low body temperature in a young infant with any severe sign such as fast breathing, chest in drawing, bulging fontanelle, lethargy, reduced movement, not feeding or sucking breast milk, convulsions, etc.

### 3.3.1 Patterns of manifestation

Most infected infants do not have any abnormal findings on clinical examination at birth. The natural history of children perinatally infected with HIV fits into one of the following three categories:

#### Category I: Rapid progressors (about 25–30% of cases)

- Manifestations of HIV-infection may occur within the first few months of life;
- OI and neurological manifestations are usual clinical features;
- Undergo a rapid downhill progression; untreated children will die within one year;
- Are thought to have acquired the infection *in utero* or in the early perinatal period.

#### Category II: Majority of paediatric infections (about 50–60% of cases)

- Develop manifestations early in life;
- Failure to thrive, recurrent bacterial infections and lymphoid interstitial pneumonitis usual presentations;
- Downhill course with death by age 3–5 years.

#### Category III: Slow progressors (about 5–25% of cases)

- Long-term survivors;
- Revelation of minor manifestations later in childhood;
- Live beyond age 8 years;
- May have had late postnatal acquisition (breastfeeding).

### 3.3.2 Clinical manifestations

In general, progression of HIV and onset of OIs occur as plasma viral load increases and CD4 count decreases. Effective prophylactic regimens against several OIs have resulted in a decline in their frequency, as well as an improvement in survival rates. Additionally, effective ARV therapy reduces the risk of development of OIs. It is essential to correctly diagnose and treat OIs since many can be life-threatening. The most common and frequent clinical manifestations of OIs are mentioned below.

#### 3.3.2.1. Failure to thrive

- May manifest as early as 4–6 months of age in perinatally infected infants;
- Measured by body weight, length/height and head circumference;
- Causes: Decreased energy intake, diarrhoea, malabsorption, chronic diseases of the heart, kidney and lungs, micronutrient deficiencies, neuroendocrine abnormalities and repeated episodes of infection.

### 3.3.2.2. Lymphadenopathy

**Causes:** Infiltration of lymph nodes by HIV (may present as persistent generalized lymphadenopathy [PGL]);

**Infections:** tuberculosis disseminated atypical mycobacterial infections, viral infections such as CMV, Epstein-Barr virus (EBV), malignancies like lymphoma and lymphosarcoma;

Persistent Generalized Lymphadenopathy WHO definition:

- Swollen or enlarged nodes > 1 cm at 2 or more non-contiguous sites;
- Without known cause;
- Definitive diagnosis is not required.

### 3.3.2.3. Respiratory manifestations

- Pneumonia and chronic lung diseases contribute to increased morbidity and mortality.
- Most children have recurrent bacterial pneumonias, but in children less than 1 year of age Pnuemocystis jiroveci pneumonia (PCP) is also frequent.
- Other HIV-related chronic lung diseases often have a similar clinical presentation, leading to over-diagnosis of TB.
- Signs and symptoms: cough, fever, dyspnoea, wheezing, ear discharge
- Recurrent infections: recurrent bacterial pneumonia; Streptococcus pneumonia is the most common organism.
- Recurrent otitis media and sinusitis are common.
- Viral causes are common.
- Chronic HIV-associated lung diseases include Tuberculosis, Lymphoid Interstitial Pneumonitis and bronchiectasis.
  - PCP causes acute life-threatening pneumonitis. PCP is the most common OI associated with HIV in children. It predominantly occurs between 3 and 6 months of age. Can occur in infants less than 12 months of age despite good CD4 count. PCP is characterized by rapidly progressive hypoxemia.

### 3.3.2.4. Gastrointestinal and Hepatobiliary

**Diarrhoea:** Acute diarrhoea is the most common cause of morbidity. It is the leading cause of death in HIV-infected children during the first year of life. Diarrhoea tends to be prolonged and is usually complicated by dehydration and malnutrition.

- **Causes:** Common infections, OIs (bacteria, virus, protozoa, fungi), malabsorption, inflammatory processes, HIV enteropathy. Persistent diarrhoea

occurs with increased frequency in children with failure to thrive, significant immunosuppression, and infants of mothers with symptomatic HIV.

**Hepatomegaly:** Hepatomegaly within three months of age in perinatally acquired infection is associated with rapid progression of disease.

- **Causes:** HIV replication in reticulo-endothelial tissue, fatty infiltration, malnutrition, viral hepatitis: Hepatitis A, Hepatitis B, Hepatitis C (rare in paediatrics), CMV, drug toxicity.

### 3.3.2.5. Parotitis

Recurrent or chronic painless unilateral or bilateral parotid swelling. Parotitis is associated with a more favourable outcome.

- **Causes:** HIV infiltration, lymphocytic infiltration

### 3.3.2.6. Oral manifestations

- Thrush (Candidiasis)
- Periodontitis
- Ulcerative gingivitis
- Oral hairy leukoplakia
- Oral or oesophageal ulcerations

### 3.3.2.7 Skin manifestations

- Common presentation in children:

Infectious (Bacterial-impetigo, scabies; viral-Herpes simplex, Herpes zoster, Molluscum contagiosum, Warts; fungal-Candida, Tinea, Onychomycosis)

Non-infectious (Seborrhoeic dermatitis, Atopic dermatitis, generalized dermatitis, Nutritional deficiency, Eczema, Psoriasis, Drug eruptions, Vasculitis, Alopecia)

### 3.3.2.8. Haematological manifestations

- **Anaemia:** Nutritional, bone marrow suppression by HIV virus or other OIs and drug side-effects (ie most commonly, ZDV) are the most common causes.
- **Thrombocytopenia:** Most commonly from bone marrow suppression by HIV itself.
- **Neutropenia,** common side-effects of ZDV (bone marrow suppression)
- **Lymphopenia** with CD4 and CD8 depletion.

### 3.3.2.9. Neurological manifestations

- HIV is a neurotropic virus that invades CNS by infecting monocytes, which cross the blood–brain barrier and establish HIV infection in macrophages and microglial cells.
- Neurological symptoms are widely prevalent, occurring at all stages of HIV infection and affecting any part of the nervous system. About 40% to 70% of HIV-infected persons develop symptomatic neurological disturbances, but the brain is most commonly affected in children. Delay in reaching developmental milestones may be an early indication of HIV infection.
- Encephalopathy and developmental delay are common in HIV-infected children and indicate advanced clinical disease. Encephalopathy may be progressive or static encephalopathy. Presentation of encephalopathy. Failure to attain or loss of motor and intellectual milestones.
- Microcephaly-impaired brain growth. Motor deficits, abnormal reflexes, spasticity, cerebellar and extra-pyramidal signs. Emotional lability, hyperactivity and lethargy. Developmental delay is common (especially gross and fine motor and language skills).
- **Causes:** CNS infiltration by HIV itself, bacterial infections such as pyogenic meningitis, OIs like toxoplasmosis, CMV, cryptococcal meningitis, TB meningitis, malignancies.

### 3.3.2.10. Cardiovascular manifestations

- Subclinical persistent disease common. Cardiomyopathy, conduction disturbances, pericardial effusion, endocarditis seen. Hemodynamic instability due to autonomic neuropathy.
- **Causes:** TB-related disease (ie pericarditis) most common, followed by HIV itself; other possibilities include immune-mediated causes, other intercurrent infections or drug toxicity.

### 3.3.2.11. Nephropathy

- More often seen in older children with symptomatic disease.
- Nephrotic syndrome is the most common presentation; others: hematuria, hypertension, renal tubular acidosis, acute renal failure, end stage renal disease.
- Various underlying renal pathology, eg minimal lesion glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy.
- **Causes:** Immune-mediated, direct viral infection, drug-induced.

### 3.3.2.12. Malignancies

- Less frequent and different from than those in adult AIDS.
- **Most common:** Non-Hodgkin's lymphoma, CNS lymphoma, leiomyoma, EBV-associated leiomyosarcoma and leukaemia. Kaposi sarcoma is very rare in children.

### 3.3.2.13. Recurrent bacterial infections

**Definition:** Two or more bacteriologically documented, systemic bacterial infections in two years, including septicemia, bacteremia, meningitis, pneumonia, or osteomyelitis.

- Iatrogenic factors often involved (eg indwelling catheters, antibiotics and cytotoxic agents).
- Clinical manifestation depends upon the site of infection. Pneumonias are the most common infections. Other infections include otitis media, abscess, sepsis, septic arthritis, meningitis and osteomyelitis.
- Manifestations are similar in HIV-infected and HIV-uninfected children.
- Always search for the causative agent to establish diagnosis.

## 3.4 Preparation of Children for ART

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

### 3.4.1 Medical preparation

The following baseline tests should be carried out to assess haematological, liver and kidney functions, as well as immune status:

- Hb, TC,DC, Platelet, ESR
- Liver functions tests (alanine transaminase)
- Renal function tests (blood urea), blood sugar
- CD4 % and count
- Chest X-ray
- Mantoux test

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. Since HIV-infected individuals remain at high risk of developing TB regardless of treatment status, a high level of vigilance is required for patients in care. If TB is confirmed and dual treatment of TB/HIV is required:

- treat any inter-current illnesses; and
- initiate Cotrimoxazole Prophylaxis in all children.

### 3.4.2 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 need to attend clinic regularly as required, as well as for inter-current 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 clinic if they have concerns or the child becomes ill.
- Children have to be weighed and their height measured regularly at each clinic visit, and dose adjustments are required as children grow and gain weight. The specific need for counselling for adolescents who are becoming sexually mature and adherence issues should also be highlighted.

## 3.5 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, although it does not provide cure. As a result, HIV is now perceived as a manageable chronic illness.

### 3.5.1 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.
- As a priority ART should be started in:
  - Infants diagnosed in the first year of life
  - In all children  $\leq 2$  years of age or children younger than 5 years of age with WHO clinical stage 3 or 4 or CD4 count  $\leq 750$  cells/mm<sup>3</sup> or CD4 percentage  $< 25\%$ , and
  - Children 5 years of age and older with WHO HIV clinical stage 3 or 4 disease or CD4 count  $\leq 350$  cells/mm<sup>3</sup>



## 3.5.2 ART Regimen

### 3.5.2.1. First-line ART for children younger than three years of age

#### Recommendations

- For infants and children younger than 3 years, the NRTI backbone for an ART regimen should be ABC + 3TC.
- An LPV/r-based regimen should be used as the first-line ART for all infected children below three years of age regardless of NNRTI exposure. The use of LPV/r pellets (3-36 months) may be useful as it circumvents cold chain requirements. If LPV/r is not available, treatment should be initiated with an NVP-based regimen. Children older than 3 years of age should receive EFV-based regimen
- Where viral load monitoring is available, consideration can be given to substituting LPV/r with EFV at 3 years of age after viral suppression is sustained.
- For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop TB while on an ART regimen containing NVP or LPV/r. Once TB therapy has been completed, this regimen should be stopped and the initial regimen should be restarted.

**Table 3.1. Summary of first-line ART regimens for children younger than 3 years**

<b>Preferred regimens</b>	ABC + 3TC + LPV/r
<b>Alternative regimens</b>	ABC + 3TC + NVP AZT + 3TC + NVP

A systematic review of two randomized controlled trials shows that children younger than 36 months have a reduced risk of discontinuing treatment and viral failure or death if they start an LPV/r-based regimen instead of an NVP-based regimen. At 24 weeks, LPV/r was demonstrated to be superior to NVP regardless of NNRTI exposure for PMTCT. But if LPV/r is not available, use an NVP-based regimen for children below 3 years and an EFV-based regimen for those above 3 years of age.

#### 3.5.2.2. First-line ART for children 3–10 years of age

- For children 3 years and older infected with HIV, EFV is the preferred NNRTI for the first-line treatment and NVP is the alternative.
- For children 3 years to below 10 years old infected with HIV, the NRTI backbone for an ART regimen should be one of the following, in preferential order:
  - ABC + 3TC
  - AZT or TDF + 3TC

**Table 3.2. Summary of first-line ART regimens for children 3–10 of years**

<b>Preferred regimens</b>	<b>ABC + 3TC + EFV</b>
<b>Alternative regimens</b>	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP

**Table 3.3. Considerations for simplifying and harmonizing ART for children with no history of treatment failure on any regimen<sup>a</sup>**

<b>Regimen containing</b>	<b>Guidance</b>	<b>Individual advantages</b>	<b>Programmatic advantages</b>
LPV/r	No need to change, but consider substituting LPV/r with NVP or EFV if there is sustained virological response on LPV/r	May improve adherence as a result of better palatability and use of fixed-dose combinations in more manageable formulations (once-daily scored tablets) Reduced risk of metabolic alterations	Aligned with adult regimens Preserve PI for second-line ART No cold-chain requirement Reduced drug cost
AZT	No need to change, but may consider changing to ABC or TDF	May improve adherence as a result of once-daily dosing (if on EFV) May reduce the risk of exacerbating anaemia	Aligned with adult regimens
ABC	No need to change, but can consider changing to TDF, especially for adolescents weighing more than 35 kg	Fixed-dose combinations can be used (if also on EFV)	Aligned with adult regimens
NVP	No need to change, but may consider changing to EFV, particularly from age 3 years onwards	May improve adherence as a result of once-daily dosing (if combined with ABC or TDF)	Aligned with adult regimens

<sup>a</sup> Defined according to the criteria for treatment failure adopted nationally, preferably using viral load testing, where feasible and available.

ABC abacavir, AZT zidovudine, ART antiretroviral therapy, d4T stavudine, EFV efavirenz, LPV/r lopinavir/ritonavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, TDF tenofovir.

### 3.5.3 Use of ARV for infant prophylaxis for HIV-exposed infants

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 prevent vertical HIV transmission is to reduce maternal viral load. All HIV-exposed babies should receive ARV prophylaxis as soon as possible after birth. Dual prophylaxis for babies with high risk of HIV is adopted to reduce the risk of HIV transmission.

#### Recommendations:

Low risk	Oral NVP for 6 weeks OR Oral AZT for 6 weeks for infants of mothers exposed to NVP in the past
High risk <sup>a</sup>	<b>Dual Prophylaxis</b> AZT <sup>b</sup> + NVP for 12 weeks

<sup>a</sup> **High risk infants** are defined as:

- Mothers not on ART or < 8 weeks of ART at delivery
- If VL is available  
VL > 1,000 copies/ml at or 4 weeks before delivery
- If VL not available  
Newly diagnosed women at delivery or postpartum

<sup>b</sup>AZT is to be given only to those infants who can come for regular follow-up of haemoglobin tests. If not feasible, then give oral NVP to high risk infants for 12 weeks.

## 3.9 Vaccination for Children Living with HIV

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/mm<sup>3</sup>.

HIV-exposed infants and children with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules. However, live vaccines should be avoided in children with advanced clinical stages and severe immunosuppression. An extra dose of measles vaccination at 6 months of age is recommended.

## 3.10 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 intakes 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.

Adequate and appropriate nutrition from the early to advanced stages of HIV infection is necessary to optimize health outcomes. Breastfeeding should be promoted and supported for optimal growth and development of infants. Infants should be exclusively breastfed for the first six 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.

ART, when clinically indicated, improves weight, growth and development of infected children and improves their life expectancy.

### 3.10.1. Set targets for energy and micronutrient intakes

Children that are growing well and 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 needs, eg chronic lung disease or chronic infections, eg TB or persistent diarrhoea (Children may or may not be on ART):*

- Children with chronic illnesses may require extra 20–30% energy each day (based on actual weight rather than expected weight for age).

These children also need ART and should be referred to a treatment site for assessment and exclusion of TB.

*Children with severe malnutrition, ie signs of visible wasting, bilateral oedema or severely impaired growth. (Children may or may not be on ART):*

- These children need 50 to 100% extra energy each day (based on actual weight rather than expected weight for age) for a limited period until weight is recovered.
- These children should be treated with therapeutic feeding, which should continue until nutritional recovery is achieved (average ~ 6–10 weeks).
- They should also be referred to an ART treatment site for assessment and exclusion of TB.
- Other OIs such as thrush, TB or cryptosporidiosis should also be excluded and treated.

## Opportunistic Infections



*Pic. 3.1. Children with severe malnutrition*



*Pic. 3.2. Cervical lymphadenopathy*



*Pic. 3.3. Child with pneumonia with distress*



Figure 3.3.2.3. Chest X-ray showing consolidation of right upper and mid-zone



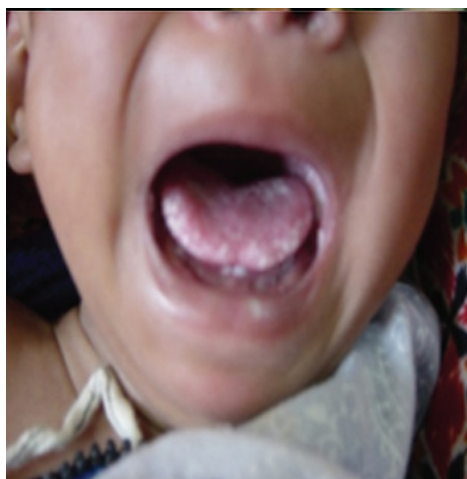
Figure 3.3.2.3c Chest X-ray showing right and left bronchiectatic changes lower zones



Pic. 3.4. Hepatosplenomegaly



Pic. 3.5. Parotid gland swelling



Pic. 3.6. Oral Candidiasis



Pic. 3.7. Pyoderma



Pic. 3.8. Tinea corporis



Pic. 3.9. Moluscum contagiosum



Pic. 3.10. Herpes Zoster



Pic. 3.11. Varicella zoster



Pic. 3.12. Severe anaemia in tongue



Pic. 3.13. Severe anaemia in palm



Pic. 3.14. Ecchymotic

# MONITORING OF PATIENTS ON ART AND MONITORING THE NATIONAL ART PROGRAMME

## 4

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## 4. MONITORING OF PATIENTS ON ART AND MONITORING THE NATIONAL ART PROGRAMME

### 4.1 Introduction

Monitoring of patients on ART is crucial for the success of any ART programme, as well as its outcome for individual patients. Monitoring ranges from programme-level monitoring to monitoring of individual patients. For programme level, treatment cascade can be used for identifying leakages in the programme. Using the cascade approach regularly and identifying leakages in the cascade help early identification of issues.

At individual level, it is very important to know the adherence status of ARV intake and to see the success of ARV treatment. Monitoring of ARV is important for timely and early recognition of drug toxicities and treatment failure and drug resistance so that necessary action can be taken to switch to the second-line or third-line drugs before it is too late. Different parameters like clinical monitoring and laboratory monitoring should be used properly to adequately monitor HIV positive people taking ARV. CD4 count, viral load, routine checks, plasma levels and resistance tests should be considered properly for correct monitoring.

Section A of this chapter deals with monitoring of patients on ART, while section B deals with ART programme monitoring, including drug resistance.

**Section A: Monitoring of patients on ART, response to ART, drug toxicities and substitution, treatment failure and switching to the second- and third-line drugs**

### 4.2 Recommended Follow-up Visits for Monitoring of Individual Patients

All new patients who have been put on ART have to pay more frequent visits to the ART centre till they are stabilized when the frequency of visits can be reduced. The national experts agreed with the concept of Differentiated Care outlines in the 2016 Guidelines with some modifications in frequency of visits in the first year.

Patients may need differentiated care according to clinical characteristics. Clinical characteristics determine the need for care and related visits to health facilities. Categories of clients and required clinical visits agreed by the programme are as shown below.

**Newly Initiated on ART:** Initial two or three preparedness counselling are must before initiating ART, but time should not be lost between these sessions and ART should be started as early as possible once the patient is ready. The suggested frequency thereafter is as below:

- 1 First month: two visits (every 2 weeks)
- 2 Thereafter, every month until client is categorized as stable
- 3 Stable patients can be dispensed drugs for three months at a time.
- 4 Patients not stable on ART need to be followed up once every month or more frequently as required.

**Stable on ART:** Stable clients are those who have received ART for **at least one year** and have no adverse drug reactions that require regular monitoring, no current illness or pregnancy, are not currently breastfeeding, have good understanding of lifelong adherence and evidence of treatment success (two consecutive VL measurements is below 1,000 copies/ml) and in absence of VL- rise of CD4 count or CD4 count more than 200 cells/mm<sup>3</sup>.

**Not stable on ART:** These are clients with treatment failure, poor adherence, OIs and adverse effects. In addition, those at risk of being lost to follow-up or returning after being lost to follow-up fall in this category. These clients should be followed up more frequently as in the first three months. Viral load should be done as indicated and client should be referred for consultation with ART clinician for adherence/OI management or possible change in ART regimen.

### 4.3 Supporting ART in the Community

People taking ART need support, not only from health facilities but also from the community. PLHIV networks, NGOs working in the community, including community-based organizations (CBOs), community health workers (CHWs) and community-based supporters can be mobilized for supporting clients for adherence, retention and follow-up for ART. The NHSP proposes a case management approach to support PLHIV.

- a. Monitoring of patients on ART
  - Clinical monitoring
    - Monthly clinical evaluation
      - weight, overall wellbeing, any fresh symptoms, routine 4-symptom screening for TB on every visit
    - Monthly treatment adherence evaluation, pill count, self-reporting
    - For adverse reactions of ART/OI drugs
    - For drug interactions, look for concomitant drugs

- For IRIS
- Immunological monitoring
  - CD4 count (every 6 months but for virologically suppressed patients, frequency can be reduced or stopped)
- Virological monitoring (at 6 months, 12 months and every 12 months)

## 4.4 Laboratory Monitoring of Patients on ART

Clinical assessment and laboratory tests are very important in assessing individuals before ART is started and then monitoring their treatment response and possible toxicity of ARV drugs. Baseline laboratory tests to be done for PLHIV before initiating ART are discussed for adults in Chapter 2 and for children in Chapter 3. This section deals with laboratory and clinical monitoring to be done for patients already on ART and coming for regular clinic visits.

**Table 4.1. Recommended tests for monitoring patients on ART (follow-up tests)**

All patients on ART need to go through CD4, Hb, TLC, DLC, ALT (SGPT), BI urea once at every six months. Drug-specific test frequency is shown below.								
Monitoring tool	Test	Baseline	15 <sup>th</sup> Day	1 <sup>st</sup> Month	2 <sup>nd</sup> Month	3 <sup>rd</sup> Month	6 <sup>th</sup> Month	Than every 6 months
On Zidovudine-based ART	CBC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
On Tenofovir-based ART	Serum Creatinine Urine for albumin	Yes	-	Yes	-	yes	Yes	Yes
Nevirapine-containing ART	ALT (SGPT)	Yes	Yes	Yes	-	-	Yes	Yes
Efavirenz-containing ART	Lipid profile	Yes	-	-	-	-	Yes	Yes
Atazanavir-containing ART	Direct and Indirect Bilirubin	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lopinavir-containing ART	Lipid Profile and Blood sugar	Yes	-	-	-	-	Yes	Yes

It is desirable to monitor patients with viral load at 6 and 12 months after initiation of ART and then viral load every 12 months once viral suppression is achieved. For stable patients with virological suppression, frequency of CD4 can be reduced or stopped. CD4 test is required for CPT initiation/ stopping CPT, and for primary and secondary prophylaxis for some OIs.

Other tests can be done earlier based on clinician's assessment/discretion and as per availability.

## 4.5 Recommendations for Viral Load Monitoring

- Routine viral load monitoring can be carried out at 6<sup>th</sup> month, at 12<sup>th</sup> month and then every 12 months thereafter if the patient is stable on ART to synchronize with routine monitoring and evaluation reporting.
- In settings where routine viral load monitoring is available, CD4 cell count monitoring can be stopped in individuals who are stable on ART and virally suppressed.

## 4.6 Monitoring and Substitutions for ARV Drug Toxicities

### 4.6.1 Guiding principles and major types of ARV toxicities

The availability of laboratory monitoring is not required for initiating ART. However, for those receiving ART, symptom-directed laboratory monitoring for safety and toxicity can be used.

Although laboratory tests are not required for initiating ART, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs. Periodic laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users) is required for all individuals or only for people at higher risk. Major toxicities of the first-line drugs are shown in Table 4.2.

**Table 4.2. Major toxicities of first-line drugs**

Drugs	Short-term Toxicities	Medium-term toxicities	Long-term toxicities
Zidovudine	Headache, nausea, vomiting, malaise, diarrhoea Bone marrow suppression Anaemia (Macrocytic)	Bone Marrow suppression Anaemia (Macrocytic) Hyper pigmentation Lactic Acidosis Proximal myopathy	
Tenofovir	Nephrotoxicity (low incidence), Fanconi syndrome and rarely Acute Renal Failure		
Efavirenz	Drowsiness, dizziness Confusion, Vivid dreams Skin Rashes Hepato toxicity (very rare)		
Nevirapine	Skin Rashes Hepatotoxicity		

**Table 4.3. Common toxicities and drugs**

Overlapping Toxicities	Drugs
<b>Bone marrow suppression</b>	Zidovudine, Cotrimoxazole, Dapsone, Pyrimethamine, Ganciclovir, Amphotericin B, Ribavirin
<b>Hepatotoxicity</b>	Nevirapine, Atazanavir, Lopinavir, Ritonavir, Isoniazid, Rifampicin, Pyrazinamide, Fluconazole, Cotrimoxazole
<b>Peripheral neuropathy</b>	Isoniazid, Alcohol
<b>Pancreatitis</b>	Cotrimoxazole, Alcohol

### Evaluation of ARV drug toxicity, general principles

- 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 like Cotrimoxazole, anti-TB drugs and other antibiotics must be ruled out before the toxicities are thought to be due to antiretroviral drugs.

### Clinical considerations

- 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 for drug toxicity and to avoid drug interactions. Table 4.4 lists the key types of toxicity and associated risk factors for the major ARV drugs and suggested management. The table gives details of adverse reactions to all ARV drugs.

**Table 4.4. Types of toxicities associated with ARV drugs**

ARV Drug	Major Type of Toxicity	Risk Factor	Suggested Management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	Do not use ABC in the presence of HLA-B*5701 allele. Substitute with AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction 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 on concomitant drugs that may prolong the PR or QRS intervals
	Indirect hyperbilirubinemia (clinical jaundice)	Presence of uridine diphosphate (UDP)-glucuronosyltransferase 1A1*28 (UGT1A1*28) allele	This phenomenon is clinically benign but may potentially cause shame. 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	Anaemia (Picture 4.1), neutropenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropenia CD4 count $\leq 200$ cells/mm <sup>3</sup>	If AZT is being used in first-line ART, substitute with TDF or ABC. Consider use of low-dose Zidovudine.
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy Lipodystrophy Myopathy	BMI > 25 (or body weight > 75 kg) Prolonged exposure to nucleoside analogues	Substitute with TDF or ABC.
DTG	Allergic reactions Liver problems	Primarily with Hep B or Hep C coinfection	Non-INSTI ART
	Insomnia, Depression Tiredness Headache	primarily in patients with pre-existing psychiatric conditions	

ARV Drug	Major Type of Toxicity	Risk Factor	Suggested Management	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia, abnormal dreams) or mental symptoms (anxiety, depression, mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	For CNS symptoms, dose at night-time, consider using EFV at a lower dose (400 mg/day) or substitute with NVP or integrase inhibitor (DTG) if EFV 400 mg is not effective in reducing symptoms. For severe hepatotoxicity or hypersensitivity reactions, substitute with another therapeutic class (integrase inhibitors or boosted PIs).	
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drug		
	Convulsions	History of seizure		
	Hypersensitivity reaction, Stevens – Johnson syndrome, Potential risk of neural tube birth defects (very low risk in humans) Male gynaecomastia (Picture 4.3)	Risk factors unknown		
LPV/r	Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	Use with caution in people with pre-existing conduction disease or those on concomitant drugs that may prolong the PR or QRS intervals	
	QT interval prolongation	Congenital long QT syndrome Hypokalaemia Concomitant use of drugs that may prolong the QT Interval		
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with NVP or RAL for children younger than 3 years and EFV for children 3 years and older. ATV can be used for children older than 6 years. If LPV/r is used in second-line ART for adults, and the person has treatment failure with NNRTI in first-line ART, consider integrase inhibitors.	
	Pancreatitis	Advanced HIV disease, alcohol Misuse		
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes		Substitute with another therapeutic class (integrase inhibitors).
	Diarrhoea			Substitute with ATV/r, DRV/r or integrase inhibitors.

ARV Drug	Major Type of Toxicity	Risk Factor	Suggested Management
NVP	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs CD4 > 250 cells/mm <sup>3</sup> in women CD4 > 400 cells/mm <sup>3</sup> in men during first month of therapy (if lead-in dose is not used)	If hepatotoxicity is mild, consider substitution with EFV, including in children 3 years and older. For severe hepatotoxicity and hypersensitivity, and in children under the age of 3 years, substitute with another therapeutic class (integrase inhibitors or boosted PIs).
	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome) (Picture 4.4)	Risk factors unknown	
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Substitute with another therapeutic class (etravirine, boosted PIs).
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factors unknown	
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years of age 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 eGFR < 50 mL/min, uncontrolled hypertension, untreated diabetes, or presence of renal failure.
	Decreases in bone mineral density	History of osteomalacia (in adults) and rickets (in 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	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	



## 4.6.2 Monitoring TDF toxicity

The renal toxicity of TDF is characterized by proximal tubular cell dysfunctions that 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 to start treatment with TDF. People with impaired eGFR at baseline ( $< 50$  mL/min) should not initiate TDF.

Serum creatinine test to detect and limit further progression of renal impairment is recommended in clients 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 ATV/r compared to when combined with LPV/r). See the clinical considerations given below.

Careful growth monitoring is recommended for children receiving treatment with TDF because of TDF-related decreases in bone mineral density (see Table 4.4).

### Clinical considerations

- Laboratory monitoring is not compulsory to start treatment with TDF.
- 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 test is routinely available, use the estimated glomerular filtration rate at baseline before initiating TDF regimens.
- TDF should not be initiated when the estimated glomerular filtration rate is  $< 50$  ml/min, or in long-term diabetes, uncontrolled hypertension and renal failure.
- Monitor growth in children using TDF.

### 4.6.3 Toxicity monitoring for other ARV drugs

#### ABC

ABC increases risk of hypersensitivity reaction and myocardial infarction in adults. HSR is associated with the presence of HLA-B-5701 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 count > 250 cells/mm<sup>3</sup> and individuals with HIV who are coinfecting with HBV or HCV.

#### EFV

The main type of toxicity of EFV is central nervous system 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 has shown that there is no overall increase in the incidence of birth defects for first-trimester EFV exposure compared with other ARV; thus, it can be used safely.

### 4.6.4 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. Major interactions with commonly used drugs are discussed below.

- When people infected with both TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV or Raltegravir can be used instead of PIs. In case it is not possible to avoid PI, use non-rifampicin-based ATT after consulting the TB treatment provider. Rifampicin is known to significantly lower plasma concentrations of DTG and increasing the dose to a twice-daily schedule may be necessary.
- **Simeprevir** and the combination of ombitasvir + paritaprevir + ritonavir plus dasabuvir should not be co-administered with any PI or NNRTI if used in

clients with Hepatitis C coinfection. **Daclatasvir** is associated with significant drug interactions with many NNRTIs and PIs, and its concomitant use requires caution, dose adjustments or consideration of alternative 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.

- NVP may decrease the concentrations of Itraconazole and ketoconazole to sub-therapeutic levels when they are used together; so, when treating fungal infections, fluconazole can be used to ensure adequate treatment.
- Most of the ARVs, mainly EFV, decreases methadone concentration, leading to withdrawal symptoms and increasing risk of relapse to opioid use; so, dose adjustment is required.
- ARVs, especially some NNRTIs and RTV-boosted PIs, may alter the effectiveness of mainly oestrogen-containing hormonal contraceptives. In such case consistent use of condom or other contraceptive method is recommended.
- Concomitant use of boosted PIs and NNRTI with antihistamine (eg astemizole and terfenadine) is associated with severe and life-threatening reactions like cardiac arrhythmias. Alternative agents like loratidine and cetirizine are preferred.
- 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 treating other conditions and the suggested management are given in Table 4.5.

**Table 4.5 Key ARV drug interactions and suggested management**

ARV drug	Key interactions	Suggested management
AZT	Ribavirin and pegylated interferon alpha-2a	Substitute AZT with TDF
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin. Adjust the dose of LPV/r or substitute with three NRTIs (for children) or replace PIs with RAL
	Halofantrine and lumefantrine	Use an alternative anti-malarial agent
	Lovastatin and simvastatin	Use an alternative cholesterol-lowering agent
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	TDF	Monitor renal function
Simeprevir	Use alternative DAA	

ARV drug	Key interactions	Suggested management
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
EFV	Amodiaquine	Use an alternative anti-malarial agent
	Methadone	Adjust the methadone dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods to prevent HIV transmission and unintended pregnancies, as EFV may lower efficacy of some long-acting hormonal contraceptives
	Astemizole and terfenadine	Use an alternative antihistamine agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA
NVP	Rifampicin	Substitute NVP with EFV
	Methadone	Adjust the methadone dose as appropriate
	Astemizole and terfenadine	Use alternative antihistamine agent
	Itraconazole and ketoconazole	Use an alternative antifungal agent
	Simeprevir	Use alternative DAA
	Ombitasvir + paritaprevir + ritonavir plus dasabuvir	Use alternative DAA

AZT: zidovudine, ATV: atazanavir, DAA: direct-acting antiviral (agent), DRV: darunavir, DTG: dolutegravir, EFV: efavirenz, LPV: lopinavir, NRTI: nucleoside reverse-transcriptase inhibitor, NVP: nevirapine, PI: protease inhibitor, r: ritonavir, TDF: tenofovir.

## 4.7 Diagnosis of Treatment Failure

### 4.7.1 Recommendations for diagnosis of treatment failure

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure.
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.
- Viral failure is defined by a persistently detectable viral load exceeding 1000 copies/mL (that is two consecutive viral load measurements within a 3-month interval with adherence support between measurements) after at least 6 months of starting a new ART regimen.
- WHO recommends a threshold of 1000 copies/mL based on the fact that the risk of HIV transmission and disease progression is very low when viral load is lower than 1000 copies/mL, and that below this threshold, viral blips or intermittent low-level viraemia (50–1000 copies/mL) can occur during effective treatment but are not associated with an increased risk of treatment failure.

- Dried blood spot specimens using venous or capillary whole blood can be used to determine the HIV viral load. A threshold of 1000 copies/mL can be used to determine viral failure when using dried blood spot samples, as defined for testing in plasma<sup>a</sup> (conditional recommendation, low-quality evidence).

<sup>a</sup> Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended for use in settings where logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

**Table 4.6. WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens**

Failure	Definition	Comments
<b>Clinical failure</b>	<p><b>Adults and adolescents</b> New or recurrent clinical event, indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment</p> <p><b>Children</b> New or recurrent clinical event, indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical conditions with the exception of TB) after 6 months of effective treatment</p>	<p>The conditions must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART.</p> <p>For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure.</p>
<b>Immunological failure</b>	<p><b>Adults and adolescents</b> CD4 count at or below 250 cells/mm<sup>3</sup> following clinical failure<sup>b</sup> or persistent CD4 levels below 100 cells/mm<sup>3</sup></p> <p><b>Children</b> Younger than 5 years; persistent CD4 levels below 200 cells/mm<sup>3</sup></p> <p>Older than 5 years Persistent CD4 levels below 100 cells/mm<sup>3</sup></p>	<p>Without concomitant or recent infection to cause a transient decline in the CD4 cell count</p> <p>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>
<b>Virological failure</b>	<p>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</p>	<p>An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed</p>

### 4.7.2 Determining treatment failure in the absence of viral load monitoring

In the absence of viral load 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. As current recommendation a single CD4 count at or below 250 cells/mm<sup>3</sup> following clinical failure is an indicator of immunological failure, though it has low sensitivity and positive predictive value for identifying individuals with virological failure.

### 4.7.3 Stopping CD4 count monitoring where viral load testing is available

Where viral load testing is routinely available and individuals are virally suppressed, long-term CD4 cell count monitoring adds little value in people who are stable on ART. The current recommendation for Nepal is to continue using CD4 testing till VL testing becomes readily available. It is important for assessing the baseline risk of disease progression, particularly for individuals presenting advanced disease, decisions regarding starting and stopping prophylaxis for OIs, and prioritization decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for people who are failing ART. The first CD4 count should be done at the 6th month and then yearly for three years and as per requirement (if VL is suppressed).

### 4.7.4 Viral load for assessing transmission risk

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

### 4.7.5 Implementation considerations

Access to ART should be the first priority for all age groups, and lack of baseline testing should not be a barrier to initiating ART. Routine viral load testing is required for monitoring of ART for all. Ensure that healthcare providers are adequately trained to conduct timely viral load testing and take appropriate clinical actions when the viral load is high: intensified adherence support and possible regimen switches. The following are the conditions for prioritizing VL tests if routine VL cannot be offered:

- pregnant and breastfeeding women, especially around the time of delivery (documented high viral load at delivery is an indication of enhanced infant prophylaxis);

- HIV-infected infants and children for whom CD4-based criteria are particularly poor and in light of the limited drug options available for lifelong treatment; infants exposed to maternal ART and/or postnatal prophylaxis (if treated with NNRTI-based regimens); and
- more frequent viral load testing in adolescents who are at the highest risk of HIV drug resistance.

However, the national programme recommends viral load monitoring for all patients on ART and has also established a second laboratory. At present, samples are transported to these sites with support from partners but programme needs to strengthen this area and take greater ownership for sustainability.

## 4.8 Second-line ART for Adults and Adolescents

### Recommendations

- The second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).
- **The following sequence of second-line NRTI options is recommended:**
  - After failure on a TDF + 3TC-based first-line regimen, use AZT + 3TC as the NRTI backbone in the second-line regimens.
  - After failure on an AZT + 3TC-based first-line regimen, use TDF + 3TC as the NRTI backbone in the second-line regimens.
  - Use NRTI backbones as an FDC as the preferred approach.
- Heat-stable FDCs of ATV/r and LPV/r are the preferred boosted PI options for the second-line ART.
- Heat-stable FDCs of DRV/r can be used as the alternative boosted PI options for the second-line ART.
- A combination of RAL plus LPV/r can be used as an alternative second-line ART regimen.

## 4.9 Second-line ART for children

### Recommendations

- After failure of the first-line LPV/r-based regimen, children younger than 3 years should be switched to a RAL-based second-line regimen.
- After failure of the first-line LPV/r-based regimen, children older than 3 years should be switched to a second-line regimen containing two NRTIs plus EFV or RAL.

- After failure of the first-line NNRTI-based regimen, children should be switched to a boosted PI-based regimen. LPV/r or ATV/r is preferred.
- After failure of the first-line regimen of ABC or TDF + 3TC (or FTC), the preferred NRTI backbone option for the second-line ART is AZT + 3TC.
- After failure of the first-line regimen containing AZT + 3TC (or FTC), the preferred NRTI backbone option for the second-line ART is ABC or TDF + 3TC (or FTC).

**Table 4.7. Preferred second-line ART regimens for adults, adolescents, pregnant women and children**

Population		Failing first-line regimen	Preferred second-line regimen <sup>e</sup>	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs <sup>b</sup> + ATV/r or LPV/r	2 NRTIs <sup>b</sup> + DRV/r <sup>c</sup>
		If AZT was used in first-line ART	TDF + 3TC (or FTC) + ATV/r or LPV/r <sup>f,g</sup>	
		If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r <sup>f,g</sup>	
Pregnant or breast feeding women		2 NRTIs + EFV (or NVP)	2 NRTIs <sup>b</sup> + ATV/r or LPV/r	2 NRTIs <sup>b</sup> + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs <sup>b</sup> + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs <sup>b</sup> + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs <sup>b</sup> + LPV/r	2 NRTIs <sup>b</sup> + RAL <sup>d</sup>
	3 years to less than 10 years	2 NRTIs + LPV/r <sup>a</sup>	2 NRTIs <sup>b</sup> + EFV	2 NRTIs <sup>b</sup> + RAL <sup>d</sup>
		2 NRTIs + EFV (or NVP)	2 NRTIs <sup>b</sup> + LPV/r	2 NRTIs <sup>b</sup> + ATV/r <sup>d</sup>
HIV and TB coinfection	If rifabutin is available	Standard PI-containing regimens as recommended for adults and adolescents		
	If rifabutin is not available	Same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is LPV/r 800 mg/200 mg twice daily) <sup>h</sup> or used RAL instead of LPV/r		
HIV and HBV coinfection		AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r) <sup>i</sup>		



<sup>a</sup> ATV/r can be used as an alternative PI for children older than 3 months of age.

<sup>b</sup> If ABC + 3TC or TDF + 3TC (or FTC) was used in the first-line failing regimen, AZT + 3TC should be used in second-line and vice versa.

<sup>c</sup> RAL + LPV/r can be used as an alternative second-line regimen in adults and adolescents.

<sup>d</sup> DRV/r can be used as an alternative PI option in special situations.

<sup>e</sup> ABC and didanosine (ddl) can be used as NRTI back-up options for adults but add complexity and cost without clinical advantages.

<sup>f</sup> DRV/r can be used as an alternative PI option.

<sup>g</sup> RAL + LPV/r can be used as an alternative second-line regimen (conditional recommendation, low-quality evidence).

<sup>h</sup> Standard LPV/r and RTV-boosted saquinavir (SQV/r) doses with an adjusted dose of RTV (that is LPV 400 mg/ RTV 400 mg or SQV 400 mg /RTV 400 mg twice daily) can be used as alternative options.

3TC lamivudine, ABC abacavir, ATV atazanavir, AZT zidovudine, d4T Stavudine DTG dolutegravir, EFV efavirenz, FTC emtricitabine, LPV lopinavir, NRTI nucleoside reverse-transcriptase inhibitor, NVP nevirapine, PI protease inhibitor, r or RTV ritonavir, RAL raltegravir. TDF Tenofovir

## 4.10 Third-line ART

### New Recommendations

- National programmes should develop policies for third-line ART.
- The third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second generation NNRTIs and PIs.
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

National programme will use Raltegravir plus Darunavir boosted with ritonavir for the third-line ART.

Patients on failing second-line regimen with no new ARV options should continue with tolerated drugs.

### Clinical considerations

The criteria for diagnosing the failure of the second-line ART are the same as those used for diagnosing the failure of the first-line ART. The demand for second- and third-line regimens will increase as access to viral load monitoring improves and the first-line ART continues to be scaled up.

## Section B: Monitoring the National ART Programme

The HIV treatment cascade—also referred to as HIV care continuum—is a system to monitor the number of PLHIV who are actually receiving clinical care and the treatment they need. It recognizes the various steps necessary for engaging PLHIV in HIV care—from an initial stage of getting tested to being able to suppress the virus through treatment. It is built around the science that when people are engaged in care and taking ART to reduce the amount of virus in their body, it makes them less likely to transmit HIV to others. By ensuring that everyone with HIV is aware of her/his infection and receiving the treatment she/he needs, we can sharply reduce new infections. Key populations (KP) are high priority in efforts to reach the ambitious 90–90–90 goals of UNAIDS by 2020. What is needed is a data-driven approach that stresses evidence-based interventions focusing on the highest risk populations in areas of highest HIV incidence. This “epidemic control” model necessitates that KP flow efficiently, consistently and sustainably through the entire HIV Continuum of Prevention, Care and Treatment (CoPCT) services. Focusing outreach efforts on individuals at greatest risk; increasing uptake of HIV Testing Services (HTS) among KP; facilitating early diagnosis of HIV infection and initiation on ART; and retaining PLHIV on treatment are the hallmarks of a strong HIV response that ultimately lowers viral suppression and achieves population-level impact.

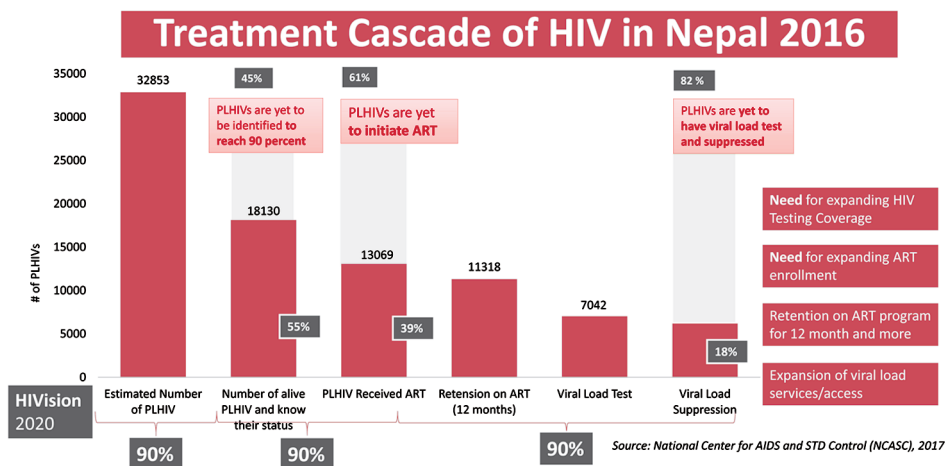


Figure 4.1. HIV treatment cascade

The HIV treatment cascade provides a framework for service providers and policymakers to examine critical questions such as the number of PLHIV getting tested and diagnosed; of those, the number enrolled in care, the number receiving ART, the number sustained on ART, and the number able to adhere to their treatment plan and achieve viral suppression. By closely examining the cascade steps, policymakers and service providers can pinpoint where gaps may exist in connecting PLHIV to sustained quality care. If service providers can keep track of when patients most commonly drop out and what populations commonly do so, it can help policymakers and service providers improve systems and services to better support PLHIV as they move from one step in the care continuum to the next.

## 4.11 Monitoring ARV Drug Resistance (HIV-DR)

WHO describes the factors broadly associated with the emergence of HIV-DR as follows:

- (i) viral factors (such as HIV subtype, replication capacity and pre-existing polymorphisms);
- (ii) drug-related factors (such as drug potency, pharmacokinetics, drug–drug interactions, tolerance and genetic barrier to resistance); and
- (iii) programme factors (such as adherence to prescribed ART, drug supply continuity and retention of patients on treatment).

Viral and drug-related factors are beyond the control of national programme managers. Monitoring of ART programme factors can alert ART clinics and national programme planners to situations that may favour population-level virological failure and/or emergence of resistance. WHO recommends that prevention of HIV-DR be integrated into the national HIV programmes through the annual monitoring of early warning indicators (EWIs) and through the implementation of HIVDR surveillance.

WHO recommends routine surveillance for HIV drug resistance (HIV-DR) in populations initiating ART and in populations on ART for 12 months and more than 48 months. The results of these surveys support the choice of recommended first- and second-line ART and pre- and post-exposure prophylaxis.

### 4.11.1 Monitoring early warning indicators for HIV drug resistance

Use of EWIs is recommended to identify deficits in programme performance that favour the emergence of HIV drug resistance. EWIs are quality of care indicators which specifically assess factors at individual ART clinics associated with emergence of HIVDR. Where widely implemented, EWIs provide the necessary programmatic context to interpret results of surveys of transmitted and acquired HIVDR and will produce evidence to help minimize the preventable emergence of HIV drug resistance and thus improve patient care and the quality of life of PLHIV. EWIs evaluate the factors associated with HIVDR prevention without requiring laboratory testing for drug resistance. It is recommended that all clinics providing ART monitor EWIs annually.

Strengthening specific aspects of ART programme delivery at site level will minimize preventable HIVDR and promote the long-term efficacy and durability of the available first- and second-line regimens.

The EWIs recommended by WHO (Table 4.8) have the strongest links to the development of HIVDR. Targets are recommended for each indicator that facilities should reach to prevent emergence of drug resistance in ART patients.

**Table 4.8. Recommended EWIs and targets**

Early Warning Indicator and Definition	Target
1. On-time pill pick-up: percentage of patients (adult or paediatric) that pickup ART no more than two days later at the first pick-up after the baseline pick-up	Red: < 80% (poor performance, below the desired level) Amber: 80–90% (fair performance, not yet at desired level) Green: > 90% (excellent performance; desired level)
2. Retention in care: percentage of adults and children known to be alive and on treatment 12 months after initiation of ART	Red: < 75% retained after 12 months of ART Amber: 75–85% retained after 12 months of ART Green: > 85% retained after 12 months of ART
3. Pharmacy stock-outs: percentage of months in a designated year in which there were no ARV drug stock-outs	Red: < 100% of a 12-month period with no stock-outs Green: 100% of a 12-month period with no stock-outs
4. Dispensing practices: percentage of adults and children prescribed or picking up mono or dual ARV therapy	Red: > 0% dispensing of mono- or dual therapy Green: 0% dispensing of mono- or dual therapy
5. Viral load suppression at 12 months: percentage of patients receiving ART at the site after the first 12 months of ART whose viral load is < 1000 copies/ml	Red: < 70% viral load suppression after 12 months of ART Amber: 70–85% viral load suppression after 12 months Green: > 85% viral load suppression after 12 months of ART

### 4.11.2 Surveys to monitor HIV drug resistance

The WHO generic protocol for monitoring acquired HIV drug resistance uses a standardized survey methodology to assess population-level virological suppression at national level and the emergence of HIV drug resistance among populations receiving treatment. Performed regularly at representative sites, these surveys provide evidence for action at programme and clinic levels to minimize HIV drug resistance. They also provide evidence to optimize the selection of the first- and second-line ART regimens.

The WHO generic protocol for surveillance of pre-treatment HIVDR provides nationally representative estimate of HIV drug resistance in populations initiating therapy. Performed regularly at representative ART clinics, these surveys support national decision-making regarding the choice of the first-line regimens.

The WHO generic protocol for surveillance of transmitted HIV drug resistance provides estimates of transmitted HIV drug resistance in recently infected populations, and the results should contribute to ART policy decisions, including guidelines on ART regimens and HIV prophylaxis.

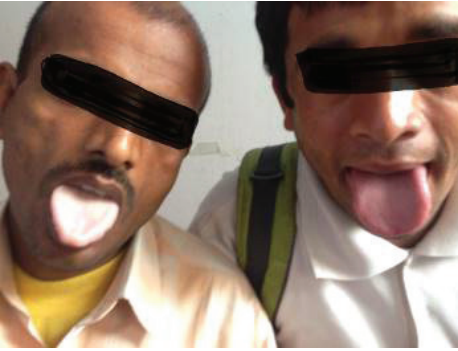
The WHO generic protocol for surveillance of HIV drug resistance among children under 18 months of age can provide estimates of national prevalence of HIV drug resistance among infants diagnosed with HIV infection through early infant diagnosis testing. The results assess differences in HIV drug resistance prevalence between populations exposed to ARV drugs for the elimination of vertical HIV transmission and those with unknown exposure to support the selection of optimal first-line ART for this population.

## 4.12 ART Programme Structure

The national ART programme is now run from sixty-six ART sites in fifty-nine districts. Each of these sites has a medical officer from the health system, while some additional staff are provided by the global fund grant at high load centres. The programme has also started decentralizing the drug provision through ARV drug distribution centres.

The programme agreed that the patients stable on ART can also be linked out to the ART drug dispensing centres being established in many parts of the country and these patients will need to come to their parent ART centres once in six months for clinical evaluation/CD4/VL testing as per protocol. These drug dispensing centres will only dispense drugs to stable patients, monitor adherence, look for adverse effects of ARV drugs or some OIs and refer them to parent ART centre as per need. These centres will get drugs from their parent centre and these centres cannot initiate new patients on ART or change the drug regimen on their own.

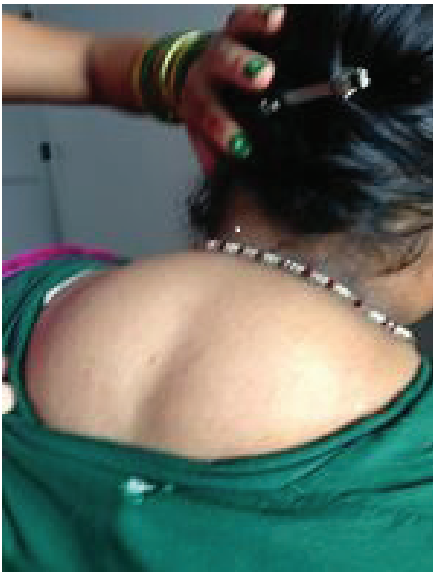
### ARV Drug Toxicities



*Pic. 4.1. Anaemia caused by AZT*



*Pic. 4.3. Gynaecomastia caused by EFV*



*Pic. 4.2. Lipodystrophy caused by d4T*



*Pic. 4.4. Maculopapular rash caused by NVP*

# ADHERENCE TO ART, RETENTION ACROSS THE CONTINUUM OF CARE

## 5

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## 5. ADHERENCE TO ART, RETENTION ACROSS THE CONTINUUM OF CARE

### 5.1 Introduction

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 patient- 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. 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 of HIV. With the commencement of ART irrespective of CD4 count, patients will be on ARV for longer time, and many may be feeling well and may not always see the rationale for high level of adherence. Therefore, the role of increased patient education and support is critical.

### 5.2 Retention on ART, Barriers to Adherence, Challenges for Adherence and Strategies to Optimize Adherence to ART

There are certain barriers to adherence that need to be addressed during ART. In *Barriers to and Facilitators of Antiretroviral Therapy Adherence in Nepal* (Wasti, *et al.*, 2012), the major barriers to ART adherence are grouped into five interwoven categories: (i) economic, (ii) individual patient-related, (iii) sociocultural, (iv) healthcare provision and system, and (v) drug-related.

Money appeared to be the biggest constraint on getting ARV refills transported every month and getting some laboratory tests done.

The individual factors include forgetting doses, being away from home, change in daily routine, depression or other illnesses, and substance or alcohol use. This also included the belief that they can control HIV through their own self-will, meditation, etc. Lack of family support acted as a barrier to adherence, and family quarrels stopped them from taking medication,

Medication-related factors may include adverse events and the complexity of dosing regimens, such as those for children. Health system factors include distance to health services; long waiting time to receive care and obtain prescription refills; receiving only one month's supply of drugs; pharmacy stock-outs; burden of direct and indirect costs of care; and negative attitude and behaviours of health care service providers. Side-effects of ART were one of the most discussed themes in this study.

Prevalence of HIV-related prejudices and discriminations in the community is also important barrier to adherence. Another key issue is non-disclosure of HIV status, when persons living in a household may have to hide their drugs and take them in secrecy; so, disclosure counselling is a key tool to support people to become adherent. Assisted partner notification is recommended by WHO as a tool for supporting disclosure as a way to minimizing adherence barriers and promoting partner testing.

Women generally have better health-seeking behaviour and are more adherent than men. There are also specific challenges around adherence in very young children and adolescents.

Several studies among PLHIV show that undiagnosed and untreated depression is a major barrier to good adherence. Therefore, mental health assessments should be built into adherence support activities.

Specific population groups face additional challenges to adherence, and these should be considered while implementing the recommended strategies. The recommendations by specific population groups are as follows:

- **Pregnant and postpartum women**

- Concerns about how ART affects the health of the foetus;
- Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence;
- Pill burden because of other medications prescribed during pregnancy;
- Stress and urgency related to delivery;
- Social factors related to pregnancy, as during the first few days after delivery, may not allow women to take medicines or women after delivery may go to stay at their parents' house away from the ART centre;
- Dealing with the diagnosis of HIV infection (many women learn about their HIV infection during routine screening during pregnancy);
- Suboptimal understanding of HIV, ART and elimination of vertical HIV transmission (eVT), lack of partner disclosure and support, and fear of prejudice and discrimination;
- Poor quality clinical practices, gaps in provider knowledge and training, poor access to services and health workers' attitudes; and
- Lack of follow-up and transfer to ART clinic after delivery.

- **Adolescents**

- Issues relating to disclosure to peers or partners;
- Concerns about safety of medications;



- Adverse effects of ARV;
- Peer pressure and perceived need to conform;
- Not remembering to take medications;
- Inconsistent daily routine;
- Transition from paediatric to adolescent care includes assuming increased responsibility for their own care, which may lead to treatment interruptions because of forgetfulness;
- Inability to navigate the healthcare system; lack of links between adult and paediatric services;
- Inadequately skilled healthcare providers; and
- Depression and substance use

- **Infants and children**

- Suboptimal HIV care and treatment for family members, resulting in suboptimal care for children and loss of primary caregiver in the family;
- Lack of nutrition support;
- Limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, frequent dosing requirements and difficulty in swallowing tablets (57–59); and
- Inadequately skilled healthcare providers.

- **Key populations at risk of HIV (FSW, MSM, MSW, TG, PWID)**

Key populations (KP) are marginalized people who, because of the prejudice and discrimination related to their behaviours, may not visit health facilities regularly.

- KP at risk of HIV may face multiple challenges to access health services that include economic as well as social causes.
- MSM, MSW and TG people require special attention because of prejudice and self-stigma and social circumstances of these KP.

- **Migrants and their spouses**

- Many migrants take ART from other countries and when they return to Nepal for brief period while on vacation or work, it is difficult to get the same regimen and this may affect adherence. A cross-referral mechanism with most commonly visited countries may be established for continuity of drugs during their stay in Nepal.

## 5.3 Strategies to Optimize Adherence to ART, Programme-related Strategies

### Providing adherence counselling

Routine adherence assessments and counselling strategies, patient education and counselling are essential strategies to optimize retention and adherence. Adherence counselling is essential both before and after ART initiation as it helps patients gain a better understanding of their disease and builds a more supportive environment. In the SIDHAS project in Nigeria, adherence counselling on every clinic visit and reinforcement of adherence counselling by pharmacists, CHWs, support groups, and volunteers improved ART adherence. Adherence counselling should be provided by ART counsellor at ART centres in multiple settings (at least three counselling sessions are recommended) before initiation of ART to prepare clients for it. Adherence counselling and patient education should be done on every follow-up visit and attempt should be made to understand potential barriers to adherence by patient, which may differ from patient to patient. The intervention should be tailored accordingly.

Suggested contents of the pre-ART adherence counselling on each visit include the following:

- **First visit**
  - Conducting clinical assessment;
  - Exploring clients' 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 the 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 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 on the second visit;
- Assessing the client’s readiness by simply asking the client to answer the questions about the regimen and what he/she proposes 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 his/her role and to make follow-up arrangements with the client. A start date for “buddy support” should be established.

Preparedness for ART varies from person to person and some patients may well be prepared in two visits and others may require more visits. The counsellor has to assess this on individual basis, but minimum two counselling sessions are advisable for good adherence. The information may have to be tailored as per the client’s understanding.

### **Ongoing ART adherence counselling**

The individuals should have a follow-up adherence counselling on their scheduled visits. Adherence barriers can change over time and individual patients 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 patient on ART.

Adherence counselling should be specific to the clients who received high viral load count (> 1000 copies/ml) during routine monitoring.

### **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 transmission risk reduction; and
- Conducting a psychosocial assessment;

## 5.4 Facilitators of Adherence

Wasti, *et al.* (2012) also identifies five major facilitators of adherence to ART:

- (i) trusting health workers,
- (ii) positive beliefs about ART,
- (iii) ART as part of daily life,
- (iv) responsibilities for children, and
- (v) family and mechanical support.

Some participants are motivated to continue their ART by a 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 positive results of ART. Healthcare workers should continuously offer information and counselling to: (a) prevent patients from stopping treatment; and (b) make intake of medication a daily priority.

Family support increases the likelihood of patients to maintain optimal adherence. Particularly for women and children, family acts as a facilitator for adherence.

Healthcare workers play an important role in supporting and encouraging patients to adhere to their medication. Good relationships with care providers and trusting them improve adherence. Healthcare providers who spend time explaining things to patients 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. Supportive and interested practitioners can motivate and reinforce good practices in their patients.

### Programme-related interventions

- *Mobilizing peer counsellors:* There is direct evidence of higher levels of adherence compared to standard care. PLHIV peer volunteers can be mobilized. This can also be case managers.
- *Using mobile phone text message or web SMS:* Text messages are sent to the client's phone one way or two ways. There is direct evidence that text messages result in higher adherence compared to standard care.
- *Using reminder devices:* Strategies using calendars, alarms, system devices for disease management assistance and pagers. There is direct evidence that supporters and device reminders result in increased viral suppression.

### Supportive strategies

- Strategies minimizing prejudices and discriminations against KP, including people living with HIV in the community and encouraging PLHIV from specific KP to attend

- health facilities in concentrated epidemic settings. Organizing community events, identifying disclosed PLHIV as *positive speakers* and mobilizing them in events.
- Peersupport, along with the support of outreach teams, community-based supporters and health workers providing multidisciplinary, non-judgmental and dignified care.
  - Assessment of depression in each clinical visit using simple tools (with clinical criteria) and referring clients for management of depression.
  - Needle and syringe programme and drug substitution therapy for PWID provide further opportunities to support adherence.
  - Nutritional support to people receiving ART reduces the risk of non-adherence among food-insecure individuals. Nutritional support could include nutritional counselling, complementary food supplies, subsidizing food costs and/or food vouchers, referring clients to the shops providing food at subsidized rates.
  - Avoiding out-of-pocket payments at the point of care (such as drugs, diagnostics and clinical services), supporting transport costs, decentralizing care, and reducing the frequency of health facility visits.
  - Confidentiality and privacy and strengthening social networks, considering local cultural customs and religious beliefs.
  - Peer-based strategies among adolescents, which provides support through experience-sharing and learning from other individuals with similar problems.
  - Meetings of adherence clubs/support group of stable patients at regular interval at a healthcare facility or community venue for a brief discussion of the barriers to adherence and ways to overcome the barriers. Experienced PLHIV on ART can share their experiences related to ART, approaches for maintaining adherence and importance of retention in care. These meetings are done along with the support group meetings and can be facilitated by community-based supporters or volunteers of PLHIV organizations. Such meetings can be organized at nearby venue of an ART centre on the days with maximum patient visits.

## 5.5 Monitoring Adherence to ART in Routine Programme and Care Settings

Patients may need differentiated care according to clinical characteristics. Clinical characteristics determine the need for care and related visits to health facilities. Adherence monitoring and support with counselling is required at every visit.

The following approaches of monitoring adherence are recommended:

### a. Viral load monitoring

Viral load 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 patient-, disease- and drug-associated effects. Other approaches to monitoring adherence should, therefore, be considered as a way to providing additional information about possible causes of virological failure or to supporting adherence monitoring in settings where viral load testing is not available. National guideline recommends that, following an initial high viral load ( $> 1000$  copies/mL), an adherence intervention be carried out prior to conducting a second viral load test. According to WHO, this has been shown to lead to re-suppression in over 70% of patients. Viral load monitoring also has a high potential to motivate adherence. The counselling after a high viral load test should include the following points:

- Ensure that clients understand that the ART taken by the client is not producing or controlling the virus as VL is not controlled. Non-adherence to treatment could be a cause.
- Review the barriers of clients on 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, set the date for follow-up action points.
- Organize follow-up sessions to help the client to adhere to the action points and review the progress.
- At the end of three months, refer the clients for repeat VL test. If the client receives VL test result more than 1000 copies /ml, refer her/him to the ART clinician for regimen change.

## **b. Review of the ARV dispensing records**

Review of the ARV dispensing records (patient cards and prescriptions) provides information on when PLHIV pick up their ARV drugs. Receiving ARVs at irregular intervals may indicate non-adherence to ART; however, in some angles 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 clients 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 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 adherence. Adherence percentage can be calculated on the basis of the pill count as follows:

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

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

### 5.6 Advice to Patient on ART Who 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 long-term outcome. 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 as soon as the patient notices that the dose is missed.
- 2 For the next dose:
  - i. If the client is taking twice-daily dose (every 12 hours):
    - If the patient is scheduled to take his/her next dose in less than 4 hours, he/she is not recommended to take that dose. He/she must wait for 4 hours (from the time he/she has taken the missed dose) to take the next dose. Thereafter, the patient can follow the regular dosing schedule.
  - ii. If the client is taking once-daily dose (every 24 hours):
    - If the patient is scheduled to take his/her next dose in less than 12 hours, he/she is not recommended to take that dose. He/she must wait for 12 hours (from the time he/she has 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, he/she can take the regular dose at the scheduled time.
    - If the patient remembers to take the missed dose on the next scheduled time, he/she should take only the scheduled dose. It is strictly not recommended to take two doses at a time.

## 5.7 Retention across the Continuum of Care

Continuum of care represents a continuum in which all the services necessary for a PLHIV exists across the continuum of life. Positive test at HIV testing marks the entry into the continuum and death, including bereavement, and is the end of the continuum. The role of an HIV case manager is critical to supporting a person across the continuum as they negotiate changes in their health, social and economic status over lifetime. For example, a person who is routinely adherent may become poorly adherent if she/he migrates or there is bereavement in the family. Adherence counselling should take into account such life events.

Early linkage of PLHIV to care is critical; delay of days or weeks with people already being ill with TB or other OIs increases the risk of mortality. PLHIV require screening for TB, cotrimoxazole prophylaxis and IPT as per the indication. For PLHIV who are receiving treatment, uninterrupted ART and continual monitoring are essential for sustained viral suppression and optimal treatment outcomes.

Each ART centre needs to draw its own cascade from the step of enrolment in care onwards and see how to plug gaps at different points in this cascade. A regular review of cascade monitoring every quarter can give an idea about performance of each centre and about the overall programme. Patient tracking can involve contacting patients on telephone, including mobile phone text messaging, physically visiting their place of residence, or both, and is often conducted by CHWs. Those with suspected failure in form of declining CD4 or high VL need to reinforce the adherence before switching to the second-line regimen.





# MANAGING COMMON HIV-RELATED COINFECTIONS AND COMORBIDITIES

## 6

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## 6. MANAGING COMMON HIV-RELATED CO-INFECTIONS AND COMORBIDITIES

### 6.1 Introduction

Various coinfections, comorbidities and other health conditions are common among PLHIV. The presence of these conditions often plays a vital role in their treatment and care, including the timing and choice of ARV drugs. Prior to the widespread use of the potent combination ART, OIs are the most important cause of morbidity and mortality in this population. OIs are defined as infections that are more frequent or more severe because of immunosuppression in HIV-infected persons. In the early 1990s, the use of chemoprophylaxis, immunization and better strategies for managing acute OIs contributed to improved quality of life and improved survival. Subsequently, widespread use of potent ART has had the most profound influence on reducing OI-related mortality in HIV-infected persons.

### 6.2 Cotrimoxazole Preventive Therapy

Cotrimoxazole Preventive Therapy (CPT) should be implemented as an integral component of a package of HIV-related services. PLHIV should be evaluated for possible need for prophylaxis at the time of preparing for ART or even in areas without ART accessibility.

Cotrimoxazole (CTX) 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)

Cotrimoxazole prophylaxis for adults should be started for:

- HIV-infected with CD4 count  $< 350$  cells/mm<sup>3</sup>
- All adults with severe and advanced HIV disease (WHO stage 3 or 4)

The regimen is:

- One DS tablet (160TMP/800SMX) every day; or
- Two SS tablets (80TMP/400SMX) every day

Cotrimoxazole prophylaxis for infants, children and adolescents with:

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

Continuation of Cotrimoxazole prophylaxis should be as follows:

- Lifelong (irrespective of the CD4 count) if client is not on ART

Cotrimoxazole must be discontinued in the following situations:

- severe cutaneous reactions, such as Stevens-Johnson syndrome, renal and/or hepatic failure, and severe haematological toxicity.
1. Timing of Cotrimoxazole prophylaxis in relation to ART initiation: Since the most common initial side-effect of Cotrimoxazole and ART (especially Nevirapine and Efavirenz) is rash, it is recommended to start Cotrimoxazole prophylaxis first and to initiate antiretroviral therapy two weeks later if the individual is stable on Cotrimoxazole and has no rash. Do NOT start Cotrimoxazole and ART at the same time.
  2. For Cotrimoxazole 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 two 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 6.1 Protocol for cotrimoxazole desensitization among adults and adolescents**

<b>Day 1</b>	<b>80 mg sulfamethoxazole + 16 mg trimethoprim (2 ml of oral suspension)</b>
<b>Day 2</b>	160mg sulfamethoxazole + 32mg trimethoprim (4ml of oral suspension)
<b>Day 3</b>	240mg sulfamethoxazole + 48mg trimethoprim (6ml of oral suspension)
<b>Day 4</b>	320mg sulfamethoxazole + 64mg trimethoprim (8ml of oral suspension)
<b>Day 5</b>	One single-strength sulfamethoxazole-trimethoprim tablet (400mg sulfamethoxazole + 80mg trimethoprim)
<b>Day 6 onwards</b>	Two single-strength sulfamethoxazole-trimethoprim tablets or one double strength tablet (800mg sulfamethoxazole + 160mg trimethoprim) a Cotrimoxazole oral suspension is 40mg trimethoprim + 200mg sulfamethoxazole per 5ml.

Follow-up of clients on Cotrimoxazole prophylaxis should occur every month during the initial stage once the person is stable on prophylaxis:

- Monitor for toxicity, clinical events and adherence.
- Lab tests of haemoglobin and white blood counts only as indicated.

Adherence counselling on Cotrimoxazole can be useful to help prepare clients for ART in the future and solve the barriers to medication adherence.

Use an alternative antibiotic for treating breakthrough bacterial infections among PLHIV receiving Cotrimoxazole prophylaxis, while continuing Cotrimoxazole.

For toxoplasmosis and PCP infections, prophylaxis should be suspended and full active treatment initiated. Cotrimoxazole prophylaxis should be started after the treatment course.

**Table 6.2. Criteria for initiation and discontinuation of cotrimoxazole prophylaxis**

Population	Recommendation	
	Criteria for initiation of cotrimoxazole prophylaxis	Criteria for discontinuation of cotrimoxazole prophylaxis
Adults (including pregnant women) with HIV	<ul style="list-style-type: none"> <li>• Initiate in all with severe/advanced HIV disease (WHO clinical stage 3 or 4) or CD4 count <math>\leq 350</math> cells/mm<sup>3</sup></li> <li>• In settings with a high prevalence of malaria and/or severe bacterial infections; initiate in all regardless of WHO clinical stage or CD4 cell count</li> </ul>	<ul style="list-style-type: none"> <li>• May be discontinued in those who are clinically stable, with evidence of immune recovery and/or viral suppression on ART</li> <li>• In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued</li> </ul>
Children and adolescents with HIV	<ul style="list-style-type: none"> <li>• Initiate in all regardless of WHO clinical stage or CD4 cell count</li> <li>• 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 <math>\leq 350</math> cells/mm<sup>3</sup></li> </ul>	<ul style="list-style-type: none"> <li>• In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued until adulthood</li> <li>• 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 and/or viral suppression on ART</li> </ul>
HIV-exposed uninfected infants	<ul style="list-style-type: none"> <li>• Initiate in all starting at 4–6 weeks after birth</li> </ul>	<ul style="list-style-type: none"> <li>• Until the risk of HIV transmission ends or HIV infection is excluded</li> </ul>
People living with HIV and TB	<ul style="list-style-type: none"> <li>• Initiate in all with active TB regardless of CD4 cell count</li> </ul>	<ul style="list-style-type: none"> <li>• Until criteria for discontinuation in adults or children are met</li> </ul>

### 6.3 Prevention, Screening and Management of TB among Adults

Among PLHIV, TB is the most frequent life-threatening OIs and a leading cause of death accounting for about a third of all mortality. ART should be provided to all PLHIV with active TB disease.

HIV care settings should implement the WHO Three I's strategy:

- Intensified TB case-finding,
- Isoniazid Preventive Therapy (IPT) and
- Infection control at all clinical encounters.

The lifetime risk of someone with latent TB developing TB in HIV negative individual is 5–10%, whereas in a HIV positive individual it is up to 50%. Managing TB among HIV-infected individuals, thus, is one of the major responsibilities of all ART clinicians.

### 6.3.1 Intensified case finding

As TB is one of the most common OIs among the HIV-infected people, TB screening should be performed for all new HIV-infected clients on their first visit using a TB screening questionnaire, a full initial history, and physical examination and these should be continued on every visit.

#### Box 6.1. Key screening questions

1. Has the client been currently coughing? Yes/No
2. Has the client been having night sweats? Yes/No
3. Has the client been experiencing weight loss? Yes/No
4. Has the client been having fever? Yes/No

If the answer is "Yes" to question 1: GeneXpert should be used rather than conventional microscopy, culture and drug susceptibility testing (DST) as the initial diagnostic test in individuals suspected of have HIV-associated TB.

For people suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (pleural fluid, cerebrospinal fluid, lymph nodes and other tissues).

If the answer is "No" to question 1 and "Yes" to any other question, continue investigation for tuberculosis according to clinical signs.

If the answer is "No" to all questions, stop investigation for tuberculosis provide IPT.

Ask the client to report immediately if any of the above-mentioned symptoms occur.

### 6.3.2. Isoniazid Preventive Therapy (IPT)

Preventive therapy against TB is the use of anti-TB drugs in individuals with latent *Mycobacterium tuberculosis* infection regardless of CD4 cell count or ART status in order to prevent the progression to active disease. HIV is the most powerful risk factor for progression from latent infection to active disease. Use of IPT can reduce the number of HIV patients developing active TB.

All patients should be screened for active TB (by asking about symptoms, physical examination and sputum examination; CXR may be done routinely if available as part of screening; CXR and GeneXpert should be done in all symptomatic pts). This should be done on every visit to ART centre using the screening tool for TB.

IPT should only be used in patients in whom active TB has been excluded, active patient follow-up is possible and high-level adherence can be attained and should be provided for six months to all clients, including children who have completed TB treatment.

## Key recommendations for initiating IPT:

- Those with liver disease, active alcohol use, jaundice, habitual treatment defaulter, prior Isoniazid resistance, peripheral neuropathy, unexplained illness should be excluded.
- Cotrimoxazole and ART should not be started at the same time as IPT.
- Monthly supply of IPT drugs should be provided.
- Providing IPT to PLHIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

## IPT Regimen:

*For adults:* Isoniazid 300mg daily for 6 months, Vitamin B6 25mg/day (pyridoxine) should be given together with IPT for 6 months.

*For children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening and have no contact with a TB case:* Such children should receive six months of IPT (10mg/kg/day). In children living with HIV 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 six months of IPT if the evaluation shows no TB disease.

## Follow-up visits while on IPT:

- Client must be seen every month for adherence check, side-effect check and medication refill.
- Client must be asked about symptoms of breakthrough TB on each visit. If any symptom occurs, evaluate for TB.

## 6.3.3 TB treatment among PLHIV

### All PLHIV with TB need ART.

- All HIV-infected patients with diagnosed active TB should be put on TB treatment immediately.
- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of CD4 count.
- Anti-tuberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (2 weeks, if CD4 < 50 cells).
- 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 patients with active TB disease.

### ARV drug choice in TB coinfection

- First-line treatment option is TDF/3TC plus Efavirenz. Use AZT if contraindication to TDF.
- Use regular dose of Efavirenz during ATT.
- Nevirapine can be used for those who are unable to take EFV. Rifampicin decreases Nevirapine levels by hepatic induction, which potentially can lead to lower anti-HIV efficacy. There are also concerns of additive liver toxicities. In case where Nevirapine is required, full dose of Nevirapine should be given from day one. However, with close monitoring NVP-containing regimens may be considered. One exception is that women with baseline CD4 > 250 should not be given NVP along with Rifampicin.

Patients already receiving ART when they develop TB should adjust the regimen to be compatible with TB treatment. Following completion of anti-tubercular therapy, the ART regimen can be continued or changed, depending upon the clinical and immunologic status of the patient.

### Second-line ART and TB coinfection

Use of Rifampicin with boosted PI-based regimens is inappropriate due to well recognized drug–drug interactions. For patients who need anti-tuberculosis treatment while on boosted PI regimen, Rifampicin needs to be substituted with Rifabutin and the standard PI-based ART regimen maintained. Rifabutin dose of 150mg once a day should be taken with LPV/r-containing ART. The same NRTI backbones are recommended for adults and adolescents. Raltegravir (RAL) can be used during the ATT period to avoid interaction with PIs if Rifabutin is not available.

## 6.4 TB Coinfection in Children

HIV increases the risk of activation of TB in latently infected children (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 depressed immunity. Extrapulmonary, disseminated TB and drug-resistant tuberculosis are seen more frequently with HIV.

Up to 25% of TB in children is extrapulmonary. The most common sites are the lymph nodes (LN), 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 or NVP mean that co-treatment in children under 3 years is challenging. Triple nucleoside therapy offers a suitable option for children who require TB treatment while already receiving ART (Table 6.3.).

**Table 6.3. Recommended ART regimens for children who need TB treatment**

<b>Recommended regimens for children and adolescents initiating ART while on TB treatment</b>		
<b>Younger than 3 years</b>		Two NRTIs + NVP, ensuring that dose is 200 mg/m <sup>2</sup> or Triple NRTI (AZT + 3TC + ABC)
<b>3 years and older</b>		Two NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)
<b>Recommended regimen for children and infants initiating TB treatment while receiving ART</b>		
<b>Child on standard NNRTI-based regimen (two NRTIs + EFV or NVP)</b>	Younger than 3 years	Continue NVP, ensuring that dose is 200 mg/m <sup>2</sup> or Triple NRTI (AZT + 3TC + ABC)
	3 years and older	If the child is receiving EFV, continue the same regimen If the child is receiving NVP, substitute with EFV or Triple NRTI (AZT + 3TC + ABC)
<b>Child on standard PI based regimen (two NRTIs + LPV/r)</b>	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC) or Substitute NVP for LPV/r, ensuring that dose is 200 mg/m <sup>2</sup> or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose (Super boosting)
	3 years and older	<b>If the child has no history of failure of an NNRTI-based regimen:</b> Substitute with EFV or Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose <b>If the child has a history of failure of an NNRTI-based regimen:</b> Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r consider adding RTV to achieve the full therapeutic dose Consider consultation with experts for constructing a second-line regimen

## 6.5 Hepatitis B and C

Viral hepatitis is an increasing cause of morbidity and mortality among PLHIV, including those on ART. A comprehensive approach includes prevention, hepatitis B and hepatitis C screening, hepatitis B vaccination, and treatment and care for people with HIV coinfecting with hepatitis B and/or hepatitis C.

### 6.5.1 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 the interactions between the drugs used for treating HIV and HCV infections.

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 coinfecting 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 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/mm<sup>3</sup>). The decision to start ART among HCV coinfecting should follow the same principle as mono-infected HIV.

HCV infection among persons with HIV coinfection can be treated with DAAs like Sofosbuvir, Daclatasvir, Ledipasvir, which are known to be more effective, of shorter duration depending on genotype and have far fewer side-effects (refer to the National Hepatitis C Guidelines). Potential harmful effects of antiretroviral 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 coinfecting persons, including those with cirrhosis, the benefits of ART outweigh the 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 elevation of AST/ALT may prompt careful evaluation for other causes of liver impairment (eg alcoholic hepatitis, hepatobiliary disease), and may require short-term interruption of the ART regimen or specific drug suspected of causing the elevation.

## Drug–drug interactions in persons with HIV/HCV coinfection

Assessment of potential drug–drug interactions is of critical significance in HIV-infected persons who are about to start HCV treatment. Careful consideration of such interactions is important to avoid toxicity and to ensure efficacy of the regimens used to treat both HIV and HCV in order to avoid development of ARV resistance and to increase the likelihood of sustainable virological response (SVR).

Interactions between NRTIs have been reported in persons treated with dual IFN/RBV-based therapy, though interferon-based therapy is no longer used for hepatitis C treatment. The use of AZT is associated with an increased risk of toxicities, and these drugs are, therefore, contraindicated. Abacavir (ABC) can be used with RBV. Tenofovir and emtricitabine (FTC) or lamivudine (3TC)-based regimens are appropriate.

Additional drug–drug interactions must be considered when using other DAAs. If patients are commencing ART and DAAs are not being considered, standard first-line ART may be used (as long as this does not include zidovudine). Efavirenz may also be used, but the dose of telaprevir must be increased.

### 6.5.2 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.

Adult, adolescents and children with chronic hepatitis B and clinical evidence of cirrhosis (or cirrhosis based on non-invasive APRI test score  $> 2$  in adults) should be treated regardless of ALT, HBeAg status or HBV DNA level. The recommended drugs TDF with 3TC or FTC are active against HBV. For mono-infection with HBV TDF single agent is recommended.

Tenofovir should be recommended for using hepatitis coinfecting patients; otherwise, hepatitis B flare 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 HBsAg and, if negative, should be vaccinated with hepatitis B.

## 6.6. Cryptococcal infection

Cryptococcal disease in HIV infected patients 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/ml, and most

cases occurs when the CD4 count falls below 50 cells/ml. Cryptococcal disease in PLHIV most commonly presents as a sub-acute meningitis or meningo-encephalitis with the following symptoms:

- Fever
- Malaise
- Headache
- Neck stiffness and photophobia (i.e. meningeal symptoms in 25-30%)
- Altered mental status/confusion, personality changes, memory loss (encephalopathic symptoms)
- Impaired consciousness and coma
- Focal signs, including cranial nerve palsies

### 6.6.1. Laboratory Diagnosis

Laboratory evaluation for cryptococcal disease should be carried out in patients with advanced immunosuppression ( $CD4 < 100$ ) with a history of persistent headache and/or clinical features of meningitis, altered mental status or focal neurological deficits. A lumbar puncture should be performed; CSF opening pressure should be measured as it is above 200mm H<sub>2</sub>O in more than 75% of patients. Rapid CSF cryptococcal antigen (CrAg) assay or rapid serum CrAg (either LA or LFA) should be carried out as it has more sensitivity than Indian ink staining (if not available, Indian ink coloration needs to be performed). Evaluation of symptomatic patients for cryptococcal antigen is extremely useful to decrease HIV related mortality.

### 6.6.2. Treatment and Secondary Prophylaxis

Untreated Cryptococcal disease is Fatal.

## • Cryptococcal infection treatment

	Preferred therapy	Alternative therapy	Comments
<p><b>Induction phase</b></p> <p>2 weeks or until CSF sterile</p> <p>Followed by consolidation phase</p>	<p><b>Cryptococcal meningitis, non CNS extra-pulmonary cryptococcosis and diffuse pulmonary disease</b></p> <p>Amphotericin B IV (0.7-1mg/kg/day)</p> <p>+ Flucytosine p.o. (25mg/kg every 6 hours)</p> <p><b>Non CNS cryptococcosis with mild-to-moderate symptoms or focal pulmonary cryptococcosis:</b></p> <p>Fluconazole 400mg/day (800mg day 1)</p>	<p><b>In decreasing order of efficacy</b></p> <p><b>Preferred alternative:</b> Amphotericin B IV (0.7-1mg/kg/day)</p> <p>+ Fluconazole 800mg/day IV or p.o.</p> <p><b>Option 2 (less efficient)</b></p> <p>5FC (25mg/kg every 6 hours)</p> <p>+ Fluconazole 800mg/day IV or p.o.</p> <p><b>Option 3 (least efficient)</b></p> <p>Fluconazole 1200mg/day</p>	<p>Amphotericin B therapy should be administered in qualified health facilities capable of close clinical and laboratory patient monitoring.</p> <p>Dosage of amphotericin B and flucytosine should be adjusted to creatinine clearance rate.</p> <p>Opening CSF pressure should always be measured at initiation of treatment and when a lumbar puncture is performed. Repeated LP are essential to effectively manage raised intra-cranial pressure.</p> <p>Corticosteroids and mannitol are ineffective to decrease intracranial pressure in cryptococcal meningitis.</p>
<p><b>Consolidation phase</b></p> <p>8 weeks</p> <p>Followed by maintenance phase</p>	<p>Fluconazole 400mg/day (800mg day 1)</p>	<p><b>If induction phase with fluconazole 1200mg/day: consolidation with fluconazole 800mg/day</b></p>	
<p><b>Maintenance phase</b></p> <p>At least 12 months; fluconazole can be stopped in patients who have been on ART and have CD4 consistently above 100 cells/mm<sup>3</sup> for at least 6 months. If there is fall in CD4 count, fluconazole should be restarted again.</p>	<p>Fluconazole 200mg/day</p>		

- **Supportive care**

Management of the unconscious patient should be as per standard guidelines with attention to airways, nursing care and nutrition. Patients with worsening headache or those with a deteriorating consciousness should be assessed for increased intracranial pressure (ICP). Raised ICP causes most deaths (> 90% in the first 2 weeks) in PLHIV with CM and is likely to be a problem in patients with opening CSF pressure > 250 cm H<sub>2</sub>O.

The principal intervention in patients with symptomatic raised ICP is repeated LP (daily if patient symptomatic, alternate days if no symptom) with subtraction of 20-30ml until CSF pressure falls below 200 cm H<sub>2</sub>O on 3 consecutive LP.

- **Monitoring**

Repeat LP to confirm clearance of infection is not necessary in patients with clinical improvement by 2 weeks of treatment. A repeat LP may be necessary if new symptoms develop in patients after 2 weeks of treatment; ICP should be assessed and India ink stain repeated on the CSF. Patients failing fluconazole therapy should be treated with amphotericin.

### 6.6.3 ART Initiation in Patients with CM

Patients with CM should be prepared for ART. ART should probably be started after the patient stabilizes to avoid severe IRIS, usually after about 4 weeks of induction and consolidated treatment with amphotericin B –containing regimens combined with flucytosine or fluconazole. Although nevirapine drug levels are increased markedly by fluconazole, patients appear to tolerate the two drugs well. Extra vigilance in monitoring patients on a nevirapine based ART regimen and fluconazole is however recommended. Recurrence of CM is unlikely in patients who attain immune reconstitution on ART; maintenance or suppressive therapy should therefore be discontinued in patients who have achieved a CD4 count > 100 cells/mm<sup>3</sup> for at least 6 months and have completed the consolidation phase of treatment (12 months).

Maintenance therapy should be recommenced in patients who have had CM and who develop ARV treatment failure with CD4 < 100 cells/mm<sup>3</sup>.

- **CM during Pregnancy**

Patients with suspected CM should be investigated and managed in the same way as non-pregnant women.

Fluconazole and itraconazole should be avoided in the first trimester because of teratogenicity; absent other options patients should be treated with fluconazole as per schedule above. The pregnancy should be monitored clinically as well as using ultrasonography where possible.

**Routine screening for cryptococcal meningitis for HIV-infected adults (Annex 3).**

## 6.7 Malaria

People with HIV with immunosuppression living in malaria-endemic areas are at high risk of 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 a rapid diagnostic test.

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

## 6.8 Sexually Transmitted Infections and Cervical Cancer

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

Furthermore, HIV infection alters the natural history of STI. The objectives of diagnosing and managing STI include identifying the infection, 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 Annex 4 for etiological management of STI.)

### 6.8.1 Cervical cancer

It is a preventable disease and is curable if diagnosed and treated early. Women living with HIV have a higher risk of pre-cancer and invasive cervical cancer. The risk and persistence of human papillomavirus infection increase with the decreasing CD4 count and increasing HIV viral load.

Invasive cervical cancer is a WHO HIV clinical stage 4 condition. Women living with HIV should be followed closely for evidence of pre-cancerous changes in the cervix, regardless of ART status or CD4 count and viral load. Cervical cancer screening leads to early detection of precancerous and cancerous cervical lesions, which will prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management of pre-cancerous and cancerous lesions should



be provided. WHO guidance covers human papillomavirus 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 to routine HPV immunization.

## 6.9 Vaccines for PLHIV

PLHIV should be assessed for eligibility for vaccination at all stages of care. HIV-exposed infants and children and young adults with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules. Those with more severe immunosuppression may be at higher risk of complications from live vaccines.

Inactivated vaccines are more effective among people receiving ART and those without immunosuppression, but they are safe and can be used with some efficacy in all groups.

## 6.10 Preventing and Managing Other Comorbidities and Chronic Care for PLHIV

### 6.10.1 Screening for and care of noncommunicable diseases

PLHIV are at increased risk of developing a range of noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, hypertension, chronic lung disease and some types of cancer. With effective ART, PLHIV are 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. Many ARV drugs like Efavirenz and lopinavir are associated with lipid and glucose abnormalities.

Chronic HIV care provides an opportunity for screening, monitoring and managing NCDs, especially through primary care. 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.

### 6.10.2 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 relate to general mental health that can be relevant to PLHIV. Screening for depression can be undertaken on a clinic visit using a staff nurse or health staff, with a clear referral pathway to a counsellor or a psychiatrist.

# ELIMINATION OF VERTICAL TRANSMISSION (eVT)

# 7

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## 7. ELIMINATION OF VERTICAL TRANSMISSION (eVT)

### 7.1 Introduction

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

The PMTCT service in Nepal has been integrated in maternal and neonatal health services since 2009 in the districts with community-based PMTCT services and has reached 70% of the districts and close to 50% of the health facilities by the end of 2016. The recently endorsed 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, and the indicators are reflected in the National Health Sector Strategy 2015–2020.

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

### 7.2 Prevention, Treatment and Care

The Government of Nepal has been scaling up eVT services in hospitals, primary health care centres and health posts. The role and responsibilities of the institutions concerned, follow-up mechanism for babies born to HIV positive mothers, and supporting agencies like community care centres have been mentioned in the PMTCT SOP 2012.

A comprehensive and integrated **four-pronged approach** to 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.

HIV testing services is the gateway for HIV treatment, care and prevention. For successful implementation of the eVT programme, the following elements should be included as part of ANC:

- Health information and inter-personal 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 with ART services to HIV positive pregnant women,
- Counselling on infant feeding,
- Discussion of family planning choices following delivery,
- Diagnosis and treatment of STI,
- Counselling for testing for TB and malaria.

### **Risk Factors for Mother-to-Child Transmission of HIV:**

The most important risk factor for vertical transmission is the amount of HIV virus in the mother's blood, ie viral load. The risk of transmission to the infant is greatest when the viral load is high, which is often the case with recent HIV infection or advanced (WHO Stage 3 or 4) clinical disease.

**Table 7.1. Factors that may increase the risk of vertical transmission of HIV**

Pregnancy	Labour and Delivery	Infant Feeding
<ul style="list-style-type: none"> <li>• High maternal viral load (new HIV infection or advanced clinical disease)</li> <li>• Viral, bacterial or parasitic placental infection (eg malaria)</li> <li>• Sexually transmissible infections (STI)</li> <li>• Maternal malnutrition (indirect cause)</li> </ul>	<ul style="list-style-type: none"> <li>• High maternal viral load (new HIV infection or advanced clinical disease)</li> <li>• Rupture of membranes more than 4 hours before labour begins</li> <li>• Invasive delivery procedures that increase contact with mother's infected blood or body fluids (eg episiotomy, caputus skull during foetal scalp monitoring)</li> <li>• First infant in multiple birth</li> <li>• Chorioamnionitis (eg from untreated STI or other infections)</li> </ul>	<ul style="list-style-type: none"> <li>• High maternal viral load (new HIV infection or advanced clinical disease)</li> <li>• Duration of breast feeding</li> <li>• Mixed feeding (ie any food or fluids in addition to breast milk)</li> <li>• Breast abscess, nipple fissures, mastitis</li> <li>• Poor maternal nutritional status</li> <li>• Oral disease in the baby (eg thrush or sores)</li> </ul>

### 7.2.1 Elimination of vertical transmission of HIV

- HIV testing algorithm should be followed for all pregnant to lactating women to confirm their HIV status.
- Provider-initiated testing and counselling (PITC) for pregnant women in antenatal care is a key component to:
  - eliminate vertical transmission of HIV;
  - integrate HIV testing with other key tests (for viral hepatitis, syphilis, etc) as relevant to the setting; and
  - retest HIV negative pregnant women who are in a serodiscordant sexual relationship; who are sexual partners of males from a key population, or who have a known HIV risk.
- Efforts should be made to reduce the time between HIV diagnosis and ART initiation and ART for MTCT transmission should be initiated urgently without waiting for CD4 count or other tests.
- The greatest risk of vertical transmission occurs at intrapartum period (ie during delivery), when the foetus comes in contact with maternal blood or cervical secretions and foetal and maternal blood mix after the placenta separates from the uterus.
- After the onset of labour, transmission risk increases with the length of time the membranes have been ruptured. Higher risk of vertical transmission during labour

and delivery is also associated with other causes of acute chorioamnionitis, eg resulting from untreated STI or other lower genital tract infections, and invasive delivery techniques that increase the baby's contact with the mother's blood. In addition, premature infants are more likely to become infected than full-term infants.

- Instrumental vaginal delivery should be avoided. These include operative or manipulative vaginal delivery (including forceps or vacuum extraction, breech extraction and manipulations during vaginal delivery of multiple pregnancy) and increase the risk of mixing of foetal and maternal blood.

Certain services, such as PMTCT services providing ART for all pregnant and postpartum women living with HIV, are programmatically organized to conduct HIV testing, provide a diagnosis and offer immediate initiation of ART. In these programmes, it may not always be feasible to retest at a different site, although it should usually be feasible for a different provider to conduct retest on a new specimen. If the HIV status is the same upon retesting, the person's HIV positive status should be considered verified.

**Viral load monitoring to pregnant to breastfeeding women on ART:** Although treatment monitoring using viral load is important for all people on ART, it may be especially valuable for pregnant and breastfeeding women for whom there is added benefit in terms of eVT. ARV prophylaxis is recommended for HIV-exposed infants at higher risk of acquiring HIV. A maternal viral load above 1000 copies/mL during the last few weeks before delivery is a reliable determinant of increased transmission risk. Viral load testing during pregnancy is a useful tool for clinical decision-making, and as viral load testing is introduced on a national scale, pregnant and breastfeeding women should be prioritized for access.

### 7.2.3 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 viral load. 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 PLHIV mothers since March 2014 based on recommendations of the WHO Consolidated Guidelines June 2013. The following three elements of eVT should be considered for women identified HIV positive during labour and postpartum period:

- provide ARV therapy to the mother and the baby following delivery;
- implement safe delivery practices;
- provide ongoing counselling and support on safer infant feeding; and
- provide counselling and support for EID at birth and at six week of age (follow the EID protocol).

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

## First-line ART for pregnant and breastfeeding women

Providing an optimized, FDC first-line ART regimen of TDF + 3TC + EFV in single pills to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits.

**Table 7.2. 1st-line ART regimen for treating pregnant women**

Timing	ARV(s)
Start ASAP in pregnancy <b>regardless of clinical stage, or CD4 count or duration of pregnancy</b> and continue throughout pregnancy, labour, delivery, breastfeeding and postpartum period and <b>lifelong</b>	TDF + 3TC + EFV FDC in single pill

Clinical assessment will be the same for both pregnant women found infected with HIV and non-infected pregnant women. Additional considerations include the gestational age of pregnancy, clinical findings and the ART regimen being used.

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

### 7.2.4 Maternal prophylaxis and treatment for OIs

Maternal prophylaxis and treatment for OIs (antenatally, during labour and delivery, and postpartum) subject to the precautions listed in Table 7.3, the risk of life-threatening infections among women with a low CD4 count or clinical features of immunosuppression warrants prophylaxis against OIs.

Women who fulfil the following criteria for Cotrimoxazole (TMP-SMX) prophylaxis for PCP and toxoplasmosis should commence 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  $CD4 < 350/mm^3$

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

**Table 7.3. Prophylaxis and treatment of OIs in pregnant women**

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

Although trimethoprim is hypothetically teratogenic to the baby during the first trimester of pregnancy, cotrimoxazole prophylaxis should be commenced 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 foetus.

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



## IPT for TB can be prescribed as for non-pregnant PLHIV.

### 7.2.5 Neonatal/infant prophylaxis:

- HIV-exposed children with low risk** (whose mothers are on ART and maternal viral load is suppressed) should receive **six weeks of infant prophylaxis with either NVP or AZT prophylaxis**. In case of past exposure to NVP in previous pregnancy, syp AZT shall be used for prophylaxis with close monitoring of haemoglobin.
- HIV-exposed children with high risk** (whose mothers have received ART for less than 8 weeks, VL is more than 1000 copies, mother diagnosed as positive during labour and delivery and even breastfeeding) should receive **dual prophylaxis with NVP and AZT for 12 weeks**.

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

**Table 7.4. Infant NVP or AZT prophylaxis for low risk**

Infant age	Daily dose
Birth <sup>a</sup> to 6 weeks	
Birth weight 2000 – 2499g <sup>a</sup>	10mg once daily
Birth weight > 2500g	15mg once daily

**Table 7.5. Infant NVP and AZT prophylaxis for high risk**

Infant age	NVP Daily dose	AZT Daily dose
Birth <sup>a</sup> to 6 weeks		
Birth weight 2000 – 2499g <sup>a</sup>	10mg once daily	10mg twice daily
Birth weight > 2500g	15mg once daily	15mg twice daily
6 weeks to 12 weeks		
	20mg once daily	60mg twice daily

<sup>a</sup> Infants weighing < 2000 g should receive mg/kg dosing; the suggested starting dose is 2mg/kg once daily for NVP and 4mg/kg per dose twice daily.

Nepal has chosen dual prophylaxis for high risk babies but it will be given only if regular haemoglobin monitoring is possible; otherwise, only syp NVP will be given for 12 weeks in such cases.

## 7.2.6 Immediate newborn care includes the following:

- Maintaining 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 gloved hand or gauze before cutting.
- Using suction only when meconium-stained liquid is present; using mechanical suction at less than 100mm Hg pressure.
- Wiping the infant dry with a towel, wrapping with warm cloth, and giving the baby to the mother for skin-to-skin contact.
- Determining the mother’s infant feeding choice, encouraging breastfeeding according to the national breastfeeding protocol.
- Administering vitamin K, and Bacille Calmette Guérin (BCG; tuberculosis) vaccine according to the national guidelines.
- Administering first dose of infant Nevirapine within 6 to 12 hours of delivery.
- Regardless of the mother’s HIV status, keeping all infants warm after birth and handling them with gloves until maternal blood and secretions have been washed off.

## 7.2.7 Postpartum care of HIV-infected women

When providing postpartum care to women infected with HIV, health care workers may follow routine protocols, but several areas require additional attention.

*Immediate Postpartum Care:* Community-based service providers should ensure that women who are infected with HIV and have given birth at health facility return for postpartum appointments or are visited at home on the 1<sup>st</sup>, 3<sup>rd</sup> and 7<sup>th</sup> day after delivery.

As a minimum, women should be evaluated in the 1<sup>st</sup> week after the birth and again at the 6<sup>th</sup> week. More frequent monitoring at home will assist in adherence to neonatal Nevirapine prophylaxis and to maternal ART and/or cotrimoxazole 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 uterine involution,

- Monitor for signs of puerperal infection,
- Monitor 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 in safe breastfeeding;
- Assess family support for breastfeeding;
- Identify any risk factors for mixed feeding, and counsel and manage as appropriate;
- Ensure women take good care of her breasts to prevent abscesses, nipple fissures and mastitis; if fever or other signs of breast infection or inflammation are present, advise or refer them promptly for treatment.

The postpartum period is essential to link the women who are 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 done so. 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,
- Antiretroviral treatment,
- 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 CBO and FBO programmes;
- 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;
- Faith-based organization’s support;
- Community service providers will be provided close to community, and they will be able to care for PLHIV throughout the continuum of HIV infection and they 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.

### **7.2.8 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, and breastfeeding continued at least for 12 months, for 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.

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 additional risk for 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 express breast milk be given.

### **7.2.9 Establishing and managing linkages**

eVT needs multidisciplinary and multi-sectoral 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 like 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 supplement and complement the expansion of eVT services. At the same time, involvement of local partners and community workers is crucial to track pregnant PLHIV women to adhere to treatment, have safer delivery, receive NVP and CPT prophylaxis for baby and do EID testing at birth and 6 weeks of age. It is crucial to ensure that the mother–baby pair follow up regularly for EID, as well as timely ART initiation for children found positive, immunization, and nutritional counselling take place.

### **Linkages between 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.

- Auxiliary Nurse Midwives and paramedics can support clinical follow-up, supervise and support adherence to any prescribed treatment (eg prophylaxis against OIs), and provide information on health promotion, disease prevention.
- Specialists in HIV who provide clinical ART treatment 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 with specific health needs, such as family planning, treatment of STI, or assistance with substance abuse.
- Linkage with disease-specific programmes, such as those for people with tuberculosis.
- Linkage with nutritional support programmes for mothers and children are especially important for PLHIV.

### **Linkages to CBOs:**

- Linkages to CBOs can provide resources to help women who are HIV-infected and their families to cope with isolation, social prejudice, and the emotional pressures that often accompany diagnosis of HIV.

NGOs often provide HIV-related and non-HIV care and support services for PWID, FSW, gay men and other MSM, MSW, TG people and other KP, and are a valuable resource for mothers who are HIV-infected and their families.

## **7.3 General Care for PLHIV**

General care for PLHIV includes basic HIV prevention, promoting the health of PLHIV, and screening, prophylaxis and management of HIV-related coinfections and comorbidities.

WHO has produced summary guidelines on the 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:

- i Psychosocial counselling and support;
- ii Disclosure and partner notification;
- iii CTX prophylaxis;
- iv TB counselling, screening and preventive therapy;
- v Preventing common fungal infections;
- vi Treatment of STI and supporting reproductive health needs, including prevention of, and screening for, cervical cancer;

- vii Preventing malaria (CTX, bed-nets and particularly preventing malaria among pregnant women);
- viii The use of vaccines for prevention of pneumococcal disease, influenza, hepatitis B, and yellow fever;
- ix Provision of adequate nutrition;
- x Family planning services;
- xi Elimination of vertical transmission;
- xii Needle and syringe programmes for people who inject drugs; and
- xiii Water, sanitation and hygiene.

## 7.4 Prevention of Unintended Pregnancies in HIV-infected Women

Many PLHIV experience strong pressure from their families, communities and health providers to give up the idea of having children either because of the risk of HIV transmission to the baby or because of concern for the welfare of 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.

### 7.4.1 Reproductive decision-making for PLHIV

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 of unplanned, unintended pregnancy;
- take into account the woman's and couple's previous and current contraceptive practices; and,
- Dual method use—when effective contraceptive method for pregnancy prevention combined with a barrier method for STI and HIV transmission prevention—is recommended in a “Condom PLUS” approach;

- **Preconception counselling for PLHIV:**
  - Preconception counselling should be provided to all couples where one or both partners are HIV positive. This helps couples to achieve conception when both of them are in good health and nutritional status and HIV transmission risk is minimized:
  - If on ART, advise to achieve maximal viral suppression with complete adherence to ART for over 6 months for those on ART before attempting conception. PrEP can also be used for women, along with viral suppression in partner with early ART.
  - Limit attempts to conceive/unprotected sex to the most fertile days of the woman's monthly cycle. This is to reduce the chance of transmitting the infection to uninfected partner or super-infection.
  - Discuss the chance of transmitting HIV to the child during pregnancy, birth or breastfeeding.
  - Counsel on the infant feeding recommendation to breastfeed while taking ARVs or while practising safe sex.
  - Counsel on the need for having good general health and nutritional status during conception.
  - Discuss the impact on the family of having another child.
- For discordant couples where the woman is HIV negative and the man HIV positive, cover the following issues as part of the preconception counselling:
  - Discuss the risk of HIV transmission from man to woman.
  - PrEP could be recommended when implemented in Nepal.
  - Discuss the increased chances of transmitting HIV to the child during pregnancy, birth or breastfeeding if the woman becomes infected right before or during pregnancy or while she is breastfeeding. Emphasize the need to always use condom consistently.
  - Encourage repeat HIV testing for the woman while attempting to conceive and throughout pregnancy.
  - Discuss option of sperm washing, if available (currently limited availability in Nepal).
- For discordant couples where the woman is HIV positive and the man HIV negative, cover the following issues as part of preconception counselling:
  - Discuss the risk of HIV transmission from woman to man.
  - PrEP could be recommended when implemented in Nepal.
  - Explain that artificial insemination is the safest conception option.

- Promptly refer to eVT services after conception. If not already on ART, begin ART as soon as possible according to the National Guidelines.
- Remind women living with HIV that pregnancy places an additional burden on her body and overall health; so, she should be careful to limit her pregnancies and space them adequately so that she has time to recover between pregnancies. Furthermore, women with HIV are at greater risk of having preterm births, stillbirths and low birth weight babies. However, with current ART and early and appropriate care, it is possible to have a healthy pregnancy and a healthy baby. Inform that initiating ARVs early and proper adherence can dramatically decrease the risk of a mother passing HIV to her baby during pregnancy, delivery and breastfeeding.

### 7.4.2 Contraceptive methods

Contraceptive options for women infected with HIV are similar to those of women who are HIV negative and include:

- barrier methods (male and female condoms, diaphragms, spermicides);
- hormonal methods (oral, injectable or implantable);
- intrauterine contraceptive device (IUD);
- female and male sterilization (tubal ligation and vasectomy);
- lactational amenorrhoea method; and
- fertility awareness-based methods.

Contraceptive effectiveness is the most important consideration for most PLHIV, but not all methods are equally effective. Women who use no method at all may have a risk of pregnancy as high as 85% over a one-year period.



**Table 7.6. Contraceptive methods for PLHIV**

FP Methods	Effectiveness	Recommendations
<b>Male and Female Condom</b>	Prevent transmission of STI and HIV in addition to preventing pregnancy – called “dual protection”	<p>Condoms are highly recommended for family planning for PLHIV, either alone or, preferably, in combination with another contraceptive method.</p> <p>A “Condom Plus” approach, which promotes use of condoms to prevent HIV/STI transmission and an additional contraceptive method to help prevent pregnancy more reliably, is recommended</p>
<b>Oral (Combined Hormonal) Contraceptives</b>	<p>Highly effective pregnancy prevention. Failure rate is around 1% if pills taken on time.</p> <p>Effect of ARVs on hormonal contraceptives, PIs, particularly Ritonavir and NNRTIs, Nevirapine (NVP), Efavirenz (EFV) can affect liver enzymes, either speeding up or slowing down the metabolism of contraceptive hormones. Similarly, contraceptives may reduce the efficacy of some, but not all, PI ARVs.</p>	<p>Women with HIV infection can use hormonal oral contraceptive (OCPs) without any restriction.</p> <p>OCPs should generally not be used by HIV-infected women on ART, which includes ritonavir or ritonavir-boosted PIs.</p>
<b>Injectable (Progestogen-Only) Contraceptives</b>	<p>Pregnancy rate for injectable is less than 1% under both “perfect” and “typical” uses.</p> <p>NVP has been found to reduce serum progesterone levels by about 20%, but without reduced contraceptive efficacy.</p>	<p>Injectable progestogen is a suitable form of contraception for women with HIV infection, including those on ART.</p> <p>The consistent use of condoms is recommended to prevent transmission of HIV and other STI.</p>
<b>Progesterone Implants</b>	Pregnancy rate and interactions with ARVs are similar to those seen with injectable progesterone.	Same recommendation as with the injectable progesterone
<b>Intra-Uterine Contraceptive Devices (IUCD)</b>	<p>Highly effective long-term method of contraception with a failure rate of less than 1%.</p> <p>IUDs are safe for PLHIV, with no impact on disease progression or clinical well-being.</p>	<p>IUD may be either initiated or continued in HIV positive women who are clinically well (either WHO Stage 1 or 2 or already on ART).</p> <p>A woman who develops symptomatic illness (WHO Stage 3 or 4) while using an IUD can continue to use the device provided she is stable on ART.</p> <p>The consistent use of condoms must be recommended to prevent transmission of HIV and other STI.</p>

<b>Emergency Contraception</b>	<p>Emergency contraceptive pills (ECPs) are the most common method of emergency contraception after unprotected intercourse.</p> <p>There are no data on interaction between ECP and ARVs. ECPs contain a higher dose of hormones than regular OCPs; so, their effectiveness in pregnancy protection may not be significantly affected by ARV drugs.</p>	<p>For HIV positive women who have unprotected sex and may be at risk of an unwanted pregnancy, access to emergency contraception is essential.</p> <p>Providers who offer emergency contraception should also help women to choose a regular contraceptive method and counsel them about how to use the method correctly and when to begin using it.</p>
<b>Male or Female Sterilization</b>	<p>For women and couples with HIV who already have children and have decided to have no more, female or male sterilization may be a popular option.</p>	<p>Sterilization is recommended for PLHIV; informed voluntary choice is essential.</p> <p>Careful infection control is essential during the procedure, especially if the man or the woman is immunocompromised.</p> <p>The consistent use of condoms must be recommended to prevent transmission of HIV and other STI.</p>
<b>Methods based on Fertility Awareness</b>	<p>Identification of the fertile days of the menstrual cycle either by observing signs of fertility (eg cervical secretions, basal body temperature) or by counting the days of the cycle.</p> <p>These methods require extremely high motivation, discipline and diligence. Pregnancy rates with “perfect” use are 2–5%, but are typically between 12% and 22%.</p>	<p>PLHIV who do not want to have children should be counselled to consider other more reliable methods of contraception.</p> <p>The consistent use of condoms must be recommended to prevent transmission of HIV and other STI.</p>



# ANNEXES

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## Annex 1. WHO clinical staging of HIV disease in adults, adolescents and children

Adults and adolescents <sup>a</sup>	Children
<b>Clinical stage 1</b>	
Asymptomatic	Asymptomatic
Persistent generalized lymphadenopathy	Persistent generalized lymphadenopathy
<b>Clinical stage 2</b>	
Moderate unexplained weight loss (< 10% of presumed or measured bodyweight)	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)	Herpeszoster
Herpeszoster Angular cheilitis	Lineal gingival erythema Recurrent or alulceration
Recurrent oral ulceration	Papular pruritic eruption Fungal nail infections
Papular pruritic eruption Fungal nail infections	Extensive wart virus infection Extensive molluscum contagiosum
Seborrhoeic dermatitis	Unexplained persistent parotid enlargement
<b>Clinical stage 3</b>	
Unexplained severe weight loss (> 10% of presumed or measured bodyweight)	Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained chronic diarrhoea for longer than 1 month	Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent
Unexplained persistent fever (intermittent or constant for longer than 1 month)	Or constant, for longer than 1 month)
Persistent oral candidiasis	Persistent or oral candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia Pulmonary tuberculosis	Oral hairy leukoplakia
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)	Lymph node tuberculosis Pulmonary tuberculosis
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Severe recurrent bacterial pneumonia
Unexplained anaemia (< 8g/dl),	Acute necrotizing ulcerative gingivitis or periodontitis
Neutropenia (< 0.5x10 <sup>9</sup> /l) and/or chronic thrombocytopenia (< 50x10 <sup>9</sup> /l)	Unexplained anaemia (< 8g/dl), neutropenia (< 0.5x10 <sup>9</sup> /l) or chronic thrombocytopenia (< 50x10 <sup>9</sup> /l)
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including Bronchiectasis

Adults and adolescents <sup>a</sup>	Children
<b>Clinical stage 4<sup>c</sup></b>	
IV wasting syndrome Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal 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) 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 Salmonella) Invasive cervical carcinoma Atypical disseminated leishmaniasis	Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy Pneumocystis (jirovecii) pneumonia Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) Chronic herpes simplex infection (or 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 more than 1 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

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

<sup>b</sup> For children younger than 5 years, moderate malnutrition is defined as weight-for-height  $< -2$  z-score or mid-upper arm circumference  $\geq 115$  mm to  $< 125$  mm.

<sup>c</sup> 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.

<sup>d</sup> For children younger than 5 years of age, severe wasting is defined as weight-for-height  $< -3$  z-score; stunting is defined as height-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.

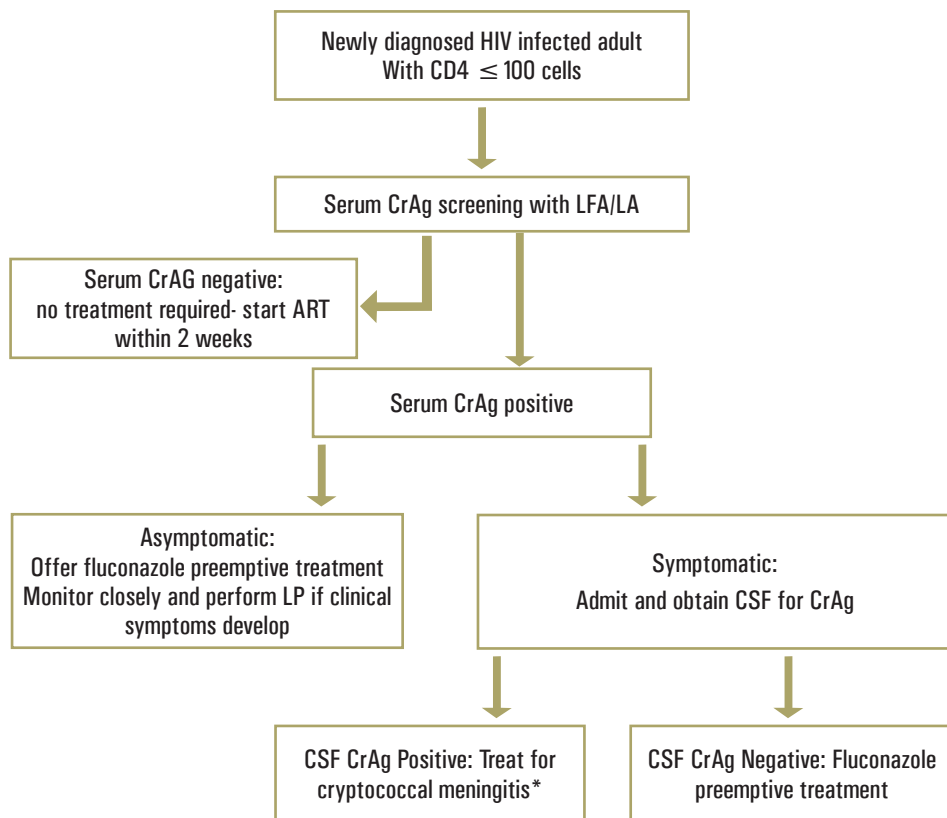
## Annex 2. Dosages of recommended antiretroviral drugs

### For adults and adolescents

Generic name	Dose
<b>Nucleoside reverse-transcriptase inhibitors (NRTIs)</b>	
Abacavir (ABC)	300 mg twice daily or 600mg once daily
Emtricitabine (FTC)	200mg once daily
Lamivudine (3TC)	150 mg twice daily or 300mg once daily
Zidovudine (AZT)	250 – 300mg twice daily
<b>Nucleotide reverse-transcriptase inhibitors (NtRTIs)</b>	
Tenofovir (TDF)	300mg once daily
<b>Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)</b>	
Efavirenz (EFV)	600mg once daily
Nevirapine (NVP)	200 mg once daily for 14 days, followed by 200 mg twice daily
<b>Proteases inhibitors (PIs)</b>	
Atazanavir + ritonavir (ATV/r)	300 mg + 100 mg once daily
Darunavir + ritonavir (DRV/r)	800mg + 100mg once daily or 600mg + 100mg twice daily
Lopinavir/ritonavir (LPV/r)	400mg/100mg twice daily
	<p><b>Considerations for individuals receiving TB therapy</b></p> <p>In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r (LPV 800mg + RTV 200mg twice daily or LPV 400 mg + RTV 400mg twice daily) or SQV/r (SQV400mg + RTV400mgtwicedaily), with close monitoring.</p>
<b>Integrase strand transfer inhibitors (INSTI)</b>	
Dolutegravir (DTG)	50mg once daily
Raltegravir (RAL)	400mg twice daily

For adolescents weighing less than 35kg, Please refer Annex 6-9.

### Annex 3. Routine screening for cryptococcal meningitis for HIV-infected adults



\*Defer ART for 4 weeks if AMPB and Fluconazole are used for treatment. Defer ART for 4-6 weeks if only Fluconazole is used and there is resolution of the symptoms.

**Fluconazole preemptive treatment:** 800 mg (12mg/kg/day if below 19 years) per day for 2 weeks followed by 400 mg per day (6mg/kg/day up to 400-800mg/day if below 19 years) for 8 weeks followed by 200mg per day for at least one year and until CD4 counts goes above 100 for at least six months (defer ART for 4–6 weeks).



## Annex 4. Etiological Management of STI

STI	Treatment for non-pregnant	Treatment for pregnant
Syphilis	<p><b>Primary Syphilis</b> Benzathine Penicillin G, 2.4 million IU (IM single dose) Or Procaine benzylpenicillin 1.2 million IU (IM daily for 10 days) <i>If client allergic to penicillin:</i> Tab. Doxycycline 100 mg (twice daily for 15 days)</p> <p><b>Late Latent Syphilis</b> Benzathine Penicillin G, 2.4 million IU (IM once weekly for three consecutive weeks) Or Procaine benzylpenicillin 1.2 million IU (IM daily for 21 days) <i>If client allergic to penicillin:</i> Tab. Doxycycline 100 mg (twice daily for 30 days)</p>	<p>Same as non-pregnant for Penicillin</p> <p><i>If client allergic to penicillin:</i> Tab. Erythromycin 500 mg (four times for 14 days)</p>
Gonorrhoea	<p>Inj. Ceftriaxone 250mg IM (single dose) Or Tab. Cefixime 400mg (single dose)</p>	Same as non-pregnant
Chlamydial infection	<p>Tab. Azithromycin 1 gm (single dose) <i>Since Chlamydial infection cannot be ruled out, it has to be treated along with Gonorrhoea</i></p>	Same as non-pregnant
Chancroid	<p>Tab. Azithromycin 1 gm (single dose) Or Inj. Ceftriaxone 250mg IM (single dose) Or Tab. Ciprofloxacin 500mg (twice a day for three days)</p>	Same as non-pregnant
Lymphogranuloma Venerum	<p>Tab. Doxycycline 100mg (twice daily for 14days) Or Tab. Erythromycin 500mg (four times for 14 days) Or Tab. Tetracycline 500mg (four times for 14 days)</p>	Tab. Erythromycin 500mg (four times for 14 days)

Granuloma Inguinale (Donovanosis)	<p>Tab. Azithromycin 1 gm on first day, then 500 mg once a day</p> <p>Or</p> <p>Tab. Doxycycline 100mg (twice daily)</p> <p>Or</p> <p>Tab. Erythromycin 500mg (four times)</p> <p>Or</p> <p>Tab. Tetracycline 500mg (four times)</p> <p>Or</p> <p>Tab Trimethoprim 80mg/Sulfamethoxazole 400mg (2 tab twice daily)</p> <p><b><i>Treatment should be continued until all lesion have completely epithelialized</i></b></p>	
Bacterial Vaginosis/ Trichomoniasis	<p>Tab. Metronidazole 400mg (twice daily for seven days)</p> <p>Or</p> <p>Tab. Tinidazole 500mg (twice daily for five days)</p>	
Candidal vaginosis	<p>Clotrimazole Vaginal Pessary 200mg (intravaginal for three days)</p> <p>Or</p> <p>Tab Fluconazole 150mg (single dose)</p>	Clotrimazole Vaginal Pessary 100mg (intravaginal for atleast six days)
Herpes genitalis	<p><b>For first episode</b></p> <p>Acyclovir 400 mg (three times a day for seven days)</p> <p>Or</p> <p>Acyclovir 200 mg (five times a day for seven days)</p> <p><b>For recurrent episodes</b></p> <p>Acyclovir 400 mg (three times a day for seven days and then twice daily for one year)</p> <p><b>For severe infection</b></p> <p>Acyclovir 5-10mg/kg IV every eight hours for five to seven days or until clinical resolution</p>	Same as non-pregnant
Genital wart	<p>Podophylline 25%</p> <p>Or</p> <p>Trichloroacetic acid (TCA 80-90%)</p> <p>Or</p> <p>Physical method (Cryo-therapy, Electro-cautery, Surgical excision, Laser therapy)</p>	TCA or surgical ablation

## Annex 5. Syndromic management of STI

Syndromes	Management
Urethral Discharge Syndrome (UDS)	<p><b>To treat Gonococcal infection, use</b></p> <p>Cefixime 400 mg orally, as a single dose OR Ceftriaxone, 250mg by intramuscular injection as a single dose</p> <p>PLUS</p> <p><b>To treat Chlamydial infection, use</b></p> <p>Azithromycin, 1gm orally, as a single dose OR Doxycycline, 100mg orally twice daily for seven days</p>
Scrotal Swelling Syndrome (SSS)	<p><b>To treat Gonococcal infection, use</b></p> <p>Ceftriaxone, 250 mg by intramuscular injection as a single dose OR Tab. Cefixim 400mg PO stat</p> <p>PLUS</p> <p><b>To treat for Chlamydia infection, use</b></p> <p>Doxycycline, 100 mg orally, twice daily for 10 days</p> <p>Supportive therapy: bed rest, antipyretics and analgesics, and scrotal support until local inflammation and fever subside</p>
Vaginal Discharge Syndrome (VDS)	<p><b>To treat Cervicitis (due to NG and CT), use</b></p> <p>Cefixime, 400mg orally, as a single dose OR Ceftriaxone, 250mg by intramuscular injection, as a single dose</p> <p>PLUS</p> <p>Doxycycline, 100mg orally, twice daily for seven days OR Azithromycin, 1gm orally, as a single dose OR Erythromycin, 500mg orally, four times daily for seven days</p> <p><b>To treat Vaginitis (BV, TV), use</b></p> <p>Metronidazole, 400mg orally twice daily for seven days OR Tinidazole, 500mg orally twice daily for five days</p> <p><b>To treat for Candidiasis, use</b></p> <p>Fluconazole, 150mg orally, as a single dose OR Miconazole or clotrimazole, 200mg vaginal pessaries intravaginally daily for three days OR Clotrimazole, 500mg vaginal pessaries intravaginally as a single dose OR Nystatin vaginal pessaries 100000IU intravaginally daily for 14 days</p>

Syndromes	Management
Lower Abdominal Pain Syndrome	<p><b>To treat Gonococcal infection, use</b> Ceftriaxone, 250mg by intramuscular injection. As a single dose</p> <p>PLUS</p> <p><b>To treat Chlamydia infection, use</b> Doxycycline, 100mg orally, twice daily for 14 days OR Erythromycin, 500mg orally, 4 times a days for 14 days</p> <p>PLUS</p> <p><b>To treat Anaerobic infection, use</b> Metronidazole, 400mg orally twice daily for 14 days</p>
Neonatal Conjunctivitis Syndrome	<p><b>To treat Gonococcal conjunctivitis, use</b> Ceftriaxone, 50 mg/kg by intramuscular injection as a single dose, to a maximum of 125 mg total dose OR Spectinomycin, 25 mg/kg by intramuscular injection as a single dose, to a maximum of 75 mg total dose</p> <p>PLUS</p> <p><b>To treat Chlamydial conjunctivitis, use</b> Erythromycin syrup, 50 mg/kg per day orally, in four divided doses for 14 days</p>
Genital Ulcer Disease Syndrome (GUDS)	<p><b>Treatment for Syphilis, use</b> Benzathine benzylpenicillin G, 2.4 million IU by intramuscular injection as a single dose OR Procaine benzylpenicillin, 1.2 million IU by intramuscular injection, daily for 10 consecutive days</p> <p>PLUS</p> <p><b>Treatment for Chancroid, use</b> Azithromycin 1 gram oral single dose OR Erythromycin 500 mg six hourly orally for seven days OR Ciprofloxacin 500 mg twice daily for three days OR Inj. Ceftriaxone 250 mg IM single dose</p> <p><b>To treat for the first clinical episode of Genital herpes, use</b> Acyclovir, 400 mg orally, three times daily for seven days OR Acyclovir, 200 mg orally, five times daily for seven days</p>
Inguinal Bubo Syndrome	<p><b>To treat Chancroid, use</b> Azithromycin, 1 g orally as a single dose OR Inj Ceftriaxone 250mg IM Stat OR Ciprofloxacin, 500 mg orally, twice daily for three days</p> <p>PLUS</p> <p><b>To treat for LGV, use</b> Doxycycline, 100 mg orally, twice daily for 14 days OR Erythromycin, 500 mg orally, four times daily for 14 days</p>

## Annex 6. Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing among children

Drug	Strength of tablets (mg)	Number of tablets by weight band morning and evening												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	AM	PM	AM	PM
AZT/3TC	Tablet (dispersible) 60mg/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	1	1
AZT/3TC/NVP	Tablet (dispersible) 60mg/30mg/50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	1	1
ABC/AZT/3TC	Tablet (dispersible) 60mg/60mg/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	1	1
ABC/3TC	Tablet (dispersible) 60mg/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	3	3	1	1

## Annex 7. Simplified dosing of child-friendly solid formulations for one-daily dosing in children

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	Table (scored) 200mg	.	.	1	1.5	1.5	200	25–34.9 kg
	Table (double scored) 600mg	.	.	One third	One half	Two thirds	600	
ABC/3TC	Table (dispersible) 60/30mg	2	3	4	5	6	600 + 300	1

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

b The double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.

## Annex 8. Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	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	AM	PM	AM	PM	AM	PM		AM	PM
<b>Solid Formulations</b>														
3TC	Table (dispersible) 30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	150	1	1
AZT	Table (dispersible) 60mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
ABC	Table (dispersible) 60mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
NVP <sup>a</sup>	Table (dispersible) 50mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200	1	1
LPV/r <sup>b</sup>	Table (heat stable) 100mg/25mg	-	-	-	-	2	1	2	2	2	2	100/25	3	3
<b>Liquid formulations</b>														
AZT	10mg/ml	6ml	6ml	9ml	9ml	12ml	12ml	-	-	-	-	-	-	-
ABC	20mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-	-	-	-
3TC	10mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-	-	-	-
NVP <sup>a</sup>	10mg/ml	5ml	5ml	8ml	8ml	10ml	10ml	-	-	-	-	-	-	-
LPV/r <sup>b</sup>	80/20mg/ml	1ml	1ml	1.5ml	1.5ml	2ml	2ml	2.5ml	2.5ml	3ml	3ml	-	-	-

<sup>a</sup> 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 recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose (Fillekes Q, et al. Is nevirapine dose escalation appropriate in young, african, HIV-infected children? AIDS, 2013, ahead of press (<http://www.ncbi.nlm.nih.gov/pubmed/23595153>, accessed 17 July 2013). doi: 10.1097/QAD.0b013e3283620811) More definitive evidence is expected from an ongoing trial.

<sup>b</sup> 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 or crushed.

## Annex 9. Simplified harmonized dosing for currently available TDF formulation for children

Drug	Size of powder scoop (mg) or strength of tablet (mg)	Number of scoops/tablets by weight band once daily					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		
TDF <sup>a</sup>	Oral powder scoops 40 mg/scoop	.	.	3	.	.	300 mg	1 (200 mg) <sup>b</sup> or 1 (300 mg)
	Tablets 150 mg or 200 mg	.	.	.	1 (150 mg)	1 (200 mg)		

<sup>a</sup> Target dose: 8 mg/kg or 200 mg/m (maximum 300 mg). The Paediatric Antiretroviral Working Group developed this guidance to harmonize TDF dosing with WHO weight bands and to reduce the numbers of strengths to be made available. The WHO generic tool was used based on the target dose provided by the manufacturer's package insert. In accordance with the standard Paediatric Antiretroviral Working Group approach, dosing was developed ensuring that a child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

<sup>b</sup> 200-mg table should be used for weight 25-29.9 kg and 300 mg tablets for 30-34.9 kg.



## Annex 6. Simplified dosing of isoniazid (INH) and cotrimoxazole (CTX) prophylaxis

Drug	Strength of tablets oral liquid (mg or mg/5 ml)	Number of tablets by weight band once daily					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		
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	25–34.9 kg
	Suspension 200/40 per 5ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	.	.
CTX	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
	Tablets (scored) 800/160 mg	.	.	.	One half	One half	800/160 mg	1
INH/CTX/B6 <sup>a</sup>	Tablets (scored) 960 mg/300 mg/25 mg	.	.	.	One half	One half	960 mg/300 mg/25 mg	1

<sup>a</sup> This formulation is currently awaiting regulatory approval, and a scored junior tablet (480 mg/150 mg/12.5 mg) is also under development.

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