

# National Consolidated Guideline for Treating and Preventing HIV in Nepal



2014



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

Supported by:



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## ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
AIDS	acquired immuno deficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AZT	zidovudine(also known as ZDV)
BMI	body mass index
CD4	T-lymphocyte cell bearing CD4 receptor
d4T	stavudine
DBS	dried blood spot
ddI	didanosine
DNA	deoxyribonucleic acid
DRV	darunavir
DRV/r	darunavir/ritonavir
EFV	efavirenz
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FTC	emtricitabine
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immune deficiency virus
HSV	herpes simplex virus
INH	isoniazid
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir

LPV/r	lopinavir/ritonavir
MDR	multidrug-resistant TB, resistant to at least isoniazid and rifampicin
MTCT	mother-to-child transmission (of HIV)
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OST	opioid substitution therapy
PCR	polymerase chain reaction
PI	protease inhibitor
PCP/PJP	Pneumocystis (jirovecii) pneumonia
PMTCT	prevention of mother-to-child transmission of HIV
PrEP	pre-exposure prophylaxis of HIV
RAL	raltegravir
RBV	ribavirin
RIF	rifampicin
RNA	ribonucleic acid
RTV	ritonavir
sd-NVP	single-dose nevirapine
TAM	thymidine analogue mutation
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
WHO	World Health Organization



## Acknowledgements

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### Foreword

Treatment for HIV has evolved over the years and current evidence demonstrates the multiple benefits of antiretroviral therapy. Since the inception of Nepal's ART programme in 2004 under the leadership of the Ministry of Health & Population, National Center for AIDS & STD Control, country has taken many measures to scale up ART with the objective of reaching everyone who needs treatment. Development of this 'National Consolidated Guideline for Treating and Preventing HIV in Nepal' is another mile stone, which emphasizes that earlier treatment has a dual advantage – keeping infected people healthier longer and dramatically reducing the risk of virus transmission to others.

This guideline demonstrates that Nepal has adopted most of the recommendations in WHO 'Consolidated guidelines on the use of Antiretroviral Drugs for treating and preventing HIV infection' published in June 2013. I am very thankful to all the members of the guideline development group and the members of the Technical Working Group on HIV Testing, Counseling, Treatment, care and PMTCT. I would also like to thank WHO Country Office Nepal for providing technical support to develop this guideline.

I strongly encourage all the partners working in the field of HIV in Nepal to utilize this guideline appropriately and together push the HIV epidemic in Nepal into irreversible decline.

Dr Dipendra Raman Singh

Director



## Executive Summary

### National Consolidated Guideline for Treating and Preventing HIV in Nepal

With the objective of providing updated, evidence-based clinical recommendations outlining a public health approach to providing ARV drugs for HIV treatment and prevention in the context of the continuum of HIV care, Ministry of Health and Population, National Center for AIDS & STD Control revised the National ART Guidelines developed in 2012, based on the recommendations adopted to Nepal context from WHO “Consolidated Guideline on The use of ARV Drugs for Treating and Preventing HIV Infection” (June 2013).

Comprehensive guidance is now provided on using ARV drugs across age groups and populations of adults, pregnant and breastfeeding women, adolescents, children and key populations. The guidelines also aim to consolidate and update clinical, service delivery and programmatic guidance.

New technologies, including CD4 point-of-care testing, and new service delivery approaches allow HIV testing and treatment monitoring to be diversified and decentralized. Simple, safer, once-daily, single-pill ARV regimens that are suitable for use in most populations and age groups have become more affordable and more widely available. With this new guideline Nepal is moving towards earlier initiation of triple-drug regimens and simplified programming for the prevention of mother-to-child transmission of HIV (PMTCT) that emphasizes the long-term health of pregnant women and mothers living with HIV and preventing HIV infection among their children.

The new clinical recommendations in this guideline expanded:

- eligibility for treatment initiation with CD4 threshold of 500 cells/mm<sup>3</sup> or less for adults, adolescents and children older than 5 years;
- ART is recommended to be initiated regardless of CD4 count for:
  - people with active Tuberculosis disease who are living with HIV;
  - people with both HIV and hepatitis B virus infection with severe chronic liver disease;
  - HIV-positive partners in sero-discordant couples;



- pregnant and breastfeeding women, and
- children younger than five years of age.
- Viral load testing is now recommended as the preferred approach to monitor ART response and diagnosing treatment failure, complementing clinical and immunological monitoring of people receiving ART.

When to start ART in people living with HIV	
Topic and population	Recommendations
When to start ART in adults and adolescents	<ul style="list-style-type: none"> <li>• ART should be initiated in all individuals with HIV with CD4 count <math>\leq 500</math> cells/mm<sup>3</sup> regardless of WHO clinical stage.</li> <li>• ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in the following situations:               <ul style="list-style-type: none"> <li>- Individuals with HIV and active TB disease</li> <li>- Individuals co-infected with HIV and HBV with evidence of severe chronic liver disease</li> </ul> </li> <li>• Partners with HIV in sero-discordant couples should be offered ART to reduce HIV transmission to uninfected partners.</li> </ul>
When to start ART in pregnant and breastfeeding women	<ul style="list-style-type: none"> <li>• All pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), as lifelong treatment.</li> </ul>
ARVs and duration of breastfeeding	<ul style="list-style-type: none"> <li>• Mothers known to be infected with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first 6 months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding. Breastfeeding should be stopped once a nutritionally adequate and safe diet without breast-milk can be provided.</li> </ul>
When to start ART in children	<ul style="list-style-type: none"> <li>• ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count and infants diagnosed in the first year of life.</li> <li>• ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count <math>\leq 500</math> cells/mm<sup>3</sup>, regardless of WHO clinical stage.</li> <li>• ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection.</li> </ul>

What ART regimens to start	
Topic and population	Recommendations
First-line ART regimens for adults	<ul style="list-style-type: none"> <li>• First-line ART should consist of two nucleoside reverse- transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).</li> <li>• TDF + 3TC + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART</li> <li>• If TDF + 3TC + EFV is contraindicated or not available, one of the following options is recommended: <ul style="list-style-type: none"> <li>- AZT + 3TC + EFV</li> <li>- AZT + 3TC + NVP</li> <li>- TDF + 3TC + NVP</li> </ul> </li> <li>• Nepal should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities.</li> </ul>
First-line ART for pregnant and breastfeeding women and their infants	<ul style="list-style-type: none"> <li>• A once-daily fixed-dose combination of TDF + 3TC + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies to lifelong treatment.</li> <li>• Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be also given six weeks of infant prophylaxis with daily NVP. Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum</li> </ul>
First-line ART for children younger than 3 years of age	<ul style="list-style-type: none"> <li>• A LPV/r-based regimen should be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with an NVP-based regimen.</li> <li>• Where viral load monitoring is available, consideration can be given to substituting LPV/r with an NNRTI after virological suppression is sustained.</li> <li>• For infants and children infected with HIV younger than three years, ABC + 3TC + AZT is recommended as an option for children who develop</li> </ul>

Topic and population	Recommendations
	<p>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.</p> <ul style="list-style-type: none"> <li>• For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC + 3TC or AZT + 3TC.</li> </ul>
<p>First-line ART for children 3 years of age and older (including adolescents)</p>	<ul style="list-style-type: none"> <li>• For children infected with HIV three years of age and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative.</li> <li>• For children infected with HIV three years to less than 10 years old (and adolescents weighing less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order: <ul style="list-style-type: none"> <li>- ABC + 3TC</li> <li>- AZT or TDF + 3TC</li> </ul> </li> <li>• For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order: <ul style="list-style-type: none"> <li>- TDF + 3TC</li> <li>- AZT + 3TC</li> <li>- ABC + 3TC</li> </ul> </li> </ul>
<p><b>Monitoring ART response and diagnosis of treatment failure</b></p>	
<p><b>All populations</b></p>	<ul style="list-style-type: none"> <li>• Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure.</li> <li>• If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.</li> </ul>
<p><b>Second-line ART - what ARV regimen to switch to</b></p>	
<p>What ARV regimen to switch to in adults and adolescents (includes pregnant and breastfeeding women)</p>	<ul style="list-style-type: none"> <li>• Second-line ART for adults should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI).</li> <li>• The following sequence of second-line NRTI options is recommended:</li> </ul>

Second-line ART - what ARV regimen to switch to	
Topic and population	Recommendations
	<p>After failure on a TDF + 3TC -based first-line regimen, use AZT + 3TC as the NRTI backbone in second-line regimens.</p> <ul style="list-style-type: none"> <li>- After failure on an AZT or d4T + 3TC-based first-line regimen, use TDF + 3TC as the NRTI backbone in second-line regimens.</li> <li>- Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach.</li> <li>- Heat-stable fixed-dose combinations ATV/r and LPV/r are the preferred boosted PI options for second-line ART.</li> </ul>
What ARV regimen to switch to in children (including adolescents)	<ul style="list-style-type: none"> <li>• After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI.</li> <li>• After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be undertaken.</li> <li>• After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI.</li> <li>• After failure of a first-line regimen of ABC or TDF + 3TC, the preferred NRTI backbone option for second-line ART is AZT + 3TC.</li> <li>• After failure of a first-line regimen containing AZT or d4T + 3TC the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC.</li> </ul>

## 01

# HIV TESTING, COUNSELLING AND LINKING PEOPLE FOR HIV CARE

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## Introduction

The overall HIV testing and counselling goal for the national HIV programme is to identify as many people living with HIV as early as possible after acquiring HIV infection, and link them appropriately in a timely manner to prevention, care and treatment services. The people tested who are not infected should be linked to appropriate prevention services, such as dropping centers for female sex workers, male sex workers and transgender women, harm reduction services for those who use drugs, and encourage to retest at a later time.

Diverse models of HIV testing and counselling services are available in Nepal to increase access to HIV diagnosis, including testing services in health care facilities, free standing sites and a range of community-based approaches.

### **Box 1.1. HIV testing and counselling: guiding principles**

1. All forms of HIV testing and counselling need to be voluntary.
2. Have to adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services.
3. Mandatory testing is never appropriate, whether that coercion comes from a health care provider or from a partner or family member.
4. Informed consent must be given (verbal consent is sufficient and written consent is not required), and has a right to decline testing.
5. Must maintain confidentiality. Although confidentiality should be respected, it should not be allowed to reinforce secrecy, stigma or shame. Shared confidentiality with a partner or family members and trusted others and with health care providers is often highly beneficial.
6. Services must be accompanied by appropriate and quality pre-test counselling and post-test counselling.
7. Quality assurance mechanisms and supportive supervision and mentoring systems should be in place to ensure the provision of high-quality testing and counselling.
8. Connection to prevention, care and treatment services that are acceptable, accessible and effective are critical for appropriate follow-up services, including long- term prevention and treatment support.

Testing algorithm for Nepal is detailed out in Chapter 8.

## 1.2. Facility-based HIV Testing and counselling

In Nepal currently mainly two types of facility-based HIV testing and counselling services are available:

- i. health facility based
- ii. stand-alone HTC services

In health facility based HTC services voluntary client-initiated (CITC) and provider initiated testing and counselling (PITC) are carried out.

Provider-initiated testing and counselling should be recommended for:

- adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB; and HIV-exposed children, children born to women living with HIV and symptomatic infants and children; for people presenting with sexually transmitted infections, hepatitis; to all pregnant women attending antenatal care settings; for key populations (notably men who have sex with men, transgender people, sex workers, people who inject drugs and migrant workers).

HTC services are mainly provided by NGOs, cater to key population groups. The HTC services catering to key populations could be considered as a community-based approach. At facility-based HIV testing centers “Testing algorithm for facility-based testing” should be carried out by the trained personnel.

## 1.3. Community-based Testing

Overall Objective of the community-based HTC (CBHTC) service is to contribute to the country targets for HIV testing in Nepal by involving community. In community-based testing, organization & management of the testing sites, conduct of pre & post-test counselling can be done by the trained, competent community workers while testing of clients will be performed by a trained laboratory personal according to the National algorithm, and confirmatory test results will be provided to clients.

Recording and reporting of the testing have to be done as per the National standards, and testing sites have to participate in external quality assurance mechanism conducted by National Public Health Laboratory.

Community based HTC can be performed both at facility and community settings. Nepal may implement following modes of CBHTC; however new innovation can always be employed over-time to suit the local context and needs:

1. Stand-alone or multi-service- HTC facilities within the community that are not directly attached to other specific health services. These HTC centers target the key populations and can be tailored to other populations - spouses of migrants, adolescents, sero-discordant couples, people with specific needs, for the persons with disabilities. Multi-service HTC facilities in addition to HTC may provide family planning services, STI management facilities, OST services, primary health care services.
2. Outreach - refers to services offered outside of a fixed site, such as workplace (e.g. in factories) or mobile centers during events (e.g. World AIDS Day, musical events, sports events). Outreach facilities may provide additional services other than HTC, e.g. family planning services, STI management facilities etc.
3. Home-based - refers to the service in which the HTC service provider physically goes to the home of a potential client or known patients to offer HTC. In Nepal it is recommended for “Index client”, i.e. HTC service providers only visit the homes of an identified HIV positive client to provide HTC services to family members.

#### **1.4. HIV Testing and counselling in specific populations and settings**

##### **1.4.1. Couples**

Couple testing and counselling can identify sero-concordant positive couples who can be linked to treatment. It also identifies couples with sero-discordant HIV test results who can benefit from HIV prevention interventions. Services should be offered to married and cohabiting couples, premarital couples, and any other partnerships. When found positive mutual disclosure should be encouraged. Meanwhile service providers must be aware of the potential for intimate partner-based violence and should support individuals when they do not want to test with their partners and for mutual disclosure.



### 1.4.2. Pregnant and postpartum women

Provider-initiated testing and counselling for pregnant women should be offered in every antenatal care setting and linkage to prevention and care are needed to promote the mother's health and prevent new paediatric infections. At antenatal care settings group pre-test counselling can be offered but post-test counselling should be individual. Antenatal screening of HIV can be coupled with syphilis testing. If any postpartum woman was not screened for HIV during her antenatal period, postpartum screening for HIV should be performed. Partner testing is highly recommended when a pregnant or postpartum woman found positive. If applicable, screening of other children for HIV has to be conducted.

### 1.4.3. Infants and children

Summary of recommended testing approaches for infants and children are provided in Table 1.1. HIV-exposed infants and children younger than 18 months should be tested using virological tests (EID - Early Infant Diagnosis), within 6 weeks of birth so that those already infected with HIV can start ART.

Provider-initiated testing and counselling is recommended for all children who are malnourished, have TB, or have other signs or symptoms of HIV infection.

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

Category	Test required	Purpose	Action to be taken
Well, HIV-exposed infant	Virological testing at 6 weeks of age	To diagnose HIV	Start ART if HIV - infected
Infant – unknown HIV exposure	Maternal HIV serological test or infant HIV serological test	To identify or confirm HIV exposure	Need virological test if HIV-exposed
Well, HIV-exposed infant at 9 months	HIV serological test	To identify infants who have persisting HIV antibody or have seroreverted	Those HIV seropositive need virological test and continued follow up; those HIV negative, assume uninfected, repeat testing required if still breastfeeding

Category	Test required	Purpose	Action to be taken
Infant or child with signs and symptoms suggestive of HIV infection	HIV serological test	To confirm exposure	Perform virological test if <18 months of age
Well or sick child seropositive >9 months and <18 months	Virological testing	To diagnose HIV	PCR +ve– start HIV care and ART
Infant or child who has completely discontinued breastfeeding	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, need to start HIV care, including ART

Older children should be told of their HIV-positive status and their parents or caregiver’s status if appropriate; younger children should be told their status incrementally to accommodate their cognitive skills and emotional maturity, in preparation for full disclosure.

#### 1.4.4. Adolescents

Adolescents (10-19 years) are considered as a vulnerable population in Nepal. They can acquire HIV infection in two ways—through vertical or horizontal. Horizontal transmission occurs in two ways: sexual and parenteral transmission (injecting drug use, unsafe surgical procedures and blood transfusion). Adolescents living with HIV can be long-term survivors of vertical transmission, some who are on treatment, as well as slow progressors (not on treatment).

However, a significant proportion has not been diagnosed and linked to care due to loss to follow-up (LTFU) or poor coverage of PMTCT programmes.

HTC for adolescents offers many important benefits. Adolescents who learn that they have been diagnosed with HIV are more likely to obtain emotional support and practice preventive behaviours to reduce the risk of transmitting HIV to others, and more likely to obtain HIV treatment and care. Early access to care can help them to feel better and to live longer, than if they present for care when their disease is already at an advanced stage. Access to HTC is also important for adolescents who do not have HIV, to reinforce prevention messages and facilitate access to prevention services and commodities.

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

In Nepal the adolescents 18 years or more can give consent on their own for testing. For adolescents less than 18 years parents or guardians and specially for adolescents from key populations their older peers can give consent for HTC.

#### **1.4.5. Specific populations**

Recommendations for HIV testing and counselling for these key populations and vulnerable groups emphasize consent and confidentiality as well as ensuring that HIV testing and counselling is part of a comprehensive prevention, care and treatment programme, including partner counseling and testing.

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

<b>Who to test</b>	<b>When to test</b>	<b>Where to test</b>
People with signs or symptoms of HIV infection, including TB patients	Integrate in health care encounter provider-initiated HIV-testing and counselling in health facilities	HTC centers, Sexually transmitted infection clinics, TB clinics, medical wards, other clinics,
Partners of people with HIV	As soon as possible after partner diagnosis. For the negative person in sero-discordant couples, offer re-testing every 6–12 months	HTC centers, Sexually transmitted infection clinics.
Families of index cases	As soon as possible after the family member is diagnosed	HTC centers community-based (home-based testing)
Key populations: people who inject drugs, men who have sex with men, transgender people and sex workers	Every 6–12 months	HTC centers, Sexually transmitted infection clinics, community-based services for key populations and harm-reduction services
Pregnant women	At the first antenatal care-visit - provider- initiated HIV testing and counselling	Antenatal care settings
Migrant workers	On their return to place of origin and before departure to destination. If any signs and symptoms of HIV infection	HTC centers, Sexually transmitted infection clinics, community-based services for key populations

#### **1.4.6. Blood donors**

Primarily donated blood units are screened for HIV according to national algorithms. Under specific conditions (mainly where the fresh blood transfusions are 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.

#### **1.4.7. Surveys/ Research**

When conducting HIV testing for surveys and research purposes, ethical clearance should be obtained from the Nepal Health Research Council before initiating it. National algorithm for HIV testing should be followed with the similar test kits 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 used. The diagnostic testing process should also include high-quality counselling and referral to services, as with other diagnostic HIV testing encounter.

### **1.5. Linking people diagnosed with HIV to care and treatment**

HTC must be accompanied by assured linkage to prevention, treatment, care and support services, including, but not limited to pre-ART, CD4 cell count testing and services for ART, TB, STIs, PMTCT, and family planning services. This enables both early assessment of their eligibility for ART and timely initiation of ART as well as access to interventions to prevent further transmission of HIV, prevent other infections and comorbidities and thereby to minimize loss to follow-up. It is the responsibility of HTC providers to ensure that individuals or couples are linked to appropriate prevention, treatment, care and support services.

Several good practices such as providing on-site or immediate CD4 testing with same-day results; assisting with transport if the ART site is far from the HIV testing and counselling site; involving community outreach workers to identify the people lost to follow-up; ensuring support from peers or experienced patients; and using new technologies, such as mobile phone text messaging can improve linkage to care.



## 02

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

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## 2.1. Introduction

At present, 3 or more ARV drugs are recommended worldwide for the treatment of people with HIV infection known as highly active antiretroviral therapy (HAART). HAART brought a revolutionary change in the treatment of HIV infected people and this disease has been transformed into a chronic condition. Although the use of antiretroviral therapy is not the final solution to HIV prevention and care programs, treatment and prevention have been proven to be inextricably linked. ART dramatically decreases the chance of transmitting the virus from unsafe sex, from mother-to child, occupational exposure in health care providers and non-occupational exposure. The delivery of effective care and antiretroviral treatment for people living with HIV in the poorest countries is considered an urgent priority and is now an integral part of HIV transmission prevention programs.

## 2.2. HIV Prevention based on ARV drugs

### 2.2.1 ART for prevention among sero-discordant couples

In sero-discordant couple HIV-positive partner should start ARV irrespective of the CD4 count for their own health as well as to reduce HIV transmission to uninfected partner.

### 2.2.2. Post-exposure prophylaxis (PEP) for occupational and non-occupational exposure to HIV

Post Exposure Prophylaxis is one of the major ways to reduce the risk of HIV infection in someone exposed to the virus either occupationally or through sexual intercourse. It is the 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. In the health sector, post-exposure prophylaxis should be provided as part of a comprehensive package of universal precautions that reduces the risk of acquiring diseases by exposure of personnel to infectious hazards at work. The majority of occupational exposures do not lead to HIV infection. The risk of HIV transmission following skin puncture from a needle or other sharp object that was 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 (e.g. suture) needles than with hollow bore (eg-blood drawing) needles. Similarly, the smaller the size of hollow bore needle, the less 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 about 0.09%.

### *Indications for Post Exposure Prophylaxis*

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 (infected body fluids -semen, cervicovaginal secretions, blood, non-infectious body fluids include faeces, saliva, urine and sweat)
  - b. Exposure to non-intact skin or mucus membranes to potentially infectious body fluids
4. The exposure occurred is less than 72 hours previously.
5. The exposure is not part of chronic exposure (prevention support needed instead).
  - The current recommended duration of post-exposure prophylaxis for HIV infection is 28 days, and the first dose should be offered as soon as possible within 72 hours after exposure.
  - First aid immediately after potential exposure is provided in Annex 2.1
  - HIV Antibody testing (rapid or ELISA) should be used to monitor for seroconversion, and test should be performed at baseline and at 3 and 6 months post exposure.
  - Testing for other bloodborne diseases - such as hepatitis B and C - is also important; depending on the nature of the risk and the local prevalence, if testing is available.
  - In the process of seeking informed consent for HIV post-exposure prophylaxis, people who have been exposed to HIV must be made fully aware of the following:
    - The risk of acquiring HIV infection from the specific exposure;
    - What is known and not known about the efficacy of PEP;

- The importance of taking a HIV test and of receiving appropriate post-test counseling (although testing 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;
- People already living with HIV should be referred for treatment of their infection, and if they had started PEP the medicine should be stopped when the diagnosis is confirmed;
- If PEP regimen comprised of Zidovudine, baseline hemoglobin test should be performed on the exposed person. NVP should not be used for PEP due to risk of hepatotoxicity.
- The importance of adhering to medicine - what to do if they forget or vomit a dose (see ART adherence section)
- The common side effects that 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 continue 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 following sexual assault - PEP for the victim of rape can be made available if required.
- PEP for non-occupational exposure other than rape - for non-occupational exposure other than rape, clinician will decide on a case-by case basis whether PEP should be provided.
- Drugs for PEP should be made available in every hospital so that treatment can be immediately initiated.

## Drug regimens for PEP

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

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

\*AZT + 3TC in case of intolerance/contraindication to TDF+3TC

### 2.2.3 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 interventions that best suit their needs at different times. Combining approaches may also result in synergies that have greater impact than single interventions alone. Although ARV drugs play a key role in HIV prevention, they should be used in combination with an appropriate mix of the following.

- **Other biomedical interventions** that reduce HIV risk practices and/or the probability of HIV transmission per contact event, including the following:
- **Male and female condoms**- Male condoms reduce heterosexual transmission by at least 80% and offer 64% protection in anal sex among 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 programmes** are highly associated with a reduction in HIV transmission through injecting drug use.
- **Opioid substitution therapy with methadone or buprenorphine** is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviour and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART.

- **Behavioural interventions** 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 behaviour that increases the risk of HIV and increase 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 interventions** affect access to, up take of and adherence to behavioural and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reform, measures to reduce stigma and discrimination, the promotion of gender equality and prevention of gender-based violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

### **2.3.Preparing People living with HIV for ART.**

Before people start ART, it is important to confirm the diagnosis according to the National algorithm, have a detailed discussion with them about their willingness and readiness to initiate ART, the ARV regimen, dosage and scheduling, the likely benefits and possible adverse effects and the required follow-up and monitoring visits. For children with HIV, this conversation should directly involve the care takers and include discussion about disclosing their HIV status. Initiation of ART should always consider nutritional status, any co-morbidities and potentially interacting medications for possible contraindications or dose adjustment.

## *Evaluation of patients before starting Antiretroviral Therapy*

A detailed evaluation is essential prior to initiating antiretroviral therapy and should aim to:

- assess the clinical stage of HIV infection.
- identify past HIV-related illnesses.
- identify current HIV-related illnesses that will require treatment.
- identify co-existing medical conditions and treatments that may influence the choice of therapy.

Before initiating therapy, the following evaluations should be performed:

- A history including past illnesses with emphasis on OIs and other conditions
- Psychological and psychiatric history.
- Assessment of family and social support
- Practices regarding safe sex and injecting drug use
- Physical examination

### **Physical examination and lab tests before initiating ARV Therapy:**

- Vital signs: Pulse, BP, respiration, including temperature, pallor, cyanosis, icterus, oedema, clubbing, lymphadenopathy, JVP
- Body weight of the patient
- Skin: look for Herpes Zoster, HIV dermatitis and other skins conditions.
- Oropharyngeal mucosa: look for candidiasis, and hairy leucoplakia, Kaposi sarcoma.
- Examination of abdomen, heart, lungs, neurological, musculoskeletal and genitourinary systems.

### **Laboratory Tests:**

- 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 GeneXpert, Microscopy, Chest X ray,
- CD4 cell count

For women, cervical pap smear or other method of cervical cancer screening, if available.

The choice to accept or decline ART ultimately lies with the individual person or his or her care taker, and if they choose to defer initiation, it is the responsibility of the clinicians and ART counsellor of the ART clinic to counsel the patient adequately so that patient understand the repercussions of not accepting ART not only for the individual, but also for the family and to the society. If there is mental health problem, substance use or other problems that are major barriers to adherence, appropriate support should be provided, and readiness to initiate ART should be reassessed at regular intervals. A wide range of patient information materials as well as community and peer support can help the person's readiness and decision to start therapy.

People starting treatment and care takers should understand that the first ART regimen offers the best opportunity for effective viral suppression and immune recovery, and that successful ART requires them to take the medications exactly as prescribed. They should be advised that many adverse effects are temporary or may be treated, or that substitutions can often be made for problematic ARV drugs. People receiving ART and care takers should also be asked regularly about any other medications they take, including herbal remedies and nutritional supplements.

People receiving ART should understand that while the ARV drugs reduce the risk of HIV transmission, they cannot be relied on to prevent other people from acquiring infection. They should be given advice on safe sex (including condom use) and avoidance of other high-risk activities, such as sharing of injecting equipment, to prevent transmitting HIV to other people.

#### **2.4. What to expect in the first 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 opportunistic infections and/or immune reconstitution inflammatory syndrome (IRIS) may develop, as well as early adverse drug reactions, such as drug hypersensitivity, especially in the first three months of ART. ART significantly decreases mortality overall, but death rates are also highest in the first three months of ART. These complications are commonest when the people starting ART already have advanced HIV disease with severe immuno deficiency and existing co-infections and/ or

co-morbidities, severely low haemoglobin, low body mass index and very low CD4 counts or are severely malnourished.

### 2.4.1. 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 care provider to potential adherence problems or primary non-response to ART, and consideration should be given to continue prophylaxis for opportunistic infections such as co-trimoxazole preventive therapy and Isoniazid preventive therapy. As long as the viral load remains below the level of detection, no need to be concerned even with decreases in CD4 T cells.

#### *Influencing factors*

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

These include:

- Concurrent infections
- Leucopenia of varying etiology especially caused by ARV itself and steroids or other immunosuppressive therapies
- Extreme exertion
- Surgical procedures
- pregnancy can also lead to lower values
- Even diurnal variation occurs; CD4 T cells are lower at noon, & highest in the evening around 8 p.m.
- Psychological stress seems to play a negligible role, even though patients often assume the contrary

Kinetics of CD4 T cells on ART - A biphasic increase in CD4 T cells occurs following the initiation of ART, with a rapid increase in first three to four months and a much slower rise there after. 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 are 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. Age is also important. The larger the thymus and the more active the process of thymopoiesis, the more significant the rise in CD4 T cells is likely to be; due to age-related degeneration of the thymus, CD4 T cells in older patients do not increase as much as in younger ones. However, very poor CD4 T cell count recovery in young and very good recovery in old age is also seen in exceptional cases. The generative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.

It is possible that some antiretroviral therapies such as ddI + tenofovir are associated with less immune reconstitution than others.

### **2.4.2. Viral Load**

Within the first few weeks of therapy the viral load should start decreasing and after 6 months viral load test should be done to evaluate the response to ARVs.

### **2.4.3. Immune reconstitution inflammatory syndrome (IRIS)**

A spectrum of clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery brought about by a response to ART. It is a widely recognized phenomenon that occurs among 10–30% of the people initiating ART, usually within the first 4–8 weeks after initiating therapy.

#### **It may present in three different ways:**

- Persistent antigen (paradoxical IRIS) - worsening of treated opportunistic infection or progression of proliferative disease in patient with cancers; when an opportunistic infection or tumour diagnosed before, initially responds to treatment but then deteriorates after ART starts;
- Viable pathogens (unmasking IRIS) - unmasking of previously subclinical, untreated infections in which initiating ART triggers disease that is not clinically apparent before ART,



eg: MAC, CMV, Viral hepatitis B/C, Herpes simplex (Figure 2.1.), Herpes zoster (Figure 2.2.), Kaposi sarcoma, PML, Cryptococcus, PCP, Sarcoidosis, Toxoplasmosis, Leshmaniasis, Leprosy, pulmonary and extrapulmonary Tuberculosis (Figure 2.3.)

- Non-AIDS-defining illnesses/An autoimmune disease- eg: Graves disease, SLE, Vasculitis, Reiter Syndrome, Relapsing Guillain-Barre syndrome, Rheumatoid arthritis, Polymyositis, Alopecia universalis, Cerebral aneurysms, Hyperergic reaction (against tattoos, foreign bodies)

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

- Active OI
- OI treatment failure
- Side effect from ARV
- HAART treatment failure (resistance)

The clinical spectrum is diverse, and IRIS has been reported for many different infections, tumors 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 opportunistic infections or tumors, a shorter duration of therapy for opportunistic infections before ART starts and increasing CD4 and decreasing viral load very rapidly after ART are the main risk factors.

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.

The most important steps to reduce 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 opportunistic infections before ART, especially TB, Cryptococcus and CMV, and optimal management of opportunistic infections before initiating ART.

Timing of ART in people with opportunistic infections requires balancing a greater risk of IRIS after early initiation against continuing high mortality if ART is delayed.

### **IRIS treatment**

If not severe, symptomatic treatment eg: NSAIDs.

Decrease immune response by:

- Immuno suppressive agents eg: corticosteroids 1-2 mg/kg usually 1 to 2 weeks, sometimes up to 12 wks
- Continuing HAART and OI therapy + steroids
- Treat OI for standard period or longer
- If already stopped OI treatment, reintroduction of OI treatment may help to decrease antigen load

## **2.5. ART for adults and adolescents**

### **2.5.1. When to start ART**

Early treatment initiation is associated with clinical and HIV prevention benefits, improving survival and reducing the incidence of HIV infection at the community level. As per the recommendations provided in the 2013 WHO guidelines, Ministry of Health, National Center for AIDS and STD Control recommends that National HIV programmes provide ART to all people with a confirmed HIV diagnosis with a CD4 count of 500 cells/mm<sup>3</sup> or less. It is also recommended to initiate ART in people with active TB disease and HBV co-infection with severe liver disease, all pregnant and breastfeeding women with HIV, and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count.

It is very important that physician working at ART centres in Nepal must follow recent national guideline. The newly enrolled PLHIV to ART should be started on new recommended regimen. The PLHIV who started ART on different ARV regimens sometime ago and clinically as well as immunologically responding adequately must be continued on the same regimen unless there is indication to change ARV either because of severe adverse effects or treatment failure. ART clinicians must rationally substitute the drugs in 1<sup>st</sup> line regimen and this should be documented all the time in patient card. Substitution of drugs should be done only when there is severe side-effects and change of treatment

regime to 2<sup>nd</sup> line should be done when there is virological failure. It should be understood by ART clinicians that timely and appropriate switching of ARV regimen is important, and but frequent and irrational change of ARV drugs or regimen may lead to treatment failure and or drug resistance.

**Table 2.1. Summary of recommendations on when to start ART in adults, adolescents, pregnant and breastfeeding women**

Population	Recommendation
<b>Adults and adolescents<sup>a</sup></b> (≥ 10 years)	<b>Initiate ART if CD4 cell count ≤500 cells/mm<sup>3</sup></b> <ul style="list-style-type: none"> <li>• <b>As a priority</b>, initiate ART in all individuals with severe/ advanced HIV disease (WHO clinical stage 3 or 4)</li> </ul>
	<b>Initiate ART regardless of WHO clinical stage and CD4 cell count</b> <ul style="list-style-type: none"> <li>• Active TB disease<sup>b</sup></li> <li>• HBV co-infection with severe chronic liver disease<sup>c</sup></li> <li>• Pregnant and breastfeeding women with HIV</li> <li>• HIV-positive individual in a sero-discordant partnership (to reduce HIV transmission risk)</li> </ul>

<sup>a</sup> There is insufficient evidence and/or favourable risk–benefit profile to support initiating ART at a CD4 cellcount >500 cells/mm<sup>3</sup> or regardless of CD4 cell count or WHO clinical stage in the following situations: individuals with HIV older than 50 years, individuals with HIV-1 infected or co-infected with HIV-2, individuals with HIV coinfecting with HCV and key populations with HIV with a high risk of transmission (such as people who inject drugs, men who have sex with men, transgender people and sex workers). ART initiation in these populations should therefore follow the same principles and recommendations as for other adults with HIV.

<sup>b</sup> TB treatment should be initiated first, followed by ART as soon as possible afterwards (and within the first eight weeks of initiating TB treatment). For those with a CD4 count less than 50 cells/mm<sup>3</sup>, ART should be provided within two weeks of starting TB treatment.

<sup>c</sup> There is insufficient evidence and/or favorable risk-benefit profile to support initiating ART in everyone co-infected with HIV and HBV with a CD4 count >500 cells/mm<sup>3</sup> or regardless of CD4 cell count or WHO clinical stage. Initiating ART regardless of CD4 count is therefore recommended among people with evidence of severe chronic liver disease, who are at greatest risk of progression and mortality from liver disease. For people without evidence of severe chronic liver disease, ART initiation should follow the same principles and recommendations as for other adults. Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and de-compensated stages. De-compensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

### 2.5.2. What ART regimen to start with (first-line ART)

Using simplified, less toxic and more convenient regimens as fixed-dose combinations is recommended for first-line ART. Once-daily regimens comprising a non-thymidine NRTI backbone (TDF + 3TC) and one NNRTI (EFV) are maintained as the preferred choices in adults, adolescents and children older than three years. For children younger than three years, a PI-based regimen is the preferred approach.

**Table 2.2. Summary of first-line ART regimens for adults and adolescents**

First-line ART	Preferred first-line Regimens	Alternative first-line Regimens <sup>ab</sup>
<b>Adults (including pregnant and breastfeeding women and adults with TB and HBV co-infection)</b>	TDF + 3TC + EFV	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP Special circumstances <sup>c</sup> Regimens containing ABC, and boosted PIs
<b>Adolescents (10 to 19 years) ≥35 kg</b>		AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP ABC + 3TC + EFV (or NVP) Special circumstances ABC + 3TC + EFV ABC + 3TC + NVP
<b>Adolescents &lt;35 kg</b>	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + EFV TDF + 3TC + NVP

<sup>a</sup> For adolescents, using d4T as an option in first-line treatment should be discontinued and restricted to special cases in which other ARV drugs cannot be used and to the shortest time possible, with close monitoring. For children, d4T use should be restricted to the situations in which there is suspected or confirmed toxicity to AZT and lack of access to ABC or TDF. The duration of therapy with this drug should be limited to the shortest time possible. Adolescents who are already taking ABC- containing regimens can safely substitute TDF for ABC, if this is needed for programmatic reasons. Despite a lack of direct evidence, consideration can also be given to substituting ABC or TDF for AZT with the goal of simplifying and harmonizing treatment regimens across age groups.

<sup>b</sup> ABC or boosted PIs (ATV/r, DRV/r, LPV/r) can be used in special circumstances.

<sup>c</sup> 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 for other reasons.

The guidelines emphasized the importance of avoiding d4T as a preferred option in first-line regimens because of its well-known mitochondrial toxicity using regimens that are potentially less toxic and more suitable for most people, preferably as fixed-dose combinations given the clinical, operational and programmatic benefits. These recommended regimens had better toxicity profiles than d4T but were considered comparable in terms of efficacy, since there was no evidence that AZT is virologically superior to d4T, AZT superior to TDF, TDF superior to d4T or ABC, or EFV superior to NVP.

### **New recommendations**

- First-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI)
  - TDF + 3TC + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART .
  - If TDF + 3TC + EFV is contraindicated or not available, one of the following options is recommended:
    - AZT + 3TC + EFV
    - AZT + 3TC + NVP
    - TDF + 3TC + NVP
- Nepal has taken necessary action to phase out use of d4T as a drug in first-line regimen because of its well-recognized metabolic toxicities.

### **2.5.3. First-line ART for Adolescents**

For adolescents infected with HIV, EFV is the preferred NNRTI for first-line treatment and NVP is the alternative. In determining the choice of NNRTI for first-line therapy, consider the dosing characteristics of EFV (once-daily) and NVP (twice-daily) and how this is suitable with the NRTI backbone. For example, if the recommended regimen is a twice-daily option using a fixed-dose combination of NRTI then NVP may be a better choice. For adolescents with HBV, the preferred backbone was TDF + 3TC.

In HIV infected adolescents weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:

- TDF + 3TC
- AZT + 3TC
- ABC + 3TC

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

TDF has got the advantages of once-daily dosing. TDF-containing fixed-dose combinations are currently only available in adult, un-scored tablets for once-daily use. At or above 35 kg, the dose of TDF in adult dual and triple fixed-dose combinations and the dose of EFV in adult triple fixed-dose combinations are acceptable for use in adolescents. ABC or boosted PIs can be used in special circumstances. ABC can be used once daily is available as a fixed-dose combination with 3TC for different age groups and harmonizes with TDF from a resistance perspective.

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

## 2.6. General care for people living with HIV

Apart from treatment with ARV drugs and proper treatment of different opportunistic infections, co-morbidities and some malignancies, People living with HIV require different kinds of care without which good quality of life for long period may not be possible. For that purpose following care should be provided adequately.

### 2.6.1. Nutritional care and support

Low energy intake combined with increased energy demands because of HIV infection 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 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 (body mass index 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), counseling and support should be an integral component of HIV care and 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 appropriate food 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.

### **2.6.2. Palliative care: symptom management and end-of-life care**

Through out all stages of HIV disease, and when receiving treatment, people living with HIV may experience various forms of pain and other discomfort. Care providers should identify and treat the under lying cause when possible, while controlling the pain. Further, effectively managing the side effects of ART is important to support adherence.

## Figures



*Figure 2.1. Verrucous Herpes Simplex Ulcer*



*Figure 2.2. Severe Herpes Zoster with secondary infection*



*Figure 2.3. Tubercular IRIS*



## 03

## ARV DRUGS FOR HIV TREATMENT FOR INFANTS AND CHILDREN

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### 3.1. Introduction:

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

Staging of severity of Pediatric HIV disease classifies the disease using WHO clinical criteria into four stages- asymptomatic, mild, moderate, and severe disease. Degree of immuno suppression is also classified into three stages according to severity of CD4 counts vary with age during the first 5 years of life, the cut-offs for this immunologic indicator differs from those cut-offs used for adults.

Antiretroviral drugs should be used properly so as to avoid development of drug resistance and restore or maintain the immune status. It is recommended to start potent first-line antiretroviral regimens and convenience once-daily dosing and the use of fixed -dose combinations should be chosen whenever possible.

Adherence to treatment is dependent on the commitment of the caregiver. Children have special counseling needs; older children, especially adolescents, need to understand their diagnosis if they are to adhere to antiretroviral therapy. Disclosure of HIV status to a child needs to be handled with care and 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 up to five years and to increase the CD4 count threshold for ART initiation to  $\leq 500$  cells/mm<sup>3</sup> in children 5 years and older, aligning with the new threshold in adults.

### 3.2. Diagnosis of HIV infection

The laboratory diagnosis of infants and children is presented in Chapter 8 – Laboratory diagnosis. For infants and children aged less than 18 months where access to laboratory testing 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
  - <sup>a</sup>Diagnosis of AIDS-indicator condition(s) can be made or

<sup>a</sup>*AIDS indicator conditions include some but not all HIV pediatric clinical stage 4 such as Pneumocystis pneumonia, cryptococcal meningitis, severe wasting or severe malnutrition, Kaposi sarcoma, extrapulmonary tuberculosis.*

- the infant is symptomatic with two or more of the following:
  - <sup>b</sup>Oral thrush
  - 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 immuno suppressive 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 opportunistic infections. 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 pediatric and adult HIV infection:

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

<sup>b</sup>As per IMCI definition:

- Creamy white to yellow soft small plaques on red or normally colored 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 indrawing, stridor or any of the IMCI general danger signs; i.e., lethargic or unconscious, not able to drink or breastfeed, vomiting, and presence or history of convulsions during current illness; responding to 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 manifestations

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 three categories:

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

- Manifestations of HIV-infection may occur within the first few months of life.
- Opportunistic infection and neurological manifestations are usual clinical features.
- Undergo a rapid downhill progression; untreated die within 1 year.
- Are thought to have acquired the infection in-utero or in the early perinatal period.

Category II: Majority of pediatric infections (about 50-60% of cases)

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

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

- Long term survivors.
- These children reveal minor manifestations later in their 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 opportunistic infections (OIs) occurs 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 OI's are mentioned below.

### 3.3.2.1. Failure to thrive (Figure 3.1.)

- 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, diarrhea, malabsorption, chronic diseases of the heart, kidney and lungs, micronutrient deficiencies, neuroendocrine abnormalities and repeated episodes of infection.

### 3.3.2.2. Lymphadenopathy(Figure 3.2.)

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

### 3.3.2.3. Respiratory Manifestations

- Pneumonia and chronic lung diseases contribute to the increased morbidity and mortality.
- Most children present with recurrent bacterial pneumonias, but in children less than 1 year of age PCP (PJP) 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, dyspnea (Figure 3.3), wheezing, ear discharge.
- Recurrent infections: recurrent bacterial pneumonia- *Streptococcus pneumoniae* is the most common organism.
- Recurrent otitis media and sinusitis are common as well.
- Viral causes are common.
- Chronic HIV associated lung diseases include Tuberculosis, Lymphoid Interstitial Pneumonitis and bronchiectasis.
  - o *Pneumocystis jiroveci* pneumonia (PCP) causes acute life threatening pneumonitis. PCP is the most common OI

associated with HIV in children. It predominantly occurs between 3-6 months of age. Can occur in infants less than 12 months of age despite good CD4 counts. PCP is characterized by rapidly progressive hypoxemia.

#### 3.3.2.4. Gastrointestinal and Hepatobiliary

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

Causes: Common infections, opportunistic infections (bacteria, virus, protozoa, fungi), malabsorption, inflammatory processes, HIV enteropathy. Persistent diarrhea occurs with increased frequency in children with failure to thrive, significant immune suppression, and infants of mothers with symptomatic HIV.

- Hepatomegaly: Hepatomegaly within 3 months of age in perinatally acquired infection is associated with rapid progression of disease – Figure 3.6

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

#### 3.3.2.5. Parotitis

- Recurrent or chronic painless unilateral or bilateral parotid swelling. Parotitis is associated with a more favorable outcome. Causes: HIV infiltration, lymphocytic infiltration. (Figure 3.7)

#### 3.3.2.6. Oral manifestations

- Thrush (Candidiasis) (Figure 3.8)
- 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, Molluscumcontagiosum, Warts; fungal- Candida, Tinea, Onychomycosis). (Figure 3.9 - 3.13)  
Non-infectious (Seborrheic dermatitis, Atopic dermatitis, Generalized dermatitis, Nutritional deficiency, Eczema, Psoriasis, Drug eruptions, Vasculitis, Alopecia)

### 3.3.2.8. Hematological Manifestations

- Anemia: Nutritional, bone marrow suppression by HIV virus or other opportunistic infection and drug side effect (i.e. most commonly ZDV) are the most common causes. (Figure 3.14 - 3.16)
- Thrombocytopenia: Most commonly from bone marrow suppression by HIV itself.
- Neutropenia, common side effect of ZDV (bone marrow suppression).
- Lymphopenia with CD4, 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 (esp. gross and fine motor and language skills)

Causes: CNS infiltration by HIV itself, bacterial infections such as pyogenic meningitis, opportunistic infections 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 (i.e. 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.
- Most common presentation - Nephrotic syndrome; others: hematuria, hypertension, renal tubular acidosis, acute renal failure, end stage renal disease.
- Various underlying renal pathology e.g. minimal lesion glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy.  
Causes: Immune-mediated, direct viral infection, drug-induced.

### 3.3.2.12. Malignancy

- Less frequent and different from than those in adult AIDS.
- Most common: Non Hodgkin's lymphoma, CNS lymphoma, leiomyoma, EBV associated leiomyosarcoma and leukemia. Kaposi sarcoma 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 (e.g. indwelling catheters, antibiotics and cytotoxic agents).
- Clinical manifestation depends upon the site of infection. Pneumonias are the commonest infections. Others 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 antiretroviral therapy

Prior to initiating on ART, it is important that the clients and their care givers be prepared adequately.

#### 3.4.1. Medical Preparation

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

- Full blood count
- Liver functions tests (do alanine transaminase )
- Renal function tests (do serum creatinine)
- CD4 % and count
- Chest X-ray
- Mantoux test

ALL children enrolled into care or those being assessed for ART should be screened for TB. This should be taken into account history of TB in the child's immediate family. Since HIV infected individuals remain at high risk of developing TB disease regardless of treatment status a high level of vigilance of TB is required for patients in care. If TB is confirmed and dual treatment of TB/HIV required.

- Treat any inter-current illnesses.
- Initiate Cotrimoxazole Prophylaxis in all children.

#### 3.4.2. Counseling

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 clinical regularly as required and as well as for inter-current conditions.

- When and how to administer the drugs
- Possible adverse effects of the ARV drugs intended for use, how to recognize them and what to do should they arise
- Care takers should be encouraged to bring a child on treatment back to clinic if they have concerns or the child becomes ill.

### 3.5. Anti-Retroviral Therapy for Infants and Children

The advent of potent antiretroviral therapy has dramatically reduced rates of mortality and morbidity and has improved the quality of life of infants and children living with HIV although it does not provide a 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 below 5 years of age regardless of WHO clinical staging or CD4 count.
- ART should be initiated in all HIV-infected children 5 years of age and older with CD 4 count  $\leq 500$  cells/mm<sup>3</sup>, regardless of WHO stage.
- ART should be started in all children with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD 4 count.
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive diagnosis of HIV infection.

#### 3.5.2. ART Regimen

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

- WHO 2013 consolidated guidelines has recommended LPV/r-based regimen to be used as first-line ART for all children infected with HIV younger than three years (36 months) of age, regardless of NNRTI exposure. If LPV/r is not feasible, treatment should be initiated with a NVP-based regimen. For children less than 10 kg of weight LPV/r liquid formulation is available. Liquid LPV/r requires a cold chain during transport and storage. Currently heat-stable formula of LPV/r pellets is available and under consideration for approval. By 2015 countries may have access to it. Therefore considering the Nepal's conditions especially due to difficulties encountered in storage of liquid LPV/r in most of

the settings NVP-based regimen is recommended as the 1st line regimen. When LPV/r heat-stable formula of pellets are available for the programme LPV/r based regimen can be used as first-line ART.

- Viral load monitoring of these patients is very important. When the 1<sup>st</sup> line given was NVP based regimen substitution of it with LPV/r should be done if virological suppression is not sustained. When the 1<sup>st</sup> line given was LPV/r based regimen substituting LPV/r with an NNRTI can be done after virological 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.
- For infants and children infected with HIV younger than three years, the NRTI backbone for an ART regimen should be ABC or AZT + 3TC.
- d4T will be phased out and in case of severe anemia while starting, ABC should be started. Children on d4T should be switch to appropriate NRTIs.

**Table 3.1. First-line ART regimens for children younger than three years**

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

Young children with HIV who are exposed to NNRTIs used for PMTCT have demonstrated viral resistance which comprises the response to NVP-containing first line ART. New evidence has become available for this age group suggesting the superiority of a LPV/r based regimen regardless of PMTCT exposure.

### 3.5.2.2. First-line ART for children three years and older (including adolescents)

- For children infected with HIV three years and older (including adolescents), EFV is the preferred NNRTI for first-line treatment and NVP is the alternative.
- For children infected with HIV three years to less than 10 years old (or adolescents less than 35 kg), the NRTI backbone for an ART regimen should be one of the following, in preferential order:
  - ABC + 3TC
  - AZT or TDF + 3TC
- For adolescents infected with HIV (10 to 19 years old) weighing 35 kg or more, the NRTI backbone for an ART regimen should align with that of adults and be one of the following, in preferential order:
  - TDF + 3TC
  - AZT + 3TC
  - ABC + 3TC

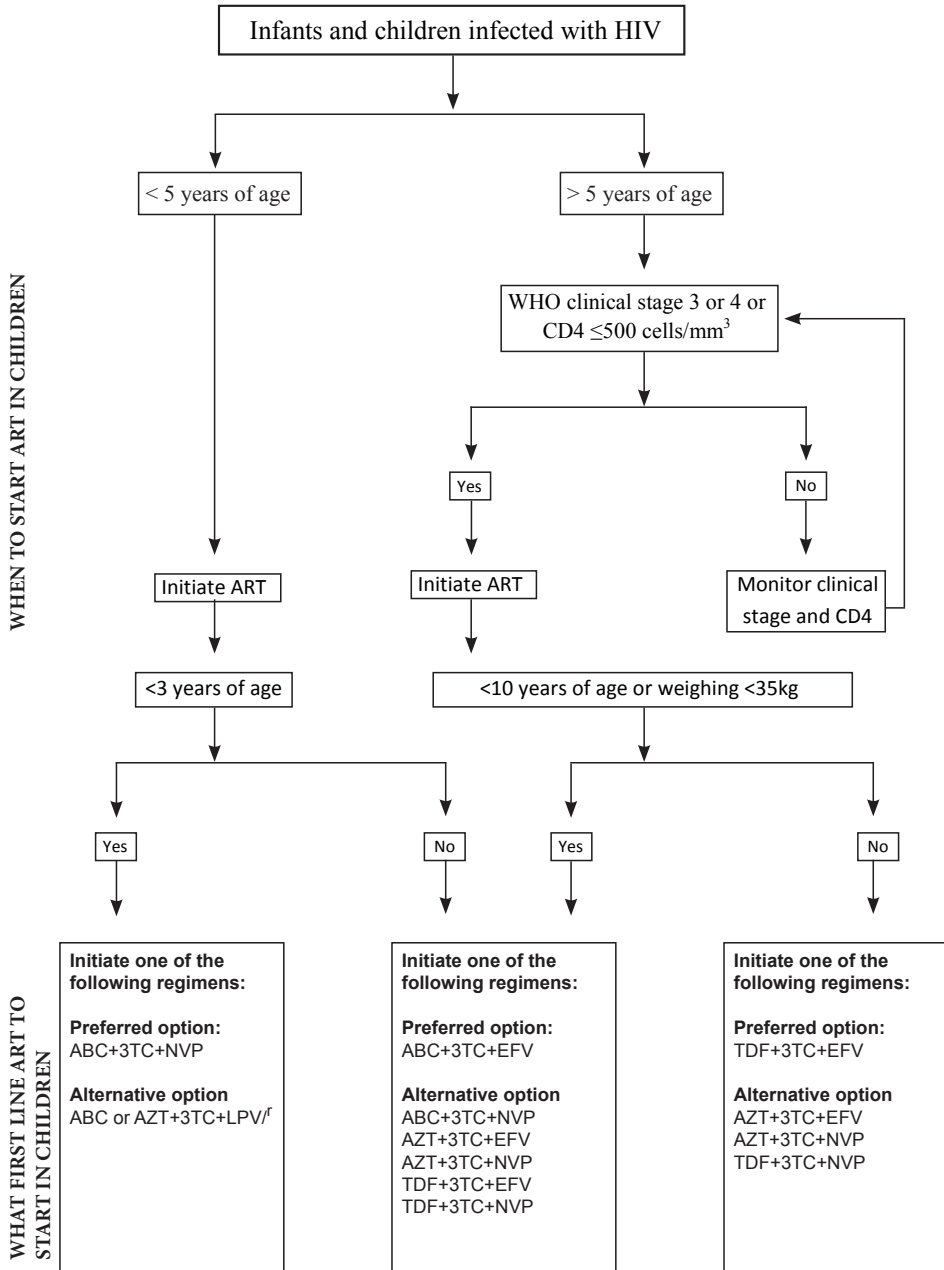
Children have to be weighed regularly at clinic visits, and dose changes are required as children grow and/ or gain weight.

**Table 3.2. Summary of recommended first-line ART regimens for children and adolescents**

	Children 3 years to less than 10 years and adolescents <35 kg	Adolescents (10 to 19 years) ≥35 kg
Preferred	ABC <sup>1</sup> + 3TC + EFV	TDF + 3TC + EFV <sup>1</sup>
Alternatives	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + EFV TDF + 3TC + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC + NVP

<sup>1</sup>These recommendations apply to children and adolescents who are initiating first-line ART.

## Algorithm for recommendations for children



### 3.6. Monitoring response to ART and 2nd line ART for children

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure.
- If viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.

**Table 3.3.WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens**

Failure	Definition
Clinical failure	New or recurrent clinical event indicating advanced or severe immuno deficiency (WHO clinical stage 3 and 4 clinical condition with exception of TB) after 6 months of effective treatment
Immunological Failure	Younger than 5 years: Persistent CD4 levels below 200 cells/mm <sup>3</sup> or <10% Older than 5 years: Persistent CD4 levels below 100 cells/mm <sup>3</sup>
Virological Failure	Plasma viral load above 1000 copies/ml based on two consecutive viral load measurements after 3 months, with adherence support

#### 3.6.1. Second-line ART for children, including adolescents

- After failure of a first-line NNRTI-based regimen, a boosted PI plus two NRTIs are recommended for second-line ART; LPV/r is the preferred boosted PI.
- After failure of a first-line LPV/r-based regimen, children younger than 3 years should remain on their first-line regimen, and measures to improve adherence should be under taken.
- After failure of a first-line LPV/r-based regimen, children 3 years or older should switch to a second-line regimen containing an NNRTI plus two NRTIs; EFV is the preferred NNRTI.
- After failure of a first-line regimen of ABC or TDF + 3TC, the preferred NRTI backbone option for second-line ART is AZT + 3TC.
- After failure of a first-line regimen containing AZT or d4T + 3TC, the preferred NRTI backbone option for second-line ART is ABC or TDF + 3TC.

**Table 3.4. Recommended first and second-line ART regimens for children including adolescents**

	Children	First-line ART regimen	Second-line ART regimen
LPV/r-based first-line regimen	Younger than 3 years	ABC + 3TC + LPV/r	No change
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV
		AZT + 3TC + LPV/r	ABC or TDF <sup>a</sup> + 3TC + EFV
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + LPV/r
		TDF <sup>a</sup> + 3TC + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF <sup>a</sup> + 3TC + LPV/r

<sup>a</sup> TDF can only be given to children > 2 years.

### 3.7. Vaccination for children living with HIV

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 is recommended at 6 months of age.

### 3.8. Cotrimoxazole Preventive therapy (CPT)

Cotrimoxazole prophylaxis reduces morbidity, hospital admissions and death in children infected with HIV. Cotrimoxazole should be administered routinely to all HIV exposed children from the age of 6 weeks until HIV status is determined and depending on WHO clinical staging and immunosuppression.

### 3.9. Isoniazid Preventive therapy (IPT)

- 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 should receive six months of IPT (10 mg/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.
- All children living with HIV, after successful completion of treatment for TB disease, should receive isoniazid for an additional six months.

### 3.10. Nutritional Care and Support of HIV-Infected Children

HIV infection can impair the nutritional status of infected children from early in life. Growth faltering and reduction in length and height often occurs even before opportunistic infections or other symptoms in almost all infected children. Early nutritional advice and active support is 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 infections is necessary to optimize health outcomes. Antiretroviral treatment (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;*

*(This 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 needs appropriate energy intake according to his/ her 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, varied diet.



*Children with conditions with increased energy needs e.g. chronic lung disease or chronic infections e.g. TB or persistent diarrhea. 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.

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*Children with severe malnutrition i.e. signs of visible wasting, bilateral edema 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 opportunistic infections such as thrush, TB or cryptosporidiosis should also be excluded and treated.

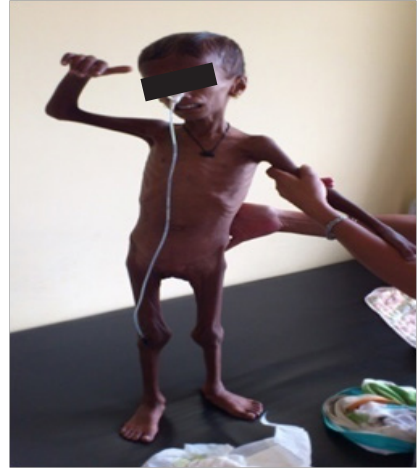


Figure 3.1 - Children with severe malnutrition



Figure 3.2 Cervical lymphadenopathy

Figure 3.3 Child with pneumonia with distress



Figure 3.4 Chest X-ray showing consolidation of right upper and mid-zone



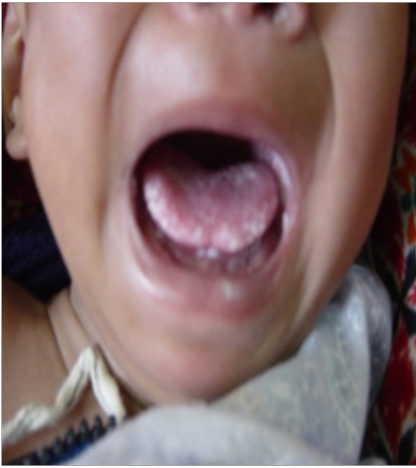
Figure 3.5 Chest X-ray showing right and left bronchiectatic changes lower zones



*Figure 3.6 hepatosplenomegaly*



*Figure 3.7 Parotid gland swelling*



*Figure 3.8 Oral Candidiasis*



*Figure 3.9 Pyoderma*



*Figure 3.10 Tinea corporis*



*Figure 3.11 Moluscum contagiosum*



*Figure 3.12 Herpes Zoster*



*Figure 3.13 Varicella zoster*



*Figure 3.14 Severe anemia in tongue*



*Figure 3.15 Severe anemia in palm*



*Figure 3.16 Ecchymotic*

## 04

## MONITORING RESPONSE TO ART, DIAGNOSIS OF TREATMENT FAILURE, SWITCHING TO 2<sup>nd</sup> AND 3<sup>rd</sup> LINE DRUGS AND MONITORING HIV DRUG RESISTANCE.

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## 4.1. Introduction

Regular monitoring of HIV positive people who started ARV is very important to know the adherence status of ARV intake and to see the success of ARV treatment. Monitoring of ARV is also very important for timely and early recognition of drug toxicities and treatment failure, drug resistance so that necessary action to switch to 2<sup>nd</sup> or 3<sup>rd</sup> line drug can be taken 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 to monitor correctly.

## 4.2. Monitoring and substitutions for ARV drug toxicities

### 4.2.1 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 the 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 people at higher risk. Table 4.1 lists key types of toxicity and associated risk factors for the major ARV drugs.

**Table 4.1 Types of toxicities associated with first-, second-,third-line ARV drugs**

ARV Drug	Major type of toxicity	Risk factor	Suggested management
ABC	Hypersensitivity reaction	Presence of HLA-B*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT or d4T. If ABC is being used in secondline ART, substitute with TDF or AZT which ever has not been used in first line.

ARV Drug	Major type of toxicity	Risk factor	Suggested management
ATV/r	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing conduction disease Concomitant use of other drugs that may prolong the PR interval	
	Indirect hyperbilirubinaemia (clinical jaundice) Nephrolithiasis and risk of prematurity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drugs Risk factors unknown	LPV/r or DRV/r. If boosted PIs are contraindicated & NNRTIs have failed in first-line ART, consider integrase inhibitors
AZT	Anaemia (Figure 4.1), neutropaenia, myopathy, lipoatrophy or lipodystrophy	Baseline anaemia or neutropaenia CD4 count $\leq 200$ cells/mm <sup>3</sup>	If AZT is being used in first-line ART, substitute with TDF or ABC
	Lactic acidosis or severe hepatomegaly with steatosis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	If AZT is being used in second-line ART, substitute with d4T
d4T	Peripheral neuropathy, lipoatrophy or lipodystrophy (Figure 4.2.)	Older age CD4 count $\leq 200$ cells/mm <sup>3</sup> Concomitant use of isoniazid or ddI	If d4T is being used in first-line ART, substitute with TDF or AZT or ABC If d4T is being used in second-line ART (after TDF or ABC are used in first-line ART), substitute with AZT
	Lactic acidosis or severe hepatomegaly with steatosis, acute pancreatitis	BMI >25 (or body weight >75 kg) Prolonged exposure to nucleoside analogues	

ARV Drug	Major type of toxicity	Risk factor	Suggested management
EFV	Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	NVP. If the person cannot tolerate either NNRTI, use boosted PIs
	Hepatotoxicity	Underlying hepatic disease HBV and HCV coinfection Concomitant use of hepatotoxic drug	If LPV/r is used in first-line ART for children, use an age- appropriate NNRTI (NVP for children younger than 3 years and EFV for children 3 years and older). ATV can be used for children older than 6 years
	Convulsions	History of seizure	
	Hypersensitivity reaction, Stevens-Johnson syndrome Potential risk of neural tube birth defects (very low risk in humans) Male gynaecomastia (Figure 4.3.) Electrocardiographic abnormalities (PR and QT interval prolongation, torsades de pointes)	Risk factors unknown People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR interval	



ARV Drug	Major type of toxicity	Risk factor	Suggested management
LPV/r	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 second-line ART for adults, use ATV/r or DRV/r. If boosted PIs are contraindicated and the person has failed on treatment with NNRTI in first-line ART, consider integrase inhibitors
	Pancreatitis	Advanced HIV disease	
	Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidaemia or severe diarrhoea Hepatotoxicity	Risk factors unknown	
NVP	Severe skin rash and hypersensitivity reaction (Stevens-Johnson syndrome ) (Figure 4.4.)	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 First month of therapy (if lead-in dose is not used) Risk factors unknown	

ARV Drug	Major type of toxicity	Risk factor	Suggested management
RAL	Rhabdomyolysis, myopathy, myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis	Limited options are available
	Tubular renal dysfunction, Fanconi syndrome	Underlying renal disease, Older age BMI <18.5 (or body weight <50 kg)	If TDF is being used in first-line ART, substitute with AZT or d4T or ABC
TDF		Untreated diabetes mellitus Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	If TDF is being used in second-line ART (after d4T + AZT use in firstline ART), substitute with ABC or ddI
	Decreases in bone mineral density	History of osteomalacia and pathological fracture Risk factors for osteoporosis or bone loss	
	Lactic acidosis or severe hepatomegaly with steatosis		
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity	
	Exacerbation of hepatitis B (hepatic flares)	Discontinuation of TDF due to toxicity	Use alternative drug for hepatitis B treatment (such as entecavir )

### 4.2.2. Monitoring TDF toxicity

TDF nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney disease.

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. However, in high-risk people (older or have underlying renal disease, long-term diabetes or uncontrolled hypertension concomitant with boosted PIs or nephrotoxic drugs) it is advised to detect and limit further progression of renal impairment.

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

#### Clinical considerations

- Laboratory monitoring is not compulsory to start treatment with TDF.
- Routine blood pressure monitoring 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

### 4.2.3. Toxicity monitoring for other ARV drugs

#### AZT

AZT is associated with a risk of haematological toxicity, and measuring haemoglobin mainly among adults and children with low body weight, low CD4 counts and advanced HIV disease is recommended before initiating ART. AZT should be avoided as first-line therapy in people with HIV with severe anaemia (haemoglobin  $<7.0$  g/dl) at base line.

#### NVP

Although measurement of liver enzymes has very low predictive value for NVP-containing regimens, monitoring hepatic enzymes is recommended if feasible, especially for women with HIV who have CD4 cell counts  $>250$  cells/mm<sup>3</sup> and individuals with HIV who are

co-infected 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.

#### **4.2.4. Drug substitutions for ARV drug toxicity**

Drug regimen or single agent substitutions may be required for drug toxicity and to avoid drug interactions. See section 4.2.5

#### **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.

#### **4.2.5 Key ARV drug interactions**

It is very important to be aware of all the drugs that the patient with HIV is taking when initiating ART and also when adding new drugs in patients taking ART. There are several key drug interactions.

A key consideration for managing coinfection with TB and HIV is contraindication of drug combination that includes rifampicin and PIs. When people coinfecting with TB and HIV are receiving a boosted PI, rifampicin may need to be substituted with rifabutin. If rifabutin is not available, LPV/r and SQV/r can be used for the duration of TB treatment. In case if it is not possible to avoid Protease inhibitor another option is to use non rifampicin based ATT and better to consult TB expert eg- streptomycin + ETH + INH + Ofloxacin initial phase followed by INH + ETH for 8 months.

AZT has been associated with an increased risk of anaemia and hepatic de-compensation with Ribavirin and peg interferon alpha-2a used for treating HCV. AZT in people co-infected with HCV and HIV 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 could 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. Similar result is expected with Buprenorphine also.

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 recommended.

Concomitant use of boosted PIs and NNRTI with antihistamine (eg: astemizole and terfenadine) are associated 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 & 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 people with HIV.

**Table 4.2. Key ARV drug interactions and suggested management**

ARV DRUG	Key interactions	Suggested management
AZT	Ribavirin and peg- interferon alfa-2a	First-line: substitute AZT with TDF Second-line: substitute AZT with d4T
Boosted PI(ATV/r, LPV/r)	Rifampicin	Substitute rifampicin with rifabutin Adjust the PI dose or substitute with three NRTIs (for children)
	Lovastatin and simvastatin	Use an alternative dyslipidaemia agent (for example pravastatin)\
	Estrogen-based hormonal contraception	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
EFV	Amodiaquine	Use an alternative antimalarial agent
	Methadone	Adjust the methadone dose as appropriate
	Estrogen-based hormonal contraception	Use alternative or additional contraceptive Methods
	Astemizole and terfenadine	Use an alternative anti-histamine agent
	Rifampicin	Substitute NVP with EFV
	Itraconazole and ketoconazole	Use an alternative antifungal agent (for example fluconazole)

### 4.3. Laboratory monitoring before and after initiating 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.

**Table 4.3. Laboratory monitoring**

First Year	Subsequent Years
<b>2<sup>nd</sup> week</b> - CBC and Liver Function tests (ALT if on NVP)	<b>Quarterly</b> - CBC
<b>Month 1, 2, &amp; 3</b> – CBC, LFT if on NVP, Other necessary investigation if and as required	<b>Every 6 months</b> - CD4 Cell count, LFT If on Tenofovir, creatinine and urinalysis for proteinuria. Other tests as needed
<b>Month 6</b> - CBC, platelets, LFTs, CD4 Cell Count, Viral load Test, If on Tenofovir, creatinine and urinalysis for proteinuria	<b>Month 18</b> – viral load test and repeat 12 monthly
<b>Month 12</b> – CBC, LFT, CD4 Cell count Other tests as needed	<b>Annually</b> - Fasting lipids and blood glucose for those on protease inhibitors

**Table 4.4. Recommended and desirable laboratory tests at HIV diagnosis and monitoring on ART**

Phase of HIV Management	Recommended	Desirable (if feasible)
HIV diagnosis	HIV serology, CD4 cell count TB screening	HBV (HBsAg) serology <sup>a</sup> HCV serology Cryptococcus antigen if CD4 count <100 cells/mm <sup>3</sup> <sup>b</sup> Screening for sexually transmitted infections. Assessment for major non-communicable chronic diseases and co-morbidities <sup>c</sup>
Follow-up before ART	CD4 cell count (every 6–12 months)	
ART initiation	CD4 cell count	Haemoglobin test for AZT <sup>d</sup> Pregnancy test Blood pressure measurement Urine dipsticks for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF <sup>e</sup> Alanine aminotransferase for NVP <sup>f</sup>

Phase of HIV Management	Recommended	Desirable (if feasible)
Receiving ART	CD4 cell count (every 6 months) HIV viral load (at 6 months after initiating ART and every 12 months thereafter)	Urine dipstick for glycosuria and serum creatinine for TDF <sup>c</sup>
Treatment failure	CD4 cell count HIV viral load	HBV (HBsAg) serology <sup>a</sup> (before switching ART regimen if this testing was not done or if the result was negative at baseline).

<sup>a</sup> If feasible, HBsAg testing should be performed to identify people with HIV and HBV coinfection and who therefore should initiate TDF-containing ART.

<sup>b</sup> Can be considered only in settings with a high prevalence of cryptococcal antigenaemia (>3%).

<sup>c</sup> Consider assessing the presence of chronic conditions that can influence ART management such as hypertension and other cardiovascular diseases, diabetes and TB.

<sup>d</sup> Among children and adults with a high risk of adverse events associated with AZT (low CD4 or low BMI).

<sup>e</sup> Among people with a high risk of adverse events associated with TDF: underlying renal disease, older age group, low BMI, diabetes, hypertension and concomitant use of a boosted PI or potential nephrotoxic drugs.

<sup>f</sup> Among people with a high risk of adverse events associated with NVP, such as being ART-naïve, women with HIV with a CD4 count >250 cells/mm<sup>3</sup> and HCV co-infection. However, liver enzymes have low predictive value for monitoring NVP toxicity.

#### 4.4. Diagnosis of treatment failure

##### New recommendations

- **Viral load testing is a more sensitive and early indicator of treatment failure and is the gold standard for monitoring the response to ARV drugs. Viral load is strongly recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure**
- **Where viral load is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.**

*Special notes: Treatment failure is defined by a persistently detectable viral load exceeding 1000 copies/ml (that is, two consecutive viral load measurements within a three-month interval, with adherence support between measurements) after at least six months of using ARV drugs.*

#### 4.5. What ART regimen to switch to (second-line ART )

When the antiretrovirals fail to slow down the replication of the virus in the body a change of treatment is needed. Increased viral load or HIV-related illnesses or decrease in CD4 count are signs of treatment failure. Failure can occur as a result of drug resistance, poor adherence, poor drug absorption or a weak combination of drugs.

Where viral load testing is available, drugs may be changed as soon as the viral load rises but this could mean running out of treatment options more quickly or recommend monitoring the trend of the viral load before making a decision to change however, this approach may increase the risk of developing resistance to certain drugs, which can limit future treatment options. Where viral load testing is not available, the WHO staging system for HIV disease that determines the stage of HIV infection based on clinical symptoms and CD4 count may be used instead.

Using a boosted PI + two NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART

#### 4.5.1. Second- line ART for Adults and adolescents

##### New recommendations

- **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 second-line regimens.**
- **After failure on an AZT + 3TC–based first-line regimen, use TDF + 3TC as the NRTI backbone in second-line regimens.**
- **Use of NRTI backbones as a fixed-dose combination is recommended as the preferred approach**
- **Heat-stable fixed-dose combinations of ATV/r and LPV/r are the preferred boosted PI options for second-line ART**

**Table 4.5 Summary of preferred second – line ART regimens for adults and adolescents**

<b>Target Population</b>		<b>Preferred second-line regimen<sup>a</sup></b>
<b>Adults and adolescents (≥10 years)</b>	If AZT was used in first-line ART	TDF + 3TC + ATV/r or LPV/r
	If TDF was used in first-line ART	AZT + 3TC + ATV/r or LPV/r
<b>Pregnant women</b>	Same regimens recommended for adults and adolescents	



Target Population		Preferred second-line regimen <sup>a</sup>
HIV and TB Co-infection	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) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400 mg/400 mg twice daily) In a special situation if Protease inhibitor cannot be avoided and rifabutin is not available use of non refampicin based ATT can be considered.
HIV and HBV Co-infection	AZT + TDF + 3TC + (ATV/r or LPV/r)	

<sup>a</sup>ABC and ddI can be used as NRTI backup options but add complexity and cost without clinical advantages. DRV/r can be used as an alternative PI and SQV/r in special situations, but neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is in development.

#### 4.6. Third-line ART

##### New recommendations

- National programmes should develop policies for third-line ART
- 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.

Resource poor countries have financial constraints that limit the adoption of third line regimens.

##### Clinical considerations

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

monitoring improves and first-line ART continues to be scaled up. The costs of potential third-line drugs, such as DRV, ETV and RAL, are not well established in resource-limited settings but are expected to be higher than those of first- and second-line regimens.

## 4.7. Monitoring HIVDR

### 4.7.1. Monitoring early warning indicators for HIV drug resistance

Use of Early Warning Indicators (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 people living with HIV. EWIs evaluate factors associated with HIVDR prevention without requiring laboratory testing for drug resistance. It is recommended that all clinics providing ART monitor EWI annually.

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

The EWIs recommended by WHO given below, are those that can be integrated most easily into national programme and have the strongest links to the development of HIVDR. The targets are recommended for each indicator that facilities should reach to prevent emergence of drug resistance in ART patients.

**Table 4.6. - Recommended EWIs and the Targets**

Early Warning Indicator and definition	Target
<b>1. On-time pill pick-up - % of patients (adult or paediatric) that pick-up ART no more than two days late at the first pick-up after the baseline pick-up.</b>	Red : <80% (poor performance, below the desired level) Amber : 80 – 90% (fair performance, not yet at desired level) Green : >90% (excellent performance; desired level)

Early Warning Indicator and definition	Target
<b>2. Retention in care - % of adults and children known to be alive and on treatment 12 months after initiation of ART.</b>	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
<b>3. Pharmacy stock-outs - % of months in a designated year in which there were no ARV drug stock-outs.</b>	Red : <100% of a 12-month period with no stock-outs Green : 100% of a 12-month period with no stock-outs
<b>4. Dispensing practices - % of adults and children prescribed or picking up mono or dual ARV therapy.</b>	Red : >0% dispensing of mono- or dual therapy Green : 0% dispensing of mono- or dual therapy
<b>5. Viral load suppression at 12 months - % of patients receiving ART at the site after the first 12 months of ART whose viral load is &lt;1000 copies/ml.</b>	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

Other than monitoring EWIs, WHO also recommends the countries to conduct surveys to monitor acquired, pre-treatment, transmitted HIV drug resistance and surveillance of HIVDR among infants under 18 months of age. Nepal has already initiated monitoring EWIs.

#### 4.7.2. 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 the 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 the programme and clinic level to minimize HIV drug resistance. They also provide evidence to optimize the selection of first- and second-line ART regimens.

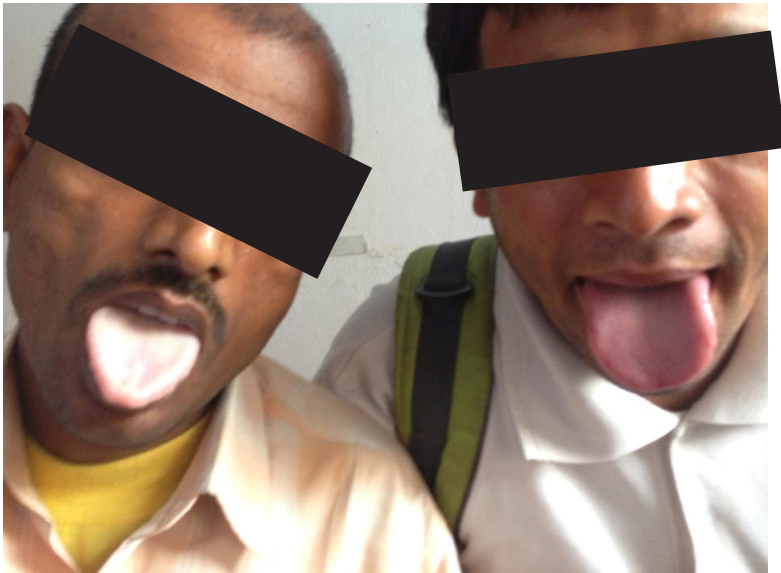
The WHO generic protocol for surveillance of pre-treatment HIVDR provides nationally representative estimate of HIV drug resistance in populations initiating therapy. Performed regularly at representative ART clinics, these surveys support national decision-making regarding the choice of 1st line regimens.

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 PMTCT and those with unknown exposure to support the selection of optimal first-line ART for this population.

**Figures :**



*Figure 4.1 Anaemia caused by AZT*



*Figure 4.2. Lipodystrophy caused by d4T*



*Figure 4.4. Maculopapular rash caused by NVP*



*Figure 4.3. Gynaecomastia caused by EFV*



## 05

# MANAGING COMMON CO-INFECTIONS AND CO-MORBIDITIES

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## 5.1. Introduction

Various co-infections, comorbidities and other health conditions are common among people living with HIV. 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 wide spread use of potent combination antiretroviral therapy (ART), opportunistic infections (OIs) are the most important cause of morbidity and mortality in this population. OIs have been 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, the widespread use of potent ART has had the most profound influence on reducing OI-related mortality in HIV infected persons.

## 5.2. Co-trimoxazole preventive therapy

1. Co-trimoxazole preventive therapy (CPT) should be implemented as an integral component of a package of HIV-related services. The PLHIV should be evaluated for the possible need of 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 should be started for:

- HIV infected adults with CD4 count  $<500$  cells/mm<sup>3</sup>
- All adults who have had an episode of PCP
- All adults with symptomatic HIV disease or Clinical stage 2, 3 or 4

The regimen is:

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

Continuation of Cotrimoxazole prophylaxis as follows:

- Lifelong (irrespective of the CD4 count)



Cotrimoxazole can be discontinued in the following situations:

- severe cutaneous reactions, such as Stevens-Johnson syndrome, renal and/or hepatic failure, and severe hematological toxicity.
2. Timing of Cotrimoxazole prophylaxis in relation to ART initiation: Since the most common initial side effect of cotrimoxazole and antiretroviral therapy (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.
  3. For Cotrimoxazole intolerance, consider the following alternatives:
    - Dapsone 100 mg once daily is the first choice, or.
    - In cases 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 percent of clients may again tolerate TMP/SMX.

### **Protocol for co-trimoxazole desensitization among adults and adolescents**

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

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 hemoglobin and white blood counts, only as indicated.

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

Use an alternative antibiotic for treating break through bacterial infections among individuals living with HIV 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.

### 5.3. Prevention, screening and management of TB among adults

Among people living with HIV, TB is the most frequent life-threatening opportunistic infection and a leading cause of death. ART should be provided to all people with HIV 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 life time risk of someone with latent TB developing TB disease 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 the ART clinician.

#### 5.3.1. Intensified case finding

As TB is one of the most common opportunistic infection among the HIV infected people, TB screening should be performed for all new HIV infected clients at their first visit using a TB screening questionnaire, a full initial history and physical examination.

#### Box – 5.1. Key screening questions

1. Has the client been coughing for > 2 weeks? Yes/No
2. Has the client been having night sweats for > 2 weeks? Yes/No
3. Has the client lost > 3kg during the last 4 weeks? Yes/No
4. Has the client been having fever or “evening rise in temperature” for > 2 weeks?  
Yes/No

*If “Yes” to question 1: do sputum tests for AFB stain and continue evaluation of client including CXR. Xpert MTB/RIF (Gene Xpert) should be used as the initial diagnostic test in individuals suspected of have HIV –associated TB.*

*If “No” to question 1 and “yes” to any other question: continue investigation for tuberculosis according to clinical signs.*

*If “No” to all questions: stop investigation for tuberculosis and repeat TB screening in 3 months at follow-up visit.*

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

### 5.3.2. Isoniazid Preventive Therapy (IPT)

Preventive therapy against TB is the use of anti-TB drugs(s) 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 newly registered 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 Gene Xpert should be done in all symptomatic pts). IPT should only be used in pts in whom active TB has been excluded, active patient follow up is possible and high-level adherence can be attained.

#### *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.
- A tuberculin skin test (TST) is not a requirement for initiating IPT in people living with HIV. PLHIV who have a positive TST benefit more from IPT, TST can be used where feasible to identify such individuals.
- Cotrimoxazole and ART should not be started at the same time as IPT.
- DOT is not needed for IPT.
- 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-*

Isoniazid 300 mg daily for 6 months, Vitamin B6 25 mg (pyridoxine) should be given together with IPT for 6 months. Children should receive Isoniazid 5mg/kg daily.

Follow-up visits while on IPT:

- Client must be seen every month for adherence check, side effect check and medication refill.
- Ask about symptoms of breakthrough TB at each visit. If any occur, evaluate for TB.

### 5.3.3. TB treatment among PLHIV

All PLHIV with TB need ART.

- All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately;
- ART should be started in all TB patients, including those with drug-resistant TB, irrespective of the CD4 count;
- Antituberculosis treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment.
- The HIV-positive TB patients with profound immuno suppression (such as CD4 counts less than 50 cells/mm<sup>3</sup>) should receive ART immediately within the first two weeks of initiating TB treatment;
- In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission of HIV.
- Immune reconstitution inflammatory syndrome (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.

ART drug choice in TB co-infection:

- First line treatment option is AZT/3TC or TDF/3TC plus Efavirenz (600mg once daily).
- Dose increase of Efavirenz is no longer recommended during ATT.
- The first alternative is AZT/3TC plus Abacavir.
- The second alternative is AZT/3TC or TDF/3TC plus Nevirapine for those unable to take EFV or ABC. Rifampicin decreases Nevirapine levels by hepatic induction, which potentially could lead to lower anti-HIV efficacy. There are also concerns of additive liver toxicities. In case where Nevirapine 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- co-infection***

Use of Rifampicin with boosted PI-based regimens is inappropriate due to well recognized drug-drug interactions. For patients who need antituberculosis treatment while on boosted PI regimen, needs to substitute Rifampicin with Rifabutin, and maintain the standard PI-based ART regimen. Rifabutin dose of 150mg once a day should be taken with LPV/r containing ART. Same NRTI backbones are recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800/200 mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV 800 mg + RTV 200 mg twice daily, with close clinical and hepatic enzyme monitoring). If PI cannot be avoided use of non-rifampicin based ART can be considered.

### **5.4. TB co-infection in children**

HIV increases the risk of activation of TB in latently infected children (10-30 times risk). HIV increases the susceptibility to both the primary infection (more common in children) as well as to reactivation of TB (more in adults) due to depressed immunity. Extra pulmonary, disseminated TB and drug-resistant tuberculosis is 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 for 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 5.1.).

**Table 5.1. Recommended ART regimens for children who need TB treatment**

Recommended regimens for children and adolescents initiating ART while on TB treatment		
<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)	
Recommended regimen for children and infants initiating TB treatment while receiving ART		
<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
	3 years and older	If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV or Triple NRTI (AZT + 3TC + ABC) or Continue LPV/r; consider adding RTV to achieve the full therapeutic dose  If the child has a history of failure of an NNRTI-based regimen: 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

## 5.5. Hepatitis B and C

Viral hepatitis is an increasing cause of morbidity and mortality among people living with HIV, 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 co-infected with hepatitis B and/or hepatitis C.

### 5.5.1. HIV/HCV co-infection

Co-infection with HIV and HCV poses a challenge because of the large number of persons affected, the negative impact of HIV on the natural history of HCV infection, and the therapeutic challenges of dealing with interactions between the drugs used for treating HIV and HCV 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 co-infection. As the management of these infections is complex, it is advisable to provide treatment in an integrated fashion by clinicians familiar with the treatment of both infections.

In HIV/HCV co-infected 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 co-infection. 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>). In these situations, since HCV RNA suppression is greater in co-infected persons with CD4 counts higher than 450 cells/mm<sup>3</sup>, it may be preferable to initiate ART and delay therapy for HCV until CD4 counts increase as a result of ART.

HCV infection among persons with HIV co-infection can be treated with PEG-IFN/RBV. These persons can also be treated with PEG-IFN/RBV and boceprevir, telaprevir or simeprevir (for genotype 1 infection) and may also be treated with sofosbuvir/

RBV or PEG-IFN/RBV/sofosbuvir. Persons co-infected with HCV/HIV treated with PEG-IFN/RBV with or without an additional agent (PI or sofosbuvir) who require treatment for HIV should receive compatible ART. Persons with HIV require special consideration regarding the selection of an antiretroviral regimen. The safety profile in HCV/HIV-1 co-infected subjects treated with sofosbuvir is similar to that observed in HCV-mono-infected subjects. Elevated total bilirubin (grade 3 or 4) occurs extremely commonly in persons treated with sofosbuvir and atazanavir as part of the antiretroviral regimen. Tipranavir/sofosbuvir is not recommended but darunavir/ritonavir, efavirenz, emtricitabine, raltegravir, rilpivirine and tenofovir have been tested and no dose adjustment is currently recommended.

Simeprevir is not recommended to be used with several HIV treatment regimens, including cobistat, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, nevirapine, delavirdine, etravirine and any HIV PI-containing regimen.

ART among people co-infected with HCV should follow the same principles as in HIV mono-infection. Initiating ART regardless of CD4 cell count was not recommended because of lack of evidence regarding the benefit of ART for persons with a CD4 count higher than 500 cells/mm<sup>3</sup>.

The choice of ART for persons with co-infection is the same as for those with HIV alone. Potential harmful effects of antiretroviral drugs include their hepatotoxic effects. Several studies have shown that hepatotoxicity as a result of ART maybe worsened in the presence of concomitant HCV infection. For most HIV/HCV co-infected persons, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury.

Raised liver enzymes may be the result of ART-induced drug toxicity and/or opportunistic infections, making interpretation of liver enzyme elevations more problematic than for patients with HCV infection alone. ALT and 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 (e.g. 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 co-infection**

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 the 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 FN/RBV-based therapy. The use of ddI, d4T and 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 direct acting antiviral drugs (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, d4T or ddI). Efavirenz may also be used but the dose of telaprevir must be increased. Boceprevir can be administered with raltegravir (RAL), TDF plus FTC; pharmacokinetic data also support the use of etravirine, rilpivirine and maraviroc as alternatives. Telaprevir can be used with either RAL or standard-dose RTV boosted atazanavir; pharmacokinetic data also support etravirine, rilpivirine and maraviroc as alternatives.

### **Monitoring of therapy in persons with HIV/HCV co-infection**

IFN-based regimens are associated with a reversible CD4 decline (average 140 cells/mm<sup>3</sup>) and a high rate of treatment discontinuation due to side effects. CD4 count monitoring is therefore recommended in co-infected persons on treatment. A higher risk of haematological suppression is also present in HIV-infected individuals; these are important dose-limiting side-effects, especially with co-administration of certain ARV drugs.

Monitoring during IFN and RBV treatment with or without PI therapy is therefore recommended at multiple time points. Additional time points may be required for persons with evidence of side-effects and in persons at highest risk (for example, persons with cirrhosis and HIV, and those on PI therapy). Additional monitoring of liver function is recommended in persons with cirrhosis - albumin, bilirubin and coagulation tests. Persons with evidence of neutropenia, thrombocytopenia and an aemia require 1–2-weekly monitoring.

## 5.6. 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 occur 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, personality changes, memory loss (encephalopathic symptoms)

Signs include : Fever, Confusion, impaired consciousness and coma

Focal signs: cranial nerve palsies

### 5.6.1. Laboratory Diagnosis

Laboratory evaluation for cryptococcal disease should be carried out in patients with advanced immunosuppression with a history of persistent headache and/or clinical features of meningitis, altered mental status or focal neurological deficits. Where possible a lumbar puncture should be performed; a raised CSF opening pressure is common often exceeding 200mm H<sub>2</sub>O in more than 75% of patients. Analysis of CSF generally demonstrates mildly elevated levels of serum protein, low-to-normal glucose concentrations, and pleocytosis consisting mostly of lymphocytes. Some HIV-infected patients will have very few CSF inflammatory cells, but an India ink or Gram's stain preparation often will demonstrate numerous yeast forms. The opening pressure in the CSF may be elevated, with pressures  $\geq 25$  cm H<sub>2</sub>O occurring in 60 to 80% of patients.

Evaluation of symptomatic patients for cryptococcal antigen is extremely useful, but may not be available in all care settings.

Blood fungal culture positive in 75% and indicative of disseminated disease.

## 5.6.2. Treatment and Secondary Prophylaxis

**Untreated cryptococcal disease is fatal.**

### *Preferred Treatment Regimen*

- Induction: initial treatment is with Amphotericin B (0.7 - 1.0 mg/kg/d) for 2 weeks or until the patient is clinically stable. Amphotericin B therapy should be administered in qualified health facilities capable of close clinical and laboratory patient monitoring. In facilities incapable of administering Amphotericin B sole, treatment with Fluconazole (400-800 mg/d for 12 weeks) may be an alternative, although treatment failure and mortality are high.
- Consolidation phase: Fluconazole 400-800 mg/d for 8 weeks
- Maintenance/suppressive phase: Fluconazole 200 mg/d
- Discontinuation of Fluconazole: Fluconazole can be stopped in patients who have been on ART and have documented immune reconstitution as shown by CD4 consistently above 100 cells/mm<sup>3</sup> for at least 6 months.

### *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 principle intervention in patients with symptomatic raised ICP is repeated daily LP until CSF pressure falls below 200 cm H<sub>2</sub>O.

### *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.

### *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 8 weeks of anti fungal treatment. 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  $> 100\text{cells/mm}^3$  for at least 6 months and have completed the consolidation phase of treatment.

Maintenance therapy should be recommenced in patients who have had CM and who develop ARV treatment failure with CD4  $< 200\text{-}100\text{ cells/mm}^3$ .

### 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.

## **5.7.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 five years of age and pregnant women are at particular risk of severe malaria and its complications. People living with HIV 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.

## **5.8. Sexually transmitted infections and cervical cancer**

HIV, other sexually transmitted infections and non-sexually transmitted infections of the reproductive tract frequently coexist. Most of these

infections are asymptomatic, especially among women. However, even asymptomatic sexually transmitted infections can cause complications, be transmitted to sexual partners and enhance HIV transmission. Further, HIV infection alters the natural history of sexually transmitted infections. The objectives of diagnosing and managing sexually transmitted infections include identifying the infection and providing appropriate treatment and preventing transmission. Screening, diagnosis and treatment of sexually transmitted infections should be offered routinely as part of comprehensive HIV care among adults and adolescents.

### **5.8.1. 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 papilloma virus infection increases with 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 that will prevent serious morbidity and mortality. Thus, all women with HIV should be screened for cervical cancer regardless of age. Immediate management for pre-cancerous and cancerous lesions should be provided. WHO guidance covers human papilloma virus vaccination and prevention, screening and treatment and palliative care of cervical cancer.

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

## **5.9. Vaccines for people living with HIV**

People living with HIV 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.

## **5.10. Preventing and managing other co-morbidities and chronic care for people living with HIV**

### **5.10.1. Screening for and care of non-communicable diseases (NCDs)**

People living with HIV are at increased risk of developing a range of non-communicable diseases including cardiovascular disease, diabetes, chronic lung disease and some types of cancer. With effective ART, people living with HIV are also living longer and experiencing NCDs associated with ageing. Both HIV and NCDs require health systems that can deliver effective acute and chronic care and support adherence to treatment.

Chronic HIV care provides the opportunity for screening, monitoring and managing NCDs, especially through primary care. Integrating interventions such as nutrition assessment, dietary counseling and support, smoking cessation, promoting exercise, monitoring bloodpressure and where available cholesterol as part of HIV care provide opportunities for reducing the risks of NCDs among people living with HIV.

### **5.10.2. Mental health**

People living with HIV and their carers may have a wide range of mental health needs. The most common mental health comorbidities among people living with HIV include depression, anxiety, dementia and other cognitive disorders and substance use disorders. HIV care settings provide an opportunity to ensure the detection and management of mental disorders among people living with HIV. Treatment or lack of treatment for these conditions can affect adherence to ARV drugs, retention in care and may involve potential side effects and drug interactions. Recommendations related to general mental health that can be relevant to people living with HIV.

## 06

# PREVENTION OF MOTHER TO-CHILD TRANSMISSION

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## 6.1.Introduction

Mother-to-child transmission (MTCT) is the most frequent source of HIV infection in children in Nepal. The HIV services are already being integrated up to sub-health post level and in some district up to PHC level and now the PMTCT services are increasingly becoming core elements of maternal, neonatal and child health services.

- 761,661 pregnancies per year
  - Estimated 0.09% prevalence of HIV among pregnant women
  - 679 pregnancies estimated to occur in HIV positive women every year
  - Estimated rate of transmission 25-45%:  
136 to 306 babies infected annually
- \* Data sources- NCASC 2013 estimations

National HIV/AIDS strategy 2011-2016 has committed to reduce new HIV infections in children by 90% by 2016 compared to 2010 baseline, and Nepal Investment plan 2014-2016 proposed investments for pregnant women and their partners through comprehensive antenatal care (ANC), including health education and HTC, at the lowest health facilities.

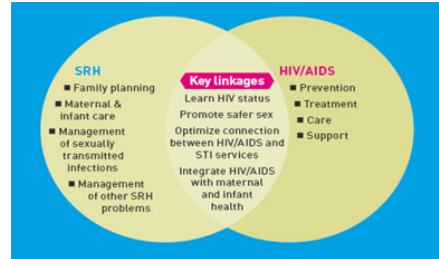
The programme will be integrated and delivered through reproductive health services (integrating with antenatal care services). The HIV testing will be available at these health facilities where the ANC, FP and STI services are available and linked with ART services. To maximize the coverage, benefit and synergy, PMTCT will be integrated in MNH programme under Family Health Division.

A comprehensive and integrated four prong approach for preventing HIV infection in infants and young children will be strengthened.

- Prevent HIV infection among women of childbearing age;
- Prevent unintended pregnancies among women living with HIV;
- Prevent HIV transmission from infected mothers to their infants:
  - antiretroviral treatment 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.



**Figure 6.1. Key linkages between Sexual and Reproductive Health services and HIV services**



Source: WHO, UNFPA, UNAIDS, IPPF. *Sexual and Reproductive Health and HIV/AIDS: A Framework for Priority Linkages* (2005).

Table 6.1. summarises the maternal and infant factors that may increase the risk of HIV transmission during pregnancy, labour, delivery and breast feeding.

The most important risk factor for MTCT is the amount of HIV virus in the mother's blood - 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.

Where viral load assays are not available, low CD4 T-cell counts are similarly associated with increased risk of antenatal and intrapartum transmission.

**Table 6.1. Factors that may increase the risk of MTCT 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 (e.g. 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 (e.g. episiotomy, fetal scalp monitoring)</li> <li>▪ First infant in multiple birth</li> <li>▪ Chorioamnionitis (e.g. from untreated STI or other infection)</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 (i.e. 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 (e.g. thrush or sores)</li> </ul>

## 6.2. Prevention of HIV transmission from HIV infected mothers to their infants

Globally, the greatest risk of MTCT occurs at intrapartum period (i.e. 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 MTCT during labour and delivery is also associated with other causes of acute chorioamnionitis – e.g. resulting from untreated STIs 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 includes, operative or manipulative vaginal delivery (including forceps or vacuum extraction, breech extraction and manipulations during vaginal delivery of multiple pregnancy) increase the risk of mixing of foetal and maternal blood.

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

- Health information and education – including safer sex practices and HIV
- HIV testing and counselling, including partner HIV testing and
- Counselling and support on Aama programme, new born care,
- Diagnosis and treatment of STIs
- Interventions to reduce the risk of MTCT
- Infant feeding counselling and support
- Counselling for TB and Malaria
- Discussion of family planning choices to be used following delivery

The government of Nepal has been scaling up PMTCT services in the hospitals, PHCC, health posts and sub-health posts. The role and responsibilities of the concerned institutions, follow up mechanism to the baby born from HIV positive mother, and supporting agencies like community care centres (CCC) have been mentioned in the PMTCT SOP. (PMTCT SOP; Section 2, 3 and Section 5.4).

### 6.2.1. Providing treatment and care for HIV positive pregnant women

Nepal has chosen Option B+ as recommended in the WHO consolidated guidelines-June 2013, which recommends that all HIV-infected pregnant women are immediately started life-long ART regardless of WHO clinical stage and CD4 cell count. Programs need to put methods in place to support these women for rapid evaluation as soon as possible. The three elements of PMTCT during labour and post-partum are:

- providing ARV therapy to the mother, and to the baby following delivery,
- implementing safer delivery practices,
- providing ongoing counselling and support on safer infant feeding

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

Practical considerations in scaling up PMTCT services, including ARV regimens, include:

- access to and the availability of HIV counselling and testing services;
- the timing of the first antenatal visit, which affects the stage of pregnancy each woman is diagnosed;
- the HIV-infected women who are aware of their status;
- the frequency of antenatal visits, which affects follow-up care and counselling, and monitoring adherence to ARV medication;
- the proportion of births occurring in health care facilities or attended by a skilled birth attendant;and
- access to early HIV-related care at postpartum, including in the community settings.

The procedure for clinical care for HIV positive pregnant women is given in the clinical care for women with HIV section in the PMTCT SOP.

**Table 6.2. Recommendations for National PMTCT programme**

National PMTCT programme	Pregnant and breastfeeding women with HIV	HIV-exposed infant
Use lifelong ART for all pregnant and breastfeeding women (“Option B+”)	Initiate ART and maintain after delivery and cessation of breastfeeding regardless of WHO clinical stage or CD4 cell count.	Breastfeeding 6 weeks of infant prophylaxis with once-daily NVP

### 6.2.2. First-line ART for pregnant and breastfeeding women

A once-daily fixed-dose combination of TDF + 3TC + EFV is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age.

Providing an optimized, fixed-dose combination first-line ART regimen of TDF + 3TC + EFV to all pregnant and breastfeeding women with HIV provides important programmatic and clinical benefits, including the following.

- Ease of implementation - The same simplified ART regimen is administered to all pregnant women (regardless of “eligibility” for treatment) and continued after cessation of breastfeeding.
- Harmonized regimens - The optimized first-line fixed-dose combination regimen can be harmonized with guidelines for ART in non-pregnant adults.
- Increased coverage of ART - This ensures that immuno-compromised women who do not have access to CD4 testing receive appropriate ART without delay.
  - Vertical transmission benefit: Provides coverage with ART to maximize the prevention of infant infections.
  - Maternal health benefit: Will delay disease progression over the course of treatment.
- Acceptability: Reviews conducted for these guidelines have generally indicated strong community preference and acceptability for this approach.
- Sexual prevention benefit: ART will reduce sexual transmission of HIV to sexual Partners.

**Table 6.3. Recommended 1st-line ART regimen for treating pregnant women**

Timing	ARV(s)
Start ASAP in pregnancy and continue throughout pregnancy, labour and delivery and postpartum, for life	TDF + 3TC + EFV

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

### Box 6.1. Management of labour and delivery to reduce risk of MTCT

- Ensure continuous support for the mother during labour
- Ensure good infection prevention practice
- Provide regular monitoring of progress of labour using partograph (vital signs, maternal and foetus well-being)
- Provide ARVs to mother according to agreed protocol
- Minimise vaginal examinations
  - Perform cervical examination only when absolutely necessary, and with appropriate clean technique
- Use non-invasive foetal monitoring to assess need for early intervention
- Treat signs of infection in the mother
- Minimise episiotomies, tears, and instrumental delivery
- Minimise risk of postpartum haemorrhage
  - Active management of the third stage of labour
    - Give oxytocin IM within one minute after delivery
    - Use controlled cord traction to deliver placenta
    - Perform uterine massage
  - Repair genital tract lacerations carefully and promptly
  - Carefully remove all products of conception
- Provide proper cord care – do not “milk” cord blood towards baby
- Provide immediate newborn care, minimize use of suctions to avoid trauma of upper airway
- Provide postpartum care for mother, with careful monitoring for infection

#### 6.2.3. Neonatal/infant care & prophylaxis

Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum. Ensure that the NVP is available through health worker or community home based care worker, if the mother plan to deliver at home or health facility with no PMTCT services.

**Table 6.4. Simplified infant prophylaxis dosing recommendations:**

Infant age	Daily dose
Birth <sup>a</sup> to 6 weeks • Birth weight 2000–2499g <sup>a</sup> • Birth weight >2500g	10 mg twice daily 15 mg twice daily First dose should be given within 6 to 12 hours of birth or as soon as possible thereafter.

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

In the rare instance where the mother has poor adherence or discontinues treatment, but continues to breastfeed, the following should be prescribed (Infant Nevirapine daily until 1 week after cessation of breastfeeding):

**Table 6.5. Extended infant NVP dosing recommendations**

Infant age	Nevirapine dose
*Birth to 6 weeks	
• Birth weight 2000–2499 g	10 mg once daily
• Birth weight >2500 g	15 mg once daily
>6 weeks to 6 months	20 mg once daily
>6 months to 9 months	30 mg once daily
>9 months to end of BF	40 mg once daily

\* Low birth weight infants should receive mg/kg dosing, suggested starting dose is 2 mg/kg once daily.

Immediate newborn care includes the following:

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

#### 6.2.4. Postpartum care of women who are HIV-infected

When providing postpartum care to women infected with HIV, health care workers may follow routine protocols, but several areas require additional attention (for detail see PMTCT SOP chapter 5, SOP-14).

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

As a minimum, women should be evaluated 1 week after the birth and again at 6 weeks. 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 weeks 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 to safely breastfeed
- Assess family support for breastfeeding; identify any risk factors for mixed feeding, and counsel and manage as appropriate
- Ensure women take good care of her breast 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 woman who is HIV-infected to comprehensive care that will support her health, prevent complications and improve her ability to live with HIV, if she has not already 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 opportunistic infections
- Antiretroviral treatment
- Management of symptoms and palliative care
- Simple management of common HIV- or ART-related symptoms (including nausea, vomiting, fatigue and skin problems) can ease discomfort.

- Nutritional counselling, care and support
- Personal and environmental hygiene
- Social and psychosocial support

In many communities, PLHIV face stigma and discrimination and therefore reluctant to disclose their status to partners, family or friends. 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
- 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 Home-based care - Community home-based care provides services to PLHIV are expanding in Nepal. They are available to care for PLHIV throughout the continuum of HIV infection and can assist at diagnosis, during times of illness, around the start or continuation of ART, in follow-up from hospitalisation or during the terminal stages of the disease.

The advantages of home-based care for patients and families, and for communities and the health care system include:

- o Care is provided in a familiar, supportive environment that allows for continued participation in family life
- o Medical and transportation expenses are reduced
- o Closer and more frequent follow-up by a health care worker may be possible, especially for those living far from health facilities
- o The local community may be involved in care for PLHA, and this may help counter myths, misconceptions, stigma, discrimination and rejection
- o The demands on the health care system are reduced

### **6.2.5 Recommendations on breastfeeding and infant feeding**

The mothers known to be infected with HIV should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter, and continue breastfeeding same as mother without HIV.



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 also facilitate infection occurring during breastfeeding, and is suggested to avoid breastfeeding until complete cure or give expressed breast milk.

### **6.3. Establishing and managing linkages**

PMTCT needs multidisciplinary and multi-sectoral initiatives. Linkages with various agencies are very important for ensuring adequate resources – human, financial and material – are available and allocated to care and support services. Related sectors like education, health, women and children and social welfare should all be involved in HIV awareness and prevention, care and support services. In addition, the NGO and private sector partners supplement and complement in the expansion of PMTCT services.

#### **6.3.1 Linkages between MNH and clinical HIV services:**

- MNH services are an important entry point for accessing PMTCT interventions, mainstreaming of the PMTCT services in MNH commence in phase-wise manner.
- The ANMs and paramedics can be supported for clinical follow-up, supervise and support adherence to any prescribed treatment (e.g. prophylaxis against OIs), and provide information on health promotion, disease prevention.
- Specialists in HIV who care for adults and children, provide clinical supervision and ART, and be aware of the need of community level support.

#### **6.3.2 Linkages with other health programmes for special needs:**

- Linkage with specific health needs, such as family planning, treatment of STIs, 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.

#### **6.3.3 Linkages to community-based organisations:**

- Linkages to community-based organisations who can provide the resources to help women who are HIV-infected and

their families cope with the isolation, social stigma, and the emotional pressures that often accompany a diagnosis of HIV.

- NGOs often provide HIV related and non-HIV care and support services for IDUs, FSWs and other KPs, and are a valuable resource for mothers who are HIV-infected and their families.

#### 6.4. Maternal prophylaxis and treatment for opportunistic infections

Maternal prophylaxis and treatment for opportunistic infections (antenatally, during labour and delivery and postpartum) subject to the precautions listed in Table 6.6, 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 2, 3 or 4 disease, irrespective of CD4 cell count or
- WHO Stage 1 disease with CD4 <500/mm<sup>3</sup>

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

**Table 6.6. Prophylaxis and treatment of opportunistic infection in pregnant women**

Pneumocystis pneumonia (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 fetal deaths and fetal 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>

Influenza vaccine Mycobacterium avium 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>- Chest X-ray should be done 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 nevertheless commence irrespective of the gestational age. This is because the benefits of the protective effect 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 new-born baby. Careful monitoring of the baby should be undertaken, but TMP-SMX should not be discontinued prior to delivery if required for maternal health.

Isoniazid preventive therapy (IPT) for TB should be prescribed in accordance with recent National TB/HIV Guidelines.

## 6.5. Prevention of unintended pregnancies in HIV-infected women

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

Some PLHIV may prefer to prevent pregnancy, either to delay their childbearing until they are clear about quality-of-life issues and access to ART, or to avoid childbearing due to the complexity 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.

### 6.5.1. 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 have access to quality services to implement these choices.

Family Planning Counselling for PLHIV should:

- assess the fertility intentions and desired family size
  - balance the desire for pregnancy against the risks, consequences and choices related to an unplanned, unintended pregnancy
  - 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.
  - Pre-conception counseling for PLHIV
- o Pre-conception counseling 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 or eligible for ART, advise to achieve maximal viral suppression with complete adherence to ART for over 6 months for those on ART, before attempting conception.
  - 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 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 practicing 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 pre-conception counseling:
  - Discuss the risk of HIV transmission from the man to the woman.
  - 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 the 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 the pre-conception counseling:
  - o Discuss the risk of HIV transmission from the woman to the man.
  - o Explain that artificial insemination is the safest conception option
  - o Promptly refer to PMTCT services after conception. If not already on ART, begin ART as soon as possible according to National guidelines.
  - o 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 she has time to recover between pregnancies. Further, women with HIV are at greater risk of having preterm births, still births and low birth weight babies. However, with current ART and early and appropriate care, it is possible to have a healthy pregnancy and healthy baby. Inform that initiating ARVs early and proper adherence can dramatically decrease the risk of a mother passing on HIV to her baby during pregnancy, delivery and breastfeeding.
- Counselling should help women or couples with HIV to examine a number of factors, which may influence their choice of contraceptive method:

- o The safety of the method
- o Its effectiveness in preventing pregnancy
- o Whether it is appropriate for short-term or long-term use, or whether it is likely to be permanent
- o Possible side effects of the method, including side effects related specifically to the woman being infected with HIV
- o How easy it will be to use
- o Whether it is affordable, with easy access to future supplies
- o If a woman is postpartum, what effect the method may have on breastfeeding
- o How it may interact with medications, especially ARVs
- o Whether it provides protection from HIV and STI transmission
- o Whether partner involvement or negotiation are required.

### 6.5.2. 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);
- the intra-uterine contraceptive device (IUD);
- female and male sterilisation (tubal ligation and vasectomy);
- the 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. Note that women who use no method at all may have a risk of pregnancy as high as 85% over a one year period.

**Table 6.7. Contraceptive methods for PLHIV**

FP Methods	Effectiveness	Recommendations
<b>Male and Female Condom</b>	prevent transmission of STIs and HIV in addition to preventing pregnancy – called “dual protection”	Condoms are highly recommended for family planning for PLHIV – either alone or, preferably, in combination with another contraceptive method A “Condom Plus” approach is recommended which promotes use of condoms to

FP Methods	Effectiveness	Recommendations
		prevent HIV/STI transmission and an additional contraceptive method to help prevent pregnancy more reliably.
<b>Spermicides</b>	have lower contraceptive efficacy than other barrier methods and they do not protect against STIs. Don't prevent HIV transmission.	Not recommended. Spermicides have been shown to increase transmission of HIV. Even in couples where both are HIV infected, spermicide use could lead to increased risk of super-infection with different strains.
<b>Diaphragm</b>	Like the female condom, the diaphragm has the advantage of being controlled by the woman, and can be inserted several hours before intercourse. Does not prevent HIV transmission.	Not recommended for PLHIV.
<b>Oral (Combined Hormonal) Contraceptives</b>	Highly effective pregnancy prevention. Failure rates are around 1% if pills taken on time. Effect of ARVs on Hormonal Contraceptives - PIs particularly Ritonavir and the 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.	Women with HIV infection can use hormonal OCPs without any restriction. OCPs should generally not be used by HIV infected women on ART which includes ritonavir or ritonavir-boosted PIs.

FP Methods	Effectiveness	Recommendations
	Studies have confirmed that IUDs are safe for PLHIV, with no impact on disease progression or clinical well-being.	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. The consistent use of condoms must be recommended to prevent HIV and other STI transmission.
<b>Injectable (Progestogen-Only) Contraceptives</b>	Pregnancy rates for injectable is less than 1% under both “perfect” and “typical” use. NVP has been found to reduce serum progesterone levels by about 20%, but without reduced contraceptive efficacy.	Injectable progestogen is a suitable form of contraception for women with HIV infection, including those on ART. The consistent use of condoms is recommended to prevent HIV and other STI transmission.
<b>Progesterone Implants</b>	Pregnancy rates 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>	Highly effective, long-term method of contraception with a failure rate of less than 1%.	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).
<b>Emergency Contraception</b>	Emergency contraceptive pills (ECPs) are the most common method of emergency contraception after unprotected intercourse. There are no data on interaction between ECP and ARVs. ECPs contain a higher dose of hormones than regular OCPs, so	For HIV-positive women who have unprotected sex and may be at risk of an unwanted pregnancy, access to emergency contraception is essential. Providers who offer emergency contraception should also help women to choose a regular



FP Methods	Effectiveness	Recommendations
	their effectiveness in pregnancy protection may not be significantly affected by ARV drugs.	contraceptive method and counsel them about how to use the method correctly and when to begin using it.
<b>Male or Female Sterilisation</b>	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.	Sterilization is recommended for PLHIV; informed voluntary choice is essential. Careful infection control is essential during the procedure, especially if the man or woman is immunocompromised. The consistent use of condoms must be recommended to prevent HIV and other STI transmission.
<b>Lactational Amenorrhoea Method</b>	The lactational amenorrhoea method is a temporary option that can be used by women who are a) in the first 6 months following delivery, b) exclusively breast feeding, and c) continue to have no menstruation.	HIV positive women must receive careful counselling regarding the advantages and disadvantages. The consistent use of condoms must be recommended to prevent HIV and other STI transmission.
<b>Methods Based on Fertility Awareness</b>	Identification of the fertile days of the menstrual cycle, either by observing signs of fertility (e.g. cervical secretions, basal body temperature) or by counting the days of the cycle. These methods require extremely high motivation, discipline and diligence. Pregnancy rates with “perfect” use are 2-5%, but are typically between 12% and 22%.	PLHIV who do not want to have children should be counselled to consider other, more reliable methods of contraception. The consistent use of condoms must be recommended to prevent transmission of HIV and other STIs.

Medical eligibility for contraceptive methods in HIV infection medical eligibility for contraceptive methods for clients with HIV/AIDS and recommendations for contraceptive use for women taking antiretroviral therapies is provided in Annex 6.3.

## 07

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

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## 7.1. Introduction

WHO defines treatment adherence as ‘the extent to which a person’s behavior-taking medications, following a diet and/or executing lifestyle changes –corresponds with agreed recommendations from a health care provider’. Adherence implies an active collaboration between the patient and provider in designing a medical regimen that addresses the needs of the individual patient within the social context of his/her life. The client plays a more active role in his/her treatment and makes a commitment to follow the prescribed regimen as closely as possible.

For ART a high level of sustained adherence is necessary to –

1. Suppress viral replications and improve immunological and clinical outcome
2. Decrease the risk of developing ARV drug resistance and
3. Reduce the risk of transmitting HIV

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.

## 7.2. Adherence to ART, barriers to adherence and interventions to optimize adherence to ART

Maintaining high level adherence is not an easy task, so every ART service provider needs to help their clients to identify the barriers of adherence, to address the barriers effectively and maintain the optimum adherence.

### 7.2.1. Barriers of Adherence

**Table 7.1: Barriers of adherence**

Factors related to barriers of adherence	Barriers for adherence
Individual factors	Forgetting doses, being away from home, changes in daily routines, depression, illnesses, lack of interest or desire to take the medications, substances and alcohol use limited knowledge on the course of HIV infection and treatment
Medications related factors	Adverse events, the complexity of dosing regimens, the pill burden, and dietary restrictions, lack of clear information or instruction on medication,
Health system related factors	Requiring people with HIV to visit health services frequently to receive care and obtain refills; travelling long distances to reach health services; and bearing the direct and indirect costs of care. Interrupted ARV drug supply lack of continuity of care

## 7.2.2. Specific Challenges for maintaining optimal adherences

Following are the possible challenges which need to address in specific population/situation for maintaining optimum adherence:

### Pregnant and postpartum women

- Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence
- Dealing with the diagnosis of HIV infection (many women learn about their HIV infection during routine screening during pregnancy)
- Concerns about how ART affects the health of the fetus
- Pill burden because of other medications prescribed during pregnancy
- The number of clinic visits during pregnancy
- Fear of disclosure of HIV status to partners
- Long waiting times at clinics
- Lack of follow-up and transfer to other clinics after delivery

### Adolescents

- Potentially large pill burden if they are treatment-experienced
- Stigma and fear of disclosure
- Concerns about safety of medications
- Adverse effects of ARV
- Peer pressure and perceived need to conform
- Not remembering to take medications
- Inconsistent daily routine
- The transition from pediatric to adolescent care presents include assuming increased responsibility for their own care (which may lead to treatment interruptions because of forgetfulness)
- An inability to navigate the health care system; lack of links between adult and pediatric services
- Inadequately skilled health care providers
- Depression and substance use

### Infants and children

- The limited choice of pediatric formulations
- Poor palatability of liquid formulations
- High pill or liquid volume burden
- Large pill size
- Frequent dosing requirements, dietary restrictions,

- Difficulties in swallowing tablets and adverse effects
- Loss of primary caregiver
- Commitment and involvement of a responsible caregiver
- Parents and other family members of children living with HIV
- Suboptimal HIV care and treatment for family members resulting in suboptimal care for the child.

### **Mental health disorders**

- Mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans
- Uncontrolled depressive symptoms

### **Substance use disorders**

- Alcohol and other drug use could be associated with forgetfulness, poor organization and diversion of monetary and time priorities

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

Key populations at risk of HIV face multiple challenges to access health services. Peer-support along with the supports of outreach teams, peer educators and health workers providing multidisciplinary, non-judgmental and respectful care, are necessary to address their needs.

### **Imprisonment**

- Diminish trust and predispose individuals to poor financial and social support both during and after imprisonment
- Substance use disorders
- Have the additional risk of acquiring TB, resulting in high morbidity and mortality rates in the absence of efficacious HIV and TB treatment

### **7.2.3. Interventions to optimize adherence to ART**

*a. Program-level interventions for improving adherence to ART include:*

1. Avoiding imposing out-of-pocket payments at the point of care
2. Using fixed-dose combination regimens for ART
3. Strengthening drug supply management systems to reliably forecast, procure, and deliver ARV drugs and prevent stock-outs.

*b. The individual-level adherence intervention:*

Efforts to support and maximize adherence should begin before ART is initiated. Initial patient education should cover basic information about HIV, the ARV drugs, expected adverse effects, preparation for treatment and adherence to ART.

1. Adherence preparation should not delay treatment initiation, when prompt action is necessary.
2. An individual adherence plan should be developed and monitored according to the need of the individual patient.
3. Informing and encouraging people receiving ART and their families and peers by health care providers including Community and Home Based Care (CHBC) workers.

*c. Using Reminders*

- The use of mobile phone text messages as reminders for taking ARV. Text messaging should clearly be provided as part of an adherence support package.
- Other patient reminder tools include alarms, phone calls, diaries and calendars are used for reminders about the timing of ARV drugs, drug dosage and appointments

*d. Substance use and mental health interventions*

- Improving well-being by treating depression and managing substance use disorders improves HIV treatment outcomes.
- WHO recommends co-treatment of depression and substance use disorders irrespective of HIV status,
- Other services for people living with HIV who use drugs, such as needle and syringe exchange programs, drug dependence treatment and peer outreach, provide opportunities for supporting treatment adherence.

*e. Nutritional support*

- HIV programs should ensure optimal health outcomes in food-insecure settings.
- Nutritional supports include nutritional counseling, cash transfers and subsidizing food costs and/or food vouchers.

*f. Financial support*

- Financial support may include reimbursement for the costs of receiving HIV care (including drugs, diagnostics, clinical services and transport vouchers)
- Programs for reducing the costs of care for people living with HIV

that would include avoiding out-of-pocket payments at the point of care, decentralizing and coordinating care and exploring opportunities to minimize health facility visits.

### 7.3. Monitoring adherence to ART in routine program and care settings

**Adherence monitoring visits are recommended as follow :**

First Month: two visits (every 2 weeks)

Second and third month: two visits (every month)

Fourth month onwards: one visit every three months

More frequent visits are needed to schedule if patients develop symptoms or experience difficulty in maintaining adherence

**Following approaches of for monitoring adherence are recommended:**

*a. Viral load monitoring*

The viral load does not directly monitor the adherence but poor adherence might be one of the causes of treatment failure. WHO recommends that viral; load monitoring must be combined with other methods of measuring treatment adherence.

*b. Review of the ARV dispensing records*

Review of the ARV dispensing records provide information on when people living with HIV pick up their ARV drugs. When people receive supply of their ARVs at irregular intervals, this may indicate non-adherence to ART; however, in some angles receiving the supply of ARVs in a regular interval only may not indicate proper adherence to ART. So, this approach also should be combined with other methods of measuring adherence. However, in absence other strong mechanisms of monitoring, this is one of the options.

*c. Self-report*

Self-report includes asking patient or their care givers how many doses of ARVs, the patient has missed or forgot to take their doses since the last visit or within a specific period in the past.

*d. Pill counts*

Counting the remaining pills in the container and comparing with the numbers of the 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 center while collecting the supply for the next period. CHBC or community team can also count the pills on their visit and assess the adherence. Adherence percentage can be calculated on the basis of pill count as follow:

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

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

### **Advice to patient on ART, who missed ARV dose :**

All doses should be taken exactly as per the instructions of the treating doctor. However, it is likely that clients forget to take their regular doses. Following are the recommendations in such situations.

1. Recommended to take the pill immediately when patient notices that the dose is missed
2. For the next dose:

### **If the client is taking twice daily dose (every 12 hours ):**

1. If the patient is scheduled to take his/her next dose in less than four hours, he/she is not recommended to take that dose. He/she must wait four hours (from the time he/she has taken the missed dose) to take the next dose. Then after that patient can follow the regular dosing schedule

### **If the client is taking once daily dose (every 24 hours)**

2. 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. Then after that patient can follow the regular dosing schedule
3. 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.
4. If the patient remembers to take the missed dose on the next scheduled time, it is recommended to take the scheduled dose only. It is strictly not recommended to take two doses at a time.

#### 7.4. Retention across the continuum of care

Continuum of care represents a continuum in which all the services necessary for a person living with HIV across the continuum of life.

Positive test at HIV testing marks the entry into the continuum and death including bereavement is the end of the continuum. According to their needs of ART in the continuum, all PLHIV at the time of their HIV- positive diagnosis can be grouped into two broad categories:

Who do not have immediate indications for ART: Care visits provide opportunities for screening, prevention and treatment of other conditions and comorbid illnesses (screening for TB, co- trimoxazole prophylaxis, isoniazid preventive therapy), PMTCT and clinical and laboratory monitoring to allow timely initiation of ART once the indications arise.

PLHIV not eligible for ART: Rapid linkage to care is critical; delays of days or weeks with people already being ill with TB or other opportunistic infections increases the risk of mortality. For PLHIV who are receiving treatment, uninterrupted ART and continual monitoring are essential for sustained viral suppression and optimal treatment outcomes.

#### 7.5. Good practices for retention across the continuum of care

Optimizing retention in HIV care requires interventions at multiple levels, improving the understanding of barriers and innovative strategies to address them, such as:

1. Bringing services closer to communities - where feasible, reduces the indirect costs of care for the people living with HIV and their families and improves retention.
  - a. Waiting times at the facility during consultation are frequently high, especially in the busy central or regional hospitals. Reorganizing services, by providing appointments, triage, separating clinical consultation visits from visits to pick up medicine, integrating and linking to all the services required for PLHIV and family-focused care may reduce waiting times at the health facility. Waiting time should be utilized by conducting edutainment activities, that include playing interactive games, showing videos etc.

2. Follow up of the PLHIV not eligible for ART-Such PLHIV may not attend ART centers regularly and may return to care only when they become symptomatic. Regularly following up these individuals is important to ensure continual monitoring and timely initiation of ART. Providing co-trimoxazole prophylaxis free, on-site or immediate CD4 testing with same-day results and peer support improve retention in care. Annex7.1. summarizes the factors related to the health system and people receiving ART influencing retention and adherence and potential interventions.

### 7.6. Good practices in providing chronic care

As HIV begins to become a manageable, chronic condition, current health delivery systems can be reorganized to provide chronic care.

The recommended steps are:

1. Follow-up visits should be scheduled and planned. Planned chronic care models provide opportunities for prevention, early identification of issues and timely intervention. NGO with CHBC and prevention program can coordinate with HIV care centers and provide supports.
2. PLHIV networks and supports groups' orientation and mobilization is necessary for providing broad support to PLHIV from their communities and health care teams to stay in care, adhere to treatment and cope with stigma.
3. PLHIV and their families need to be informed about HIV infection and the anticipated side effects of medicines and supported to adhere to treatment. Care related counseling of the PLHIV and care giver is necessary.
4. A patient registry serves a reminder function for follow-up services. Health care teams can use it to identify people's needs, to follow-up and plan care, to monitor responses to treatment and to assess outcomes for both individuals and for the overall treatment cohort.
5. Chronic care requires integrating and linking related services to ensure comprehensive and consistent patient management over time, including providing related services in single settings, systems to share information and effective referrals across settings and providers. This also likely to reduce missed opportunities for initiating ART, enhance long-term adherence support and optimize patient retention in care.
6. Programs for HIV, sexual and reproductive health, maternal and child health, TB and drug dependence need to collaborate to successfully implement ART and related services at different levels of the health system.



## 08

## LABORATORY SERVICE

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## 8.1 Introduction

Laboratory support is crucial in all the areas of HIV management specially in diagnosis and monitoring of response to antiretroviral.

### Human Immunodeficiency Virus (HIV) -types and subtypes

HIV is a member of the genus *Lentivirus* which belongs to family *Retroviridae*. HIV infects CD4 T lymphocyte helper cell which is the vital cell of the immune system. When CD4 T- cell count decline below a critical level, cell-mediated immunity is lost, and the infected person becomes progressively more susceptible to opportunistic infections and leads to AIDS. CD4 T-lymphocyte count and viral load test is done to assess the HIV progression and immune status of the person.

HIV has two major types, HIV Type 1 (HIV-1) and HIV Type 2 (HIV-2). Both the infections can be detected using the antibody based rapid tests, ELISA and western blot. It is also important to know HIV subtypes that are present in the region.

1. HIV-1 is the most common and pathogenic strain of the virus. HIV-1 can be divided into groups M, N, and O and P. The epidemic is dominated by Group M, which is composed of subtypes A – K.
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 in the country, the laboratory (test site) should contact NPHL for further investigation.

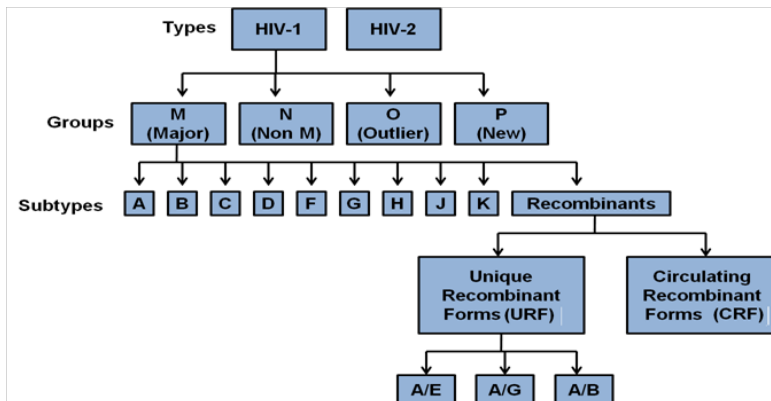


Figure: 8.1. HIV virus types and subtypes

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, vaginal fluid etc. The laboratory confirmation of HIV infection is needed at different settings to ensure the HIV status.

- Blood and blood products safety
- Screening of donors of sperms, organs and tissues.
- Diagnosis of HIV infection in clinically suspected cases.
- HIV counseling and testing (HTC).
- Research and surveys.

## HIV progression

Upon entry into human cells (including peripheral blood mononuclear cells), the HIV-1 RNA is converted into complementary DNA (cDNA) by reverse transcription. These linear cDNA strands are then integrated into the host cell genome, thus representing the pro-viral form of HIV-1. From the pro-viral DNA, m-RNA is transcribed which is used to synthesize the proteins required to make new viral particles. These proteins and viral RNA are packaged in the host's cytoplasm and released from the cell, completing the life cycle of the virus.

In primary infection with HIV, the virus in the blood can be demonstrated by nucleic acid-based test (PCR for pro-viral DNA and real time PCR for viral RNA quantification), antigen testing or culture. Antibodies to HIV are detectable within four to eight weeks of infection by commonly employed tests and in virtually all infected individuals within six months. Once antibodies appear in the blood, they persist for the lifetime.

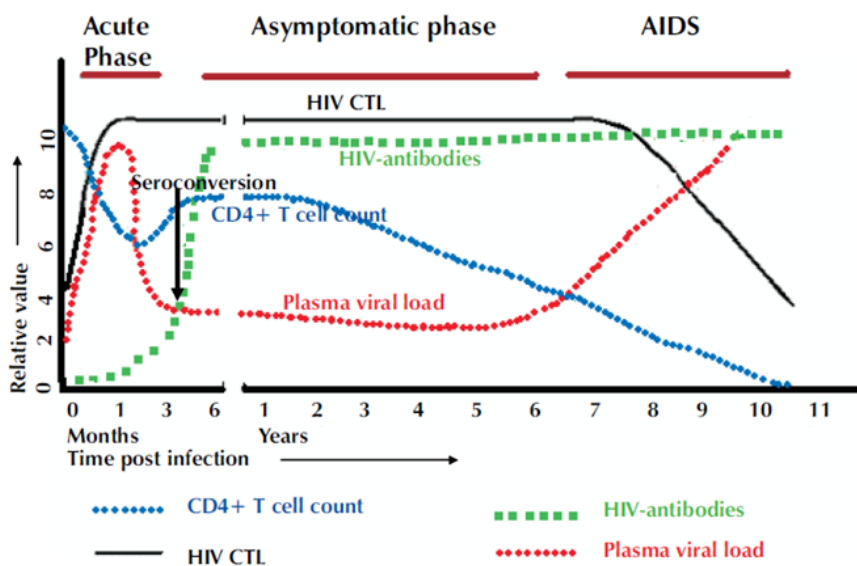


Figure 8.2. Laboratory markers during HIV-1 disease progression

## 8.2. Spectrum of HIV diagnosis

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

- Antibodies to HIV (Rapid test, ELISA, and Western Blot)
- HIV nucleic acid (DNA/RNA PCR)
- HIV antigen (Antigen test)

### 8.2.1. Antibodies for HIV detection

#### *Rapid HIV Tests*

HIV rapid tests are based on three immunologic formats (Immuno concentration, Immuno chromatography, Particle agglutination). Most HIV rapid tests contain antigens to HIV-1 and HIV-2 and detect antibodies to both. Some rapid test detects HIV-1 and HIV -2 infection separately.

#### *Enzyme Linked- Immunosorbent Assay (ELISA)*

A common feature of all varieties of ELISA is the use of enzyme conjugates that bind to specific HIV antibody and substrates/ chromogens that produce colour in a reaction catalyzed by the bound enzyme conjugate. Most ELISA detect antibodies to HIV-1 and HIV-2 and suitable for the sites with large number of samples.

#### *Western Blot (WB)*

It is based on capturing different antibodies present in the serum in a single test. This method uses longer strip on which different HIV antigens are separated. When patient serum which contains different antibodies is mixed with strip containing different antigens, antigen antibody reaction occurs and test result is read based on presence of major antibodies in the serum.

### 8.2.2. HIV Nucleic acid detection - HIV DNA PCR test

HIV DNA PCR test is based on polymerase chain reaction (PCR) which is used for early detection of HIV infection and considered as gold standard technique for early infant diagnosis. Through this technique HIV provirus is detected and used for early HIV infection in children (below 18 months) and/or with “indeterminate” antibody profile results. The presence of integrated HIV proviral DNA can be detected by a PCR that targets a segment of the highly conserved gene. Clinical studies have indicated that detection of HIV proviral DNA in whole blood specimens by PCR is highly sensitive and specific.



### 8.2.3. 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. Monoclonal antibodies specific to the protein are mixed with the blood to be analyzed.

## 8.3. Testing algorithms

### 8.3.1. Early infant diagnosis & diagnosis of children

Diagnosis of HIV infection in babies born to HIV-infected mothers cannot be confirmed by conventional antibody tests. The presence of anti-HIV antibody in the new born may not necessarily indicate primary infection. It may be due to the presence of passively transmitted anti-HIV antibodies from the mother to the uninfected child. These maternal antibodies may persist in the infant for as long as 18 months. Hence, virological assays such as HIV DNA-PCR 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 spots (DBS) samples, which have considerable advantages in settings where sample transportation and storage are problematic.

- Routine virological test of all HIV-exposed infants 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
- 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 six weeks of last breastfeeding, who have now stopped breastfeeding for more than six weeks
  - Children between 9 and 18 months of age who have completely stopped breastfeeding for more than six weeks

and whose HIV antibody test is positive using a rapid antibody assay

- To confirm any positive initial virological test

### Diagnostic Algorithms for EID

#### a) 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 Dried Blood Spot (DBS) is collected and sent for HIV DNA PCR at NPHL.

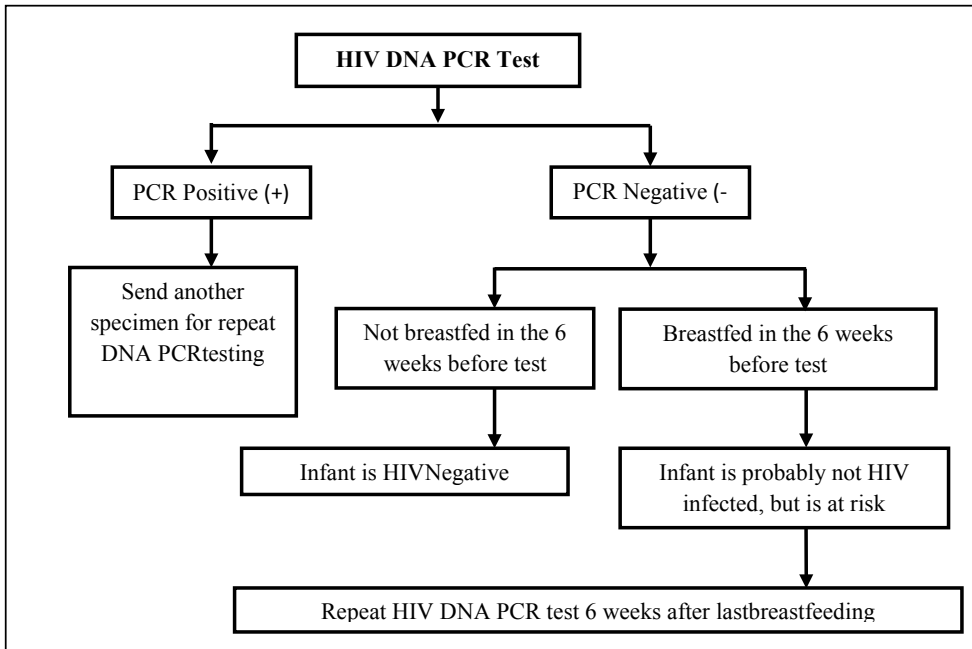


Figure 8.3. Strategy for Diagnosis of HIV in Infants (6 weeks to <9 months)

#### b) Diagnosis of HIV in babies 9-18 months old known to be HIV exposed

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 rapid test first. If the rapid test is positive, then send DBS specimen or whole blood for the DNA PCR test. He/she may have maternal antibodies or may be HIV infected.

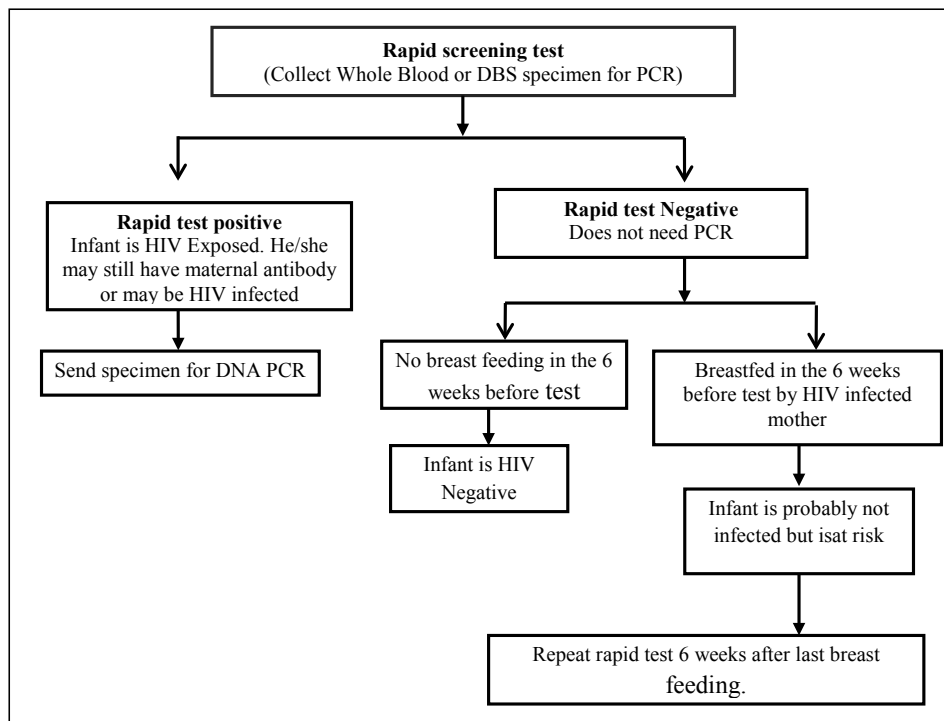


Figure 8.4. Strategy for Diagnosis of HIV in babies (9 to 18 months old)

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 positive HIV status.

### c) Diagnosing HIV infection in breastfeeding infants

If an infant is breastfeeding, the infant 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 6 weeks or longer after complete cessation of breastfeeding.

If the child is between 9-18 months of age, HIV antibody testing can be performed prior to virological testing as a cost saving measure. Children, who no longer have HIV antibody at this age, do not need virological testing. If breast feeding occurred in the previous six weeks, further tests are needed.

Negative PCR results should always be confirmed at age 18 months with an antibody test.

Positive PCR results at any stage indicate HIV infection, but require confirmation by second DNA PCR as soon as possible.

## 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 likely to exclude HIV infection. An antibody test at 18 months is done to confirm that child is not infected.

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

After an initial positive, if a 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 the child is currently breastfeeding or has recently stopped breastfeeding but became infected close to the time of weaning. It can take six weeks to detect HIV antibody. In this case, antibody testing should be repeated more than six weeks 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 the child was breastfed within the last six weeks.

### 8.3.2. Adults and adolescents

Nepal has adopted serial testing algorithm based on antibody testing using Rapid diagnostic kits for whole blood, serum or plasma.

The results of the first test determine whether additional testing is required. If the first test shows a non-reactive result, the tested sample will be reported as “HIV Negative.” If the first test shows a reactive result, the sample will be tested further by a second test; if the second test shows a reactive result, the tested sample will be reported as “HIV Positive.”

When two test results disagree (the first is reactive and second is non-reactive), the finding is called “discordant.” In this case, a third test must be performed; the result of the third test will be the final test result.

The first test used in a serial HIV testing algorithm should be highly sensitive so that all positive samples will be identified as positive. The second test should be highly specific so that all true negative samples will be identified as negative.

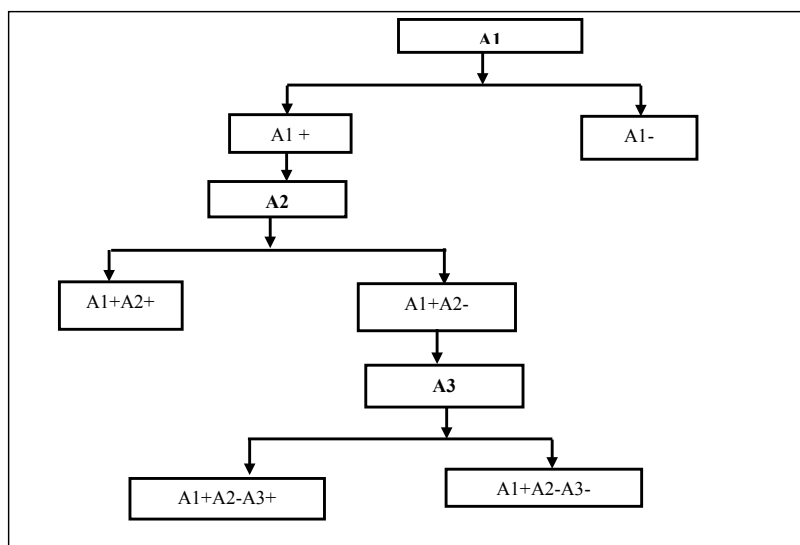


Figure 8.5. - Serial testing algorithm

A1: Screening Rapid test (Determine HIV-1/2)

A2: Confirmatory Rapid test (Uni-Gold HIV)

A3: Tiebreaker Rapid test (Stat pak HIV-1/2)

Note: Above mentioned RDTs have been evaluated by NPHL based on National Scenario.

TEST 1	TEST 2	TEST 3	HIV Status
Non-reactive			Negative
Reactive	Reactive		Positive
Reactive	Non-reactive	Non-reactive	Negative
Reactive	Non-reactive	Reactive	Positive

**Table 8.1. Sensitivity and specificity of commonly used Rapid HIV Test Kits**

Rapid HIV Test Kits	Sensitivity (Percentage)	Specificity (Percentage)
Determine HIV-1/2	100(95.5-100.0)	99.4(96.7-100.0)
Uni-Gold HIV	100 (95.5-100.0)	100.0(97.9-100.0)
HIV-1/2 STAT-PAK	100 (98.8 - 100)	99.3 (98.1 - 99.9)

*Source- WHO 2009. HIV Assays: Operational Characteristics Report 16: Rapid Tests*

Where HIV diagnosis is done using ELISA test kits, the sensitivity and specificity of the kits should be similar to rapid test kits used in the national HIV testing algorithm. The reactive sample from first ELISA test should be confirmed using other ELISA kits capturing another antibodies or RDT with sensitivity and specificity equal to second and third RDTs used in current national algorithm. At present NPHL has evaluated Determine, Uni-Gold and Stat pak so these kits are being used in case other kits to be included in algorithm the same evaluation process will be done by NPHL.

### 8.3.3. Community-based testing

In community-based testing, testing will be conducted by a trained laboratory staff. The same national testing algorithm will be followed. Pre-test and post-test counseling will be provided by the trained community worker. To ensure the quality of test performance, addition to internal quality control measures, laboratory staff will prepare the DBS samples of all positives and 10% of negative samples to be sent to reference laboratory (regional or National Public Health Laboratory).

## 8.4. Laboratory monitoring before and after initiating ART

- Haematological and bio-chemical monitoring
- Immunological Monitoring
- Virological Monitoring

### 8.4.1. Haematological and bio-chemical monitoring

Many of the ARV drugs have potential toxicity and careful monitoring of patients by laboratory investigation for ARV drugs used in treatment has crucial role in good clinical management.

- Didanosine (DDI) and Stavudine (D4T) are responsible for Pancreatitis and hepatotoxicity.
- Zidovudine (AZT) is responsible for neutropenia, megaloblastic anemia.
- Tenofovir (TDF) may lead to renal failure

#### Hematological tests

A complete blood count (CBC) including hemoglobin, total leucocyte count (TLC) and differential leucocyte count (DLC) is required for monitoring the effects of ART in the body.

#### Biochemical tests

According to ART regimen used, different biochemical test including ALT, urea, creatinine, cholesterol, serum electrolytes, serum lactate and glucose level measurements are required to monitor the side-effects of different ARV used for treatment.

### 8.4.2. Immunological Monitoring - CD4 T lymphocyte counts

Immunological monitoring refers the CD4 T lymphocyte count which is the hallmark of body's Immune status. CD4 count also provides the information either to initiate the ARV or not and its monitoring.

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

- Concurrent infections,
- Leucopenia of varying etiology especially caused by ARV itself and steroids or other immuno suppressive therapies.
- Extreme exertion,
- Surgical procedures
- Pregnancy can also lead to lower values.
- Even diurnal variation occurs; CD4 T cells are lower at noon, & highest in the evening around 8 p.m.
- Psychological stress seems to play a negligible role, even though patients often assume the contrary.

### Available CD4 T lymphocyte count platforms in Country:

- BD FACS Count and BD FACS caliber
- Partecyflow
- Pima (Point of care Testing)

### 8.4.3. Virological Monitoring - HIV RNA PCR (Viral load)

Once the ARV is initiated, regular viral load test provides the information on progression of HIV infection and function of ARV in body. The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection.

Apart from methodological variability a host of other factors may influence levels of viral load including

- vaccinations and concurrent infections. During active OIs viral load is often high. Viral load can also increase significantly during syphilis and declines after successful treatment.
- Following immunizations, i.e., for influenza or pneumococcus, the viral load may be transiently elevated. As the peak occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization.

It should be noted that not every increase is indicative of virologic treatment failure and resistance. Slight transient increases in viral load, or blips, are usually of no consequence, as numerous studies in the past have shown. The possibility of mixing up samples always has to be considered. Unusually implausible results should be double-checked with the laboratory, and if no cause is found there, they need to be monitored – people make mistakes. Should there be any doubt on an individual result; the lab should be asked to repeat the measurement from the same blood sample.

It is predicted that with successful therapy a fall of 1.5 to 2 log in plasma viral load occurs within 4-6 weeks. With successful ART, it should become undetectable in four to six months of therapy.

Viral load is measured using a variety of commercial kits based on nucleic acid testing (NAT). Currently, various methods of determining plasma virus load include quantitative RT-PCR, branched DNA technology and NASBA.



## Influencing factors

Apart from methodological variability a host of other factors may influence levels of viral load including

- vaccinations and concurrent infections. During active OIs viral load is often high. Viral load can also increase significantly during syphilis and declines after successful treatment.
- Following immunizations, i.e., for influenza or pneumococcus, the viral load may be transiently elevated. As the peak occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization.

It should be noted that not every increase is indicative of virologic treatment failure and resistance. The possibility of mixing up samples always has to be considered. Unusually implausible results should be double-checked with the laboratory.

## 8.5. Laboratory Diagnosis of Common Opportunistic Infections (OIs)

The most common OIs seen in people living with HIV are *M. tuberculosis*, *Pneumocystis carinii (jiroveci)*, *Candida albicans* and *Cryptococcus neoformans*. The common OIs diagnosed in Nepal includes pneumonia, pulmonary Tuberculosis, meningitis (mostly Cryptococcal), oral candidiasis, Hepatitis B and C, skin lesions - Herpes simplex, Herpes Zoster, molluscumcontagiosum, papularpruritic eruption, candida dermatitis, folliculitis. The less common OIs detected are lymphoma (non-CNS), CNS lymphoma, possible PML, TB of the abdomen and TB osteomyelitis or joint infections.

**Table 8.2. Common viral, bacterial, parasitic and mycotic opportunistic infections**

Group	Opportunistic Infections
Bacterial	<ul style="list-style-type: none"> <li>• Streptococcal infection (mainly <i>S. pneumoniae</i>)</li> <li>• Mycobacterial infections (tuberculosis)</li> <li>• Mycobacterial avium complex</li> <li>• Salmonellosis</li> </ul>
Parasitic	<ul style="list-style-type: none"> <li>• Toxoplasmosis (<i>Toxoplasma gondii</i>)</li> <li>• Cryptosporidiasis ( stool , ZN stain modified)</li> <li>• Isosporiasis</li> <li>• Generalized strongyloidiasis</li> </ul>

Group	Opportunistic Infections
<b>Mycotic</b>	<ul style="list-style-type: none"> <li>• <i>Pneumocystis jirovecii</i> (pneumonia)</li> <li>• Candidiasis</li> <li>• Cryptococcosis neoformans</li> </ul>
<b>Viral</b>	<ul style="list-style-type: none"> <li>• Cytomegalo virus (CMV)</li> <li>• Herpes simplex</li> <li>• <i>Varicella zoster</i></li> <li>• Human papilloma virus, genital warts</li> <li>• <i>Molluscum contagiosum</i></li> <li>• Oral Hairy Leukoplakia (OHL)</li> <li>• Progressive Multifocal Leukoencephalopathy (PML)</li> </ul>
<b>Malignancies</b>	<ul style="list-style-type: none"> <li>• Cervical carcinoma, Kaposi sarcoma</li> <li>• B-cell lymphoma or non-Hodgkin's lymphoma</li> </ul>

In general, the following laboratory methods are used to diagnose the STIs and OIs.

- Microscopy (Microscopic examination)
- Culture
- Serology
- Antigen detection
- Nucleic acid detection

The sensitivity and specificity of these different approaches vary according to specimen type and organism assayed. Nucleic Acid Amplification tests (NAATs) are the most sensitive methods, and culture the most specific.

### **Microscopy (Microscopic examination)**

Directly visualizing the organism on smear prepared under the microscope. Examples: Wet mount for *Trichomonas vaginalis*, Candida (budding cells), Bacterial vaginosis (BV), Gram staining for gonococcus, KOH for fungal infections, Acid fast staining for Tuberculosis.

### **Gram Staining**

The Gram stain is particularly useful in the presumptive diagnosis of bacterial as well as fungal opportunistic infections. Properly Gram-stained preparations can quickly give considerable information that can be applied immediately to patient care. The Gram stain is useful in the diagnosis of gonorrhea, candidal vulvovaginitis, and bacterial

vaginosis, and in the assessment of urethritis, cervicitis, and other infections characterized by mucosal discharge. Both the numbers of polymorphonuclear leukocytes (PMNs) and microbial flora present can be assessed.

## Culture

It is one of the primary diagnostic methods of microbiology and used as a tool to determine the cause of infection by letting the agent multiply in a predetermined medium. It has advantage of drug sensitivity profile useful to treat patient specifically. Culture can be performed to detect *Neisseria gonorrhoea*, yeast and others.

## Nucleic Acid (DNA/RNA) Detection

A nucleic acid amplification test (NAAT) is a molecular technique used to detect the microorganism by identifying the genome (DNA or RNA) of microorganism. These tests were developed for early detection when antibody based tests fail to do so. A nucleic-acid amplification test uses a series of repeated reactions to make numerous copies of the DNA or RNA that makes it easier to detect. Nucleic acid amplification tests like PCR are used to detect gonorrhoea and *Chlamydia trachomatis* infection.

There are multiple methods that fall in this group, that includes Polymerase chain reaction, reverse transcriptase PCR (RT-PCR), Transcription mediated amplification, Branched DNA (quantiplexbDNA), and ligase chain reaction.

## Serology

There are several serology techniques that can be used depending on the antibodies being studied. These include ELISA, agglutination, precipitation, complement-fixation, and fluorescent antibodies. Serological tests such as RPR and TPPA are important in the diagnosis of Syphilis.

### 8.6. Expanding diagnostic services to point-of-care settings

- Antibody testing - Rapid test using blood: up to Primary Health Care and community-based setting;
- CD4 T lymphocyte count – PIMA: up to district health facilities;
- Viral Load test – Automated Viral load testing: up to regional level;

## 8.7. Laboratory Quality Assurance in HIV Testing

Quality system is a part of overall quality management that aims to ensure consistency, reproducibility, traceability, reliability and efficiency of products or services. Organizational management and structure, Quality standards, Documentation, Training and Assessment are the major components of quality system. Laboratories that conduct HIV testing should have a functioning internal quality control and participation on HIV EQAS program.

### 8.7.1. Internal Quality Control

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

### 8.7.2. External Quality Assurance

External Quality Assurance (EQA) is the assessment of laboratory quality of laboratory by reference laboratory, higher authority or independent agency. EQA leads to correction and improvement of the laboratory quality. EQA can be done through proficiency panel testing, Retesting or on site monitoring.

- a) External Quality Assessment Scheme (EQAS) for HIV - Retesting for HIV

All the positive and 10% of total negative tested samples in Dried Blood Spot (DBS) papers from testing sites are sent to reference laboratory ( currently NPHL) for retesting as a part of EQAS. The samples in DBS paper are received at NPHL in monthly basis, tested following same algorithms as in site and reports from NPHL 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 a part of EQA for CD4 count and

viral load. The results are sent to respective external agencies and summary report with feedback is received by NPHL. This helps to assess the testing performance of laboratory.



## 9

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## Annex 1

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

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

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 body weight)	Unexplained persistent hepatosplenomegaly
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)	Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Herpes zoster	Herpes zoster
Angular cheilitis	Lineal gingival erythema
Recurrent oral ulceration	Recurrent oral ulceration
Papular pruritic eruption	Papular pruritic eruption
Fungal nail infections	Fungal nail infections
Seborrhoeic dermatitis	Extensive wart virus infection
	Extensive molluscum contagiosum
	Unexplained persistent parotid enlargement
<b>Clinical stage 3</b>	
Unexplained severe weight loss (>10% of presumed or measured body weight)	Unexplained moderate malnutrition <sup>b</sup> not adequately responding to standard therapy
Unexplained chronic diarrhoea for longer than 1 month	Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (intermittent or constant for longer than 1 month)	Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)
Persistent oral candidiasis	Persistent oral candidiasis (after first 6 weeks of life)
Oral hairy leukoplakia	Oral hairy leukoplakia
Pulmonary tuberculosis	Lymph node tuberculosis
	Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)	Severe recurrent bacterial pneumonia
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis	Acute necrotizing ulcerative gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10 <sup>9</sup> /l) and/or chronic thrombocytopaenia (<50 x 10 <sup>9</sup> /l)	Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10 <sup>9</sup> /l) or chronic thrombocytopaenia (<50 x 10 <sup>9</sup> /l)



Adults and adolescents <sup>a</sup>	Children
<b>Clinical stage 3</b>	
	Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis
<b>Clinical stage 4<sup>c</sup></b>	
HIV wasting syndrome	Unexplained severe wasting, stunting or severe malnutrition <sup>d</sup> not responding to standard therapy
<i>Pneumocystis (jirovecii) pneumonia</i>	<i>Pneumocystis (jirovecii) pneumonia</i>
Recurrent severe bacterial pneumonia	Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)	Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis	Extrapulmonary tuberculosis
Kaposi sarcoma	Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)	Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month)
Central nervous system toxoplasmosis	Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy	HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis	Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection	Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis	Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis	Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)	Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Lymphoma (cerebral or B-cell non-Hodgkin)	Cerebral or B-cell non-Hodgkin lymphoma
Symptomatic HIV-associated nephropathy or cardiomyopathy	HIV-associated nephropathy or cardiomyopathy
Recurrent septicaemia (including nontyphoidal <i>Salmonella</i> )	
Invasive cervical carcinoma	
Atypical disseminated leishmaniasis	

<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 length-for-age/height-for-age <-2 z-score; and severe acute malnutrition is either weight for height <-3 z-score or mid-upper arm circumference <115 mm or the presence of oedema.

## **Annex 2.1.**

### **First aid immediately after potential exposure**

The aim of first aid is to reduce contact time with the source person's blood, body fluids or tissues and to clean and decontaminate the site of the 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 will 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:**

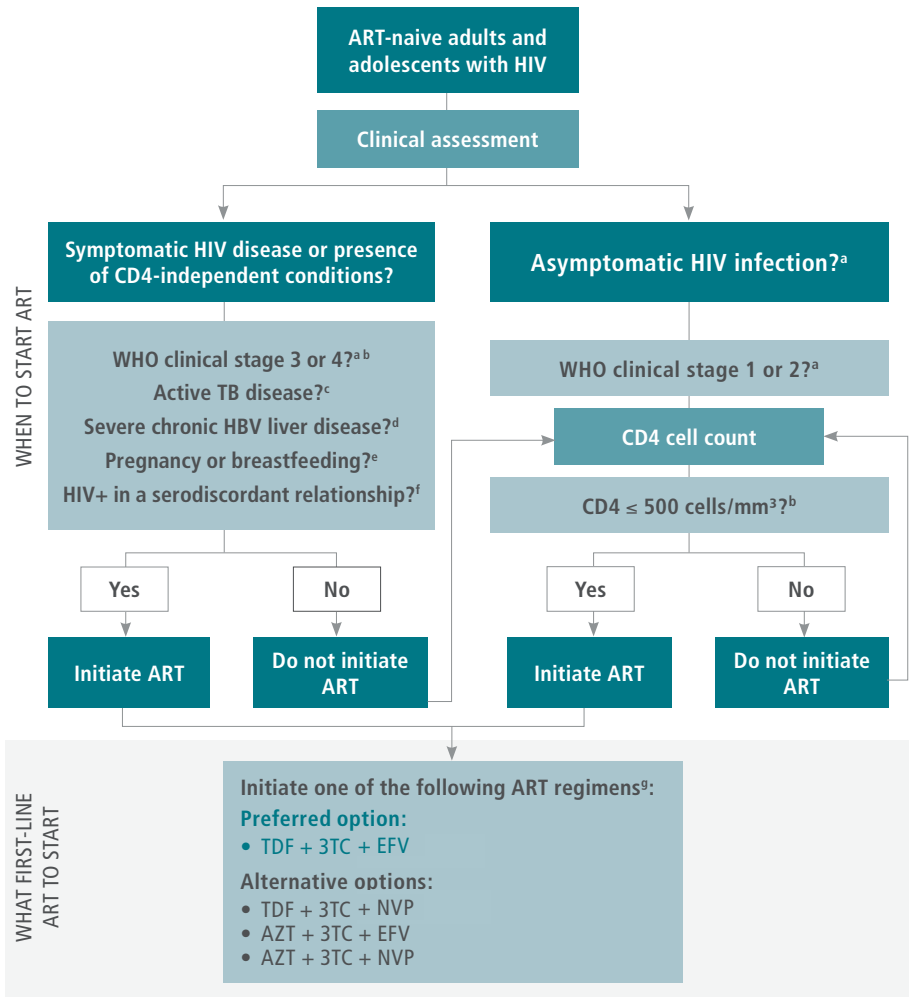
- Irrigate the exposed eye immediately with water or normal saline.
- Sit in a chair, tilt the head back and have a colleague gently pour water or normal saline over the eye, pulling the eyelids up and down to make sure the eye is cleaned thoroughly.
- If contact lenses are worn, leave these in place 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 the normal manner. This will make them safe to wear 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.

## Annex 2.2

## Algorithm for the 2013 recommendations for adults and adolescents



<sup>a</sup> Annex 1 lists the WHO clinical staging for HIV disease.

<sup>b</sup> ART initiation in individuals with severe or advanced symptomatic disease (WHO clinical stage 3 or 4), regardless of CD4 cell count, or with CD4 count  $\leq 350$  cells/mm<sup>3</sup>, regardless of clinical symptoms, should be prioritized.

<sup>c</sup> Active TB disease refers to the time when TB breaks out of latency and causes disease. Latent TB infection refers to the period of time when the immune system has been successful in containing the *Mycobacterium tuberculosis* and preventing disease.

<sup>d</sup> Severe chronic liver disease includes cirrhosis and end-stage liver disease and is categorized into compensated and decompensated stages. Decompensated cirrhosis is defined by the development of clinically evident complications of portal hypertension (ascites, variceal haemorrhage and hepatic encephalopathy) or liver insufficiency (jaundice).

<sup>e</sup> A HIV-serodiscordant couple is a couple in which one of the sexual partners is HIV-positive and one is HIV-negative. Although one partner is currently HIV-negative, this does not mean that this partner is immunized or protected against getting HIV in the future.

<sup>g</sup> For adolescents weighing less than 35 kg, refer to the algorithm for children in annex 4 which indicates the appropriate first-line ART regimen options.

## Annex 2.3

### Dosages of recommended antiretroviral drugs<sup>a</sup>

#### Dosages of antiretroviral drugs for adults and adolescents

Generic name	Dose
<b>Nucleoside reverse-transcriptase inhibitors (NRTIs)</b>	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Didanosine (ddl)	400 mg once daily (>60 kg) 250 mg once daily (≤60 kg)
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Stavudine (d4T)	30 mg twice daily
Zidovudine (AZT)	250–300 mg twice daily
<b>Nucleotide reverse-transcriptase inhibitors (NtRTIs)</b>	
Tenofovir (TDF)	300 mg once daily
<b>Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)</b>	
Efavirenz (EFV)	600 mg once daily
Etravirine (ETV)	200 mg twice 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)	800 mg + 100 mg once daily or 600mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily
	<b>Considerations for individuals receiving TB therapy</b> In the presence of rifabutin, no dose adjustment required. In the presence of rifampicin, adjusted dose of LPV/r (LPV 800 mg + RTV 200 mg twice daily or LPV 400 mg + RTV 400 mg twice daily) or SQV/r (SQV 400 mg + RTV 400 mg twice daily), with close monitoring.
<b>Integrase strand transfer inhibitors (INSTIs)</b>	
Raltegravir (RAL)	400 mg twice daily

<sup>a</sup> For adolescents weighing less than 35 kg, see the next page for weight-based dosing for ARV formulations for children.

## Annex3.1

### Weight-based dosing for antiretroviral formulations for children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on antiretroviral drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing. For simplification and ease of implementation, doses are expressed per weight-band rather than per kilogram or per square meter of body surface area. In some cases the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to ensure that in no case would a child receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. For simplification, Antiretroviral drugs that are no longer considered preferred or alternative options for children such as didanosine and saquinavir are no longer included in the dosing guidance. Antiretroviral drugs and formulations are available from several companies, and the dose strengths of tablets, capsules and liquid formulations may vary from the information given here. National programmes should ensure that any product procured for use is approved and of appropriate quality and stability.

#### General principles

The principles followed in developing the simplified tables include the following;

- It is preferable to use an age-appropriate fixed dose combination for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided where possible, especially if volumes are large – such as above 10 ml.
- Dispersible tablets (or tablets for oral solution) are the preferred solid oral dosage forms, since each dispersible tablet can be made into liquid at the point of use.
- In general, young children should be switched to available solid oral dosage forms as soon as they are tolerated.
- Where children have to use adult formulations, care must be taken to avoid underdosing. Adult tablets that are scored are more easily split. For tablets that are not easily split, it is recommended that this be done in the dispensing pharmacy using appropriate tablet cutters.

- Some tablets such as LPV/r heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split or crushed, since they lose bioavailability.
- Different dosing between morning and evening doses should be avoided where possible.
- Children have to be weighed at each clinic visit, and dose changes are required as children grow and /or gain weight.

**Table 1. 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												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	AM	PM				
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	3	1	1
AZT/3TC/ NVP	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	3	1	1
ABC/ AZT/3TC	Tablet (dispersible) 60 mg/60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	3	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	0.5	0.5	1
d4T/3TC	Tablet (dispersible) 6 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	1	1	1
d4T/3TC/ NVP	Tablet (dispersible) 6 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	2.5	2.5	3	3	3	4	4	4

**Table 2. Simplified dosing of child-friendly solid formulations for once-daily dosing in children**

Drug	Strength of tablets (mg)	Number of tablets or capsules by weight band once daily					Strength of tablet (mg)	Number of tablets or capsules by weight band once daily
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		
EFV <sup>a</sup>	Tablet (scored) 200 mg	–	–	1	1.5	1.5	200	2
	Tablet (double scored) <sup>b</sup> 600 mg	–	–	one third	one half	two thirds	600	2/3
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 + 300	1

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

<sup>b</sup> 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.



**Table 3. 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			AM	PM		
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM					
<b>Solid formulations</b>																
3TC	Tablet (dispersible) 30 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	3	3	150	1	1
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	3	3	300	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	3	3	300	1	1
NVP <sup>a</sup>	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2	2.5	2.5	2.5	3	3	200	1	1
LPV/r <sup>b</sup>	Tablet (heat stable) 100 mg/25 mg	–	–	–	–	2	1	1	2	2	2	2	2	100/25	3	3
<b>Liquid formulations</b>																
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	12 ml	–	–	–	–	–	–	–	–
ABC	20 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	6 ml	–	–	–	–	–	–	–	–
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	6 ml	–	–	–	–	–	–	–	–
NVP <sup>a</sup>	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	10 ml	–	–	–	–	–	–	–	–
LPV/r <sup>b</sup>	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2 ml	2.5 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–

<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 (Fililekes 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.

**Table 4. Simplified harmonized dosing for currently available TDF formulations for children**

Drug	Size of powder scoop (mg) or strength of tablet (mg)	Number of scoops or 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	25–34.9 kg
	Tablets 150 mg or 200 mg	–	–	–	1 (150 mg)	1 (200 mg)		1 (200 mg) <sup>b</sup> or 1 (300 mg)

<sup>a</sup> Target dose: 8 mg/kg or 200 mg/m<sup>2</sup> (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 tablets should be used for weight 25–29.9 kg and 300 mg tablets for 30–34.9 kg.

**Table 5. Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX) prophylaxis**

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of scoops or 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
CTX	Suspension 200/40 per 5ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400/80 mg	–	one half	one half	1	1	400/80 mg	2
	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.

## Annexe 6.1.

### 6.1. Site Requirements for conducting PMTCT services

#### 6.1.1. Sites offering full PMTCT services (Hospitals)

**Human Resources and Capacity:** A core team, trained on all aspects of PMTCT, consisting of

- 1 midwife, with ready access to an obstetrician/gynaecologist and HIV clinician
- 1 - 2 staff nurses, with ready access to a doctor with skills in clinical HIV medicine
- 2 - 3 trained counsellors/nursing staff, according to the case load
- 1 laboratory technician (or other health worker accredited to conduct rapid testing)

The team should also explore, encourage and promote the involvement of NGOs, CBOs, PLHIV network and community based health volunteers, who will also receive training. Community based health workers are an essential part of the PMTCT team

**Infrastructure (Space):**

- An appropriate room for counselling, offering audible and visual materials, privacy and containing basic furniture to sit and talk comfortably.
- Two additional rooms to accommodate one-on-one and couples counselling, as well as small group pre-test counselling.

**Equipment and supplies:**

- Appropriate equipment, test kits and supplies for HIV testing
- Essential drugs for PMTCT services
- Health education materials, condom supplies and a penis model
- Supplies for infection prevention (universal precautions)
- Updated list of referral institutions including contact name, eligibility requirements, location, hours of operation, telephone number and any fees.
- Appropriate record keeping, monitoring and evaluation forms
- Refrigerator for storing test kits requiring a “cool” chain, with appropriate back-up energy source and temperature monitoring

#### 6.1.2. Community-based PMTCT services and support

**Human Resources and Capacity:** Health Facility staff (HA, SN, ANM, AHW), and community based health worker (FCHV or CHBC worker) who are:

- trained on all community aspects of PMTCT, and
- involved in the PMTCT activities in the PHC, HP or sub-health post.

**Infrastructure:**

- An appropriate room for counselling, offering audible and visual materials, privacy and containing basic furniture to sit and talk comfortably.

**Equipment and supplies:**

- Essential drugs for delivering the “Minimum Standard” PMTCT Protocol
  - Fixed dose combination tablets
  - NVP paediatric suspension 50mg/5ml
- Access to a refrigerator for storing NVP paediatric suspension with appropriate back-up energy source and temperature monitoring
- Health education materials, condom supplies and a penis model
- Supplies for infection prevention (universal precautions)
- After hours contact details for supervising health centre including contact name, telephone number and location of residence.

## Annex 6.2

### PMTCT Programme Monitoring

Monitoring is regular tracking of key programme elements. Monitoring of the PMTCT programme will help to:

- Assess programme performance
- Detect and correct performance problems
- Make more efficient use of PMTCT programme resources

Monitoring information is used for decision-making about PMTCT programmes at local, national and global levels. The monitoring of the PMTCT Programme is covered by the HMIS and HIV/AIDS M&E framework, however the UN Universal Access initiative recommends that country level M&E focuses on the coverage levels of the following programme interventions:

- Provision of information on PMTCT to pregnant women attending antenatal care
- HIV testing for pregnant women attending antenatal care, including those previously confirmed to be infected with HIV
- Provision of ARV prophylaxis for pregnant women living with HIV, to reduce the risk of MTCT
- Provision of ART for eligible pregnant women living with HIV, for their own health and to reduce the risk of MTCT
- Provision of co-trimoxazole prophylaxis for infants born to women living with HIV
- Infant feeding counselling and support at the first infant follow-up visit for mothers living with HIV
- Referral and enrolment of women living with HIV into comprehensive CT&S
- Virological HIV testing within two months of birth for infants born to women living with HIV

## Annex 6.3

**Medical eligibility for contraceptive methods in HIV infection medical eligibility for contraceptive methods for clients with HIV and AIDS**

Contraceptive Method	Condition		ARV therapy		
	HIV-Infected	AIDS	NRTIs	NNRTIs	Ritonavir
DMPA	1	1	1	1	1
NET-EN	1	1	1	2	2
Implants	1	1	1	2	2
Oral Contraceptives	1	1	1	2	3
IUCD	Starting	3*	2/3*	2/3*	2/3*
	Ongoing	2	2	2	2
Condoms	No restrictions: use with hormonal contraception is encouraged to prevent HIV/STI transmission				
ECPs	No restrictions				
Sterilization	No reasons to delay: delay in cases of acute HIV infection				
FAB methods	Can use if menstrual cycle is regular: Encourage continued use of condoms outside the fertile window to prevent STI/HIV transmission.				
LAM	Advise on the risk of transmission: exclusive breastfeeding reduces risk compared to mixed feeding.				
Spermicides and diaphragm	Use is not recommended, may increase risk of HIV transmission/super infection.				
<b>Definitions</b>					
Category 1: No restrictions on Use					
Category 2: Benefits generally outweigh the risks					
Category 3: Risks generally outweigh the benefits: seek specialist advice before using					

\* Category 2 if client with AIDS is clinically well on ARV therapy; otherwise category 3.

### Summary of recommendations for contraceptive use for women taking antiretroviral therapies

If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method										
CONDITION	CATEGORY							CLARIFICATIONS		
	COC	P/R	CIC	POP	DMPA	NET-EN	LNG /	LNG-IUD		
I = initiation, C = continuation										
<b>ANTIRETROVIRAL DRUGS</b>										
<b>NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)</b>										
ABACAVIR (ABC)	1	1	1	1	1	1	1	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>c</sup> There is no known interaction between antiretroviral therapy and IUD use. However, severe or advanced HIV clinical disease (WHO stage 3 or 4) as a condition is classified as Category 3 for insertion and Category 2 for continuation. Asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) is classified as Category 2 for both insertion and continuation.
TENOFOVIR (TDF)	1	1	1	1	1	1	1	2/3 <sup>c</sup>	2 <sup>c</sup>	
ZIDOVUDINE (AZT)	1	1	1	1	1	1	1	2/3 <sup>c</sup>	2 <sup>c</sup>	
LAMIVUDINE (3TC)	1	1	1	1	1	1	1	2/3 <sup>c</sup>	2 <sup>c</sup>	
<b>NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS</b>										
EFAVIRENZ (EFV)	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>c</sup> There is no known interaction between antiretroviral therapy and IUD use. However, severe or advanced HIV clinical disease (WHO Stage 3 or 4) as a condition is classified as Category 3 for insertion and Category 2

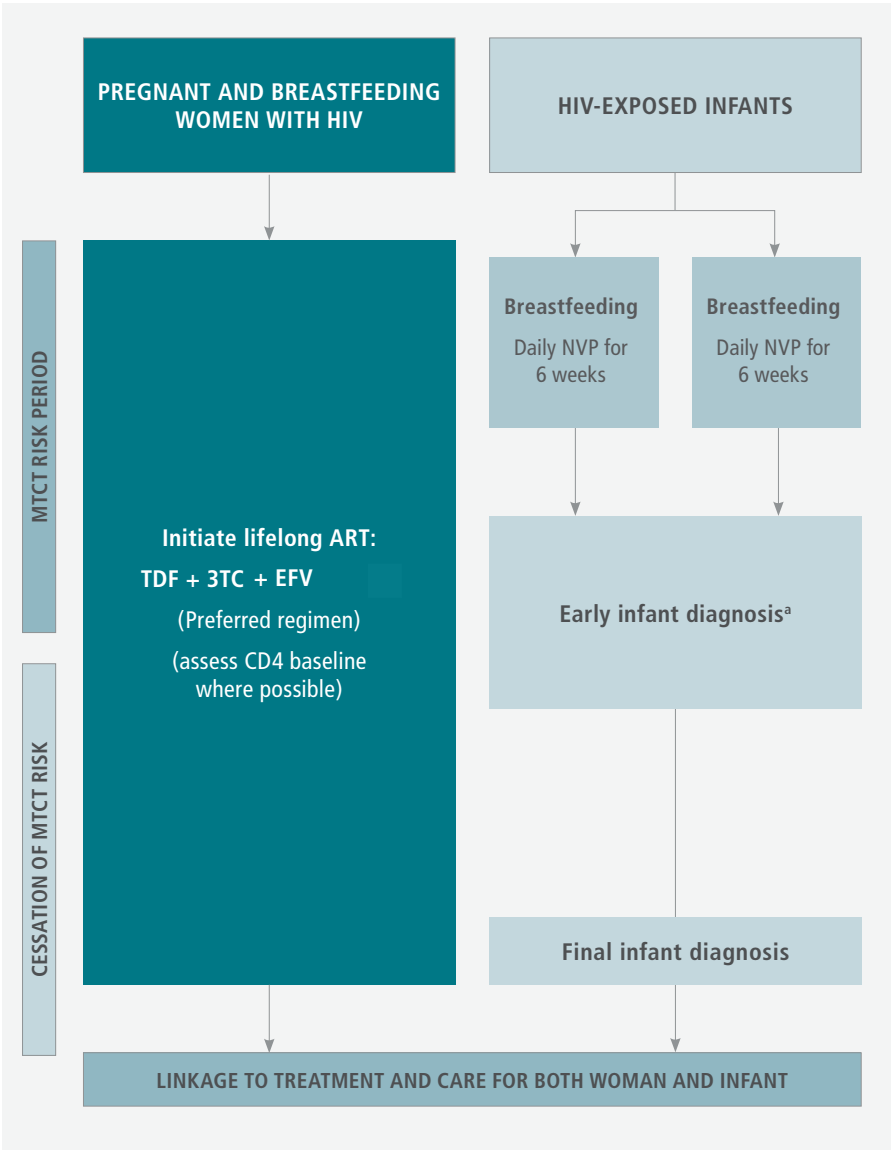
NEVIRAPINE (NVP)	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1 <sup>l</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>f</sup> Antiretroviral drugs have the potential to either decrease or increase the levels of steroid hormones in women using hormonal contraceptives. Pharmacokinetic data suggest potential drug interactions between some antiretroviral drugs (particularly some NNRITIs and ritonavir-boosted protease inhibitors) and some hormonal contraceptives. These interactions may reduce the effectiveness of the hormonal contraceptive.
<b>PROTEASE INHIBITORS (PIs)</b>										
RITONAVIR-BOOSTED ATAZANAVIR (ATV/r)	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1 <sup>l</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>f</sup> There is no known interaction between antiretroviral therapy and IUD use. However, severe or advanced HIV clinical disease (WHO stage 3 or 4) as a condition is classified as Category 3 for insertion and Category 2 for continuation. Asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) is classified as Category 2 for both insertion and continuation.
RITONAVIR-BOOSTED LOPINAVIR	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1 <sup>l</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>d</sup> Antiretroviral drugs have the potential to either decrease or increase the levels of steroid hormones in women using hormonal contraceptives. Pharmacokinetic data suggest potential drug interactions between some antiretroviral drugs (particularly some NNRITIs and ritonavir-boosted protease inhibitors) and some hormonal contraceptives. These interactions may reduce the effectiveness of the hormonal contraceptive.
RITONAVIR-BOOSTED DARUNAVIR (DRV/r)	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1 <sup>l</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	
RITONAVIR (RTV)	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2 <sup>d</sup>	1 <sup>l</sup>	2 <sup>d</sup>	2 <sup>d</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	
<b>INTEGRASE INHIBITORS</b>										
RALTEGRAVIR (RAL)	1 <sup>l</sup>	1 <sup>l</sup>	1 <sup>l</sup>	1 <sup>l</sup>	1 <sup>l</sup>	1 <sup>l</sup>	1 <sup>l</sup>	2/3 <sup>c</sup>	2 <sup>c</sup>	<sup>f</sup> There is no known interaction between antiretroviral therapy and IUD use. However, severe or advanced HIV clinical disease (WHO stage 3 or 4) as a condition is classified as Category 3 for insertion and Category 2 for continuation. Asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) is classified as Category 2 for both insertion and continuation.

CIC: combined injectable contraceptives; COC: combined oral contraceptives; DMPA: depot medroxyprogesterone acetate; IUD: intrauterine device; LNG/ETG: levonorgestrel and etonogestrel implants; LNG-IUD: levonorgestrel-releasing IUD (20 µg/24 hours); MEC: Medical eligibility criteria for contraceptive use (WHO publication); NET-EN: norethisterone enantate; P: combined contraceptive patch; POP: progestogen-only pills; R: combined contraceptive vaginal ring; STI: sexually transmitted infection.

## Annex 6.4

### Algorithms for pregnant and breastfeeding women

Lifelong ART for all pregnant and breastfeeding women with HIV (Option B+)





## Annex 6.5

### Readiness assessment checklist: moving towards ART for pregnant and breastfeeding women

This guideline recommends that all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment. It is useful to refer to this readiness assessment checklist, which addresses a range of issues from national policy to facility readiness.

Recommended timing key:



Before implementation



Early in implementation



During implementation

<b>POLITICAL COMMITMENT &amp; POLICY ENDORSEMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Full-time MoH staff responsible for PMTCT (national & subnational)			
Functional technical working group inclusive of stakeholders from MNCH, PMTCT, and HIV treatment, including health care workers and people living with HIV			
<b>FINANCIAL CONSIDERATIONS</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Costing of current PMTCT strategy			
Costing of ART for all pregnant and breastfeeding women,			
Conduct resource gap analysis			
Increased programme funding needs reflected in budget			
Demonstration of national financial commitment			
<b>SERVICE DELIVERY MODEL</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Defining minimum package of services to provide ART to all pregnant and breastfeeding women			
Assessment of system capacity (infrastructure, human resources, and commodities) to decentralize ART to MNCH settings, including absorbing women with HIV and their families			

<b>SERVICE DELIVERY MODEL</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Timing and location of transition between PMTCT and long-term treatment services has been determined			
Systematic identification of ART clients who become pregnant and linkage to MNCH			
Testing and treating partners and family members within MNCH			
Referral of stable ART clients at current ART facilities to new decentralized ART sites			
<b>HUMAN RESOURCE CAPACITY</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
National endorsement of task shifting/sharing for ART maintenance			
Assessment of human resource capacity (nurse, midwife, pharmacy, lab) to support ART scale-up			
Core competencies in HIV management for each health worker cadre			
Training strategy for ART provision to support rapid scale-up			
Updating of national in-service and pre-service curricula			
Strategy for retention, retraining, and continuing professional development of health workers, especially those providing in PMTCT/ART			
<b>ART REGIMEN CHOICE</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Simplification and harmonization of PMTCT and adult treatment regimens			
Plan for alternate regimen for pregnant women not tolerant of 1st-line ART			
Optimization of 1st-line regimen for infants			
Establishment of pharmacovigilance system, where appropriate			
<b>SUPPLY CHAIN MANAGEMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Supply chain gap assessment including quantification, distribution and stock management			
18 month forecast, quantification, and supply plan developed			
Stock management of ART in MNCH settings (training, capacity, and security)			
<b>SUPPLY CHAIN MANAGEMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
If modifying 1st line regimen, plan to for using ARVs already ordered			
Revised supply chain management system (consumption, forecasting, and distribution)			

<b>MONITORING, EVALUATION, AND DATA USE</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Antenatal care (ANC) and PMTCT register allows for documentation of initiation versus those already on ART			
ART register allows for documentation of pregnancy and breastfeeding status			
Tools and registers in MNCH allow for cohort monitoring of maternal ART retention and exposed infant retention in care			
Pregnant and breastfeeding women initiated on ART in MNCH settings are included in site and national level ART M&E systems			
System to track and measure linkages and transition between MNCH and long-term HIV care & treatment for mother and infant (for example, a mother-baby longitudinal registry, unique identifier)			
Program evaluation designed to detect early successes and challenges, and to assess longer term maternal and infant outcomes, including mother-to-child transmission			
Routine data quality assurance			
Harmonization of PMTCT and ART M&E systems and data review processes			
Standardized file or card for pregnant and breastfeeding women with HIV and exposed infants			
<b>SITE SUPERVISION AND QUALITY MANAGEMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Routine site supervision and clinical mentoring for quality of care			
Continuous quality improvement process for the PMTCT program			
<b>HIV TESTING AND COUNSELLING IN PMTCT SETTINGS</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Quality assurance measures for rapid HIV testing in all PMTCT sites			
Policy decision on treatment of discordant couples			
Couples HTC and follow-up of discordant couples incorporated into PMTCT			
Strategy to link or register male partners with HIV in ART program			
<b>COUNSELLING ON ART INITIATION AND ADHERENCE</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Specialized messaging and support services for pregnant and Breastfeeding women initiating ART			
Structures to expedite preparation for ART initiation			
Alternative protocols developed for women not in need ART for their own health who decline treatment for life			
<b>LABORATORY AND CLINICAL MONITORING</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Treatment monitoring capability for toxicity			
Availability of baseline CD4 (point of care or reliable sample transport)			
Algorithm for CD4 and/or viral load monitoring			

<b>INFANT DIAGNOSIS AND PEDIATRIC TREATMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
EID capacity paralleling PMTCT programme scale-up			
Strengthening of "EID cascade" – early diagnosis, rapid results return, active case finding of infants infected with HIV and initiation of treatment			
Retention of HIV exposed infants through end of breastfeeding including assuring final diagnosis			
Expand access to pediatric treatment			
<b>RETENTION IN CARE AND TREATMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
System to ensure that ALL pregnant and postpartum women with HIV are enrolled in ongoing HIV care and/or treatment			
Models of service delivery that consider harmonized mother-infant pair follow-up			
Facility- and community-based services to support adherence and trace defaulters			
Innovative solutions to improving the accessibility of ART			
<b>FAMILY PLANNING</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Assessment of family planning service availability and commodities			
Access to and uptake of voluntary family planning services in settings providing ART			
<b>COMMUNITY INVOLVEMENT</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Women living with HIV are engaged in the planning, implementation and monitoring at national, subnational and community levels			
Community-based activities and services to support PMTCT scale-up and retention			
Community structures to support orphans and vulnerable children			
<b>ROLL-OUT STRATEGY</b>	<b>Completed</b>	<b>In Process</b>	<b>Not yet started</b>
Roll-out strategy has been planned			
Real-time evaluation of implementation in order to inform further scale-up			

Acronyms used: MoH (Ministry of Health); MNCH (maternal, newborn, and child health); M&E (monitoring and evaluation); HTC (HIV testing and counselling); and EID (early infant diagnosis).

## Annex 7.1

### Factors related to health system and people receiving ART influencing retention and adherence with potential interventions (WHO, 2013)

A. Factors related to the health system	
Factors	Recommended interventions
High direct and indirect costs of receiving care	<p>Decentralize ART</p> <p>Provide ART and related diagnostics and services free of charge at the point of care Schedule facility visits by the clients.</p> <p>Reduce waiting time at the facility:</p> <ul style="list-style-type: none"> <li>• Provide appointments</li> <li>• Separate clinical consultation or first visits from appointments for picking up ARV and other medicines</li> <li>• Link, integrate and coordinate care</li> <li>• Family-focused care (organizing services around the needs of the family) when appropriate</li> <li>• Optimize pharmaceutical supply management systems</li> <li>• Use fixed-dose combinations to simplify forecasting and supply management systems to forecast, procure and deliver ARV drugs.</li> </ul>
Stock-outs of ARV drugs	<ul style="list-style-type: none"> <li>• Optimize pharmaceutical supply management systems</li> <li>• Use fixed-dose combinations to simplify forecasting and supply management systems to forecast, procure and deliver ARV drugs.</li> </ul>
System for monitoring retention in care	Implement systems for patient monitoring across the continuum of care, including cohort analysis and patient tracking systems
System for transferring people across different points of care	<ul style="list-style-type: none"> <li>• Interlink patient monitoring systems across services for HIV, TB, maternal and child health and PMTCT;</li> <li>• System for transitioning from pediatric to adolescent and adult services and from maternal and child health and TB services to chronic HIV care</li> <li>• Set up referral directory for transfer of patient from one point of care to another</li> </ul>
Pill burden and complex ARV drug regimens	Use fixed-dose combinations to reduce the pill burden and simplify the regimens

<b>A. Factors related to the health system</b>	
<b>Factors</b>	<b>Recommended interventions</b>
Poor relationship between patient and care provider	<ul style="list-style-type: none"> <li>• Train health workers on how to: reduce stigma; improve treatment preparedness, adherence and retention; provide adherence support and care for key populations</li> <li>• provide simplified approaches for educating patients and their families</li> </ul>
Educating people in HIV care	<ul style="list-style-type: none"> <li>• Task shifting and sharing task among clinic team members</li> <li>• Using PLHIV as patient experts and peer supporters</li> <li>• Use team approach to care (Engage all level health care providers for educating people in HIV care)</li> </ul>
Adverse drug effects	<ul style="list-style-type: none"> <li>• Provide knowledge to PLHIV on possible adverse effects of ARV</li> <li>• Educate how and when to self-manage adverse effects and when to return to the clinic</li> </ul>
<b>B. Factors related to the people receiving HIV care</b>	
<b>Factors</b>	<b>Recommended interventions</b>
Forgetfulness, life stress, stigma and discrimination	<ul style="list-style-type: none"> <li>• Send text messages to keep patients engaged</li> <li>• Provide peer and family support</li> <li>• Link to community support group</li> <li>• Use CHBC workers, FCHV for patient education and community activities</li> </ul>
Comorbidity, substance and alcohol use disorders and mental health disorders	<ul style="list-style-type: none"> <li>• Provide adequate referral to manage HIV with mental health disorders, alcohol and other substance use disorders</li> <li>• Link with community and social support</li> <li>• Provide referral to OST centers</li> <li>• Mobilize CHBC workers for identification and referral</li> <li>• Conduct TB screening and refer for further investigations</li> </ul>
Patient knowledge and beliefs related to HIV infection, its course and treatment	<ul style="list-style-type: none"> <li>• Provide education and counseling to patients and their families</li> <li>• Conduct activities related to treatment literacy in the community</li> <li>• Engaged the community engagement through DACC and other informal networks like VACC</li> <li>• Engaged PLHIV networks, CHBC workers and positive prevention activists</li> </ul>

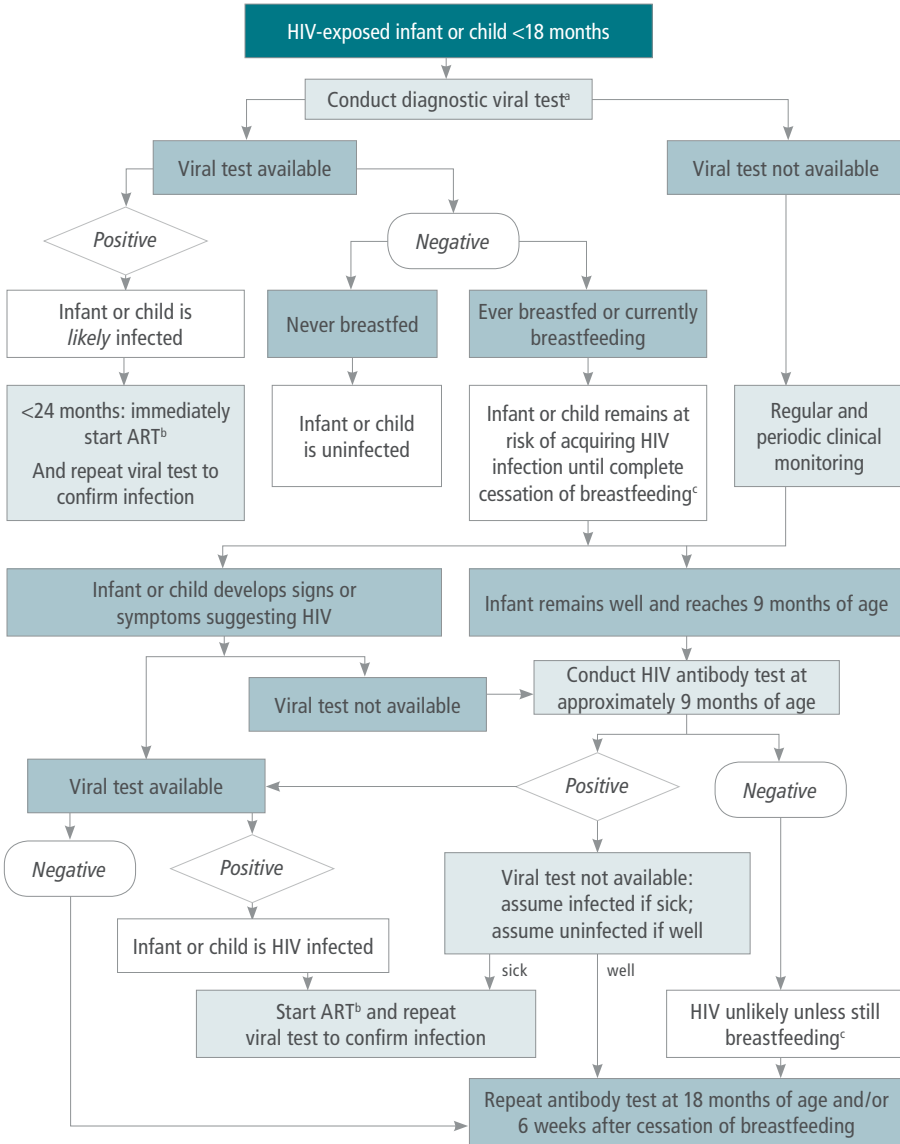
## Annex 8.1

### Laboratory Network at different level of health care delivery system for HIV

Health care level	Laboratory services	Human Resources
National	<ul style="list-style-type: none"> <li>• Enzyme Immuno Assays for diagnosis</li> <li>• Higher Throughput CD profiles</li> <li>• HIV RNA viral load testing</li> <li>• HIV DNA early infant diagnosis</li> <li>• Microbiology, biochemistry and haematology laboratory monitoring</li> </ul>	Microbiologist/ Virologist Senior Medical lab specialist Senior Medical Technologist Medical lab technologist
Regional level	<ul style="list-style-type: none"> <li>• Enzyme Immuno Assays for diagnosis</li> <li>• Medium throughput CD4 profile</li> <li>• Microbiology, biochemistry and haematology laboratory monitoring</li> </ul>	Microbiologist/Virologist Senior Medical lab specialist Senior Medical Technologist Medical lab technologist
Central level hospital	<ul style="list-style-type: none"> <li>• Enzyme Immuno Assays for diagnosis</li> <li>• Medium throughput CD4 profile</li> <li>• Microbiology, biochemistry and haematology laboratory monitoring</li> </ul>	Microbiologist/Virologist Senior Medical lab specialist Senior Medical Technologist Medical lab technologist
Zonal level	<ul style="list-style-type: none"> <li>• Enzyme Immuno Assays for diagnosis</li> <li>• Medium throughput CD4 profile</li> <li>• Microbiology, biochemistry and haematology laboratory monitoring</li> <li>• DBS protein Saver card for External quality assurance</li> </ul>	Senior Medical Technologist Medical lab technologist Senior Medical lab technician Medical lab technician
District level	<ul style="list-style-type: none"> <li>• Enzyme Immuno Assays for diagnosis</li> <li>• Serial Rapid HIV testing for diagnosis</li> <li>• Low throughput (portable) CD4</li> <li>• DBS protein Saver card for External quality assurance</li> </ul>	Medical lab technologist Medical lab technician Medical lab Assistant

## Annex 8.2

## Algorithm for early infant diagnosis



<sup>a</sup> For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks).

<sup>b</sup> Start ART, if indicated, without delay. At the same time, retest to confirm infection.

<sup>c</sup> The risk of HIV transmission remains as long as breastfeeding continues.



# 10

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