# NATIONAL GUIDELINES ON THE MANAGEMENT OF HIV/AIDS

**Department of Public Health**
**Ministry of Health**
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# FOREWORD

This publication of the 3rd National Guidelines for Management of HIV/AIDS marks another milestone in the nation's response to HIV/AIDS. With the implementation of these guidelines, Bhutan will be increasing the baseline CD4+T lymphocyte count for initiation of Antiretroviral therapy (ART) from 350 cells/$mm^3$ or below to 500 cells/$mm^3$ to reap the benefits of early treatment initiations. Earlier treatment brings the dual advantage of keeping people healthier longer and reducing the risk of virus transmission to others. This guideline now recommends that pregnant women and children under the age of five years start treatment immediately after diagnosis. Treatment will also be offered to HIV positive person, in a sero-discordant relationship irrespective of the CD4 count to reduce the risk of transmission. With the right therapy, started at the right time, people with HIV can now expect to live long and healthy lives. They are also able to protect their sexual partners and infants as the risk of transmitting the virus is greatly reduced.

The guidelines were prepared keeping in view our country's context. The content of this document are a synthesis of the WHO recommendations and is formulated to suit the needs of our country. With the increase in the CD4 threshold for treatment initiation, more people with HIV will be put on treatment and will require appropriate management. This document provides health care professionals with the knowledge base that will assist in providing the appropriate treatment and management of HIV/AIDS.

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# List of Acronyms

| | |
|---|---|
| AIDS | Acquired Immunodeficiency Syndrome |
| ANC | Antenatal Clinic |
| ART | Antiretroviral Therapy |
| BHU | Basic Health Unit |
| CDC | Centre for Disease Control |
| CMV | Cytomegalovirus |
| CNS | Central Nervous System |
| CSF | Cerebro Spinal Fluid |
| CST | Care, Support and Treatment |
| DOPH | Department of Public Health |
| DOTS | Directly Observed Treatment Short Course |
| EID | Early Infant Diagnosis |
| ELISA | Enzyme Linked Immunoassay |
| FNAC | Fine Needle Aspiration Culture |
| GFATM | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| GI | Gastro Intestine |
| HBV | Hepatitis B Virus |
| HCT | HIV Counselling and Testing |
| HCV | Hepatitis C Virus |
| HCW | Health Care Worker |
| HISC | Health Information Service Centre |
| HIV | Human Immunodeficiency Virus |
| HSV | Herpes simplex virus |
| IDU | Injecting Drug Users |
| IRS | Immune Reconstitution Syndrome |
| JDWNRH | JigmeDorjiWangchuck National Referral Hospital |
| KS | Kaposi Sarcoma |
| LDH | Lactate Dehydrogenase |
| LIP | Lymphoid Interstitial Pneumonia |
| MAC | *Mycobacterium aium* complex |
| MCH | Maternal Child Health |
| MDG | Millennium Development Goal |
| MoH | Ministry of Health |
| MRI | Magnetic Resonance Image |
| MSM | Men who have Sex with Men |
| MSTF | Multi Sectoral Task Force |
| MTCT | Mother To Child Transmission |
| NACP | National STI, HIV and AIDS Prevention &Control Programme |
| NGO | Non-Government Organization |
| NHAC | National HIV/AIDS Commission |
| NNRTI | Non Nucleoside Reverse Transcriptase Inhabitors |
| NRTI | Nucleoside Reverse Transcriptase Inhabitors |
| NSP | National Strategic Plan |
| OCP | Oral Contraceptive Pill |
| OHL | Oral Hairy Leukoplakia |
| OI | Opportunistic Infection |
| PCP | Pneumocystis carinii pneumonia |
| PCR | Polymerase Chain Reaction |
| PEP | Post Exposure Prophylaxis |
| PIs | Protease Inhabitors |
| PMTCT | Prevention of Mother-To-Child Transmission |
| RNA | Ribonucleic Acid |
| SOPs | Standard Operating Procedures |
| STI | Sexually Transmitted Infection |

| | |
|---|---|
| TB | Tuberculosis |
| TPHA | Treponema pallidum haemagglutination |
| VCT | Voluntary Counselling and Testing |
| VDRL | Venereal Disease Research Laboratory |
| RPR | Rapid Plama Regain |
| WHO | World Health Organization |
| DNA | Deoxyribonucleic Acid |
| EBV | Epstein-Barr Virus |

## Chapter I

## HIV TESTING AND COUNSELLING

# *Introduction*

People access HIV treatment, care and prevention through the gateway of HIV testing and counseling. It is estimated that globally about half of the people living with HIV do not know their HIV status. The people who do know their status often test late, this could mean that many people start treatment when they are already significantly immune compromised, resulting in poor health outcomes and ongoing HIV transmission. The overall HIV testing and counseling goal for the National HIV/AIDS Control Programme is to intensify the HIV diagnostic facilities to detect as many people as possible at the earlier stage of the infection and subsequently make linkage to the continuum of care.

Rapid HIV antibody testing facilities are available in all the district hospitals including some BHUs and the free standing Health Information and Service Centers (HISCs) in four major towns. ELISA testing facilities are currently available only in the national and regional referral hospitals including some district hospitals in strategic locations.

All forms of HIV testing and counseling will be voluntary. However, the provider initiated testing and counseling (PITC) are provided to the individual clients based on their existing health conditions such as for patients with tuberculosis (TB), sexually transmitted infections (STI) and ante-natal clinic (ANC) attendees. Similarly for the general population the HIV testing is offered adhering to the five C's as follows:

- *Consent* - HIV testing is initiated only after obtaining an informed consent.
- *Confidentiality*- HIV counseling and testing services are kept confidential
- *Counseling*- HIV counseling and testing services must be accompanied by pre-test information and post-test counseling.
- *Correct test*- HIV counseling and testing providers should strive to provide high-quality and quality assured testing services
- *Connection to care & treatment*- Connections to prevention, care and treatment services include the provision of referral system for appropriate follow-up, including treatment, care and support services.

**Pre-Test Counselling:**

- Make an appointment for the test result
- Basic information about the potential benefits of testing
- Pre-test counseling performed after obtaining informed consent
- Basic information about HIV and its transmission
- Risk assessment and risk reduction plan
- Basic information about the test result
- Condom use including demonstration

**Post Test Counselling**

- Consider possible exposure in window period – including any risks, which may have occurred since pre-test counselling
- Reinforce information on transmission, safer sex and other practices
- Explanation of their result
- Emphasize the client's requirement of subsequent testing with appointment if necessary
- Partner notification if positive
- Providing continuum of counselling and psychosocial support

- Referral if required

**HIV testing and counselling services provided in the health facilities**

Trained counselors are available in all hospitals including the Health Information Service Centers (HISC) to provide voluntary counseling and testing services. They also carry out patient monitoring and follow-up for continuum of care as well as recording and reporting of the HIV data including quarterly VCT reporting.

HIV testing facilities are available in all the health facilities including HISCs in four major towns of Thimphu, Phuentsholing, Gelephu and SamdrupJongkhar. The different level of HIV testing facilities are as follows:

**Table 1**

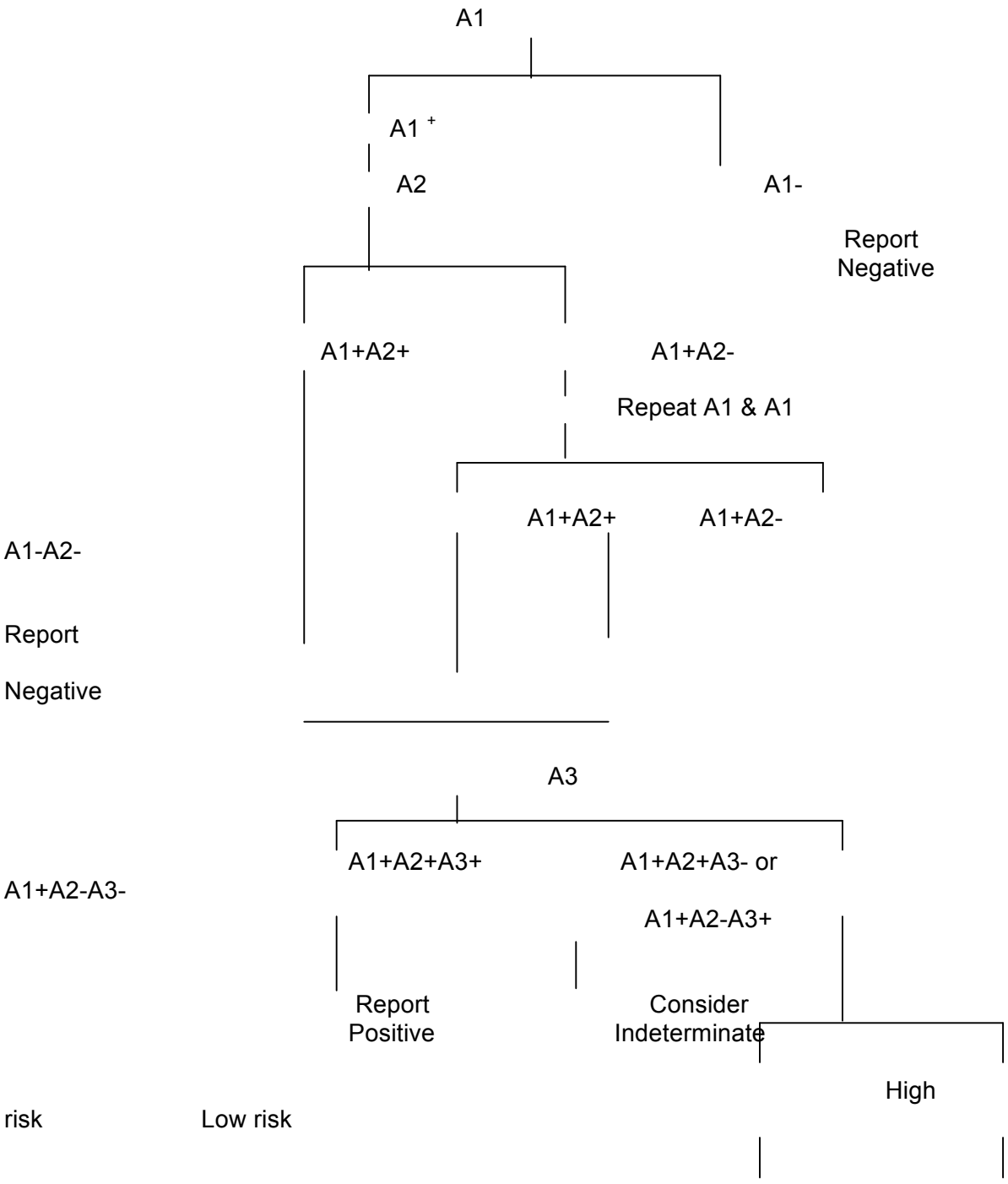
| Health Facility Level | HIV Testing Services | Human Resource | Remarks |
|---|---|---|---|
| National Referral Hospital | • Rapid diagnostic test<br>• Enzyme-linked Immunoassay (ELISA)<br>• CD4 count<br>• PCR-DNA for viral load estimation*<br>• PCR-RNA test for Early Infant diagnosis (EID)*<br>• | Laboratory Specialists, Laboratory Technologists, Laboratory Technicians | HIV confirmation is done at the National Reference Laboratory (PHL) |
| Regional Referral Hospital | • Rapid diagnostic test<br>• Enzyme-linked Immunoassay (ELISA)<br>• CD4 count | Laboratory Technologists, Laboratory Technicians | |
| District/General Hospital | • Rapid diagnostic test | Laboratory Technologists, Laboratory Technicians | ELISA and CD4 count testing available at hospitals located in strategic areas. |
| Basic Health Unit I | • Rapid diagnostic test | Laboratory Technicians | |
| Basic Health Unit II | • Rapid diagnostic test | Trained Health Assistants, Basic Health Workers | |
| Health Information and Service Center (HISC) | • Rapid diagnostic test | Trained counselor (Health Assistant/Basic Health Worker) | |

***EID and viral load testing are currently not available but there are plans to establish the facilities very soon***

**Testing algorithm**

HIV testing and confirmation procedures will be as per the national protocol. All testing centers will use the standard operating procedures (SOP) for initial screening (A1) at their facilities using the rapid test kits or ELISA wherever feasible. **The test will be repeated for all the initial reactive (IR) tests.** If the repeat test is reactive, the samples will be sent to the Public Health Laboratory for a confirmatory test. Tests A2 and A3 are carried out at the PHL.

**HIV Testing and Confirmation Algorithm**




**Test Stage/Kit**

a. A1: Rapid/ELISA at primary testing center
b. A2: ELISA (HIV 1/2 Ab/Ag combo) at confirmatory test center
c. A3: Gelatin particle agglutination test (GPA) at confirmatory test center

**Summary of testing approaches for infants**

Any infant born to infected mothers should be tested for HIV as in the following table:

**Table 2**

| Category | Test Provided | Testing Period/Frequency | Service Availability | Action |
|---|---|---|---|---|
| Healthy, HIV exposed baby | Virological testing (EID) | • At 6 wks after birth<br>• (Refer EID algorithm under Paediatric section) | JDWNRH | Start ART immediately if positive but confirm with a second sample |
| Healthy, HIV exposed infant | Serological test (Rapid/ELISA) | 12 months and above | All health facilities | Repeat at 18 months if positive |
| Healthy, HIV exposed baby | Serological test (Rapid/ELISA) | 18 months | All health facilities | For confirmation of HIV status |

**Viral load testing and EID**

It is strongly recommended that all HIV-exposed infants, and all infants with unknown or uncertain HIV status, should have an HIV virological test performed at 4–6 weeks of age or at the earliest opportunity thereafter. All infants with an initial positive virological test result should be started on ART without delay and, at the same time, a second specimen should be collected to confirm the initial positive virological test result.

To reduce the cost of virological testing, a serological test should be done for HIV-exposed infants and children age 9 to 18 months. Only those with reactive serological assays should have a virological test to confirm HIV infection and determine who needs ART.

| Target population | Time of EID/VLT & Frequency |
|---|---|
| 1. Exposed Children | Antibody Screening at 18 months & EID at 4-6 weeks after delivery |
| 2. Pregnant Women | Baseline, 6 months and yearly thereafter |
| 3. WHO clinical stage 1 & 2 and CD4+ count between >350-<500 $mm^3$ | Baseline, 6 months and yearly thereafter |
| 4. WHO clinical stage 3 & 4 | Baseline, 6months and yearly thereafter |
| 5. VL count >1000 copies/$mm^3$ but CD4 count within normal range without OIs. | Advise Drug Resistance Testing (DRT) |
| 6. Suspected Drug Resistance (normal CD4 count & signs of OIs) | Baseline, 6months and yearly |

# Chapter II

# ANTI RETROVIRAL THERAPY (ART)

## Introduction

The primary aim of ART is the prevention of mortality and morbidity associated with chronic HIV infection. This goal is best accomplished by using effective ART to maximally inhibit HIV replication so that plasma HIV RNA levels (viral load) remain below that detectable by commercially available assays. Durable viral suppression improves immune function and quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. The effectiveness and tolerability of ART has improved significantly over the last 15 years. A further aim of treatment is the reduction in sexual transmission of HIV and for some patients may be the primary aim. The use of ART to prevent mother-to-child transmission is universally accepted and is addressed in this guideline under the PMTCT.

## Goals of Therapy

| | | |
|---|---|---|
| a | ***Clinical Goals*** | Prolongation of life and improvement in the quality of life |
| b | ***Virological Goals*** | Reduction of plasma viral RNA to undetectable levels (<50 copies per mL) especially in the first few months of therapy to limit the risk of treatment failure. |
| c | ***Immunological Goals*** | Restore and preserve immunologic function which is assessed by CD4 T cell count. The 'normal value is 800-1050 cells/$mm^3$ |
| d | ***Therapeutic Goals*** | Rationalize the sequencing of drugs to achieve clinical, virological and immunological goals while maintaining treatment options, limiting drug toxicity and facilitating adherence. |
| e | ***Epidemiologic Goals*** | Reduce transmission of HIV. |

The ultimate aim of ART is to achieve and maintain undetectable levels of plasma HIV RNA and CD4 counts in the normal range.

## Definition of ART

*It is a combination treatment with three or more anti-retroviral agents to suppress viral replication in order to prolong and improve the quality of life*.

## Prerequisites for Starting ART

The following services are essential for starting ART:

a. Access to HIV voluntary counselling and testing and follow up counselling services. This also includes psychological support and adherence to treatment.
b. A well-equipped medical centre for diagnosis and management of opportunistic infections.
c. Reliable laboratory services capable of carrying out investigations such as CBC, biochemistries, CD4 counts, culture facilities and viral load estimations.
d. Drugs: reliable, affordable and sustained supply of anti-retrovirals and drugs for prophylaxis and treatment of opportunistic infections (OIs).

## Clinical evaluation of the patient

Prior to initiating the treatment:

- Complete history and physical examination
- Detailed clinical examination of the patient should aim to assess the clinical staging of the HIV infection
- Conduct routine laboratory investigations: CD4+ T lymphocyte count
- Identify past and current HIV related illnesses that would require treatment
- Identify coexisting medical conditions which may influence the choice of therapy

For WHO Clinical Staging – Please refer to Annex 6 Page -

**History**

Medical history should include the following questions:

- When and where the diagnosis of HIV was made
- Source and route of infection (e.g. IDU, homosexual, heterosexual, etc.)
- Current and past signs and symptoms of HIV
- Past medical treatment of established diseases
- Treatment and/or contact with tuberculosis
- History of Sexually Transmitted Infections (STIs),
- Previous ART received, if any
- Pregnancy and Oral Contraceptive Pills (OCP) use
- Sexual history and social habits

**Physical Examinations**

- Weight of the patient
- Skin: look for herpes, Kaposi's Sarcoma (KS), pruritic papular eruptions, dermatitis, etc.
- Lymphadenopathy
- Oropharyngeal mucosa: look for oral candidiasis, herpes simplex, oral hairy leukoplakia (OHL), KS
- Cardio vascular system and respiratory system
- Abdomen: look for hepatosplenomegaly/ascites/any other mass
- Central nervous system: assess the mental status and look for any localizing signs
- Eyes/fundus examination
- Genital/gynaecological examination

## Table 1.Laboratory Examinations

| Important | Supplementary |
|---|---|
| • *HIV serology (ELISA) and HIV RNA (when available)*<br>• *CD4+T lymphocyte count and CD4 percentage*<br>• *Complete blood count*<br>• *Blood chemistry: e.g. RFT/Electrolytes, LFT, Blood sugar and lipid profil.*<br>• *Chest X-ray*<br>• *Hepatitis B and C*<br>• *STI profile* | • *Urine: routine and microscopy*<br>• *Ultrasonography*<br>• *PAP smear* |

**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.

*Table:* Standardized eligibility for starting ART

| When to start ART in People Living with HIV | |
|---|---|
| **Adults and Adolescents** | • As a priority ART should be initiated in all individuals with severe/advanced HIV disease (WHO Clinical Stage 3 or 4) or CD count ≤ 350 cells/mm$^3$.<br><br>• **Initiate ART if CD4 cell count ≤ 500 cells/mm$^3$**<br>• *ART should be initiated in all individuals with HIV regardless of WHO Clinical Stage or CD4 cell count in the following situations:*<br><br>- Individuals with HIV and active TB disease<br>- Individuals coinfected with HIV and HBV with evidence of severe chronic liver disease<br>- HIV positives in a serodiscordant relationship<br>- Pregnancy |

**What ART to start with?**

2 NRTIs remain the integral component of ART with either an NNRTI or Ritonavir boosted Lopinavir. This guideline now recommends Tenofovir and Lamivudine as the NRTI backbone of the first line therapy. The two NNRTI'S available are Nevirapine and Efavirenz. Efavirenz is safe to use in the first trimester of pregnancy.

Tenofovir is well tolerated, it has no interaction with Zidovudine or Stavudien and its use harmonizes the regimen with HIV and HBV co-infection. It also has advantage of once a day dosing.

Table 3:This guideline recommends the use of the following combination of drugs as the first line regimen:

| What ART/ARV regimens to start with | |
|---|---|
| **Population** | **Recommendations** |
| **First line ART regimens for Adults and Adolescents** | • TDF + 3TC + EFV (preferred option)<br><br>• If TDF + 3TC + EFV is contraindicated or not available, one of the following options is recommended:<br><br>• TDF + 3TC + NVP<br>• AZT + 3TC + EFV<br>• AZT + 3TC + NVP |

**Table 4:Drugs,form, usual adult dose, food effects and toxicities of the ARVs used in the guideline**

| Drug Name | Form | Usual Adult Dose | Food effects | Toxicity |
|---|---|---|---|---|
| ***Nucleoside Reverse Transcriptase Inhibitors*** | | | | |
| Zidovudine (AZT) | 300 mg tab<br>10mg/mL syrup | 300 mg bid | No effect | *Anemia, neutropenia,* headache, asthenia, GI intolerance, lacticacidosis |
| Lamivudine (3TC) | 150mg<br>10mg/mL syrup | 150 mg bid or 300 mg od | No effect | Minimal. |
| Tenofovir (TDF) | 300 mg tab | 300 mg qd | No effect | Nephrotoxicity |
| TDF + 3TC (FDC) | 300mg + 300mg | One daily | No effect | |
| ***Non-Nucleoside Reverse Transcriptase Inhibitors*** | | | | |
| **Nevirapine (NVP)** | 200 mg tabs<br>10mg/mL syrup | 200 mg od x 14 d, then 200 mg bid | No effect | *Rash*, increased ALT/AST, *hepatic necrosis*, esp. in females with a baseline CD4 >250 cells/mm³ |
| **Efavirenz (EFV)** | 600 mg tabs | 600 mg hs | Take on an empty stomachduring the first2-3 wks | *Rash, insomnia, confusion, loss of concentration, abnormal dreams, dizziness,↑cholesterol, ↑triglycerides* |
| ***Protease Inhibitors*** | | | | |
| **Lopinavir/Ritonavir (LPV/r) boosted PI** | LPV 200 mg + RTV 50 mgtab | 400 mg LPV + 100 mg RTV (2 tabs) bid or 800 mg LPV +200 mg RTV (4 tabs) qd | No effect | *GI Intolerance*, (esp. diarrhea), increase in ALT/AST, asthenia, Fat redistribution, hypertriglyceridemia, hyperglycemia |

**What ART regimen to switch to (second - line ART)**

- Second - line ART for adults should consists of two nucleoside reverse transcriptase inhibitors (NRTIs) + a ritonavir boosted PI:

  The following sequence of second-line NRTI options are recommended:

  - ✓ after failure on a TDF + 3TC -based first line regimen, use AZT + 3TC as the NRTI backbone in second line regimen,
  - ✓ after failure on an AZT + 3TC based first line regimen, use TDF + 3TC as the NRTI backbone in second line regimen
- Boosted PI for second line ART is Lopinavir/Ritonavir (LPV/r).

# Chapter III

# MONITORING ANTI RETROVIRAL THERAPY

Clinical assessment and laboratory tests play a key role in assessing individuals before ART is initiated and then monitoring their treatment response and possible toxicity of ART.

**Clinical Monitoring**

Enquiry should be made about (*the acronym ABCD*):

A - Appetite
B - Body weight
C - Complaints related to ART and OIs
D - Disease progression

Furthermore, at every visit, the patients should be screened for tuberculosis by asking history of:

- ✓ cough,
- ✓ fever,
- ✓ night sweats, and
- ✓ weight loss.

**Laboratory Monitoring**

Routine laboratory monitoring should be done including CBC, LFT, RFT, Blood glucose and Serum lactate to monitor the adverse effects of the drugs, monthly for three months.

**Immunological Monitoring**

CD4 count should be done at the fourth month of starting therapy and then every six months. Immunological failure is indicated by a fall of CD4 counts more than 30% from the initial value or a return to or below pre-therapy baseline.

**Virological Monitoring**

See goals of therapy for HIV infection (if viral load testing facilities are available)

### *Monitoring includes*

- Pre ART laboratory tests, laboratory test at ART initiation and test when receiving ART for follow up
- Identification/diagnosis of clinical, immunological and virological failure.
- Monitoring of ART toxicities and their management

The following table summarizes the monitoring required.

*Table1: Recommended and desirable laboratory tests at HIV diagnosis and monitoring on ART*

| Phase of HIV management | Recommended | Desirable (if feasible) |
|---|---|---|
| **Pre ART** | CD4 cell count (every 6 months) | |
| **ART initiation** | CD4 cell count<br><br>Viral load | Haemoglobin test for AZT<br>Pregnancy test<br>Urine dipstick for glycosuria and estimated glomerular filtration rate (eGFR) and serum creatinine for TDF<br>Alanine aminotransferase for NVP |
| **Receiving ART** | CD4 cell count (4 months after initiation and then every 6 months)*<br><br>HIV viral load (at 6 months after initiating ART and every 12 months thereafter) | Urine dipstick for glycosuria and serum creatinine for TDF |
| **Treatment failure** | HIV viral load<br><br>CD4 cell count | HBV (HBsAg) serology (before switching ART regimen if this testing was not done or if the result was negative at baseline)<br>Drug resistance testing |

**Exepect the CD4 count to rise by 50 within 4 months of initiation of ART and thereafter increases at the rate of 50-100 per year.*

*Table2: WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens*

| Failure | Definition | Comments |
|---|---|---|
| Clinical failure | New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition) after 6 months of effective treatment | The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART.<br>Certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure |
| Immunological failure | CD4 count falls to the baseline (or below) *<br>or<br>Persistent CD4 levels below 100 cells/mm$^3$ | Without concomitant or recent infection to cause a transient decline in the CD4 cell count. |
| Virological failure | Plasma viral load above 1000 copies/mL based on two consecutive viral load measurements after 3 months, with adherence support | An individual must be taking ART for at least 6 months before it can be determined that a regimen has failed |

**CD4 count falls to less than 30% of the baseline.*

**Table3: Monitoring the toxicities associated with the antiretroviral agents available in Bhutan**

| ARV Drug | Major Types of Toxicity | Risk Factors | Suggested Management |
|---|---|---|---|
| AZT | Anaemia, Neutropenia, myopathy, lipodystrophy | Baseline anaemia or Neutropenia CD4count≤200cells/$mm^3$ | If AZT is being used in first-line ART, substitute with TDF |
| | Lactic acidosis or severe hepatomegaly with steatosis | BMI>25(or bodyweight >75kg) Prolonged exposure to nucleoside analogues | |
| EFV | Persistent central nervous system toxicity (such as abnormal dreams, depression or mental confusion) | Depression or other mental disorder(previous or at baseline) Day time 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. | |
| | Convulsions | History of seizure | |
| | Hypersensitivity reaction, Stevens-Johnson syndrome<br><br>Male gynaecomastia | Risk factor unknown | |
| LPV/r | ECG abnormalities | People with pre-existing conduction system disease | If LPV/r is used in the second line ART for adults, use ATV/r or DRV/r. Seek Expert Advice |
| | Hepatotoxicity | Underlying hepatic disease HBV and HCV co infection Concomitant use of hepatotoxic drugs | |
| | Pancreatitis | Advanced HIV disease | |
| | Risk of prematurity, lipoatrophy or metabolic syndrome, dyslipidemia or severe diarrhea | Risk factor unknown | |

*Table4: Toxicity and Management*

| ARV drug | Major Types of Toxicity | Risk Factors | Suggested Management |
|---|---|---|---|
| **NVP** | Hepatoxicity | Underlying hepatic disease<br><br>HBV and HCV co infection<br><br>Concomitant use of hepatotoxic drugs<br><br>CD4 cell >250 cells/mm3 in women<br><br>CD4 > 400 cells/mm3 for men<br><br>First month of therapy (if lead-in dose is not used) | EFV. If the person cannot tolerate either NNRTI, use boosted PIs |
| | Severe skin rash and hypersensitivity reaction (Stevens-Johnson Syndrome) | Risk factors unknown | |
| **TDF** | Tubular renal dysfunction, Fanconi syndrome | Underlying renal disease<br><br>Old age<br><br>BMI < 18.5 (or body weight <50 kg)<br><br>Untreated diabetes mellitus<br><br>Untreated hypertension<br><br>Concomitant use of nephrotoxic drugs or a boosted PI | If TDF is being used in first line ART substitute with AZT<br><br>If TDF is being used in second line ART (after AZT use in first line ART), substitute with ABC or ddI.<br><br>Seek Expert Advice |
| | Decrease in bone mineral density | History of osteomalacia and pathological fracture<br><br>Risk factors for osteoporosis or bone loss | |
| | Lactic acidosis or severe hepatomegaly with steatosis | Prolonged exposure to nucleoside analogues<br><br>Obesity | |
| | Exacerbation of hepatitis B (hepatic flares) | Discontinuation of TDF due to toxicity | Use alternative drug for hepatitis B treatment (such as entecavir) |

## Chapter IV

## Management for people living with HIV/AIDS at various levels of Health facility

All levels of health care delivery systems in Bhutan can contribute to the management and treatment of people living with HIV/AIDS (PLHA). The Basic Health Units, District Hospitals and the Referral Hospitals should work in close coordination in providing comprehensive care and support services.

**HIV care and treatment team**

At the hospitals, to ensure the continued support and care, the HIV care treatment teams should take the lead role. The HIV positive people should be informed about the team and the responsibilities of each member. This helps in building confidence among the people and reduce stigma or minimize discriminatory experiences in the health setting.

The membership of the teams should be left to the local decision to appoint most appropriate staffs. The following are the components of the core team and their respective responsibilities at the hospital level.

**1. Medical Officer (MO)**

***Responsibility****:* The MO will be the overall in charge and delegate responsibilities to his subordinates and identify focal persons in the hospital. Later after the refresher training on HIV care and support, the MO can offer test for HIV. The MO is also responsible for reporting collective data to the District Health Officer (DHO) who in turn will report to the National Program.

**2. Laboratory**

***Responsibility:*** The Laboratory will be responsible for doing all the tests and record keeping and report to DMO.

**3. Pharmacy**

***Responsibility:*** The Pharmacy will be responsible for providing antiretroviral therapy (ART), ARV stock keeping, record keeping and reporting to MO/specialist in charge.

**4. Ward In charge (indoor)**

***Responsibility:*** The Ward In charge will be responsible for care & support to the HIV positive admitted patients, record keeping & reporting to the MO.

**5. Reproductive Health Unit**

***Responsibility***: The RHU will be responsible for Counseling & Testing, record keeping, follow up and reporting to the MO.

**6. Out Patient Department, ACO**

***Responsibility:*** The ACO will be responsible for referring the clients with symptoms/ potential patients to the RHU/DMO. Later after the training on counseling and testing, ACO can offer test and report to DMO.

**The following briefly outlines the scope of care and treatment at each level of health care system.**

**At Basic Health Unit (BHU) :**

a) **Patient suspected with HIV/AIDS:** If facilities are available for HIV testing, perform a rapid test after proper counselling. If found reactive, arrange for transfer of sample or refer the patient to the nearest hospital where arrangements can be made for transfer of samples for confirmation to the Public Health Laboratory.
If testing facilities are not available and a patient is suspected of suffering from HIV/AIDS based on signs and symptoms, make arrangement for shipment of samples or patient referral to the nearest hospital.

**b) Patient is already diagnosed to have HIV infection but without signs of AIDS and not on ART**

- Follow up closely (at least three monthly) and advice on healthy living
- Counsel for safe sex and correct and consistent use of condoms
- Screen for TB with the WHO questionnaires
- Record the clinical staging at each visit
- If there are any signs of AIDS or OIs (*see clinical staging of HIV infection)* the patient should be referred to the District hospital.
- Fill up the relevant forms and report accordingly to the schedule to the Care ,Support and Treatment(CST) Unit at JDWNRH

**Patient is on ART and OI prophylaxis**

- Visit or call the patient to the BHU every month
- Ensure the patient's adherence to treatment
- Ensure the patient gets his/her regular medications
- Ensure that the patient takes the medications at the right interval
- Counsel and educate the patient about safe sex
- Check for adverse effects of ARVs
- Record and report to CST,JDWNRH as per the required schedule

**Refer the patient to the District Hospital if there are signs of:**

- Drug intolerance/toxicity
- Jaundice
- Losing weight despite treatment
- Opportunistic infections, other complications of HIV and suspicion of any malignancy

**At District Hospitals (DH) or hospitals:**

**a) Patient not on ART:**

- HIV testing of the suspected patient after proper counselling
- If positive, refer the patient to Referral Hospital (RH) or nearby hospital with facilities for CD4 count testing or arrange for samples to be shipped for CD 4 count
- Initiate treatment as per the criteria set out in this guidelines in consultation with a medical specialist
- Follow WHO clinical staging of HIV infection for the diagnosis of AIDS
- Voluntary counselling and testing (VCT) of the sexual partner
- If the patient is already on ART, ensure an adequate stock of medications and reinforce the importance of adherence.
- Monitor drug toxicity and if a change in the regimen is indicated refer the patient to the Regional Referral Hospital (RRH).

**b) Patient already on ART**

- Follow the BHU procedures
- Look for evidence of drug intolerance/toxicity
- Refer the patient for CD4 count every six months

**At Regional/National Referral Hospital:**

- Reconfirm the diagnosis
- Screen for OIs
- Carryout relevant investigations, including CD4 count/Viral load
- Patient is started on OI prophylaxis or ART depending on the CD4+T cell count.
- Review the patient after two weeks of starting ART (if on Nevirapine) to look for its side effects (hepatotoxicity) and to increase its dose if there is no such adverse effect.
- Review the patient after four weeks of starting ART to monitor side effects and to reinforce adherence.
- After initiating ART the patient can be sent back to the hospital with an instruction to send the blood sample for CD4 cell counting after four months and every six months thereafter.

## Chapter V

## Care, Support and Treatment Unit

***Care, Support and Treatment Unit, JDWNRH***

Roles and Responsibilities:

The Care, Support and Treatment Unit at JDWNRH will serve as the nodal unit to coordinate care and treatment of PLHAs across the country. It has been set to mainly ensure better coordination and as well as ensure continuous health services to the PLHAs. Its main responsibilities are

1. Liaising with the Public Health Laboratory to ensure confirmatory test of reactive samples from district are done timely and results communicated to the Districts

2. Assign unique identifier code for newly confirmed HIV positives and enter the record into the database.

3. Advice and guide delivery of positive results to clients by counsellors in the fields

4. Ensure appropriate recording and reporting of HIV case details

5. Ensure timely and regular reporting on HIV case follow up to the CST by the districts

6. Ensure that timely CD4 tests are done

7. Coordinate with the Pharmacy Unit, JDWNRH to ensure proper and adequate forecasting of drugs to ensure a steady supply of ARVs

8. Updating and maintaining database of PLHAs

9. Report quarterly to the National STI & HIV/AIDS on the status of the PLHAs based on indicators developed by NACP.

10. To discuss in person all the new cases being initiated on ART with the treating physician and those on ART with specific problems.

** For all recording and reporting forms to CST refer Annex (7).*

## Chapter VI

## CO-INFECTION

### Hepatitis B co-infection

Hepatitis B virus infection is an important infection in HIV-infected individuals because of the influence of HIV on the natural history of HBV infection. HIV/HBV (HBV co-infection) increases the rate of progression to cirrhosis and liver cancer by four to five folds. The mortality of the patients with the above situation is approximately ten times higher than that of patients with either infection alone. There is accumulating evidence that ART greatly reduces progression to cirrhosis and death in coinfection individuals. As the prognosis of HIV has now dramatically improved the specific consideration for treatment of individuals co-infected with HIV/HBV has increased its importance.

### Treatment

The aim of the HBV treatment is to suppress HBV viral replication and to achieve sustained disease amelioration and to prevent cirrhosis of liver, liver cell failure and hepato cellular carcinoma. Initiate ART in all HIV infected individuals who are coinfected with HBV with severe chronic liver disease, regardless

of WHO clinical stage and CD4 cell count. In the absence of a severe liver disease ART should be initiated as per the standard recommendations. The ART regimen should include 2 drugs active against HBV i.e. Tenofovir and Lamivudine (as in this guideline). This treatment should be continued indefinitely. The end of point to assess treatment response are:

1. Normalization of ALT
2. Loss of HBeAg with or without the appearance of anti HBeAg and
3. Undetectable serum HBV … by a reliable assay

**Hepatitis C co-infection**

The significance of hepatitis C virus co-infection in HIV-infected populations has become apparent since AIDS-related mortality has reduced in the era of ART. Cirrhosis develops in approximately 20% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable. Risk factors for development of significant liver disease include older age at the time of infection, male, obesity, and concomitant alcohol use. HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly those with CD4 cell count < 200 cells/$mm^3$. Unlike HIV and HBV, there is a chance of cure of HCV infection with specific antiviral.

**Treatment**

All patients with chronic Hepatitis C should be assessed for treatment with pegylated interferon alpha – 2a plus Ribavirin for 48 weeks. Therapy can be discontinued when HCV RNA is undetectable. The evaluation and the management of HIV/HCV coinfection should be carried out by an expert in a specialized centre. The role of a new drug generically known as fosobuvir is promising. The cost of treatment with this agent is currently an issue.

# Chapter VII

# OPPORTUNISTIC INFECTIONS (OIs)

OIs are the leading cause of morbidity and mortality in patients with HIV infection. Approximately 80% of AIDS patients die as a direct result of an infection other than HIV, with bacterial infections heading the list. While causative agents characteristically are opportunistic organism such as *Pneumocystis jirovecii*, *Mycobacterium avium* complex, CMV and other organisms that do not ordinarily cause disease in the absence of a compromised immune system, they also include common bacterial and mycobacterial organisms.

Potent ART has decreased the outcome of the OIs, and ART has dramatically improved the prognosis of HIV.The occurrence of OIs depends on the level of CD4+T lymphocyte count (*see figure below)*

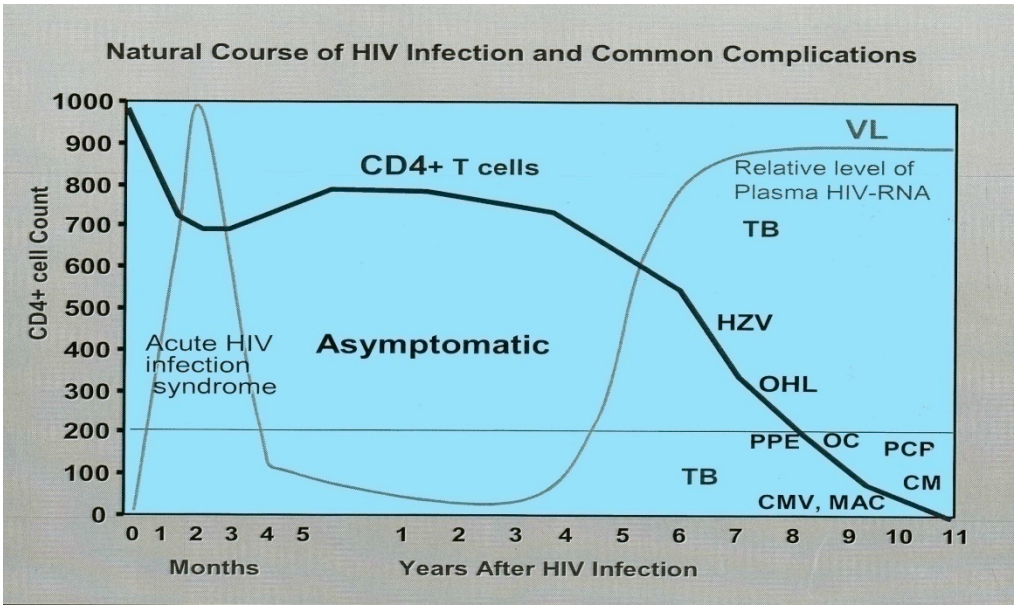



*Figure: Natural course of HIV infection and common complications*

**Opportunistic infections and HIV/AIDS**

- Most patients are diagnosed with HIV infections when they present with an opportunistic infection.
- OIs can be a result of re-activation of previous infections as the immune system is weakened.
- OIs accelerate HIV infection
- OIs can be prevented and treated successfully.
- Identification, prevention and treatment of OIs can significantly decrease morbidity and mortality.

**Prophylaxis:**

- **Primary:** to prevent even first occurrence of infection

- **Secondary:** to prevent a second occurrence of an infection that has already occurred at least once (prevention of recurrence).

**Mycobacterial infection**

## Tuberculosis

*M. tuberculosis* is especially frequent among HIV infected patients. Primary as well as reactivated disease occur.

**Impact of TB on HIV**

- TB is the leading AIDS-related opportunistic infection.
- HIV disease progresses more rapidly in patients with TB, the level of plasma viraemia increases during active TB and successful treatment of tuberculosis brings back the plasma viraemia to the baseline.

**Impact of HIV on Tuberculosis**

- The lifetime risk of HIV infected patients developing TB is 50% as compared to HIV negative patients which is 5-10%.
- HIV increases not only the risk, but also the rate of progression of recent or latent *M. tuberculosis* infection to disease.
- Increases the incidence of extra-pulmonary/disseminated TB.

- HIV increases the incidence of MDR-tuberculosis.
- TB-ART co-treatment involves higher pill burden and increased adverse drug reactions.
- TB/HIV infection is associated with high mortality rate.

**TB can manifest at any stage of HIV infection irrespective of the CD4 count. Extra-pulmonary dissemination is common. In advanced AIDS, clinical and radiological features of tuberculosis can be atypical.**

**Diagnosis**

- Chest X-ray: classic presentation with apical cavitatory disease
- Sputum AFB for three days
- Culture for AFB (even if the smear is negative)
- To confirm MAC (instead of MTB) blood culture is necessary
- Tuberculin Skin Test (TST): CDC recommends TST using 5 tuberculin units of PPD for HIV infected person who have not had a prior positive test (induration ≥ 5mm at 24 to 48 hours). TST should be repeated annually if initial tests were negative. And, also following immune reconstitution when CD4 count increases to >200/$mm^3$. Positivity of TST decreases with progression of HIV/AIDS.
- It is important to do a TST for evidence of latent TB in all PLHIVs. It is recommended that any anergic patient with HIV infection who is at high risk for TB (residents of prisons or jails, injection drug users (IDU), and homeless individuals) should be given 6 months course of isoniazid.

**DO NOT START ART** in a patient with TB simultaneously, the reasons being:

- ✓ Immune reconstitution syndrome (IRS)
- ✓ Overlapping drug toxicity
- ✓ Adherence problem due to high pill burden
- ✓ Difficulty in identifying the culprit drug in case of skin reactions

**Treatment of tuberculosis**

- ✓ The standard regimen is: **2HRZE + 7HR**
- ✓ Treatment with INH should receive $B_6$ supplementation.
- ✓ Treatment should be prolonged if the clinical response is slow.

12 months' regimen or longer is recommended for TB meningitis, spinal TB, TB of the bones and military TB

**Prophylaxis of tuberculosis for the households**

- Household contacts of the patients should be screened for TB with sputum exam for AFB and possible chest X-ray.
- Patient with active TB should be started on treatment immediately and the patient should be isolated.
- Consider DOT to improve adherence and treatment success.

**ART in TB/HIV**

- First line:

  2NRTIs + EFV (600mg every 24 hours) – TDF + 3TC + EFV

- Alternative line:

  2NRTIs + NVP (200mg 12 hourly) – TDF + 3TC + NVP

Protease inhibitors are not recommended for Rifampicin based anti-tubercular regimen.

**Mycobacterium avium complex (MAC)**

- MAC is an acid fast atypical mycobacterium
- MAC infection probably indicates an acute infection with organisms that are ubiquitous in the environment in both in soil and water.
- The presumed portals of entry are the gastrointestinal and respiratory tracts.
- MAC infection is a late complication of HIV infection, occurring in patients with CD4 cells count of <50 cells/$mm^3$

**Presentation**

*Fever, weight loss, night sweats, and diarrhoea with or without abdominal pain.*

1. It is a disseminated disease with gastrointestinal, neurological, dermatological and respiratory manifestations.

**Diagnosis**

1. **Definitive:** Blood culture (positive in 90-95%)
2. **Probable:** By demonstrating the organisms in stool, bone marrow specimen, liver and skin biopsy.
3. Disseminated MAC should be confirmed by clinical assessment or blood culture as AFB stain cannot differentiate between MTB and non-tubercular mycobacteria.
4. Pulmonary MAC shows infiltrates on chest X-ray

**Treatment and Prophylaxis**

| Treatment | Prophylaxis |
|---|---|
| • Clarithromycin 500mg 12 hourly P.O. or Azithromycin 500mg OD plus Ethambutol 15mg/kg P.O. for 12 months.<br>• In severe cases, consider adding a third drug with ciprofloxacin 500 to 700mg BD P.O. and/or Amikacin 500mg IV daily for the first two to three months.<br>• *Clarithromycin and Azithromycin for this indication can be procured on named patient basis.* | **Primary prophylaxis:**<br>• CD4 count <50 cells /$mm^3$ in patients who are asymptomatic.<br>• Clarithromycin 500mg P.O. 12 hourly or azithromycin 1000-1250mg P.O. per week.<br>• Restarting primary prophylaxis when - CD4 decrease to ≤ 50 cells/$mm^3$.<br>• Discontinuation of primary prophylaxis - patients who have responded to ART with increase in CD4 count to > 100 cells/$mm^3$ for at least three month. |

**Prevention of Recurrence**

- Patients with disseminated MAC should receive lifelong secondary prophylaxis or maintenance therapy (unless immune reconstitution occurs following ART) with Clarithromycin (or azithromycin) plus Ethambutol.
- Discontinuation of secondary prophylaxis- sustained CD4 increase of more than 100 cells per $mm^3$ for ≥ 6 months in response to ART after12 months of therapy for MAC is completed and if there are no symptoms or signs attributable to MAC.

## Viral infection

**Cytomegalovirus infection (CMV)**

- CMV retinitis occurs frequently and accounts for 85% of CMV disease in patients with AIDS.
- CMV pneumonitis, encephalitis, polyradiculomyalopathy, dementia, oesophagitis and colitis are other manifestations.
- Usually occurs in patients with CD4<50 cells/$mm^3$.
- Opacifications of retina, areas of haemorrhages, exudates and periphlebitis are the ophthalmologic findings.
- Bilateral in 50% of the patients and retinal detachment occurs in 25%.

**Diagnosis**

- Fundus examination by an experienced ophthalmologist
- CMV PCR (*if available*) often positive in vitreous and aqueous humor.

**Treatment and Prophylaxis**

Treatment can be local or systemic and is administered in two phases: induction and maintenance. This treatment should be carried out by an expert ophthalmologist in a specialized centre.

| Treatment | Prophylaxis |
|---|---|
| • Ganciclovir - 5mg/kg IV infusion over 1 hour, 12 hourly for 2-3 weeks.<br>• Maintenance - 5mg/kg IV infusion of Ganciclovir over one hour daily for 3 days a week or 1000mg P.O. three times daily.<br>• Local treatment – Ganciclovir intra-vitreal injection 200-2000 micrograms weekly. | **Primary prophylaxis:**<br>• Not recommended<br><br>**Secondary Prophylaxis:**<br>• Valganciclovir can be used |

**Herpes simplex infection**

Herpes simplex virus (HSV) type 1 and type 2 of this common virus affect humans. Type 1 HSV produces mucosal lesions, predominantly of the head and neck, while type 2 is a sexually transmitted urogenital infection.

The source of infection is a case of primary or active recurrent disease. Primary infection normally occurs as gingivitis in infancy. It may present as keratitis, viral paronychia, ('Whitlow'), vulvovagitinitis, cervicitis or balanitis.

Recurrent disease involving reactivation of HSV from latency in the dorsal root ganglion produces the classical 'cold sore' or herpes labialis. Prodromal hyperaesthesia is followed rapidly by vesiculation, postulation and crusting. Recurrence can be precipitated by UV rays, menstruation or fever of any cause. Type 2 (genital disease) is a common cause of recurrent, painful genital ulceration especially in females.

**Diagnosis**

- Multiple, painful grouped vesicles/pustules on an erythematous base is a reliable clinical finding.
- Differentiation from other vesicopapular or pustular lesion requires demonstration of the virus by PCR or culture from vesicular fluid (*if available*).

**Treatment**

| Treatment |
|---|
| • Administration of acyclovir (400mg P.O. 8 hourly) for one week is usually effective. For more severe disease, IV acyclovir 5mg/kg q8h, is recommended.<br>• Relapses are frequent, and acyclovir, 400mg P.O. 12 hourly, may prevent their recurrence.<br>• HSV can become resistant to acyclovir, in which case foscarnet, 40mg/kg IV q8h for 10-14 days, or one dose of cidofovir, 5mg/kg IV should be used.<br>• *Acyclovir, foscarnet and cidofovir may be procured on Named Patient Basis for the above indication* |

**Varicella Zoster Infection:**

VZV may cause typical dermatological lesions or disseminated infection. It may also cause encephalitis, which is more common with ophthalmic distribution of facial nerve.

**Treatment**

| Treatment |
|---|

Acyclovir, 10mg/kg IV q8h for 7-14 days, is the recommended therapy. For milder cases, administration of acyclovir 800mg P.O. 5 times a day for one week is usually effective.

## Fungal Infections

### Pneumocystis jirovecii (previously known as Pneumocystiscarinii pneumonia - PCP)

- *Pneumocystis jirovecii* is an opportunistic fungal pulmonary pathogen that is an important cause of pneumonia in an immuno-compromised host. Its natural habitat is the lungs. Droplets transmission can also occur. PCP occurs when CD4 count is below 200 cells/$mm^3$.
- Typical manifestation of PCP is a triad of dry cough, breathlessness on exertion and fever.
- Chest X-ray shows symmetrical pulmonary infiltrates. 10-20% of the patients show no radiological changes. Pleural effusion is not common.
- Laboratory study shows low oxygen saturation.
- Lactate dehydrogenase is usually >500mg/dl.
- Sputum and broncheoalveolar lavage (BAL) may demonstrate the parasite (if available).

### Treatment

**Treatment**

**Preferred Regimen**

- Cotrimoxazole (Trimethoprim 15-20mg/kg + Sulphamethoxazole 70-100 mg per kg per day) P.O. or IV (if severe) in 3-4 divided doses for 21 days) i.e.4 tablets of 480mg three times daily for 21 days.
- If $PaO_2$<70mm Hg or A-a gradient >35mm Hg then add a glucocorticoid - Prednisolone 40mg 12 hourly for five days => 20mg 12 hourly for 5 days => 20mg daily for 11 days.
- For patients who experience adverse events, consider de-sensitization or dose reduction or adopt an alternative regime.

**Alternative Regimen**

- For patients allergic to Sulphonamides – clindamycin 600-900mg 6 hourly or 300-450mg P.O. 6 hourly + Primaquine 15-30mg per day for 21 days.
- *Clindamycin can be procured on named-patient basis for the above indication*

### Prophylaxis

**Prophylaxis**

**Indications:**

- CD4 <200 cells/$mm^3$ or CD4 percentage < 14%
- Prior PCP or history of AIDS defining illness or fever of unknown origin >2 weeks
- Past history of oral thrush

**Preferred regimen:**

- Cotrimoxazole 80/400mg, 2 tabs daily

**Alternative regimen:**

- Dapsone 100mg daily or 50mg twice a day if allergic to cotrimoxazole
- Dapsone 50mg/day plus Pyrimethamine 50mg weekly + Leucrorin
- Aerosolized Pentomidine 300mg monthly (only via respigard II nebulizer)
- Atoravuone 1500mg every day

*Prophylaxis may be discontinued if the CD4 count is stable at ≥ 200 cells/$mm^3$ for three to six months.Reintoduce prophylaxis if CD4count falls <200 cells/ $mm^3$*

### Candidiasis

- Candidiasis is common in HIV infected host
- Location of the infection can be oral, oesophageal or vaginal.
- Commonly seen in patients with CD4 <200 cells/$mm^3$.

### Treatment and Prophylaxis

| Treatment | Prophylaxis |
|---|---|

| | |
|---|---|
| • Oral and vaginal candiasis usually respond to local therapy with troches or cream.<br>• For patients who do not respond, fluconazole 100-200mg daily for 1-2 weeks is the treatment of choice.<br>• Oesophageal candidiasis - Fluconazole 200mg daily for 14-21 days.<br>• Fluconazole can be procured on named patient basis for the above indication<br>**Alternatives are:**<br>• Itraconazole cap. 200mg BD with meals.<br>• Amphotericin B 0.3mg/kg per day IV for 2-3 weeks.<br>• *Itraconazole and Amphotericin B can be procured on named patient basis for the above indication* | **Primary prophylaxis:**<br>• Not recommended<br><br>**Secondary Prophylaxis:**<br>• Fluconazole 100-200mg daily or Itraconazole oral solution 100-200mg daily.<br>• Discontinuation secondary prophylaxis if the patient on ART and has CD4 >200 cells/mm$^3$ for more than three months |

**Cryptococcus neoformans**

- Cryptococci are yeast-like fungi which are ubiquitous.
- The sources of infection are the bats and birds.
- It is the leading cause of meningitis in AIDS patients.
- It can present as acute primary illness or reactivation of previously dormant disease.

**Clinical features include**

- Fever, headache, meningism (stiff neck in <25%), diplopia and mental status changes.
- It can also present as pulmonary or cutaneous illness.
- Cryptococcus meningitis has a high mortality, the cause of death being raised intracranial pressure (ICP).

**Diagnosis**

- High CSF pressure
- Few lymphocytes
- High protein
- Normal or slightly low sugar
- Numerous cryptococci in India ink preparation
- CSF crypto-antigen is positive in over 95% of cases
- Serum antigen and CSF culture can also be used for the diagnosis

**Treatment and Prophylaxis**

| Treatment | Prophylaxis |
|---|---|
| • Most cases are seen when CD4 count is below 50 cells per mm$^3$.<br>• Amphotericin B 0.7mg/kg q6h IV for 2-3 weeks followed by Fluconazole P.O. daily for 8-10 weeks and then Fluconazole 200mg per day (indefinitely).<br>• Liposomal Amphotericin B is the preferred choice of formulation in renal insufficiency. | **Primary prophylaxis:**<br>• Not recommended routinely because of lack of survival benefits associated with prophylaxis, drug interaction, drug resistance and the cost.<br><br>**Secondary Prophylaxis:**<br>• Itraconazole 200mg per day until CD4 count ≥ 200 cells per mm$^3$ for more than 3 months in response to effective ART. |

**Histoplasmosis**

- Histoplasmosis is an airborne fungal infection.
- Suspect histoplamosis in patient with fever, lymphadenopathy, hepatosplenomegaly and weight loss. It can also present as gram negative septicaemia.

**Diagnosis**

- Blood and sputum culture are positive in 85% of the cases but it takes two to four weeks.
- Identification of the organism in the clinical specimens- discharges, FNAC.
- Pancytopenia develops due to bone marrow suppression.

**Treatment and Prophylaxis**

| Treatment | Prophylaxis |
|---|---|
| • Amphotericin B, 0.5mg/kg IV daily for a total dose of 0.5-1.0gm followed by Itraconazole 300mg P.O. BD for three days for induction therapy followed by 200mg P.O. BD indefinitely.<br>• Discontinuation of Itraconazole is possible if sustained increase in CD4 count is observed (more than 100-200 cells/$mm^3$) for more than six months. | **Secondary Prophylaxis:**<br>• Itraconazole 200mg OD<br>• Alternative agent is amphotericin B 1mg/kg per week.<br>• No sufficient data to make recommendations at present to discontinue secondary prophylaxis. |

**Aspergillosis**

- *Aspergillusfumigatus* is the common cause of aspergillosis. This fungal infection is identified by gross and microscopic examination. This infection can involve the lung, CNS, heart, kidneys, and the paranasal sinuses.
- There are two clinical forms of aspergillosis in AIDS patients, viz. invasive pulmonary and febrile diffuse meningo-encephalitis.
- Respiratory manifestations include pseudomembranous tracheitis or pneumonia.

**Diagnosis**

Definitive diagnosis requires biopsy of the tissue involved, or positive culture from a normally sterile site.

**Probable:** Two positive sputum cultures or one positive bronchoscopy in an appropriate host.

| Treatment |
|---|
| • Voriconazole is the treatment of choice.<br>• Amphotericin B, 1.0mg/kg/day IV for 2 weeks.<br>• Fluconazole 200mg P.O. BD for three days then 400mg per day for a minimum of 2 weeks. |

**Penicilliosis**

- Penicilliosis is caused by *P. marneffi*. It presents with fever, skin and mucosal lesions (papules, pustules, or nodules).
- Lymphadenopathy and wasting from endemic areas (Northern Thailand and Southern China) with CD4 count <50 cells/$mm^3$.
- The diagnosis is established by the evidence of pathogen in culture, smear, or histopathology; most frequent with Wright stain of skin scraping, node biopsy or marrow aspirate. Smears show elliptical yeast, some with the characteristically clear central septation.

**Treatment**

| Treatment |
|---|
| **Preferred regimen:**<br>• Severe - Amphotericin B 0.6mg/kg per day for 2 weeks, then Itraconazole 200mg P.O. BD for 10 weeks.<br>• Mild to moderately severe - Itraconazole 200mg BD.<br><br>**Maintenance:**<br>Itraconazole 200mg per day for lifetime or CD4 count more than 100 cells per $mm^3$ for more than 6 months in response to<br>ART |

**Protozoal infections**

**Toxoplasma gondii**

- Typically causes multiple CNS lesions and presents with encephalitis and focal neurological signs.
- The disease represents reactivation of previous infection and the serological test is usually positive.

Often the diagnosis relies on response to empirical treatment as seen by clinical response and reduction in the size of the mass lesion.

**Imaging:** MRI is the best radiographic technique for the diagnosis of cerebral toxoplasmosis

**Treatment and Prophylaxis**

| Treatment | Prophylaxis |
|---|---|
| • Sulphadiazine 25mg/kg p.o.q for 6 weeks + Pryimethamine 100mg p.o on day 1 followed by 75mg daily is the therapy of choice<br>• For patients who are allergic to Sulphonamides, Clindamycin (600mg IV or P.O. q8h) can be used.<br>• Treatment is continued for at least six weeks | **Primary prophylaxis:**<br>• CD4 count <100 cells per $mm^3$ and Toxoplasma IgG positive.<br>• Drug of choice - Cotrimoxazole 480mg, 2 tabs daily<br><br>**Discontinuation of primary prophylaxis:**<br>• CD4 count >200 cells/$mm^3$ for more than three months.<br>• Restart when CD4 count is less than 100-200 cells/$mm^3$ |

| Additional Treatment | Prophylaxis |
|---|---|
| • Dexamethasone if there is evidence of cerebral oedema.<br>• Anti-convulsants in case of seizures, but not as prophylaxis in all patients. | **Secondary prophylaxis:**<br>• Drug of choice - Cotrimoxazole 480mg, 2 tabs daily<br><br>**Discontinuation of secondary prophylaxis:**<br>• Patient on ART with no symptoms and CD4 more than 200 cells/$mm^3$ ≥ 6 months provided initial therapy for six weeks or more has been completed and the patient is asymptomatic.<br>• Restart secondary prophylaxis when CD4 count is <200/$mm^3$. |

***N.B.*** *Primary and secondary prophylaxis in toxoplasmosis are strongly recommended*

**Other Protozoal infections:**

- Cryptosporidium
- Cyclospora
- *Isospora belli*
- Microsporidia
- Strongyloides

**Central nervous system manifestation of HIV/AIDS**

CNS infection is common in HIV patients when CD4 count is <100cells/$mm^3$. Neurologic complications of AIDS can occur as primary result of HIV, secondary neurologic complications and immunonologic complication.

**Primary Result of HIV**

- Aseptic meningitis
- Chronic meningitis

- Encephalitis
- Cognitive disorder/ dementia
- Polyneuropathy

**Secondary Neurologic Complications**

- Opportunistic infections.
- Secondary neoplasm.
- Vascular disease.

**Immunologic Complications**

- Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Mononeuropathy

**Cryptococcal meningitis:***See under fungal infections*
**Toxoplasmosis/Toxoplasma encephalitis**: *See protozoal infections*
**CMV retinitis:***See viral infection*

**Tubercular meningitis**

**The treatment regimen of TB meningitis is the same as for immunocompetent host and the duration of the treatment should be 12 months.**

Glucocorticoids are indicated particularly if:

- Evidence of raised intracranial pressure
- Altered sensorium and focal neurological signs
- Spinal TBM

**Gastrointestinal Manifestation in HIV/AIDS**

Gastrointestinal manifestations used to be very common in patients with HIV/AIDS before the ART era but with the initiation of ART, the manifestations have become less common. HIV related GI disorders can present in many forms.

The GI manifestations include:

- Dysphagia/ odynophagia
- Diarrhoea with or without abdominal pain
- Anorexia
- Vomiting

**Dysphagia/ Odynophagia**

Causes: Candida, CMV, HSV, other fungal infections, TB infection, and drug induced oesophagitis.

| **Treatment** |
|---|
| • Empirical treatment of oesophageal candidiasis is with fluconazole 100 (up to 400mg P.O.) for 14 to 21 days.<br>• If the patient doesn't respond, give a course of acyclovir 200-800mg five times a day for 2-3 weeks (suspected HSV infection).<br>• If no improvement, patient may be referred for oesophagoscopy to rule out CMV infection which is treated with Ganciclovir. |

**Diarrhoea**

Diarrhoea is still a common problem in the era of ART. It is caused by organisms like microsporidium, cryptosporidium, MAC, CMV, *E.histolytica*, *G.lamblia*, *Strongyloides*, *Salmonella, Shigella*, *C. jejuni*, Clostridium species. Idiopathic diarrhoea is common.

**Diagnosis**

- Stool examination for parasites, fungi, WBC and RBC, and modified AFB stain
- Febrile patients with CD4 counts<100 cells/$mm^3$ need blood culture for MAC infection.

**Treatment**

| Treatment |
|---|
| • In acute diarrhoea - Cotrimoxazole or quinolones (short course)<br>• For chronic diarrhoea - Depending on the suspected aetiology, Cotrimoxazole, quinolones, or Metronidazole and Albendazole may be used.<br>• The initiation of ART alone stops diarrhoea in majority of the cases. |

**Cutaneous Manifestations of HIV/AIDS**

Cutaneous manifestations are very common in HIV/AIDS and have a very broad and diverse spectrum. In this section only those manifestations which are commonly encountered with HIV/AIDS are considered. They are:

**Viral:**

- **Exanthema of acute retroviral syndrome** – maculopapular rashes seen in acute retroviral syndrome and is self-limiting.
- **Chronic herpetic ulcers**- usually present as painful orolabial or genital lesions and persist for more than a month. Acyclovir is the drug of choice.
- **Herpes Zoster**- vesicular eruptions along the nerve distribution can occur in normal CD4 counts. Acyclovir is prescribed.
- **Oral Hairy Leukoplakia (OHL)** is caused by the Epstein Barr Virus (EBV). Reported in more than 20% of HIV patients, and is a marker of HIV infection. It occurs when CD4 count is < 100cells/$mm^3$. Hyperplastic whitish plaques are seen on the lateral sides of the tongue which are difficult to scrape off as opposed to *Candidial lesions of the tongue, oral and buccal lesions which can be easily scraped off with a tongue depressor*. It is usually bilateral and is a premalignant condition.
- Molluscumcontagiosum: multiple umbilicated follicular lesions which can occur in any part of the body, except the palms and the soles. No specific treatment is required as initiation of ART controls the lesions.

**Fungal:**

**Proximal subungualonychomycosis –** is a fungal infection of the proximal nail bed. Itraconazole given in pulse therapy is this management of this condition.

**Oral candidiasis**- *see fungal infections*
**Penicilliosis**- *see fungal infections*

**Bacterial:**

- Staphylococcusaureus infections
- Impetigo
- Folliculitis
- Furunculosis
- Acne vulgaris

*Prescribe antibiotics as per the sensitivity pattern.*

**Others:**

- **Eosinophillic folliculitis**- unknown aetiology and pathogenesis; small pink to red, oedematous, folliculocentric papule occur symmetrically above the nipples. Treatment: Prednisolone

- **Psoriasis**- It is one of the markers of HIV infection. Existing psoriasis gets flared up with HIV infection. Treatment is as for the immunocompetent host.
- **Pruritic papular eruptions (PPE)** - common finding in AIDS patients and is also a marker of HIV infection. It occurs in patients with CD4 <50 cells/$mm^3$.
- **Icthyosis and xerosis** are common in advanced HIV infection. These are extremely pruritic dermatoses characterized by red or skin coloured. Treatment is symptomatic.

**Associated Neoplasms**

**Kaposi 's sarcoma (KS)**

Kaposi's sarcoma usually presents as liposomal cutaneous lesion; the GI tract and lungs are the visceral organs involved.

**Treatment**

Local therapy with liquid nitrogen or intra-lesional injection with alitretenoin or vinblastine has been used. Cryotherapy or radiation may be useful as well. Systemic therapy involves chemotherapy (e.g. liposomal doxorubicin, paclitaxel, liposomal daunorubicin, thalidomide, retinoids), radiation, and interferon α.

**Lymphoma**

- Lymphomas commonly associated with AIDS are non-Hodgkin's lymphoma, CNS and systemic lymphoma, and lymphoma of B-cell origin.
- EBV appears to be the associated virus.

**Cervical and peri-anal neoplasm**

- Both HIV infected men and women are at high risk for human papilloma virus-related disease.
- Certain human papilloma virus subtypes, such as 16 & 18 are oncogenic.
- Cancer can also arise from peri-anal condylomaaccuminata.
- Screening for vaginal dysplasia with a Papinicolaou stain is indicated every six month and if results are normal annually afterwards.

# Chapter VIII

## IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

### Definition

*Clinical deterioration following initiation of ART believed to be related to restored ability to mount an inflammatory response due to restoration of pathogenic specific immunity.*

- Also occurs following re-initiation or change to more potent ART.
- It has a temporal association with the initiation of ART (5-6 weeks)
- Commonly known as immune reconstitution syndrome (IRS) also known as immune recovery syndrome
- Incidence: 17-25% in three large retrospective studies.

### Diagnosis

Initiation, re-initiation or change to a more effective combination of ART with associated increase in CD4 cell count and/or decrease in viral load after excluding:

a. Worsening of known infection due to inadequate or inappropriate therapy.
b. New infections not known to be associated with IRIS (e.g. bacterial sepsis).
c. Reactions to medications.

### Infective IRIS can present as one of the two forms

a. **Paradoxical IRS** in which patients on anti-microbial treatment for an infection experience clinical deterioration related to the infection after starting ART **OR**

b. **Unmasking IRIS:** in which a previously present, but clinically undetected, and therefore untreated infection, becomes apparent after starting ART, and the clinical presentation is usually inflammatory in nature.

### IRIS prevention

- WHO currently recommends starting ART two weeks to two months after TB treatment with patients with CD4 cells count<200 cells /mm3 but delaying ART in patients with higher CD4 cell counts.
- Optimal timing of ART introduction in patients with TB and cryptococcal meningitis is needed.
- Unmasking forms of IRIS might be prevented by thoroughly screening for OIs and commencing patients on OI treatment before starting ART.
- Paradoxical IRIS: shorter delay between starting treatment for TB and cryptococosis and ART has been identified as risk factor, i.e. the chances of developing IRIS is higher if the interval between initiation of ART and TB treatment or treatment of cryptococosis is short.

### Management and treatment of Mild IRIS

- NSAIDs can be used in cases in which mild inflammation or fever cause patient discomfort.
- Abscesses may be drained.
- Inflamed and painful nodes may be excised.
- Inhaled steroids may alleviate mild pulmonary inflammations that cause bronchospasm or cough.

### Glucocorticoids

- Mortality benefit has been demonstrated for
  - ✓ Bacterial meningitis
  - ✓ TB meningitis
  - ✓ TB pericarditis
  - ✓ Severe typhoid fever
  - ✓ PCPwith moderate to severe hypoxemia

**Management and treatment of severe IRIS with glucocorticoids**

- Glucocorticoid therapy to suppress inflammatory response is the most commonly use treatment for IRIS.
- Recommended dose of prednisolone is 10-40mg P.O. and 1- 2mg per day and if severe for 1-2 weeks after which it should be tapered.
- Some patients experience relapse of symptoms when glucocorticoid is tapered or discontinued in which case, months of treatment may be required.
- In viral hepatitis-associated IRIS, glucocorticoids may cause harm. Their use for this form of IRIS is ill-advised.

In some patients the potential risks of steroids are high (e.g. patient with Kaposi's sarcoma), provided an IRIS does not seem to be life threatening, counselling, reassurance and symptomatic and supportive management without the use of glucocorticoids is a safer option.

**NSAIDs**

- NSAIDs may provide symptomatic relief in patients with IRIS manifestations that are not severe.
- Favourable responses are reported in cryptococcal IRIS with lymphadenitis, MAC IRIS and paradoxical TB-IRIS.
- The adverse effects of the NSAIDs - GI ulceration and worsening of renal functions in patients with HIV-associated nephropathy should be borne in mind.

**IRIS in TB**

For patients with tuberculosis, IRIS has been reported to occur in as many as 30% in the developed world. The syndrome is characterized by fever, worsening pulmonary lesions (X-ray findings) and expanding CNS lesions, serositis (pleural and pericardial effusions). Mean duration for development of the syndrome is about 60 days. These reactions are usually self limiting, although in some cases a short course of glucocorticoids may be helpful to reduce inflammation for severe respiratory and CNS symptoms. Initiation of ART can also unmask previously undiagnosed infections by augmenting the inflammatory response. In general, ART should not be discontinued for immune reconstitution syndrome.

**IRIS in MAC**

Symptoms of IRIS in MAC is characterised by increase in symptoms of lymphadenitis and granulomatous inflammations, cutaneous lesions, endobroncheal tumours, small bowel involvement, and paravertebral abscess. Cultures are usually negative.

**Treatment**

- Glucocorticoids 1 mg/kg for one month and then tapering off gradually.
- Appropriate antimicrobial therapy.
- Local surgical drainage where indicated.

**IRIS in CMV**

IRIS in CMV is seen in the form of:

- Vitreitis, retinitis, retinal detachment, neovascularisation, proliferative vitreo retinopathy.
- Parotitis.
- Pneumonitis.

**Treatment**

- Topical anti-inflammatory therapy.
- Periocular steroids.
- Ganciclovir implants.
- Prophylactic CMV therapy.

**IRIS in Cryptococcosis**

Patients suffering from cryptococcosis show increase in intracranial pressure, CSF pleocytosis, high protein, negative culture, cerebral infarction, enlarged lymph nodes, cavitatory or necrotizing pneumonia and subcutaneous abscesses in IRIS.

**Treatment**

- Antifungal therapy to lower fungal burden.
- Manage increased intracranial pressure.
- Anti-inflammatory drugs.

**IRIS in PCP**

IRIS develops early in patients with PCP after startingART (median duration of about 2 weeks if primary prophylaxis was not received). It presents as granulomatous pneumonitis on X-ray.

**Treatment**

a. Cotrimoxazole with ART.
b. Symptomatic.
c. Glucocorticoids may be indicated

## Chapter IX

## POST EXPOSURE PROPHYLAXIS (PEP)

This chapter covers consideration and initiation of antiretroviral post-exposure prophylaxis (PEP) in occupational and non-occupational settings.

**Definition**

*The set of services that are provided to manage the specific aspects of exposure to HIV and help prevent HIV infection in a person exposed to the risk of getting infected by the HIV.*

*PREVENTION IS PRIMARY!*
*Protect patients....protect healthcare personnel.....promote quality healthcare*

**Rationale for PEP**

Administration of ARTs soon after exposure will inhibit viral replication and dissemination, and tip the balance in favour of the host's defense mechanisms to clear the inoculums

***PEP should be initiated as soon as possible, within hours and no later than 72 hours***

**Indications**

PEP is indicated in the following circumstances:

- break in the skin by sharp object (including both hollow bore and cutting needles or broken glassware) that is contaminated with blood, visibly body fluids, or other potentially infectious material, or that has been in the source patient's blood vessel.
- bite from an HIV infected patients with visible bleeding in the mouth that causes bleeding in the health care worker (HCW)
- splash of blood, visible body fluid or other potential infectious material to a mucosal surface (mouth, nose or eyes)
- a non intact skin (e.g. dermatitis, chapped skin, abrasions, or open wound) exposure to blood, body fluid, or other potentially infectious material.

**Universal Precaution**

- standards developed to prevent exposure and transmission of disease in an occupational setting
- UNIVERSAL means: everyone everywhere, and always!!

**Management**

- first aid
- do not panic
- immediate management: wash skin with soap and water and flush mucous membranes with water

**Counselling including the assessment of the risk of the infection**

- assessment of infection risk
- types of exposure: percutaneous, mucous membrane, non intact skin and bites resulting in blood exposure
- body substance
- blood
- body fluids
- potentially infectious fluid or tissue

**Table 1**

| Definitely infectious | Potentially infectious | Non-infectious (unless visibly bloody) |
|---|---|---|
| Blood<br>Semen<br>Vaginal secretions<br>Breast milk | CSF<br>Synovial fluid<br>Pleural effusion<br>Amniotic fluid<br>Peritoneal fluid | Saliva<br>Tears<br>Sweat<br>Urine<br>Faeces |

**Other factors to be considered in an occupational exposure**

- Source person: (a) presence of HBsAg(b) presence of HCV antibody
- If the source is unknown, assess epidemiologic and clinical evidence
- Other risk factors:
  - ✓ HIV viral load
  - ✓ the length of exposure time: tenfold drop in infectivity every 9 hours with the initiation of PEP
  - ✓ the glove use
  - ✓ hollow bore versus solid bore needle: large diameter needle are associated with increased risk

**HIV testing**

- Enzyme immunoassay (ELISA) - consider rapid test if ELISA cannot be done within 24-48 hours
- Evaluate for infection status with approved rapid HIV antibody test
- Remember to obtain the source persons informed consent and maintain confidentiality
- If exposure source is unknown, information on circumstances, disease prevalence may be epidemiologically assessed for likelihood of HIV transmission.

## The prescription of ART

- **When should PEP be started?**
  - ✓ PEP should be initiated as soon as possible, preferably within hours of exposure..

- **How long to continue?**
  - ✓ For four weeks (28 days) as inferred by case controlled studies and recommended by CDC guidelines

**Three Drug Regimen**

Preferred regimen - 2 NRTIs + Boosted PI (TDF + 3TC + LPV/r)
Alternate regimen - TDF+3TC+EFV

**HIV PEP services would include the following as a core package**

- Reporting incidence and possible referral capacity
- Risk assessment
- Counselling services for providing PEP
- Pre and post HIV test and counselling (for both the exposed person and the source person)
- Drug adherence and managing side effects
- Preventing the risk of transmission
- Initial testing of exposed individuals
- Testing of the source person when possible
- Providing PEP medications which includes the initial dose and the doses for 28 days (the full course)
- Support and follow up
- Appropriate record keeping and documentation

**PEP is NOT indicated:**

- If the exposed person is HIV positive from previous exposure
- If the exposure does not pose a risk of transmission
- Exposure of intact skin to potentially infectious body fluids
- Any exposure to non infectious body fluids, faeces, saliva, urine and sweat
- Exposure to body fluids from a person known to be HIV negative unless this person is identified as being a high risk for recent infection and thus likely to be within the window period
- If the exposure occurred more than 72 hours previously

**Administration Procedures in case of an occupational exposure.**

1. Provide first aid as per the guideline
2. Register
3.Inform the incharge of the unit and the appropriate Hospital authority (Med. Superintendent/Med.Officer including the CST,JDWNRH and the program)
4. Immediate evaluation by a physician on a decision for requirement of possible exposure prophylaxis
5. If not known, HIV testing of the exposed and the source person
6. Follow up on the case by a physician with update to the Administration/Program.

# Chapter X

# ADHERENCE

***Definition***

Adherence was defined for the first time as an *extent to which patients' behavior coincides with medical/health advice*. Subsequently it was defined as *the extent to which the patients continue with an agreed mode of treatment*.

Adherence to ART has been correlated strongly with HIV viral suppression, reduced rates of resistance, an increase in survival, and improved quality of life. A low adherence is strongly associated with detectable viremia, progression to AIDS and death. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team.

Some of the factors associated with poor adherence are:

- Lack of patient education
- Poor patient and clinician relationship
- Stigma and discrimination against the patient and their families
- Alcohol and substance abuse
- Mental depression/low mood
- Fear of disclosure
- High pill burden
- Adverse events related to drugs
- Inability of the patient to identify their medications
- Paucity of regular supply of ART
- Being too ill
- New medical problems
- Lack of family support

**How to improve adherence?**

The health worker must be prepared to assess the patients' readiness to adhere, offer advice and monitor progress at every contact.

In order to improve adherence, health care provider must:

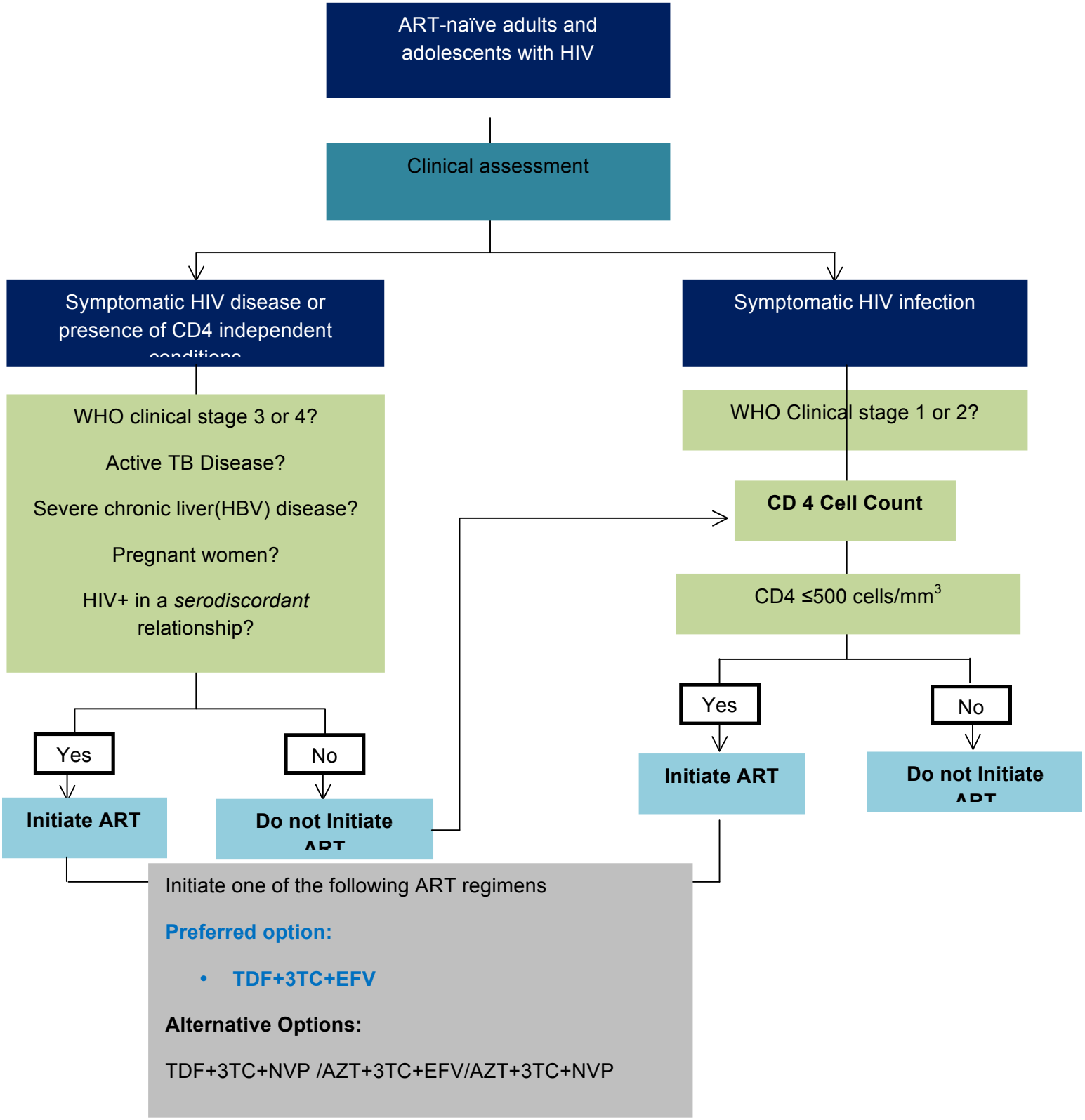
- give written instructions about the drugs prescribed in the manner that the patient understands
- explain the possible side effects about the medicines
- reinforce regular follow up visits
- encourage and show hope
- seek peer support of peer educators on treatment known as "expert patient" and community treatment groups if any exists.
- Explain clearly to the patient the consequences of poor adherence.

**How to assess adherence?**

Simplify regimens, dosing and food requirement, e.g.

- Advice to take every 12 hours, not as B.D.
- what time do you take the medicines normally
- with meals or without meals
- Any dose missed or delayed in the last one to two weeks
- concomitant medication(s)
- Physical inspection of remaining drugs of the patient and reinforcing the ideal manner in which ART is to be administered.

## Algorithm for treatment and management of HIV in adults and adolescents




**WHO clinical staging of HIV disease in adults, adolescents**

| |
|---|
| Asymptomatic<br><br>Persistent generalized lymphadenopathy |
| Moderate unexplained weight loss (<10% of presumed or measured body weight)<br><br>Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)<br><br>Herpes zoster<br><br>Angular cheilitis<br><br>Recurrent oral ulceration<br><br>Papular pruritic eruption<br><br>Fungal nail infections<br><br>Seborrhoeic dermatitis |
| Unexplained severe weight loss (>10% of presumed or measured body weight)<br><br>Unexplained chronic diarrhoea for longer than 1 month<br><br>Unexplained persistent fever (intermittent or constant for longer than 1 month)<br><br>Persistent oral candidiasis<br><br>Oral hairy leukoplakia<br><br>Pulmonary tuberculosis<br><br>Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)<br><br>Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis<br><br>Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x $10^9$/l) and/or chronic thrombocytopaenia (<50 x $10^9$/l) |
| HIV wasting syndrome<br><br>Pneumocystis (jirovecii ) pneumonia<br><br>Recurrent severe bacterial pneumonia<br><br>Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)<br><br>Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)<br><br>Extrapulmonary tuberculosis<br><br>Kaposi sarcoma<br><br>Cytomegalovirus infection (retinitis or<br><br>infection of other organs)<br><br>Central nervous system toxoplasmosis |

| |
|---|
| HIV encephalopathy |
| Extrapulmonary cryptococcosis, including meningitis |
| Disseminated nontuberculous mycobacterial infection |
| Progressive multifocal leukoencephalopathy |
| Chronic cryptosporidiosis |
| Chronic isosporiasis |
| Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis) |
| Lymphoma (cerebral or B-cell non-H |
| odgkin) |
| Symptomatic HIV-associated nephropathy or cardiomyopathy |
| Recurrent septicaemia (including nontyphoidal Salmonella) |
| Invasive cervical carcinoma |
| Atypical disseminated leishmaniasis |

## Chapter XI

## PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (PMTCT)

**Overview of Mother To Child Transmission (MTCT)**

The pregnant women form an important target group for the country to address towards reduction of HIV infection cases. In addition pregnancy is associated with significant maternal morbidity and mortality if proper care is not provided. Infected children die early without interventions and uninfected children are left without parents. Society has to bear the loss of working people and the expense of looking after the orphans. With proper implementation of PMTCT activities in all health care settings for pregnant women, we can reduce the incidence of HIV transmission from mother children (vertical transmission).

**Rationale for PMTCT**

The estimated number of perinatally acquired AIDS cases in the world had decreased dramatically over the last two decades. This is predominantly due to the implementation of prenatal HIV testing with antiviral therapy given to the pregnant woman and then to her neonate.

However, more than 90% of the world's 2.5 million children living with HIV/AIDS were infected through MTCT. Without interventions, rate of transmission is 25-45% in the developing countries. Combination of early diagnosis,, effective ART, safer obstetric practice and no breast feeding, counseling and support can reduce the risk to less than 2%.

With the proper inception of the PMTCT program in Bhutan from 2005, the incidence of HIV transmission from mother to child in the group who received ART prophylaxis is zero till date in the babies who were tested.

The PMTCT 2013 Guidelines recommends that the ART needs to start early in the course of disease in all pregnant patients in order to have the greatest impact on disease transmission, morbidity and mortality. Breast milk transmission can be prevented by replacement feeding.

.

*Table 1: Factors that can potentially increase the risk for MTCT at different stages of pregnancy*

| Pregnancy/postpartum stage | Factors | Risk of transmission* |
|---|---|---|
| **Pregnancy** | • High maternal viral load<br>• Viral, Bacterial, or placental infection (e.g. Malaria)<br>• Sexually transmitted infections (STIs)<br>• Maternal malnutrition | 5-10% |
| **Labour& Delivery** | • High Maternal viral load<br>• Rupture of membranes more than 4 hours before labour begins<br>• Invasive delivery procedures that increase contact with mother's infected blood or foetal scalp monitoring<br>• Chorioamnionitis (from untreated STI or other infection) | 10-20% |
| **Breastfeeding** | • High Maternal viral load (new or advanced HIV/AIDS)<br>• Longer duration of breastfeeding.<br>• Early mixed feeding (e.g. food or fluids in addition to breast milk)<br>• Breast abscesses, nipple fissures, mastitis.<br>• Poor maternal nutritional status<br>• Oral disease in the baby (e.g. Thrush or sores) | 10-20% |

*Risks without any intervention

**Effect of pregnancy on HIV-disease progression**

All studies so far have not shown pregnancy to have any effect on the progression of HIV disease. Even repeated pregnancy does not have significant effect on the clinical or immunological course of HIV viral infection.

**Effect of HIV on pregnancy outcomes**

Although maternal morbidity and mortality rates are not increased in seropositive asymptomatic women.

| | |
|---|---|
| **First line ART for Pregnant Women** | • TDF + 3TC + EFV is recommended as first-line ART in pregnant women, including pregnant women in the first trimester of pregnancy.<br>• Infants of mothers who are receiving ART should receive six weeks of infant prophylaxis with AZT (twice daily). Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum. |

However, reported adverse fetal outcomes include preterm delivery, fetal growth restriction, and stillbirth were seen more common among HIV-infected women compared with non-HIV infected women.

There are no studies that indicate an increase in the frequency of birth defects related to HIV infection. HIV is not an indication for termination of pregnancy.

**Key points to note for comprehensive PMTCT package**

**1. Diagnosis/Testing**

- All pregnant women attending ANC should be offered HIV testing and counselling preferably in the first trimester of pregnancy and if missed should be offered during the subsequent visits.
- Women who had not attended any ANC should be screened for HIV during labour or immediately after birth
- ANC diagnosis of HIV should be linked with routine MCH service and with involvement of focal person in each Hospital.
- Repeat testing is recommended in the high risk group between 30-36 weeks.

**2. Care during the antenatal period**

- All pregnant women should have routine ANC care.
- Complicated cases should be managed by the core team.
- Screen for Tuberculosis
- Rule out opportunistic infections

It is recommended to form a core team at each health facility for PMTCT service as listed below:

- All obstetricians/ physician/Midwife/ANM/AN/HA
- All pediatrician/nurse
- 1-2 trained counselors, according to the local case load
- 1-2 staff nurses
- 1 Lab Technician
- 1 Pharmacist/pharmacy technician

**Antiretroviral Therapy**

- All the HIV positive pregnant women should be started on ART irrespective of CD4 count or the WHO clinical stage as soon as possible. They should follow the same regimen like adults and adolescents (TDF+3TC+EFV).
- Give folic acid (5mg) daily for all women receiving ART before 12 completed weeks
- If the CD4+ T-cell count is <200/mm3, primary prophylaxis for P. jiroveci (formerly P. carinii) pneumonia is recommended with Sulfamethoxazole-trimethoprim or Dapsone.

**Monitoring of the Pregnant Patient**

- Montly CBC, RFT, LFT
- Viral load and CD4+ quantification are determined each trimester
- Increasing viral load on ART may need resistance testing
- Screen for Tuberculosis and opportunistic infections

**Management of Labour and delivery**

**Mode of delivery**

- All HIV positive pregnant women will be delivered by elective caesarean section at 39 completed weeks in comprehensive EmOC centers (facilities where C/Section are available).
- Routine vaginal delivery will be promoted once the viral load facilities are available (less than 1000 copies/ml of blood).
- **Emergency caesarean section** will be offered to all HIV positive mothers coming with labour or ruptured membranes with less than 4 hours duration.
- All HIV positive mothers coming with labour and ruptured membranes with ***more than 4 hours*** duration should be allowed for vaginal delivery with the following precautions:
  a. Avoid episiotomy as far as possible.
  b. Reduce the number of internal examination
  c. Not to use fetal scalps monitoring.
  d. Avoid prolong labour.
  e. Avoid instrumental delivery as far as possible.

**Immediate newborn care consists of the following:**

- Wipe infant's mouth, eyes and nostrils with gauze when the head is delivered.
- Clamp cord immediately after birth, and avoid milking the cord. Cover the cord with gloved hand or gauze before cutting.
- Use gentle suction only when meconium-stained liquid is present. Use either mechanical suction or bulb suction.
- All babies should be given an immediate warm water bath with mild soap wearing protective gloves. Once the initial bath is given, then no need to wear gloves for handling the baby.
- Immunization at birth should be like at any other routine one including Vitamin K.
- **Start syrup AZT 2mg per body weight every 6 hours for 6 weeks.**
  i. **>35 wks – 4mg/kg/dose twice a day x 6 wks**
  ii. **30 – 35wks – 2mg/kg/dose BID x 2 wks then 3mg/kg BID x 4 wks**
  iii. **< 30wks – 2mg/kg/dose BID x 4 wks then 3mg/kg**

**Feeding of the baby**

- The Government policy advocates no breast feeding for all the HIV infected mothers.
- The government supports for supplementary feeding for two years for every baby after birth.
- The concerned focal person in each hospital should facilitate the procurement and supply of the infant formula for every baby.

**Postpartum care**

- Immediate postpartum care should be like the routine care.
- Give breast milk suppression to the mother as follows:
  - ✓ Tab pyridoxine 100mg-once a day for 5 days.
  - ✓ Advice mother to use firm bra for breast support.
  - ✓ Use Paracetamol for analgesia.
- Subsequent post natal visits should be also like routine ones.
- Teach and explain the mothers to dispose body secretions and fluids properly.
- **All mothers on ART should continue for same medication for life long. After six weeks they should be followed up in adults clinics**

**Sexual and Reproductive Health**

- Educate for condom use as dual protection (STIs, including HIV, and for family planning)
- Support the mother's choice of contraceptive method. If family size is completed, recommend for permanent method of family planning by the couple
- Ensure for routine Paps smear screening

# Chapter XII

# PEDIATRIC HIV/AIDS MANAGEMENT

## Introduction

In the absence of any interventions, about a third of children born to HIV infected mothers will be born with HIV or infected through breastfeeding. Children born with HIV have very high mortality. They are over four times more likely to die by the age of two than children born without HIV. The clinical manifestations of HIV infection in children are different from those in adults. The immune system of young children, who are infected perinatally, is immature and hence dissemination throughout the various organs may occur very early. Organs such as the brain may be susceptible to the effects of the virus in a manner different from the ones observed in adults. Even the pattern of opportunistic infections in children is different from those in adults. Children tend to suffer from primary infection while adults are more likely to suffer from reactivation of infection as their immunity wanes in response to advanced HIV-infection. Therefore it is important to start treatment and management of infants with HIV as early as possible.

## Key differences between adults and children

- Young children have immature immune systems, and if HIV-infected, are particularly susceptible to common childhood and opportunistic infections. They may experience a rapid progression of HIV disease if treatment is delayed.
- Maternal HIV antibodies can be passed to the child and last for up to 18 months, so HIV antibody testing does not reliably indicate HIV infection in children under 18 months of age. Positive HIV antibody testing in this time period can indicate exposure to HIV or HIV infection in the child and, where possible, should be followed up with a viral test.
- Children are at risk of acquiring HIV by breastfeeding from HIV-infected mothers. Negative HIV antibody testing in a child who stopped breastfeeding at least 6 weeks prior to the test usually indicates the child is not HIV-infected.
- In young children normal CD4 counts are higher, age-dependent, and more variable than in adults. For children under 5 years of age, it is best to use %CD4 rather than absolute count.
- ART drugs are handled differently in children's bodies, affecting the doses that are needed. ART medicine dosages must be adjusted as the child grows.
- It can be challenging to communicate effectively with children about their HIV status, about the care they need, and to support their adherence to ART. As children grow, the counselling they receive must evolve as well.

## Diagnosis of HIV-infection in children

Tests for antibodies do not establish the presence of HIV infection in infants because of transplacental transfer of maternal antibodies to HIV. Maternal HIV antibody transferred can persist for as long as 18 months in children born to HIV-infected mothers; therefore a virologic test should be used to diagnose HIV in infants and children younger than 18 months. All infants with an initial positive virological test result should be started on ART without delay and, at the same time, a second specimen should be collected to confirm the initial positive virological test result. Currently there are no facilities for virological test for early infant diagnosis (EID). Arrangements have to be made to ship samples aboard until the country is able to establish the facilities for EID. Therefore it is imperative that the Care, Support and Treatment is informed beforehand to organize the possible shipment of samples for EID.

Although HIV antibody test can be reliably used only after 18months in a child to diagnose HIV, it can however be useful to exclude HIV infection in children. A negative HIV antibody test in a known HIV-exposed infant can be used for excluding HIV infection if there is no ongoing exposure. However a child is suspected to have HIV infection if the child exhibits any clinical features as described in WHO clinical staging. When DNA- PCR test becomes available, we should test the baby's blood at 4- 6

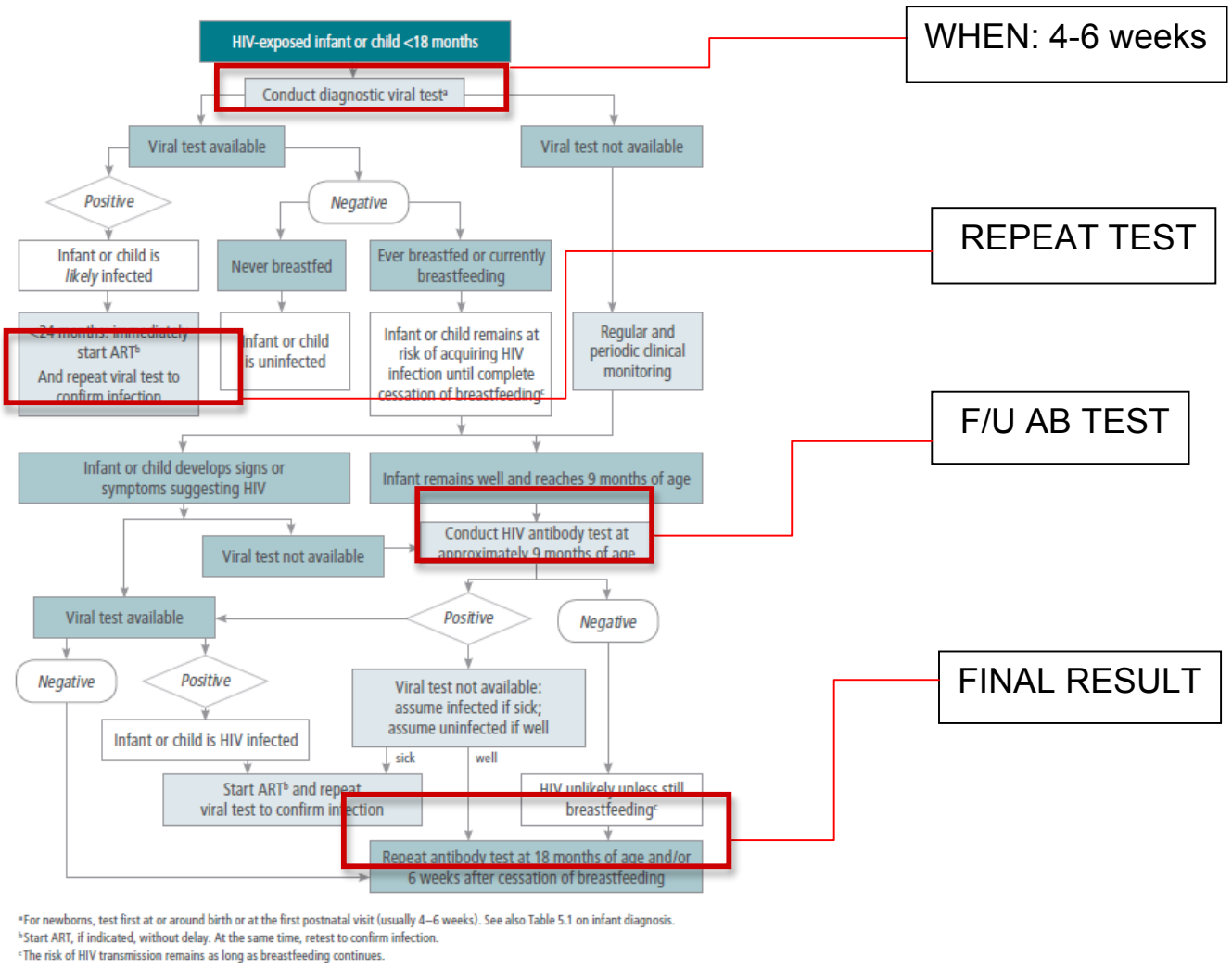
weeks. If not, it is thereafter confirmed by a HIV anti- body testing after 18 months of age.

**Summary of recommend testing approaches**

**Table 1: Summary of recommended testing approaches for infants**

| Category | Test required | Purpose | Action |
|---|---|---|---|
| Well,HIV-exposed infant | Virological testing at 4-6 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 (at last immunization, usually 9 months) | To identify infant 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 |
| 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 | Reactive - 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 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. |

**Algorithm for EID**




[a]For newborns, test first at or around birth or at the first postnatal visit (usually 4–6 weeks). See also Table 5.1 on infant diagnosis.
[b]Start ART, if indicated, without delay. At the same time, retest to confirm infection.
[c]The risk of HIV transmission remains as long as breastfeeding continues.

**Presumptive Diagnosis if EID is unavailable**

If the child is < 18 months and has symptoms and signs that are suggestive of HIV infection and there is no virologic testing available, it is possible to make a presumptive diagnosis by addressing the following issues:

| |
|---|
| A presumptive diagnosis of severe HIV disease should be made if:<br>The infant is confirmed HIV antibody positive;<br>and<br>Diagnosis of any AIDS-indicator condition (s) can be made;<br>or<br>The infant is symptomatic with two or more of the following:<br>• Oral thrush<br>• Severe pneumonia;<br>• Severe sepsis. |
| Other factors that support the diagnosis of severe HIV disease in an HIV sero-positive infant include:<br>Recent HIV-related maternal death; or advanced HIV disease in the mother; |

**Signs or conditions that may indicate possible HIV infection:**

HIV's clinical expression in children is highly variable. Many HIV-infected children develop severe HIV-related signs and symptoms in the first year of life. Other HIV-infected children remain asymptomatic or mildly symptomatic for more than a year and may survive for several years ( rapid and slow progressors respectively )

Suspect HIV if any of the following symptoms, signs, and/or clinical events are present, as they are not common in children without HIV:

- *Recurrent infection:* three or more severe episodes of a bacterial infection (such as pneumonia, meningitis, sepsis, cellulitis) in the past 12 months.

- *Oral candidiasis* : After the neonatal period the presence of oral thrush is highly suggestive of HIV infection when it is occurring when there has been no antibiotic treatment, lasting over 30 days despite treatment, recurring, extending beyond the tongue, or presenting as oesophageal candidiasis.

- *Chronic parotitis:* unilateral or bilateral parotid swelling for >14 days, with or without associated pain or fever.

- *Generalized lymphadenopathy*: enlarged lymph nodes in two or more extra-inguinal regions without any apparent underlying cause.

- *Hepatomegaly with no apparent cause*: in the absence of concurrent viral infections such as cytomegalovirus (CMV).

- *Persistent and/or recurrent fever: fever* (>38°C) lasting >7 days, or occurring more than once over a period of 7 days.
- *Neurological dysfunction*: progressive neurological impairment, microcephaly, delay in achieving developmental milestones, hypertonia, or mental confusion.
- *Herpes zoster (shingles*): painful rash with blisters confined to one dermatome on one side.
- *HIV dermatitis*: erythematous papulular rash. Typical skin rashes include extensive fungal infections of the skin, nails and scalp, and extensive molluscum contagiosum.
- *Chronic suppurative lung disease.*
- Signs or conditions very specific to HIV-infected children:
  Strongly suspect HIV-infection if the following conditions, which are very specific to HIV, are present: pneumocystis pneumonia (PCP), oesophageal candidiasis, lymphoid interstitial pneumonia (LIP), and in girls, acquired recto-vaginal fistula.
- Moderate or severe malnutrition: weight loss or a gradual but steady deterioration in weight gain from expected growth, as indicated on the child's growth card. Suspect HIV particularly in breastfed infants <6 months old who fail to thrive.

**Anti-Retroviral Therapy**

**When to start**

| | |
|---|---|
| **Children** | ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.<br><br>ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≤500 cells/$mm^3$, regardless of WHO clinical stage.<br><br>ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count. |

| | |
|---|---|
| | ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection. |

**What to start**

| | |
|---|---|
| **First line ART for children younger than 3 years of age** | • AZT + 3TC + LPV/r (preferred option)<br>• AZT + 3TC + NVP (alternative option) |
| **First line ART for Children 3 -10 years of age or >35 Kgs.** | • AZT +3TC + EFV (preferred option)<br>• AZT +3TC + NVP (alternative option) |
| **Children > 10 yrs or > 35kgs** | • Follow Adult regime - TDF+3TC + EFV |
| **Special Circumstances** | • d4T +3TC+LPV/r<br>• d4T +3TC+NVP |

**Refer to Annexure 5 for drug dosing*

**WHO Paediatric Clinical Staging for HIV**

In a child with diagnosed or highly suspected HIV infection, the clinical staging system helps to assess the degree of damage to the immune system, and to plan treatment and care options. The stages determine the likely prognosis of HIV and are a guide when to start, stop, or switch ARV therapy.

The clinical stages identify a progression sequence from least to most severe (number 1 through 4) - the higher clinical stage, the poorer the prognosis. For classification purposes, once a stage 3 clinical condition has occurred, the child's prognosis will likely remain in stage 3 and will not improve to stage 2, even once the original condition is resolved, or a new stage 2 clinical condition appears. Antiretroviral treatment with good adherence dramatically improves prognosis.

The clinical staging events can also be used to identify the response to ARV treatment if there is no easy or affordable access to viral load or CD4 testing.

(Refer to Annexure 6 for WHO clinical staging)

***Managing common co-infections and co-morbidities***

The natural history of opportunistic infections among children might differ from that observed among HIV-infected adults. Opportunistic infections among HIV-infected children more often reflect primary infection with the pathogen. In addition, among children with perinatal HIV infection, the primary infection with the opportunistic pathogen is occurring after HIV infection is established when the child's immune system might already be compromised. This can lead to different manifestations of disease associated with the pathogen among children than among adults. For example, young children with TB are more likely to have extra pulmonary and disseminated infection than adults, even without concurrent HIV infection. This section provides a brief overview of the most common and important conditions.

**Pneumonia in HIV-infected or exposed children**

- HIV-infected/exposed children are at significantly increased risk of developing pneumonia
- History and diagnosis of very severe, severe and non-severe pneumonia is the same in HIV-infected/exposed children as in HIV-negative children
- Provide same treatment to HIV-infected/exposed children with pneumonia.
- For severe and very severe pneumonia one should use a combination of Ampicillin or Crystalline Penicillin and Gentamicin as first line. If this fails use ceftriaxone as 2nd line or Ciprofloxacin and Gentamicin.

- In addition, all HIV-exposed/infected children 1-12 mo age with features of pneumonia and severe pneumonia should receive additional oral Co-trimoxazole in high doses, TMP 5 mg/kg + SMX 25 mg/kg 4 times/day for 21 days as for treatment of PCP.
- If bacterial pneumonia, response is fast within 3-5 days. Delayed responses only after 5-7 days would favour PCP though other disorders (Foreign body, complicated bacterial pneumonias, asthma, Tuberculosis, inappropriate antibiotics, resistant organisms, underlying LIP, bronchiectasis, etc.) need to be evaluated as usual.

**Table 2: Differential Diagnosis of Child with Cough or difficulty breathing in HIV positive**

| Diagnosis | Features In Favour |
|---|---|
| Pneumocystis pneumonia (PCP) | Mild fever<br>Hypoxia and degree of respiratory distress (Fast breathing, Chest retractions) disproportionate to findings on auscultation<br>On irregular or not on routine Co-trimoxazole (TMP-SMX) prophylaxis |
| Lymphoid Interstitial Pneumonia LIP | Persistent cough with or without mild-severe exertional breathlessness.<br>Clubbing, stunted growth, generalized lymphadenopathy, bilateral parotid enlargement, hepatosplenomegaly.<br>Normal respiratory tract examination or localized bilateral crepitations/ rhonchi.<br>Features of corpulmonale with evidence of right heart failure (Cough/ breathlessness, raised JVP, tender hepatomegaly, bilateral pitting pedal edema, prominent 2nd heart sound on auscultation |
| Pulmonary TB | Failure to thrive;<br>Persistent non-remittent cough (lasting >30 days)<br>Weight loss<br>Persistent fever poorly responsive to appropriate antibiotics and Antimalarials<br>Decreased activity/weakness.<br>Contact with an adult with diagnosed TB or presenting with persistent non-remittent cough, weight loss and persistent fever especially an immediate family member |
| Bronchiectasis | Persistent cough with productive purulent sputum, hemoptysis<br>Persistent fever<br>Clubbing, malnutrition, persistent localized coarse crepitations |

**Diarrhoea in an HIV infected child**

Acute diarrhoea should be managed the same as in non-HIV infected children, though as mentioned, HIV-infected children are more prone to persistent diarrhoea.

**Persistent Diarrhoea in HIV-infected children**

Persistent or chronic diarrhoea is described as diarrhoea (loose or watery stools, >3 times a day) of 14 days or more in duration. The differential diagnosis of persistent diarrhoea in HIV-infected children includes opportunistic infections (viral, bacterial, protozoal, parasites), secondary conditions (allergies, lactose intolerance), HIV-related medication side effects, and nutritional deficiencies.. Therefore, an empirical treatment approach is needed.

**The presence of unexplained persistent diarrhoea places an HIV-infected child into WHO Stage 3 disease, thereby making the child eligible for ART**.

**Investigations**

Investigations that may support a diagnosis are listed below:

| Investigation | Comment |
|---|---|
| Stool microscopy for WBCs/ 5-10 hpf and specific etiologies | Stool WBC/hpf> 10 suggests Shigella, Entamoebahistiolytica, CMV or Invasive E.coli<br>Stool WBC/hpf 0 suggests normal or Cryptosporidia, Cyclospora, Giardia lamblia, MAC<br>Specific organisms may be identified such as giardia lamblia and entameoba. |
| Stool for modified ZN stain | Cryptosporidia, Cyclospora |
| Stool pH and reducing Substances | Stool pH < 5.5 and reducing substances positive suggests lactose intolerance |
| Stool for ova and cysts | Helminthiasis, EntamoebaHistolytica |
| CD4 Count/ CD4 % | CD4 < 50/$mm^3$: consider Disseminated CMV, Disseminated MAC<br>CD4 < 100/$mm^3$:Cryptosporidosis, chronic Microsporidiosis |

**Hepatitis in HIV-Infected child**

Hepatomegaly and mildly elevated liver enzymes are common in HIV infected children, though chronic or progressive liver disease is unusual. Hepatitis could occur in children infected with HIV due to:

a. Co-infections with Virus (Hepatitis A,B.C,D, E, CMV, EBV,etc )
b. Co-infections with MAC and complications of Cryptosporidia..
c. Drug toxicity
d. Fatty liver

**Hematological Manifestations**

Pediatric HIV disease is associated withdifferent hematological abnormalities presenting as pallor, neutropenia, lymphopenia, thrombocytopenia and eosinophelia.Thrombocytopenia can be present with petechiae and ecchymosis and may be diagnosed as Immune Thrombocytopenia. Alteration of hematological profile occurs due to the virus itself,opportunistic infections,drugs side effects or antibody mediated cellular destruction.

**Hematological Abnormalities**

**Table 3.Clinical manifestations and underlying mechanism**

| Hematological Abnormality | Mechanisms |
|---|---|
| **Anemia** | • Auto-immune antibodies that cause destruction of erythrocytes,Suppression of the bone marrow by drugs used in treatment of HIV-infection (e.g. AZT) or of associated infections(i.e. Ganciclovir, Cotrimoxazole; nutritional deficiency (folic acid, vitamin B12, micronutrients) |
| **Thrombocytopenia** | • Immune-mediated destruction of platelets, nutritional deficiency (i.e. vitaminB12 deficiency) |
| **Neutropenia** | • immune-mediated destruction of leukocytes |
| **Lymphopenia** | • Bone marrow suppression due to altered cytokine production,CD4+apoptosis induced byHIVreplication |
| **Eosinophilia** | • Shifting of immune response fromTh1 to Th2 cytokineprofile. |

**Cardiac Manifestation**

- HIV infection does not increase the risk of developing congenital cardiac malformations. However, cardiovascular diseases do seem to develop in HIV-infected children, and they are often clinically silent.
- The cardiac manifestations include cardiomegally, congestive cardiac failure, non-bacterial thrombotic endocarditis, cardiomyopathy, pericardial effusion, cardiac tamponade, conduction disturbances and sudden death.
- Cardiomyopathy is frequently present in patients with encephalopathy. The factors that have been implicated in the causes of cardiomyopathy include primary HIV disease, immune-mediated reactions, intercurrent infections and drug toxicity
- Cardiomyopathy decreases the survival rates and is one of the clinical indicators of starting ARV drugs.

**Neurological Manifestation**

- Primary CNS infection by HIV is quite common as it is a neurotropic virus.
- Two forms of encephalopathy exist- Progressive and static.
- HIV leads to myriad of CNS problems of varied etiology that are both infectious and non-infectious.

According to the CDC revised system, the diagnosis of encephalopathy requires one of the following progressive findings to be present for at least 2 months in the absence of other identifiable causes.

- Failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychiatrical tests.
- Impaired brain growth or microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by CT or MRI, with serial imaging required in children less than 2 years of age.

Acquired symmetric motor deficit manifested by two or more of the following paresis, pathological reflexes,ataxia or gait disturbances.

- CT may show evidence of cortical atrophy, prominent sulci, and enlarged ventricles and decreased attenuation of white matter suggestive of progressive mutifocalleucoencephalopathy.

**Nephropathy**

- The proportion of HIV-infected children who have nephropathy is variable and is more in adolescent.
- The manifestations or renal disease associated with AIDS include proteinuria, hematuria hypertension, renal tubular acidosis, acute renal failure and progression to end-stage renal disease.
- In the initial stages, the patient could be asymptomatics, although laboratory evidence of nephropathy can be found on investigations.
- Histological changes inAIDS nephropathy reveal focal segmental glomerulosclerosis, minimal lesion glomerulonephritis, IgA nephropathy.
- Nephropathy may be due to direct infection of the virus, immune complex vasculitis, or as a result of various opportunistic infections or drugs.

**Prognostic indicators**

- In the underdeveloped countries the age at diagnosis and the type of clinical presentation are the only clinical factors related to prognosis.
- Infants who develop symptoms in the first year of life manifest the fastest progression of illness with worst outcome.
- Similarly, the occurrence of opportunistic infections, progressive encephalopathy or hypogammaglobunemia at any age often carries a poor prognosis.
- In contrast, generalized lymphadenopathy, hepatosplenomegaly, parotitisare associated with a more favorable outcome.
- **Viral load** is the most important prognostic marker of the risk of progression. But the availability and the cost are constraints. It is predicted that a favorable clinical outcome is most likely if virus replication is maximally suppressed before the immune system is irreversiblydamaged.

**Prophylaxis for HIV-infected Children**

- Cotrimoxazole Prophylaxis

**Co-trimoxazole preventive therapy starting at 6 weeks of age**

Co-trimoxazole prophylaxis prevents pneumocystis pneumonia (PCP) in infants and reduces morbidity and mortality among infants and children living with, or exposed, to HIV. Co-trimoxazole protects against common bacterial infections, toxoplasmosis, and malaria.

All children born to HIV-infected mothers should receive Co-trimoxazole prophylaxis starting at 6 weeks after birth, or at first encounter with the health care system.

**When to Discontinue CTX**

| Group | Discontinue Cotrimoxazole |
|---|---|
| HIV-exposed children | Give CTX until HIV infection has been ruled out and the baby is no longer breast-feeding. |
| Children less than 5 years living with HIV | Maintain on CTX prophylaxis until age 5 years irrespective of clinical and immune response |
| HIV-infected children on ART and> 5 years old | CTX can be stopped only when clinical or immunological indicators confirm restoration of the immune system for more than 6 months i.e. in a child > 5 years of age with a CD4 count of > 500 cell/mm3 on two occasions not less than 3 months apart (as per adult guidelines |

**Isoniazid (INH) Preventive Therapy (IPT) for children less than 5 years**

An HIV-positive infant or child with no evidence of TB, especially in resource limited settings with high prevalence of TB, should be given INH preventive therapy to reduce the incidence of TB and death among these children.

INH should be given for 6 months at a dose of 10mgs/kg/ day to a maximum of 300mgs per day.

All HIV-positive children that successfully complete treatment for TB disease should receive INH for an additional 6 months.

**Decrease the burden of TB in people living with HIV with the Three I's for HIV/TB**

1. Establish Intensified TB case-finding.
2. Introduce Isoniazid prevention therapy (IPT).
3. Ensure TB Infection control in health care and congregate settings.

**Summary of Opportunistic infections**

*Table 4: Summary of clinical diagnosis and management of common opportunistic infections in children*

| Opportunistic Infections | Clinical and lab manifestations | Diagnosis | Treatment |
|---|---|---|---|
| **Pneumocystis jiroveci pneumonia (PCP)** | Dry cough, tachypnea, dyspnea, cyanosis | Chest X-ray: bilateral diffuse parenchymal infiltrates with "ground-glass" or reticulogranular appearance.<br>Associated with a high level of lactate dehydrogenase (LDH).<br>Microscopy of induced sputum by bronchoalveolar lavage (BAL): GMS stain- stains cyst wall in brown or black, Wright stain: stains the trophozoites and intracysticsporozoites in pale blue | TMP/SMX 15-20 mg/kg/day of TMP in 3-4 divided dose for 21-day course<br>Steroids e.g. prednisolone can be used for severe acute PCP |
| **Candidiasis** | Oral candidiasis: creamy white curd-like patches that can easily | Oral candidiasis:<br>KOH preparation demonstrates budding yeast | Oral candidiasis<br>Clotrimazole oral 10 g or<br>Nystatin 400,000 600,000 units 5 |

| | | | |
|---|---|---|---|
| | be scraped off with inflamed underlying mucosa.<br>Esophageal candidiasis: odynophagia, dysphagia, and/or retrosternal pain. | cells.<br>Esophageal candidiasis: Barium swallow show cobblestone appearance.<br>Endoscopy show small white raised plaques to elevated confluent plaques with hyperemia and extensive | times daily 7–14 days.<br>or<br>Oral fluconazole 3-6 mg/kg once daily 7–14 days.<br>Esophageal candidiasis<br>Oral fluconazole 3-6 mg/kg once daily 14–21 days. |
| **Cryptococcosis** | Meningoencephalitis manifestation: fever, headache, altered mental status, nuchal rigidity<br>Disseminated manifestation: persistent fever with translucent umbilicated papules which may resemble molluscum | Elevated intracranial pressure and elevated CSF protein and mononuclearpleocytosis.<br>India ink stain of CSF should show budding yeast.<br>Cryptococcal antigen can be detected in CSF or serum by latex agglutination test.<br>Wright stain of skin scraping shows budding yeast. | Induction therapy:<br>Amphotericin B (0.7-1.5 mg/ kg/day) plus flucytosine (25 mg/kg/dose four times daily) for 2 weeks.<br>Consolidation therapy:<br>Fluconazole 5–6 mg/kg/dose twice daily for 8 weeks.<br>Maintenance therapy:<br>Fluconazole 3–6 mg/kg/day. |
| **Herpes simplex** | HSV gingivostomatitis: fever, irritability, superficial painful ulcers in the gingival, oral mucosa and perioral area.<br>HSV encephalitis: fever, alteration of consciousness, abnormal behavior. | HSV gingivostomatitis is diagnosed by clinical evaluation.<br>HSV encephalitis is diagnosed by detection of HSV DNA in the CSF.<br>HSV | HSV gingivostomatitis:<br>oral acyclovir 20 mg/kg/dose three times daily<br>or<br>intravenous acycolovir 5-10 mg/kg/dose three times daily for 7-14 days.<br>Disseminated HSV or encephalitis: intravenous acyclovir 10 mg/mg/dose or 500 mg/m2/dose three times daily for 21 days. |
| **Herpes Zoster** | Primary varicella infection: Generalized pruritic vesicular rash.<br>Herper zoster: Painful rash with fluid-filled blisters, dermato-maldistribution | Use clinical diagnosis.<br>If clinical diagnosis is not clear then Giemsa staining (Tzanck preparation) of cell scrapings from lesions can be done.<br>show multinucleated giant cells suggestive of VZV (Note that this is also seen in HSV infection). | Primary varicella infection:<br>intravenous acyclovir 10 mg/ mg/dose or 500 mg/m2/dose three times daily for 7 days in children with moderate to severeimmuno-suppresion.<br>Oral formulation should be used only in a child with mild immunosuppression.<br>Herper zoster:<br>Oral acyclovir 20 mg/kg/dose four times daily (max 800 mg/ dose) for 7 days |
| **Cytomegalovirus** | CMV retinitis:<br>Young HIV-infected children are frequently asymptomatic and discovered on routine examination. Older children present with floaters or loss of vision.<br>Extraocular CMV disease: CMV colitis, CMV esophagitis, CMV pneumonitis, CMV hepatitis. | Diagnosis of CMV retinitis is based on clinical appearance with white and yellow retinal infiltrates and associated retinal hemorrhages.<br>Extraocular CMV disease:<br>recover of virus from tissues or histopathology demonstrates characteristic “owl’s eye” intranuclear inclusion bodies or positive staining with CMV monoclonal antibodies biopsy | Ganciclovir intravenous 5 mg/kg/dose twice daily for 14-21 days followed by lifelong maintenance therapy. |
| **Mycobacterium avium complex (MAC)** | Fever, night sweats, weight loss, fatigue, chronic diarrhoea and abdominal pain.<br>Laboratory findings: neutropenia, elevations in alkalialkaline | Definitive diagnosis: isolation of organism from blood or specimens from normally sterile sites.<br>Histology demonstrating macrophages-containing acid-fast bacilli is a suggestive finding | ART should be provided to restore immune function.<br>Treatment with at least 2 drugs:<br>Clarithromycin 7.5-15 mg/kg twice daily (max 500 mg/dose) plus Ethambutol 15-25 mg/kg/ |

| | | | |
|---|---|---|---|
| | phosphatase or lactate dehydrogenase. | | day once daily (max 1 g/dose). Consider adding a third drug e.g. Amikacin or ciprofloxacin in severe cases. Duration of treatment: at least 12 months |
| **Cryptosporidiosis** | Subacute or chronic watery diarrhoea often associated with cramps, nausea and vomiting | Modified Kinyoun acid-fast stain of stool: small oocyst (4–6 µm in diameter) | Effective ART is the only treatment that controls persistent cryptosporidiosis. Supportive care with hydration, correction of electrolyte abnormalities, and nutritional supplementation. Nitazoxanide is approved for treatment (age 1–3 years 100 mg twice daily, age 4–11 year 200 mg twice daily |

**Nutrition**

A child has increased energy needs associated with HIV infection, which requires a proactive approach to nutritional support after 6 weeks

- From the time of first infection, energy needs increase by about 10%
- In HIV-infected children with chronic conditions such as LIP, persistent diarrhoea, HIV-related malignancies, and during infections such as TB, energy needs can increase by about 25-30%
- During and following periods of severe malnutrition, energy requirements may increase by 50-100% in order to recover weight

These increased requirements are over and above normal energy and protein requirements that are needed by all children to support normal growth and development

**Infant Feeding/Replacement Feeding:**

Breastfeeding is associated with significant additional risk of HIV transmission from mother-to child. The risk of transmission is about 20-35% with breast feeding up to six months. These risk further increases to 30-45% if breastfeeding is continued to 24 months. The Royal Government of Bhutan has thus decided to counsel all HIV positive mothers not to breastfeed and that the Government will supply infant formula for the first two years of life. All HIV infected mothers will be counseled for formula feeding and provided with formula milk support till 24 months of age.

**Approximate amount of formula needed per day**

| Age in months | Weight in kilos | Approximate amount of formula per 24 hours | Approximate number of feeds |
|---|---|---|---|
| 1 | 3 | 450 ml | 8*60 ml |
| 2 | 4 | 600 ml | 7*90 ml |
| 3 | 5 | 750 ml | 6*120 ml |
| 4 | 5+ | 750 ml | 6*120 ml |
| 5 | 6 | 900 ml | 6*150 ml |
| 6 | 6+ | 900 ml | 6*150 ml |

In the first two months of life advise the mother to feed at least 8 times in 24 hours. Therefore the number of feed may be decreased to 6 times in 24 hours.

**Commercial infant formula requirements**

The amount of milk that needs to be given for each baby at various age is given below. However should the mother ask for more she may be given as extra one or two tins provided it is documented that her baby is growing well.

| Months | 500g tins needed per month | 450g tine needed per month |
|---|---|---|
| 1 | 4 tins | 5 tins |
| 2 | 6 tins | 6 tins |
| 3 | 7 tins | 8 tins |
| 4 | 7 tins | 8 tins |
| 5 | 8 tins | 8 tins |
| 6 | 8 tins | 9 tins |
| 7-8 | 7 tins | 8 tins |
| 9-11 | 6 tins | 6 tins |

**Monthly requirements of milk (approximately)**

| Age in months | Milk feeds per day | Cow's milk, water and sugar to make home prepared formula per day | Commercial formula needed per month |
|---|---|---|---|
| 1 | 450 | 300 ml milk + 150 ml water + 30g sugar | 4*500g tins |
| 2 | 600 | 400 ml milk + 200 ml water + 40g sugar | 6*500g tins |
| 3 | 750 | 500 ml milk + 250 ml water + 45g sugar | 7*500g tins |
| 4 | 750 | 500 ml milk + 250 ml water + 45g sugar | 7*500g tins |
| 5 | 900 | 600 ml milk + 300 ml water + 56g sugar | 8*500g tins |
| 6 | 900 | 600 ml milk + 300 ml water + 56g sugar | 8*500g tins |
| **Total for 6 months** | | 92 Liters of milk + 9 kg of sugar | 40 * 500g (20 kg) |

**Up to 6 Months of Age**

- Give formula feeds only
- Other foods or fluids are not necessary
- Prepare correct strength and amount just before use. Use milk within two hours and discard any left over
- Cup feeding is safer than bottle feeding
- Clean the cup and utensils with hot soapy water
- Give these amounts of formula 6 to 8 times per day *

**6 months up to 12 months**

- Give about 1-2 cups (500 ml) of full cream milk or infant formula per day
- Give milk with a cup, not a bottle
- If no milk is available, give 4-5 feeds per day
- Give 3 adequate servings of nutritious complementary foods plus one snack per day (to include protein,
- mashed fruit and vegetables). Each meal should be 3/4 cup*.
- If possible, give an additional animal-source food such as liver or meat.

**12 month up to 2 years**

- Give 3 adequate nutritious feeds plus 2 snacks per day (each meal should be 1 cup).
- If possible, give an additional animal-source food, such as liver or meat.
- Give fruit or vegetables twice every day
- Give about 2 cups (250 x 2=500 ml) of full cream milk or infant formula per day. If
- no milk is available, give 4-5 feeds per day.
- Feed actively with own plate and spoon

**Disclosure for children**

Disclosure of HIV diagnosis to infected children is a complex process that presents a challenge to both families and health care providers. Obstacles to disclosure of HIV diagnosis to children include:

- Fears regarding a decrease in the child's will to live
- Fears regarding retaliation or discrimination based on stigma
- Parental guilt about prenatal transmission of HIV infection
- Child's difficulty keeping a secret
- Parent's denial and/or difficulty confronting their own illness.

**Disclosure of HIV infection status to children should take into consideration**

- Their age, psychosocial maturity, the complexity of family dynamics, and the clinical context.
- The exact diagnosis and prognosis of the disease.
- Child's ability to cope with knowledge of life-threatening infection
- Child's circumstances- e.g. when informing school going children- discrimination in schools, communities, and families remains a serious problem.
- Disclosure of HIV status to children should include continued counselling about disclosure and its impact, for both the child and parents.
- Disclosure may be partial or complete depending on the age and level of functioning of the child. Partial disclosure aims to describe what's happening to the body and what treatments will help to resolve this, rather than naming the virus or illness. Complete disclosure involves open discussion about the virus, infection, and all other issues relating the HIV infection. This must be done together with the child and parent/caregiver.
- Counselling for disclosure is an ongoing process and the health care provider needs to work with the child on every visit. Ideally the caregiver should be the one to disclose information to the child.

- Disclosure to children should be done little by little, encouraging questions, providing truthful answers, and making the child understand they can comeback with more questions at any time.
- Counselling the caregiver for guidance on disclosure of HIV status is important component of the counseling process. Counselling techniques used should be individualized based on the child's age, maturity, clinical and social circumstances; and should facilitate the child's capacity to cope with their illness.

*(Refer to VCT guidelines)*

Chapter XIII

# PHARMACOLOGY OF ANTI RETROVIRALS

Substantial advances have been made in antiretroviral therapy since the introduction of the first agent, Zidovudine, in 1987. Greater knowledge of viral dynamics through the use of viral load and resistance testing has made it clear that combination therapy with maximally potent agents will reduce viral replication to the lowest possible level and decrease the likelihood of emergence of resistance. Thus, administration of combination antiretroviral therapy, typically comprising at least three antiretroviral agents, has become the standard of care.

Six classes of antiretroviral agents are currently available for use: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs),non nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, and integrase inhibitors.

Combinations of three anti-retrovirals typically two reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or boosted protease inhibitor is referred to as ***highly active antiretroviral therapy*** (***ART***). These drug regimens have produced sustained reductions in viral load often to levels below the limit of detection, and have been associated with improvements in CD4 cell counts, immune function, and clinical well-being.

**Nucleoside reverse transcriptase inhibitors (NRTIs)**

Nucleoside Reverse Transcriptase Inhibitors targets the HIV enzyme reverse transcriptase. Acting as alternative substrate, they compete with physiological nucleosides which in turn get incorporated into viral DNA.
NRTIs are easy to take, does not have significant interaction with food and once daily dosing is sufficient for most of these drugs. Overall tolerability is good. Lamivudine, zidovudine and tenofovir are the NRTIs available in Bhutan for the treatment of HIV infection.

**Lamivudine (3TC)**

*(Available as 150mg tablets and 10mg/mL syrups.)*

Lamivudine is well tolerated and considered the safest of NRTIs. It is also effective against Hepatitis B virus. Use in pregnancy is extensive and well established.

## Dose

- 150mg BD or 300mg once daily orally; no interaction with food
- Dose adjustment is required with reduced creatinine clearance

## Side Effects

- Side effects are minimal
- Infrequent complications include headache, nausea, diarrhoea, abdominal pain and insomnia.
- Class related side effect of lactic acidosis and steatosis are listed but not clear if it can be attributed to 3TC therapy.

**Zidovudine (AZT)**

*(Available as 300mg tablets and 10mg/mL syrup)*

Zidovudine was the first antiretroviral agent to be made available and it still holds an important place as one of the most widely used antiretroviral agents as a component of ART. It is also used as a monotherapy to prevent vertical transmission from mother to child.

## Dose:

- 300mg 12 hourly (>70kg weight) or 200mg 8 hourly
- No interaction with food

## Side Effects

Bone marrow suppression (macrocytic anaemia and neutropenia) is a most common serious side effect which occurs within a few weeks of starting treatment. Other less serious but frequently seen side effects include asthenia, fever, malaise, dizziness, headache, abdominal pain, anorexia, dyspepsia, taste disturbance, diarrhoea, nausea, vomiting, and rashes. Class related side effects such as lactic acidosis and severe hepatomegaly with steatosis have been reported as rare, but can be fatal; myopathy due to mitochondrial toxicity may occur. Pancreatitis, convulsions, and pigmentation of nails, skin, and oral mucosa may also occur.

**Tenofovir (TDF)**

*(Available as 300mg capsules)*

TDF belongs to a distinct class of nucleotide reverse transcriptase inhibitors (NRTIs). It forms the mainstay of triple regimen in patients with HBV coinfection owing to its established efficacy against HBV.

## Dose

- 300 mg once a day orally to be taken with food; the dose of Tenofovir is expressed in terms of its ester desoproxil fumarate which is equivalent to 136 mg Tenofovir.
- Dose adjustment is required in case of renal impairment as follows:
    - Cc 30-49mL/minute, 300mg every 48 hours
    - Cc 10-29mL/minute, 300mg twice a week

## Side Effects

The most common side effects associated with Tenofovir include nausea, vomiting, diarrhea, and asthenia. Less frequent side effects include hepatotoxicity, abdominal pain, peripheral neuropathy, myalgia and skin rashes. Hypophosphatemia is also common. Nephritis, nephrogenic diabetes insipidus, renal impairment, acute renal failure, and effects on the renal proximal tubules, including Fanconi syndrome is a concern. There have also been reports of raised liver enzymes, hepatitis, hypertriglyceridaemia, hyperglycaemia and neutropenia.

## Precaution

Tenofovir should be used with caution, and doses modified, in patients with renal impairment. Renal function and serum phosphates should be monitored before treatment is started, every 4 weeks during the first year of therapy, and then every 3 months; in patients with a history of renal impairment or who are particularly at risk, more frequent monitoring may be needed.

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

As with the nucleoside analogs, the target enzyme of NNRTIs is reverse transcriptase. In contrast to the NRTIs, they are not false building blocks, but rather bind directly and non-competitively to the enzyme, at a position in close proximity to the substrate binding site for nucleosides.

The currently available NNRTIs in Bhutan are nevirapine and efavirenz. The simple dosing and the overall good tolerability are some of the advantages.

**Nevirapine (NVP)**

*(Available as 200mg tablets and 10mg/mL syrup)*

Nevirapine is one of the most commonly used NNRTI as a component of ART. It is also used for PMTCT.

## Dose

200 mg once daily for the first 14 days; then increased to 200 mg twice daily if there is no rash. If rash is seen, the dose should not be increased till the rash resolves. It is readily absorbed after oral administration and has no significant interaction when taken along with food.

## Side effects

The most common adverse effect of nevirapine is skin rash, usually occurring within the first 6 weeks of starting therapy. Severe and life-threatening skin reactions including Stevens-Johnson syndrome and, more rarely, toxic epidermal necrolysis have been reported. Severe hepatotoxicity, including hepatitis and hepatic necrosis, has occurred and may be more prevalent in women and patients with high CD4 cell counts at the start of treatment. Other common adverse effects include nausea, vomiting, diarrhoea, abdominal pain, fatigue, drowsiness, and headache.

## Drug Interactions

- Rifampicin, protease inhibitors and oral contraceptives decrease the level of nevirapine.
- Use of nevirapine with ketoconazole and oral contraceptives is not recommended.

## Caution

- Use of nevirapine with ketoconazole and oral contraceptives is not recommended.
- Therapy should be interrupted in patients who developmoderate to severe liver functions test results.
- Therapy should be reinstated with a 14 day once daily dosing when liver function returns to normal.
- If liver function worsens nevirapine should be discontinued.

**Efavirenz (EFV)**

*Available as 600mg tablets*

Efavirenz is used as an alternative to Nevirapine when Nevirapine is not tolerated or contraindicated and vice versa.

## Dose

As capsules

Adult and child 40kg and over – 600mg OD

Child 33-39 kg - 400mg OD
Child 25-32kg – 350mg OD
Child 20-24kg – 300mg OD
Child 15-19kg – 250mg OD
Child over 3 years / 10 – 14kg – 200mg OD

Bioavailability of Efavirenz from the oral solution is less than that from the capsule and so proportionately higher doses should be used.

As an oral solution;

Adult and child 40kg and over 720mg OD

Child 33-39 kg – 510mg OD

Child 25-32kg – 450mg OD
Child 20-24kg – 360mg OD
Child 15-19kg – 300mg OD
Child over 3 years / 10 – 14kg – 270mg OD

Dose should preferably be taken at bed time to reduce occurrence of CNS side effects.

## Side Effects

The most common adverse effects associated with efavirenz are skin rashes and CNS disturbances. CNS symptoms include dizziness, headache, insomnia or somnolence, impaired concentration, abnormal dreaming, and convulsions. Symptoms resembling psychoses and severe acute depression have also been reported. Other adverse effects include nausea and vomiting, diarrhoea, fatigue, and pancreatitis. Raised liver enzyme values have been noted, particularly in patients with viral hepatitis. Raised serum-cholesterol and -triglyceride concentrations have been reported.

## Precautions

- Efavirenz is contra-indicated in patients with severe hepatic impairment, and should be used with caution, and liver enzymes values monitored, in patients with mild to moderate liver disease.
- Caution should be exercised in patients with a history of seizures or psychiatric disorders. Efavirenz should be discontinued if a severe skin rash, associated with blistering, desquamation, mucosal involvement, or fever, develops.
- Monitoring of plasma-cholesterol concentrations may be considered during Efavirenz treatment.

## Drug Interactions

Efavirenz both induces and, to a lesser extent, inhibits the cytochrome P450 enzyme system, exerting a variable effect on concentrations of concurrently administered drugs that utilize this enzyme system.

### Protease Inhibitors (PIs)

PIs prevent viral replication by inhibiting the activity of protease enzyme used by HIV to cleave nascent proteins for final assembly of new virions**.** The current practice of using boosted PIs is because the concentration of one PI is increased by many folds when boosted with a booster dose of PI such as ritonavir which is a potent inhibitor of the isoenzyme 3A4, a subunit of the hepatic enzyme cytochrome P450. This useful interaction between ritonavir and the other PIs simplifies daily regimens by reducing the frequency and number of pills to be taken every day, in many cases independent of food intake.

### Lopinavir/Ritonavir (LPV/r)

*Available as 200/50mg tablets or 400/100mg*

**LPV/r** is a co-formulation of Lopinavir and Ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster).

## Dose

Adults: 400/100mg twice a day to be taken after meals

## Side Effects

Diarrhoea in 15-25% nausea and abdominal pain, class side effects: insulin resistance, fat accumulation and hyperlipidemia, elevated trasaminases.

### Drug Interactions

Drug interactions with PIs are numerous and difficult to predict. Ritonavir is the most potent inhibitor of liver enzymes and is most likely to reduce the hepatic metabolism.

- Plasma concentration of Lopinavir decreased with Efavirenz and Nevirapine; once a day dosing of LPV/r may not suffice
- Concentration of Lopinavir decreased with Rifampicin
- Concentration of clarithromycin increased; dose reduction should be considered in renal failure
- Concentration of atorvastatin increased; uselowest possible dose of 10mg/day or use alternatives such as pravastatin,

- Concentration of hormonal contraceptives decreased, use alternative contraception.
- Increases concentration of ergot alkaloid; may lead to ergotism

**Drugs for Opportunistic Infections**

Most of the drugs for the treatment of Opportunistic infections are not available on the Essential Drugs List. They are usually procured on Named Patient Basis (*Form II duly signed by the treating Specialist*) by the Pharmacy Department of the JDWNRH and delivered to the patients or the health centres wherever required. The drugs are expensive therefore they should be ordered only for use for the indication(s) as specified in this guideline.

**Amphotericin B**

*(Powder for injection: 50mg vial)*

## Indications

- Oesophageal and oral candidiasis resistant to azole derivative.
- Cryptococcal meningitis.
- Histoplasmosis and coccidioidomycosis.
- Aspergillosis and penicillinosis.

## Dose

- Oesophageal and oral candidiasis : 0.5- 1mg/kg/day until symptoms resolve.
- Histoplasmosis and coccidioidomycosis: 0.5-1mg/kg/ day for at least 6 weeks.
- Penicillinosis: 0.6 - 1mg/kg/day for 7-14 days or until there is clinical resolution.

## Side Effects

Common adverse effects which occur during or following intravenous infusion of amphotericin B include headache, nausea, vomiting, chills, fever, malaise, muscle and joint pains, anorexia, diarrhoea, and gastrointestinal cramp. Hypertension, hypotension, cardiac arrhythmias including ventricular fibrillation and cardiac arrest, skin rashes, flushing, anaphylactoid reactions including bronchospasm and dyspnoea, blurred vision, tinnitus, hearing loss, vertigo, gastrointestinal bleeding, liver disorders, peripheral neuropathy, and convulsions have been reported occasionally. Partial reversible deterioration of renal function, progressive normochromic anaemia and thrombocytopenia are less common.

## Precautions

Concomitant administration of other nephrotoxic drug should be avoided.

1. **Azithromycin**(Capsule:250mg**,** Powder for Oral Suspension: 200mg/ml)

## Indications

Treatment and prophylaxis of *Mycobacterium avium* complex (MAC) infection

## Dose

- Treatment of MAC infection; 500mg once daily until the symptoms resolve
- Prophylaxis: 1.2g once a week indefinitely
- To be taken on empty stomach one hour before food or two hours after

## Side Effects

Gastrointestinal disturbances such as abdominal discomfort and cramp, nausea, vomiting, and diarrhoea are common but not as severe as erythromycin. Severe hypersensitivity reactions and photosensitivity occur rarely.

Transient reductions in neutrophil counts have been seen in patients receiving azithromycin. Pain and inflammation may occur at the site of intravenous infusions.

### Fluconazole

*(100mg tablet, Oral suspension 10mg/ml)*

## Indications

- Treatment and prophylaxis of cryptococcal meningitis: Following treatment with amphotericin B either for two weeks or until the condition improves fluconazole 800mg oral or intravenous for 2 days followed by 400mg once a day for 8 weeks and then reduced to 200mg OD.
- Treatment of oesophageal and resistant oropharyngeal candidiasis: 200mg initial loading dose followed by 100mg once a day until the symptoms resolve.
- Vaginal candidiasis: 150mg stat
- Treatment and maintenance of coccidiodomycosis: 400mg orally in patients not tolerating amphotericin B.

## Side Effect

Gastrointestinal tract side effects such as abdominal pain, diarrhoea, flatulence, nausea and vomiting, and taste disturbance are common. Other adverse effects include headache, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy.

## Drug Interactions

Dose should be increased by half if co administered with Rifampicin.

### Ganciclovir

*(Capsule 250mg, Powder for injection 500mg/vial)*

## Indications

Treatment of cytomegalovirus end organ disease: 5mg/kg by slow IV infusion twice a day for two to three weeks or until the symptoms resolve. Treatment and maintenance of CMV retinitis: 5mg/kg by slow IV infusion twice a day for two to three weeks followed by maintenance dose of 5mg/kg once a day.

## Side Effects

The most common adverse effects of intravenous Ganciclovir are haematological and include neutropenia and thrombocytopenia; anaemia also occurs. Other adverse effects occurring in patients given intravenous Ganciclovir include fever, rash, and abnormal liver function tests. Irritation or phlebitis may occur at the site of injection due to the high pH.

## *Common Complications of ART*

Patients on ART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. About 25 % of patients stop therapy within the first year on ART because of side effects.

The patient should be counselled in detail on the potential side effects, so that he or she is in a position to recognize them and to consult his physician in time. This can save livesand prevent the irreversible damage of side effects, such as polyneuropathythrough early diagnosis. Some of the notable side effects of ART are highlighted as follows:

## Lactic Acidosis

Lactic acidosis is a rare but life-threatening complication attributed to NRTIs. NRTIs are thought to cause mitochondrial toxicity via inhibition of the mitochondrial DNA polymerase. It occurs most frequently on treatment with Stavudine (no longer used in Bhutan), less in patients on Zidovudineand lamivudine.

The clinical symptoms, including fatigue, nausea and vomiting, abdominal pain, weight loss and dyspnoea, are non-specific and may develop acutely or more gradually. Blood results show elevated lactate levels with or without metabolic acidosis. CPK, LDH, lipase, amylase, γGT and the anion gap may be increased; serum bicarbonate may be decreased.

Risk factors are obesity, female, pregnancy and therapy with ribavirin or hydroxyurea, a diminished creatinine clearance, acquired Riboflavin and thiamine deficiency and a low CD4 cell nadir.

## Management

- Warrants discontinuation of NRTIs
- Monitor in intensive care unit
- Correct acidosis with IV sodium bicarbonate
- Assist respiratory chain function with riboflavin and thiamine.

## Lipodystrophy

Lipodystrophy, also referred to as “fat redistribution syndrome”, consists of two components thatmay be seen together or independently: fat accumulation and fatatrophy. Fat accumulation is seen within the abdominal cavity(Crix-belly), the upper back (buffalo hump), and the breast (gynaecomastia). Sometimes patients may have cushingoid appearance despite the absence of measureable abnormalities in adrenalfunction. Another feature of fat redistribution is lipoatrophy with loss of buccal fat, and thinning of extremities and buttocks. Fat accumulation is frequently associated with PI therapy while lipoatrophy is more closely linked with NRTI therapy, especially d4T/ddI combination.

## General recommendations include following:

**Dietary changes and life style modifications**:

- Low fat diet and aerobic exercises.
- Regimen change: replacement of protease inhibitors with NNRTI or replacement of Zidovudinewith Tenofovir.
- Metformin 500mg BD improves insulin sensitivity and may result in weight loss and decreased intra-abdominal fat in patient with obesity and insulin resistance.

## Peripheral polyneuropathy

Peripheral polyneuropathy is mainly caused by the NRTIs mainly Zalcitabine, Didanosine and Stavudine. It usually presents with a distal symmetrical distribution and sensorimotor paralysis. Patients complain of paresthesia and pain in their hands and feet, and often, with Zalcitabine (not used in Bhutan), about perioral dysesthesia. The symptoms often begin gradually after several months of therapy. HIV infection itself can lead to peripheral polyneuropathy, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients must be informed that they should consult their treating physician as soon as possible if the typical complaints develop. This adverse effect is now less of a longer a concern since we do not use any of the drugs that causes this side effect.

Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus, malnutrition, or treatment with other neurotoxic drugs, e.g. INH, should be addressed in the appropriate manner. The nucleoside offending NRTI should be avoided in such cases.

## Hyperlipidemia

Changes in triglycerides and/or cholesterol blood levels havebeen observed very frequently, even in the absence of fat redistribution. It is an important concern with ART, due to the potential for premature arteriosclerosis and coronary artery disease. With PI based regimen there is usually an increase in triglycerides, cholesterol, and LDL cholesterol. Triglyceride levels may increase to > 1000mg/dl, levels associated with an increased riskof both pancreatitis and arteriosclerosis.
Lipid profile should be monitored every six months and risk assessment done atleast once a year.

## Risk factors

Assessment needs to include a review of other cardiovascular risk factors:

- History of arteriosclerosis (stroke, coronary artery disease)
- Hypertension (need for anti-hypertensives)
- HDL cholesterol less <40mg/dl
- Family history
- Age

## Management

- Initiate non-drug therapy unless there are extreme elevations
- Switch from PI based regimen to Nevirapine based; Efavirenz is less effective
- A suitable lipid lowering agent should be used

## Gastrointestinal side effects

Gastrointestinal side effects are the most common side effects of almost all antiretroviral drugs - nucleoside analogs, NNRTIs and particularly protease inhibitors can occur especially during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhoea, nausea and vomiting. Heartburn, abdominal pain, bloating and constipation may also occur. Nausea is a common symptom with Zidovudine-containing regimens; diarrhea occurs frequently with Zidovudine, and all PIs, including Lopinavir/r.
In most cases, symptoms occur at the beginning of therapy. Patients should be informed that these side effects usually resolve after four to six weeks of treatment. If gastrointestinal side effects occur for the first time after longer periods on ART, other causes such as gastritis and infectious diarrhoea are likely.

## Allergic Reactions

Allergic reactions are frequent during ART. They occur with all NNRTIs, as well as with NRTI and some PIs.
The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include myalgia (sometimes severe), fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. Severe reactions such as the Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) or anicteric hepatitis are rare. Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases > 5 times the upper limit of normal) or fever > 39°C.

## Management

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Anti-histamines may be helpful. Prophylactic treatment with glucocorticosteroids or anti-histamines has been shown to be of no benefit for the

prevention of Nevirapine allergy. Following a severe allergic reaction, the drug responsible for the reaction should never be given again.

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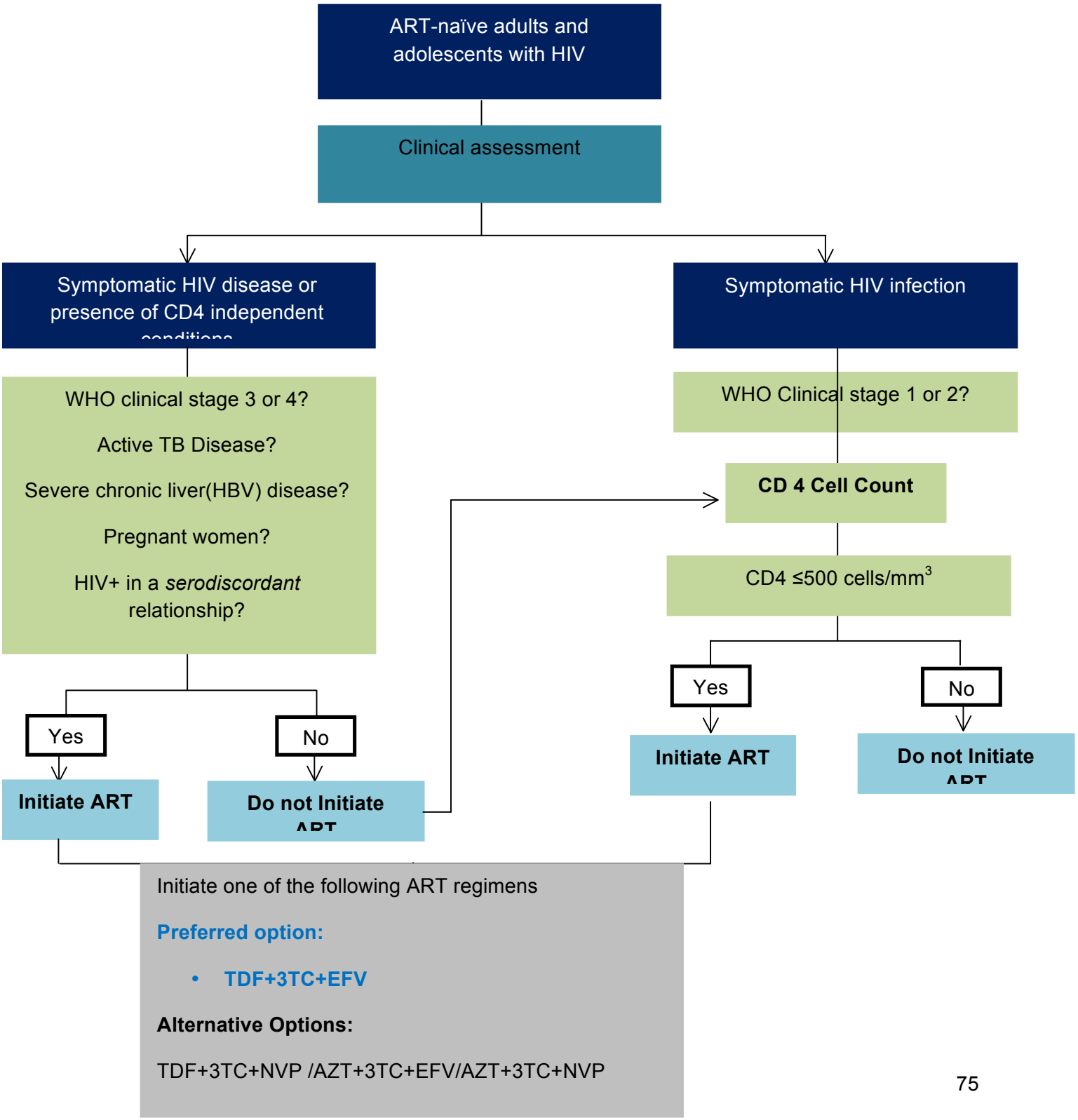
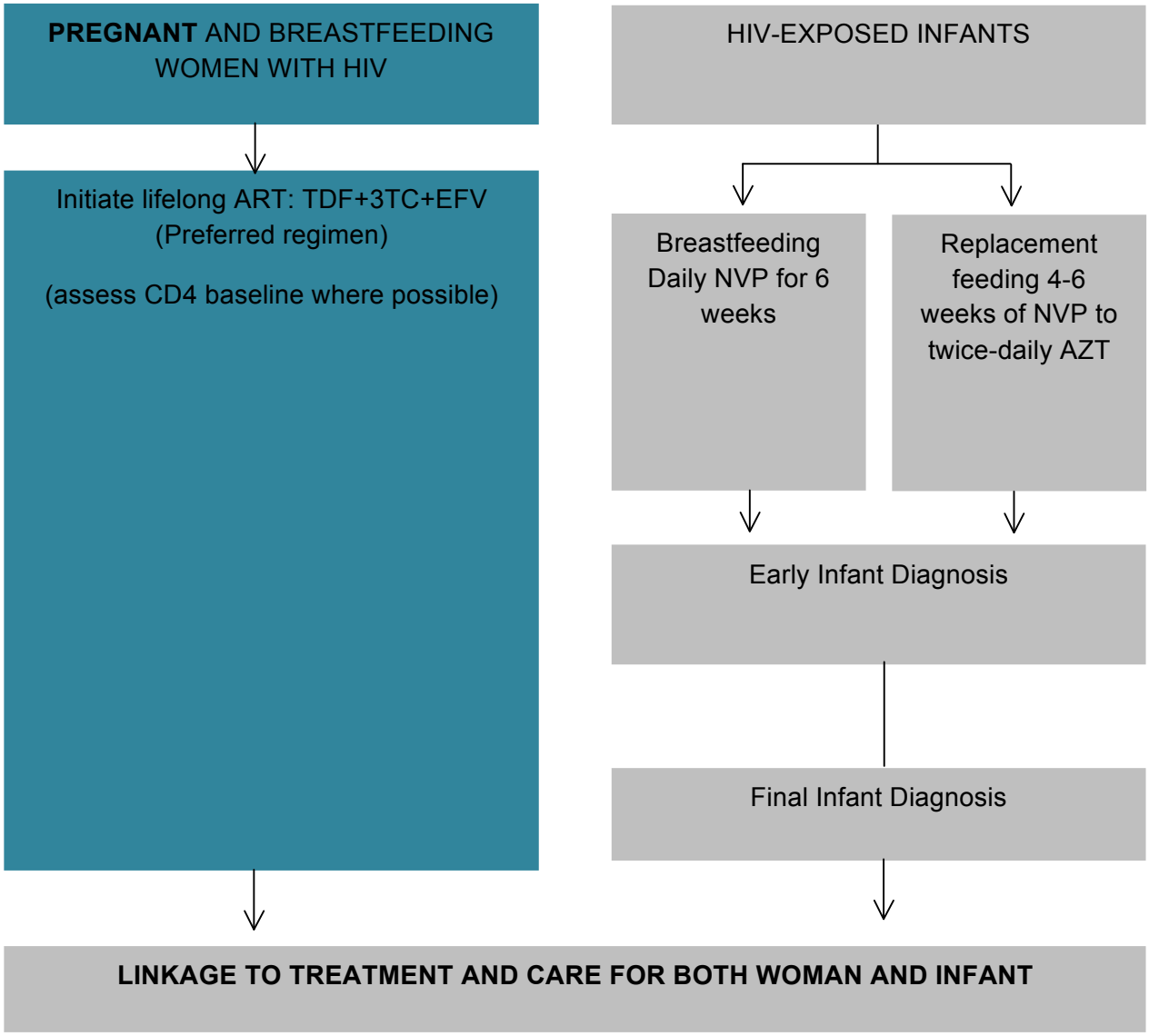
## *Annexures*

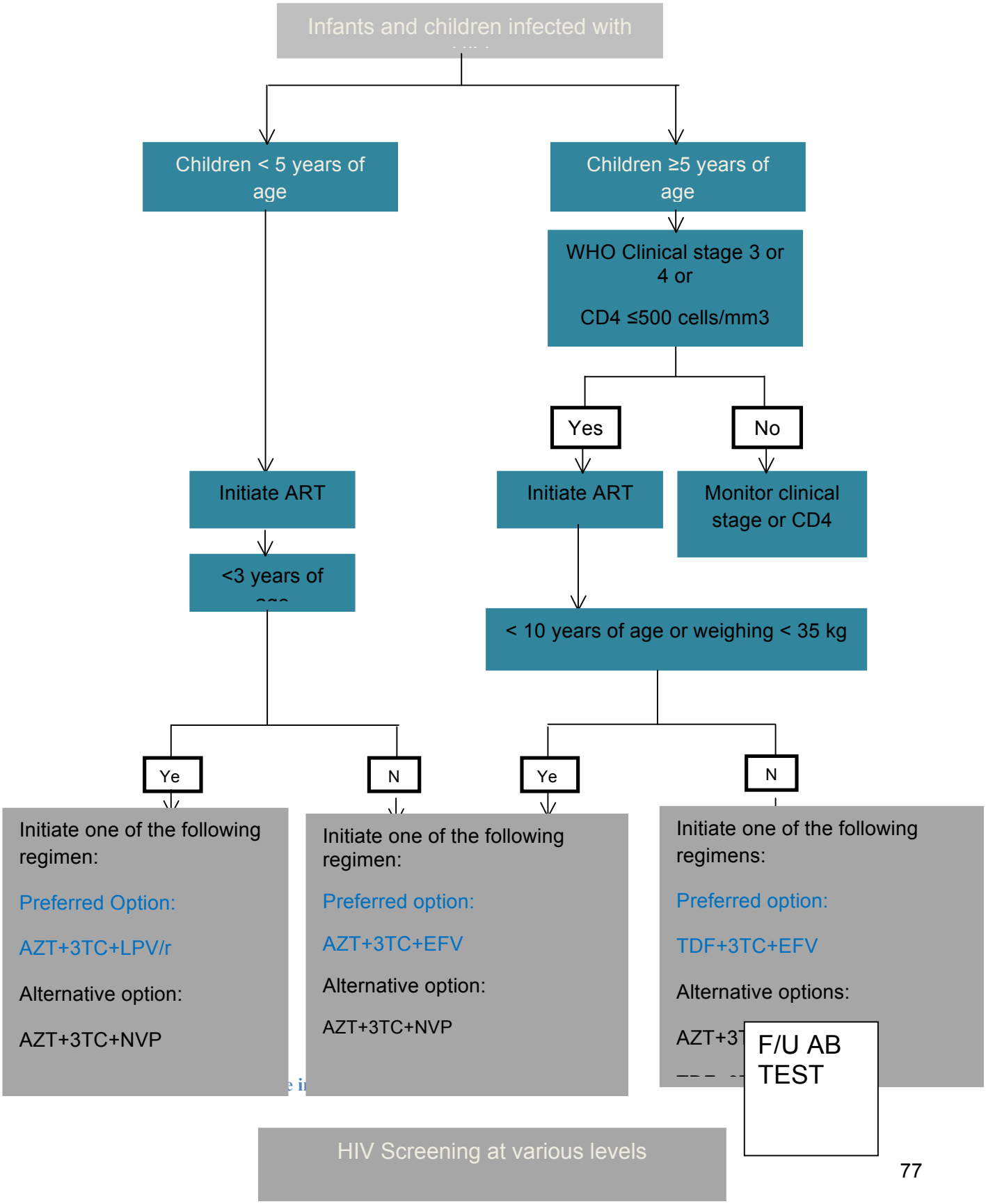
### Annex 1. Algorithm for treatment and management of HIV in adults and adolescents

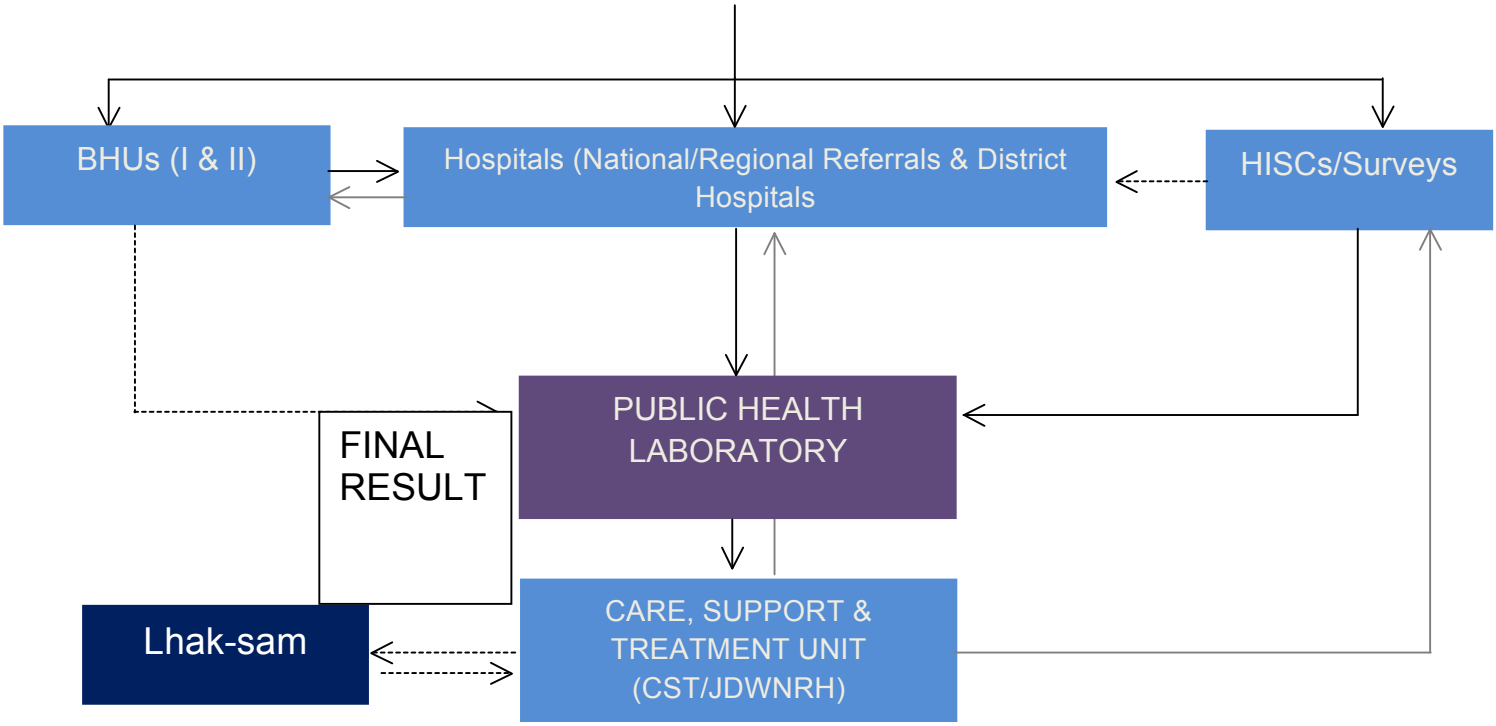


**Annex 2. Algorithm for the treatment and management of Pregnant women (Option B+)**



## Annex 3. Algorithm for Treatment and Management of Children infected with HIV






***Annex 5: Dosages of recommended antiretroviral drugs for Children by WHO***

The principles followed in developing the WHO 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, WHO recommends 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** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **3-5.9kg** | | **6-9.9kg** | | **10-13.9 kg** | | **14-19.9kg** | | **20-24.9kg** | | | **25-34.9kg** | |
| | | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | | **AM** | **PM** |
| AZT/3TC | Tablet (dispersible) 60 mg/30mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300/150 | 1 | 1 |
| AZT/3TC/NVP | Tablet (dispersible) 60 mg/30mg/50 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300/150/200 | 1 | 1 |
| D4T/3TC | Tablet (dispersible) | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300/300/150 | 1 | 1 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 mg/30mg | | | | | | | | | | | | | |
| D4T/3TC/NVP | Tablet (dispersible) 6 mg/30mg/50 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | | 4 | 4 |

**Table 2.Simplified dosing of child-friendly fixed dose 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 adult tablet *mg)** | **Number of tablets or capsules by weight band once daily** |
|---|---|---|---|---|---|---|---|
| | | | **10-13.9 kg** | **14-19.9kg** | **20-24.9kg** | | **25-34.9kg** |
| EFV[a] | Tablet scored) 200mg | | 1 | 1.5 | 1.5 | 200 | 2 |
| | Tablet (double scored )[b]600 mg | | One third | One half | Two thirds | 600 | 2/3 |

a EFV is not recommended for children younger than 3 years and weighing less than 10 kg. FDA approval for use in children less than 3 years weighing more than 3.5 kg was granted during the finalisation of these
guidelines (3.5-5 kg two 50 mg capsules; 5-7.5 kg three 50 mg capsules; 7.5-15 kg one 200 mg capsule), however more data are urgently needed to inform recommendations for use of EFV in this age group.
b The double-scored tablet has two score lines on one side of the tablet and one score line on the other side, enabling the tablet to be divided into thirds and halves as needed.

**Table 3.Simplified dosing of child-friendly fixed dose 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** |
|---|---|---|---|---|---|---|---|---|
| | | **3-5.9kg** | **6-9.9kg** | **10-13.9 kg** | **14-19.9kg** | **20-** | | **25-34.9kg** |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | **24.9kg** | | | | |
| | | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | **AM** | **PM** | | **AM** | **PM** |
| Solid formulations | | | | | | | | | | | | | | |
| 3TC | Tablet (dispersible) 30mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 150 | 1 | 1 |
| AZT | Tablet (dispersible) 60 mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 300 | 1 | 1 |
| NVP[a] | Tablet (dispersible) 50mg | 1 | 1 | 1.5 | 1.5 | 2 | 2 | 2.5 | 2.5 | 3 | 3 | 200 | 1 | 1 |
| LPV/r[b] | Tablet (heat stable) 100mg/25mg | | | | | 2 | 1 | 2 | 2 | 2 | 2 | 100/25 | 3 | 3 |
| Liquid Formulations | | | | | | | | | | | | | | |
| AZT | 10mg/ml | 6ml | 6ml | 9ml | 9ml | 12 ml | 12ml | | | | | | | |
| 3TC | 10mg/ml | 3ml | 3ml | 4ml | 4ml | 6ml | 6ml | | | | | | | |
| NVP[a] | 10mg/ml | 5ml | 5ml | 8ml | 8ml | 10 ml | 10ml | | | | | | | |
| LPV/r[b] | 80/20mg/ml | 1ml | 1ml | 1.5 ml | 1.5 ml | 2ml | 2ml | 2.5ml | 2.5ml | 3ml | 3ml | | | |

a 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. More definitive evidence is expected from an ongoing trial.
b 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** | **Number of scoops or tablets by** | **Strength of adult** | **Number of tablets by** |
|---|---|---|---|---|

| | strength of tablets (mg) | weight band once daily | | | | | tablet (mg) | weight band |
|---|---|---|---|---|---|---|---|---|
| | | 3-5.9kg | 6-9.9 kg | 10-13.9.9 kg | 14-19.9kg | 20-24.9kg | | 25-34.9kg |
| TDF | Oral powder scoops 40mg/scoop | | | 3 | | | 300mg | 1(200mg)[a] or 1 (300mg) |
| | Tablets 150mg or 200mg | | | | 1 (150 mg) | 1(200 mg) | | |

a 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 9INH) and co-trimoxazole (CTX) prophylaxis**

| Drug | Strength of tablets or oral liquid (MG or mg/5ml | Number of scoops or tablets by weight band once daily | | | | | Strength of adult tablet *mg) | Number of tablets by weight band |
|---|---|---|---|---|---|---|---|---|
| | | 3-5.9kg | 6-9.9kg | 10-13.9 kg | 14-19.9 kg | 20-24.9 kg | | 25-34.9kg |
| INH | 100mg | 0.5 | 1 | 1.5 | 2 | 2.5 | 300 | 1 |
| CTX | Suspension200/40 per 5ml | 2.5ml | 5 ml | 5ml | 10ml | 10ml | | |
| | Tablets (dispersible)100/20mg | 1 | 2 | 2 | 4 | 4 | | |
| | Tablets (scored)400/80 mg | | One half | One half | 1 | 1 | 400/80mg | **2** |
| | Tablets (scored) 800/160 | | | | One half | One half | 800/160 | **1** |

**Table 6.Simplified dosing for urgently needed ARV drugs for children recommended by the pediatric Antiretroviral Working group**

| Table 6.Simplified dosing for urgently needed ARV drugs for children recommended by the paediatric Antiretroviral Working group | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Drug** | **Strength of table or sprinkle sachet or capsule (mg)** | **No of tablets or sprinkle capsules/sachets by weight band** | | | | | | | | | | | |
| | | **3-5.9kg** | | **6-9.9kg** | | **10-13.9kg** | | **14-19.9kg** | | **20-24.9kg** | | **25-34.9kg** | |
| | | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM | AM | PM |
| LPV/r sprinkles | 40mg/10mg | 2 | 2 | 3 | 3 | 4 | 4 | 5 | 5 | 6 | 6 | | |
| AZT/3TC/LPV/r | 30mg/15mg/40mg/10mg | 2 | 2 | 3 | 3 | 4 | 4 | 5 | 5 | 6 | 6 | | |
| TDF/3TC | 75mg/75mg | | | | | 1.5 | | 2 | | 2.5 | | 3-3.5[a] | |
| TDF/3TC/EFV | 75mg/75mg/150mg | | | | | 1.5 | | 2 | | 2.5 | | 3-3.5 | |
| TDF/3TC adult double scored | 300mg/300mg | | | | | one third | | One half | | Two Third | | 1 | |
| TDF/3TC/EFV adult double scored | 300mg/300mg/600mg | | | | | one third | | One half | | Two Third | | 1 | |

a 3 tablets for 25-29.9 kg and 3.5 tablets for 30-34.9 kg.

## *Annexure 6. WHO clinical staging of HIV disease in adults, adolescents and children*

| **Adults and adolescents** | **Children** |
|---|---|
| **Clinical stage 1** | |
| **Asymptomatic**<br><br>**Persistent generalized lymphadenopathy** | Asymptomatic<br><br>Persistent generalized lymphadenopathy |
| **Clinical stage 2** | |
| **Moderate unexplained weight loss (<10% of presumed or measured body weight)** | Unexplained persistent hepatosplenomegaly |

| | |
|---|---|
| **Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)**<br><br>**Herpes zoster**<br><br>**Angular cheilitis**<br><br>**Recurrent oral ulceration**<br><br>**Papular pruritic eruption**<br><br>**Fungal nail infections**<br><br>**Seborrhoeic dermatitis** | Recurrent or chronic upper respiratory tract infections<br><br>(otitis media, otorrhoea, sinusitis, tonsillitis)<br><br>Herpes zoster<br><br>Lineal gingival erythema<br><br>Recurrent oral ulceration<br><br>Papular pruritic eruption<br><br>Fungal nail infections<br><br>Extensive wart virus infection<br><br>Extensive molluscum contagiosum<br><br>Unexplained persistent parotid enlargement |
| **Clinical stage 3** | |
| **Unexplained severe weight loss (>10% of presumed or measured body weight)**<br><br>**Unexplained chronic diarrhoea for longer than 1 month**<br><br>**Unexplained persistent fever (intermittent or constant for longer than 1 month)**<br><br>**Persistent oral candidiasis**<br><br>**Oral hairy leukoplakia**<br><br>**Pulmonary tuberculosis**<br><br>**Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)**<br><br>**Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis**<br><br>**Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x $10^9$/l) and/or chronic thrombocytopaenia (<50 x $10^9$/l)** | Unexplained moderate malnutritionb not adequately<br><br>responding to standard therapy<br><br>Unexplained persistent diarrhoea (14 days or more)<br><br>Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month)<br><br>Persistent oral candidiasis (after first 6 weeks of life)<br><br>Oral hairy leukoplakia<br><br>Lymph node tuberculosis<br><br>Pulmonary tuberculosis<br><br>Severe recurrent bacterial pneumonia<br><br>Acute necrotizing ulcerative gingivitis or periodontitis<br><br>Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x $10^9$/l) or chronic thrombocytopaenia (<50 x $10^9$/l)<br><br>Symptomatic lymphoid interstitial pneumonitis Chronic HIV-associated lung disease, including bronchiectasis |
| **Clinical stage 4** | |
| **HIV wasting syndrome** | Unexplained severe wasting, stunting or severe |

| | |
|---|---|
| **Pneumocystis (jirovecii ) pneumonia**<br><br>**Recurrent severe bacterial pneumonia**<br><br>**Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)**<br><br>**Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)**<br><br>**Extrapulmonary tuberculosis**<br><br>**Kaposi sarcoma**<br><br>**Cytomegalovirus infection (retinitis or**<br><br>**infection of other organs)**<br><br>**Central nervous system toxoplasmosis**<br><br>**HIV encephalopathy**<br><br>**Extrapulmonary cryptococcosis, including meningitis**<br><br>**Disseminated nontuberculous mycobacterial infection**<br><br>**Progressive multifocal leukoencephalopathy**<br><br>**Chronic cryptosporidiosis**<br><br>**Chronic isosporiasis**<br><br>**Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)**<br><br>**Lymphoma (cerebral or B-cell non-H**<br><br>**odgkin)**<br><br>**Symptomatic HIV-associated nephropathy or cardiomyopathy**<br><br>**Recurrent septicaemia (including nontyphoidal Salmonella)**<br><br>**Invasive cervical carcinoma**<br><br>**Atypical disseminated leishmaniasis** | Malnutrition not responding to standard therapy<br><br>Pneumocystis (jirovecii ) pneumonia<br><br>Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)<br><br>Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)<br><br>Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)<br><br>Extrapulmonary tuberculosis<br><br>Kaposi sarcoma<br><br>Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month)<br><br>Central nervous system toxoplasmosis (after the neonatal period)<br><br>HIV encephalopathy<br><br>Extrapulmonary cryptococcosis, including meningitis<br><br>Disseminated nontuberculous mycobacterial infection<br><br>Progressive multifocal leukoencephalopathy<br><br>Chronic cryptosporidiosis (with diarrhoea)<br><br>Chronic isosporiasis<br><br>Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)<br><br>Cerebral or B-cell non-Hodgkin lymphoma<br><br>HIV-associated nephropathy or cardiomyopathy |

***Annexure 7***

## *HIV CARE MASTER FORM*

**1. Patient Identification Data (Write complete information)**

**Patient Id Code** ☐☐☐ ☐☐ ☐☐ ☐☐ ☐☐ ☐☐

Patient No Code No Date Month Year

Name: _____

Age _____ Sex: ☐ Male ☐ Female ID card no._____

Local Address: _____

Permanent Address: _____

Contact number: _____

Date confirmed HIV+ test: ☐☐ ☐☐ ☐☐ Place: _____

**Entry point** (services referring the patient for HIV care): ☐ 1-VCT ☐ 2 -ANC ☐ 3-TB ☐ **4-**Inpatient
☐ 5- Outpatient ☐ 6**-** MTCT ☐ 6-STI ☐ 7-Blood donor ☐ **8-** Others _____

| **2. Personal History** | | **3. Family History at the start** | |
|---|---|---|---|
| Risk factors for HIV infection | ☐ Heterosexual<br>☐ MSM<br>☐ IDUs<br>☐ Blood Transfusion | Marital status: | ☐ Single<br>☐ Married/Living<br>☐ Divorce/separate<br>☐ Widowed ☐ Others…… |

| ☐ Mother-to-Child<br>☐ Others | Family members: partner/ children | Age/ sex | HIV +/- /unknown | ART Y/N | Regist. No if in care |
|---|---|---|---|---|---|
| | | | | | |

**Education**: ☐ Non-literate
☐ Primary School
☐ Secondary School
☐ College and above
☐ Others ……..(Specify)

**Employed:** ☐ Yes ☐ No

**Alcoholism:** ☐ Habitual
☐ Social
☐ No Use

Performance scale: A- Normal activity; B- bedridden <50% of the day during last month; C- bedridden > 50% of the day during last month

| **4. Antiretroviral treatment history** | |
|---|---|
| Was ART received before?<br><br>☐ Yes ☐ No<br><br>If yes:<br>☐ PMTCT<br>☐ PEP<br>☐ ART | Initial CD4 Count/Baseline……..Place of ART Initiation……..<br><br>Drugs & Duration; |

| **5. Antiretroviral Treatment** | |
|---|---|
| **Treatment started** | |

| ☐ AZT+3TC+NVP<br>☐ AZT+3TC+EFV<br>☐ d4T+3TC+NVP<br>☐ d4T+3TC+EFV<br>☐ TDF+3TC+NVP<br>☐ TDF+3TC+EFV | Date | Substitution, switch or stop | Reason (code) | Date restart | New regimen |
|---|---|---|---|---|---|
| | | | | | |

**Reasons SUBSTITUTE**: 1 toxicity side effects, 2 pregnancy, 3 risk of pregnancy, 4 newly diagnosed TB, 5 new drug available, 6 drug out of stock, 7 other reason (specify)

**Reasons for SWITCH:** 1 clinical treatment failure, 2 immunological failures, 3 virologic failures

**Reasons STOP:** 1 toxicity side effects, 2 pregnancy, 3 treatment failure, 4 poor adherence, 5 illness hospitalization, 6 drug out of stock, 7 patient lack of finance, 8 patient decision, 9 planned treatment interruption, 10 others

**6. Tuberculosis treatment during HIV care**

| **Disease class** (tick) | **Regime**(tick) | **TB registration** |
|---|---|---|
| | | District:_____ |
| ☐ Pulmonary TB | ☐ New treatment | |
| | | Health Centre: _____ |
| ☐ Smear-positive | ☐ Retreatment | |
| | | TB number: _____ |
| ☐ Smear-negative | ☐ MDR | |
| | | Treatment outcome: ☐ Cure ☐ Rx completed |
| ☐ Extrapulmonary | | |
| | Date start TB Rx: | ☐ Rx failure ☐ Died ☐ Default ☐ Transfer out |
| Site:…… | | |
| | | Date:…… |

| | | |
|---|---|---|
| ☐ Past history of TB | | |

**7. Reasons for stopping follow-up**

| | |
|---|---|
| Death | Date of death: ☐☐ ☐☐ ☐☐ |
| Lost to follow-up(>3 months) | Date last visit: ☐☐ ☐☐ ☐☐ |
| Transferred out | Date: ☐☐ ☐☐ ☐☐ |
| | New clinic:…….. |

**8. PRE-ART FOLLOW-UP**

| Date of visit | Date next visit | Weight (kg) &height | WHO stage | **IPT prophylaxis** | Lab Results | | | | | **TB Screening** |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CD4 | LFT | RFT | TLC | Others (specify) | |
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***Instructions and codes:**

**Date:** ALL DATES: **DD/MM/YY**

**Performance scale:** A- Normal activity; B- bedridden <50% of the day during last month; C- Bedridden > 50% of the day during last month

TB screening: All patients should be screened for TB at every visit as per the TB/HIV guidelines and insert Yes/No accordingly. If TB status is confirmed please indicate as TB confirmed in the same box.

## 9. ANTIRETROVIRAL TREATMENT FOLLOW-UP

| Date of visit | Date next visit | Weight (kg) & height | WHO stage | Performance scale | OIs | CPT Prophylaxis | Adherence* >95 %, 80-95%, <80 % | ART S/E – code | Lab results | | | | | Outcomes* | TB Screening |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | CD4 | HB | ALT& AST | TLC | Others (specify) | | |
| | | | | | | | | | | | | | | | |
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**Opportunistic infections:** Enter one or more codes − Tuberculosis (TB); Candidiasis (C); Diarrhea (D); Cryptococcocal meningitis (M); Pneumocystis Carinii Pneumonia (PCP); Cytomegalovirus disease (CMV); Penicilliosis (P); Herpes zoster (Z); Genital herpes (H); Toxoplasmosis (T); Other-specify
**Adherence:** Check adherence by asking the patient if he/she has missed any doses. Also check the bottle/blister packet. Write the estimated level of adherence (e.g. >95% = < 3 doses missed in a period of 30 days; 80-95% = 3 to 12 doses missed in a period of 30 days; < 80% = >12 doses missed in a period of 30 days

**ART S/E; Side effects:** Enter one or more codes − S=Skin rash; Nau-nausea; V=Vomiting; D=Diarrhoea; N=Neuropathy;J=Jaundice; A=Anemia; F=Fatigue; H=Headache; Fev=Fever; Hyp=Hypersensitivity; Dep=Depression; P=Pancreatitis; L=Lipodystrophy; Drows=Drowsiness; O=Other− Specify **Outcome:1-same; 2-Improved; 3-Deterioted**