Guideline for Management of HIV/AIDS in Adults

Ministry of Health
Royal Government of Bhutan

HIV/AIDS & STI Control Program
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Program Manager
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forward</td>
<td>i</td>
</tr>
<tr>
<td>Preface</td>
<td>iii</td>
</tr>
</tbody>
</table>

**Chapter 1:**
- Introduction                                                           | 1     |
- General Principles for the use of HAART                               | 3     |
- HAART Drugs                                                            | 7     |

**Chapter 2:**
- Adherence                                                             | 10    |
- Continuum of care for people living with HIV/AIDS                      | 12    |
- Pregnancy                                                              | 14    |
- Breast - feeding                                                      | 16    |

**Chapter 3:**
- Management of Opportunisitic Infections (OI’s)                         | 17    |
- in HIV infected patients                                              | 17    |
- Treatment Failure                                                     | 31    |

**Chapter 4:**
- Drugs Information                                                     | 33    |
- Antiretro Viral Drugs                                                  | 36    |
- Drugs for Opportunistic Infections                                    | 41    |

**Chapter 5:**
- Occupational Transmission of HIV                                      | 44    |
- Drugs Abbreviations                                                   | 50    |
- References                                                            | 52    |
FOREWORD

The Royal Government of Bhutan has initiated treatment of Bhutanese people living with HIV/AIDS with antiretroviral medicines. These medicines can prolong and improve quality of lives of HIV infected people, although there is yet no known cure for HIV/AIDS. Under the dynamic leadership of our beloved king, people living with HIV in Bhutan are fortunate to have accessibility to free treatment services for the expensive ARV drugs. Government of Bhutan is committed in providing comprehensive treatment and care for PLWHA. However, treading the path of good prevention program will only ensure long terms benefits. Treatment services should, therefore be used as an entry point to enhancing HIV prevention services among our communities. Hence, it is essential to link treatment services to prevention programs.

Scaling up treatment services is fraught with difficulties. HIV infection in the country is expected a steep rise in the coming years with improved surveillance system and increased uptake for voluntary counselling and testing. With this, number of PLWHA requiring ARV treatment will be on continuous rise. As of now 29 people are already on the treatment since the start of the treatment program 2005. HIV/ AIDS treatment is a chronic problem and require life long treatment unlike other infectious diseases that need short term interventions. Treatment of HIV/AIDS has a huge cost implications. With high mortality and morbidity related to HIV/AIDS, burden on health care system will increase. Besides, a good adherence to treatment is challenging and poses the risk of making HIV resistant to available ARV drugs. Health system must also be able update the health workers on the fast changing evidence based practices in the field of HIV/AIDS.

However, HIV treatment services also provide us with the opportunity to improve health systems. Counselling, Adherence programs, monitoring and referral mechanisms of the patients are integral part of HIV treatment. Ethical duties of the health care providers such as protecting the information of the clients are ce-
ntre to HIV/AIDS treatment and care. All these are positive approaches and a change that can be used in dealing with other health problems as well. I am happy to introduce the first guideline for Management of HIV/AIDS in adults in Bhutan. I am sure this book will serve a good use for providing quality treatment for the PLWHA in Bhutan.
PREFACE

The Royal Government of Bhutan recognized the seriousness of this pandemic and acted early on. The STD/AIDS Control program was established in 1988, five years before the first case of HIV infection detected in 1993. Despite the numerous preventions measures undertaken, numbers of cases continue to rise steadily. As of November 2008, Bhutan is home to 160 cases of HIV, of this 31 died of HIV/AIDS related complications. While prevention is still considered as the best way of combating the epidemic, the government has taken initiatives to provide treatment services the infected people to improve the quality of life and reduce mortality and morbidity associated with HIV/AIDS. Therefore, in June 2004, the National HIV/AIDS Commission endorsed the proposal to provide free HAART to all Bhutanese living with HIV/AIDS. Following this directive, the management of HIV/AIDS in adults. The main objective of the guideline is to provide standard approach for the use of:

1. Highly Active Anti Retroviral Therapy (HAART) as a part of comprehensive HIV/AIDS care.
2. Prophylaxis and treatment of Opportunistic infections in patients with HIV/AIDS.

HAART drugs do not cure HIV (Human Immunodeficiency Virus): they only temporarily suppress viral replications and improve symptoms. Effective therapy requires the simultaneous use of three or more drugs. The need for early drug treatment should, however, be balanced against the development of toxicity. Bhutan has chosen a triple drug regime of AZT, 3TC, NVP as the first line of treatment. Which are in conformity to regional practice, the cut off CD 4 count lesser than 200 cell/cubic mm will be use for initiating the treatment.

Currently HAART is started at Jigmi Dorji Wangchuck National Referral Hospital as it is the only centre equipped with facilities for CD 4 count. However, treatment services for HIV/AIDS are essentially a decentralized approach like any other health services. The efforts are continuing to upgrade the diagnostic and laboratory facilities and also the skill of the health care providers to deliver defective treatment services for people living with HIV/AIDS.
1.     Introduction:

AIDS was recognized in Los Angeles, USA in 1981 in five healthy homosexuals suffering from pneumocystis carinii pneumonia (PCP) and in other 26 individuals with Kaposi sarcoma (KS). In 1983 Human Immuno Deficiency virus was isolated from a patient with lymphadenopathy. In 1984 causative organism of AIDS was identified and in 1985 ELISA test was developed to diagnose antibody to the HIV virus. HIV prevalence rates in Asia may seems low but figure are high. UN AIDS and WHO estimates 4.9 million people were living with HIV in Asia 2007, including the 440,000 people who became newly infected in 2007. Over all, there are 9 million Asian have been infected with HIV. Approximately 2.6 million men, more than 950,000 women and almost 3,60,000 children have died of AIDS related diseases.

The first case of HIV infections in Bhutan was detected in 1993. Despite the numerous preventive measures undertaken the number of cases continues to rise steadily. As of November 2008, there are 160 cases detected in the kingdom. Of this 31 died of HIV/AIDS related complications. While preventions is still considered as the best way of combating the epidemic, the government is committed to provide comprehensive treatment and care services to people already infected and affected. Therefore, in June 2004, the National HIV/AIDS Commission endorsed the proposal to provide free HAART to all Bhutanese living with HIV/AIDS. Following this directive, the National HIV/AIDS and STI Control Program has come up with this guideline to strengthen the HIV/AIDS related services for the benefit of those affected.
1.1 Scope of this Guideline
This guideline is particularly intended for:
   a. Physicians and other health care providers in Bhutan
   c. The guidelines will require updating from time Source of reference for people living with HIV/AIDS.

1.2 Objectives:
   a. To provide standard approach for the use of
      • Highly Active Anti Retroviral Therapy (HAART) as a part of comprehensive HIV/AIDS care.
      • Prophylaxis and treatment of opportunistic infections in patients with HIV/AIDS.
   b. To be source of reference for physicians, Health care providers, AIDS Program Managers and Health
   c. Planners involved in the National HIV/AIDS Program.

1.3 Goals of Therapy of HIV infection
   a. Clinical Goals:
      • Prolongation of life and improvement in quality of life.
   b. Virologic Goals:
      • Greatest possible reduction in viral load preferably (Below<20-50 copies/ml) as long as possible to halt disease progression and prevent or delay progression.
   c. Immunologic Goals:
      • Immune reconstitution that is both quantitative (CD4 cell count in normal range) and qualitative (pathogen specific immune response is present)
   d. Therapeutic Goals:
      • Rational sequencing of drugs in a fashion that achieves clinical, virologic, and immunologic goals while maintaining treatment options, limit drug toxicity and facilities adherence.
e. Epidemiologic Goals:
   - Reduce HIV transmission

2. General Principles for the use of HAART
   a. The viral replication is quite high i.e 10 particles are produced and destroyed every day. Despite this high level of replication patient usually remain symptomatic for many years.
   b. The ongoing viral replication leads to progressive immune system damage resulting in susceptibility to opportunistic infections, malignancy and ultimately death.
   c. Plasma HIV RNA indicates the magnitude of HIV replication and associated rate of CD4 destruction. So the estimation of CD4 cells at regular intervals (6 monthly) should be done along with clinical monitoring of the patient in resource constrained country like Bhutan.
   d. Treatment decision should be individualized by CD4-T cell count.
   e. The goal of the therapy should be maximal achievable suppression of HIV replication.
   f. The most effective ways to establish durables suppression of replication is the simultaneous of a combination of effective antiretroviral drugs.
   g. HAART use in combination therapy regimen should be in an optimal schedule and dosage.
   h. Women should receive optimal HAART regardless of pregnancy status unless a drug is contraindicated.
   i. Same principle of HAART applies to HIV infected children.
   j. HIV infected persons even those whose viral loads are below detectable limit, should be considered infectious. Therefore they should be counselled to avoid sexual and drug use behaviour that are associated with either transmission or acquisition of HIV or other infectious pathogens.
2.1 Prerequisites
The following services are essential for starting HAART:

a. Accesses to HIV voluntary counselling, testing and follow up counselling services.
   This also includes psychological support and adherence to treatment.

b. A well equipped medical centre for identification and management of OI’s.

c. Reliable laboratory services capable of carrying out investigations such as CBC, Biochemistry, and CD 4 count.

d. Drugs: reliable, affordable and sustainable supply of HAART and drugs for prophylaxis and treatment of OI’s.

2.2 Clinical Evaluation of the Patient
- Complete history and physical examination.
- Routine laboratory investigations.
- CD4+T-Lymphocyte count and percentage/total lymphocyte count (TLC)
- Details clinical examination of the patient should aim to assess the clinical staging of the HIV infection (see 3.3)
- Identify past and current HIV related illnesses that would require treatment.
- Identify coexisting medical condition which may influence the choice of therapy.

2.3 History
Medical history should include the following questions:
- When and where the diagnosis of the HIV 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 Disease (STI’s)
- Previous HAART received, if any.
- Pregnancy and Oral contraceptive Pill (OCP) used
- Social habits and sexual history.
2.4 Physical Examination:
- Weight of the patient
- Skin – look for herpes, Kaposi Sarcoma (KS), Dermatitis
- Lymphadenopathy
- Oropharyngeal mucosa: look for oral candidacies, OHL, KS
- CVS and Respiratory System
- Per Abdomen- look for hepatosplenomegaly
- CNS – look for localizing signs and mental status
- Eye- including funduscopy
- Genitalia/Gynecological examination

2.5 Clinical Staging HIV infection

Table 1:

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Symptoms</th>
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<tr>
<td>Stage I</td>
<td>Asymptomatic or Persistent Generalized Lymphadenopathy (PGL) and/or normal activity.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Weight loss&lt;10% minor mucocutaneous conditions, zoster&lt;5 years, resurrent URI’s and/or asymptomatic + normal activity.</td>
</tr>
<tr>
<td>Stage II</td>
<td>weight loss&lt; 10% Unexplained diarrhoea&gt;1 month, unexplained fever? 1 month, thrush, oral hairy leukoplakia (OHL), Pulmonary TB in past year or severe bacterial infection and /or bedridden&lt;50% of the days in the past month.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>CDC defined AIDS and/or bedridden&gt; 50% of the days in the past moth (for CDC classification see Annexure)</td>
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2.6 Investigations  

b. Essentials:
- HIV serology (confirmed by ELISA)
- CD 4 T lymphocyte count with percentage.
- Complete Blood count.
- Blood chemistry e.g RFT/electrolytes, LFT, Blood sugar, lactate level,
- Chest X-ray.

c. Frequency of CD4 count:
1. Before initiating HAART:
   The rate of fall of C count is 60-100 cells every 6 months. Patients with <350 cells /mm3 should be monitored every 3 months  
2. After CD4 should be done at the 4th month and then every months

d. Supplementary:
- Urine Routine and Microscopy
- Hep C and B serology
- VDRL testing
- Pap Smear
- Culture facilities: blood, urine, sputum and fungi
- Modified stool for AFD
- Ultrasonography

It is very important to confirm the diagnosis of HIV infection according to WHO/CDC guidelines. Incase of doubtful results, it should be reconfirmed in a reference laboratory.

2.7 When to start HAART?
The rationale of starting HAART is to prolong and improve quality of life maintaining CD4 T count to a acceptable level and maximal suppression of virus replication as long as possible: because with currently available HAART, eradication of HIV is not likely. Indication for initiating HAART is based on the WHO/CDC guidelines. Patients with CD T cell count<200/mm3 should be treated.
2.8 Criteria with CD 4 cell count:
1. any patient with CD 4 counts < 200 cells/mm³
2. All WHO stage IV disease (AIDS defining Diagnosis)
3. WHO stage III disease with consideration of using CD 4 count < 350 cells/mm³ (patient with CD 4 counts of 200-350 cells/mm³ but with OI).

2.9 Where to start HAART?
Initially HAART has to be started only at a centre equipped with facilities for CD 4 count and laboratory diagnostic facilities for opportunites infections. These facilities are currently available at JDWNRH only.

3. HAART Drugs.
HAART drugs do not cure HIV (human Immunodeficiency virus): they only temporarily suppress viral replications and improve symptoms. Effective therapy requires the simultaneous use of three or more drugs. The need for early drug treatment should, however, be balanced against the development to toxicity.

a. Nucleoside Reverse Transcriptase inhibitors
   - Abacavir (ABC)
   - Didanosine (ddI)
   - Lamivudine (3TC)
   - Stavudine (d4T)
   - Tenifovir (TDF)
   - Zidovudine (ZDV or AZT)

b. Non-Nucleoside Reverse Transcriptase inhibitors
   - Efavirenz (EFV or EFZ)
   - Nevirapine (NVP)

c. Protease Inhibitors
   - Indinavir (IDV)
   - Lopinavir/Ritonavir (LPVRTV)
   - Nelfinavir (NFV)
   - Ritonavir(RTV)
   - Saquinavir(SQV)
3.1 Factors to be considered prior to starting HAART:

- Patient readiness and willingness to start therapy should be established and a simplified treatment plan that a patient can commit to.
- Adherence: patient knows the importance of taking medication and the impact of non-compliance.
- Possible side effects and drugs toxicity should be discussed in advance.
- Inform patient of the immune Reconstitution Syndrome.
- Advice on food issues with the pills they take.

3.2 Choice of Regimens

HAART with single or dual regimen is not recommended due to rapid emergence of drug resistance. Monotherapy with AZT or NVP is recommended for the prevention of mother to child transmission of HIV. For triple therapy two NRTI’s generally form the backbone of most combinations. Regimen containing two nucleosides and a non-nucleoside RT inhibitor has been adopted by most of the developing world. Regimens containing triple nucleosides were never chosen because of their efficacy, cost and Abacavir hypersensitivity reactions, and regimens containing protease inhibitors are kept as secondary options, mainly due to their cost, high pill counts, side effect profile and some requiring cold chain for storage.

a. First Line regimen for adults and adolescents in Bhutan.

2 NRTI’s + 1 NNRTI
- AZT + 3TC + NVP
For patient who are allergic to NVP, should be switched over to EFV
- AZT + 3TC + EFV

b. Second Line Regimen for adults and adolescents in Bhutan.

In case of AZT related persistent GI intolerance or severe haematological toxicity and NVP related severe hepatotoxicity switch over to.
- D4T + 3 TC + EFV
In case of AZT related persistent GI intolerance or severe hematological toxicity and EFV related severe hepatotoxicity switch over to:

- D4T + 3 TC + NVP

Note: Pregnant women developing hepatotoxicity due to NVP, a switch to PI preferably NFV or SQV id recommended.

1.3 Monitoring Therapy

When HAART initiated there should be clinical monitoring from time to time. The patient should be advised to visit clinic to two weeks after initiating HAART. The clinicians then can monitor any side effects and reinforce adherence to the therapy. The patient should be advised to visit the clinic monthly for prescription refill and then once every six months for CD4 count. During each visit, the clinician should enquire about:

- Any new symptoms that may be related to drug toxicity.
- Any symptoms of opportunistic infections.
- Symptoms related to progression of HIV.
- Assess the need for further counselling.

Table 2.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Monitor</th>
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<tbody>
<tr>
<td>2 weeks</td>
<td>To increase to dose and monitor NVP side effect by doing LFT</td>
</tr>
<tr>
<td>4 weeks</td>
<td>Monitor SE and reinforce adherence and/or change the drug</td>
</tr>
<tr>
<td>Every month 6 Months</td>
<td>Prescription refill and reinforce adherence, CD4 count</td>
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4. Adherence

Unlike other chronic diseases, the rapid replication and mutation rate of HIV mean that very high levels of adherence are required to achieve durable viral suppression of viral load. Non-adherence can lead to resistance, which can then limit therapeutic options.

HIV viral suppression, reduced rate of resistance, and improved survival has been correlated with high rates of adherence to HAART. Since it is a lifelong treatment, great commitment is required from both the patient and the healthcare provider. Some of the factors associated with poor adherence are:

- Adverse events related to drugs.
- Poor patient and clinician relationship
- High pill burden
- Forgetfulness
- Mental depression
- Lack of patient education
- Inability of the patient to identify their dedication.
- Drug toxicity
- Being too ill
- New medical problems

4.1 Important determinants of adherence to HAART in our setting.

- Quality of initial and continuing counselling resulting in well-informed decision and commitment by the patient to start and maintain HAART.
- Availability of assessable, knowledgeable and committed medical terms.
- The assurance of affordable and continued supply of antiretroviral medications
- Low pill burden and convenient dosing.

The willingness of the patient to start therapy is very important. Patient should be explained about the importance of taking regular doses and the consequences of non-compliance.
4.2 In order to improve adherence a health care provider must:
   - Written instructions about the medications prescribed.
   - Explain possible side effects.
   - Educate patient family and follow up visits.
   - Simplify treatment regime by reducing the number of pills, frequency and minimizing side effects.

4.3 How to assess adherence
   - Enquire number of doses missed in the last 7 days.
   - Enquire about of doses missed since last visit.
   - Enquire about the dose timing.
   - Enquire about correct dosing.
   - Physical inspection of the remaining drugs of the patients

4.4 Management of patients who has missed his/her medication:
If the patient has missed his /her medication for more than a month, they should be counselled and a clinical examination for OI’s and CD4 count should be carried out soon. HAART should be initiated as soon as possible. Once started, HAART should never be stopped even if the CD4 count is normal.

4.5 Monitoring efficacy and toxicity of HAART
The efficacy of HAART is indicated by clinical improvement of the patient, and by rise in CD4 cell count.

a. Clinical Monitoring
Clinical indicators of response to therapy are:
   - A- Appetite
   - B-Body weight increase
   - C- Complaints related to HAART, OI’s and disease progression are less.
b. Laboratory Investigations

Routine laboratory monitoring should be done including CBC, LFT, RFT, blood glucose, and serum lipids to monitor adverse effects of the drugs, monthly for the initial 3 months. CD4 count should be done at the 4th month of starting therapy and then every 6 months. Immunological failure is indicated by a fall in CD4 counts more than 30 percent from the initial value or a return to, or below, the pre therapy baseline.

5. Continuum of care for people living with HIV/AIDS

All levels of health care delivery systems in Bhutan will contribute to the management and treatment of people living with HIV/AIDS. The BHU’s district Hospitals and the referral Hospital will work in close co ordinations in providing comprehensive care and support services. The following briefly outlines the scope of care and treatment at each level of the health care system:

5.1 Management at the BHU level.

a. Patients suspected to be suffering from HIV/AIDS:

If a health worker suspects a patient to be suffering from HIV/AIDS with the following signs and symptoms:

- Chronic diarrhoea
- Loss of weight
- Non healing and frequent oral thrush
- Fever
- Lymphadenopathy
- Recurrent herpes infection
- Vulvo vaginitis
- Skin lesion

Then, if facilities are available to do HIV testing –perform a rapid test after proper counseling and refer the patient to the District Hospital.

b. Patient is already diagnosed HIV positive but without signs of AIDS and not on HAART.

- Follow up three monthly.
- Counsel for safe sex and condom distribution
• Any sign of AIDS or Opportunistic infection refer to the District Hospital.

c. **Patient is on HAART and Opportunistic infection Prophylaxis**
   • Monthly visit the patient or call the patient to the BHU.
   • Ensure that patient adherences to the treatment.
   • Ensure that patient gets his or her regular medication
   • Ensure that the patient takes medication at the right interval.
   • Advise patient that CD4 count has to be done every six months.
   • Counsel and educate on the importance of safe sex.

Refer the patient to the District Hospital if there are signs of:
• Drug toxicity and intolerance
• Jaundice.
• Losing weight despite the medications.
• Any sign of opportunistic infections.

**5.2 Management at the District Hospitals**

a. **Patient not on HAART**
   • HIV test of the suspected patients should be carried out after proper counselling.
   • Follow WHO classification for the diagnosis of HIV/AIDS.
   • Voluntary counselling and testing of the sexual partner should be done.
   • If found positive, refer the patient to the Referral Hospital for CD4 count.
   • If the patient is put on HAART ensure regular supply of drugs and adherence to medications.
   • Monitor drug toxicity and if a change in the regimen is required, refer the patient to the Referral Hospital.

b. **Patient already on HAART**
   • Follow BHU procedures
   • Look for signs of drugs toxicity or intolerance. If it cannot be managed at the District Hospital then refer.
   • Refer the patient 6 monthly for CD4 count.
• Opportunistic infections like Tuberculosis, skin infections, fungal infections can be treated at the District Hospital. If found to be unresponsive to treatment, refer.

5.3 National and Regional Referral Hospital:
• Diagnosis is confirmed.
• Patient screened for OI’s.
• Laboratory investigations completed.
• CD4 count done.
• Patient’s started on OI prophylaxis and HAART depending on CD4 count.
• First and second (2nd and 6th week) follow up dine at the referral hospital.
• When found HIV positive patient is referred back to the district hospital with the advice to send the blood sample for CD4 count at the 4th month and the every 6 months.

6. Pregnancy
  a. Women with specific reference to pregnancy
• When initiating HAART for women of reproductive age, the indication for initiation of therapy and the goals of treatment are same as for the adults and adolescents.
• For women who is pregnant, an additional goal of therapy is prevention of mother to child transmission (PMTCT), with a goal of viral suppression to less than 1000 copies/ml to reduce risk of transmission of HIV to foetus and newborn.

b. HAART in Pregnancy:
• The regimen should include antiretroviral agents known to reduce MTCT.
• AZT, 3TC and NVP are known to reduce MTCT so a combination of AZT, 3TC should be the first line agents.
• Dose should be same as in non pregnant women.
• Stavudine, and ddI should be avoided due to potential risk of lactic acidosis.
• PI’s are associated with the development of glucose in-
tolerance and diabetes.
- Nelfinavir and saquinavir are commonly used PI’s in developed countries
- AZT/3TC/NVP is the first line of HAART in pregnancy with close monitoring of LFT till the 18th week of therapy.
- In case of patient evidence of Nevirapine hepatotoxicity: consider substituting with either by NGV or SQV.

6.1 Women first diagnosed with HIV infection during pregnancy (ANC):

a. Not on HAART:
- Assess the CD4 count to find the progression of the disease.
- Delay HAART for at least 12 weeks of pregnancy in patient whose CD4 count is 200cell/mm3, as it is not a medical emergency.
- For women who are severely ill initiate therapy with a combination of AZT/3TC/NVP.

b. No indication for HAART but indicated for PMTCT:
- Start HAART from 28 weeks of pregnancy with AZT 300mg every 12 hours.
- NVP 200mg at onset of labour.
  - Infant receives single dose of NVP 2mg /kg at 48-72 hours.
- AZT 2mg/kg IV, then 1 mg hourly until delivery.
  - Infant receives AZT 2mg/kg every 6 hours for 6 weeks.
- AZT 600mg PO at onset of labour, then 300mg PO every three hours until delivery.

c. Already on HAART:

i. In Early pregnancy
The following three options should be offered:
- Temporarily discontinue treatment until the first trimester.
• Continue same therapy.
• Change to a different drug regime if the regime contains a drug which is contraindicated.

ii. In late Pregnancy (>36 weeks)
• Continue the same the drugs.
• Encourage caesarean Section /Hospital Delivery.

iii. Presents in Labour
• NVP 200mg at onset of labour.
  - Infant receives single dose of NVP 2mg /kg at 48-72 hours.
• AZT 2mg/kg iv, then 1mg/kg hourly until delivery.
  - Infant receives AZT 2mg/kg every 6 hours for 6 weeks.
• AZT 600mg PO at onset of labour, then 300mg PO every three hours until delivery plus 3TC 150mg 3TC 150mg PO at onset of labour and 150mg 12 hourly until delivery.

iv. Presents in Post Delivery
• Mothers who are already on HAART should continue
• Mothers who were given HAART for PMTCT should stop after 6 weeks
• Initiate 6 weeks AZT protocol for the infant
• Evaluate infant for HIV infection when feasible.
• Evaluate mother for indication of HAART

v. Caesarean Section
• It should be performed at 38 weeks of pregnancy if indicated only.

7.0 Breast-feeding:
• No breast feeding for infants and young child of the HIV infected mothers from birth.
• Children born to these mothers will be fed by formula milk recommended by the ministry of Health.
• The cost for the formula feed will be borne by the Royal government of Bhutan.
**Guideline for the Management of HIV/AIDS in adult in Bhutan**

**a. Adolescents:**
Children over 13 years, infected with HIV by sexual route or intravenous drug use should receive treatment as per adult guidelines. Children below 13 years who are infected with HIV perinatally or parenteral route (blood and blood products) should receive HAART as per paediatric guidelines.

**CHAPTER-3**

**8. Management of Opportunistic infections (OI’s) in HIV infected Patients**
Opportunistic infections are caused by organisms in an immunocompromised host, which otherwise normally do not occur in an immunocompetent host. When the CD4 count starts falling, these organisms, which normally do not cause disease, get an opportunity to infect the immunodeficient host. Occurrence of OI’s depends on the rate of fall of CD4 T lymphocyte counts.

The occurrence of opportunities infections depends on the rate of fall of CD4 T lymphocyte count. HIV infected patients are very prone to OI’s once the CD4 count drops below 200 cell/mm3. The commonest infections are Tuberculosis, Pneumosystic Carinii Pneumonia (PCP), fungal other skins infections. This section deals with OI’s system wise in frequency of their occurrence.

**8.1 Respiratory System**
Respiratory System is the commonest system affected by OI’s. The following are the commonest respiratory system OI’s affected by OIS.

**a. Tuberculosis (TB)**
TB can manifest at any stage of the disease irrespective of CD4 counts. The risk of active TB with latent infection is increased 100 folds by HIV infection. HIV promotes TB at all CD strata but clinical features vary on CD4 counts. With CD4 count >350cell/
mm3, lung lesions are typical with upper lobe infiltration and cavi-
tations but CD4 count below 50 cell/mm3, extra pulmonary TB is
common. TB is associated with in increased rival road and more
rapid progression of HIV infection (Refer graph below).

**Diagnosis:**
- Chest X-ray.
- Sputum AFB X 3 day
- Culture for AFB if positive after two months of DOTS
  and, if the CD4 is very low and to differentiate between
  MAC and MTB.
- PPD (50-65% false negative).

**Important Note:**
DO NOT START HAART in a patient with TB simultaneously
due to the following reasons:
- Immune Reconstitution Syndrome (IRS).
- Overlapping drug toxicity.
- Adherence due to pill load.

**Treatment:**
- Always start ATT with category 1 (exclude Streptomycin, start with HERZ)
- Rifampicin should always be included in the ATT during
  the continuation phase
- Follow DOTS protocol.
- HAART can be started 2-8 weeks after starting ATT.
- Inpatient where CD4 count is below 50 cells/mm3, HAART may have to be delayed by several weeks de-
  pending on the clinical judgment.
- Follow the guidelines as below:
  i. CD4 count 200 cell/mm3, start HAART after 8 weeks
     of ATT with AZT + 3TC + EFV (increase EFV dose to
     800mg once daily)
  ii. CD4 count 200-350 cell/mm3, consider HAART after
      initial TB treatment with AZT +3TC +EFV.
  iii. CD4 over 350 cells/mm3, no HAART.

The Duration of treatment is a minimum of 9 months.
b. Pneumocystic Carinii Pneumonia (PCP)
- Pneumocysts is an opportunistic fungal pulmonary pathogen that is an important cause of pneumonia in an immunocompromised host. PCP occurs when CD4 count is below 200 cells/mm³. Air borne transmission can occur.
- Typical manifestation of PCP is a triad of dry cough, breathlessness on exertion and fever.
- Chest X-ray shows symmetrical pulmonary infiltrates. 10-20% patient show no X-ray changes.
- Laboratory studies show low oxygen saturation. PCP occurs when the CD4 count is below 200 cells/mm³.
- Lactate dehydrogenase (LDH) is usually >500mg/dl.
- Sputum and bronchoalveolar lavage (BAL) may demonstrate the parasite.

Treatment:
- **Preferred regimen**
  i. Cotrimoxazole: Trimethoprim 15-20mg/kg + Sulphamethoxazole 70-100mg/kg iv for 21 days (in three divided doses).
  OR
  Cotrimoxazole 960mg (Double Strength) three times daily for 21 days. Prophylaxis with the preferred regime is continued till the CD4 count is stable over 200 cells/mm³.
  ii. Corticosteroids: for patients with hypoxemia prednisolone 40mg b.d. for 5 days then 40mg o.d. for 5 days then 20mg till completion.
- **Alternative Regimen**
  i. Patient allergic to Sulphamethoxazole: Trimethoprim 15-20mg/kg PO+ Dapsone 100mg daily for 21 days.
  ii. Clindamycin 600-900mg IV 6 hourly or 300-450mg PO 6 hourly + Primaquine 15-30mg/days for 21 days.

**Prophylaxis:**
- PCP prophylaxis should be started if the CD4 count is below 20 cells/mm³
1. Cotrimoxazole 80/400mg 2 tabs daily.
2. Dapsone 100mg o.d. in Cotrimoxazole allergy.

**Alternative Regimes Include:**

3. Dapsone 50mg/day + pyrimethamine 50mg/week.
4. Dapsone 200mg/week + pyrimethamine 75mg/week.
5. Allergy to both cotrimoxazole and dapsone, Azithromycin (250mg) 4-5 capsules a week.

Prophylaxis may be discontinued if the CD4 count is stable over 200cells/mm3 for 3-6 months.

c. **Mycobacterium Avium Complex (MAC)**

It is an acid fast atypical mycobacteria. It can cause disseminated disease among patients with advanced HIV infection who are not on HAART and where the CD4 counts is <100cells/mm3.

- Occurs when CD4 counts is below 50cells/mm3
- The symptoms are: fever, night sweats, weight loss, and diarrhoea with or without abdominal pain.
- It is a disseminated disease involving gastrointestinal, CNS, skin and respiratory symptoms are late in the disease.
- Manifest as anaemia, leucopenia and raised serum alkaline phosphatase.

**Diagnosis:**

**Definitive**

- Blood culture (positive in 90-95%)

**Probable:**

- By demonstrating organism in stool, bone marrow specimen, liver and skin biopsy.
- Sputum and stool culture are insensitive and non specific.
- Modified AFB stain.
- Pulmonary MAC show infiltrate on chest X-ray.
Treatment:

1. Clarithromycin 500mg b.d. PO + Ethambuto 15mg/kh PO for 12 months
   In severe cases consider adding a third drug with Ciprofloxacin 500-750mg b.d. PO and/or Amikacin 500mg IV o.d for the first 2.-3 months.

Prophylaxis:

1. Clarithromycin 500mg b.d PO or Azithromycin 1.0-1.25g PO weekly.
   Discontinued prophylaxis when CD4 count is over 100cells/mm3 for more than 6 months; restart if it is less than 100cells/mm3.

d. Histoplasmosis
   • It is a fungal infection caused by a fungus Histoplasma Capsulatum. It is also spread as an air borne infection.
   • Usually present when CD4 count is below 100cells/mm3
   • Symptoms are fever, weight loss, fatigue, and respiratory symptoms. Can manifest like gram negative septicaemia.
   • Can mimic TB lymphadenopathy.

Diagnosis:

Definite
   • Blood culture and sputum culture (85%) and takes two to four weeks.
   • Identification of the organism in the clinical specimen-FNAC, discharges.

Treatment:
   • Amphotericin B IV 0.7mg/kg/day for 10 days.
   • Continue with fluconazole 200mg BD for 12 weeks and then maintenance treatment with 200mg OD life long.

e. Nocardiosis
   • Nocardiosis is a saprophytic bacteria which can cause
Guideline for the Management of HIV/AIDS in adult in Bhutan

Pneumonia and disseminated disease. Nornardia asteriodes is commonly associated and disease in HIV patients.

- Chronic or symptomatic sputum production with constitutional symptom and local lymphadenopathy.
- CNS manifestations: can present as brain abscess.
- Chest X-ray shows nodules or cavity.

**Diagnosis:**
- Modified AFB stain.
- Culture and gram stain

**Treatment:**
- Cotrimoxazole: TMP-SMX-5-15 mg/kg/day IV for 3-6 weeks then continue PO for 6 months.

**Alternative regimen, in case of cotrimixazole allergy:**
- Augmentin 1000mg tid for 6 months

**f. Aspergillosis**
- Aspergillus fumigates is a common cause of aspergillosis. It is a fungal infection. It is identified by gross and microscopic examination.
- There are two clinical forms of aspergillosis in Aids patients namely invasive pulmonary and febrile, diffuse meningoencephalitis.
- Respiratory manifestations include pseudomembranous tracheitis or pneumonia

**Diagnosis:**
Definitive: positive histology positive culture, or positive culture from a normally sterile site.
Probable: two positive sputum cultures or one positive bronchoscopy + appropriate host.

**Treatment:**
1. Amphotericin B 1.0mg/kg/day Iv for two weeks.
2. Fluconazole 200mg PO bd for three days then 400mg/
Guideline for the Management of HIV/AIDS in adult in Bhutan

day for minimum of 2 weeks.

8.2 Central Nervous System manifestation of Hiv/AIDS.
CNS infection is common in HIV patients when CD4 count is < 100 cells/mm³. Neurologic complications of AIDS can occur as primary result of HIV, secondary neurologic complications and immunologic complication.

a. Primary Result of HIV
- Aseptic meningitis
- Chronic meningitis
- Encephalitis
- Cognitive disorder/ dementia
- polyneuropathy

b. Secondary Neurologic Complications
- Opportunistic infections.
- Neoplasm.
- Vascular disease.
- Nutritional/ Metabolic Disorder.

c. Immunologic Complications:
- Acute inflammatory Demyelinating Polyneuropathy (AIDP)
- Chronic inflammatory Demyelinating Polyneuropathy (CIDP)
- Mononeuropathy

d. Cryptococcal Meningitis
- Caused by Cryptococcus neoformans.
- Most cases are seen in patients when CD4 counts are below 50 cells/mm³
- Clinical features are: fever, headache, meningismus (stiff neck < 25%), visual changes mainly diplopia, and myalgia.
- It can present as acute primary illness or reactivation of previously dormant disease.
- Sources are bats or birds.
• Mortality is 60% due to raised intracranial pressure.

**Diagnosis:**

**CSF analysis**
- High CSF pressure (ICP)
- Few lymphocytes
- High protein
- Normal or slightly low sugar
- Numerous Cryptococcus organisms in India ink preparation.
- CSF crypto antigen is positive in over 95% of the cases.

**Treatment**
- Amphotericin B 0.7-1.0mg/kg/day for 10-14 days IV then fluconazole 400mg o.d. for 8 weeks.
- Raised ICP: fast clinical deterioration, mortality 93% in two weeks.
- Daily lumbar puncture (LP).
- No role of steroids.

**Prophylaxis/Suppressive therapy:**
- Fluconazole 200-400mg o.d and discontinue when CD4 count is more than 100-200cells/mm3 for over 6 months.

**e. Toxoplasmosis/Toxoplasmaencephalitis**
- Common cause of focal brain lesion in AIDS and it occurs in patients with low socioeconomic groups.
- Transmitted by ingestions of raw or undercooked meat that contain cysts or ingestion of water or food contaminated with oocytes.
- Transplacental transmission is possible.
- Occurs in patients whose CD4 count is <100cells/mm3

**Diagnosis:**
- Clinical manifestations includes: headache, fever, stiff neck, localizing signs, altered sensorium, cranial nerve
-25-

Guideline for the Management of HIV/AIDS in adult in Bhutan

- palsies and seizures.
  - Made on clinical grounds in tropical countries with therapeutic response within a few days of starting therapy.
  - CT scan shows multiple ring enhancement lesions.

**Treatment:**
Preferred Regimen: Primethamine 100-200mg, the 50mg/day + Sulphadiazine 4-8g/day/cotrimoxazole.
Alternative: Primethamine + Azithromycin 600mg/day
Suppressive treatment:
Pyrimethamine 25-75mg + Sulphadiazine 0.5-1.0mg/day
Alternative: Pyrimethamine + Azithromycin 600mg/day

f. Tuberculous Meningitis
The treatment of Tuberculosis Meningitis in same as immunocompetent host but the duration should be increased to 9-12 months.
Steroids should be included in the following circumstances:
  - Symptoms of raised ICP
  - Altered sensorium
  - Increased incidence when CD4 count is < 50cells/mm3
  - Retinal detachment (RD) in 70% of cases after 1 month.

**Treatment:**
  - Should be started immediately.
  - IV acyclovir 10-20mg/kg every 8 hours OR
  - IV ganciclovir 5mg/kg 12 hourly 1-12 weeks.
  - Maintenance acyclovir 800mg 5 times daily PO for 1-2 months (for ARN: prednisolone 60-100mg PO 24 hours after acyclovir for 2 months with topical steroids and cycloplegic agents)

b. Cytomegalovirus Retinitis (CMV)
  - Most common retinal infection in AIDS.
  - Occurs in one third of AIDS patient
  - Usually occurs in patient with CD4 count below 50 cell/mm3
  - Opacification of retina, area of haemorrhages, exudates, necrosis, and peripherebilitis.
• Bilateral in 50% of patient with 25% retinal detachment.
• Diagnosis is clinical as serology is not helpful.

**Treatment:**
- ganciclovir 5mg/kg Iv over 1 hour infusion 12 hourly for 2-3 weeks.
- Maintenance 5gm/kg IV infusion over one hour o.d. five days a week OR 1000mg PO t.i.d. (100-150, 000)
- Local treatment: ganciclovir intravitral injection 200-2000Mcg in 0.1 ml weekly.

**8.4 Gastrointestinal Manifestation in HIV/AIDS**
Gastrointestinal manifestations used to be very common in patients with HIV/AIDS before the HAART era but with the initiation of HAART, the manifestations are less common. HIV related GI disorders can present in many forms. The GI manifestations include:
- Dysphagia/ Odynophagia
- Diarrhoea
- Anorexia
- Vomiting

**a. Dysphagia/Odynophagia**
Causes: Candida, CMV, HSV, other fungal infections, TB infections, and drug induced oesophagitis.

**Treatment:**

i. Empirical treatment for oesophageal candidacies with Fluconazole 200-800mg/ day for 7 days.
ii. If the patient does not respond, give a course of Acyclovir 200-800mg five times a day for 2-3 weeks (suspected HSV infection)
iii. If no improvement, patient may be referred for oesophagscopy to rule out CMV infections which is treated with Ganciclovir as other CMV infections.
b. Diarrhoea
Diarrhoea is still a common problem in the era of HAART. It is caused by organism like microsporidium, cryptosporidium, MAC, CMV, E. histolytica, G. Lambia, Strongyloides, salmonella, shigella, C. jejuni, clostridium species. Most of the time it is idiopathic.

**Diagnosis:**
- Stool examination for parasites, fungi, WBC & RBC/Modified AFB.
- Febrile patients with CD4 counts <100 cells/mm3 needs blood culture for MAC.

**Treatment:**
- In acute diarrhoea: Cotrimoxazole or Quinolones.
- For chronic diarrhoea: depending on the aetiology, cotrimoxazole Quinolones, or metronidazole and Albendazole may be used.
- The initiation of HAART alone stops diarrhoea in majority of the cases.

1.5 Coetaneous Manifestations of HIV/AIDS
- Coetaneous 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:

a. Viral
- Exanthem of acute retroviral syndrome – maculopapular rashes seen in acute retroviral syndrome and is self limiting.
- Chronic herpetic ulcers- usually seen as orolabial or genital lesions and persists for more than a month. It is painful, acyclovir is prescribed.
- Herpes Zoster- vesicular eruptions along the never distribution. Can occur in normal CD4 counts. Acyclovir is prescribed.
- Oral Hairy Leucoplaikia- caused by the Epstein Barr Virus (EBV). Reported in more than 20% of HIV patients,
Guideline for the Management of HIV/AIDS in adult in Bhutan

and is marker of HIV infection. Occurs when CD4 count is < 100 cells/mm³. Hyperplastic whitish plaques on the sides of the tongue which are difficult to remove. Usually bilateral and is precancerous.

- Molluscum contagiosum- multiple umbilicated follicular lesions which can occur in any part of the body, except the palms and soles. No specific treatment but with initiation of HAART the lesions can be controlled.

b. Fungal
- Proximal subungul onychomycosis – is a fungal infection of the proximal nail bed. Itraconazole ‘pulse therapy’.
- Oral candidiasis- refer GI manifestations
- Penicilosis- presents with fever, skin lesions, and wasting in patients with CD4 counts< 50 cells/mm³. Diagnosis is established by culture and smear of penicillium marneffei. Amphotericin B 0.7 mg/kg for two weeks IV in severe cases, itraconazole 200 mg PO b.d in mild to moderate cases, maintenance 200 mg o.d for life time.

c. Bacterial:
- Staph. Aureous infections
- Impetigo
- Folliculities
- Furunculosis
- Acne vulgaris
Prescribe antibiotics as per the sensitivity pattern!

d. Others:
- Eosinophilic folliculitis- unknown etiology 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 popular Eruptions (PPE)- common complaint, marker of HIV progression, occurs in patients with CD4
count < 50 cells/mm³. Ecthyosis and xerosis are common in advanced HIV. Extremely pruritic dermatosis characterized by red or skin colored non confluent micro papules on a dry skin. Involves wide spread areas, most commonly the trunk, extremities and skin folds. Symptomatic treatment. Amitriptyline may be helpful. May disappear with the initiation of HAART and with increase in CD4 count.

- Kaposi’s sarcoma- occurs in the palate, gingival, tongue and the skin. Low prevalence in the Asians. Commonly associated with HSV 8 infection. It cannot be cured. HAART decreases the tumour load.

8.6 Immune Reconstitution inflammatory Syndrome (IRIS)

Also known as:
- Immune Reconstitution syndrome (IRS)
- Immune Restoration Syndrome.
- Immune Recovery Syndrome
- Paradoxical Reaction.

IRIS is produced by the worsening of opportunistic infections due to improved immune response. This occurs 2-5 weeks after successful HAART and is common with TB, MAC CMV retinitis, PCP, Cryptococcal meningitis and dermatitis, bronchitis and herpes zoster.

IRIS in TB:
For patients with TB this syndrome has been reported to occur in as many as 30% in the developed world. The Syndrome is characterized by fever, worsening pulmonary lesion (X-ray examination) and expanding CNS lesions, serositis (pleural and pericardial effusion). Mean time of development is 60 days. These reactions are usually self limiting, although in some cases a short course of corticosteroids may be helpful to reduce inflammation for severe respiratory and CNS symptoms. Initiation of HAART can also unmask previously undiagnosed infections by augmenting the inflammatory response. In general, HAART should not be discontinued for immune Reconstitution Syndrome.
IRIS in MAC:
Increase in symptoms of lymphadenitis and granulomatous inflammations, cutaneous lesions, endobronchial tumours, small bowel involvement, paravertebral abscess, negative blood culture.

Treatment
- Corticosteroids 1mg/kg for 1 month and taper,
- Antimicrobial therapy
- Local surgical drainage.

MAC prophylaxis in low CD4 count patients before starting HAART is unclear.

IRIS in CMV
- Vitreitis, retinitis, retinal detachment, neovascularization, proliferative vitreo retinopathy,
- Parotitis.
- Pneumonitis

Treatment
- Topical anti inflammatory therapy.
- Periocular steroids
- Ganciclovir implants
- Prophylastic CMV therapy

IRIS in Cryptococcosis
Increase in intracranial pressure, CSF pleocytosis, high protein, negative culture, cerebral infarction, enlarged lymph nodes, cavitatory or necrotizing pneumonia and subcutaneous abscesses.

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

IRIS in PCP
Develops early after starting (median time=2 weeks if primary prophylaxis in not received). Presents as granulomatous pneumonia on X-ray.
Treatment:
- Cotrimoxazole with HAART

9. Treatment failure
Definition: Antiretroviral treatment failure can be defined as a sub optimal response to therapy.

Factors causing treatment failure includes regimen complexity, adherence, intolerance and toxicity, sub optimal pharmacokinetics, inadequate antiretroviral potency, and drug resistance. Treatment failure is associated with:

a. **Virologic failure:**
Virologic failure can be defined as incomplete or lack of HIV RNA response to antiretroviral therapy. Incomplete virologic response can be defined as repeated HIV RNA > 400 copies/ml after 24 weeks or > 50 copies/ml by 48 weeks of treatment in a naïve patient.

b. **Immunologic failure:**
Immunologic failure can be defined as a failure to increase the CD4 cell count by 25-50 cells/mm3 above the baseline count over the first year of therapy, or a decrease to below the baseline CD4 cell count on therapy. Mean CD4 cell count in a naïve patient approximately increases by 150 cells/mm3 in a year (John Hopkins pg.64).

c. **Clinical progression:**
Clinical progression can be defined as the occurrence or recurrence of HIV related events (after at least 3 months on an antiretroviral regimen), excluding immune Reconstitution Syndrome (IRS).

9.1 Assessment of antiretroviral treatment failure and changing therapy.
In general, the cause of treatment failure should be explored by, reviewing the medical history and performing a thorough physical examination to assess the signs of clinical progression. Initial
assessment of treatment failure includes:

- Adherence (adherence to regimen)
- Medication intolerance (symptomatic treatment or change of medications).
- Pharmacokinetic issues (food/fasting requirement, recent history of GI symptoms, drug-drug interactions)
- Suspected drug resistance: resistance testing (this is not possible in a resource constrained country like Bhutan).

9.2 Change of therapy due to treatment failure

Once treatment failure is diagnosed, whether it is virologic or immunologic failure the regime has to be changed. The entire regime has to be changed from a first line to a second line combination regime. A single drug should not be added or changed to a failing regime. The second line regimen should include all three new drugs, in order to increase the likelihood of treatment success. The change should be carried out base on the following table (source: WHO Guide).

<table>
<thead>
<tr>
<th>First line regime</th>
<th>Second Line Regime for Treatment failure</th>
<th>Alternative second Line regime for treatment failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT+3TC+EFV or NVP</td>
<td>RTV enhanced Pl+deT/ddl</td>
<td>RTV enhanced Pl+ ABC/ddl NFV +ABC/ddl or d4T/ddl</td>
</tr>
<tr>
<td>AZT +3TC +ABC</td>
<td>NNRTI+ LPV/r +d4/ddl</td>
<td>RTV enhanced Pl + d4 T/ddl</td>
</tr>
<tr>
<td>AZT+ 3TC+RTV enhanced Pl or NFV</td>
<td>NNRTI +d4T/ddl</td>
<td>NNRTI+ABC/ddl</td>
</tr>
</tbody>
</table>

Table 5
10. DRUG INFORMATION.
Common and important complications of HAAT.

a. Lactic Acidosis:

It is primarily a complication of d4T, ddl or both: AZT is a less frequent cause. The initial clinical manifestations of lactic acidosis are variable and may include non-specific GI symptoms: weight loss, anorexia, nausea, vomiting, abdominal pain, and diarrhea without dramatic elevation of hepatic enzymes, and in some cases dyspnoea and/or fatigue.

- Metabolic acidosis (pH<7.25)
- Blood lactate >5mmol/L
- Type A: Anaerobic
  - Tissue hypoxia
- Type B: Aerobic
  - Malignancy, glycogen storage diseases, certain myopathies, mitochondrial toxicity.
- Lactate levels >9mmol/l
  - Widespread energy deficits contribute to organ failure
  - Mortality exceeds 75%.

Risk Factors:

- Risk factors include duration of NRTI exposure, female gender, and obese, acquired riboflavin and thiamine deficiency.
- Recovery from hyperlactatemia may be prolonged; mean of 62 days (range 7-176 days)

Treatment:

- Discontinue NRTIs
- Monitor in intensive care unit
- Correct acidosis:
  - Sodium bicarbonate
- Assist respiratory chain function with supplementation:
  - Riboflavin
  - Thiamine
Therapeutic doses of various nutritional supplements, such as riboflavin, thiamine, may be tried to assist respiratory chain function. No data support their efficacy, although cases of recovery have been reported.

**b. Lipodystrophy**
Lipodystrophy, also referred to as “lipodystrophy syndrome” “fat redistribution syndrome”, consists of two components that may be seen together or independently: fat accumulation and fat atrophy. Fat accumulation is seen within the abdominal cavity (Crix-belly), the upper back (buffalo hump), the breast (gynaecomastia). Sometimes patients may have cushingoid appearance despite the absence of measurable abnormalities in adrenal function. 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/ddl combination.

**Evaluation:**
- Patient perception
- Physical Examination, serial photography.

**Treatment:**
- Low fat diet and aerobic exercise
- Metformin (500mg twice daily) improves insulin sensitivity and results in weight loss and decreased intra-abdominal fat in patients with fat accumulation and insulin resistance.
- Regimen changes: switch from PI to an NNRTI or ABC, TDF or AZT may lead to gradual improvements in lipoatrophy.

**c. Insulin Resistance**
Insulin resistance (impaired uptake of glucose by muscle and inhibition of hepatic gluconeogenesis), hyperglycemia, diabetic ketoacidosis and exacerbation of diabetes mellitus are common with
P1 based HAART. Insulin resistance occurs in 40% of the patients and hyperglycemia has been reported in 3-17% of patients treated with P1’s. The reversibility of these events is currently unknown, due to limited data.

**Screening:**
- Routine fasting blood glucose measurement at regular intervals during treatment.
- Asking patients to report immediately the occurrence of suspected signs and symptoms as polydipsia, polyuria or polyphagia can be useful.
- Some guideline recommend fasting blood glucose levels at baseline and at 3-6 Months intervals.

**Risks:**
Risk assessment should include:
- Risk factors for diabetes and arteriosclerosis.
- Smoking
- Hypertension, obesity and dyslipidemia.

**Treatment:**
- Most cases can be managed with diet and exercise.
- Metformin has the advantage of improving insulin resistance and decreasing. visceral fat accumulation with a possible reduction in cardiovascular risk.
  Alternate method is to switch HAART to a non-P1 based regimen.

**d. Hyperlipidemia**
Changes in triglycerides and/or cholesterol blood levels have been observed very frequently, even in the absence of fat redistribution. It is an important concern with HAART, due to the potential for premature arteriosclerosis and coronary artery disease. Most P1’s have this effect but the rate with SQV is low or nil. With P1 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 risk of both pancreatitis and arteriosclerosis.
**Risk:**
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 <40mg/dl.
- Family history
- Age.

**Monitoring**
- Lipid profile should be repeated at 6 months and then with a frequency depending on the 6 month values and risk assessment (at least once per year)

**Treatment:**
- Imitate non drug therapy unless there are extreme elevations
- Switch therapy: P1 to NVP or ABC: EFV is less effective
- A suitable lipid-lowering agent should be used.

11. **Antiretro Viral Drug.**
a. Nucleoside Reverse Transcriptase Inhibitors.
   i. **Lamivudine (3TC)**

**Dose:**
- 150mg bd or 300mg once daily (no interaction with food)

**Available formulations:**
- Oral suspension: 10mg/ml
- Tablets: 150mg, 300mg.

**Side effects:**
- Safest NRTI
- Infrequent complications include headache, nausea, diarrhea, abdominal pain and insomnia.
- Use in pregnancy is extensive and well established.
- Alopecia
- Class side effect of lactic acidosis and steatosis are listed but not clear whether it is due to 3TC therapy.
**Drug interactions:**
Cotrimoxazole increase levels of 3TC, however no dose adjustment is necessary due to the safety profile of 3TC.

**ii. Stavudine (d4T)**

**Dose:**

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>wt&lt;60kg</th>
<th>wt&gt;60kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>30mg bd</td>
<td>40mg bd</td>
</tr>
<tr>
<td>26-50</td>
<td>15mg bd</td>
<td>20mg bd</td>
</tr>
<tr>
<td>10-25</td>
<td>15mg od</td>
<td>20mg od</td>
</tr>
</tbody>
</table>

Children < 30kg: 1mg/kg bd  
Children > 3kg: using the adult recommended dosage (no interaction with food)

**Available formulations:**
- Oral solutions: 1mg/ml
- Capsules: 15, 20, 30 and 40mg

**Side effects:**
Lactic acidosis with hepatic steatosis (high), peripheral neuropathy and pancreatitis, which are dose related (reduced dose to half) and may resolve if therapy is withdrawn, lipodystrophy (high) are some of the common side effects. Other less common side effects include headache, abdominal pain, weight loss, cough, rash, diarrhea, studies show good tolerability and pharmacokinetics in pregnancy, however avoid combination of d4T and ddl due to increased risk of lactic acidosis and hepatic steatosis.

**Drug Interactions:**
- avoid concomitant use with Zidovudine because of antagonist actions.
- avoid use with ddC, ddl, ethionamide, ethambutol, INH, phenytoin, hydralazine, and long term metronidazole due to possible risks of peripheral neuropathy.
iii. Zidovudine (ZDV or AZT)

Dose:
- 300mg bd (>70kg weight or tolerated) or 200mg tid
- IV-2mg/kg IV over 1hour, then 1mg/kg/hour until delivery
- (No interaction with food).

Available formulations:
- Oral solutions: 10mg/ml
- Capsules: 100 and 250mg
- tablets: 300mg
- IV solutions: 10mg/ml

Side effects:
Bone marrow suppression within 2-3 months (depends on dose and duration of treatment and stage of disease), fingernail discolouration (2-6 weeks), class related lactic acidosis and hepatic steatosis to a lesser extent than other NRTI’s, GI intolerance, altered taste, rare dose related myopathy due to mitochondrial toxicity, advocated for pregnant women beyond first trimester to prevent vertical transmission.

Drug Interaction:
- other drugs causing bone marrow suppression e.g Cotrimoxazole, dapsone, amphotericin B should be used with caution.
- Probenecid increases the levels of AZT but concurrent administration is limited due to high incidence of rash due to probenecid.

b. Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
   i. Nevirapine (NVP)

Dose:
200mg daily for the fist 14 days, then 200mg bd. (Note: patients experiencing a rash during the lead - in should not increase the dose until the rash has resolved)
- No interaction.
**Available formulations:**
Oral suspension: 10mg/ml  
Tablets: 200mg

**Side effects:**
Life threatening coetaneous reactions 3-6% (Stevens - Johnson syndrome), and thepatoxicity 13% (high CD4), usually during the initial 8 weeks (patient should be warned to report hypersensitivity symptoms: fever, rash 10-16%, arthralgias, or myalgias), maculopapular and erythematous rash.

**Drug Interactions:**
- Rifampicin, protease inhibitors and oral contraceptives decrease the level of Nevirapine.  
- Macrolides increase the level of Nevirapine.  
- Use of Nevirapine with Ketoconazole and Oral contraceptives is not recommended.

**Important:**
- If severe rash or rash with constitutional symptoms develop, therapy should be discontinued. If rash develops within the first 14 days of therapy, dose should not be increased to twice daily.  
- Therapy should be interrupted in patients who develop moderate to severe liver functions test results. Therapy should be reinstated with a 14 day once daily dosing when LFT returns to normal.  
- If LET recur nevirapine should be discontinued.

**ii. Efavirenz (EFV/EFZ)**

**Dose:**
- 600mg once daily taken in the evening to reduce CNS side effects that common in the first 2-3 weeks.  
- < 40kg = 400mg od (Empty stomach).
Available formulations:
- Syrup: 30mg/ml
- Tablets: 50, 100, 200, 600mg

Side Effects:
Approximately 15-27% develop rash, which is usually morbilliform and dose not require discontinuation of the drug. More severe reactions that require discontinuation are blistering and desquamating rashes (1-2%), CNS (noted in about 52% of patients): dizziness, delusions depression, bad dreams. False positive urine cannabinoid test, increased aminotransferase levels, contraindicated in pregnancy in the first trimester.

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.

c. Protease Inhibitors (PI)
i. Lopinavir/Ritonavir (LPV/r)
Dose:
- Adults: 400/100mg (3caps) twice a day (with food)

Available formulations:
- Oral suspension: 80mg/ml LVP + 20mg/ml RTV
- Capsules: 133/33mg (= 133.3mg of LVP +33.3 of RTV in each capsule)

Side effects:
Diarrhoea in 15-25% nausea and abdominal pain, class side effects: insulin resistance, fat accumulation and hyperlipidemia. Elevated trasaminase (SGOT and SGTP).

Drug Interactions
- LPV/r should not be administrated together with Rifampicin, Simvastatin, Atorvastatin, Lovastatin, Midazolam and Saquinavir (in vitro antagonism)
• Bioavailability of clarithromycin increased, reduced dose of clarithromycin in renal failure
• Bioavailability of atorvastatin increased to 450 times, use lowest dose 10mg/day or use alternatives such as pravastatin,
• Bioavailability decreased, use alternative contraception.

12. DRUGS FOR OPPORTUNISTIC INFECTIONS

i. Amphotericin B

Available formulations:
• Powder for injection: 50mg vial

Indication:
• 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 have resolved.
• 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:
Chills, fever and vomiting are common during infusion. Anaphylaxis, muscle and joint pains, headache and anorexia may also occur. These effects are often marked in the first days of treatment. Partial reversible deterioration of renal function, progressive normochromic anemia, selective leukopenia and thrombocytopenia are less common,
**Drug Interactions:**
- Concomitant administration of other nephrotoxic drugs should be avoided

ii. Azithromycin

**Available formulations:**
- Capsule: 250mg
- Powder for Oral Suspension: 200mg/ml

**Indications:**
- Prophylaxis against Mycobacterium Avium Complex

**Dose:**
- Prophylaxis against Mycobacterium Avium Complex: 1.2 - 25g (depending on tablet strength availability) once a day indefinitely.
- Should be taken one hour before or two hours after food.

Side Effects: Majorities are GI in origin including nausea, abdominal discomfort, vomiting, flatulence and diarrhea. Allergic reactions such as rash and photosensitivity have been reported. Ototoxicity has been reported in-patient receiving high doses for prolonged periods. Reversible elevations in transaminase levels have been reported.

**Drug Interactions:**
Increases the plasma levels of cyclosporin, digoxin and Warfari.

iii. Fluconazole

**Available formulations:**
- Tablets: 50mg, 100mg, 200mg
- Suspension: 50mg/5ml, 200mg/5ml
- Solution for infusion: 2mg/ml in 25ml and 100ml ampoule

**Indications:**
- Treatment and prophylaxis of cryptococcal meningitis
- Treatment of oesophageal and resistant oropharyngeal candidiasis, and vaginal candidiasis.
- Treatment and maintenance of coccidiodomycosis.
Guideline for the Management of HIV/AIDS in adult in Bhutan

**Dose:**
Cryptococcal meningitis: following treatment with Amphotericin B for either two weeks or until the conditions has improved: Fluconazole 800mg either orally or IV for two days followed by 400mg once a day for 8 weeks, reduced to 200mg oral once a day thereafter.

- Oesophageal and resistant oropharynadeal candidiasis: 200mg as an initial loading dose followed by 100mg daily until symptoms have resolved. Doses of up to 400mg daily have been used in very resistant cases.
- Vaginal candidiasis: 150mg as single oral dose.
- Coccidiodomycosis: 400mg orally or IV daily in patients unable to tolerate Amphotericin B.

**Side Effects:**
Nausea is frequently reported; vomiting and abdominal distension and discomfort have also been reported. Elevation of hepatic enzymes levels occurs in a small percentage of the patients and is reversible in the early stages. Treatment should be discontinued if signs of hepatic disease develop.

**Drug Interactions:**
- The dose of fluconazole should increased by one half if co administered with Rifampicin.

  **iv. Ganciclovir.**

**Available formulations:**
- Capsules: 250mg
- Powder for injection: 500mg vial

**Indications:**
Treatment of Cytomegalovirus end organ disease and maintenance of CMV retinitis

**Dose:**
- 5mg/kg/by slow IV infusion over 1 hour twice a day for 14-21 days or until symptoms has resolved.
- In CMV retinitis, it should be followed by oral medica-
iv gancyclovir should be given at a dose of 5mg/kg daily thereafter.

**Side effects:**
Anemia, leukopenias (especially neutropenia) and thromcytopenia, Fever, rash, abnormal liver functions test, raised blood urea concentrations, psychosis, convulsions and coma occurs sometimes.

**Drug Interaction:**
Concomitant administration with Zidovudine and other myelosuppressive drugs have been associated with severe haematological abnormalities.

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**CHAPTER-5**

13. Occupational Transmission of HIV

a. Health care workers and laboratory workers:
There is a small but definite occupational risk of HIV transmission to Health care workers, laboratory workers and people working with HIV containing materials. A total of 23 studies of needle sticks among health care workers demonstrated HIV transmission in 20 out of 6135 HIV infected source (0.33%). with mucosal surface exposure, there was one transmission in 1143 exposure (0.09). There was no transmission on skin exposure in 2712 incidents.

Till June 2003, 57 health care workers in USA who occupationally acquired HIV seroconversions has seroconverted. Among the confirmed cases 23 were nurses, 20 lab technicians and six physicians. All transmission was through blood and body fluids expect 3 lab technicians and who were exposed to viral culture. Exposures were per cutaneous in 5 and both in 2 cases. There were no confirmed cases of sero conversion in surgeon with exposure to suture needles. Risk of conversion is higher in following circum-

---
stances:
- Deep injury.
- Visible blood in the device.
- Needle placement in the vein or artery.
- Source with late HIV infection (due to high viral load).

**Risk of Viral Transmission with Sharps injury from Infected Source**

<table>
<thead>
<tr>
<th>Source</th>
<th>prevalence (U.S general populations)</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>HBV sAg</td>
<td>2.0-0.3%</td>
<td>1-6%</td>
</tr>
<tr>
<td></td>
<td>0.05-0.1%</td>
<td>22-31%</td>
</tr>
<tr>
<td>HCV</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

**13. POST EXPOSURE PROPHYLAXIS (PEP)**

Post-exposure prophylaxis (or PEP) means taking antiviral medications as soon as possible after exposure to HIV, so that the exposure will not result in HIV infection. These medications are only available with a prescription. Treatment should continue for 4 for weeks, if tolerated.

Preventing accidental exposure to blood and other body fluids of HIV infected patients through universal precautions is priority in reducing the risk of HIV transmission to health care workers. Ensure workplace safety, a policy of precaution; management, treatment and monitoring of accidental exposures to health care workers should be developed. HCWs who have exudative lesions and weeping dermatitis should refrain from direct care of the HIV positive patients. HIV specialist should be consulted immediately before starting PEP.

**a. Rationale for HIV PEP**

Considerations that influence the rationale and recommendations for PEP include
- The pathogenesis of HIV infection, particularly the time
course of early infection;
• The biological plausibility that infection can be prevented or ameliorated by using antiretroviral drug;
• Direct or indirect evidence of the efficacy of specific agents used for prophylaxis
• The risk and benefit of PEP to exposed HCW.

b. Efficacy of Antiretrovirals for PEP in Human Studies.
Little information exists from which the efficacy of PEP in humans can be assessed. Seroconversion is frequently following an occupational exposure to HIV-infected blood; therefore, several thousand of exposed HCP gold need to enroll in a prospective trial to achieve the statistical power necessary to directly demonstrate PEP efficacy.

c. Objectives of PEP
• To provide recommendations for the management of accidentally exposed health care workers (HWC).
• To recommend the selection of Highly Active Anti-Retroviral Therapy (HAART) for PEP.
• To provide guidance on monitoring and registrations of accidental exposures.
• Make available the ARV prophylaxis to the HCW within 1-2 hours of exposure.

d. PEP Recommendation and Choice of HAART regimen.
Recommendation are based on the type of exposure, HIV statues of the source, or if the status is unknown, the risk status of the source.

e. Treatment of an Exposure Site
• Wounds and skin sites that have been in contact with blood or body fluids should be washed with soap and water.
• Mucous membranes should be flushed with water.
• A 70% Alcohol solution should be used as disinfectant for washing.

f. HIV PEP for percutaneous injuries
Table 3.
### Table 4

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Source: HIV+, Low Risk*</th>
<th>Source: HIV+, High Risk</th>
<th>Source: HIV status unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not severe solid needle, superficial.</td>
<td>2 drug PEP AZT + 3TC</td>
<td>3 Drug PEP</td>
<td>Usually none, consider 2 drug PEP*</td>
</tr>
<tr>
<td>Severe: Large bore, deep injury, and visible blood in device, needle in patient artery or vein.</td>
<td>3 drug PEP AZT +3TC + LPV/r</td>
<td>3 Drug PEP</td>
<td>Usually none, consider two drug PEP***</td>
</tr>
</tbody>
</table>

* Low Risk: Asymptomatic HIV, retain patient for test but result may/may not be disclosed
** Concern for drug resistance: initiate prophylaxis without delay.
*** Consider 2 drug PEP if source is high risk for HIV or exposure is from an unknown source with HIV infection likely

* HIV PEP for mucous membrane and non intact skin exposure***

**Table 4**
** Consider if source has HIV risk factors or exposure from unknown source where HIV infected source is likely.
*** Non intact skin: dermatitis, abrasion and wound.

h. Monitoring and Counseling the Health Care Worker (HCW)

- Testing of HCW serology performed at the time of injury, repeated at 6 weeks, 3 months, 6 months and 12 months if positive for HCV.
- Precautions to prevent sexual transmission: HCW should practice safe sex or abstain until serology is negative at 6 months post exposure. The greatest risk within the first 6-12 weeks.
- Time: PEP should be initiated as quickly as possible preferably within 1-2 hours of exposure and up to 36 hours of post exposure. Some guidelines extend the time up to 72 hours. PEP should be given for a period of 28 days.
- Side effects: Many HCW experience side effects like nausea, fatigue, headache, diarrhea and they should be advised not to discontinue. If the side effects are severe a change in regimen may be offered.
- Breast-feeding: consider temporary cessation of breastfeeding during PEP.

i. Testing in the source patient.

- The IV test for the source patient is not mandatory considering the window period. (Refer VCT Guideline).

j. How is PEP taken?
PEP should be started as soon as possible after exposure to HIV. The medications used in PEP depend on the exposure to HIV. The following situations are considers serious exposure:
- Exposure to a large amount of blood.
Blood came in contact with cuts or open sores on the skin.
Blood was invisible on a needle that stuck someone.
Exposure to blood from someone who has high viral load (a large amount of virus in the blood).

k. The bottom line.

Post-exposure prophylaxis (PEP) is the use of antiviral drugs as soon as possible after exposure to HIV, to prevent HIV infection. PEP can reduce the rate of infection in healthcare worker exposed to HIV by 79%.
The benefits of PEP for non-occupational exposure have not been proven. This use of PEP is controversial because some people fear it will encourage unsafe behaviors.

PEP is a four-week program of two or three antiviral medications, several times a day. The medications have serious effects that can make it difficult to finish the program. PEP is not 100% effective; it cannot guarantee that exposure to HIV will not become a case of HIV infection.

**CDC Classification 1993**

<table>
<thead>
<tr>
<th>CD4 cell category</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) &gt; 500/mm³</td>
<td>A1</td>
<td>B1</td>
<td>C2</td>
</tr>
<tr>
<td>(2) 200-499/mm³</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>(3) &lt; 200/mm³</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>
### Guideline for the Management of HIV/AIDS in adult in Bhutan

<table>
<thead>
<tr>
<th>Category A</th>
<th>Category B</th>
<th>Category C</th>
</tr>
</thead>
</table>
| • Asymptomatic HIV infection  
  • Persistent generalized lymphadenopathy\(^1\) (PGL)  
  • Acute primary HIV illness  

\(^1\)Nodes in 2 or more extrainguinal sites, at least 1 cm in diameter for >3 months | • Symptomatic, not A or C conditions  
• Examples include but not limited to:  
- bacillary angiomatosis  
- candidiasis, vulvovaginal persistent > 1 month, poorly responsive to treatment  
- candidiasis, oropharyngeal  
- cervical dysplasia, severe or carcinoma in situ.  
- constitutional symptoms e.g. fever - (38.5\(^\circ\)) or diarrhoea > 1 month  
  
  ◆ the above must be attributed to HIV infection or have a clinical course or management complicated by HIV. | • candidiasis: oesophageal, trachea, bronchi.  
• coccidiodomycosis, extrapulmonary  
• Cervical cancer, invasive  
• cryptosporidiosis, chronic intestinal > 1 month  
• CMV retinitis, or CMV in other than liver, spleen nodes  
• HIV encephalopathy  
• Herpes simplex with mucotaneous ulcer > 1 month  
• Histoplasmosis  
• Kaposi sarcoma  
• M. Avium  

<table>
<thead>
<tr>
<th>Drug Abbreviations:</th>
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<tbody>
<tr>
<td>3TC = Lamivudine</td>
</tr>
<tr>
<td>ABC = Abcavir</td>
</tr>
<tr>
<td>AZT = Zidovudine</td>
</tr>
<tr>
<td>ZDV = Zidovudine</td>
</tr>
<tr>
<td>EFV = Efavirenz</td>
</tr>
<tr>
<td>EFZ = Efavirenz</td>
</tr>
<tr>
<td>LPV/r = Lopinavir/Ritonavir</td>
</tr>
<tr>
<td>T-MP-SMX = Trimethoprim + Sulphamethoxazole</td>
</tr>
<tr>
<td>HGC = Hard Gelatin Capsule</td>
</tr>
</tbody>
</table>
SGC = Soft Gelatin Capsule
NRTI: Nucleoside Reverse Transcriptase Inhibitors
PI: Protease inhibitors

HAART : Highly Active Anti Retroviral Therapy
HIV: Human Immuno Deficiency Virus
AIDS: Acquired Immuno deficiency syndrome
CDS: Cluster of Differentiation
RNA: Ribonucleic acid
OI: Opportunistic infections
CBC: Complete blood count
TLC: Total; lymphocyte count
PGL: Persistent generalized lymphadenopathy
URL: Upper respiratory infection
OHL: Oral hairy leukoplakia
IVDU: Intravenous drug users
STI: Sexually transmitted infection
OCP: Oral Contraceptive pills
KS: Kaposi sarcoma
-AFD: Acid fast bacilli
PMTCT: Prevention of mother to Child Transmission
MTCT: Mother to Child Transmission
PEP: Post Exposure prophylaxis
HCW: Health Care Workers
MAC: Mycobacteriu Avium Complex
IRS: Immune Reconstitution Syndrome
PCP: Penumocystic Carinii pneumonia
CMV: Cytomegalo virus
EBV: Epstein Barr Virus
PPE: Pruritic Papular Eruptions
References


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9. CDC. Public Health Service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. MMWR 1990; 39 (No. RR-1).

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11. CDC. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendation for postexposure prophylaxis. MMWR 1998;47 (No. RR-7)


