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- Post-exposure prophylaxis
- Preventing mother to child transmission of HIV

Learning Objectives

At the end of this module you should:

- Understand the principles of ART
- Name the ARV drugs recommended for ART in Zimbabwe
- Understand the side effects of ARVs
- Limitations of ART
- When to start ARVs, what to start with, when to change, What to change to
- Post-exposure prophylaxis.
Introduction

The benefits of highly active antiretroviral therapy (HAART) have been widely documented. With effective management of persons with HIV infection it is possible to delay the onset of AIDS-defining illnesses and to provide a high quality productive life. It is possible to prevent the occurrence of some opportunistic infections and opportunistic cancers with ART. Chronic debility and death may be delayed with effective treatment and therefore infected persons, who are usually in the most productive period of their life, may remain productive for longer periods. Numerous chemotherapeutic agents effective in reducing the viral load in persons with HIV infection are now available, and numerous combinations of these agents have been recommended as being effective in treating infected persons.

However, despite the emergence of a large number of antiretroviral agents, HIV infection remains incurable and the mainstay in the control of the epidemic remains primary prevention (Table 1).

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health education</td>
<td>▪ Inform and educate the public about the nature of HIV and other STIs including danger of infection, complications, modes of transmission, methods of prevention and treatment</td>
</tr>
<tr>
<td>Promote safer sexual behaviour</td>
<td>▪ Abstain from sexual activity altogether</td>
</tr>
<tr>
<td></td>
<td>▪ Delay sexual debut until one has found one’s lifelong mutually faithful partner</td>
</tr>
<tr>
<td></td>
<td>▪ Have sex only with one’s lifelong mutually faithful partner</td>
</tr>
<tr>
<td></td>
<td>▪ Avoid situations that may promote casual sexual liaisons</td>
</tr>
<tr>
<td>Promote safer sexual activity</td>
<td>▪ Abstain from sexual activity altogether</td>
</tr>
<tr>
<td></td>
<td>▪ Use condoms if engaging in casual sex</td>
</tr>
<tr>
<td></td>
<td>▪ Use condoms correctly and consistently</td>
</tr>
<tr>
<td></td>
<td>▪ Engage in non-penetrative sexual activities</td>
</tr>
<tr>
<td></td>
<td>▪ Promote and provide condoms widely</td>
</tr>
<tr>
<td>Promote early STI-care seeking</td>
<td>▪ Promote good STI-care seeking behaviour</td>
</tr>
<tr>
<td></td>
<td>▪ Make STI services accessible and acceptable</td>
</tr>
<tr>
<td>Promote voluntary counseling and testing for HIV</td>
<td>▪ Knowing one’s HIV status has been shown to promote behaviour change provided appropriate education and counselling are also provided</td>
</tr>
</tbody>
</table>
Prevention of opportunistic infections - Training Course for Health Care Providers

### Goals of ART

The aims of antiretroviral therapy (ART) are:

- Maximal and durable suppression of replication of HIV,
- Restoration and/or preservation of immune function,
- Reduction of HIV-related morbidity and mortality,
- Improvement of quality of life.

### Principles of antiretroviral therapy

The management of HIV infection has become increasingly complex because of the large numbers of available drugs and drug combinations, and because of the toxicity associated with drug therapy. In addition, some antiretroviral drugs may not be used in combination with drugs commonly used for treating infections such as tuberculosis. The monitoring of response to therapy, currently based on measuring the amount of virus present in plasma (HIV plasma viral load), is a complex and costly procedure and clinical surrogate markers of viral load are not currently available. It should be stated that ART is required for life in persons with HIV infection. Therefore treatment compliance and strict adherence to treatment regimens and schedules is necessary. Finally it is known that viral resistance to the drugs emerges readily, hence the need for continued vigilance and monitoring.

The guiding principles for good ART include efficacy, freedom from serious adverse effects, ease of administration and affordability of the drugs and drug combinations. Ongoing viral replication drives the disease process and leads to immunological suppression, hence a target for ART is to reduce viral replication. Viral replication may be assessed by measuring periodically the plasma viral load and the effect on the immune system may be assessed by measuring the number of CD4+ lymphocytes present in peripheral blood.
Health personnel that will be involved in managing persons on ART need to be trained and should have an in-depth knowledge about antiretroviral agents and their side effects.

**Mechanism of action**

Antiretroviral agents act by blocking the enzymes responsible for the replication and functioning of HIV. Currently available antiretroviral drugs belong to three classes:

- **Reverse transcriptase inhibitors (RTIs)** – these drugs block HIV reverse transcriptase and prevent the copying of the viral genetic code (RNA) into the genetic code (DNA) of infected host cells
- **Protease inhibitors (PIs)** – these drugs block the enzyme protease and prevent the assembly and release of HIV particles from infected cells
- **Fusion inhibitors** - these drugs block the fusion of HIV with the CD4 cell membrane and hence prevent the entry of HIV RNA into the cell

Within the class of reverse transcriptase inhibitors there are three types of drugs, the nucleoside reverse transcriptase inhibitors (NsRTIs), the nucleotide reverse transcriptase inhibitor (NtRTI), and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The different categories of antiretroviral drugs are shown in Table 2. Very recently a new agent that inhibits the fusion of HIV with the cell membrane has been launched. This drug, enfuvirtide, is only available for parenteral administration and is not widely available.

**Efficacy and safety**

For optimal efficacy a combination of several drugs should be used. A number of combinations have been shown to produce lasting suppression of HIV replication.
HIV replication & points of action for ARVs

All antiretrovirals have class specific side effects and individual drugs may cause specific side effects. In addition, significant drug interactions may occur when using some antiretrovirals in combination with each other and with other drugs as well.

Table 2: Classes of Antiretroviral Drugs

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitors</th>
<th>Non-nucleoside Reverse Transcriptase Inhibitors</th>
<th>Protease Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>Nevirapine (NVP)</td>
<td>Saquinavir* (SQV)</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>Efavirenz (EFV)</td>
<td>Ritonavir (RTV, r)</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>Delavirdine (DLV)</td>
<td>Indinavir (IDV)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td>Amprenavir (APV)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td></td>
<td>Lopinavir/ritonavir L(PVr)</td>
</tr>
</tbody>
</table>

Other classes of ARVs:
- Nucleotide reverse transcriptase inhibitors – tenofovir
- Fusion inhibitors – enfuvirtide

Adding a small dose of ritonavir to other protease inhibitors, such as saquinavir, indinavir and lopinavir may enhance their action. A lower dose of the drug may then be used and the drug may be administered twice a day rather than three times a day.
A number of these drugs are available as combination products. By prescribing drugs available in combination products, it may be possible to reduce the number of “pills” a patient has to take each day and to improve adherence.

- **Saquinavir** – if used as the only protease inhibitor in a combination regimen should be in the form of the soft gel capsule. Hard gel capsules should only be used in combination with ritonavir or nelfinavir.

**Tools to achieve the goals of Therapy**
- Maximization of adhere to ART
- Rational combinations of drugs
- Preservation of future treatment options
- Use of resistance testing when appropriate

**Limitations of Antiretroviral Therapy**
- Incompetence potency
- Drug toxicity
- Drug interactions
- Drug resistance
- Adherence
- Cost

**Critical questions in ART**
- When to start?
- What to start?
- When to change?
- What to change?

**When to start ARV therapy**

<table>
<thead>
<tr>
<th>Table 5.4: WHO Staging System for HIV Infection and Disease in Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Stage I:</strong></td>
</tr>
<tr>
<td>1. Asymptomatic</td>
</tr>
<tr>
<td>2. Persistent generalised lymphadenopathy</td>
</tr>
<tr>
<td><em>Performance Scale 1: Asymptomatic, normal activity</em></td>
</tr>
<tr>
<td><strong>Clinical Stage II:</strong></td>
</tr>
<tr>
<td>1. Weight loss less than 10% body weight</td>
</tr>
<tr>
<td>2. Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular stomatitis)</td>
</tr>
<tr>
<td>3. Herpes zoster within the last 5 years</td>
</tr>
<tr>
<td>4. Recurrent upper respiratory tract infections, e.g., bacterial sinusitis</td>
</tr>
<tr>
<td><em>And/or Performance Scale 2: Symptomatic but normal activity</em></td>
</tr>
<tr>
<td><strong>Clinical Stage III:</strong></td>
</tr>
<tr>
<td>1. Weight loss more than 10% body weight</td>
</tr>
</tbody>
</table>
2. Unexplained chronic diarrhoea for more than 1 month
3. Unexplained prolonged fever, intermittent or constant, for more than 1 month
4. Oral candidiasis
5. Oral hairy leukoplakia
6. Pulmonary tuberculosis within the past year
7. Severe bacterial infections such as pneumonias, pyomyositis

*And/or Performance Scale 3: Bed-ridden for less than 50% of the day during the last month*

<table>
<thead>
<tr>
<th>Clinical Stage IV:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. HIV wasting syndrome – weight loss of more than 10%, and either unexplained chronic diarrhoea for more than 1 month, or chronic weakness or unexplained prolonged fever for more than 1 month</td>
</tr>
<tr>
<td>2. <em>Pneumocystis</em> pneumonia (PCP)</td>
</tr>
<tr>
<td>3. <em>Toxoplasmosis of the brain</em></td>
</tr>
<tr>
<td>4. Cryptosporidiosis with diarrhoea for more than 1 month</td>
</tr>
<tr>
<td>5. Extrapulmonary cryptococcosis</td>
</tr>
<tr>
<td>6. Cytomegalovirus (CMV) disease of an organ other than liver, spleen or lymph nodes</td>
</tr>
<tr>
<td>7. Herpes simplex virus (HSV) infection, mucocutaneous for more than 1 month, or visceral of any duration</td>
</tr>
<tr>
<td>8. Progressive multifocal leukoencephalopathy (PML)</td>
</tr>
<tr>
<td>9. Any disseminated endemic mycosis such as histoplasmosis, coccidiodomycosis</td>
</tr>
<tr>
<td>10. Candidiasis of the oesophagus, trachea, bronchi or lungs</td>
</tr>
<tr>
<td>11. Atypical mycobacteriosis, disseminated</td>
</tr>
<tr>
<td>12. Non-typhoid salmonella septicaemia</td>
</tr>
<tr>
<td>13. Extrapulmonary tuberculosis</td>
</tr>
<tr>
<td>14. Lymphoma</td>
</tr>
<tr>
<td>15. Kaposi’s sarcoma</td>
</tr>
<tr>
<td>16. HIV encephalopathy – disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing slowly over weeks or months, in the absence of concurrent illness or condition other than HIV infection that could account for the findings</td>
</tr>
</tbody>
</table>

*And/or Performance Scale 4: Bed-ridden for more than 50% of the day during the last month*

If CD4 testing is available
- WHO stage 4 disease irrespective of CD4 cell count
- WHO stage 1,2,3 with CD4 counts below 200

**If CD4 testing is unavailable, use total lymphocyte count (TLC)**
- WHO stage 4 irrespective of total lymphocyte count
- WHO stage 2 or 3 disease with a total lymphocyte count below 1200
Individualization of ARV Therapy

<table>
<thead>
<tr>
<th>General factors</th>
<th>Patient specific factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count</td>
<td>Interest in taking drugs</td>
</tr>
<tr>
<td>Viral load</td>
<td>Co-morbidities</td>
</tr>
<tr>
<td>Presence or absence of symptoms</td>
<td>Financial barriers</td>
</tr>
</tbody>
</table>

**Potential for adherence**

What to start with?

**First line treatment for adults:**

- Stavudine 30/40mg orally twice daily, plus
- Lamivudine 150mg orally twice daily, plus
- Niverapine 200mg orally daily for two weeks and then 200mg orally twice daily

**NB:** Stavudine 30mg for those less than 60kg body weight,
       Stavudine 40mg for those above 60kg body weight.

**Alternative first line treatment for adults:**

- Zidovudine 300mg orally twice daily plus,
- Lamivudine 150mg orally twice daily, plus
- Nevirapine 200mg orally daily for 2 weeks and then 200mg orally twice daily thereafter.

**Activity 1**

This is an individual exercise.

1. What are the 3 main classes of ARV drugs?
2. Name at least one drug in each class.

When to change?

The treatment regimen may need to be changed if there has been treatment failure or if the patient is unable to tolerate the drugs due to toxicity. Patients in whom it is felt that treatment needs to be changed should be referred for specialist opinion.

In the event of treatment failure:

Patients that fail to respond to first treatment should be treated with a different regimen that contains drugs that were not included in the first regimen, see list of drugs in Table 2 above.
These patients may be treated with the second line treatment regimen described above provided they are not receiving rifampicin.

**In the event of drug toxicity:**

If the patient has drug toxicity, therapy may be altered as follows:

Change of a single drug in a multi-drug regimen is permitted, i.e., the offending drug may be replaced with an alternative drug of the same class.

If a patient reacts to stavudine replace with zidovudine and vice versa,

If a patient reacts to nevirapine replace with efavirenz 600mg once daily.

**When to change therapy?**

- **a) Virologic failure**
  - Less than 1.0 log reduction VL by 8 weeks
  - Failure to fully suppress (<50/ml) VL by 4-6 months
  - Repeated detection of VL after initial suppression
  - Any reproducible significant increase of VL

- **b) Immunologic failure**
  - Persistently declining CD4 cell counts

- **c) Clinical deterioration**
  - Stage 4 disease

- **d) Drug intolerance**

**Why does Treatment Fail?**

- Baseline resistance or cross-resistance
- Use of less potent antiretroviral regimens
- Sequential monotherapy
- Poor adherence
- Drug level and drug interactions
- Tissue reservoir penetration
- Other, unknown reasons
Correlation Between Optimal Therapeutic Response and Adherence to HIV Therapy

% patients with HIV RNA <500 c/mL at least twice

- <70%: 12
- 70%-<80%: 24
- 80%-<90%: 47
- 90%-<95%: 64
- 95%-100%: 84

Adherence level

Mantel-Haenszel trend test, p=0.001

n = 232


What to change to?

Second line treatment for adults

A second line regimen is to be used only when there is documented evidence of treatment failure with the first line regimen, i.e., if there is evidence 6 months after commencing first line treatment of falling CD4+ lymphocyte counts, or rising HIV plasma viral load, or if there is worsening of symptoms and signs of opportunistic infection or cancer. The second line treatment regimen should only be initiated after consultation with a specialist. Patients who fail to respond to first line treatment should be treated with a different regimen that contains drugs that were NOT included in the first regimen.

NOTES:

1. Zidovudine and stavudine should not be taken together
2. Didanosine should be taken on an empty stomach; the patient should not take food two hours before and one hour after taking the medication
3. Patients taking indinavir should take at least 1.5 litres of water a day in order to prevent the formation of renal calculi. Indinavir should be taken 1 hour before or two hours after taking food
4. Patients receiving rifampicin should not be given indinavir
5. All patients with HIV infection, unless it is known that the CD4+ lymphocyte counts are more than 200 / mm$^3$, should take, on a long term basis, cotrimoxazole 2 tablets orally once daily to prevent other opportunistic infections
6. Combination products can enhance adherence by reducing the pill burden that the patient has to take.

**Activity 2**

This is an individual exercise.

1. What are the reasons for treatment failure in ART?

**Patients with HIV infection who have TB and in whom ART is indicated**

Tuberculosis is the commonest opportunistic infection encountered among persons with HIV infection in Zimbabwe. Since the advent of the pandemic of HIV infection, TB has re-emerged as a serious public health problem. Studies have shown that up to 50% of persons with HIV infection develop TB and that up to 85% of persons with TB have HIV infection. The rifamycin antibiotics, rifampicin and rifabutin, are highly active against TB, however they interact adversely with some antiretroviral agents such as protease inhibitors, and therefore cannot be used concomitantly with some ART regimens.

Patients with HIV infection and TB may be treated with the first line treatment recommendations described above. It is recommended that ART be commenced in those patients with extra-pulmonary TB and / or CD4 counts of less than 200 cells. The ART may be delayed until the intensive phase of TB therapy is over or may be started as soon as TB therapy is tolerated.

All patients that are already on ART and develop TB while on ART should be referred for assessment and advice on management. The following treatment may be given to patients with HIV infection and TB:

- Stavudine 30/40 mg orally twice daily, Plus
- Lamivudine 150 mg orally twice daily, Plus
- Nevirapine 200mg orally daily for two weeks and then 200mg orally twice daily
NOTES:

All patients with HIV infection and TB, unless it is known that the CD4+ lymphocyte counts are more than 200 / mm$^3$, should take cotrimoxazole 2 tablets orally once daily to prevent opportunistic infections.

**Antiretroviral therapy during pregnancy**

ARVs may be used in pregnant women provided certain precautions are kept in mind:

- It is preferable to commence ART after the first trimester of pregnancy so as to minimize the possible risk of teratogenesis
- Certain drugs, such as, efavirenz should **not** be used during pregnancy and in women at risk of falling pregnant
- NsRTIs and NNRTIs cross the placenta and there is a potential for mitochondrial toxicity in the foetus
- By reducing the maternal HIV plasma viral load with highly active antiretroviral therapy the risk of transmission of infection to the baby is reduced
- Do not use the combination of Stavudine and Didanosine in pregnant women as there is an increased risk of lactic acidosis with this combination of drugs

With treatment during pregnancy there is a theoretical risk of drug resistance occurring in the baby and of masking the diagnosis in the child particularly while less than 6 weeks of age. Resistance development after a single dose of Nevirapine has been reported however the resistance is lost after a year. The following treatment regimen is recommended for pregnant women after the first trimester:

- **Stavudine 30/60 mg orally twice daily, Plus**
- **Lamivudine 150 mg orally twice daily, Plus**
- **Nevirapine 200mg orally daily for two weeks and then 200mg orally twice daily**
Antiretroviral therapy in children
The principles of ART in children are similar to those in adults. However, there are certain important points that need to be considered when addressing this issue. These are:

- Prevention of mother-to-child transmission of HIV should take high priority
- Babies born to mothers with HIV infection should receive cotrimoxazole prophylaxis from the age of 4 to 6 weeks
- Nutritional support is a crucial intervention in managing HIV infected children
- The interpretation of CD4+ lymphocyte counts and HIV viral loads differs from that for adults
- Viral load measurement is not necessary for monitoring and is not predictive of disease progression in children
- The diagnosis of HIV infection using the standard ELISA antibody tests may be misleading and may be a simple indication if the mothers transferred antibodies. These tests are only reliable after the child has reached the age of 15 months. Prior to the age of 15 months it is necessary to perform a PCR test for HIV. If the HIV test is negative before the age of 15 months the infant does not have HIV infection but is at risk of infection if breast-feeding is continued.

Criteria for Initiating ART in children
(SEE MODULE 14 AS WELL FOR MORE DETAILS)
It is advisable to commence ART in the following categories of HIV infected children:

- All children regardless of age who have:
  - AIDS-defining opportunistic infections,
  - wasting,
  - failure to thrive,
  - encephalopathy,
  - malignancy,
  - recurrent septicemia
  - recurrent meningitis
- All children with rapidly declining CD4+ lymphocyte counts and levels approaching moderate or severe immune suppression, i.e., when 15 to 24% of all peripheral blood lymphocytes are CD4+ lymphocytes
- All children in whom the HIV viral load is above 100000 copies / ml or there is a 5 fold rise in viral load over a period of observation in children less than 2 years of age and a 3 fold rise in children more than 2 years of age
Recommendations for children need to take into consideration the age and weight of the child, the availability of paediatric formulations of medications, palatability of medications and the effect of food on absorption of drugs. Symptomatic children with HIV infection should be treated as follows:

**First line regimen in children**

**Stavudine** – over 3 months, under 30kg - 1mg/kg every 12 hours
30kg and over - adult dose (30mg every 12 hours preferably at least 1 hour before food for under 60kg and 40mg every 12 hours for over 60kg.

**OR**

**Zidovudine** – less than 28 days of age – 4mg/kg orally twice daily
4 weeks to 13 years - 180mg/m² orally twice daily

**PLUS**

**Lamivudine** - Age less than 30 days - 2mg/kg orally twice daily
Age more than 30 days or weight less than 60kg - 4mg/kg orally twice daily
More than 60kg weight (Maximum dose) - 150mg orally twice daily

**PLUS**

**Nevirapine** - Age 15-30 days: First 2 weeks - 5mg/kg orally daily
Next 2 weeks – 120mg/m² orally twice daily
Then - 200mg/m² orally twice daily

Age >30 days: First 2 weeks - 120mg/m² orally twice daily
Then - 200mg/m² orally twice daily

Where there is evidence of treatment failure or suspected treatment failure, refer to a specialist for change of regimen.

**MONITORING PATIENTS ON ART**

Patients on ART need close monitoring to assess treatment compliance and adherence to treatment regimen, tolerance and side effects of the medications and efficacy of the treatment.
Initial evaluation

Before commencing ART all patients should have a detailed history taken, a physical examination carried out (See Table 5), and basic laboratory tests performed.

Prior to commencing ART it is essential to perform some laboratory tests. These include:

- HIV serology – No patient should be started on ART without first establishing that the patient is infected with HIV
- Full blood count – It is necessary to have a baseline haemoglobin, peripheral blood white cell count, lymphocyte count and red cell indices performed
- Liver function tests
- Blood urea, electrolytes and creatinine
- Urinalysis – Urine chemistry and microscopy should be performed
- Chest x-ray – It is essential to search for tuberculosis in all patients prior to commencing ART

If it is possible, also arrange to have the following tests performed prior to commencing ART:

- CD4+ lymphocyte count
- HIV viral load
- Syphilis serology
- Hepatitis B virus screening
- Pregnancy test

Table 5: Important clinical findings to note prior to initiating ART

<table>
<thead>
<tr>
<th>From the history note the following:</th>
<th>From the examination note the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of diagnosis of HIV infection</td>
<td>Patient’s weight</td>
</tr>
<tr>
<td>Current symptoms</td>
<td>Mental state of patient</td>
</tr>
<tr>
<td>Past illnesses and treatments</td>
<td>Presence of oral candidiasis, oral Kaposi’s sarcoma, oral hairy leukoplakia</td>
</tr>
<tr>
<td>History of past TB</td>
<td>Presence of lymphadenopathy, skin Kaposi’s sarcoma, herpes zoster scars, dermatitis</td>
</tr>
<tr>
<td>History of TB contacts</td>
<td>Presence of chest signs</td>
</tr>
<tr>
<td>Current symptoms suggestive of TB</td>
<td>Presence of abnormality in the CVS, GIT, abdomen, CNS, fundi</td>
</tr>
<tr>
<td>Past or current symptoms of STI</td>
<td>Abnormalities in the genital tract</td>
</tr>
<tr>
<td>Possibility of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Social habits and sexual history</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring treatment compliance

Strict adherence (at least 90% adherence) to recommended treatment regimens is important if treatment efficacy is to be expected. The importance of counselling and the provision of accurate information to all patients is an important determinant of treatment compliance. Information on side effects should be provided and patients should be told what to expect from the treatment. A treatment timetable, e.g., like the TB card, should also be provided and patients and carers should be instructed how to fill out the card. Counselling should be provided at each visit and patients should be allowed to seek help between visits as well. Patients should be encouraged to bring with them all tablet containers at each visit. Providers should carry out a tablet count in order to determine whether the medications have been taken as per schedules provided.

Monitoring drug side effects

A patient on ART may develop new symptoms while on treatment. These symptoms may be indicative of intercurrent illnesses, adverse drug side effects, or immune reconstitution syndrome. All patients should be examined carefully at each visit and a diagnosis should be made. Any intercurrent illness should be treated appropriately.

Once ART has been commenced the patient should be seen 2 weekly for a month after initiating treatment, and then every month for 3 months. The patient should be provided with written and verbal information on side effects that may occur and should be requested to report immediately for examination should side effects occur. Side effects may be class specific or drug specific. Most side effects are mild and most occur within the first 15 days of initiating ART.

Class-specific side effects of antiretroviral agents

Mild side effects such as headache, fatigue, gastrointestinal upsets and diarrhoea occur fairly frequently, but the serious side effects occur rarely. Usually these are worst in the first 2 weeks of treatment and can be treated symptomatically with paracetamol, anti-emetics, or antidiarrhoeal agents such as loperamide.
Nucleoside reverse transcriptase inhibitors

- Reversible fatty change in the liver (hepatic steatosis)
- Lactic acidosis
- Deranged metabolism of fats

Protease inhibitors

- Body fat redistribution with “cushingoid appearance”
- Abnormal glucose tolerance and worsening diabetic control
- Deranged fat metabolism with elevation of triglycerides and cholesterol
- Bleeding episodes in persons with haemophilia

Non-nucleoside reverse transcriptase inhibitors

- Skin rashes that may be mild or life-threatening
- Hepatitis and rarely liver failure

Side effects of specific antiretroviral agents

The side effects of specific antiretrovirals are summarized in Table 6:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side effects</th>
<th>Action to be taken</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Anaemia, neutropenia, sepsis</td>
<td>Monitor FBC</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Pancreatitis, peripheral neuropathy, diarrhoea</td>
<td>Monitor, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>Oral ulceration, peripheral neuropathy</td>
<td>Observe, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Pancreatitis, peripheral neuropathy</td>
<td>Monitor, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Usually nil</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Severe hypersensitivity reactions</td>
<td>Withdraw drug immediately and give alternative. Do not restart drug as this can be fatal</td>
</tr>
<tr>
<td><strong>NNRTIs:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Abnormal liver function tests, severe hypersensitivity reactions</td>
<td>If LFTs suggestive of hepatitis or if jaundice present discontinue; if rash severe discontinue</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>CNS symptoms</td>
<td>Monitor, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Headaches</td>
<td>Monitor, withdraw drug if symptoms are severe</td>
</tr>
</tbody>
</table>
Prevention of opportunistic infections

<table>
<thead>
<tr>
<th>PIs:</th>
<th>Symptoms are severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>GI intolerance, diarrhoea</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Pancreatitis, hepatitis, skin sensitivity, circumoral paraesthesia, nausea vomiting, diarrhoea Monitor, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Renal stones, headaches, blurred vision, jaundice, rash, metallic taste in mouth Monitor, withdraw drug if symptoms are severe</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Diarrhoea                                                May be necessary to give loperamide</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>GI intolerance, diarrhoea, rash, circum-oral paraesthesia</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir</td>
<td>GI intolerance</td>
</tr>
</tbody>
</table>

**Monitoring efficacy of ART**

Efficacy of ART may be monitored by assessing clinical improvement as well as immunologic function and HIV viral load. The ideal would be to monitor on a regular basis the CD4+ lymphocyte count and the HIV viral load. However these tests are not widely available throughout the country and are also extremely costly to perform. It is necessary to make an assessment of response to treatment through regular careful clinical examinations backed where possible by simple laboratory tests.

**Clinical monitoring**

Clinical monitoring on its own has not yet been validated, but studies are on going. The following clinical indices suggest that the patient is responding to ART:

- The patient feels better and has more energy to perform daily tasks. This may be assessed quantitatively by calculating the Karnoffsky performance score at each visit
- The patient is gaining weight – Record the patients weight at each visit
- There is an improvement in symptoms and signs of the original presenting illness
- Infections such as oral thrush, hairy leukoplakia, genital herpes, skin rash, molluscum contagiosum have improved
- There has been an improvement in chronic diarrhoea
- There has been an improvement in Kaposi's sarcoma or other malignancy
- The patient is free of new moderate or severe infections

The following symptoms and signs may be indicative of treatment failure or poor response to treatment. However before diagnosing treatment failure it is important to assess adherence to treatment. If adherence has been satisfactory then the following clinical criteria may indicate treatment failure:

- Patient feels he is deteriorating with loss in energy levels and loss in activity level and a deteriorating Karnoffsky performance score
- Loss of weight
- Worsening of symptoms and signs of original presenting illness
- Development of new and recurrent minor opportunistic infections such as oral thrush, hairy leukoplakia, genital herpes, skin rash, molluscum contagiosum
- Return or worsening of chronic diarrhoea
- Return of features of HIV encephalopathy
- Exacerbation of Kaposi's sarcoma
- Appearance of new moderate or severe infections or malignancy
- Development of bacterial pneumonia or tuberculosis with other AIDS-defining illnesses

**Immunological, peripheral blood CD4+ lymphocyte monitoring**

With successful ART the rate of increase in CD4+ lymphocyte levels depends on the initial CD4+ lymphocyte count. If the CD4+ lymphocyte count was very low to start with, e.g., if the initial CD4+ lymphocyte count was less than 50 / mm³, then it can take more than one year to increase to more than 200 / mm³. Persistently declining CD4+ lymphocyte counts as measured on two occasions and clinical deterioration as described above is suggestive of treatment failure.

**Virological, HIV viral load monitoring**

The HIV viral load decreases to undetectable levels within 6 months of successful ART. However this response also depends on the initial, pre-treatment, viral load. The viral load
measurement is useful in assessing treatment failure. If there has been a three-fold increase in the viral load from the lowest point following treatment, then this is an indication of treatment failure. In such situations it is necessary to review the treatment regimen and consider changing the regimen.

**Monitoring of ART in children**

In children growth and development are important clinical monitoring indicators. These are assessed using growth charts. Laboratory indices of CD4+ lymphocyte counts and HIV viral load levels may also be used in assessing response to therapy.

**Changing ART in children**

In the event of treatment failure or drug toxicity there may be a need to change or modify therapy. If therapy is to be changed then drugs that have not been used in the first regimen should be used. Note that in the presence of neurodevelopmental deterioration the new regimen should contain at least one drug that is known to penetrate the blood brain barrier, i.e. zidovudine, stavudine or nevirapine. The following clinical criteria warrant consideration of a change in antiretroviral therapy:

- Disease progression, occurrence of new opportunistic infections and advancement from one paediatric HIV clinical category to another
- Occurrence of new symptoms and signs and HIV-related diseases
- Progressive neurodevelopmental deterioration (i.e., repeated demonstration of two or more of the following: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction)
- Growth failure, i.e., persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation

In the event of treatment failure the ART regimen should be changed and drugs that were not used previously should be used. However change of regimen should only be undertaken if poor adherence is not the cause of failure, in which case treatment should be withheld until all adherence issues have been addressed.
Prevention of opportunistic infections

PREVENTING OPPORTUNISTIC INFECTIONS

Immunosuppressed persons are prone to develop opportunistic infections such as *Pneumocystis carinii* pneumonia, toxoplasmosis and bacterial lower respiratory tract infections and bacterial skin infections. Studies have shown clearly that taking chemoprophylaxis in the form of cotrimoxazole and isoniazid (INH) on a long-term basis may prevent many of these infections.

Cotrimoxazole chemoprophylaxis can potentially prevent the following opportunistic infections:

- *Streptococcus pneumoniae* pneumonia
- Non-typhoid salmonelloses
- *Pneumocystis carinii* pneumonia
- Cerebral toxoplasmosis
- Nocardiosis
- Isosporiasis

It is therefore recommended that all persons with HIV infection who are to commence on ART should also receive:

Cotrimoxazole (sulphamethoxazole 800 mg and Trimethoprim 160 mg) once daily orally. This treatment is continued indefinitely or until such a time that the CD4+ lymphocyte counts are greater than 200 / mm³.

POST-EXPOSURE PROPHYLAXIS

In persons who have been accidentally exposed to HIV through needle-stick inoculation or through contamination of mucous membranes by secretions it has been shown in a limited number of studies that immediate administration of antiretrovirals may prevent infection from occurring. In this situation ART needs to be continued for one month. The following guidelines should be followed in the event of accidental occupational exposure to material,
i.e., blood, secretions, excretions, that may contain HIV. Occupational exposure to potentially infectious material may occur through an injury with a sharp object that has been used on a patient or through the contamination of mucous surfaces with patients’ blood or secretions.

The following types of exposures should be considered for post-exposure prophylaxis:

- Needle-stick injury or injury with a sharp object used on a patient
- Mucosal exposure of the mouth or eyes by splashing fluids
- Broken skin exposed to a small volume of blood or secretions

**Prevention of occupational exposure in health facilities**

All health facilities in the private and public sector should adopt a policy for the prevention of occupational accidental exposure to blood borne pathogens. Health facilities should implement universal precautions for the prevention of exposure to potentially infectious material. The programme should include training of all employees in handling and disposal of infectious material. All personnel should be made aware of the risks involved in improper handling of such material and the steps necessary for preventing exposure should be clearly displayed in posters.

The greatest risk for accidental exposure is with the handling sharp objects that have been used on patients. All personnel should be taught how to safely handle sharp objects and how to safely dispose of them. Messages should address promote avoid re-capping of needles, using “sharps bins” for disposing of sharps, and taking care in performing procedures.

Health personnel should also be conscious that blood and secretions from patients may be infectious and that simple contamination of unbroken skin does not comprise a significant risk but contamination of intact mucous surfaces of the mouth and eyes does. The health facility should ensure the continuous supply of education materials, disposable syringes and needles and sharps bins.
**Procedure to be followed in the event of injury with a sharp object**

In the event of an injury with a sharp object such as a needle or scalpel that has been used on a patient or in the event of a mucous surface being contaminated with blood or secretions from a patient the following steps should be followed:

1. Wash exposed area thoroughly with soap and water.
2. Rinse eye or mouth with plenty of water if contaminated.
3. Report the injury to a senior member or staff or the supervisor.
4. Take antiretroviral drugs recommended for post-exposure prophylaxis immediately – these should be started within 1 hour if possible and at the latest within 72 hours of the exposure (persons presenting after 72 hours of exposure should also be considered for post exposure prophylaxis).
5. Ascertain the HIV status of the patient and the injured health worker after providing appropriate counselling – the standard rapid HIV antibody tests that are currently used in the Voluntary Counselling and Testing programme should be used and the results of tests should be obtained as quickly as possible.
6. Depending on the results of the HIV tests the following actions should be taken:

   - If the source patient is HIV negative no further post-exposure prophylaxis is necessary for the exposed health worker.
   - If the exposed health worker is HIV positive no further post-exposure prophylaxis is necessary for the health worker, but the health worker should be referred for further counselling and management on a long-term basis his/her HIV infection which has not occurred as a result of the exposure.
   - If the health worker is HIV negative and the source patient is HIV positive then continue antiretrovirals for a period of one month; repeat the health worker’s HIV tests at 3 months and at 6 months after the initial test, if the health worker should seroconvert during this time then provide appropriate care and counselling and refer for expert opinion and long term treatment.
   - If the health worker refuses to be tested, he or she may have no claim for possible future compensation.
7. If it is not possible to determine the HIV status of the source patient then assume that the source is positive and proceed according to guidelines in the previous bullet.

8. Determine the health workers hepatitis B virus immune status and if non-immune institute hepatitis B virus vaccination.

**Antiretroviral Drugs to be used in Post-Exposure Prophylaxis**

Dual therapy can be used as it has been shown to work but we are recommending triple therapy in line with our general recommendations for HIV infection.

Immediately after exposure all exposed health workers should take:

- **Zidovudine 300 mg orally twice daily, Plus**
- **Lamivudine 150 mg orally twice daily, Plus**
- **Protease Inhibitor e.g. Indinavir 800mg orally three times a day or Lopinavir –400/Ritonavir -100mg twice a day**

Counseling regarding side effects should be given to the healthcare worker.

This regimen is continued until the results of HIV tests for patient and injured health worker are known:

If the source is HIV negative or the health worker is HIV positive then drug administration should be discontinued.

If the health worker is HIV negative and the source is HIV positive or the source’s HIV status is not determined then continue this regimen for 4 weeks.

**Alternate antiretroviral regimens** for post-exposure prophylaxis may be used such as:

- **Stavudine 40 mg orally twice daily if body weight is more than 60 kg, or 30 mg orally twice daily if body weight is less than 60 kg for 4 weeks, Plus**
- **Didanosine 400 mg orally once daily if body weight is more than 60 kg, or 250 mg orally once daily if body weight is less than 60 kg for 4 weeks, Plus**
- **Indinavir 800mg orally three times a day or Lopinavir 400mg/Ritonivir 100mg twice a day.**
Post-sexual exposure prophylaxis

There is not enough evidence to recommend prophylaxis against infection following casual sexual exposure. However in the event that there has been sexual abuse or rape then it is recommended that the victim be counseled and provided with the drugs recommended for post-occupational exposure prophylaxis. It is important to try and determine the HIV status of the perpetrator. If this is not possible then it may be assumed that the perpetrator is HIV positive and the victim is provided with the treatment as listed in the preceding paragraph.

PREVENTING MOTHER-TO-CHILD TRANSMISSION OF HIV

There is sufficient evidence that mother-to-child transmission of HIV may be prevented substantially by giving the mother and the infant ART. Studies have shown that zidovudine given to the mother in last trimester of pregnancy and to the baby during the first 6 weeks of life, or alternatively nevirapine given in a single dose to the mother during labour and in a single dose to the infant soon after birth, substantially reduce the rate of mother-to-child transmission of HIV. In addition it has also been shown that treating the pregnant woman adequately with antiretroviral agents during pregnancy reduces the rate of mother-to-child transmission of HIV. Combination of antiretroviral agents has also been shown to reduce the transmission rate. These approaches reduce the rate of mother-to-child transmission of HIV by about 50% provided the baby does not breast feed.

The role of breast-feeding in the mother-to-child transmission of HIV is significant. However the risks of not breast-feeding far out-weigh the benefits and hence it is important to counsel and educate the mother so that she can make an informed choice.

Formula feeding may be an acceptable alternative to breast-feeding provided hygienic standards of formula feeding can be maintained. The Ministry of Health and Child Welfare has already launched the programme for the prevention of mother-to-child transmission of HIV and readers are advised to follow the Ministry’s guidelines on this topic.
Antiretroviral regimens for the prevention of mother to child transmission of HIV

Nevirapine-containing regimen

Mother: Nevirapine 200 mg orally in single dose to HIV positive mother at the start of labour, Plus

Neonate: Nevirapine 2mg/kg in a single oral dose to neonate at 48 to 72 hours after birth

If the mother receives nevirapine less than two hours before delivery then give the baby nevirapine 6 mg orally as soon as possible after birth and at 48 to 72 hours later

It is advisable that the baby is not breast-fed.

Zidovudine-containing regimen

Mother: Zidovudine 300 mg orally twice daily from the 36th week of pregnancy till labour starts and 300 mg orally 3 hourly during labour until delivery to the mother, Plus

Neonate: Zidovudine 2 mg / kg 4 times a day for 6 weeks, beginning 8 to 12 hours after birth

Zidovudine and lamivudine-containing regimen

Mother: Zidovudine 300 mg orally twice daily from the 36th week of pregnancy till labour starts and 300 mg orally 3 hourly during labour until delivery and 300 mg orally twice daily for 1 week after delivery to the mother, Plus

Lamivudine 150 mg orally twice daily from the 36th week of pregnancy until one week after delivery to the mother,

Neonate: Zidovudine 4 mg / kg orally twice daily for 1 week to the baby, Plus

Lamivudine 2 mg / kg orally twice daily for 1 week to the baby

ART in mother

All mothers should be assessed and treated according to the adult ART guidelines.