Guidelines for Antiretroviral Therapy in Zimbabwe

The National Drug and Therapeutic Policy Advisory Committee (NDTPAC)

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Ministry of Health and Child Welfare, Republic of Zimbabwe

Further copies may be obtained via the PMD offices or NDTPAC, MOHCW, PO Box CY 1122, Causeway, Harare, Zimbabwe or write to ndtpac@healthnet.zw .

The information presented in these guidelines conforms to current medical nursing and pharmaceutical practice. It is provided in good faith and hence, whilst every effort has been made to ensure that the drug doses are correct, no responsibility can be taken for errors or ommissions.

Foreword

The introduction of antiretroviral drugs has revolutionised the care and management of HIV/AIDS. Whilst they cannot cure HIV/AIDS, they have dramatically reduced mortality, morbidity, prolonged lives and improved the quality of life for those infected with HIV. Concurrently, the price of antiretroviral drugs has fallem making it possible for those in the developing countries to access antiretroviral drugs.

In Zimbabwe, we would want to see a standardised approach to treatment and management of HIV/AIDS. Remember, that once started on antiretroviral drugs, treatment is for life. It is hoped that they will promote rational use of these important and expensive drugs and avoid therapeutic anarchy. The guidelines are meant for use in the private as well as the public sector.

These guidelines will be updated as new information and evidence becomes available.

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1. Introduction

The benefits of highly effective 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 1: HIV Primary Prevention Strategies and Activities

Strategies	Activities
Public health education	- 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.
Promote safer sexual behaviour	- Abstain from sexual activity altogether. - Delay sexual debut until one has found one's lifelong mutually faithful partner. - Have sex only with one's lifelong mutually faithful partner. - Avoid situations that may promote casual sexual liaisons.
Promote safer sexual activity	- Abstain from sexual activity altogether. - Use condoms if engaging in casual sex. - Use condoms correctly and consistently. - Engage in non-penetrative sexual activities. - Promote and provide condoms widely.
Promote early STI-care seeking	- Promote good STI-care seeking behaviour. - Make STI services accessible and acceptable.
Promote voluntary counselling and testing for HIV provided.	- Knowing one's HIV status has been shown to promote behaviour change provide appropriate education and counselling are also - Provide accessible and acceptable services for the voluntary testing for HIV. - Provide HIV counselling services.
Prevent mother-to-child transmission of HIV	- Provide education and counselling to pregnant mothers. - Implement activities for the prevention of mother-to-child transmission of HIV using single-dose regimens of antiretroviral drugs such as nevirapine.

2. Principles of Antiretroviral Therapy (ART)

The management of HIV infection has become increasingly complex because of the large numbers of available drugts and drug combinations, and because of the toxicities 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.

3. Characteristics of Available Antiretroviral Drugs

3.1 Mechanism of action

Antiretroviral agents act by blocking the enzymes responsible for the reproduction and functioning of HIV. Currently available antiretroviral drugs belong to two 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. Within the class of recerse 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 administratin and is not widely available.

3.2 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.

All antiretrovirals have class specific side effects and individual drugs may cause specific side effects. The side effects of individual drugs are listed in Table 6. 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

Nucleoside Reverse Transciptase Inhibitors	**Non-nucleoside Reverse Transcriptase Inhibitors**	**Protease Inhibitors**
Zidovudine	Nevirapine	Saquinavir*
Didanosine	Efavirenz	Ritonavir
Zalcitabine	Delavirdine	Indinavir
Stavudine		Nelfinavir
Lamivudine		Amprenavir
Abacavir		Lopinavir/ritonavir

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.

4. Initiation of Antiretroviral Therapy in Adults

4.1 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, and
- Improvement of quality of life.

4.2 Considerations for initiating ART in adults

Table 3: WHO HIV Clinical Staging System

Stages 1 & 2	Stage 3	Stage 4
Asymptomatic infection	Weight loss more than 10% body weight	Pneumocystis pneumonia Recurrent pneumonia
Persistent generalized lymphadenopathy	Unexplained chronic diarrhoea for more than one month	Cryptococcal meningitis, oesophageal candidiasis
Weight loss of less than 10% body weight	Unexplained prolonged fever	Kaposi's sarcoma, lymphoma, invasive cervical cancer
Herpes Zoster	Oral candida, chronic vaginal candidiasis	HIV wasting syndrome
Minor mucocutaneous manifestations, eg, seborrhoeic dermatitis, recurrent oral ulcer, prurigo, onychomycosis	Oral hairy leukoplakia	Extrapulmonary TB Toxoplasmosis CMV Cryptosporidiosis / Isosporiasis Disseminated mycosis Histoplasmosis Atypical mycobacteriosis Non-typhoid salmonella bacteraemia
Recurrent upper respiratory tract infections	Severe bacterial infections	Herpes simplex ulcer for more than one month
	Pulmonary TB	CMV Non-typhoid salmonella septicaemia HIV encephalopathy. PML. HIV nephropathy.

Based on currently available evidence it is recommended that ART be considered in:

- Patient with WHO clinical stages 3 and 4 (see Table 3).

- Patients with HIV infection who have a peripheral blood CD4+ lymphocyte count of less than 350 / mm^3.

- Patients with a high HIV viral load, ie, more than 30000 copies / mL as measured by bDNA analysis, or more than 55000 copies /mL as measured by RT-PCR.

4.3 Using virological, immunological and clinical parameters in guiding decisions about therapy

The measurement of viral loads and CD4+ lymphocyte counts are currently not widely available in Zimbabwe and are expensive tests to perform. It is therefore recommended that the decision to commence ART may be made on the clinical findings in a person in whom HIV infection has been confirmed through standard laboratory tests for HIV antibody detection. Recommendations may change as more evidence on ART becomes available.

The following are recommendations for making decisions about ART in Zimbabwe:

A. Indications for commencing antiretroviral therapy

- HIV positive individuals who have WHO stages 3 and 4 disease (See Table 3).

- HIV positive individuals who have no symptoms or only mild symptoms but in whom the peripheral blood CD4+ lymphocyte count is less than 200 / mm^3 (See Table 3).

B. Indications for offering antiretroviral therapy

In the following category of patients the advantage and disadvantages of ART should be discussed with patients. ART should be offered to the patient if the patient is prepared to adhere to the strict treatment recommendations. It is important that patients commencing ART strictly adhere to the prescribed regimen.

- HIV positive individuals who have no symptoms or only mild symptoms but in whom the peripheral blood CD4+ lymphocyte count is between 200 / mm^3 and 350 / mm^3 and the HIV viral load is more than 30000 copies / mL as measured by bDNA analysis, or more than 55.000 copies / mL as measured by RT-PCR.

C. Indications for deferring antiretroviral therapy

In the following category of patients ART should not be commenced but discussed with patients. Patients in this category should be monitored regularly. If they develop symptoms or their CD4+ lymphocyte counts decrease then the situation should be reviewed:

- HIV positive individuals who have no symptoms or only mild symptoms but in whom the peripheral blood CD4+ lymphocyte count is more than 350 / mm^3. Such patients should be closely monitored.

- If the HIV viral load is more than 30000 copies / mL (bDNA), or more than 55000 copies / mL (RT-PCR) or increases over a period of time and if the CD4+ lymphocyte count decreases over a period of time then the patient may benefit from ART.

These guidelines for initiating ART are summarised in Table 4.

Table 4: Summary of indications for considering ART in adults with HIV infection

Clinical category	CD4+ lymphocyte count	Viral load	Recommendations
WHO stages 3 and 4 disease	Any value	Any value	Commence ART
Asymptomatic	< 200 / mm^3	Any value	Commence ART
Asymptomatic	200-350 / mm^3	Any value	Offer ART with counselling relating to pros and cons of ART
Asymptomatic*	> 350 / mm^3	Any value	Defer ART and monitor regularly

* As there are no clinical parameters that indicate CD4+ lymphocyte levels and viral loads it is necessary to perform these tests in asymptomatic HIV infected individuals.

5. Recommended Treatment Regimens for Adults

A large number of drugs and drug combinations have been used in the treatment of persons with HIV infection. The choide of drug regimen will depend on drug availability, costs of medications, side effects or the development of resistance. The following recommendations are made for the use of ART in persons with HIV infection in Zimbabwe:

5.1 Adult patients with HIV infection who have WHO clinical stages 3 and 4, or opportunistic infections, or AIDS

Triple therapy only is being recommended. Use of Protease Inhibitors in the first line regimen is not recommended.

Thus the first line treatment should consist of two nucleoside reverse transcriptase inhibitors plus one non-nucleoside reverse transcriptase inhibitor. The choice of regimen used will depend on availability and affordability. These patients should receive the following first line ART regimens.

First Line Treatment Recommendation for Adults

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

Alternative Line Treatment Recommendation for Adults

- **Stavudine 30 mg orally twice daily, plus**
- **Lamivudine 150 mg orally twice daily, plus**
- **Nevirapine 200 mg orally daily for two weeks and then 200 mg orally twice daily.**

Caution: Do not ever start Nevirapine without this gradual introduction!

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.

Second Line Treatment Recommendation for Adults

- **The second line regimen should only be initiated after consultation with a specialist as the recommendation will be based on what the patient has already been taking.**

A second line regimen is to be used only when there is documented evidence of treatment failure with the first line regimen, ie, 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 will also be required for those who do not tolerate the first line regimen due to drug toxicity.**

Consultation with a specialist in HIV care will be required for the second line regimen as the options available will be limited.

General Notes about some of the antiretroviral drugs:

1. Zidovudine and stavudine **must not** be used together.

2. Didanosine must 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 hours before or two hours after taking food.

4. Ideally rifampicin should not be used together with a protease inhibitor.

5. All patients with HIV infection, **uless 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.

5.2 When to change treatment regimens

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 contain drugs that were **not** included in the first regimen (see list of drugs in Table 2 above).

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, ie, the offending drug may be replaced with an alternative drug of the same class. In addition action should be taken according to Table 6.

Addendum:

Guidelines for Antiretroviral Therapy in Zimbabwe

For the national antiretroviral programme the first line is:

First Line Treatment for Adults:

- Stavudine 40 mg orally twice daily, plus
- Lamivudine 150 mg orally twice daily, plus
- Nevirapine 200 mg orally daily for two weeks and then 200 mg orally twice daily.

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.

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, ie, the offending drug may be replaced with an alternative drug of the same class.

If a patient reacts to **Stavudine,** then this can be replaced with **Zidovudine** and vice versa.

If patient reacts to **Nevirapine,** then they can be given **Efavirenz 600 mg orally once daily.**

Second Line Treatment Recommendation for Adults

In the event of treatment failure:

Patients that fail to respond to first line treatment should be treated with a different regimen that contains drugs that were **not** included in the first regime. The second line regimen should only be initiated after consultation with a specialist, as the recommendation will be based on what the patient has already been taking. For the national programme the regimen below is currently recommended:

- **Zidovudine 300 mg orally twice daily, plus**
- **Didanosine 200 mg, orally twice daily, plus**
- **Lopinavir / Ritonavir three capsules twice daily.**

5.3 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 TBmay 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:

- **Zidovudine 300 mg orally twice daily, plus**

- **Lamivudine 150 mg orally twice daily, plus**

- **Nevirapine <u>200 mg orally daily for two weeks</u> and then 200 mg orally twice daily**

(or use the alternative first line treatment).

Notes:

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

5.4 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 placent 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 notuse 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 ni 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:

- **Zidovudine 300 mg orally twice daily, plus**

- **Lamivudine 150 mg orally twice daily, plus**

- **Nevirapine 200 mg orally daily for two weeks and then 200 mg orally twice daily.**

5.5 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 that 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.

5.5.1 Criteria for initiating ART in children

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, ie, 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

Zidovudine	- age less than 28 days of age - 4 mg/kg orally twice daily	
	- 4 weeks to 13 years - 180 mg/m^2 orally twice daily, plus	
Lamivudine	- age less than 30 days - 2 mg/kg orally twice daily	
	- age more than 30 days or weight less than 60 kg - 4 mg/kg orally twice daily	
	- weight more than 60 kg (maximum dose) - 150 mg orally twice daily, plus	
Nevirapine	- age 15-30 days:	First 2 weeks - 5 mg/kg orally daily
		Next 2 weeks - 120 mg/m^2 orally twice daily
		Then - 200 mg/m^2 orally twice daily

- age > 30 days: First 2 weeks - 120 mg/m^2 orally twice daily
  Then - 200 mg/m^2 orally twice daily.

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

6. 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.

6.1 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 - Uruine 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

From the history note the following:

Date of diagnosis of HIV infection.
Current symptoms.
Past illnesses and treatments.
History of past TB.
History of TB contacts.
Current symptoms suggestive of TB.
Past or current symptoms of STI.
Possibility of pregnancy.
Social habits and sexual history.

From the examination note the following:

Patient's weight.
Mental state of patient.
Presence of oral candidiasis, oral Kaposi's sarcoma, oral hairy leukoplakia.
Presence of lymphadenopathy, skin Kaposi's sarcoma, herpes zoster scars, dermatitis.
Presence of chest signs.
Presence of abnormality in the CVS, GIT, abdomen, CNS, fundi.
Abnormalities of the genital tract.

6.2 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, eg, 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.

6.3 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 and then every 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.

6.3.1 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 effecgts 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.

6.3.2 Side effects of specific antiretroviral agents

The side effects of specific antiretrovirals are summarised in Table 6.

6.4 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.

Table 6: Some important side effects of antiretroviral agents

Drug	Side effects	Action to be taken
NRTIs		
Zidovudine	Anaemia, neutropenia, sepsis	Monitor FBC
Didanosine	Pancreatitis, peripheral neuropathy, diarrhoea	Monitor, withdraw drug if symptoms are severe
Zalcitabine	Oral ulceratin, peripheral neuropathy	Observe, withdraw drug if symptoms are severe
Stavudine	Pancreatitis, peripheral neuropathy	Monitor, withdraw drug if symptoms are severe
Lamivudine	Usually nil	
Abacavir	Severe hypersensitivity reactions	Withdraw drug immediately and give alternative. Do no re-start as this can be fatal!
NNRTIs		
Nevirapine	Abnormal liver function tests, severe hypersensitivity reactions	If LFTs suggestive of hepatitis or if jaundice present discontinue; if rash severe discontinue
Efavirenz	CNS symptoms	Monitor, withdraw drug if symptoms are severe
Delavirdine	Headaches	Monitor, withdraw drug if symptoms are severe
PIs		
Saquinavir	GI intolerance, diarrhoea	
Ritonavir	Pancreatitis, hepatitis, skin sensitivity, circumoral paraesthesia, nausea, vomiting, diarrhoea	Monitor, withdraw drug is symptoms are severe
Indinavir	Renal stones, headahes, blurred vision, jaundice, rash, metallic taste in mouth	Monitor, withdraw drug is symptoms are severe
Nelfinavir	Diarrhoea	May be necessary to give loperamine
Amprenavir	GI intolerance, diarrhoea, rash, circumoral paraesthesia	
Lopinavir / Ritonavir	GI intolerance	

6.4.1 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 patient's 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.

6.4.2 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, eg, if the initial CD4+ lymphocyte count was less than 50 / mm^3, then it can take more than one year to increase to more than 200 / mm^3. Persistently declining CD4+ lymphocyte counts as measured on two occasions and clinical deterioration as described above is suggestive of treatment failure.

6.4.3 Virological, HIV viral load monitoring

The HIV viral load decreases to undetectable levels within 6 monhts 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.

6.4.4 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.

6.4.5 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, ie, 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 (ie, 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, ie, 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 untill all adherence issues have been addressed.

7. 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.

Cotruimoxazole 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 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 / mm^3.

8. Post-Exposure Prophylaxis

In persons who have been accidentally exposed to HIV through needle-stick inoculation or through contamination of mucous memranes 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, ie, 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.

8.1 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 promote avoidance of 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 aducational materials, disposable syringes and needles and sharps bins.

8.2 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 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 of 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 paragraph.

8. Determine the health worker's hepatitis B virus immune status and if non immune institute hepatitis B virus vaccination.

8.3 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, eg, Indinavir 800 mg orally three times a day or Lopinavir - 400 / Ritonavir - 100 mg twice a day.

Counselling 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, 800 mg orally three times a day or Lopinavir 400 mg / Ritonavir 100 mg twice a day.

8.4 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.

9. 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 Healthy and Child Welfare has already launched a programme for the prevention of mother-to-child transmission of HIV and readers are advised to follow the Ministry's guidelines on this topic.

9.1 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, 6 mg in a single oral dose to neonate at 48 to 72 hours after birth.

If the mouther 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 tpo 72 hours later.

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

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, plus

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.

9.2 ART in mother

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