AMREF

DIRECTORATE OF LEARNING SYSTEMS

DISTANCE EDUCATION PROGRAMME

INTEGRATED HIV/AIDS PREVENTION, TREATMENT AND CARE

Unit 5
Antiretroviral Therapy in Adults and Adolescents

C·O·L

The Allan and Nesta Ferguson Trust

Unit 5: Antiretroviral Therapy in Adults and Adolescents

A distance learning course offered by the AMREF Directorate of Learning Systems

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Contents

Acronyms and Abbreviations

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immune deficiency syndrome
ANC	Antenatal care
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
C&T	Counseling and testing
C&S	Culture & sensitivity
CNS	Central nervous system
CSF	Cerebrospinal fluid
CBC	Complete blood count
d4T	Stavudine
ddC	Zalcitabine
ddI	Didanosine
DLV	Delavirdine
DFID	Department for International Development
DOT	Directly observed treatment
DOTS	Directly observed treatment strategy
EBV	Epstein-Barr virus
EHRZ	ethambutol (E), isoniazid (H), rifampicin (R), pyrazinamide
EFZ	Efavirenz (Z)
HAART	Highly active antiretroviral therapy
HSV	Herpes simplex virus
INH	Isoniazid
KS	Kaposi's sarcoma
mg	Milligram
mg/L	Milligrams/liter
NAM	Nucleoside analogue mutation
NFV	Nelfinavir
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-infl ammatory drug
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
NsRTI	Nucleoside reverse transcriptase inhibitor
PZA	Pyrazinamide
RIF	Rifampin
RNA	Ribonucleic acid
RTV	Ritonavir
SHRZE	Streptomycin (S), Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E)
STD	Sexually transmitted disease
TB	Tuberculosis
TDF	Tenofovir
TLC	Total lymphocyte count

Unit 5: Introduction

Welcome to the fifth Unit in our course on Integrated HIV/AID Prevention, Care and Support. In the last unit we discussed the common HIV Associated Conditions. In this unit we shall look at antiretroviral therapy in adults and adolescents. We shall introduce you to antiretroviral agents (their classification, modes of action and common side effects) and discuss their rational use in the management of HIV/AIDS in resource-limited settings. But first, let us look at our objectives for this unit.

Unit Objectives

By the end of this unit you should be able to:

- Describe the classification and mode of action of ARVs;
- Discuss the goals of antiretroviral therapy;
- Describe the rationale for standard treatment regimens;
- Describe the characteristics of widely used ARVs;
- Discuss the rationale and timing for ART initiation;
- Describe the preparation of a patient for ART;
- Explain the common side-effects associated with ARVs and discuss strategies to minimize/manage these side effects;
- Describe the common drug interactions between ARVs and drugs commonly used in the management of HIV disease;
- Discuss the follow-up of patients on ART;
- Discuss the common reasons for treatment failure, changing of ART regimens and stopping ART.

The Unit is made up of three sections. Section 1 will look at classification, ,mode of action of antiretroviral agents. Section 2 will discuss how to initiate ARVs in adults and adolescents, while Section 3 will look at how to monitor ART side-effects of ART, drug interactions, adherence and when to stop or change the ART regimens .

Section 1: Introduction to Antiretroviral Agents.

Introduction

Welcome to the first section of this unit. In this section we shall discuss the classification, mode of action, goals, benefits and limitations of ART. You will recall in Unit 1 Section 2, we discussed the biology of the HIV virus. Can you remember what we said? We said that the HIV disease is caused by a retrovirus which enters human cells (CD4+ T-lymphocytes) and uses them "as a factory" to reproduce itself. Like all disease causing pathogens, HIV has a life-cycle. Knowledge of this life cycle is core to understanding the mechanism of action of antiretroviral drugs. This is because the drugs used in HIV treatment target essential steps in the HIV life cycle by either blocking the step or inhibiting the enzyme required to catalyze the step.

Let's start by reviewing our objectives for this section.

Section Objectives

By the end of this section you should be able to:

- Describe the classification of ARVs;
- Explain their mode of action;
- Discuss the goals, benefits and limitations of antiretroviral therapy.

Let's start by looking at how ARV drugs are classified.

Classification of ARVs

HIV is a retrovirus. So drugs against HIV are called *anti-retroviral* drugs or ARV in short. When we give ARV drugs in the correct way, with adherence support, this is called *Antiretroviral Therapy* or ART in short.

In Unit 1 you learnt about the HIV life cycle. Can you remember the various steps in the life cycle of the virus, and how each step is accomplished? Look at Figure 1.1 on the HIV life cycle to refresh your memory.

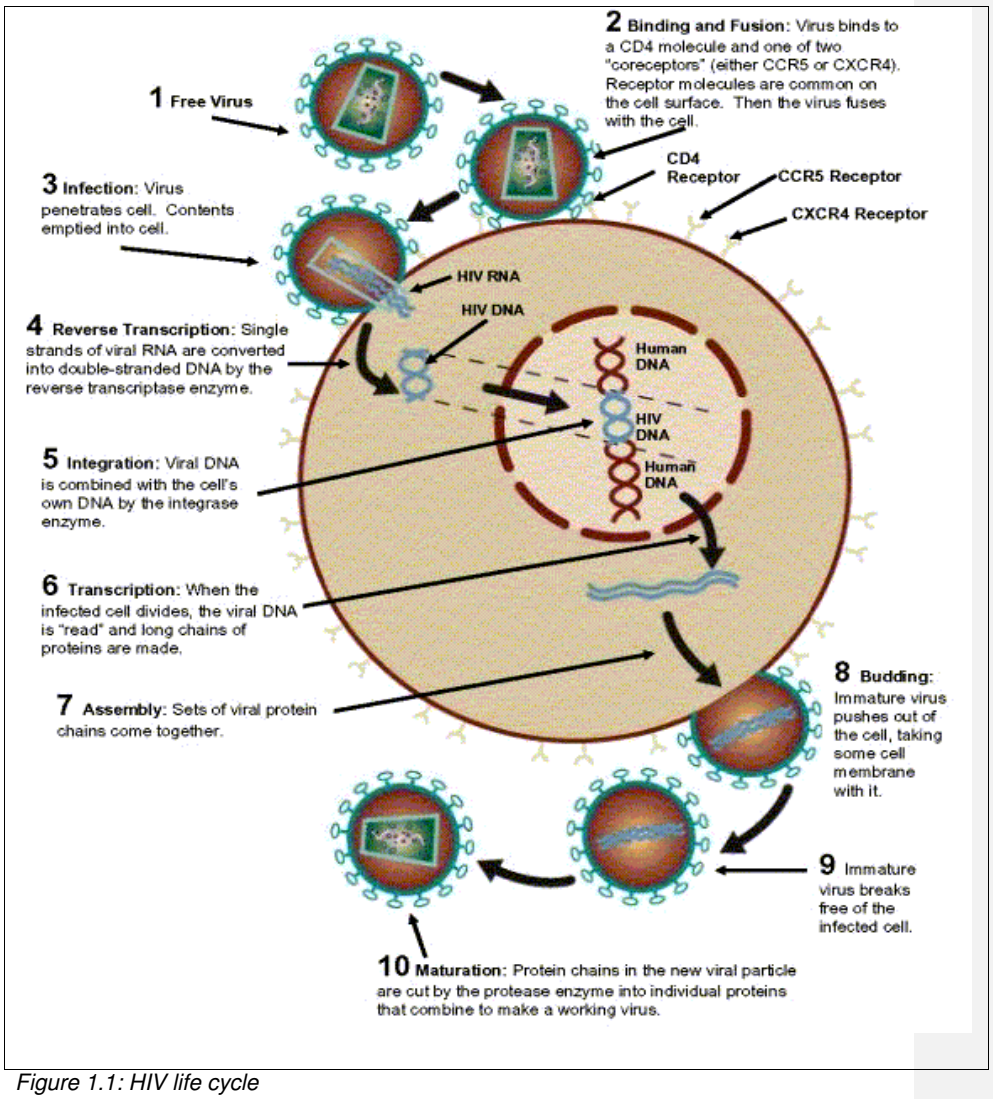


Figure 1.1: HIV life cycle

As you can see from this figure, HIV attaches itself to the CD4+ lymphocyte is through the CD4 receptor on the surface of the lymphocyte. The first drug that could inhibit HIV replication was zidovudine (AZT or ZDV). It was first used in the treatment of HIV infection in 1987. Since then, more than 25 agents have been developed that are active against HIV replication.

There are 3 main groups of antiretroviral drugs available for clinical use depending on their site of action on the HIV replication cycle. These are:

- Reverse transcript inhibitors
  - Nucleoside reverse transcriptase inhibitors (NRTI)
  - Nucleotide reverse transcriptase inhibitors (NtRTI)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors.
- Entry Inhibitors – This is a new class of antiretroviral drugs. They are at times referred to as fusion inhibitors.

These antiretroviral agents work at different steps as shown in Figure 1.2 below, to block HIV from making new copies of itself inside the cell or assembling its various parts to form a new virus.

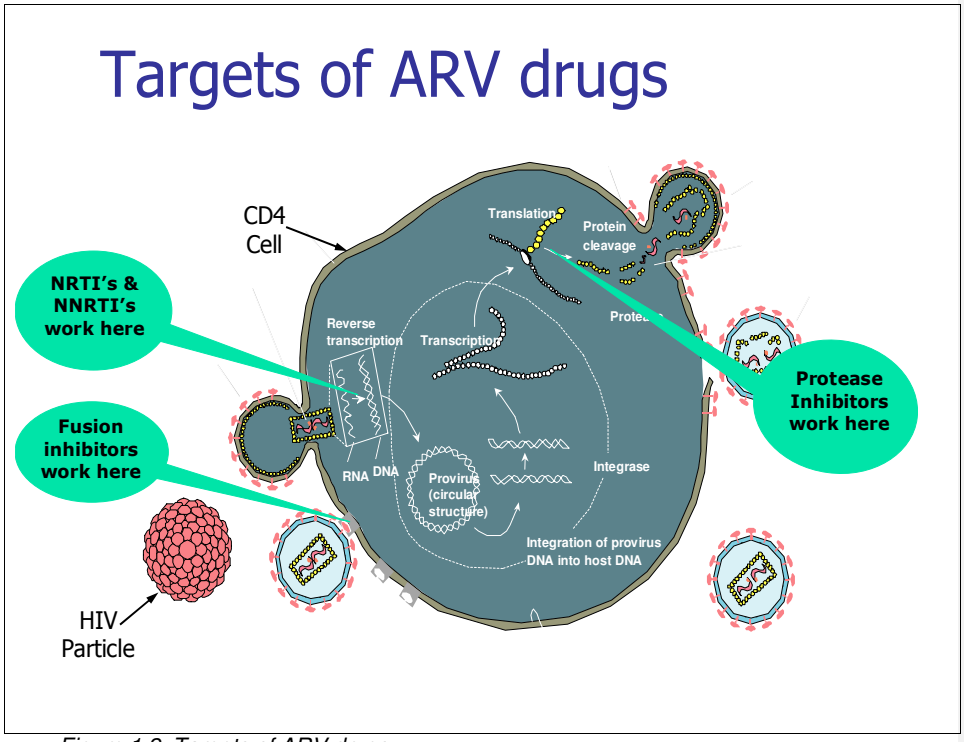


Figure 1.2: Targets of ARV drugs

Mode of Action of ARVs

As we mentioned earlier there are three main groups of ARVs available for clinical use. These are:

- Reverse Transcriptase Inhibitors;
- Protease inhibitors
- Entry Inhibitors

We shall now look at their mode of action.

Reverse Transcriptase Inhibitors

As you can see from Figure 1.1, HIV enters the CD4 lymphocyte together with genome (composed of ribonucleic acid, RNA), and several enzymes which are essential for its replication. One such enzyme is reverse transcriptase (RT), which is needed immediately the virus enters the cell. The function of reverse transcriptase is to copy (transcribe) viral RNA to viral DNA. This step is essential before the virus can be integrated into the human cell nucleus (made up of DNA).

Normally, RNA is made from DNA, however, HIV 'reverses' this process and starts making DNA from RNA through the use of this special enzyme 'reverse transcriptase'.

There are 3 classes of reverse transcriptase inhibitors (RTIs) namely:

1. Nucleoside reverse transcriptase inhibitors (NRTI)
2. Nucleotide reverse transcriptase inhibitors (NtRTI)
3. Non-nucleoside reverse transcriptase inhibitors (NNRTI)

Initially, the names of these classes appear strange, like they are designed NOT to be remembered! But it is actually quite simple. A reverse transcriptase inhibitor is named depending on whether or not it contains a molecule similar to the naturally occurring nucleotides (adenine, thymine, cytosine, and guanine). If it does, it is a nucleoside analogue, if it does not, it is a non-nucleoside.

1. *Nucleoside reverse transcriptase inhibitors (NRTIs)*

These agents act as "fake" nucleosides in the cell. They compete with the true nucleosides when viral DNA is being formed. The DNA formed containing these 'fake' nucleosides is thus abnormal and therefore viral replication is prevented. The table below has examples of the common NRTIs, with their dosages and side effects.

Table 1.1: Nucleoside analogue Reverse Transcriptase Inhibitors (NRTIs)

Drug	Dose (adults)*	Common and Important Side effects	Comments
Zidovudine (AZT, ZDV)	>12 years, 300 mg BD	Anaemia, leucopenia (low white cell counts), thrombocytopenia (low platelets-can cause bleeding)	Requires monitoring of haemoglobin and white cell count regularly during use. Has no food restrictions
Lamivudine (3TC)	>37.5 kg 150 mg BD	Very well tolerated. May be associated with hepatitis	No food restrictions
Stavudine (d4T)	<30 kg: 30 mg BD >40 kg: 40 mg BD	Peripheral neuropathy (numbness, tingling/burning sensations, weakness), fat redistribution in the body (lipodystrophy)	No food restrictions. Should not be used with zidovudine
Abacavir (ABC)	>37.5 kg or over 16 years: 300 mg BD	Hypersensitivity (fever, rash, cough, difficult breathing)	Patients and carers should be educated on the possibility of sensitivity reaction. Patient should not be re-started on ABC after a hypersensitivity reaction
Didanosine (ddI)	<60 kg, 250 mg/day >60 mg, 400 mg/day	Pancreatitis (suspect if has abdominal pain, nausea, vomiting) and peripheral neuropathy	To be taken on an empty stomach half hour before food, OR two hours after a meal
Emtricitabine (FTC)	Used in combination with tenofovir as a fixed dose preparation taken once daily	Well tolerated	Very similar to 3TC No food restrictions

*Almost all NRTIs require dose adjustment in case of renal or liver disease. Tenofovir is a nucleotide analogue reverse transcriptase inhibitor (NtRTI). It is used at a dose of 300 mg once daily and is well tolerated. It should be taken with a meal.

2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

These drugs bind directly to the reverse transcriptase enzyme and therefore inhibit its activity. They prevent the conversion of RNA to DNA. Table 1.2 lists the drugs and dosages for this class of drugs.

Table 1.2: Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Name and class of drug	Strength of preparation	Adult dosing
Efavirenz (EFZ)	Capsules, 200mg, tablets 600mg	600mg OD
Navirapine (NVP)	Tablets, 200mg	200mg BD
Delavirdine (DLV)	Capsules, 100mg	600mg OD

Two agents in this class are commonly used: Nevirapine and efavirenz.

Nevirapine

It is not affected by meals and may be taken with or without food. The main side effects of Nevirapine are a skin rash that may occur in 15 to 30% of patients. In about 7%, this rash is severe and extensive and is life threatening, which necessitates that the drug be stopped and never used again in that patient. In some patients, Nevirapine may cause hepatitis. It is therefore very important to monitor a patients liver enzymes when they are on this drug. At initiation of therapy, Nevirapine is started at a lower dose of 200mg for the first 2 weeks to reduce the risks of severe liver side effects and severe skin rash. If tolerated the dose is increased to 200 mg twice daily.

When used in combination with certain drugs, the likelihood of liver injury increases. For this reason, Nevirapine should not be used together with rifampicin. Patients with TB who are on a rifampicin-containing regimen should be given efavirenz instead of nevirapine.

Nevirapine should not be used together with rifampicin. Patients with TB who are on a rifampicin-containing regimen should given efavirenz instead

Effavirenz

This is a relatively safe drug in comparison with nevirapine, though it is more costly. It is also easier to administer, as it only requires one dose per day. Its absorption is markedly improved when taken with a fatty meal, as are its side effects. The commonest side effect of effavirenz is dizziness. The drug is therefore prescribed for bed time. It may also cause abnormal dreams, loss of sleep, increased sleepiness, confusion, hallucinations and poor concentration. These side effects usually disappear after two to four weeks of consistent use. Effavirenz may occasionally cause a rash.

In pregnancy, this drug should not be used as it has been associated with increased risk of congenital malformations in experimental animals. Female patients in the reproductive age group who are on effavirenz should be on contraceptives. It is given at a dose of 600 mg once daily (preferably at bed-time).

Nucleotide Reverse Transcriptase

The only drug in this class is Tenofovir. Its mechanism of action is similar to that of NRTI'S.

Next let us look at the second group of antiretroviral drugs, namely protease inhibitors.

Protease Inhibitors (PIs)

Protease Inhibitors work at the last stage of the virus reproduction cycle. They prevent the HIV virus from being successfully assembled and released from the infected cell.
The viral enzyme, protease, is responsible for 'assembling and maturing' newly formed viral proteins into a viable virus capable of infecting new cells. When the central part of the body cell makes parts of the HIV virus after infection, these parts have to be cut and put together in the right way before the new HIV copies can leave the cell. Protease inhibitors prevent this 'cut and putting together' from happening correctly. Thus the newly produced virus parts cannot leave the infected cell and infect other cells. PI drugs block the special substance HIV uses to put the different parts together to form a new HIV virus before it leaves the cell.

Protease Inhibitors in clinical use include the following drugs:

- ***Indinavir:*** This may cause renal stones formation. Advise patients to take at least 2 litres of water per day. It should not be taken at the same time as didanosine. If it must, make sure that you separate the two by 2 hours, to make sure it is taken on an empty stomach.
- ***Ritonavir:*** used in small doses to boost other PIs; requires refrigeration if stored for more than 30 days. The oral solution contains 12% alcohol.
- ***Saquinavir.***
- ***Nelfinavir***; main side effect is diarrhoea. Should be taken with a fatty meal to improve bioavailability.
- ***Lopinavir:*** 'Boosted' with ritonavir (i.e. Kaletra), requires refrigeration, when in storage for more than 2 months, otherwise stable at 25°C for less than 2 months.
- ***Amprenavir.***
- ***Forsamprenavir***
- ***Atazanavir***

Table1.3: Protease Inhibitors

Name and class of drug	Strength of preparation	Adult dosing
Saquinavir hard-gel (SQV)	Capsules, 200mg	600mg OD
Saquinavir soft-gel (SQV)	Capsules, 200mg	1200mg OD
Ritonavir** (RTV)	Capsules, 100mg	600mg OD
Indinavir (IDV)	Capsules, 200mg	800mg TID
Nelfinavir** (NFV)	Tablets 250mg	1250mg BD or 750mg TDS
Amprenavir^ (AMV)	Tablets, 300mg	1200mg BD
Lopinavir + Ritonavir^	Capsules (133mg Lopinavir + 33.3mg Ritonavir)	400mg Lopinavir + 100mg Ritonavir BD

*Drugs marked * are not available in Kenya and drugs marked ** are available in paediatrics formulations.*

Absorption of PI's is enhanced by a high fat diet. Once absorbed, they are metabolized by the liver and mainly excreted through faeces, though a small percentage is eliminated by the kidneys.

Common side effects of PI'S include:

- Lipodystrophy: this refers to the redistribution of body fat in which fat from the peripheral parts of the body is lost. This is accompanied by deposition of fat over the central parts of the body, mainly over the abdomen, breasts, upper back and subcutaneous tissue;
- Glucose intolerance: this results in poor glucose control and may be associated with an increased risk of diabetes;
- Elevated blood cholesterol;
- Gastro intestinal tract intolerance;
- Elevated liver enzymes.

These drugs are often reserved for use as second-line drugs in patients whose initial regimen is failing.

No antiretroviral drug or combination of drugs can completely eliminate HIV from the body. Additionally, most of the available agents have potential serious side effects and complicated dosing schedules. Therefore, the search for safer and more effective antiretroviral agents continues. Table 1.4 below gives the drugs available in Kenya.

Table 1.4: Commonly used antiretroviral drugs in Kenya

NRTI		**NNRTI**	**PI**
Nucleoside reverse transcriptase inhibitors	**Nucleotide reverse transcriptase inhibitor**	**Non-nucleoside reverse transcriptase inhibitors (NNRTI)**	**Protease Inhibitors (PI)**
stavudine (d4T) lamivudine (3TC) zidovudine (AZT) didanosine (ddI) abacavir (ABC) emtricitabine (FTC)	tenofovir disoproxil fumarate (TDF)	nevirapine (NVP) efavirenz (EFV)	lopinavir (LPV) with ritonavir (RTV) as a FDC* nelfinavir (NFV) saquinavir (SQV) Atazanavir (ATV)

* ritonavir is used as a 'helper' for another PI, to make the effect of the other PI stronger.

Having looked at the types of ARV drugs and their mode of action, lets now discuss the goals of this therapy, its benefits as well as its limitations.

Entry or Fusion Inhibitors

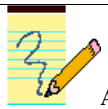
This is a new class of Antiretroviral drugs. They are at times referred to as fusion inhibitors. They function by stopping the virus from entering the CD4+ cell. Do you recall the lesson on the pathogenesis of HIV infection? During this lesson, it was mentioned that the HIV virus attacks the CD4+ cell. Well, the entry inhibitors prevent this process, by preventing the virus from entering the cell. An example of the Fusion inhibitors is Enfurvitide (T-20)

Goals of Antiretroviral Therapy (ART)

While many drugs are available for the treatment of HIV disease, none can cure HIV (i.e. completely eliminate HIV from the body). As you have seen, ARVs work by reducing viral replication (multiplication) thereby reducing the amount of virus in the body. This slows down the destruction of the immune system and other negative effects to other vital body organs. ART should be part of a comprehensive program that encompasses other aspects of care like nutritional support, opportunistic infections prophylaxis, ongoing psychosocial support and prevention of HIV transmission. Because ARVs do not cure HIV infection, treatment is life-long. It should therefore be carefully planned and discussed with the patient. Efficacy of ART can only be assured if there is strict adherence to the prescribed regimen. Regular follow-up and monitoring of treatment is required.

What Are The Goals of ART?

Before you read on, do the following activity. It should take you less than 5 minutes.

ACTIVITY

Write down the goals of ART therapy?

_____

_____

_____

I hope your answer included the following goals of ART:

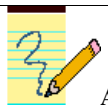
- *Restoration and preservation of immune function*: ART, by reducing the viral load decreases the killing of CD4 cells by HIV. As the number of these cells increases, this protects the patient from opportunistic infections and other HIV associated conditions.
- *Reduce the viral load as much as possible*, *for as long as possible,* in order to halt disease progression and prevent or reduce resistant variants. The key to achieving maximal viral suppression is though the use of at least 3 effective ARV drug combinations (also called highly active antiretroviral therapy-HAART), and the patient's adherence to medication.
- *Improved quality of life:* patients with HIV disease experience regular infections and other HIV related conditions that require medication and regular hospitalization, pain and discomfort, weight loss, absence from work and social activities etc. The sum effect of these conditions is to adversely affect the quality of life of PLWAs. ART, by reversing these negative effects of HIV-infection, positively influences the quality of life of patients, once again giving them the opportunity to lead normal lives.

- Reduction in HIV-related mortality and morbidity.

How can these goals be achieved?

You can achieve these goals through:

- Providing patient education, assessment and preparation prior to treatment initiation and continued support during treatment.
- Becoming knowledgeable and experienced in HIV care
- Adherence to treatment guidelines and best practice.

ACTIVITY

What do you think are the benefits of ARVs? List them down.

_____

_____

_____

_____

_____

_____

I hope your list included the following benefits of ARTs:

- They prolong life and improves quality of life;
- Households can stay intact;
- There is a decrease in the number of orphans;
- They reduce mother-to-child transmission;
- There is decreased stigma surrounding HIV infection since treatment is now available;
- Less money is spent to treat opportunistic infections and provide palliative care;
- They make HIV testing and counselling acceptable to more people;
- There is increased awareness in the community, since more people get tested;
- There is increased motivation of health workers, since they feel they can do more for HIV patients;
- Businesses can stay intact;
- They reduces absenteeism from work due to illness.

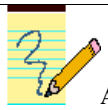
What Are The Limitations of ART?

The limitations of ART include the following:

- Antiretroviral therapy does not eliminate the virus and so there is no cure for HIV/AIDS. Treatment is life-long.
- Emergence of resistant HIV strains frequently occurs in particular if patients have poor adherence to therapy. More than 95% adherence is needed to achieve maximal suppression of the virus.
- Side effects, though not severe, occur with almost all the antiretroviral drugs. Serious complications that lead to discontinuation of treatment may also occur.
- Sexual transmission of HIV may continue to occur even if the viral load is at undetectable levels in serum. Sexual transmission of multi-drug resistant viral strains has already been documented.

Summary

Well, we have come to the end of this section. In this section we have looked at the classification of antiretroviral therapy, its mode of action, benefits as well as its limitations. I hope you now understand how ARVs work by intervening in the life cycle of HIV. Before you move on to the next section find out how much you still remember by doing the following activity.

ACTIVITY

Name two main enzymes which current ARV drugs inhibit?

_____

_____

The two enzymes are:

- Reverse Transcriptase, at the beginning of the Life Cycle
- Protease, at the end of the life cycle

If you got this answer right, well done! If not, we suggest that you revise this section again.

In the next section we shall discuss how to initiate and monitor ARVs in adults and adolescents.

Section 2: Initiating ARVs in Adults and Adolescents.

Introduction

Welcome to the second section of our unit on antiretroviral therapy. In the last section we discussed the classification of ARVs in HIV, their mode of action, benefits as well as limitations. In this section we shall explore how to initiate ARV therapy in adults and adolescents.

Section Objectives

By the end of this section you should be able to:

- Discuss the rationale for ART initiation;
- Describe how to initiate ART treatment;
- Discuss the considerations of ART in patients with TB.

Rationale For ART Initiation

Most HIV infected persons enjoy long periods of normal health before the virus overwhelms the immune system and starts to cause ill health. It is now accepted that ART should not be initiated too early in the course of the infection. On the other hand, treatment should not be delayed too long, such that the immune system is so severely destroyed as to make it difficult to recover, or until the patient's quality of life is compromised.

In general, it is opportunistic infections that cause the majority of morbidity in people with HIV and these should be aggressively treated before even considering ARVs. For example, a patient with TB, severe pneumonia or cryptococcal meningitis, who is only given ARV therapy, will almost certainly die.

The clinical benefits of taking ARV drugs are usually not apparent until six to eight weeks after commencing the therapy. Consequently, starting lifelong ARV therapy should not be seen as an emergency measure.

The decision to start therapy should therefore be based on sound medical and social criteria. Next we shall look at the criteria for starting ARV therapy.

Table 2.1 outlines the recognised advantages and risk of delaying ARV treatment.

Table 2.1: Potential risks and benefits of delaying ART

Benefits of delayed therapy	**Risks of delayed therapy**
• To avoid development of side effects which develop from long-term use of ARVs; • To delay the development of resistant virus, with the attendant risk of transmission of drug resistant virus; • To delay the occurrence of treatment failure as a result of resistant virus in a healthy patient, necessitating the use of potentially toxic or expensive ARVs; • Adherence to treatment is more difficult to maintain in a relatively well patient over prolonged duration of treatment.	• Possible risk of irreversible immune system damage; • The increased possibility of progression to AIDS.

Starting ARV therapy is not an emergency!

So what criteria should one use to start ARV therapy? Lets look at that next.

Criteria for Starting ARV Therapy

In Module 1, you learnt about the WHO Staging of HIV. Can you recall the various stages of HIV infection? It is normally not necessary to memorize what ailments constitute which WHO stage, but it recommended that you have a wall chart or table-top reference that you can consult each time you examine HIV infected patients. There are two main criteria used to start ART. These are medical and social criteria.

Medical Criteria

The medical criteria monitors the strength of a persons immune system (CD4 testing) also known as immunological monitoring. Immunological monitoring provides the most reliable information on the immune status of the patient, and therefore, is the ideal way of determining who should be started on ART. The table below provides guidance on what action should be taken at various CD4 levels.

Table 2.2: Immunological Monitoring for ART Initiation

CD4 (cells/ml)	Treatment Recommendation	Subsequent action
<200	Initiate ART	Carry out a CD4 test at 3 months and then every 6 months thereafter.
200-350	Consider treatment, particularly in case of pulmonary tuberculosis or history of severe bacterial infection. Initiate ART before CD4 falls below 200 cells/ml	If ART not initiated, CD4 test every 3 months. If ART initiated, CD4 test at 3 months and then every 6 months thereafter.
>350	Continue 'other' care: Cotrimoxazole prophylaxis, nutrition and hygiene, immunization, safer sex, psychosocial support etc	CD4 test every 6 months, or as indicated by the clinical condition of the patient.

You should only start HIV-infected adults and adolescents on antiretroviral treatment under the following conditions:

- **If CD4 testing is available, it is recommended to document baseline CD4 counts and to offer ART to patients with:**
  - WHO Stage IV disease, irrespective of CD4 cell count;
  - WHO Stage III disease if CD4 cell counts is less than <350/mm^3
  - CD4 is less than 250 at any stage

Though CD4 testing provides the ideal criteria for initiation of ART, the test is expensive to perform and may not be available in most primary care facilities. Clinical staging, however, can be used to guide decisions on when to start ART, where CD4 testing is not available.

- **If CD4 testing is not available, it is recommended to offer ART to patients with:**
  - WHO Stage IV disease, irrespective of total lymphocyte count;
  - WHO Stage III disease (including but not restricted to HIV wasting, chronic diarrhoea of unknown etiology, prolonged fever of unknown etiology, pulmonary TB, recurrent invasive bacterial infections or recurrent/persistent mucosal candidiasis), irrespective of the total lymphocyte count;
  - WHO Stage II disease with total lymphocyte count of less or equal to 1200mm cubed.

Social Criteria

This criteria determines that the patient (or parent/guardian if patient is a child) is able or willing to:

- demonstrate an understanding of the importance of strict, long term adherence to therapy and monthly attendance of the clinic;
- afford the cost of the drugs and investigations on a LONG TERM basis (if in a cost recovery program);
- identify a "treatment assistant" (family member or a friend) to support them with adherence to therapy;
- disclose their contact details and physical address (Patient Locator Card") and be contacted when they miss appointments;
- commit themselves to safer sex practices.

In addition to the above criteria, there are other requirements for starting ARV therapy. Let us discuss them too.

Other Requirements for Starting ART

If you work at a primary facility, there are other requirements that you should consider before starting ART. These are as follows:

1. HIV positive patient has a written documented HIV test;
2. Patient fits criteria to be started, if all the 7 questions have a negative response;
3. Opportunistic infections have been treated or stabilised;
4. Patient is ready for ARV therapy;

5. A supportive clinical team that is well prepared for chronic care;
6. There is a reliable drug supply.

We shall discuss each in turn.

- ***HIV positive patient with a written documented HIV test;***

According to the MOH guidelines, you should only start ARV in patients who have written documentation of a positive HIV test. If the patient has had a positive HIV test at another facility, but does not have written documentation, the test should be repeated. Do not start patients on ART if there is only a clinical suspicion of HIV infection. There is a possibility that a few patients may want to get ARV drugs to sell them. Also in the past, mistakes have also been made in assuming that a patient with severe wasting has AIDS. Yet, as you know other conditions like TB can also cause severe wasting in adults. So it is important to have adequate proof before you initiate ARTs.

- ***Patient fits criteria to be started on ART, if you can answer NO to the following questions;***

  - Does the patient have a severe illness requiring referral or a WHO stage 4 condition? You should not initiate ART during a severe acute opportunistic infection or other severe illness as it can cause a strong reaction with the opportunistic infection, thus making the symptoms suddenly worsen, and the patient can even die

  - Is the patient currently on TB treatment? Although TB is accorded a special treatment unlike other OIs, you should not give ART and TB drugs together unless you are able to assess interactions with the current regimen.

  - Is there peripheral neuropathy? Patients with burning or tingling or numbness in the feet or hands should not receive d4T which causes nerve toxicity, because this may worsen the problem of tingling and numbness.

  - Is there jaundice or known liver disease? Patients with liver disease will need an adapted regimen and should not receive a regimen that contains drugs that can cause liver toxicity, like nevirapine.

- Does the patient have a chronic disease like diabetes or heart disease? Patients with a chronic disease should be referred to a senior clinician as they require more expertise in deciding how to give ART.

- Is the patient a child? ART initiation in children needs to be done by a qualified clinician who understands how to read their CD4 values and knows the correct ARV drugs and dosing. So if you do not have this expertise you should refer the child immediately.

- Is there prior ART use (including Nevirapine for prevention of mother-to-child transmission)? You should always take a history of what kind of medication patients took before, especially ARV drugs. This will help you to determine the most suitable regimen for that patient and identify drugs that they are probably resistant to.

- ***Opportunistic infections have been treated or stabilised;***

As we have mentioned several times, any patient with severe illness should be treated first before being put on ARV. There are a few exceptions however, such as patients on TB treatment and those with OIs such as prurigo and diarrhoea which do not respond to any other treatment other than ARVs.

- ***The Patient is ready for ARV therapy;***

ARV treatment is not an emergency. It is very important that a partnership is formed between the clinician and the patient where they take responsibility for taking ARV drugs regularly.

- ***A Supportive clinical team is prepared for chronic care;***

Providing care for PLWHA requires a team approach. Do not be a lone ranger! If you are a clinician you will need to work with counsellors and lay providers to provide treatment education and support, someone to dispense the drugs correctly, and community health workers for home-based care.

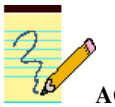
- ***There is a reliable drug supply***

Continuous levels of ARV drugs are needed to halt the virus making new copies. Patients who stop and start treatment may develop ARV drug resistance and treatment failure. You should therefore ensure that you have a reliable drug supply.

Figure 2.1 outlines what you should consider when commencing ARV therapy for adults and adolescents.

Institutional Requirements for Initiating an ART Program.

Are there institutional requirements for starting an ART program? Before you read on do the following activity. It should take 5 minutes to complete.

ACTIVITY

List some of the requirements that you believe should be met by institutions before they start an ART programme.

_____

_____

_____

_____

Well done! I believe your answer included some of the following requirements for starting an Antiretroviral Treatment Program:

- Availability of quality HIV testing services (voluntary, diagnostic as well as routine counselling and testing);
- Availability of quality antiretroviral drugs on long-term basis;
- Assurance of an adequate supply and storage of drugs, including drugs for treatment of opportunistic infections and other HIV related conditions;
- Availability of a trained multidisciplinary team, including doctors, nurses, counsellors, social workers etc;

- Availability of a system for training, continuous education, monitoring, support supervision and feedback on safe and effective management of HIV disease and antiretroviral treatment;
- Capacity to recognize and appropriately manage common HIV related conditions;
- Reliable laboratory monitoring services including routine haematological and biochemical tests for detection of drug toxicity.

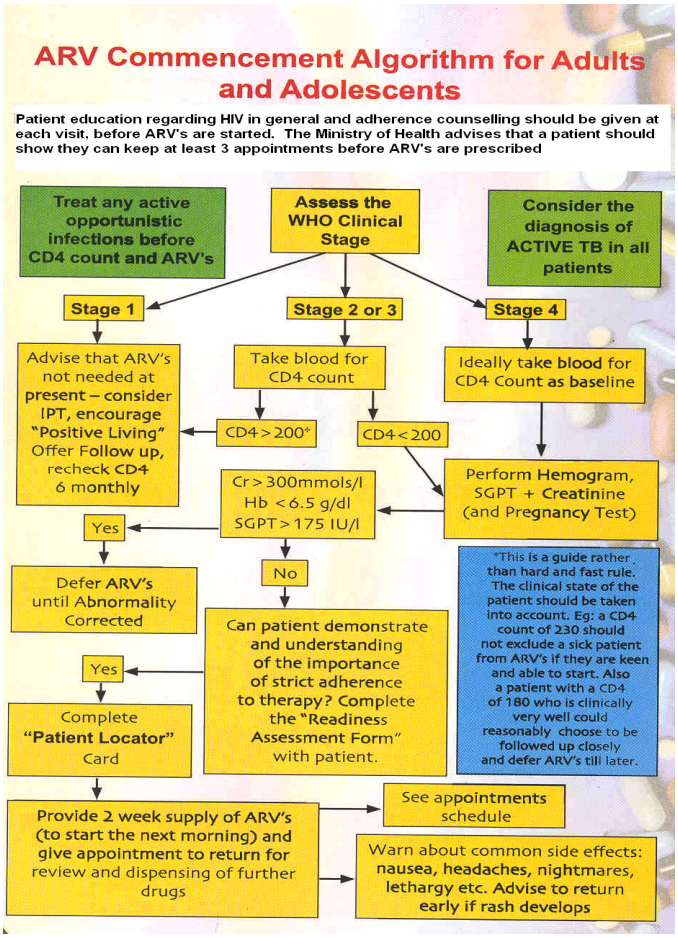


Figure 2.1: ARV commencement algorithm for adults and adolescents. (Source: MOH, 2006)

Patient Assessment and Education Prior to ART Initiation

Before any patient is started on antiretroviral therapy, they should undergo baseline clinical assessment and receive thorough education about how ART works and how to maintain adherence.

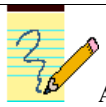
Baseline Clinical Assessment

A basic clinical assessment should include the following:

- A complete medical history;
- Physical examination;
- Laboratory investigations;
- Patient education and counselling;

Taking a complete Medical History

Once again, lets start with your thoughts on this. Complete the following activity before you read on.

ACTIVITY

What information would you gather when taking a complete medical history?

_____

_____

_____

_____

Now read through the text below and see if your ideas are included.

The complete medical history should include the following:

- Essential demographic characteristics, such as age, marital status, etc;
- The past medical history including major illness (particularly TB), hospitalization and surgeries;

- The length of time since HIV diagnosis;
- Current medication and symptoms;
- In the case of women, you should review the current or planned pregnancy and access to contraceptive services.

Physical Examination

It is important to carry out a baseline physical examination. This should include:

- Vital signs and weight;
- Examination of the skin and mouth, oral pharynx, lymph nodes and extremities;
- Examination of the lungs, heart, abdomen, nervous system, eyes, and genital tract.

Laboratory Investigation

The following table outlines the recommended investigations before initiating, and for monitoring ART.

Table 2.3: Recommended Laboratory Investigation before initiating ART

	INVESTIGATION	LEVEL AVAILABLE	OBJECTIVE	FREQUENCY
I. Absolute minimum	HIV antibody test	All levels	Diagnose HIV and initiate comprehensive care	Before ART
	Hemoglobin	All levels	Monitor degree of anemia – if severe transfuse before ART or use D4T instead of Zidovudine.	If on AZT do at baseline, 2 weeks, then monthly If not AZT baseline and then every 6 months and when indicated.
II. Basic Recommended tests	Total WBC + differential	All levels	Monitoring neutropenic side effects. Lymphocyte count where CD4 machine is not available	6 monthly
	LFTs: Alanine(ALT) or aspartate (AST)aminotransferase	District hospitals	Monitor hepatitis co- infection and hepatotoxicity	Do at baseline, at 2weeks, then monthly especially if Nevirapine is used.
	Serum creatinine and or urea	District hospitals	Monitor renal function	6 monthly and when indicated
	Serum glucose	District hospitals	Monitor hyperglycemia in	When indicated

	Pregnancy test	All levels	patients on protease inhibitors Change therapy to appropriate regimen	At base line and when indicated for all women of child bearing potential
III. Desirable test	Serum lipids CD4 cell count	District hospitals plus referral hospital Few regional hospitals	Monitoring hyperlipidemia for those on protease inhibitors Monitoring immune response to therapy	When indicated At baseline and then 6- 12 monthly

Patient Education Prior to ART Initiation

The initiation of ART should not be rushed. Remember it is not an emergency! Before you start your patients on ART you should prepare them adequately. Patient education and counselling is particularly important and should cover the following topics:

- How HIV infection affects the body;
- Prophylaxis and multivitamin supplementation;
- Antiretroviral Drugs;
- Arrangements of how patient will come for appointments ;
- Review patient's willingness to start ART;
- Community Links and Patient Support Groups.

Let's briefly discuss each point looking at the information that you should give to the patient.

- ***How HIV infection affects the body?***

You should inform the patient that HIV attacks the body's immune system and weakens the body's ability to fight off infections. Once the body's immunity is weakened, one becomes vulnerable to infections that they would normally fight off. These are called opportunistic infections**.** Most of these infections are treatable. The patient should seek early medical attention anytime they feel unwell. You should inform patients of their CD4 cell count and the importance of closely monitoring them to ensure their body defence is still working.

- ***Prophylaxis and multivitamin supplementation.***

Arrange for nutritional assessment and counselling and inform the patient that they can reduce their chances of developing opportunistic infections by taking cotrimoxazole on a daily basis, maintaining good nutrition and providing multivitamin tablets. These measures would keep them healthy and strong for longer.

- ***Antiretroviral Drugs:***

Inform the patient that antiretroviral drugs are strong medicines that fight HIV in the body and prevent the virus from destroying the body's immune system. These drugs

- are lifesaving drugs and patient's health depends on taking them every day at the right time;
- do NOT cure HIV;
- do not prevent HIV transmission to others—the patient must still use condoms and practice safer sex;
- may interact with other drugs: the patient should not take herbal medicines or over-the-counter medicines before discussing with a health care worker.

Antiretroviral drugs stop HIV from multiplying in the body, therefore, treatment with these drugs is life-long.

Demonstrate to the patient, the drug regimen with the actual drugs and show them how they should take them. Discuss possible side effects of the drugs and tell the patient what to do if they occur.

- ***Adherence and Follow-Up:***

Inform the patient of need to return to the clinic on the scheduled dates so that you can ensure that their medicines are working properly and that there are no side effects. Emphasize the importance of adherence and tell the patient that ARVs will only work properly if taken as prescribed. Missing doses, even occasionally, makes treatment ineffective, and can result in treatment failure with recurrence of illness, opportunistic infections and even death. Ask the patient what they intend to do to ensure that they do not miss taking their medicines?

***Assess Adherence Strategies**:* Ask them to identify either a member of family, friend or community health worker who can remind them to take their medication. This person should be identified and also be educated on ART. Teach the patient pill cues such as putting the tablets next to toothbrush; using a pill diary; alarm clock in the watch or phone.

- ***Arrangements of How Patient Will Come for Appointments:***

If the patient does not leave near your health facility and it is not convenient for them to commute to and from their home, refer them to the health facility nearest their home that offers ART service.

- ***Review patient's willingness to start ART:***

Has the patient demonstrated ability to keep appointments, or to adhere to other medications? Has the patient disclosed his or her HIV status? If not, encourage them to do so. Disclosure to at least 1 person who can be the treatment supporter is important. Does the patient want treatment and understand what this treatment is for? Is the patient willing and able to come for the required clinic follow-up?

- ***Community Links and Patient Support Groups:***

Advise patient on available community support groups and facilitate contact. Discuss the importance of disclosure especially to partners who may be at risk of continued exposure to HIV**.** Disclosure to a treatment supporter may be crucial in ensuring adherence and in providing emotional support**.** Discuss, encourage and facilitate testing of exposed individuals in the family and/or among sexual contacts.

- ***Continuing Counselling and Support:***

Always make time for patients to raise issues of concern to themselves that may require counselling and support.

After you conduct a thorough baseline clinical assessment, then you can now select an appropriate ARV regimen.

Choosing a ARV Regimen

Fighting the HIV virus requires a smart approach as the virus seems very clever. It needs a combined force or what is called combination therapy. It takes a combination of 3 different drugs to stop HIV from replicating and making new copies of itself rapidly. This approach offers maximum benefits with regards to providing maximum and durable viral suppression without producing unacceptable side effects. This principle has been used by the World Health Organization and many national HIV/AIDS programmes have provided guidelines on standardized ARV regimens.

Why should we use standard treatment regimens?

The reasons for using standardized treatment regimens include:

- The need to provide treatment to large numbers of PLWAs in an affordable, accessible and simplified manner;
- To simplify prescribing and prevent misuse of these potentially life-saving medicines;
- By restricting the use of ARVs to first line, second line and so on, certain ARVs are protected for use on later occasions as regimens begin to fail;
- To simplify procurement and supply of these ARVs;
- Drug combinations can be formulated as fixed dose combinations further simplifying prescribing and encouraging adherence.

The powerful combination of 3 different antiretroviral drugs is called Highly Active Retroviral Therapy or HAART. This is the standard for good therapy and has the greatest benefits for the longest time.

There are two different types of ART regimens used in the world. These are the 1st line and second line ART regimens. Lets look at each type in turn.

First-line and Second-line ART Regimens

A first-line regimen is a combination of drugs that are used in a patient who has no prior ART experience. This means that the patient has never taken ARV drugs before.

Most commonly, a first-line regimen will consist of ***two NRTIs and one NNRTI.***

The following are the 4 different first-line combinations that can be given:

d4T-3TC-NVP d4T-3TC-EFV AZT-3TC-NVP AZT-3TC-EFV

Tables 2.4 shows the standard or first-line regimen.

Table 2.4: Standard 1st Line Regime for Adults and Adolescents

Stavudine (D4T)		**Stavudine (D4T)**		**Zidovudine (AZT)**		**Zidovudine (AZT)**
+		**+**		**+**		**+**
Lamivudine (3TC)	**or**	**Lamivudine (3TC)**	**or**	**Lamivudine (3TC)**	**or**	**Lamivudine (3TC)**
+		**+**		**+**		**+**
Nevirapine (NVP)		**Efavirenz (EFV)**		**Nevirapine (NVP)**		**Efavirenz (EFV)**

Did you notice anything peculiar about these regimens? I hope you noted the following:

- That 3TC is included in all 4 regimens.
- The first drug is either d4T or AZT (but not both together).
- The last drug is NVP or EFV (not both together).
- AZT is the same as ZDV.

ARTs are always given in a combination of 3 drugs.

If well tolerated with good adherence, the patients can take the first-line treatment for several years. However, some patients eventually develop treatment failure. This means that the first-line treatment is not effective anymore. Treatment failure often occurs because of non-adherence, that is, the drugs were not taken correctly. In patients who develop treatment failure, the clinician may decide to switch to a second-line regimen.

The second-line regimen consist of 2 NRTIs + 1 PI. The second-line regimen involves taking more pills, it sometimes has food restrictions and often has more side effects than first-line regimens. Even second-line regimen can fail, if the patients do not adhere well. Table 2.5 shows the drugs used in the second line regimen.

Table 2.5: Standard 2nd Line Regime for Adults and Adolescents

Zidovudine		Zidovudine
+		+
Didanosine	or	Didanosine
+		+
Lopinavir/Ritonavir		Nelfivanir

Correct Dosage of Antiretroviral Drugs

The usual adult and adolescent dose of the following1st line antiretroviral drugs is as follows:

- Nevirapine (200mg) OD for 2 weeks then 200mg BD (first 2 weeks, it is necessary to use separate tablets)
- Stavudine(d4T) 30 mg BD
- Lamivudine (3TC) 150mg BD

As you can see, Nevirapine requires an escalating dose once daily for two weeks, then twice daily. These tablets are available in separate tablets or in fixed-dose combination tablets. A fixed-dose combination tablets is a tablet that contains all the 3 drugs. Thus in the case of the drugs listed above, there would be one tablet with 30 mg of d4T plus 150 mg of 3TC and 200 mg of NVP.

Table 2.6 Dosage of antiretroviral drugs used in the first-line ARV regimens. (Source, MOH, 2006)

	Drug	**Dose**
Note: same dose for all adolescents and adults	zidovudine (AZT)	300 mg twice daily
	lamivudine (3TC)	150 mg twice daily
	nevirapine (NVP)	200 mg once daily for 14 days, thereafter 200 mg twice daily
	efavirenz (EFV)	600 mg once daily
Same dose for adults regardless of weight	stavudine (d4T)	30 mg twice daily

As you can see in Table 2.6, in the case of nevirapine, during the first two weeks of commencing treatment, it is given in a lower dose of 200mg once daily. Then after the second week the dosage becomes 200mg twice daily. This is known as an "escalating dose" or lead-in dose.

Why is Nevirapine given in an escalating dose?

Nevirapine is given in an escalating dose to reduce its side effects. If it is given twice a day in the first two weeks it can result in a serious rash or liver problems.

Therefore, in the first two weeks the patient should take the drugs as follows:

- 1 fixed-dose combination tablet of d4T-3TC-NVP in the morning,
- 1 tablet of d4T and 1 tablet of 3TC in the evening. Sometimes both d4T and 3TC come in a single fixed-dose tablet.

Then after the first 2 weeks, the patient should take 1 fixed-dose combination tablet in the morning and one fixed-dose combination tablet in the evening.

For the first 2 weeks of treatment, the patient should receive 14 fixed-dose combination tablets d4T-3TC-NVP in one, 14 tablets of d4T, and 14 tablets of 3TC

OR

For the first 2 weeks of treatment, the patient should receive 14 fixed-dose combination tablets d4T-3TC-NVP in one and 14 tablets of fixed-dose combination tablets of d4T-3TC in one.

You now know what combination therapy you can give for 1st line and second line ART. Let us now look at what you should not give and some of the few cases where you can make an exception (see Table 2.7).

Table 2.7: Antiretroviral regimens or components that should not be offered at any time

Antiretroviral regimen or component	**Rationale**	**Exception**
Mono or dual therapy	• It facilitates Rapid development of resistance • Inferior antiretroviral activity when compared to combination with three or more antiretrovirals	Pregnant women may be given mono or dual therapy for the purpose of prevention of mother transmission of HIV (PMTCT)
Stavudine + Zidovudine	Antagonistics effects on HIV 1	No exception
Didanosine + stavudine	High incidence of toxicities-lactic acidosis (especially in pregnant women) , peripheral neuropathy , pancreatitis etc	When no other options are available and potential benefits outweigh the risks.
Lamivudine + zalcitabine	In-vitro antagonism	No exception
Atazanavir + indinavir	Potential additive hyperbilirubinemia	No exception
Efavirenz in pregnancy and in women with significant child bearing potential	Potential teratogenicity	When no other options are available and potential benefits outweigh the risks

Starting Treatment in People With Tuberculosis and HIV Co-Infection

As you read in the last unit, TB is an opportunistic infection that occurs frequently in HIV positive patients. We also mentioned earlier in this unit that opportunistic infections should be treated before starting ART.

However, TB is a special OI. This is because the duration of treatment for TB is long, usually 6-8 months, and during this time dangerous OIs can occur if the patient has very low immunity. On the other hand, drug interactions between TB drugs and ART can damage the liver or make some ARV drugs less effective, especially if patients are still taking rifampicin. In Kenya, the Ministry of Health recommends the use of rifampicin throughout the course of treatment for TB. Also, there is a high pill burden if both TB and HIV are treated at the same time. Therefore the decision to give and when to start ARVs in patients on TB treatment needs to be made by a qualified clinician.
It is recommended that people with TB/HIV complete their TB therapy prior to beginning ARV therapy unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e. a CD4 count <200/mm^3 or the presence of disseminated TB).

The recommended national first line regimen in Kenya for TB patients initiating treatment while on rifampicin is:

- ***d4t (stavudine) + 3TC (lamivudine) + EFV (efavirenz).***

However, for patients who are no longer on rifampicin the standard national first line regimen is:

- ***d4t (stavudine) + 3TC (lamivudine) + NVP (Nevirapine).***

In patients who cannot take efavirenz (such as pregnant women), a triple nucleoside regimen may be used e.g. Zidovudine + Lamivudine + Abacavir

Although Rifampicin decreases efavirenz (EFV) levels by 25%, however, standard doses of efavirenz can be used. Alternatively, abacavir (ABC) can be used with 2 NRTIs.

Nevirapine (NVP) should only be used if there is no alternative, considering the hepatotoxicity of nevirapine and the effect of rifampicin on reducing serum levels of NVP.

Except for saquinavir/ritonavir (SQV/r), protease inhibitors are not recommended during TB treatment with rifampicin due to their interactions with the later drug.

In general, when considering when to start ART in patients taking TB, you should consider the following:

> *'Is the risk of developing dangerous OI more important than the disadvantage of drug interactions and high pill burden?'*

The answer to this question will depend on the immunity of the patient in terms of:

- A very low immunity (CD4 less than 100) and patient takes TB treatment. The patient is very much at risk to develop serious OI and ART should not be postponed for more than a few weeks. You should refer the patient to a senior clinician or consider which ART regimen should be started that is compatible with TB treatment.

- A low immunity (CD4 between 200 and 350) and patient takes TB treatment. The risk to develop serious OI is still present, but we can afford to wait for 2 months. By so doing, we avoid a high pill burden and drug interactions with rifampicin.

- Start ART only after the intensive phase of TB treatment (here you need to decide which regimen or refer the patient to a senior clinician in case the continuation phase still contains rifampicin).

- Moderate immunity (CD4 more than 350) and the patient takes TB treatment. The patient does not need ART.

SUMMARY

You have now come to the end of this section. In this section we have discussed the rationale for initiating ART and noted that starting ART is not an emergency. We have also looked at the criteria and requirements for ART initiation, patient education prior to ART initiation, how to choose the correct ARV regimen and lastly the considerations that you need to make when dealing with TB patients. We hope you have found this section interesting and informative. In the next section we shall discuss how to monitor and follow-up patients on ARTs.

Its time again for you to find out how much you still remember from this lesson by answering the following questions without referring to the text. Good Luck!

Self Test 2

1. A new patient comes to the health centre because he is HIV positive and says that he needs to start ART right away. He tells you that he had a "brain infection" last year. You now have ART available. What would you do?

   A. Start preparing the patient for ART now
   B. Ask for written documentation of his HIV test and previous records
   C. Refer him for assessment

2. An HIV positive patient with chronic fever and a CD4 count of 50 comes to the health centre. What will you do?

   A. Carry out an assessment of the fever before starting ART
   B. Start ART now, because the ART will decrease the fever
   C. Give anti-malarial drugs and start ART at the same time

3. Write two standard or first-line ARV regime for adults and adolescents

_____
_____

4. When should you start ARV therapy in a patient on TB treatment?

_____
_____

ANSWERS

1. B; 2. A;

3. Write two standard or first-line ARV regime for adults and adolescents:

- *Stavudine + Lamivudine + Nevirapine (D4T/3TC/NVP); or*
- *Stavudine + Lamivudine + Efavirenz (D4T/3TC/EFV)*

4. A TB patient with very low immunity (CD4 count less than 100) or after the intensive phase.

Section 3: Monitoring of ART in Adults and Adolescents

Introduction

Welcome to the third section of this unit on antiretroviral therapy. In the last section we discussed how to initiate ARV therapy in adults and adolescents. We looked at the criteria used to start ART, the assessment and patient education that should take place before you initiate this therapy, how to choose a ARV regimen, and how and when to start ARVs in people with TB and HIV co-infection. By now we are sure you have noted that patients on ART need close monitoring. Thus in this section you will learn how to monitor and follow-up patients on ARV therapy.

Section Objectives

By the end of this section you should be able to:

- Discuss how to monitor and follow-up patients on ART;
- Identify common reasons for treatment failure;
- Explain how to change or stop ART.

Monitoring and Follow-up of Patients on Antiretroviral Therapy

It takes approximately 6-8 weeks for the clinical effects of ART to be felt by the patient or longer if the patient's immunity was too weak at the start of treatment. Some patients might even get worse initially. Thus it takes time for the immunity to recover. Antiretroviral drugs also have some side-effects which tend to occur in the initial weeks of therapy. Thus your patient needs a lot of support to ensure they do not give up the therapy all together.

Why should we monitor patients on ART? Lets start with your thoughts on this question.

ACTIVITY

List down the reasons why you think its important to monitor patients on ART.

_____

_____

_____

_____

Well done! I believe your answer included the following reasons why we monitor patients on ART.

The main goals of monitoring of patients on ART are to assess:

a) response to medication;
b) adherence to medication;
c) development of side effects to antiretroviral drugs and;
d) for recurrent or new opportunistic infections; this could imply failure of therapy if immune recovery had been achieved;
e) any psychosocial issues that may affect treatment, such as depression, substance abuse, disclosure, social support networks etc.

Supporting Patients on ARV?

The most important period of treatment support for patients is in the first three months of ARV initiations. During this period, patients are vulnerable to non-adherence for several reasons:

- Early drug toxicities may lead to treatment interruption or cessation and this may require specific intervention by the clinician;

- Ongoing viral replication is associated with a high risk of developing resistance, thus if a patient is taking the wrong daily dose, this will lead to early treatment failure and a need to shift to second line treatment, with an associated low probability of overall treatment success.

Therefore it is very important that we closely monitor the patient and show them our commitment to their well being. We also need to ensure that a clinician is easily available to the patient to address any emerging issues.

What Information Should You Gather During Monitoring?

While monitoring ARV therapy, it is important for you to gather information on the following:

- Clinical symptoms;
- Detailed past and present history;
- Other medical problems;
- Other drugs, including herbs;
- Thorough and regular physical examination.

Table 3.1 below summarises what to ask and look for when you make contact with a patient on ART.

Table 3.1: Clinical Monitoring

ASK ABOUT	**REMARKS**
How have you been?	Allow patient to express themselves freely.
Have you developed any new problems?	
Have you developed any of the following problems?	
Cough, night sweats, fever?	Exclude tuberculosis, pneumonia, malaria other OIs.
Diarrhoea, nausea, vomiting or weight loss?	Exclude infective diarrhoea, TB, other OI

Mouth sores, lack of appetite, painful swallowing?	Exclude oropharyngeal/oesophageal candidiasis and herpes
Headache, neck pain, tingling or numb or painful feet or legs? Fatigue?	Is the patient on anti-TB medication or stavudine? Exclude anaemia.
Have you developed a new skin rash?	Cotrimoxazole, nevirapine, efavirenz (rare), anti-TB
Do you have genital sores or discharge?	Exclude STI
What medications are you taking?	Assess adherence and drug interactions
How are things at home? To whom have you disclosed your HIV status ? What family support are you receiving? Have you been feeling sad or unhappy or have you lost interest in your normal activities recently?	Identify possible barriers to adherence; If sad, assess for depression.
What physical activities are you capable of doing?	Classify: WORK OR AMBULATORY OR BEDRIDDEN
Are there any other issues you'd like to talk about? Do you experience any sexual problems? In women, ask for the LMP, check for pregnancy	
LOOK	**REMARKS**
Take the patients weight, blood pressure, pulse rate, respiratory rate and temperature.	Weight gives information or response to treatment. Plot this at every visit and check the general trend.
Look for pallor	Could be due to opportunistic infections, HIV infection or AZT
Look for yellowing of eyes (jaundice)	Could be due to infections (hepatitis A or B), certain drugs (nevirapine, isoniazid or rifampicin)
Look for oral thrush?	Presence of thrush could imply disease progression.
Skin rash, enlarged lymph glands	Grade severity of rash. In case of enlarged lymph nodes, exclude TB or lymphoma
Examination of systems	Will depend on the specific complaints. It helps to palpate for the liver and spleen at very visit

Monitoring Treatment

As we mentioned earlier, patients on ART need close monitoring to assess the following:

- Adherence to the prescribed regimen;
- Tolerance and side effects of the medications;
- Efficacy of treatment.

Let us look at each in turn starting with adherence monitoring.

- **Adherence Monitoring**

Adhering to treatment is the most important factor in success of antiretroviral treatment (ART). Studies have shown that more than 95% adherence is needed to achieve maximum suppression of the virus. Less strict adherence leads rapidly to the development of viral resistance, and hence, to much earlier treatment failure. For example, missing only one tablet in a week translates to adherence of only 92.8%. It is therefore important that all patients demonstrate an understanding of adherence before starting ART.

Table 3.2 General measures that can help to increase adherence

Do not rush into staring ARV's	Make sure the patient is able to keep appointments by attending at least 3 appointments before starting ARVs. Start cotrimoxazole prophylaxis and assess adherence to it before starting ARVs.
Provide simple written information	Information on HIV in general. • How the drugs work • Not a cure for HIV • Life long treatment etc
Encourage patient to identify a treatment supporter	This can be a relative or a friend that can help and remind them to take medication
Educate patient on side effects	Give simple information. Do not overload with information, or frighten them, but knowledge that headaches, nausea etc are expected and that they will improve with time can help them to continue taking their medication.
Encourage patient to join a support group of other patients living with AIDS.	This can be very helpful to patients in addressing and also reducing stigma.
Advice patient to use reminders	Alarm clocks etc

Methods of assessing adherence

Adherence assessment should be combined with adherence counselling at every visit. The aim is to identify those patients who are having difficulties with adhering to treatment so that extra assistance can be offered to them.

Self report: This is a simple method that is widely used. Patients are asked to report their own adherence. However the way the question is asked can influence the answer.

For example asking:

Do you forget to take your tablets? Will invariably be answered by 'NO'

You should ask the question in a non-judgmental way to increase the accuracy of this method – for example:

Many people find it hard to remember to take every single dose?
-when was the last time you missed a dose?
-What things can make it hard for you to remember to take your tablets?

Pill counts: This is counting the number of pills remaining in the bottles and comparing them with the number of pills that should be remaining if adherence was 100%. If done well it can help to reassure the health care provider that adherence is good, or identify those patients that need extra support. However, if the approach is not friendly, it can promote a relationship of distrust between the patient and health worker. Patients may also be tempted to dump missed pills prior to the visit.

A trusting and supportive patient-health worker relationship is vital to enable assessment of adherence. Allocate sufficient time for a good interaction : "OBSERVE + LISTEN + TALK" and make sure the patient understands properly your indications and feels free to ask you the necessary questions to clarify all his/her doubts

Allocate sufficient time for a good interaction: "OBSERVE + LISTEN + TALK" .Make the patient feels free to ask you the necessary questions to clarify all his/her doubts.

- **Monitoring efficacy and side effects of treatment**

This is done using clinical and laboratory parameters.

Clinical visits:

The frequency of visits for clinical monitoring should be as follows:

1. The first visit should take place 2 weeks after initiating therapy. This appointment should focus on ensuring that the medicines are being taken and stored correctly. Any side effects should be noted and addressed accordingly.

2. If the patient is stable, subsequent visits should be done monthly and the focus should be on assessing the patient's clinical progress and checking for any side effects of the drugs.

3. After 6-12 months following initiation of ART, clinical appointments may be spaced at 2 to 3 month intervals in a compliant and clinically stable patient with a good understanding of the treatment. However, any patient with intercurrent problems should be able to be seen when necessary

At each visit:

- Plot the patient's weight and note the trend;
- Determine the patient's physical condition;
- Address ongoing medical problems including possibility of failure of treatment through the development of a new opportunistic infection;
- Treat intercurrent infections;
- Check drug dosages and adjust according to weight;
- The patients should be given medicines to last for 1month even when the clinic appointments are less frequent;
- Adherence should be assessed and counselling provided at each visit.

Laboratory Parameters

For assessing efficacy of treatment the following tests are used.

CD 4 lymphocyte call counts

As you already know, CD4 cells are a type of lymphocytes, which play an important role in the immune system. HIV targets these cells and uses them for replication, resulting in their death. The CD4 cell count is therefore an important laboratory marker of the strength of the immune system. Normal counts in adults range from 380-1800 cells per cubic millimetre.

CD4 cell counts, where possible, should be determined at baseline and thereafter at 6 monthly intervals. CD4 cell counts should not be measured during a concurrent infection; instead, measurement should be delayed until >2 weeks after recovery. For consistency, CD4 cell measurements in a particular patient should be carried out in the same laboratory and preferably at the same time of day.

Viral Load

Viral burden in peripheral blood can be determined by using quantitative HIV RNA assays. During the period of primary infection in adults, HIV RNA copies initially rise to high levels. Coincident with the body's humoral and cell-mediated immune response, RNA levels decline. Patients with lower HIV RNA copies have slower disease progression and improved survival compared with those with high HIV RNA copies. Where available, viral loads should be done routinely, at baseline and then 6-monthly. Viral load should be done if possible, when treatment failure is suspected.

Resistance testing

Resistance testing, where available, is recommended for persons on anti-retroviral treatment whose viral suppression is sub-optimal or viral load is increasing and CD4 cell count is declining. Currently resistance testing is not routinely available in most of the resource-limited settings.

Table 3.1 presents the schedule of clinic visits and the examinations and tests to be conducted.

Table 3.3: Schedule of clinic visits and examinations required

Visit	**Weeks**				**Months**			
Examination / Test required	**0**	**2wks**	**4wks**	**8wks**	**3mo**	**6mo**	**9mo**	**12mo**
Clinical Examination	X		X		X	X	X	X
Adherence counselling	X	X	X	X	X	X	X	X
Support group meetings			X	X	X	X	X	X
CD4+ count	X					X		X
Viral load testing****	X				X***			X
AST / ALT (particularly on patients on NVP)	X	X	X	X		X		X
Urea / Creatinine	X			X*		X***		X
Lipase ****								

* Only where clinically indicated or abnormal baseline

** Response to treatment is monitored by viral load testing at 3 months. Good adherence to successful treatment is associated with an undetectable viral load at 12 weeks. Early viral load testing can be considered at 8 weeks

*** Only for a select number of patients as deemed necessary by the physician

**** Lipase or pancreatic amylase should only be considered for patients presenting with symptoms suggestive of pancreatitis. The high incidence of false positive lipase results in asymptomatic patients as a result of HIV infection precludes the routine use of this test.

Changing Therapy

There are 3 main reasons why treatment regimen can be changed. These are

- Treatment failure;
- Treatment toxicity and/or intolerance;
- Drug interaction

Other reasons include:

- Pregnancy;

- Interruption of drug supply;
- Cost of treatment.

Let's look at the three main reasons in turn.

Treatment failure:

Antiretroviral treatment failure can be defined as a sub-optimal response to effective ART. Treatment failure can be clinical, immunological and/or virological. Let us further look at each type.

Clinical failure:

This occurs when a patient who has been doing well on antiretroviral treatment develops new opportunistic infections, or failure to resolve pre-treatment opportunistic infections when the drugs have been given for at least six months. This needs to be differentiated from an immune reconstitution syndrome, which can be seen within the first eight weeks after the initiation of ART.

Immunological failure:

Failure to significantly increase CD4 count or a persistent decline in CD4 count after a period of immune reconstitution.

Virological failure:

Failure to reduce the viral load to undetectable levels after 24 weeks; or sustained increase in viral load after full suppression.

Considerations for changing a failing regimen

As with the initiation of antiretroviral therapy, the decision to change regimens should be approached with careful consideration of several complex factors:

- Do not rush into second-line therapy;
- When changing therapy, determine whether poor adherence was responsible for the failure;

- If it is not possible to improve adherence, attempt directly observed therapy with a health worker, family member or a friend;

- If the patient is adherent, assume that resistance has developed and change therapy. If possible, cases of patients who need to change therapy should ideally be discussed in a multi-disciplinary team before reaching a decision.

- The decision to change treatment from the first line to second line should be based on clinical assessment and where available with a documented decline in CD4 count of 30% in 6 months while on ARVs.

It is vital to ensure that adherence is good in these circumstances as poor adherence is the most common cause of viral resistance. Just changing to second line will achieve little if the reason for the failure is not detected and addressed.

Choice of second line antiretroviral regimens

There is insufficient information on sequencing of treatments in absence of resistance testing. Cross-resistance is common, in particular within the same drug class, for example for zidovudine (AZT) and stavudine (d4T) or nevirapine (NVP) and efavirenz (EFV). In the absence of ARV resistance testing, W.H.O. recommends that the entire regimen be changed from a first to a second line combination regimen.

Table 3.4: Second line regimen in adults and adolescents in the event of treatment failure of the first line antiretroviral therapy regimen

Failing first-line regimen	Second-line regimen		
d4T OR AZT + 3TC + NVP OR EFV	Abacavir (ABC) + Didanosine (ddI) + Lopinavir/ritonavir (LPV/r)	***OR***	Tenofovir + Abacavir + Lopinavir/ritonavir OR Nelfinavir

As we mentioned earlier, when monitoring patients who are on ART, it's important not to confuse treatment failure with immune reconstitution syndrome.

What is Immune Reconstitution Syndrome (IRIS)?

Immune reconstitution syndrome is a strong reaction of the body's defence against a previously "quiet" opportunistic infection. In many cases, the symptoms of the immune reconstitution syndrome will be similar to the symptoms of a normal opportunistic infection. In some cases, the symptoms of an opportunistic infection in the framework of an immune reconstitution syndrome may be different from the classical symptoms of the opportunistic infection.

Usually in a person who is HIV negative, the body presents with symptoms of disease when there is a kind of 'battle' going on between the micro-organisms causing the disease and the body's the immune system. However, in a person with advanced AIDS whose immune system is thoroughly weakened, the opportunistic disease can enter the body and there will be no battle or fight. This is because the body has no CD4 left to fight. If there is no battle, then there are no symptoms. In such a person, the OI quietly continues to do harm in the body but the person may not know it because he or she does not exhibit any symptoms.

Now, when a person who has a quiet OI starts to take ARVs, the body reacts in an interesting way. First the ART makes the body's defence system stronger as a result increased CD4. As soon as that happens, the body starts to fight the OI that was already present and the patient now starts to experience sudden symptoms and may actually feel very ill. This is what is known as an immune reconstitution syndrome. Although the patient feels sick, it is a sign that the body defence is now working again, and it does not mean that the ART is bad.

So if new symptoms appear shortly after the start of ART, do not jump to conclude that it is due to failure of therapy. You should first consider immune reconstitution syndrome, drug side effects and new OIs. Typical manifestations of immune reconstitution syndrome are TB or Herpes Zoster occurring shortly after the initiation of ART. IRIS often occurs in patients with pre-existing TB which may have been detected if screening for TB had been carried out before ART initiation. Remember to always assess patients for TB prior to initiating ART.

It is very important to be able to distinguish between side effects of ART, immune reconstitution syndrome and opportunistic infections from failure of therapy. If they are not recognised and treated correctly some of these conditions, can be fatal

Changing drugs due to toxicity

Although the majority of patients will tolerate treatment fairly well, adverse drug reactions have been reported with virtually all antiretroviral drugs. Adverse drug reactions are however the most common reasons for switching or discontinuing therapy and for medication non-adherence.

Adverse drug reactions events are gross clinical or biochemical abnormalities that arise from ARV drugs, but may be precipitated or exacerbated by underlying conditions or concomitant drugs, such as:

- Combining ARVs with overlapping and additive toxicity, e.g. stavudine and didanosine;
- Co-morbid conditions that may increase risk of developing of/or exacerbate adverse events, for example, alcoholism and hepatitis B or C co-infection may increase the risk of liver toxicity;
- Drug to drug interaction may lead to an increase in dose-related toxicities, e.g. nevirapine and fluconazole.

Considerations for changing therapy due to toxicity

- Establish whether the adverse event is due to ARV or to other medication. Not all problems that arise during treatment result from ARV drugs therefore, consider other disease processes e.g. consider isoniazid as a cause of peripheral neuropathy in a patient on ARV drugs taking anti-TB drugs;
- Continue ARV if there are mild reactions; single drug substitutions may occasionally be necessary. Treatment should be stopped if severe reactions occur;
- Manage the medical event; then reintroduce ARV drugs using a modified regimen;
- In the setting of good therapeutic response, the development of a clearly definable toxicity permits single drug substitutions without compromising the overall regimen. For example, d4T can be substituted for AZT for AZT-related symptoms and vice versa. Efavirenz can be substituted for Nevirapine-related symptoms and vice versa.

We hope you now understand the reasons why we may need to change therapy. Next let us look at common side effects of ARV and how to manage them.

Common ARV Side Effects

As you well know most drugs have side effects. However not everybody who takes the drugs experiences the same side effects and to the same extent. Similarly with ARVs not everybody suffers from side effects and even those who do they differ in extent. Only a minority of patients taking ART will have serious clinical side effects that require that their treatment be discontinued. Otherwise, the majority will have non-serious but annoying side effects, especially in the beginning of therapy.

The following table summarises the ARV drug class adverse effects as well as the common adverse effects and the drugs that cause them.

Table 3.5: ARV Drug Class adverse effects

NRTIs	**PIs**
■ Peripheral neuropathy ■ Pancreatitis ■ Lipoatrophy ■ Hepatitis ■ Lactic acidosis ■ Mitochondrial toxicity	■ Lipodystrophy ■ GI Intolerance ■ Hyperglycaemia ■ Lipid abnormalities
NNRTIs	**Common Adverse Effects**
■ Rash ■ Fever ■ Nausea ■ Diarrhea ■ Hepatoxicity	■ Peripheral Neuropathy – d4T,ddI ■ Hematotoxicity - AZT ■ Hepatotoxicity - NVP ■ Diarrhea – NFV ■ Skin rash – NVP ■ Lipodystrophy – PIs, NRTIs ■ CNS disturbance – EFV ■ Hypersensitivity – ABC ■ Hyperlipidemia-PIs, d4T

Categories of Side Effects

Side effects can be divided in two broad categories:

- Side effects that are uncomfortable but not dangerous
- Potentially serious side effects
- Side effects occurring later during illness

- ***Side effects that are uncomfortable but not dangerous***

These are some of the common side effect which you should warn the patient about and advice them what to do should they occur. These include symptoms such as:

- nausea,
- headache,
- dizziness,
- diarrhoea,
- feeling tired, and
- muscle pain.

These side effects usually occur when treatment begins and then improve within 2 to 4 weeks. They are usually tolerable and can be managed symptomatically and tend to improve within a few weeks in any case. However they can affect adherence and the patient should be encouraged to persist taking the ARVs and followed up regularly to support adherence. For example, patients on Efavirenz tend to experience side effects such as, strange dreams and nightmares, mood changes, dizziness and loss of concentration. You should reassure the patient that this will go away after some weeks.

But remember that the list of all the possible side effect is long and telling the patient about all of them could confuse and discourage them. So we suggest that you learn the side effects for each drug or drug regimen so that you can prepare your patient to deal with only the specific side effects should they occur. You also need to know how to provide clinical management when the patient seeks care either because the symptoms have persisted or have become severe. Some side effects such as darkening of nails due to AZT are less common and there is no need of advising the patient about them in advance. However you should be aware of them and manage them accordingly when they occur.

- ***Potentially serious side effects***

Although rare, these side effects can be disabling and even life threatening. You should therefore warn the patient about them and tell them to seek medical attention as soon as they notice them. They include:

- Severe rash and Steven Johnson syndrome mainly caused by nevirapine or EFV;
- Yellow eyes due to hepatotoxicity mainly caused by nevirapine or EFV;
- Burning, numbness or tingling in the hands and feed (Peripheral neuropathy) mainly caused by stavudine and didanosine;
- Bone marrow suppression leading to anaemia and neutropenia caused by zidovudine;
- Severe abdominal pain, fatigue and shortness of breath (suspect pancreatitis and lactic acidosis) caused by didanosine and stavudine

- ***Side effects occurring later during illness***

These are those side effects that occur after the patient has been taking ART for several months or even years. The most common are:

- Abnormal distribution of body fat—fat gain on the abdomen, breasts, shoulders, neck (sometimes with fat lumps under the skin), as well as fat loss from legs, arms, buttocks and face (lipodystrophy).
- Lactic acidosis may also present after several months of treatment.

The following table (Table 3.6) summarises the common ARV side effects.

Table 3.6: Common ARV Side Effects

	Very common side-effects: *warn patients and suggest ways patients can manage; also be prepared to manage when patients seek care*	**Potentially serious side effects:** *warn patients about them and tell them to seek care*	**Side effects occurring later during treatment:** *discuss with patients*
d4T Stavudine	Nausea Diarrhoea	**Seek <u>care</u> urgently:** Severe abdominal pain (suspect for pancreatitis), Fatigue, shortness of breath, weight loss, abdominal pain with nausea and vomiting (suspect for lactic acidosis) **Seek <u>advice</u> immediately:** Tingling, numb or painful feet or legs or hands (suspect for peripheral neuropathy)	**Changes in fat distribution:** Arms, legs, buttocks, cheeks become THIN Breasts, belly, back of neck become FAT
3TC Lamivudine *This drug is very well tolerated*	Very Well tolerated	**May be associated with hepatitis**	
NVP Nevirapine	Nausea Diarrhoea	**Seek care urgently:** Yellow eyes, abdominal pain (suspected hepatotoxicity) Skin rash AND shortness of breath Fever	
ZDV zidovudine (also known as AZT)	Nausea Diarrhoea Headache Fatigue Muscle pain	**Seek care urgently:** Pallor (anaemia) Fatigue Shortness of breath **Seek care urgently:** Fatigue, shortness of breath, weight loss, abdominal pain with nausea and vomiting (suspect for lactic acidosis, less common than with d4T)	**Changes in fat distribution:** Arms, legs, buttocks, cheeks become THIN Breasts, belly, back of neck become FAT (less common than with d4T)
EFV Efavirenz	Nausea Diarrhoea Headache Strange dreams Difficulty sleeping Memory problems Dizziness	**Seek care urgently:** Yellow eyes Psychosis or confusion Severe skin rash	

Managing Common Side Effects

As we have already mentioned, side effects can be a big worry for your patient when they start ART for the first time. It is therefore important to reassure them and inform them and suggest ways that the patient can manage them. It will help if you tell them what they can expect. You should also make it easy for them to get advice on managing other side effects or any worries they may have.

Patients who experience side effects are more likely to stop taking their drugs correctly because they are discouraged by the side effects; if they do not take their drugs well, the therapy will not be successful. So if patients complain about side effects, you should take their complaints seriously; if not, they might start to 'forget' taking pills.

The following table outlines the management of common side effects.

Table 3.7: Management of mild side effects

Signs or Symptoms	**Response**
Nausea and Vomiting	These are common side effects in the first weeks of ART for all the drugs. Counsel patient to take drugs with food. If no AZT, reassure that this is common, usually self-limited. Treat symptomatically.
Headache	Give paracetamol. Assess for meningitis. If on AZT or EFV, reassure that this is common and usually self-limited. If headache persists, look for meningitis and other causes of headache and treat as indicated.
Diarrhoea	Diarrhoea is a frequent side effect of ART, and it occurs shortly after initiation of ART. Usually, it is self-limiting and gets better after some weeks. Hydrate. Follow diarrhoea guidelines. Reassure patient that if due to ARV, it will improve in a few weeks.
Fatigue	This commonly lasts 4 or 6 weeks especially when starting AZT.
Herpes Simplex Infection	If these persist for more than a month or are extensive, the patient has a new stage 4 condition. In a patient taking ART for months or years, this may mean the therapy does not work. Call for advice or refer
Night Sweats	These can also be due to immune reconstitution syndrome (usually within 2-3 months after starting ART), new TB in a patient doing well on ART or due to TB or other opportunistic infections in a patient failing ART
Anxiety, nightmares, psychosis, depression	This may be due to efavirenz. Give at night; counsel and support (usually lasts less than 3 weeks). Call for advice or refer if severe depression or suicidal or psychosis develops. The initial difficult time can be managed with amitriptyline at bedtime.

Blue/black nails	Reassure. It is common with AZT zidovudine.
Yellowness of the eyes (jaundice)	This could be caused by liver damage due to the drugs like nevirapine and efavirence. Stop all drugs and refer patient or manage accordingly.
Skin rash	Patients on NVP and less commonly, EFV may develop a skin rash. Dry or wet rash with fever is a dangerous side effect.
Painful muscles	AZT often causes painful muscles which occurs mostly in the beginning of treatment. It gets better after some weeks
Pallor (Anaemia)	Some patients can suddenly develop anaemia due to AZT. This is a serious side effect. Obtain a haemoglobin test and refer if haemoglobin is less than 10g/dl.
Fever	Check for common causes of fever. Patient needs further assessment as fever could be a side effect, an opportunistic or other new infection, or immune reconstruction syndrome.
Cough or difficult breathing	This could be immune reconstitution syndrome. Look for OIs especially TB and treat accordingly.
Tingling, numbness or burning in hands or feet	Mainly due to damage of the nerves called peripheral neuropathy. d4T and INH can cause peripheral neuropathy. Risk increases when both are combined. Substitute d4T with AZT in patient has no severe anaemia
Difficulty sleeping	This problem usually resolves spontaneously after the first week of treatment. It is common with efavirenz.

In summary, we can say that the good management of side effects includes:

- Discussing the common possible side effects before the person starts the medication;
- Giving advice on how to manage these side effects;
- Advising the patient on the regimen as a whole and not on each specific drug;
- Warning patients about the potentially serious side effects and telling them to seek care urgently if they occur;
- Giving immediate attention to side effects: patient should have access to the clinic even by phone;
- Advising the patient to consult you first before they stop or change treatment due to side effects;
- Initiating a discussion about side effects, even if the patient does not mention them spontaneously;
- Referring the patient if you are unable to manage serious side effects
- Referring the patient to peer-educators.

Formatted: Bullets and Numbering

If ARV side effects are potentially serious and it is necessary to discontinue the drugs, STOP ALL THE THREE DRUGS.

Changing Therapy Due To Drug Interactions

Patients with HIV are often on other medications that interact with ARVs. Before you select an antiretroviral regimen, you should take into consideration the potential drug-drug interactions and/or food interactions. A thorough review of current medications can help you in designing a regimen that minimizes undesirable interactions. You should therefore thoroughly review any drug that is added to an existing regimen, including over-the-counter pills.

For example, if a patient develops TB while on Nevirapine containing regimen, rifampicin (which significantly reduces blood levels of Nevirapine) cannot be practically avoided. It is therefore recommended that efavirenz be used instead of nevirapine. You should therefore put the patient on efavirenz. Similary, in women of child bearing age, they should be on an effective contraception and efavirenz should be changed to Nevirapine after the TB treatment.

In order to minimize drug interactions, you should:

- Ask at each visit what other medication the patient is taking;
- Educate the patient to consult before taking any medicine and to avoid over-the- counter pills;
- Avoid drugs which interact wherever possible;

Considerations for Changing a Failing Regimen

As with the initiation of antiretroviral therapy, the decision to change regimens should be approached with careful consideration of several complex factors. These factors are virologic and immunological considerations. Lets look at each in turn.

Virologic consideration for changing therapy

Ideally, ART should suppress viral replication to levels that can not be detected with HIV RNA assays. Consensus recommendations have been developed using plasma HIV RNA measurements to guide changes in antiretroviral therapy for HIV infected adults.

You should consider changing therapy if:

- HIV RNA levels drop less than 10fold (1 log) after 8 weeks of therapy
- HIV RNA has not decreased to undetectable level after 4-6 months after the therapy

Immunological consideration for changing therapy

CD4 + lymphocyte count and percentage are independent predictors of disease progression. Normal CD4 count in adults in Kenya range from 500 -1800 cells per millimetre of volume. Consider changing ART if there is a rapid and substantial decrease in absolute CD4 +-lymphocyte count (a>30% decline in < 6 months).

Discontinuation of Therapy

Under certain circumstances it may be necessary to discontinue ART, this includes the following situations:

- Consistently poor adherence for whatever reason;
- Repeated treatment interruptions;
- Severe toxicity such as lactic acidosis;
- Only consider discontinuation of therapy after exploring all potentially corrective measures with the patient, care-giver and family.

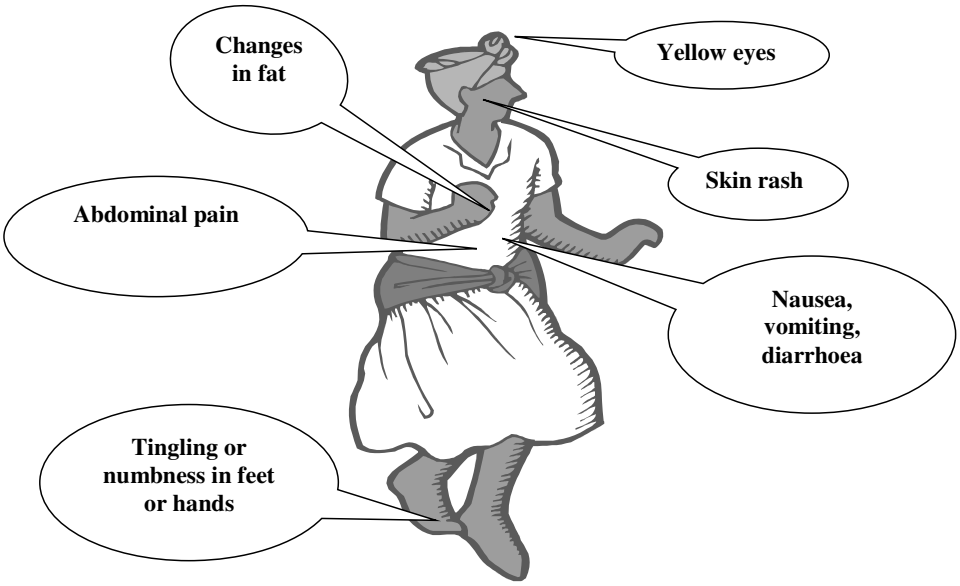
Summary

You have now come to the end of this section on how to monitor ART in adults and adolescents. We hope you have found it useful and informative and that you are now able to monitor patients on ART for side effects as well as encourage them to practice strict adherence.

We have also come to the end of this unit on ARV in adults and adolescents. Before you complete the attached assignments, find out how much you remember from the content you have just covered by completing the following exercise without referring to the text.

Self Test 3

This patient is taking d4T-3TC-NVP. Write the appropriate drug next to the side effect and put an asterisk (*) on the ones that require urgent care.



Source: MOH, 2006, Participant Manual for the Primary-level Training for Comprehensive Management of HIV Infection

Now refer to page 51 of this studyguide for the answers.

Appendix 1: List Of ARV Drug Dosages (WHO List)

NRTIs	Dosages
Lamivudine	150 mg BD
Stavudine	40 mg BD (30mg if <60kg)
Zidovudine	300mg BD
Didanosine	400 mg OD (250mg od if <60kg)
Abacavir	300 mg BD
Tenofovir	300 mg OD

NNRTIs	Dosages
Efavirenz	600 mg OD
Nevirapine	200 mg OD for 14d, then 200 mg BD
Protease Inhibitors	
Lopinavir/Ritonavir	400 mg/100 mg BD
Nelfinavir	1250 mg BD
Indinavir/Ritonavir	800 mg/100mg BD
Saquinavir*/Ritonavir	1000 mg/100mg BD

**Saquinavir hard gel to be used (Invirase™)*