

# **Clinical Tract**

**Module on**

## **Basic pharmacology of antiretroviral therapy**

## **Learning outcomes for all course participants**

After completion of this module the learner should:

- Understand the basic viral replication process and targets for drug action
- Understand the basic mechanism of action of antiretroviral drugs
- Know the different antiretroviral drug classes that are available in South Africa
- Know the basic side effects that can be seen in patients on Regimen 1 ARVs.

# 1. THE VIRAL REPLICATION PROCESS

There are different stages that the virus goes through after it has entered the human body and antiretroviral drugs use those different stages as target sites for their action.

Certain drugs interfere with the attachment and penetration of the host cell by the infecting virus while others interfere with the multiplication and release of the mature virus from the host cell.

For a good understanding of the pharmacotherapy of HIV infection it is important for one to understand the path that the virus takes once it has entered the human body and the effects thereof.

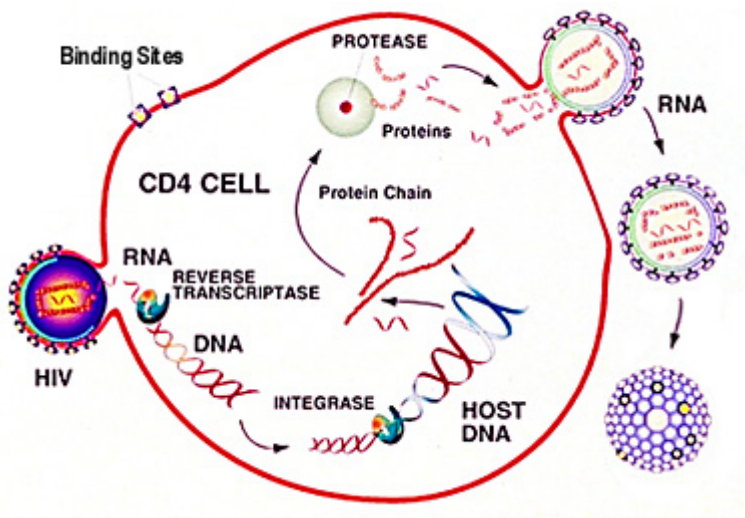


Figure 1. The viral replication process and the site of action of ARVs

# 2. CLASSES OF ANTIRETROVIRAL DRUGS (ARVs)

## Available drugs

There are three major classes of antiretroviral drugs:

1. Reverse transcriptase inhibitors:
  - Nucleoside analogues
  - Non-nucleoside analogues
2. Protease inhibitors

## Drugs under development

There are still ongoing trials for newer drug classes that will not be discussed in this module.

- Newer nucleoside reverse transcriptase inhibitors
- Newer non-nucleoside reverse transcriptase inhibitors
- Newer protease inhibitors
- Integrase inhibitors (Inhibit binding of proviral DNA to integrase, an enzyme responsible for the integration of the proviral DNA into the host genome for the formation of new viruses.)
- Fusion inhibitors
- CCR5 and CXCR4 co-receptor blockers

In theory it is possible to develop a drug to interfere with each of the stages of the viral replication process.

## 3. AN OVERVIEW OF ANTIRETROVIRAL DRUGS AVAILABLE IN SOUTH AFRICA

### Nucleoside reverse transcriptase inhibitors (NRTIs or “Nucs”)

These were the first antiretroviral drugs to be used in the treatment of HIV infection. Nucleosides are building blocks for RNA/DNA synthesis. Drugs in this class act as false building blocks and they therefore terminate the DNA chain and prevent DNA synthesis from taking place.

This group of drugs is further divided into:

- Thymidine analogues (structurally related to thymidine, a DNA building block)
- Non-thymidine analogues (structurally related to other building blocks such as adenosine, cytosine, and guanosine).

This division is according to the building block being mimicked.

These drugs were formally identified by their chemical names before their generic and trade names were used.

**Table 1. The chemical name, abbreviation and generic name of NRTIs**

Chemical name	Abbreviation	Generic name
3'-Azido-3'-deoxythymidine	AZT	Zidovudine
2',3'-didehydro-2',3'-dideoxythymidine	d4T	Stavudine
2'-deoxy-3' thiacytidine	3TC	Lamivudine
2', 3'-dideoxyinosine	ddI	Didanosine
2',3'-dideoxycytidine	ddC	Zalcitabine

**Table 2. NRTIs available in South Africa, October 2004**

<b>Analogue mimicked</b>	<b>Generic name</b>	<b>Trade names</b>
Thymidine	Zidovudine (AZT)	Retrovir Aspen-Zidovudine Zidaid
Thymidine	Stavudine	Zerit Stavir Aspen Stavudine
Non-Thymidine (cytosine)	Lamivudine (3TC)	3TC Lamaid Cipla-Lamivudine Aspen-Lamivudine
Non-Thymidine (cytosine)	Zalcitabine (ddC)	Hivid
Non-Thymidine (adenosine)	Didanosine (ddI)	Videx Aspen-Didanosine
Non-Thymidine (Guanosine)	Abacavir	Ziagen
Combination NRTI	Lamivudine/ Zidovudine	Combivir Avacomb Aspen-Lamzid

### **Non-nucleoside reverse transcriptase inhibitors (NNRTIs or “non-nucs”)**

This class of drugs is chemically diverse and act by binding to the enzyme HIV reverse transcriptase directly at a non-substrate binding site, altering the structure of the enzyme and causing physical obstruction.

**Table 3. NNRTIs available in South Africa, October 2004**

<b>Generic name</b>	<b>Trade name</b>
Nevirapine	Viramune Nevran Aspen-Nevirapine
Efavirenz	Stocrin

### **Protease inhibitors (PIs)**

Protease inhibitors bind to the viral protease enzyme and prevent it binding and cleaving its natural polyprotein substrate, thus halting production of mature, infective virions. This class of drugs work much later in the replication process.

**Table 4. PIs available in South Africa, October 2004**

<b>Generic name</b>	<b>Trade name</b>
Indinavir	Crixivan
Saquinavir	Invirase Fortovase
Ritonavir	Norvir
Nelfinavir	Viracept
Amprenavir	Agenerase
Lopinavir / Ritonavir	Kaletra

## 4. REGIMEN 1 IN THE NATIONAL PROGRAMME

Combination of 2 NRTIs and 1 NNRTI

1. Stavudine (thymidine analogue NRTI)
2. Lamivudine (non-thymidine analogue NRTI)
3. Efavirenz or Nevirapine (NNRTI)

## 5. IMPORTANT SIDE EFFECTS OF FIRST REGIMEN ANTIRETROVIRALS

The most important side effects that everybody should be aware of, are discussed in this module. In a following module the side effects are discussed in more detail.

### Class associated toxicities of the NRTIs

1. Lactic acidosis — Acid build up in the body resulting in - tiredness, weight loss, shortness of breath, stomach problems and loss of appetite. This needs urgent referral to a experienced doctor)
2. Hepatitis and steatosis — Liver problems
3. Lipodystrophy — Fat loss seen mainly on the face, arms and legs and also buttocks.
4. Associated prominence of arm and leg veins
5. Myopathy — Muscle weakness
6. Pancreatitis — Inflammation of the pancreas. This needs immediate referral to an experienced doctor.

### Side effects of the individual drugs used in Regimen 1 ARVs

#### Zidovudine

- Bone marrow suppression. Since the bone marrow produce all the cells in the blood, the cells are not enough to do their work (low white cell count, low red cell count and low platelet count). The patient might not have enough red blood cells to carry the oxygen, not enough platelets to control bleeding and not enough white cells to fight infection. This is monitored with the full blood count (FBC).
- Nausea and vomiting

#### Stavudine

- Pins and needles associated with numbness of the hands and feet. Medical terms is peripheral neuropathy.
- Pancreatitis characterised by severe stomach pain, nausea, vomiting, fever and light-headedness.

#### Lamivudine

- No clinically significant side effects.

### **Nevirapine**

- Liver toxicity – may present with stomach problems and flu like symptoms (Refer to treating doctor)
- Rash that can be mild to moderate and also severe characterised by blistering, increase in body temperature, swelling of the body and stomach problems. (Refer to treating doctor). Any patient on nevirapine developing a skin rash must immediately consult the doctor.

### **Efavirenz**

- Insomnia, dizziness, drowsiness, depression, nightmares and impaired concentration are common in the first 2-3 weeks, but they usually subside with continued therapy.
- Avoid in pregnancy and in women of childbearing age not on proper contraception. If a patient falls pregnant during treatment, she must be switched to nevirapine. If a patient has been taking efavirenz for the whole or most of the first three months of pregnancy, the risk of an abnormal baby should be explained and an option of termination of pregnancy offered.

## **6. NRTI DRUG COMBINATIONS THAT ARE NOT RECOMMENDED**

- Zidovudine and Stavudine (same class, they compete for action)
- Lamivudine and Zalcitabine (same class, they compete for action)
- Stavudine and Zalcitabine (both result in numbness of the hands and feet)
- Didanosine and Zalcitabine (both result in numbness of the hands and feet)

