

Clinical Tract

Module on

The basic pharmacology of antiretroviral drugs

LEARNING OUTCOMES FOR DOCTORS, NURSES AND PHARMACISTS

After completion of this module the learner should be able to:

- Know the drugs in the different classes
- Know the side effect profile of the different drugs and how to manage it
- Know where and how to report unexpected side-effects
- Know the important drug interactions
- Know what influences bio-availability of the different antiretroviral drugs

This module is primarily meant to be studied by medically qualified health care workers. Counsellors and data typists are welcome to read it, but should not feel discouraged if they do not understand all the information.

1. CLASSES OF ANTIRETROVIRAL DRUGS

Available drugs

There are three major classes of antiretroviral drugs:

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

2. 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).

Table 1. NRTIs available in South Africa, November 2004

Analogue mimicked	Generic name	Trade names
Thymidine	Zidovudine (AZT)	Retrovir Aspen-Zidovudine
Thymidine	Stavudine	Zerit Stavir Aspen-Stavudine
Non-Thymidine (cytosine)	Lamivudine (3TC)	3TC 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

ZIDOVUDINE

This is a thymidine analogue that inhibits reverse transcriptase enzyme actively. This drug was the first to be used in the treatment of HIV infection. It crosses the blood brain barrier and is therefore effective in treating CNS complications of HIV.

Uses

- Prevention of maternal – foetal transmission as single drug or part of combination therapy
- Paediatric HIV infection Regimen 2 (children > 3 months of age)
- Adult HIV infection regimen 2
- HIV associated dementia

Side Effects and management

- Macrocytosis is noted within a few weeks in patients on zidovudine. This phenomenon can be used as a crude indicator of adherence.
- The most common side effect is bone marrow suppression that is usually seen within 12-17 weeks of starting therapy. It can be seen as suppression of all or only one cell line (i.e. red cells, white cells and platelets). Patients may present with a pancytopenia but anaemia is the commonest presentation of bone marrow suppression. It can be reversed by treatment interruption, but in severe cases a blood transfusion might be necessary. The patient can either be rechallenged on a lower dosage of zidovudine or the regimen can be changed. Zidovudine should be discontinued when the absolute neutrophil count is $<750/\text{mm}^3$. For severe cases of bone marrow suppression, a decrease in dose or replacement with stavudine (another thymidine analogue) is usually necessary.
- Gastrointestinal disturbances usually nausea and vomiting. Seen within the 1st 6 weeks of therapy.
- Abnormal liver functions

STAVUDINE

Uses

- Adult HIV infection regimen 1
- Paediatric HIV infection regimen 1

Side Effects and management

- Peripheral neuropathy (5 - 15%). The onset is usually 8 weeks to 6 months after initiation of treatment. The incidence is increased if the drug is co-administered with drugs that give the same side effect e.g. didanosine. Peripheral neuropathy usually resolves if treatment is promptly stopped. A change in regimen or dose reduction is needed after resolution of the peripheral neuropathy. The symptoms of the peripheral neuropathy can be treated with a non-steroidal anti-inflammatory or tricyclic antidepressants e.g. amitriptyline or the newer anti-epileptics such as gabapentin.
- Pancreatitis (rare) but life threatening. It is characterised by severe stomach pain, nausea, vomiting fever and light-headedness. Antiretrovirals should immediately be stopped.

LAMIVUDINE

Uses

- Adult HIV infection regimen 1
- Paediatric HIV infection regimen 1

Side Effects

- No clinically significant side effects but can get gastrointestinal side effects
- Neutropaenia is very rare

DIDANO SINE

Uses

- Adult HIV infection regimen 2
- Paediatric HIV infection regimen 2 (> 6 months)

Side Effects

- Pancreatitis (1-9% of cases) May be fatal in 6% of cases and this may warrant discontinuation of treatment with this drug. This can occur anytime during therapy.
- Peripheral neuropathy (5-12%). Onset is usually 55-201 days after initiation of therapy with this drug.
- Gastrointestinal symptoms mainly diarrhoea – due to buffer in tablets
- Altered liver functions

ZALCITABINE

This is a cytosine analogue (synthetic pyrimidine nucleoside analogue)

Uses

- Not currently part of any SA guidelines

Side effects

- Peripheral neuropathy (17 – 31%) Seen in the 1st 6 months of therapy.
- Mouth ulcers (Aphthous ulcers) Seen in the 1st 4-6 weeks of therapy.
- Skin rash

Zalcitabine's side effects overshadow its clinical use.

ABACAVIR

Uses

- Adult and paediatric HIV infection (Salvage Regimen)
- Used in combination with other NRTIs

Side Effects and management

- Hypersensitivity syndrome (3 – 5 %) - It occurs within the first 6 weeks of starting therapy. It is a multi-organ event with the most frequent symptoms being fever, rash, gastrointestinal symptoms, respiratory symptoms (pharyngitis, dyspnoea, cough), and less commonly musculoskeletal symptoms (myalgias, arthralgias).

Once this happens, the drug should be discontinued and the patient should never be rechallenged with abacavir.

- Rash (3 – 5%)

NRTI DRUG COMBINATIONS THAT ARE NOT RECOMMENDED

- Zidovudine and Stavudine antagonise each other (both thymidine analogues). These drugs compete for phosphorylation, which is a necessary process for activation of each drug. Zidovudine therefore decreases the efficacy of stavudine because it has higher affinity for the thymidine kinase enzyme that is responsible for this process.
- Lamivudine and Zalcitabine antagonise each other (both cytosine analogues)
- Stavudine and Zalcitabine (same side effect profile – peripheral neuropathy)
- Didanosine and Zalcitabine (same side effect profile – peripheral neuropathy)

CLASS ASSOCIATED TOXICITIES OF NRTIs

- Lactic acidosis (discussed in the latter part of the module)
- Hepatic steatosis
- Lipodystrophy (peripheral fat wasting)- discussed in the latter part of the module
- Myopathy usually proximal in nature. (Patient cannot stand from a squatting position or difficulty in combing the hair)

PHARMACOKINETICS OF THE NRTIs

Table 2. Absorption and excretion of NRTIs

Drug name	Absorption	Excretion
Zidovudine	Oral bio-availability 65% Food has no significant effect	Kidney
Stavudine	Oral bio-availability 82- 86%	Kidney
Lamivudine	Oral bio-availability 85%	Kidney
Zalcitabine	Oral bio-availability 70 –90%	Kidney
Didanosine	Oral bio-availability 30 – 40% (decreases by 55% with food) should be taken 1hr before or 2hrs after meals	Kidney
Abacavir	Oral bio-availability 83%	Liver

Didanosine is available as buffered tablets. Sufficient antacid is needed and therefore at least two tablets should be taken per dose e.g. 125mg (100mg + 25mg) or 400mg (2x150mg + 100mg).

3. NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs OR “NON-NUCS”)

These drugs act by binding to the hydrophobic pocket of the HIV Reverse transcriptase enzyme, thereby altering the structure of the enzyme and thus rendering the enzyme inactive.

Table 3. NNRTIs available in South Africa in November 2004.

Generic name	Trade name
Nevirapine	Viramune
Efavirenz	Stocrin

NEVIRAPINE

Uses

- Adult HIV infection regimen 1 for females of childbearing potential not using contraception or pregnant women
- Used to prevent mother to infant HIV infection (as a single agent)

Side effects

- Hepatotoxicity – occurs in 8-18% of cases. It is more frequent in women and patients with higher CD4 cell counts. Patients may present with non-specific gastrointestinal and flu-like symptoms. These can rapidly progress to hepatomegaly, jaundice and hepatic failure within a few days. Liver function tests should be done fortnightly for the first two months and then every 3 months thereafter. If ALT and AST increase by 5 times the upper limit of the normal values, then the drug should be discontinued and only restarted once the values have normalised and the patient has no signs or symptoms of hepatitis. This condition may be fatal and therefore the above precautions should be adhered to.
- A rash occurs in about 17% of patients, mostly mild to moderate, but can be as severe as Stevens-Johnson syndrome in 0.3% of patients. Seven percent of patients have to discontinue the drug. Nevirapine must be discontinued for severe rash with desquamation or blistering, mucocutaneous involvement or rash accompanied by constitutional symptoms (fever, oedema and gastrointestinal symptoms).

The above side effects are usually seen within the first 8 weeks of treatment.

Nevirapine is usually started at half its normal dose (lead-in dose of 200mg daily) and later increased to its maximum dose after two weeks (200mg twice daily) of treatment in order to reduce the incidence of side effects.

If a patient does not tolerate the lead-in dose a dose increase cannot be done.

EFAVIRENZ

Uses

- Adult HIV infection regimen 1
- Paediatric HIV infection regimen 1 (in children > 3 years or > 10kg)

Side effects

- Neuropsychiatric manifestations (insomnia, dizziness, drowsiness, depression, nightmares and impaired concentration) are common in the first 2-3 weeks, but are severe enough to require discontinuation in only 2-5% of patients. These usually subside with continued therapy.
- Teratogenic (avoid in pregnancy and in women of childbearing age not on proper contraception). Efavirenz was teratogenic in cynomolgus monkeys and is therefore contra-indicated in pregnancy or in women of childbearing age not using contraceptives. 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 trimester, the risk of congenital abnormalities should be explained and an option of termination of pregnancy offered.

PHARMACOKINETICS OF THE NNRTIs

Table 4. Absorption and excretion of NRTIs

Generic	Absorption	Metabolism	Excretion
Nevirapine	Oral bio-availability >90%	Liver	Kidney 80%
Efavirenz	Oral bio-availability 42% Empty stomach preferably avoid high fat meal (high fat meal increase absorption by 50%)	Liver	Kidney 14-34% Faeces 16-61%

4. PROTEASE INHIBITORS (PIs)

These drugs bind to viral protease enzymes preventing the post-translational breakdown of viral polyprotein into the components required for viral assembly and budding.

DRUGS CURRENTLY AVAILABLE

Table 5. The generic and trade names of PIs currently available in South Africa

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

USES

- Lopinavir/ritonavir is used as part of second-line regimen for HIV infected adults.
- Lopinavir/Ritonavir is used as first line regimen in HIV positive children from 6 months of age.

DISADVANTAGES OF THE PIs

- Complex regimens
- Poor tolerability
- Long term side effects
- Poor CNS penetration
- Cross resistance
- Drug interactions
- Interpersonal pharmacokinetic variability

PHARMACOKINETICS OF THE PIs

All protease inhibitors are metabolised in the liver by the cytochrome p450 enzyme system. They act as either enzyme inducers or enzyme inhibitors and therefore interfere with the metabolism of other drugs. Ritonavir is the most potent inhibitor of

the liver microsomal enzymes compared to other drugs in the same drug class. This drug is frequently used as part of dual PI treatment.

Table 6. The absorption and excretion of PIs.

Generic	Absorption	Excretion
Indinavir	Oral bio-availability 65% Must be taken on an empty stomach. Food decreases absorption substantially Separate dosing with buffered didanosine by 2h	Liver
Saquinavir	Soft gel capsule: oral bio-availability unknown but better than hard gel Hard gel capsule: oral bio-availability 4%, but erratic Must be taken with food, food increases absorption	Liver
Ritonavir	Oral bio-availability unknown Must be taken with food; food increases absorption Capsule needs refrigeration Separate dosing with buffered didanosine by 2h	Liver
Nelfinavir	Oral bio-availability 20-80% Must be taken with food, food increases absorption	Liver
Amprenavir	Oral bio-availability 83% Avoid high fat meals, otherwise no meal restrictions	Liver
Lopinavir/Ritonavir	Oral bio-availability 80% Food increases absorption from 48% to 80%	Liver

DUAL PI COMBINATIONS

The rationale for using two PIs is based on their metabolic interactions. Dual PIs allow an easier dosing regimen and a lower pill burden, hence increasing adherence and reducing the likelihood of side effects. The frequently used combinations are indinavir/ritonavir (indinavir as combination therapy with ritonavir has no meal restrictions), saquinavir/ritonavir, and lopinavir/ritonavir. These combinations can be used as second line regimens or as salvage therapy.

Ritonavir inhibits the biotransformation of Lopinavir in the liver and therefore increases the plasma concentration of the latter drug. Ritonavir is a potent inhibitor of liver microsomal enzymes.

CLASS ASSOCIATED TOXICITIES

- Lipodystrophy
- Hyperlipidaemia
- Diabetes Mellitus

FREQUENT SIDE EFFECTS OF PROTEASE INHIBITORS

Table 8. Frequent side effects of PIs

Indinavir	Nephrolithiasis (kidney stones). Patients must drink at least 1.5 –2 l of water a day. (Seen within 24-48hrs of starting therapy – dose related) Asymptomatic hyperbilirubinaemia – seen early in the course of therapy. Rash, alopecia, dry skin
Saquinavir	Gastrointestinal (diarrhoea) Elevated liver transaminases
Ritonavir	Gastrointestinal Elevated liver transaminases (within 5 weeks) Parasthesias and asthenia
Nelfinavir	Diarrhoea Rash
Amprenavir	Rash (within 10 days of initiation of therapy) Gastrointestinal intolerance (within 12 weeks) Oral paresthesia
Lopinavir / Ritonavir	Class side effects

RESISTANCE PROFILE

Resistance to PIs requires multiple amino acid substitutions. Resistance patterns to PIs overlap. Cross-resistance is less problematic with nelfinavir, making rescue treatment with other PIs more likely to succeed.

5. OTHER DRUGS

HYDROXUREA

This is a cellular ribonucleotide reductase inhibitor. It depletes the available number of nucleotides, which are the building blocks for DNA. It is registered in South Africa as a cytostatic agent and not as an antiretroviral agent. It acts synergistically with the nucleoside reverse transcriptase inhibitors such as didanosine. The drug is considered to be toxic and therefore should be reserved for salvage therapy by an expert HIV clinician.

Combining this drug with stavudine and didanosine can be fatal due to the development of a fatal pancreatitis and liver toxicity (shared side effects).

Side effects

- Bone marrow suppression
- Hair loss
- Hyperpigmentation
- Peripheral neuropathy

6. RECOMMENDED ADULT ANTIRETROVIRAL DOSAGES

Table 9. Recommended adult antiretroviral dosages

Drug name	Adult dosage
Zidovudine	300 bd
Stavudine	>60 kg: 40mg bd <60 kg: 30mg bd
Lamivudine	150mg bd
Didanosine	>60kg: 200mg bd or 400mg once daily <60kg: 125mg bd or 250mg once daily
Zalcitabine	0.75mg tds
Abacavir	300mg bd
Nevirapine	200mg daily for 2 weeks then 200mg bd
Efavirenz	600mg nocté
Indinavir	800mg tds on empty stomach (low fat snack allowed)
Saquinavir	Soft gel: 1200mg tds Hard gel: 1000mg bd+ Ritonavir 100mg bd
Nelfinavir	750mg tds or 1250mg bd
Amprenavir	1200mg bd 1200mg/day + Ritonavir 200mg/day
Ritonavir	600mg bd when used as single PI 100-400mg bd when used as part of combination PI
Lopinavir / Ritonavir	3 capsules bd

Table 10. Recommended adult dosages in renal failure.

Drug	Creatinine clearance 10-50ml/min	Creatinine clearance <10ml/min
Zidovudine	Dosage unchanged	300mg/day
Didanosine	200mg daily	100mg/day
Stavudine	20mg bd	20mg/day
Lamivudine	150mg daily	50mg/day
Zalcitabine	0.75mg bd	0.75mg/day

Paediatric dosages of antiretroviral drugs depend on the age of the child, the weight and sometimes the body mass index of the child. This will be discussed in the **Paediatric antiretroviral module**.

7. HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

Three or more drugs are used together to counter the development of resistance. Drug combinations will be discussed in detail in **MODULE 8**.

- Two NRTIs + One NNRTI
- Two NRTIs + One PI
- Two NRTIs + Two PIs
- Three NRTIs (the third is abacavir)
- Two PIs

The last two options would be used as salvage regimens when other regimens have failed.

8. ANTIRETROVIRAL DRUG RESISTANCE

This is failure of the drug to achieve a desired goal of therapy due to viral resistance (mechanism described below). This is usually due to non-compliance (skipping doses), therefore counselling for adherence is crucial to avoid this complication. The viral load is the most important parameter for evaluating response to therapy. CD4 count and the clinical picture usually complement the viral load test.

There are 3 types of treatment failure:

- **Virological failure** – this is defined as
 - Failure to suppress the viral load to below 5000 copies/mL
 - A decline in viral load of less than 1 log₁₀ 6-8 weeks after initiation of treatment.
 - A viral load 0.6 log₁₀ higher than its lowest point **OR** a return to 50% of its pre-treatment value.
- **Clinical failure** is defined as disease progression with the development of opportunistic infections or malignancy.
- **Immunological failure** is defined as a 30% drop in CD4 count from peak value or a return to pre-treatment baseline or lower.

Mechanism of drug resistance

Resistance to nucleoside reverse transcriptase inhibitors (NRTIs) develops slowly with the exception of zidovudine (should therefore be used as part of a highly suppressive regimen). Cross-resistance does not occur between agents in this drug class.

Cross-resistance exists between NNRTIs. Cross - resistance is very high among currently available NNRTIs (Nevirapine and Efavirenz). HIV resistance to NNRTIs is associated with the appearance of mutations in the reverse transcriptase enzyme. Major NNRTI mutations result in treatment failure (e.g. K103N mutation). This is responsible for 20 – 50 fold resistance to all NNRTIs.

That means if a patient should develop resistance to one drug in the class, the patient will also have resistance to the other drug in this class. The NNRTI thus need to be replaced by a drug from a different class.

Marked resistance amongst protease inhibitors develops also because of mutations with amino acid substitutions at both the active enzymatic site and other regions. Viruses with mutated proteases are not very capable of replication. (Less fit)

Viruses with this major mutation are highly resistant, but are capable of replication.

9. DRUG INTERACTIONS

Shared toxicity profiles

- Peripheral neuropathy:
 - Isoniazid, didanosine, zalcitabine and stavudine
- Hepatitis
 - Rifampicin and nevirapine

Competition for metabolism

- Rifampicin is an inducer of the liver microsomal enzymes and can therefore reduce the plasma concentration of the protease inhibitors especially lopinavir/ritonavir, indinavir and saquinavir. Concurrent use of rifampicin with PIs is thus contraindicated, with the only exception a combination of saquinavir/ritonavir.
- Clarithromycin is a drug used to treat *Mycobacterium avium* infections. Its plasma concentration increases when given together with indinavir, ritonavir and saquinavir. Dose adjustments should be done when co-administering these drugs.

Anti-fungal agents

- Ketoconazole is a potent inhibitor of the liver microsomal enzymes. It can increase plasma levels of protease inhibitors like indinavir and saquinavir.
 - When given together with other protease inhibitors like ritonavir (another potent liver microsomal inhibitor), the plasma concentration of ketoconazole actually increases (same applies with co-administration with lopinavir).
- Efavirenz and nevirapine can decrease the plasma levels of ketoconazole

Lipid-lowering drugs

- Simvastatin and lovastatin should not be used together with protease inhibitors because they are metabolised by the same enzyme system. Co-administration can lead to toxic effects and therefore substitution with other safer drugs such as atorvastatin and pravastatin is recommended.

Benzodiazepines

- Benzodiazepines are anxiolytic, hypnotic and anticonvulsant drugs that can be administered in HIV positive patients.
- Examples of benzodiazepines that should not be co-administered with protease inhibitors are midazolam, triazolam, and diazepam. These agents are also metabolised by the cytochrome p450 enzyme system.
- Alternative benzodiazepines that are safer are: Lorazepam and oxazepam.

Other

- **St John's wort** - it reduces the plasma levels of PIs when taken together.
- **Non-sedating antihistamines** e.g. Terfenadine and astemizole. Protease inhibitors can increase the plasma levels of these drugs and therefore lead to toxicity (especially cardiac toxicity). Protease inhibitors have a similar effect when given together with cisapride (gastrointestinal motility agent). Cisapride has a similar cardiac effect to the non-sedating antihistamines (prolongation of the QT interval).

10. MANAGEMENT OF MAJOR DRUG COMPLICATIONS

Lactic acidosis

- This is a rare but potentially fatal metabolic complication of NRTIs, especially stavudine and didanosine. Incidence is 4-5 per 1000 patient years of therapy. It

is more frequent seen in women and those with hepatitis co-infection. The underlying cause is drug induced mitochondrial damage. The incidence of lactic acidosis increases with duration of antiretroviral treatment.

Nausea, vomiting, abdominal pain and clinical signs of acidosis characterize the clinical picture. Laboratory testing reveal a low CO₂, abnormal liver enzymes, raised amylase level, a metabolic acidosis on arterial blood gas and raised lactate levels.

Treatment is supportive. Nucleoside analogues should be stopped immediately and may not be reintroduced when lactate levels are > 5mmol/L with symptoms or > 10mmol/L. Seek the help of an expert HIV clinician.

Fat maldistribution

This is seen particularly in patients taking protease inhibitors or NRTIs. Lipodystrophy is seen in 13-84% of patients on regimens containing protease inhibitors whereas lipoatrophy may be due to mitochondrial toxicity associated with NRTIs. A big variance in reporting occurs because there is no single uniform definition for this syndrome.

Lipodystrophy is characterised by maldistribution of fat resulting in breast enlargement, increase in abdominal girth, buffalo hump and peripheral wasting. Fat loss is seen mainly on the face, arms and legs and also buttocks. with an associated prominence of arm and leg veins

Discontinuation of therapy does not always improve condition. Encourage exercise. Management includes switching to an NNTRI or discontinuation of therapy.

Insulin resistance/glucose intolerance

Glucose metabolism may be affected in a sizable portion of patients using PIs. Hyperglycemia can occur in 3–17% of patients on PIs. The incidence of new onset diabetes mellitus may be 1-6%. Insulin resistance or glucose intolerance may occur in association with lipodystrophy.

Hyperlipidemia

This condition is characterised by elevated total cholesterol, LDL cholesterol and triglycerides. It is associated with an increased incidence of coronary artery disease. Protease inhibitors have been implicated in the development of this complication.

The lipid profile of patients should be checked 6-monthly and patients should also be evaluated for other cardiac disease risk factors.

Management includes:

- Reduce fat intake (cholesterol and saturated fats)
- Exercise
- Stop smoking
- Lose weight (refer to dietician)
- Drug therapy with the fibrates or atorvastatin for severe cases.
- Monitor lipid profile 6 monthly.

11. FURTHER READING / REFERENCES

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