HIV/AIDS Training

Module 3
Anti-retroviral Therapy
June 2008

Adapted from and thanks to:
Foundation for Professional Development; Ashraf Grimwood; GF Jooste meetings; Prof Gary Maartens lectures; PATA conference; MIC and Department of Pharmacology UCT
Antiretroviral therapy

“Goal – to put as many patients on ART with good adherance”
Objectives

• Do they work? – patient’s *choice*
• What are they?
• How do they work?
• What are the side effects (adverse events)?
The “before and after” of antiretroviral therapy.
Do the drugs work? Yes they do.
Antiretrovirals calculated to extend life expectancy by 35 years

Simon Collins, HIV i-Base

An analysis from a large international cohort study from the Antiretroviral Therapy Cohort Collaboration (ART-CC) has calculated that antiretroviral treatment currently extends life expectancy for HIV-positive people to an average of 65 years. Their model used patients who start treatment when either 20 or 35 years old.

Using data from 43,000 patients from 14 cohorts from Canada, Europe and the US, the researchers estimated the life expectancy since 1996 on the basis of reported deaths within the cohorts and compared rates in treatment-naive patients starting treatment in the 1996–99 period to patients starting treatment from 2003–05.

Compared to the earlier treatment group, life expectancy for patients starting treatment in 2003-05 increased by 13 years.

Although life expectancy increased similarly in all groups there were significant absolute differences between different groups of patients,

Women had higher life expectancy than men (overall mortality rates/1000 patient years [95%CI]: 9.1 [8.2-10.1] vs 12.9 [12.3-13.6].

Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32.6 [1.1] years vs 44.7 [0.3], based on starting treatment aged 10).

Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32.4 [1.1] years for CD4 cell counts below 100 cells/mm$^3$ vs 50.4 [0.4] years for counts of 200 cells/mm$^3$ or more).
What are they?

- Many ARVs are currently available in South Africa (with more available overseas) – limited options in the Public Health sector → important for SA private sector to comply.

- All drugs, e.g., antibiotics, analgesics, antimalarials have side effects.

- Mechanism of action important for medical staff but other issues and ideas need to be discussed with patients.

- Patients exhaust M/Aid or lose it when they become unemployed.

- Pros and cons.

- Adherance, disclosure, testing of partners etc.
Antiretroviral Therapy 7:3:2*

Objectives - to understand the:

- mechanism of action of ARVs
- different drug classes and regimens
- diagnosis and management of side effects
- drug interactions & shared toxicity

* 7 drugs : 3 classes : 2 regimes
Important Terms

- ART – antiretroviral therapy
- HAART – highly active antiretroviral therapy ("triple therapy")
- NRTI – nucleoside reverse transcriptase inhibitor
- NNRTI – non-nucleoside reverse transcriptase
- PI – protease inhibitor
# ART sites in South Africa - 2008

<table>
<thead>
<tr>
<th>Province</th>
<th>No. of ART sites</th>
<th>Population - million</th>
</tr>
</thead>
<tbody>
<tr>
<td>KZN</td>
<td>75</td>
<td>10 (20.9)</td>
</tr>
<tr>
<td>WC</td>
<td>53</td>
<td>4.8 (10.1%)</td>
</tr>
<tr>
<td>GP</td>
<td>54</td>
<td>9.6 (20.2%)</td>
</tr>
<tr>
<td>EC</td>
<td>54</td>
<td>6.9 (14.4%)</td>
</tr>
<tr>
<td>LP</td>
<td>48</td>
<td>5.4 (11.3%)</td>
</tr>
<tr>
<td>MPL</td>
<td>23</td>
<td>3.5 (7.4%)</td>
</tr>
<tr>
<td>FS</td>
<td>22</td>
<td>2.9 (6.2%)</td>
</tr>
<tr>
<td>NW</td>
<td>21</td>
<td>3.4 (7.1%)</td>
</tr>
<tr>
<td>NC</td>
<td>12</td>
<td>1.1 (2.3%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>362</strong></td>
<td>± 48 million</td>
</tr>
</tbody>
</table>

**Ratio per clinic:**
- KZN: 0.13
- WC: 0.09
- GP: 0.18
- EC: 0.13
- LP: 0.11
- MPL: 0.15
- FS: 0.13
- NW: 0.16
- NC: 0.09
## When to Start?

<table>
<thead>
<tr>
<th>Early Treatment</th>
<th>Delayed Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td><strong>Benefits</strong></td>
</tr>
<tr>
<td>• Easier to control viral load</td>
<td>• Avoid negative effects on quality of life</td>
</tr>
<tr>
<td>• Less damage to immune system</td>
<td>• Avoid side effects</td>
</tr>
<tr>
<td>• Lower incidence of side effects</td>
<td>• Less risk of drug resistance</td>
</tr>
<tr>
<td>• Preserve future drug options</td>
<td>• Preserve future drug options.</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td><strong>Risks</strong></td>
</tr>
<tr>
<td>• Potential side effects</td>
<td>• Possible permanent immune system damage</td>
</tr>
<tr>
<td>• Drug resistance over time</td>
<td>• Difficult to control viral load</td>
</tr>
<tr>
<td>• Limited future drug options</td>
<td>• Increased incidence of side effects</td>
</tr>
<tr>
<td>• Negative effects on quality of life</td>
<td></td>
</tr>
</tbody>
</table>
“Guidelines”

Site manuals and Protocols

- < 350 ?
- < 200 ?
- < 250 ?
- TB ?
- Staff training and experience ?
- Pregnant ?
- Age ?
- Province ?
- Country ?
Leucocyte with new HIV viruses

- **nucleus**
- **cytoplasm**
- **budding new HIV**
Start date = initiation of ARVs

- there is only ONE start date
- this can be recorded on the appointment card, the tick sheet, the patient clerking notes and on the treatment contract

- Treatment naïve
  NEVER had ARV’s before

- Treatment non-naïve
  Patient is presently on ARV’s or has had in the past and defaulted
Predictors of mortality in patients initiating ARVs

• study at McCords Hospital, Durban, KZN 1999 – 2004 on 309 patients

• strongest predictors:
  – CD4 cell count < 50 / µl
  – haemoglobin < 8g / dl
  – a history of oral candidiasis
  – history of cryptococcal meningitis
  – TB was not a significant predictor

Bisola O et al, SAMJ March 2008 98; 3; 204 - 208
The effect of ARVs

- CD4+ T cell count
- Viral load

Days | Years | Treatment begun

Undetectable

No anti-retroviral medication

START DATE
ARV treatment

IMMUNE RECOVERY
The effect of ARVs

- CD4+ T cell count
- Viral load

Low CD4 count starts to recover

Viral load falls

START DATE
The effect of ARVs

- **CD4**$^+$ T cell count
- **Viral load**

The viral load never falls to ZERO.

Month 6
The effect of ARVs

- **CD4⁺ T cell count**
- **Viral load**

Days | Years | Treatment begun | START DATE | CHECK ADHERANCE | Undetectable | 700-1100 | 500,000 | 200
Mechanism of Action

Nucleoside reverse transcriptase inhibitors
• mimic DNA building blocks
• prematurely terminate the growing DNA chain

Non-nucleoside reverse transcriptase inhibitors
• directly block the reverse transcriptase enzyme

Protease Inhibitors
• block the protease enzyme thereby preventing budding of new virus
DNA and the Double Helix

DNA: nucleic acids

Nucleic acid analogues

adenine

thymine

guanine

cytosine

didanosine

AZT, d4T

ABC, TDF

3TC, FTC
HIV virus

- the virus codes for 3 enzymes
  - Reverse Transcriptase
  - Integrase
  - Protease
- a single HIV virus particle is called a *virion*
- it needs co-receptors for binding called CCR5 (R5) and CXC4 (X4)

any drug *that interferes* with these enzymes suppresses viral replication
HIV virus structure

1 / 10 000mm diameter

protective shell = viral envelope

envelope (Env) made of two proteins called gp120 and gp41

two strands of RNA

core = capsid

3 enzymes:
- Reverse transcriptase
- Integrase
- Protease
Drugs that inhibit Reverse Transcriptase
NRTI's (3TC, D4T) & NNRTI's (Nevirapine, Efavirenz)

Drugs that inhibit Protease
PI's (Lopinavir, Ritonavir)

HIV virus releases viral RNA & Reverse Transcriptase into CD4 cell

Production of proteins for new viruses causes cell destruction. When more cells die, than are produced by the bone marrow, thymus & spleen the body becomes depleted of CD4 cells
Approved ARV Agents Included in WHO’s ARV Guidelines

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitor</th>
<th>Non - Nucleoside Reverse Transcriptase Inhibitor</th>
<th>Protease Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NsRTI</strong></td>
<td><strong>NtRTI</strong></td>
<td><strong>NNRTI</strong></td>
</tr>
<tr>
<td>Thymidine analogues</td>
<td>Non-Thymidine analogues</td>
<td></td>
</tr>
<tr>
<td>zidovudine (ZDV, AZT)</td>
<td>didanosine (ddI)</td>
<td>tenofovir disoproxil fumarate (TDF)</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>lamivudine (3TC)</td>
<td>Nevirapine (NVP)</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
<td>Efavirenz (EFZ)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1a 1b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saquinavir (SQV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ritonavir (RTV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indinavir (IDV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lopinavir/ritonavir (LPV/r)</td>
</tr>
</tbody>
</table>

Never combine 2 thymidine analogues together eg AZT, D4T
Never combine 2 non-thymidine analogues together eg DDI, 3TC, ABC
Avoid D4T, DDI & EFV during pregnancy
Approved ARV Agents Included in WHO’s ARV Guidelines

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitor</th>
<th>Non - Nucleoside Reverse Transcriptase Inhibitor</th>
<th>Protease Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NsRTI</td>
<td>NtRTI</td>
<td>PI</td>
</tr>
<tr>
<td>Thymidine analogues</td>
<td>Non-Thymidine analogues</td>
<td></td>
</tr>
<tr>
<td>zidovudine (ZDV, AZT)</td>
<td>didanosine (ddl)</td>
<td></td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>lamivudine (3TC)</td>
<td>Nevirapine (NVP)</td>
</tr>
<tr>
<td></td>
<td>Abacavir (ABC)</td>
<td>Efavirenz (EFZ)</td>
</tr>
<tr>
<td></td>
<td>tenofovir disoproxil fumarate (TDF)</td>
<td></td>
</tr>
</tbody>
</table>

**Guidelines and Precautions:**

- Never combine 2 thymidine analogues together eg AZT, D4T
- Never combine 2 non-thymidine analogues together eg DDI, 3TC, ABC
- Avoid D4T, DDI
- Avoid EFV during pregnancy
## Antiviral regimes

<table>
<thead>
<tr>
<th>Category I</th>
<th>Category II</th>
<th>Category III</th>
<th>Category IV</th>
<th>Category V</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI Thymidine analogues</td>
<td>NRTI Non-thymidine analogues</td>
<td>NRTI</td>
<td>NNRTI</td>
<td>PI</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>Didanosine (ddI)</td>
<td>Abacavir (ABC)</td>
<td>Nevirapine (NVP)</td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>Zalcitabine (ddC)</td>
<td></td>
<td>Efavirenz (EFV)</td>
<td>Indinavir (IDV)</td>
</tr>
<tr>
<td></td>
<td>Lamivudine (3TC)</td>
<td></td>
<td></td>
<td>Ritonavir (RIV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saquinavir (SQV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Liponavir/Ritonavir</td>
</tr>
</tbody>
</table>

For initiation, combine one drug from category I, one from category II and one from category IV.
South African National Department of Health revised protocol in March 2007:

* 30mg as effective as 40mg

* reduced side effects (lactic acidosis and peripheral neuropathy)
Efavirenz [Stocrin]
Use of ARV’s in the Private sector

- it is important for all medical profession to know about DoH Provincial protocol
- Patients may be referred to the public health sector for ARV’s:
  a) run out of Medical Aid due to expenses incurred during hospital admissions related to AIDS
  b) no longer able to work due to illness and therefore no longer has a M/Aid
Available Regimens

- **First line therapy**
  1. D4T - Stavudine
  2. 3TC - Lamivudine
  3. EFV - Efavirenz or NVP - Nevirapine

- **Second line therapy**
  1. AZT - Zidovudine
  2. DDI - Didanosine
  3. Kaletra - Lopinavir/Ritonovir

Drug resistance or side effects on Regime 1

There are currently no further treatment options available in the public sector for someone who fails second line therapy!
Major Class Side Effects of ARV’s

– **NRTI**: mitochondrial toxicity
  - Lactic Acidosis
  - Peripheral neuropathy
  - Neutropaenia and anaemia

– **NNRTI**: hypersensitivity reactions
  - Hepatitis
  - Rash

– **PI**: metabolic complications
  - Glucose and cholesterol and TGs [“sugar and fats”]
  - Lipodystrophy

NB – ask patients about possible side effects
Adverse reactions

- can be divided into abnormal LABORATORY blood tests and CLINICAL abnormalities eg rash
- side effects can be divided into acute (days to weeks), subacute and chronic (weeks to months) AND common or rare
- mild (minor) or severe (major), temporary or permanent
- **Graded** according to severity:
  - Grade I and II = mild
  - Grade III and IV = severe

Remember: Common things are common!
# NRTI Dosage & Side Effects

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Nucleoside Analogue</th>
<th>Brand Name</th>
<th>Generics (SA)</th>
<th>Adult Dose</th>
<th>Common side effect profile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stavudine (d4T)</strong></td>
<td>Thymidine</td>
<td>Zerit (BMS)</td>
<td>Aspen</td>
<td>Stavir (20mg/30mg/40mg) (Cipla) (30mg/40mg)</td>
<td>&gt;60kg 40mg bid &lt; 60mg 30mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stavir(20mg/30mg/40mg)(Cipla)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generics (SA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zidovudine (AZT)</strong></td>
<td>Thymidine</td>
<td>Retrovir (GSK)</td>
<td>Aspen</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lamivudine (3TC)</strong></td>
<td>Cytosine</td>
<td>3TC (GSK)</td>
<td>Aspen Lamivudine</td>
<td>150mg bid</td>
<td>Generally well tolerated Infrequent diarrhoea; peripheral neuropathy; pancreatitis</td>
</tr>
<tr>
<td><strong>Didanosine (ddl)</strong></td>
<td>Adenosine</td>
<td>Videx (BMS)</td>
<td>Aspen</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abacavir (ABC)</strong></td>
<td>Guanosine</td>
<td>Ziagen (GSK)</td>
<td></td>
<td>300mg bid</td>
<td></td>
</tr>
</tbody>
</table>
Mitochondrial Toxicity

• The depletion of mitochondrial DNA is an effect of nucleoside analogues recognized in 1990, the effect being reversed when therapy is discontinued.

• NRTI therapy is an independent risk factor for the development of mitochondrial toxicity and correlates with its ability to inhibit mtc polymerase-γ.
Fatty acyl coA → Pyruvate → Mitochondrion → Acetyl coA → ATP

Lactate → Fatty liver

O₂

currency of energy in human body
Nucleoside Reverse Transcriptase Inhibitors (NRTI’s)
(especially D4T + ddI)

Inhibit human mitochondrial DNA γ polymerase

Hyperlactataemia and Lactic Acidosis
Lactic Acidosis

- LA is probably the **most recognisable feature of mtc dysfunction** in clinical disease, in which loss of mtc oxidative function leads to increase reliance on anaerobic metabolism and the inevitable accumulation of lactate (and thus of acid).

- LA is one of the **most severe and life-threatening** side effects of NRTI’s
Portable hand-held lactate machine

Bottle of test strips (25)*

* Remember to order MORE strips from the pharmacist when bottle nearly empty
Lactic Acidosis

- Elevated lactate is common in patients on NRTI’s (up to 20%) per annum – generally asymptomatic.

- Symptomatic hyperlactataemia without acidosis (1-2%)
- Lactic acidosis is rare (0.1% per annum)

- Higher incidence of lactic acidosis being reported in WC than in developed world (G F Jooste 11/2005)
  - 8.7/1000 pt years vs 1-2/1000 pt years
- Bicarbonate levels may be better prognostic predictor than Lactate

Risk of lactate elevation:

- zalcitabine / stavudine / didanosine > zidovudine > lamivudine / abacavir > TDF
Risk factors

- Drugs - the “D” drugs
- **Stavudine** and **Zidovudine** based HAART
- concurrent disease: liver, kidney, cardiac, anaemia, septicaemia; dehydration
- obesity - **Body Mass Index (BMI) > 28**
- female gender
- prolonged NRTI exposure: 6 – 12 months
- pregnancy
  - Inborn errors of metabolism

Negligible risk after 18 months
Lactic acidosis

- rare, about 0.1%
- high mortality
- exclude other causes
  - sepsis
  - pancreatitis
  - hepatic failure
  - cardiogenic shock
  - thiamine deficiency
Hyperlactatemia – Clinical Syndromes

Lactate (mmol/l)

- **Normal Range**: 1-2 mmol/l
- **Compensated hyperlactatemia**
  - stable over time
  - common
- ** Decompensated lactic acidosis**
  - rapidly progressive life-threatening
  - HCO < 20 mmol/l
  - rare

Symptoms:
- HCO < 20 mmol/l
Lactic Acid Management

- blood samples do NOT need to be kept on ice
- prolonged tourniquet needs to be avoided

- **Normal lactate**: less than 2 mmol/l
- **Mild**:
  - 2.5 – 5 mmol/l and bicarbonate > 20 mmol
  - monitor regularly and check blood lactate again in 3 days, then weekly till normalised
  - change stavudine to zidovudine

WC – switch d4T to tenofovir

may take up to 3 months average 51 days
Lactic Acid Management

• Moderate:
  – More than 5 mmol/l and bicarbonate greater than > 15
  – stop HAART and admit & hydrate and vitamins
  – exclude sepsis
  – only start HAART when normal – 3/12
  – NNRTI and *Kaletra®* four capsules 12 hourly

*Can use Tenofovir +3TC+ NNRTI* SOP, WC DoH October 2008
Lactic Acid Management

• Severe:
  – more than 5mmol/l and bicarbonate less than < 15mmol
  – admit and stop HAART
  – hydrate with fluids and vitamins
  – exclude sepsis
  – consider iv bicarbonate and ventilation
  – NNRTI and Kaletra® four capsules 12 hourly
  – 50% mortality

WC - Do NOT use tenofovir
<table>
<thead>
<tr>
<th>INITIAL SYMPTOMS</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>Check patient’s weight at every visit</td>
</tr>
<tr>
<td>Tender/ enlarged liver</td>
<td></td>
</tr>
<tr>
<td>Motor weakness</td>
<td></td>
</tr>
</tbody>
</table>

Maintain a high index of suspicion if these symptoms persist or get worse.
<table>
<thead>
<tr>
<th>INITIAL SYMPTOMS</th>
<th>SUBSEQUENT SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Tachypnoea and Hyperventilation</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Liver or renal failure</td>
</tr>
<tr>
<td>Bloating</td>
<td>Clotting abnormalities</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Seizures</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Cardiac Dysrhythmias</td>
</tr>
<tr>
<td>Check patient’s weight at every visit</td>
<td></td>
</tr>
<tr>
<td>Tender/ enlarged liver</td>
<td>Death</td>
</tr>
<tr>
<td>Motor weakness</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

• ensure lactate machine calibrated (for each new bottle of test strips opened)
• be able to interpret the result → advise patient accordingly:
  – Reassure
  – Revise medication and monitor → repeat in 3 days
  – Refer to hospital → STOP ARVs
SYMPTOMATIC HYPERLACTATAEMIA / LACTIC ACIDOSIS SUSPECTED

Risk factors:
- On d4T or ddl (occasionally occurs with AZT)
- Overweight (but can be normal weight)
- On ARV's > 2 months (usually > 6)
- Female
- Neuropathy

Suspicious symptoms and signs
- Unintentional recent LOW
- Anorexia
- Abdominal pain
- Nausea and vomiting
- Dyspnoea, tachypnoea without respiratory cause
- Unexplained tachycardia

Exclude other causes of acidosis
- sepsis, severe anaemia, renal or hepatic failure, pancreatitis, congestive cardiac failure (CCF), severe dehydration, thiamine deficiency, diabetic ketoacidosis (DKA), other drugs

Check lactate

Lactate < 2.5
Hyperlactataemia excluded, investigate for other causes

In patients with raised lactate check
- Blood gas
- Lipase
- LFT

Mild
Lactate 2.5-5, minimal symptoms and bicarb > 20
Switch d4T to AZT, TDF or ABC as available
Recheck lactate in 3 days, then weekly until normal
Rather stop HAART and get expert advice:
1. lactate cannot be monitored
2. symptoms severe
3. HRT other than D4T
4. abnormalities, new or lactic acidosis continue to rise after switch

Moderately severe
Lactate 5-10, and/or bicarb 15-20
Stop HAART and admit
Supportive therapy and maintain adequate hydration
(PO or IV)
Investigate for sepsis, opportunistic infections and pancreatitis
In patients who are acutely ill do blood culture and start broad spectrum antibiotic

Severe
Lactate > 10 and/or bicarb < 15
See guidelines for drug choices for restarting HAART once lactate has normalised. Consult expert. Never use d4T or ddl again.
Peripheral Neuropathy

• Diagnosis is **IMPORTANT** in order to avoid unnecessary discontinuation of NRTI therapy.

• 45% patients misdiagnosed with NRTI related peripheral neuropathy.¹

• *Symptom type* and *site* are key criteria for determining a correct diagnosis (Table).

• *Sudden onset* and *rapid progression* are often characteristic of NRTI-associated neuropathy.
### Diagnostic criteria for NRTI-induced peripheral neuropathy

<table>
<thead>
<tr>
<th>APPROPRIATE DIAGNOSIS</th>
<th>INAPPROPRIATE DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, numbness, paraesthesia</td>
<td>Weakness</td>
</tr>
<tr>
<td>Lower &gt; upper extremities</td>
<td>Upper &gt; lower extremities</td>
</tr>
<tr>
<td>Bilateral, symmetrical</td>
<td>Unilateral, asymmetrical</td>
</tr>
<tr>
<td>Distal</td>
<td>Proximal</td>
</tr>
<tr>
<td>No other causes</td>
<td>Other causes</td>
</tr>
</tbody>
</table>
Incidence

• *peripheral neuropathy* occurs in up to 35% of patients.

• *other* potential causes include HIV disease; opportunistic infections; drug treatment for HIV/AIDS; and other underlying diseases.

• it is *not* life-threatening but can be severe.

• *peripheral neuropathy*, if caused by HAART, may be reversible with prompt withdrawal or dose reduction of the offending agent.
Management

• monitor high risk patients
• **discontinue** or **reduce dosage** of implicated drugs.
• if neuropathy recurs after resumption, **permanent discontinuation** should be considered.
• provide **palliative support** as needed to reduce discomfort as needed.
• if symptoms do not resolve after a 2 month interval, look for another causative factor.
# Common shared toxicity of HAART and anti-TB therapy

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>TB DRUG/S</th>
<th>ART/HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>INH isoniaizid</td>
<td>Stavudine (d4T)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Didanosine (ddl)</td>
</tr>
<tr>
<td>Rash</td>
<td>Rif rifampicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INH INH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PZA pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>PZA Rif</td>
<td>Didanosine (ddl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zidovudine (AZT) PI</td>
</tr>
<tr>
<td>Hepatitis (42 days*)</td>
<td>Rif INH PZA</td>
<td>NNRTI’s*</td>
</tr>
</tbody>
</table>
# Common minor side effects of TB treatment

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampicin</strong></td>
<td>Nausea and loss of appetite</td>
</tr>
<tr>
<td></td>
<td>Take treatment at night</td>
</tr>
<tr>
<td></td>
<td>Orange urine – reassure patient</td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>Joint pain</td>
</tr>
<tr>
<td></td>
<td>Take aspirin 150mg tds</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>“Burning feet”</td>
</tr>
<tr>
<td></td>
<td>Pyridoxine 50 to 100mg daily</td>
</tr>
<tr>
<td></td>
<td>( each tablet 25mg )</td>
</tr>
</tbody>
</table>

PALSA PLUS 2008 page 9
# NNRTI Dosage & Side Effects

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Generic (SA)</th>
<th>Suggested Dosage</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td>Stocrin (MSD)</td>
<td></td>
<td>&gt;40kg = 600mg at night</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;40kg = 400mg at night</td>
<td></td>
<td>TERATOGENICITY - Grade D – use injectable contraceptive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exacerbation of underlying CNS problems</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vivid dreams; dizziness; insomnia; psychosis – NB warn patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Maculopapular rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatotoxicity (8% - although more recent evidence that Nevirapine and Efavirenz don’t differ much)</td>
</tr>
<tr>
<td><strong>Nevirapine (NVP)</strong></td>
<td>Viramune (BI)</td>
<td>Aspen</td>
<td>200mg once daily for 2 weeks, thereafter 200mg bid</td>
<td>Rash (17% of patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis (15%) : including necrotising hepatitis</td>
</tr>
</tbody>
</table>
### Table III. Common causes of liver abnormalities in HIV-infected patients

#### Patients not on ART
- Drugs: TB medications (rifampicin, INH, PZA), co-trimoxazole, fluconazole, antibiotics and others.
- Acute and chronic hepatitis B and C
- TB: granulomatous hepatitis, lymph nodes at porta hepatis causing obstruction
- Fatty liver
- HIV cholangiopathy
- Lymphoma
- Toxins: alcohol, alternative therapies
- Bacterial sepsis

#### Patients on ART
- All of the above
- HAAART: NRTIs cause fatty liver/steatohepatitis; NNRTIs (nevirapine > efavirenz) cause immune-mediated hepatitis; PIs may also cause drug-induced hepatitis
- Immune reconstitution inflammatory syndrome: TB, hepatitis B or C
- Hepatitis B flares on stopping 3TC or tenofovir

Exclude ALL other causes beforehand!
Hepatocellular damage

Most resolve within 2 weeks of stopping drug

Features of hepatitis as for acute viral:
- malaise
- nausea/vomiting
- jaundice
- right upper quadrant pain or tenderness

Transaminases >5 fold elevated

Fulminant course in a few

Chronic disease infrequent (eg α-methyldopa)
Hepatotoxicity as part of systemic hypersensitivity

Rash, fever and/or eosinophilia

e.g. cotrimoxazole, phenytoin, nevirapine

any of these drugs may causes a "rash"
NVP hepatotoxicity & rash

“women with CD4+ counts greater than 250 cells/mm³ were 9.8 times more likely than women with lower CD4+ counts to experience symptomatic, rash-associated, nevirapine-related hepatotoxicity”

46% of symptomatic hepatitis is rash-associated


Clinical Infectious Diseases 2004; 38(Suppl 2):S80–9
NVP Toxicity: Symptomatic Hepatic Events in 1st 6 Weeks of NVP Therapy by Baseline CD4 Count & Gender (BI)

Prof James McIntyre  Perinatal Research Unit, Bara
Changing ARVs

- a woman may be on EFV if on concurrent TB drugs; change to NVP as soon as TB drugs completed ( in 6 months )
- woman may want to conceive and start a family when she regains health
- always initiate with NVP if possible especially if woman is pregnant OR of child bearing age ( and will start a family soon )

No need to introduce NVP stepwise when switching from EFV
NVP-associated hepatitis in ANC

• NVP has 2 principal side effects: Stevens-Johnson syndrome and hepatitis
• both can be fatal (early diagnosis NB)
• 0.8% incidence of hepatitis at JHB Hospital ANC, onset insidious
• development of a rash following initiation of NVP associated with a 10 fold ↑ risk of developing hepatitis

SAMJ Feb 2008 p.116
Managing LFT toxicity

unrelated to ARV’s e.g. viral hepatitis, cholangitis

• HAART-induced exacerbation of chronic viral hepatitis

• remember other drugs especially TB

• nevirapine most hepatotoxic > > efavirenz
  – monitor ALT 2,4,8 & 12 weeks; then 3 monthly

• symptoms of hepatitis critically important - check glucose, INR
Table VI. ART toxicities and reasons for specialist referral

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Main causative drug(s)</th>
<th>When to refer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlactataemia/lactic acidosis</td>
<td>d4T &gt; ddI &gt; AZT</td>
<td>All suspected cases (see Fig. 3)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>NVP &gt; EFZ &gt; others (TB medication also an important cause)</td>
<td>Severe symptoms of hepatitis (such as jaundice and vomiting), signs of liver failure (flap, confusion, drowsiness) and patients on multiple drugs that could be causing hepatitis</td>
</tr>
<tr>
<td>Drug rash</td>
<td>NVP &gt; EFZ &gt; others</td>
<td>Severe rash – extensive involvement, mucosal involvement, blistering, desquamation or significant systemic symptoms</td>
</tr>
<tr>
<td>Myelosuppression (anaemia and neutropenia)</td>
<td>AZT</td>
<td>Symptomatic anaemia</td>
</tr>
<tr>
<td>Neupathy</td>
<td>d4T &gt; ddI</td>
<td>Neutropenia (neutrophil count &lt;1) with fever</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ddI &gt; d4T (also protease inhibitors via hypertriglyceridaemia)</td>
<td>Atypical and rapidly progressive presentations</td>
</tr>
<tr>
<td>Metabolic complications</td>
<td>Protease inhibitors (D4T can also cause impaired glucose tolerance and diabetes mellitus)</td>
<td>All cases and suspected cases</td>
</tr>
</tbody>
</table>

Severe & rare

Mild and common

Chronic
# PI Dosage & Side Effects

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Brand Name</th>
<th>Generics (SA)</th>
<th>Suggested Dosage</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir / Ritonavir</td>
<td>Kaletra (Abbot)</td>
<td></td>
<td>400mg/100mg bid (3 tabs bid)</td>
<td>Nausea, GIT side effects, Lipodystrophy, Insulin intolerance, Hypercholesterolaemia</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Invirase/ Fortovase (Roche)</td>
<td></td>
<td>1000mg + 100mg ritonavir boosting bid</td>
<td>Diarrhoea, nausea, liver enzyme (CYP450) inhibition</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir (Roche)</td>
<td></td>
<td>600mg bid (protease active dosing)</td>
<td>Diarrhoea, nausea, abdominal pain, Lipodystrophy, Hypercholesterolaemia, Insulin intolerance. <em>Very potent liver (CYP450) inhibitor</em></td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crixivan (MSD)</td>
<td></td>
<td>800mg + 100mg ritonavir bid OR 800mg tds on an empty stomach</td>
<td>Nephrolithiasis, nausea, <em>Potent liver enzyme (CYP450) inhibitor</em></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept (Roche)</td>
<td></td>
<td>1250mg bid or 750mg tds with meals</td>
<td>Diarrhoea, Lipodystrophy, Insulin intolerance, Hypercholesterolaemia</td>
</tr>
</tbody>
</table>
Lipodystrophy

- consists of *atrophic* and *hypertrophic* changes, which can co-exist
- LIPOATROPHY is a form of lipodystrophy characterised by fat *loss* in the limbs, buttocks or face
- LIPOHYPERTROPHY results in breast enlargement, *increased* visceral fat ("crix belly" or "Protease paunch") and buffalo hump on the neck
Affects

• these body shape changes are distressing to the patient
• some patients find it more difficult to cope with lipodystrophy than their HIV itself
• may make HIV positive status more recognisable
• these worries could lead to non-adherence
Causes

- little known but thought to be multi-factorial
- Increased duration of ARV’s associated with increased risk
- NRTI’s especially d4T ( stavudine )
- P.I.’s (especially in association with NRTI’s) associated with lipohypertrophy
- lipodystrophy can occur with any HAART regime
Lipodystrophy – lypoatrophy
Lipodystrophy – lypohypertrophy
Managing lipodystrophy

• modify HAART regimen
  – NNRTI instead of PI (seldom possible)
  – NRTI switch (AZT/abacavir/TDF instead of D4T)
  – resolution very slow
• exercise useful for reducing central obesity
  – Accentuates lipoatrophy
• cosmetic surgery or soft tissue augmentation by injections are effective
  ( not available in public health sector )
Associations

• increased risk for dyslipidaemia and insulin resistance

• remember to do a fasting lipogram & glucose in affected patients
HYPERLIPIDAEMIA

- PI’s can cause fasting hypertriglyceridaemia and elevated LDL cholesterol.

- ↑↑Trigs → Pancreatitis

<table>
<thead>
<tr>
<th>Triglyceride</th>
<th>2-5.5 mmol/l</th>
<th>&gt;5.5 mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-chol</td>
<td>Diet</td>
<td>Diet + fibrate</td>
</tr>
<tr>
<td>Low IHD risk</td>
<td>3-4.8 mmol/l</td>
<td>&gt;4.8 mmol/l</td>
</tr>
<tr>
<td>LDL-chol</td>
<td>Diet</td>
<td>Diet + fibrate/statin*</td>
</tr>
<tr>
<td>High IHD risk</td>
<td>3-3.3 mmol/l</td>
<td>&gt;3.3 mmol/l</td>
</tr>
<tr>
<td></td>
<td>Diet</td>
<td>Diet + fibrate/statin*</td>
</tr>
</tbody>
</table>
Lipodystrophy syndrome(s): overlapping NRTI & PI toxicities

NRTIs

d4T > ZDV/ABC

Lactate

Fat wasting (lipoatrophy) TG

PIs

↑ LDL, VLDL cholesterol
↑ Insulin resistance
↓

Visceral obesity

Dyslipidaemia

• Pre-HAART decreased cholesterol & elevated triglycerides in advanced disease

• PIs cause: elevated LDL-cholesterol reduced HDL-cholesterol elevated triglycerides

• IHD & pancreatitis (TG >11) risk

• Ritonavir, especially Kaletra, most associated
  – 5% significant elevations on Kaletra
Managing dyslipidaemia – international guidelines

Monitor fasting lipids baseline, after 3-6 months, then annually

- TG <5.6 Diet
- TG >5.6 Diet + fibrate

- LDL-chol
  - Lifestyle for all elevations
  - >4.9 (IHD > 3.4) consider fibrate/statin

Beware drug interactions statins & PI

JAIDS 2002;31:257
SA guidelines?

- Primary prevention not part of Essential Drug List [EDL]
- Secondary prevention in EDL
- Need to protect against severe ↑TG
  - TG >10 give fibrate?
Statins & PI interactions

- Atorvastatin $\uparrow$ level - low dose (5-10mg)
- Pravastatin $\downarrow$ levels modest
- Simvastatin & lovastatin $\uparrow\uparrow$ levels toxic
  - AVOID
Insulin resistance

- Up to 40% abnormal GTT on PIs
- Overt diabetes uncommon
- Insulin resistance mechanisms
  - Impaired glucose uptake
  - Central obesity & lipoatrophy from lipodystrophy (NRTIs also play a role)
Insulin resistance - management

• Monitor fasting glucose baseline, after 3-6 months, then annually

• Diabetic diet

• Exercise minimises central obesity

• Drug - metformin (watch for lactic acidosis)
Understanding and Responding to Adverse Events

- Failure to monitor, observe or act
- Delay in diagnosis
- Incorrect assessment
- Loss of patient-data or poor or inadequate note-keeping
- Failure to ensure all equipment in good working order
- Deviation from agreed upon protocols, use of incorrect protocol
- Failure to seek help
- Incorrect treatment given


Dr Dave Spencer 2008
Adverse reactions

- can be divided into abnormal LABORATORY blood tests and CLINICAL abnormalities eg rash
- side effects can be divided into acute (days to weeks), subacute and chronic (weeks to months) AND common or rare
- mild (minor) or severe (major), temporary or permanent
- Graded according to severity:
  - Grade I and II = mild
  - Grade III and IV = severe

Remember: Common things are common!
Side effects (adverse events)

- Temporary
  - AZT
    - tiredness, nausea, flu-like symptoms
- Mild (minor)
  - rash, hepatitis
- Acute
- Common
- Permanent
  - lipoatrophy
- Major (severe)
  - Lactic acidosis
  - Stevens Johnson syndrome
- Chronic
  - lipoatrophy
- Rare
  - Lactic acidosis
It is important to establish the cause of symptoms or signs:
- AIDS
- other drugs eg TB drugs
- IRIS
- Opportunistic infections
- is it due to the ARVs
Grading of abnormal ALT

- ALT = alanine transaminase
- A sensitive laboratory blood test (red top tube – clotted blood) to detect abnormal liver function
- U.L.N. = upper limit of normal
- NHLS reference range = 0 – 40
- A result over 40 is therefore ABNORMAL

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 -100</td>
<td>100 -200</td>
<td>200 - 400</td>
<td>More than 400</td>
</tr>
</tbody>
</table>

Action on results!

• Grade 1 and 2
  – continue ARVs; repeat test 2 weeks after the initial test and reassess

• Grade 3
  – continue ARVs; repeat test 1 week after initial test and reassess; if ALT still Grade 3 consult expert (stop ARVs)

• Grade 4
  – consult expert immediately before stopping ARVs
Laboratory abnormalities

<table>
<thead>
<tr>
<th>ITEM</th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>8.0-9.4 g/dL</td>
<td>7.0-7.9 g/dL</td>
<td>6.5-6.9 g/dL</td>
<td>&lt;6.5 g/dL</td>
</tr>
<tr>
<td>Absolute Neutrophil Count</td>
<td>1.0-1.5 X 10⁹/L</td>
<td>0.75-0.99 X 10⁹/L</td>
<td>0.5-0.749 X 10⁹/L</td>
<td>&lt;0.5 X 10⁹/L</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>1.25-2.5 X upper normal limit</td>
<td>&gt;2.5-5 X upper normal limit</td>
<td>&gt;5-10 X upper normal limit</td>
<td>&gt;10 X upper normal limit</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>3.0-4.51 mmol/L</td>
<td>4.52-8.48 mmol/L</td>
<td>8.49-13.56 mmol/L</td>
<td>&gt;13.56 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&gt;1-1.3 X upper normal limit</td>
<td>&gt;1.3-1.6 X upper normal limit</td>
<td>&gt;1.6-2 X upper normal limit</td>
<td>&gt;2 X upper normal limit</td>
</tr>
</tbody>
</table>
Grading of abnormal FBC

- FBC = full blood count (purple top tube – unclotted)
- diff = “differential” = looks at the number of different white blood cells
  - neutrophils (bacterial infections)
  - Lymphocytes (viral infections)
  - Eosinophils (parasitic infections)
  - basophils
  - monocytes
Differential count – neutrophils

- expressed as a percentage (%) of the total white cell count (WCC)
- e.g. total WCC = \(2.3 \times 10^9 \text{ /L (2300)}\)
- neutrophil percentage = 12%

- absolute neutrophil count = \(2300 \times \frac{12}{100} = 276\)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 to 1500</td>
<td>750 to 1000</td>
<td>500 to 750</td>
<td>Less than 500</td>
</tr>
</tbody>
</table>
Clinical abnormalities

<table>
<thead>
<tr>
<th>ITEM</th>
<th>GRADE 1 TOXICITY</th>
<th>GRADE 2 TOXICITY</th>
<th>GRADE 3 TOXICITY</th>
<th>GRADE 4 TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraesthesia (burning, tingling, etc.)</td>
<td>mild discomfort; no treatment required</td>
<td>moderate discomfort; non-narcotic analgesia required</td>
<td>severe discomfort; OR narcotic analgesia required with symptomatic improvement</td>
<td>incapacitating; OR not responsive to narcotic analgesia</td>
</tr>
<tr>
<td>Neuro-sensory</td>
<td>mild impairment (decreased sensation, e.g. vibratory, pinprick, hot/cold in great toes in focal area or symmetrical distribution)</td>
<td>moderate impairment (moderate decrease in sensation, e.g. vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical</td>
<td>severe impairment (decrease or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e. upper and lower extremities)</td>
<td>sensory loss involves limbs and trunk.</td>
</tr>
<tr>
<td>Cutaneous / Rash / Dermatitis*</td>
<td>erythema, pruritus</td>
<td>diffuse, maculopapular rash OR dry desquamation</td>
<td>vesiculation OR moist desquamation OR ulceration</td>
<td>exfoliative dermatitis OR mucous membrane involvement OR erythema multiforme OR suspected Stevens-Johnson syndrome OR necrosis requiring surgery</td>
</tr>
<tr>
<td>Regimen</td>
<td>Test</td>
<td>Frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T / 3TC / NVP</td>
<td>• CD4</td>
<td>• Staging, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• VL</td>
<td>• <strong>Baseline</strong>, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ALT</td>
<td>• Baseline, week 2, 4 and 8, thereafter 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T / 3TC / efavirenz</td>
<td>• CD4</td>
<td>• Staging, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• VL</td>
<td>• <strong>Baseline</strong>, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT / 3TC / NVP (during pregnancy)</td>
<td>• CD4</td>
<td>• Staging, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• VL</td>
<td>• 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FBC and white cell diff</td>
<td>• Baseline and monthly until delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ALT</td>
<td>• Baseline, week 2, 4, thereafter monthly until delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZT / ddI / lopinavir / ritonavir</td>
<td>• CD4</td>
<td>• Staging, 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• VL</td>
<td>• 6 monthly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FBC and white cell diff</td>
<td>• baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) thereafter. (Monthly during pregnancy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fasting cholesterol and triglyceride</td>
<td>• baseline, 6 months and thereafter every 12 months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fasting glucose</td>
<td>• Every 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Staging** = initial testing for all patients when being referred for antiretroviral therapy
- **Baseline** = testing for ARV eligible patients, at initiation of ARVs
Nevirapine initiation

• Daily for first 2 weeks: remember to
  – Cross off evening or morning dose on adherence sheet and counsel
  – Inform patient of need for blood test at 2 weeks
  – Remind patients to bring pills for pill count
  – Remind patient to bring adherence sheet

• Twice daily thereafter: remember to
  – Counsel regarding change of dosage

NB: check 2 week ALT at 4 week visit
# Adverse Drug Reaction and Product Quality Problem Report Form

**Patient Information**

<table>
<thead>
<tr>
<th>Name (or initial)</th>
<th>Age</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Reaction/Product Quality Problem**

- **Adverse reaction**
- **Date of onset of reaction**
- **Time of onset of reaction**

**Description of reaction or problem**

**Medicines/Vaccines/Devices**

<table>
<thead>
<tr>
<th>Trade name and batch No.</th>
<th>Daily dosage</th>
<th>Route</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Reasons for use</th>
</tr>
</thead>
</table>

**Adverse Reaction Outcome**

- **Death**
- **Disability**
- **Congenital anomaly**
- **Required intervention to prevent permanent impairment/damage**
- **Life-threatening hospitalisation**
- **Other**
- **Event reappeared on rechallenge**
- **Treatment of reaction**
- **Rechallenge not done**
- **Recovered**
- **Sequelae**

**Comments**

- Relevant history, allergies, previous exposure, baseline test results/lab data

**Product Quality Problem**

- **Trade name**
- **Batch No.**
- **Registration No.**
- **Dosage form and strength**
- **Expiry date**
- **Size/Type of container**

**Product available for evaluation?** Y/N

**Reporting Doctor/Pharmacist etc.**

- **Name**
- **Qualifications**
- **Address**
- **Signature**
- **Date**
- **Tel:**...

---

This report does not constitute an admission that medical personnel or the product caused or contributed to the event.
Metabolic interactions: the Cytochrome P450 enzyme system

Cytochrome P450 substrates:
- 1A2, 2C19, 2C9, 2D6, 2E1, 3A4, 5, 6

Inducer:
- rifampicin
- NNRTIs
- protease inhibitors
- antiepileptics
- St John’s wort

Inhibitor:
- protease inhibitors

Metabolite/s
- protease inhibitors
- NNRTIs
- protease inhibitors
- antiepileptics
- St John’s wort

Substrates:
- protease inhibitors
- NNRTIs
- benzodiazepines
- oral contraceptives
- HMG coA reductase inhibitors
Remember – dosage adjustment in renal failure

- formula to estimate creatinine clearance (CrCl) in ml/min:
  \[
  \frac{(140 - \text{age}) \times \text{weight (Kg)}}{0.82 \times \text{serum creatinine (µmol/L)}}
  \]

For women, multiply the GFR by 0.85

* Modified formula of Cockroft and Gault

*SAMF 8th Edition p. 15*
# Adult dosages in renal impairment

*bd = 12 hourly*

<table>
<thead>
<tr>
<th>Drug NRTI’s</th>
<th>Cr Cl 10 – 50</th>
<th>Cr Cl &lt; 10</th>
</tr>
</thead>
</table>
| Stavudine d4T | >60kg 20mg bd  
<60kg 15mg bd | >60kg 20mg daily  
<60kg 15mg daily |
| Lamivudine 3TC | 150mg daily | 50mg daily |
| Zidovudine AZT | unchanged | 300mg daily |
| Didanosine ddl | >60kg 200mg daily  
<60kg 150mg daily | >60kg 100mg daily  
<60kg 75mg daily |
Adult dosages in renal impairment

Note: Abacavir (ABC) unchanged  PI’s = protease inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cr Cl 10 - 50</th>
<th>Cr Cl &lt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TDF)</td>
<td>AVOID</td>
<td>AVOID</td>
</tr>
<tr>
<td>PI’s</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
</tbody>
</table>
Saquinavir + ritonavir

Saquinavir / Lopinavir
Intestinal CYP450 Inhibited
Increased Cmax
No effect on half life
Intestinal metabolism

• CYP 3A4 is present in the liver & the small intestine.

• Ritonavir causes a 20 fold increase in saquinavir levels- probably because of CYP3A4 inhibition at both sites.

• Grapefruit juice inhibits CYP 3A4 in the gut- increases saquinavir levels.
<table>
<thead>
<tr>
<th>ART interactions with Rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI’s</strong></td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
</tr>
<tr>
<td><strong>Nevirapine</strong></td>
</tr>
<tr>
<td><strong>Kaletra + Ritonavir</strong></td>
</tr>
<tr>
<td><em>(400/400mg bid)</em></td>
</tr>
<tr>
<td><strong>Ritonavir + Saquinavir</strong></td>
</tr>
<tr>
<td><em>(both 400mg bid)</em></td>
</tr>
<tr>
<td><strong>All the other PI’s</strong></td>
</tr>
</tbody>
</table>
6.2 WEBSITES WITH INFORMATION ABOUT DRUG AND DRUG INTERACTIONS

Food and drug interactions:
www.foodmedinteractions.com

Liverpool HIV Pharmacology Group:
www.hiv-druginteractions.org

HIV/AIDS Treatment Information Service:
www.hivatis.org

Johns Hopkins AIDS Service:
www.hopkins-aids.edu

International Association of Physicians in AIDS Care:
www.iapac.org

Medscape:
www.medscape.com
Herbal remedies

- **St Johns wort** decreases the area under the curve for indinavir by more than 50%
  - *Induction of CYP3A4 and P-glycoprotein.*

- **Garlic supplements** may decrease saquinavir levels
  - *Induction of intestinal CYP450 and P-glycoprotein*

- **In vitro evidence** that *Sutherlandia and “African potato”*
  - *Inhibits cytochrome P450*
Illicit and recreational drugs

• Limited information in the literature regarding drug interactions between illicit drugs and anti-retrovirals.

• Case reports suggest that ritonavir, by inhibition of CYP2D6, can alter the elimination of methylenedioxymetamphetamine (MDMA or ecstasy), and dramatically increase the effects and toxicity of the drug.
Mr D. T.

- 44 year old, HIV infected man
- CD4 :45 cells/mm3. WHO stage 4 (previous oesophageal candidiasis).
- 62 kgs,
- found to have disseminated tuberculosis during ARV work-up. Treated for pulmonary tuberculosis in 2000.
- current medication: co-trimoxazole 160/800mg daily; amitryptiline 25 mg nocte (for symptomatic peripheral neuropathy); ferrous sulphate 1 tablet 3 times daily and folate 5mg daily (for treatment of anaemia).
- started on TB treatment- rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin. 2 weeks later commences 1st line antiretroviral therapy: stavudine 30mg 12 hourly, lamivudine 150mg 12 hourly and efavirenz 600mg nocte.
• How many tablets is this patient taking a day?
• What important adverse effects may his treatment cause?
• What else should he be prescribed?
• Can nevirapine OR lopinavir/ritonavir combination (Kaletra®) be used with rifampicin?
Salvage therapy

• Aspen Pharmaceuticals predicts 50,000 people on salvage treatment by 2010 in Africa
• in Africa, 20 – 25% of 6 million Africans who require ARV’s are receiving them
• increasing to 50 – 60% in the next 4 years
• in 4 – 5 years ± 3.6 million Africans will be on ARV’s

Wound the virus until better treatment becomes available; drug resistant viruses are generally less virulent than the wild type

Deep salvage – keep going as long as the pt. tolerates therapy
Vaccines

- A vaccine is a substance that aims to teach the body’s immune system to disable or destroy germs, like viruses and bacteria, which cause disease.
- Scientists combine small particles that look like different parts of HIV into a sub cut injection.
- A person cannot be infected by using these particles.
- A successful HIV vaccine may teach the immune system to recognize the virus and destroy it if it enters the body.
- A vaccine in not a cure.
Vaccines

• prophylactic vaccines have been under investigation for more than 15 years.

• realistic expectations of a clinically available viable vaccine are 10 years in the future.

• therapeutic vaccines (for use in HIV infected patients in association with HAART) are currently under investigation.

• interested parties:
  • SAAVI
  • Centre for the Study of AIDS
  • The South African HIV Vaccine Action Campaigne [SA HIVAC]
Vaccines and HIV 1 infection

internet sites:

www.iavi.org

International AIDS Vaccine Initiative
Where to get drug – interaction information

• Medicines Information Centre: 021 4066829
• Websites:
  www.medscape.com
  www.hiv-druginteractions.org (Liverpool HIV Pharmacology group)
  www.hopkins-aids.edu
  www.iapac.org
  www.hivinsite.ucsf.edu
  www.tthivclinic.com
  www.unaids.org
  www.who.int
  www.sahivclinicianssociety.org
Golden rules

• ARV’s are NEVER an emergency
• Never stop, change or add to an ARV Regime without consulting an HIV specialist
• Advise patients that ALL drugs have side effects (warn patient/family especially if the CD 4 is LOW)
<table>
<thead>
<tr>
<th>TEST</th>
<th>If patient declines VCT, he/she may be putting his/her health at risk and other (include unborn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST EARLY</td>
<td>Testing LATE means patient will present with a lower CD4 result and may be more susceptible to IRIS</td>
</tr>
<tr>
<td>START TREATMENT EARLY</td>
<td>Starting ARV's when patient is very ill slows recovery time, ↑ likelihood of SE and IRIS</td>
</tr>
</tbody>
</table>
Golden Rules

• Never give EFV to a pregnant woman (avoid ARV’s in the first 3 months of pregnancy) - promote SAFE contraception
• Use NVP if woman of child-bearing age or is planning to start a family
• Do not combine NVP with TB medication as there is a risk for shared toxicity eg hepatitis
• Never combine d4T with AZT as they are both thymidine analogues
Golden rules

- Never combine 3TC with DDI as they are both non-thymidine analogues
- Never re-challenge a patient with ARV’s proven to have previously caused lactic acidosis
- Don’t use EFV if patient has a history of psychosis - side effects include insomnia, delusions, inappropriate behaviour, acute depression, somnolence and vivid dreams
Golden rules

• Take special note of safety bloods:
  - Check ALT at 2 weeks, 4 weeks and 8 weeks if patient is starting NVP even if changing from Efavirenz ( monthly if pregnant )
  - Check FBC and blood differential count if on AZT monthly for 3 months ( monthly if pregnant )

• Take note of special storage requirements of medication:
  - d4T syrup ( Zerit ) should be stored in the fridge once reconstituted and used within 30 days.
  - Kaletra should be kept under 25°C.
  - Remember to ask mom if she has a working fridge
Addendum
# Prices of ART – October 2008

<table>
<thead>
<tr>
<th>Reg</th>
<th>d4T 30mg bd</th>
<th>3TC 150 mg bd</th>
<th>3TC 300 mg daily</th>
<th>EFV</th>
<th>NVP</th>
<th>AZT</th>
<th>TDF</th>
<th>ddl</th>
<th><em>Kaletra Aluvia</em></th>
<th>TOTAL Price (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRICE</td>
<td>17.65</td>
<td>29.91</td>
<td>42.50</td>
<td>108.03</td>
<td>32.11</td>
<td>71.09</td>
<td>159.49</td>
<td>67.83</td>
<td>319.07</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>155.59</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>79.67</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>310.02</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>209.03</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>457.99</td>
<td></td>
</tr>
</tbody>
</table>

TDF = tenofovir  
1a per year = R1867.08  
1b per year = R 956.04