



HIV/Aids Training

Module 3

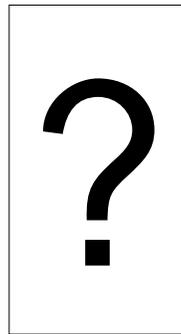
Anti-retroviral Therapy

June 2008

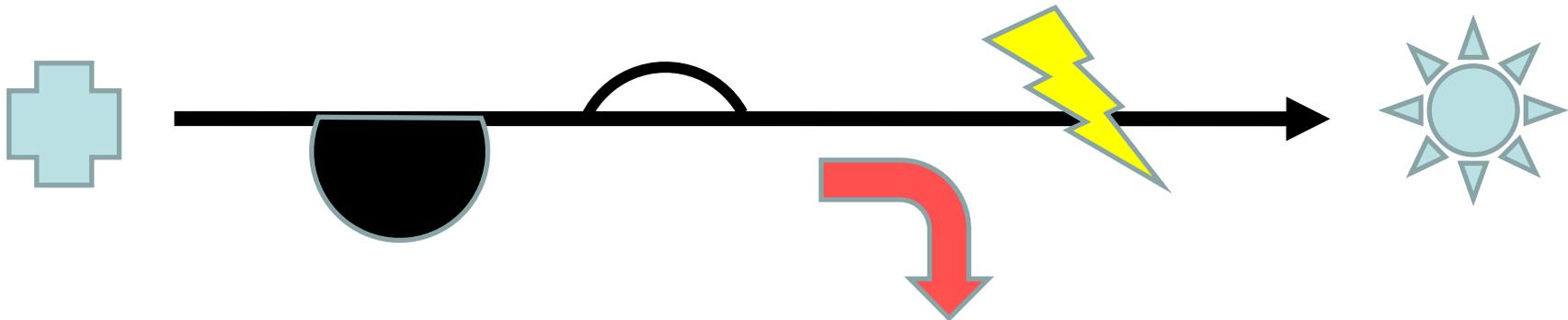
Adapted from and thanks to:

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 adherence”



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

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-naïve 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 expectancies 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/mm³ vs 50.4 [0.4] years for counts of 200 cells/mm³ or more).

HIV treatment bulletin SOUTH
Vol 1 Number 2 p.21
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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

majority

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

- all drugs eg antibiotics, analgesics, anti-malarials have side effects

pros and cons

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

Adherence, 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

Province	No. of ART sites	Population - million	Ratio per clinic
KZN	75	10 (20.9)	0.13
WC	53	4.8 (10.1%)	0.09
GP	54	9.6 (20.2%)	0.18
EC	54	6.9 (14.4%)	0.13
LP	48	5.4 (11.3%)	0.11
MPL	23	3.5 (7.4%)	0.15
FS	22	2.9 (6.2%)	0.13
NW	21	3.4 (7.1%)	0.16
NC	12	1.1 (2.3%)	0.09
TOTAL	362	± 48 million	

When to Start ?

Early Treatment

Benefits

- Easier to control viral load
- Less damage to immune system
- Lower incidence of side effects

Risks

- Potential side effects
- Drug resistance over time
- Limited future drug options
- Negative effects on quality of life

Delayed Treatment

Benefits

- Avoid negative effects on quality of life
- Avoid side effects
- Less risk of drug resistance
- Preserve future drug options.

Risks

- Possible permanent immune system damage
- Difficult to control viral load
- Increased incidence of side effects

“Guidelines”

Site manuals and Protocols

country ?

< 350 ?

< 250 ?

< 200 ?

province ?

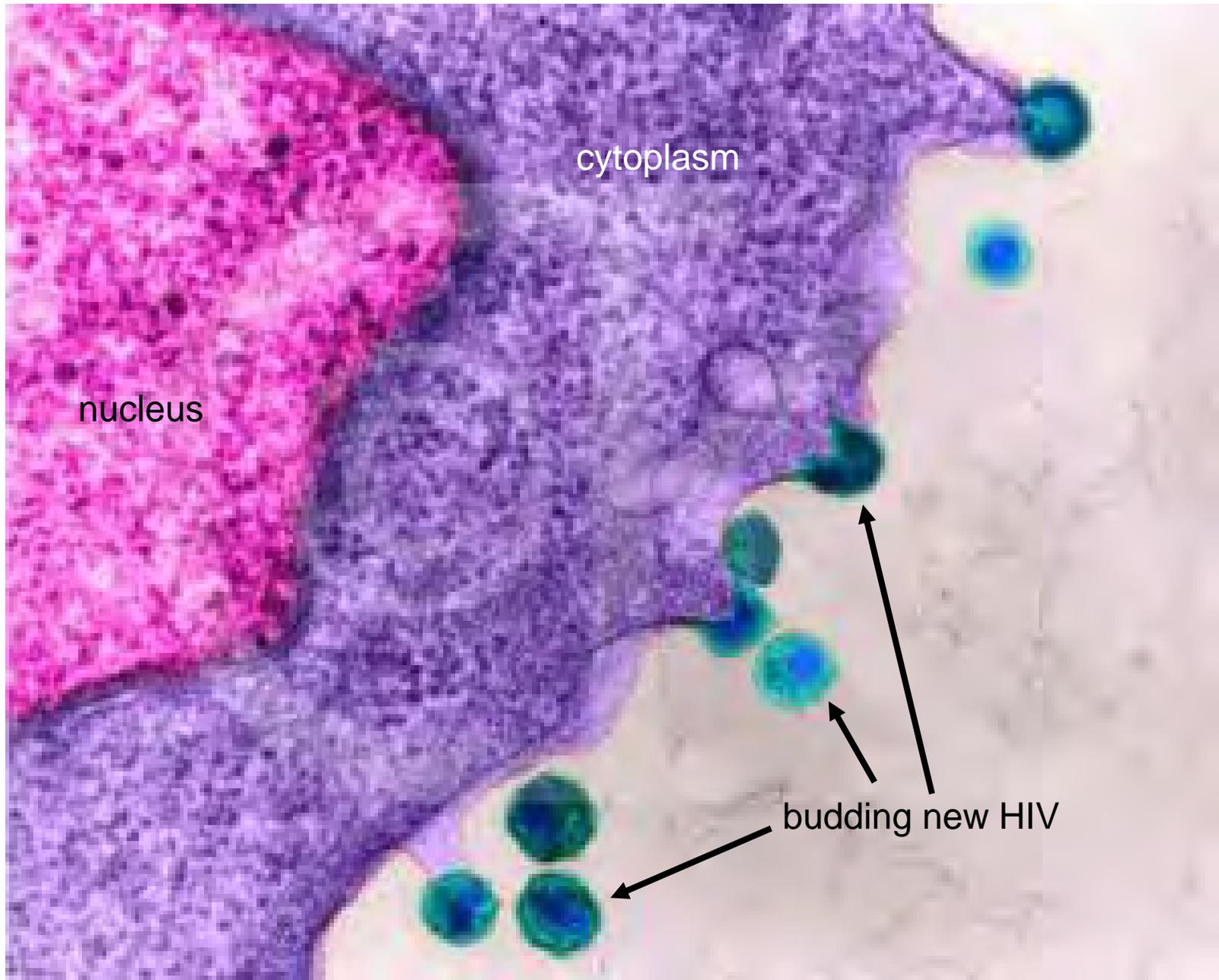
TB ?

staff training
and experience ?

pregnant ?

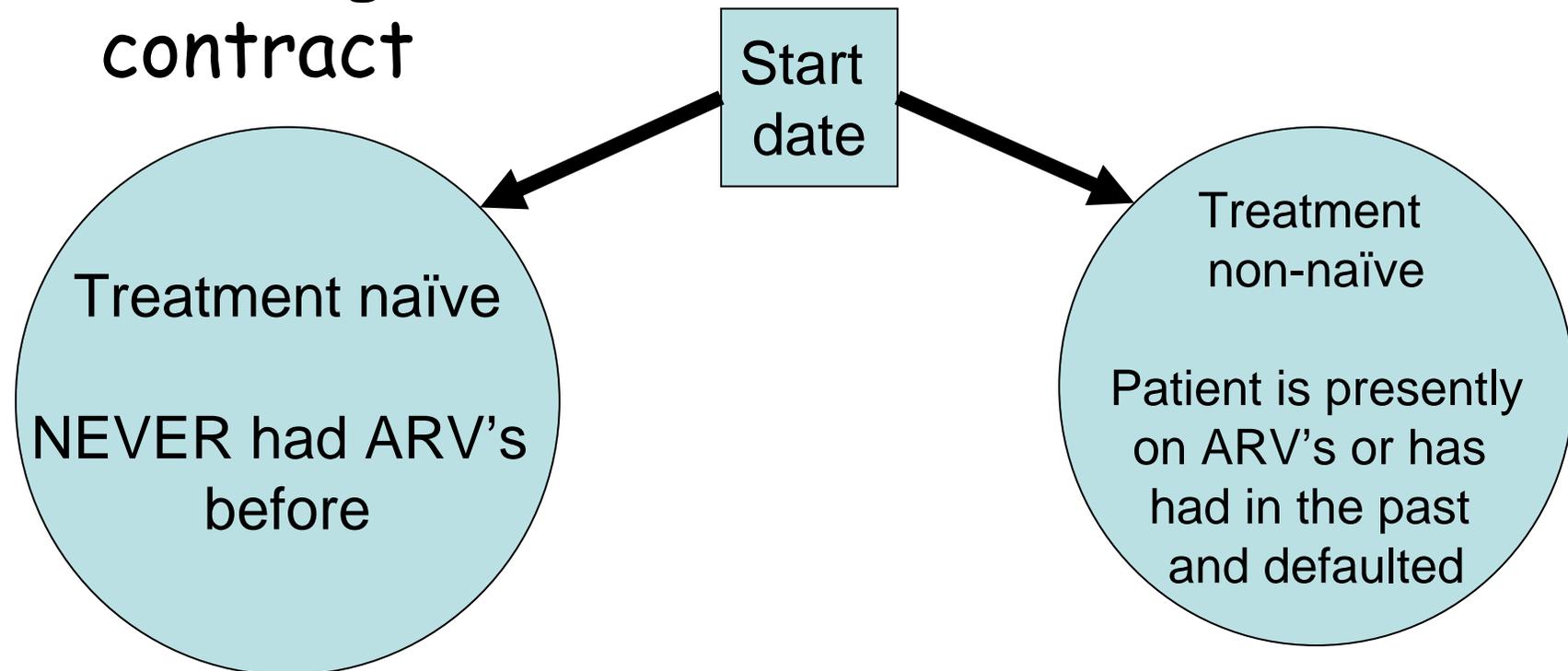
age ?

Leucocyte with new HIV viruses



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

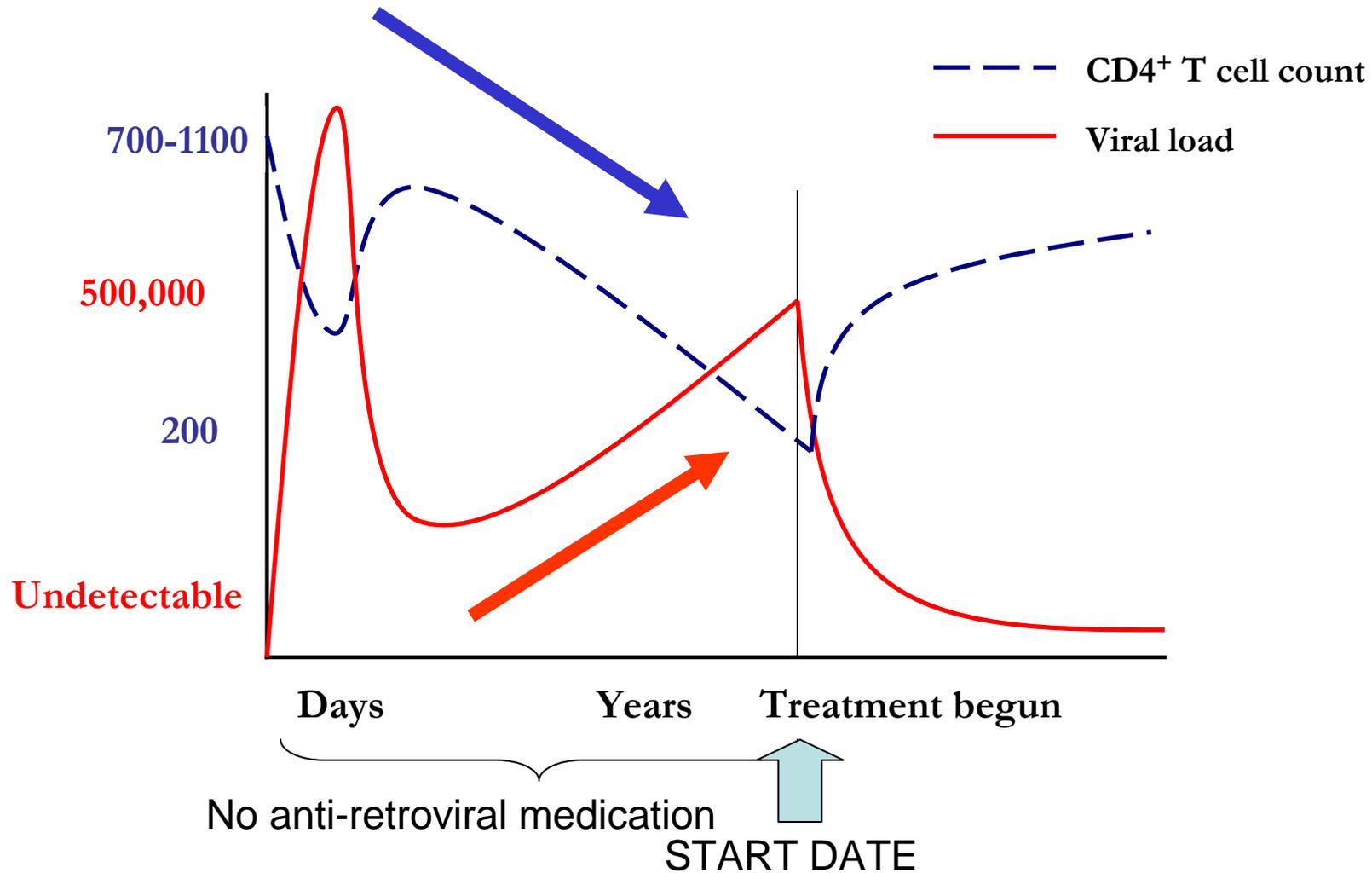


Predictors of mortality in patients initiating ARVs

- study at McCords Hospital, Durban, KZN 1999 – 2004 on 309 patients
- strongest predictors:
 - *CD4* cell count < 50 / μ l
 - *haemoglobin* < 8g / dl
 - a history of *oral candidiasis*
 - history of *cryptococcal meningitis*
 - TB was not a significant predictor

? surrogate marker for undiagnosed OI

The effect of ARVs

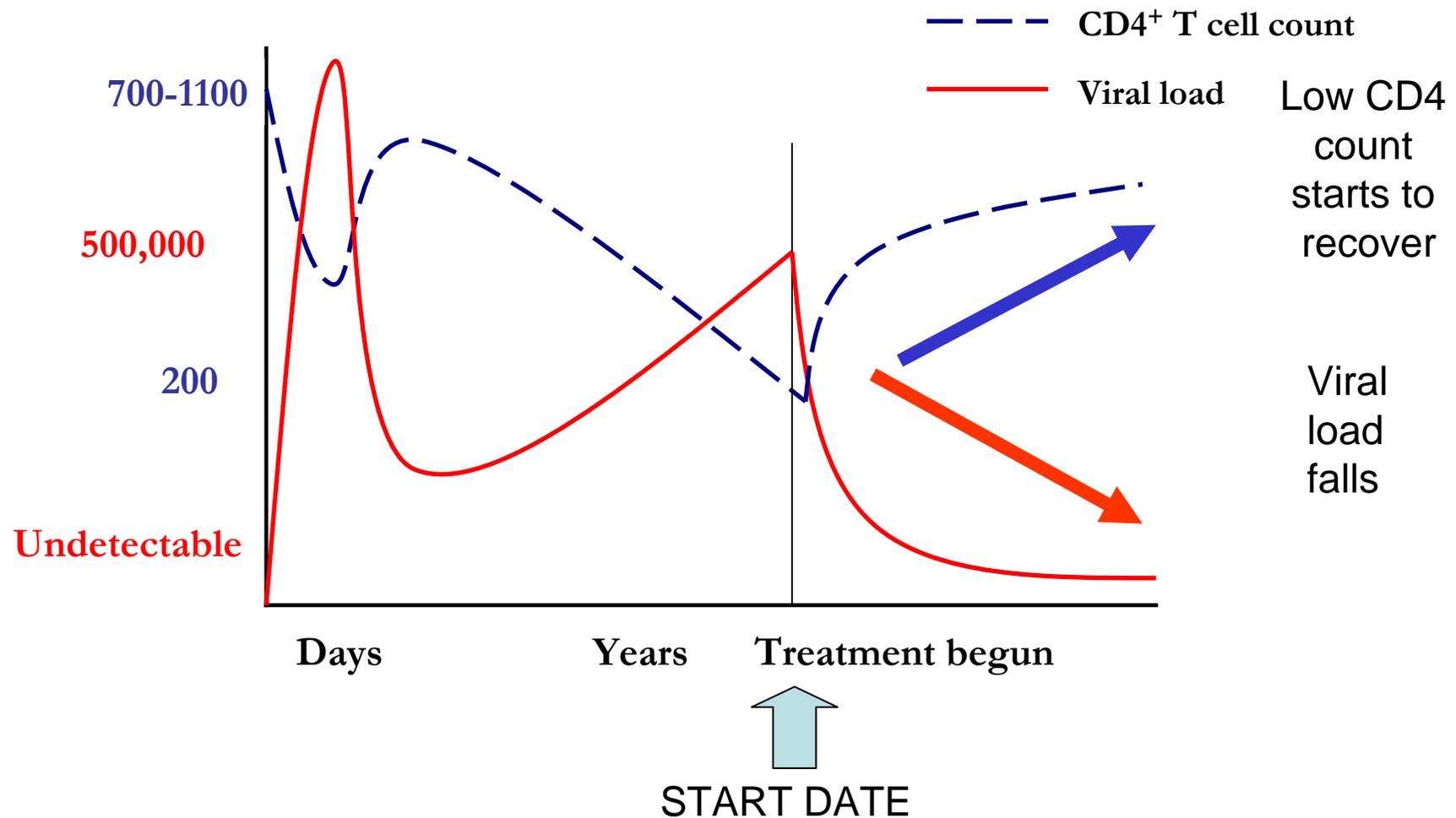


ARV treatment

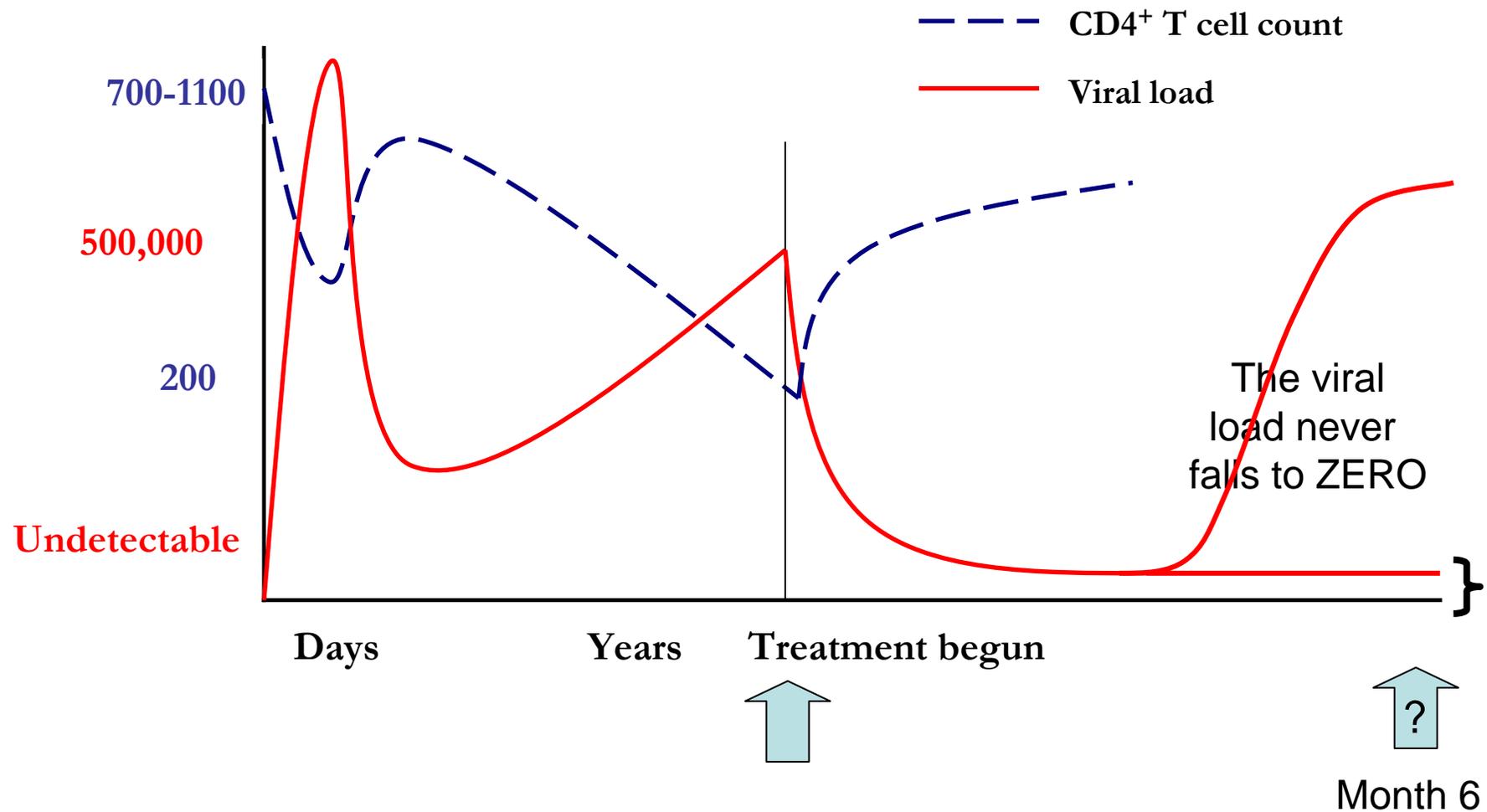
IMMUNE

RECOVERY

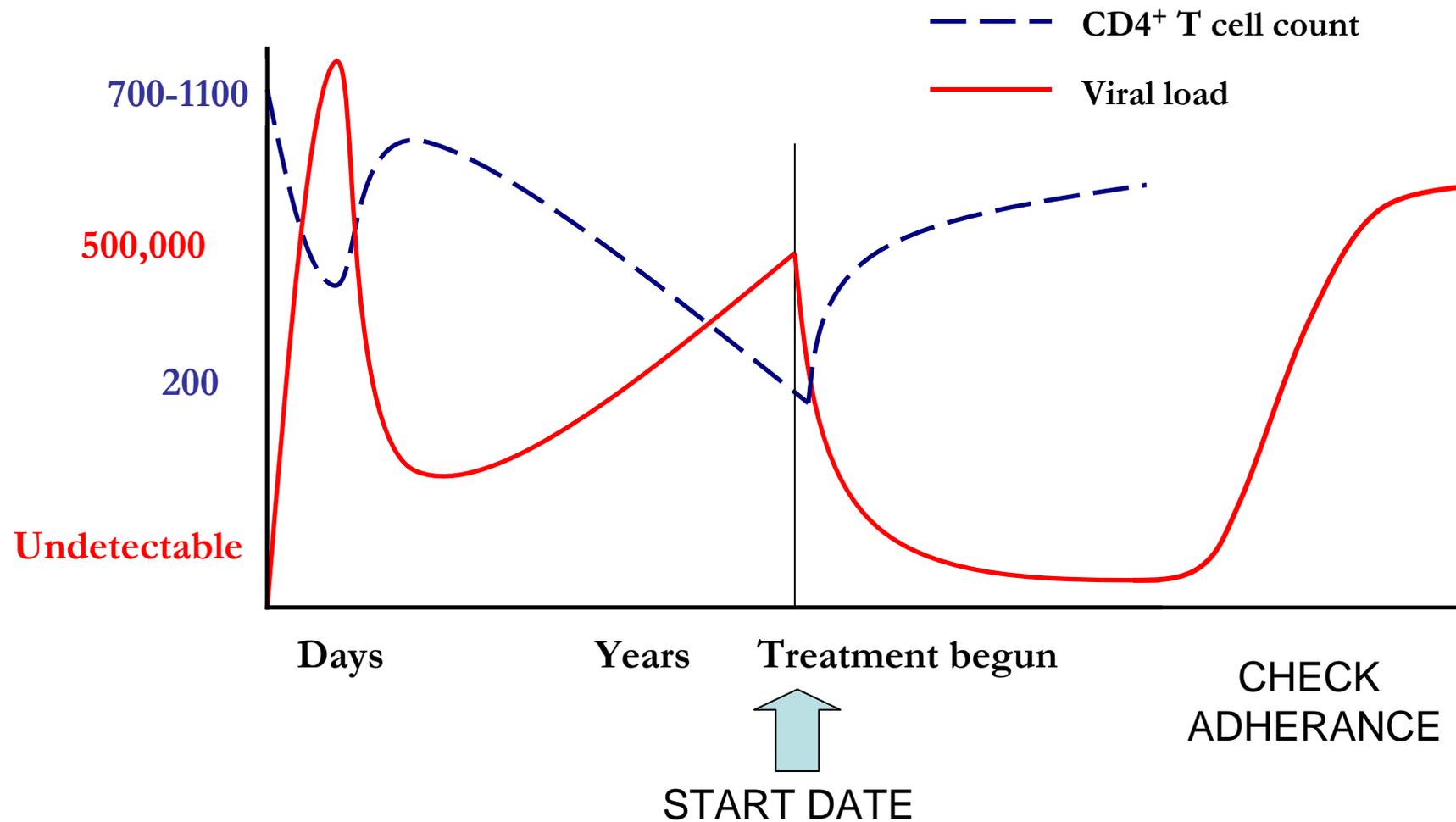
The effect of ARVs



The effect of ARVs



The effect of ARVs



Mechanism of Action

Nucleoside reverse transcriptase inhibitors

- mimic DNA building blocks
- prematurely terminate the growing DNA chain

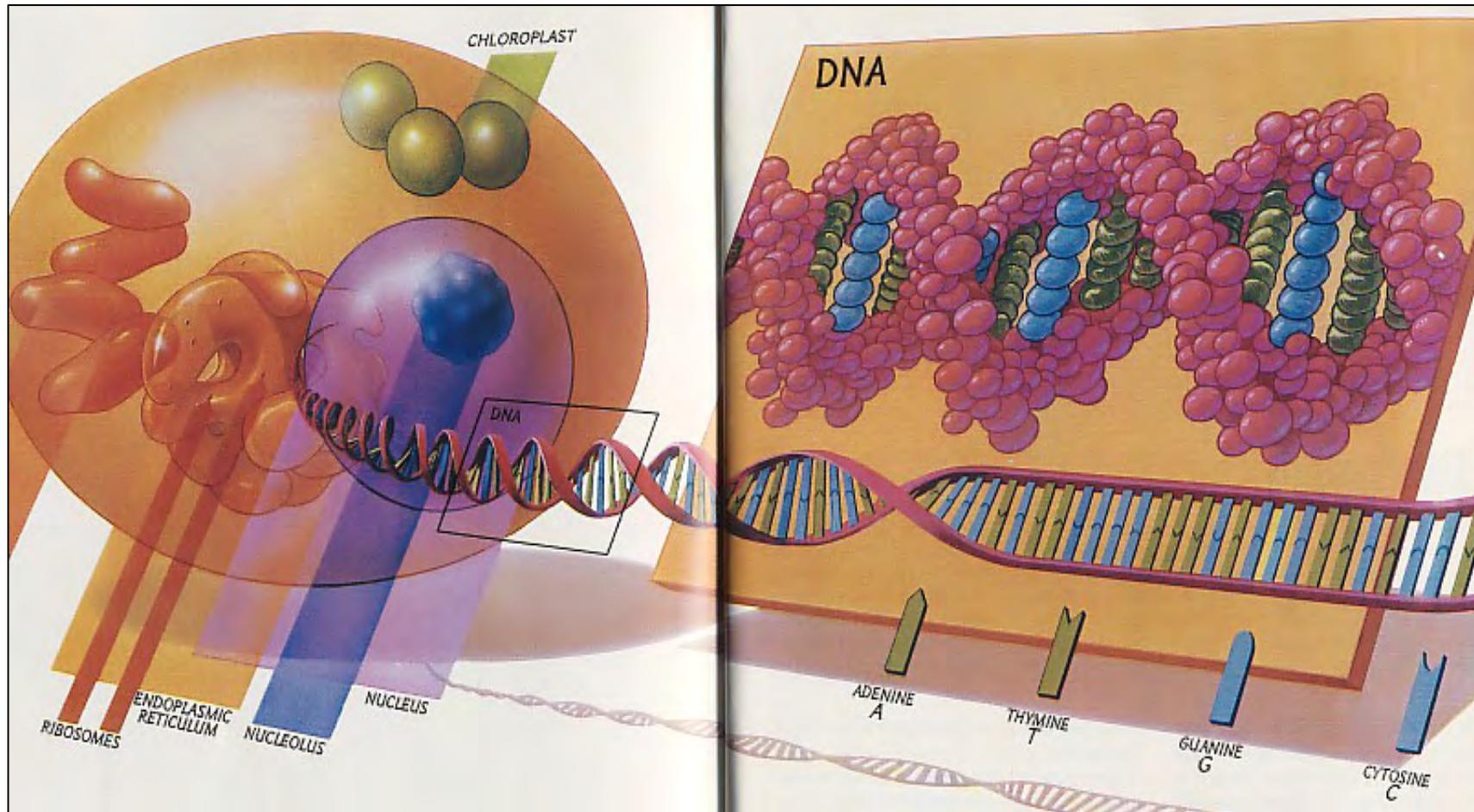
Non-nucleoside reverse transcriptase inhibitors

- 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

adenine

thymine

guanine

cytosine

Nucleic acid analogues

didanosine

AZT, d4T

ABC, TDF

3TC, FTC

HIV virus

- the virus codes for 3 *enzymes*

- Reverse Transcriptase

- Integrase

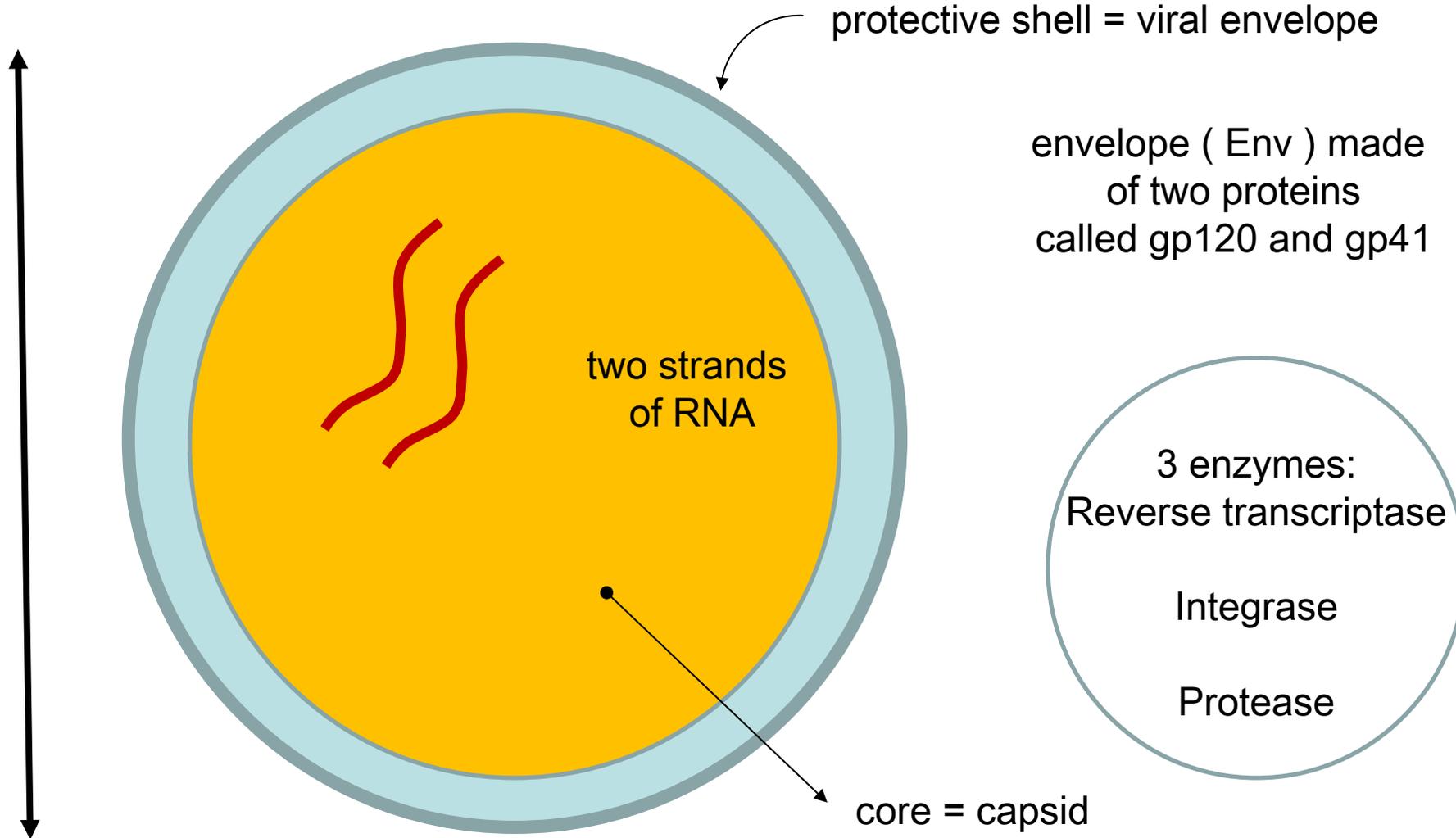
- Protease

any drug *that interferes*
with these enzymes
suppresses viral
replication

- a single HIV virus particle is called a *virion*
- it needs co-receptors for binding called CCR5 (R5) and CXCR4 (X4)

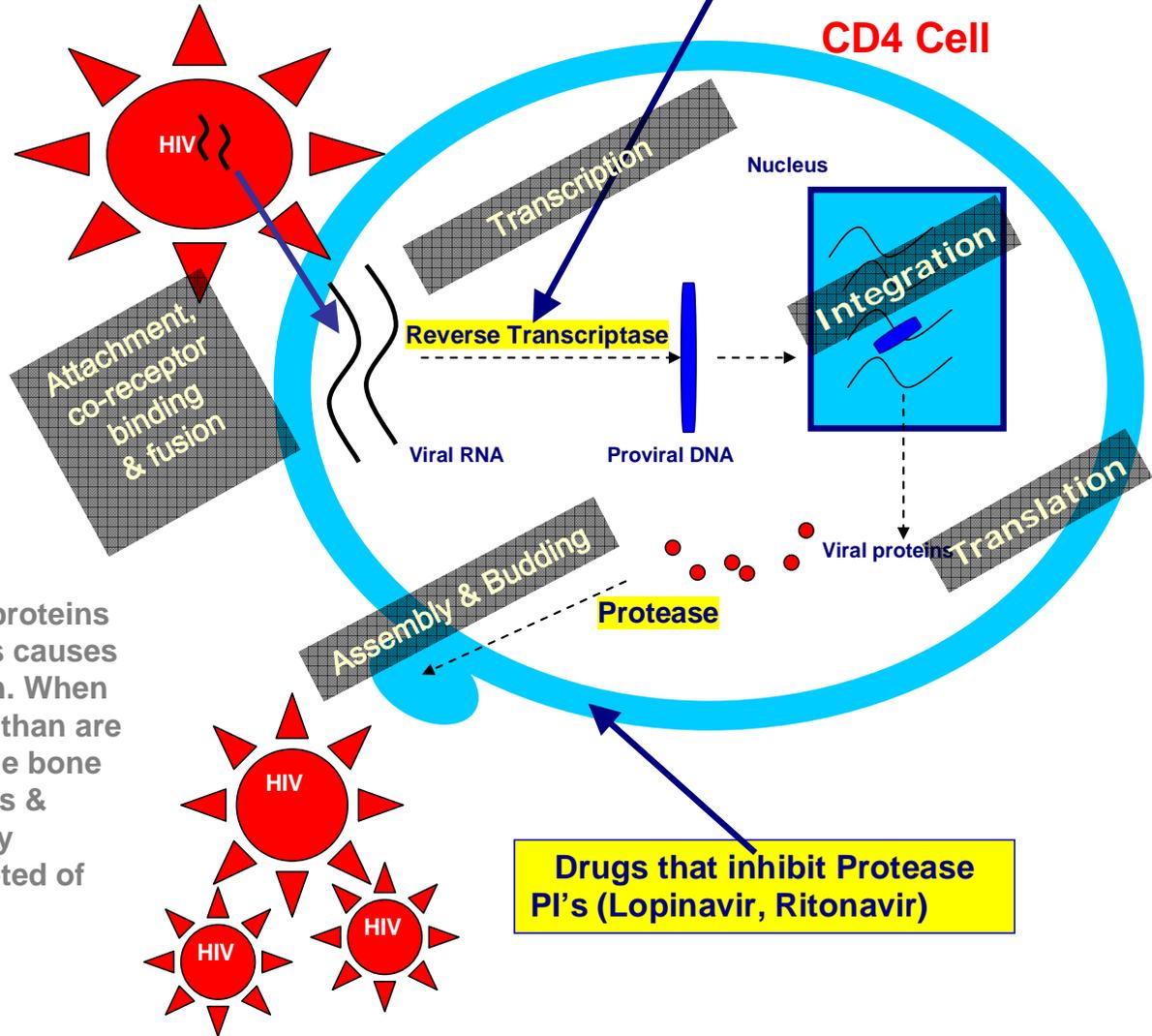
HIV virus structure

1 / 10 000mm
diameter



HIV virus releases viral RNA & Reverse Transcriptase into CD4 cell

Drugs that inhibit Reverse Transcriptase
NRTI's (3TC, D4T) & NNRTI's (Nevirapine, Efavirenz)



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

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

Approved ARV Agents Included in WHO's ARV Guidelines

Nucleoside Reverse Transcriptase Inhibitor		Non - Nucleoside Reverse Transcriptase Inhibitor		Protease Inhibitor
N _s RTI		N _t RTI		PI
Thymidine analogues	Non-Thymidine analogues			
zidovudine (ZDV, AZT) stavudine (d4T)	didanosine (ddI) lamivudine (3TC) Abacavir (ABC)	tenofovir disoproxil fumarate (TDF)		Nevirapine (NVP) Efavirenz (EFV)
			or 1a 1b	Saquinavir (SQV) Ritonavir (RTV) Indinavir (IDV) Nelfinavir (NFV) Lopinavir/ritonavir (LPV/r)

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

Nucleoside Reverse Transcriptase Inhibitor		Non - Nucleoside Reverse Transcriptase Inhibitor		Protease Inhibitor
N _s RTI		N _t RTI		PI
Thymidine analogues	Non-Thymidine analogues			
zidovudine (ZDV, AZT) stavudine (d4T)	didanosine (ddI) lamivudine (3TC) Abacavir (ABC)	tenofovir disoproxil fumarate (TDF)	Nevirapine (NVP) <u>Efavirenz (EFZ)</u>	Saquinavir (SQV) Ritonavir (RTV) Indinavir (IDV) Nelfinavir (NFV) Lopinavir/ritonavir (LPV/r)



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

Category I	Category II	Category III	Category IV	Category V
NRTI Thymidine analogues	NRTI Non-thymidine analogues	NRTI	NNRTI	PI
Stavudine (d4T) Zidovudine (AZT)	Didanosine (ddI) Zalcitabine (ddC) Lamivudine (3TC)	Abacavir (ABC)	Nevirapine (NVP) Efavirenz (EFV)	Nelfinavir (NFV) Indinavir (IDV) Ritonavir (RIV) Saquinavir (SQV) Liponavir/ Ritonavir
<p>For initiation, combine one drug from category I, one from category II and one from category IV.</p>				

Stavudine



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

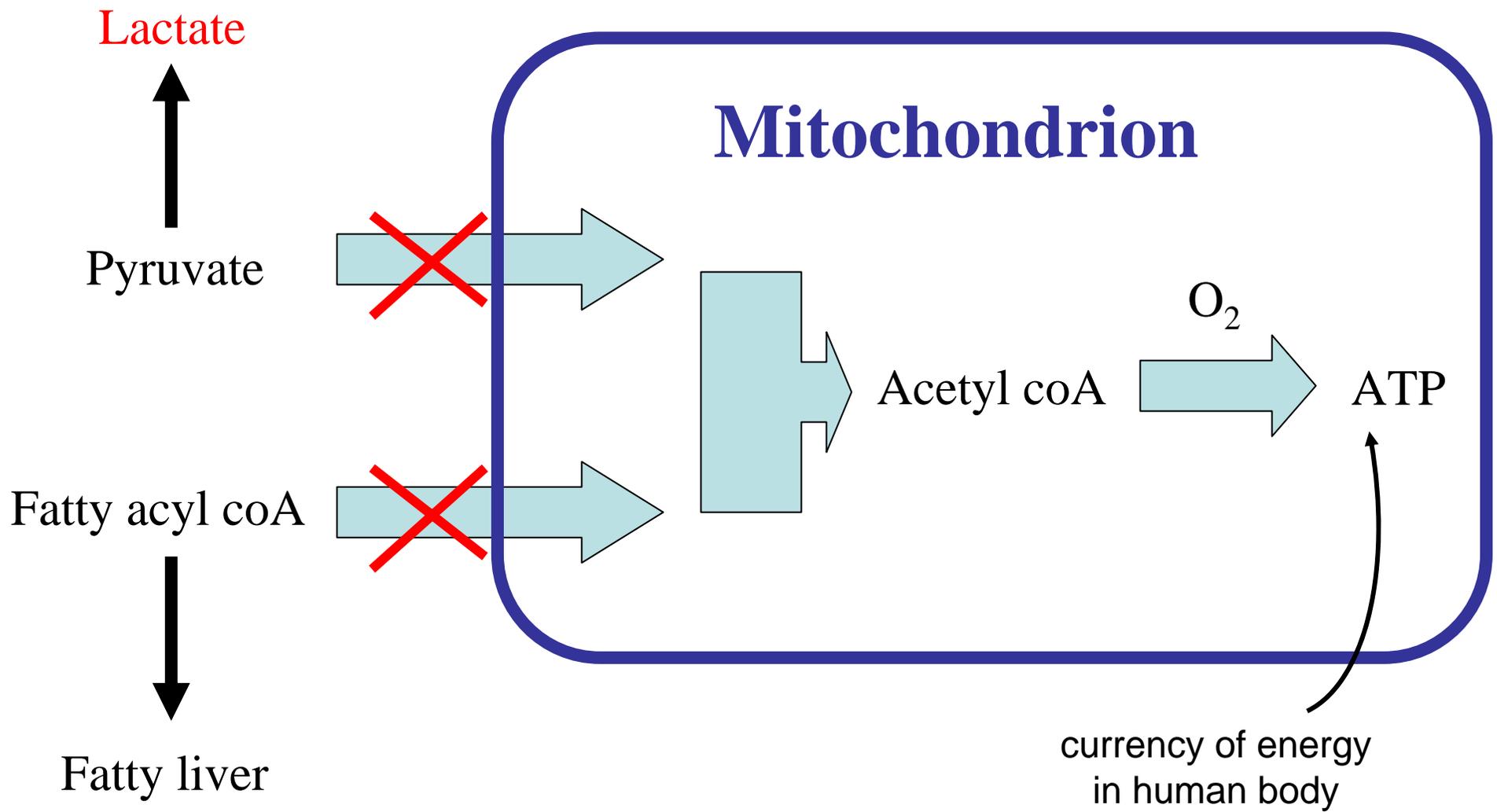
Remember : Common things are common !

NRTI Dosage & Side Effects

Chemical Name	Nucleoside Analogue	Brand Name	Generics (SA)	Adult Dose	Common side effect profile
Stavudine (d4T)	Thymidine	Zerit (BMS)	<u>Aspen</u> Stavir (20mg/30mg/40mg) <u>(Cipla)</u> (30mg/40mg)	>60kg 40mg bid < 60mg 30mg bid	Peripheral neuropathy, Lipoatrophy syndrome, Lactic acidosis <i>hepatitis (7-16%)??</i>
Zidovudine (AZT)	Thymidine	Retrovir (GSK)	<u>Aspen</u>	250mg bid 300mg bid 200mg tds	Nausea, headache, Neutropaenia, Anaemia, <i>hepatitis (7-16%)??</i>
Lamivudine (3TC)	Cytosine	3TC (GSK)	<u>Aspen</u> Lamivudine	150mg bid	Generally well tolerated Infrequent diarrhoea; peripheral neuropathy; pancreatitis
Didanosine (ddI)	Adenosine	Videx (BMS)	<u>Aspen</u>	>60 kg: 200mg bid OR 400mg daily 60 kg: 125mg bid OR 250mg daily (on empty stomach)	Nausea, diarrhoea, Nasty taste Pancreatitis Peripheral Neuropathy <i>hepatitis (7-16%)??</i>
Abacavir (ABC)	Guanosine	Ziagen (GSK)		300mg bid	Hypersensitivity reaction (+/- 5%)

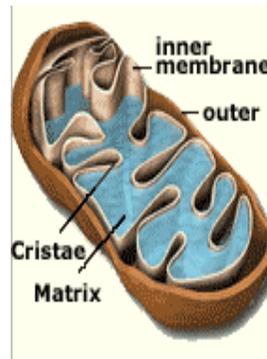
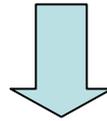
Mitochondrial Toxicity

- 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 it's ability to inhibit mtc polymerase- γ .

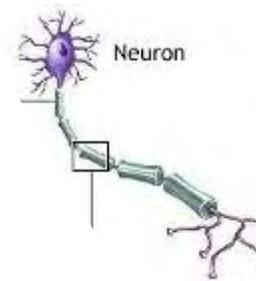
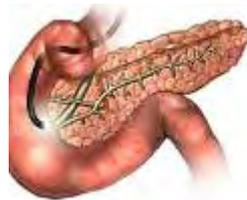
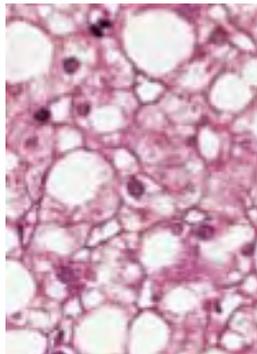
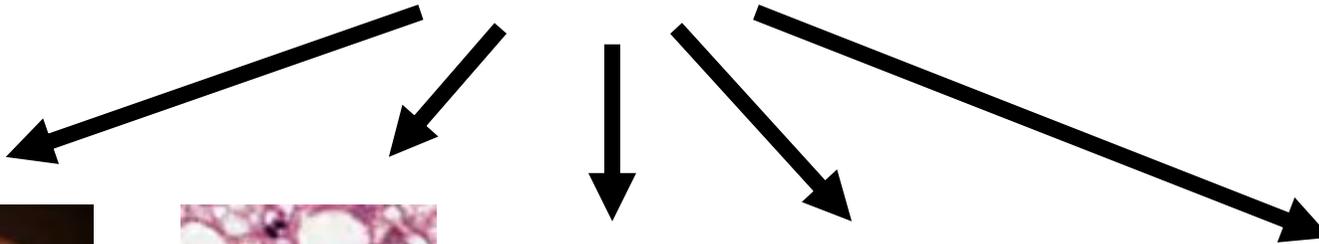


Nucleoside Reverse Transcriptase Inhibitors (NRTI's)

(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



Accutrend[®] Lactate

POINT OF CARE TESTING

Accutrend[®] Lactate

- Zur Selbstanwendung geeignet
- Suitable for self-testing
- Adatto all'autocontrollo
- Utilisable en autocontrollo
- Apto para el autocontrol
- Adequado para o autocontrollo
- Avandó für sjálfkontroll
- Voor zelfcontrole
- Eignet für egenkontroll
- Eignet für hjemmemåling
- Omseurantaos varten
- Κατάλληλο για μετρήσεις από τον ίδιο τον ασθενή
- Przydatne w samokontroli
- Vhodné pro selfmentoring

- Användningen till lagring av två saktinvardein med två datum och användarens identifikations
- Spekt fuokkaintervall
- 100 saktinvardein jaa 100 millisekond med två dato og bruger ID
- Αυτοεπιβεβαιώνεται η σωστή κλιμακωμένη βαθμίδα
- 100 minuter för användare, klockenslote, dato og brukeridentifikasjon
- Με ένδειξη 100 αποστολες/ώραν μετρήσης, valokkio με ημερομηνία και ύψος
- 2 saktinvardein του χρήστη
- 2 saktinvardein na 100 pomiarów mleczanu, z godziną, datą i identyfikacją użytkownika
- 2 saktinvardein na 100 hodnot kyseliny mliecnej včetné času a data měření a identifikaceho kódu uživatele



Roche Diagnostics®

Bottle of
test strips
(25)*



Portable hand-held
lactate machine

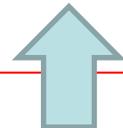
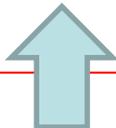
* Remember to order MORE strips from the *pharmacist* when bottle nearly empty

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



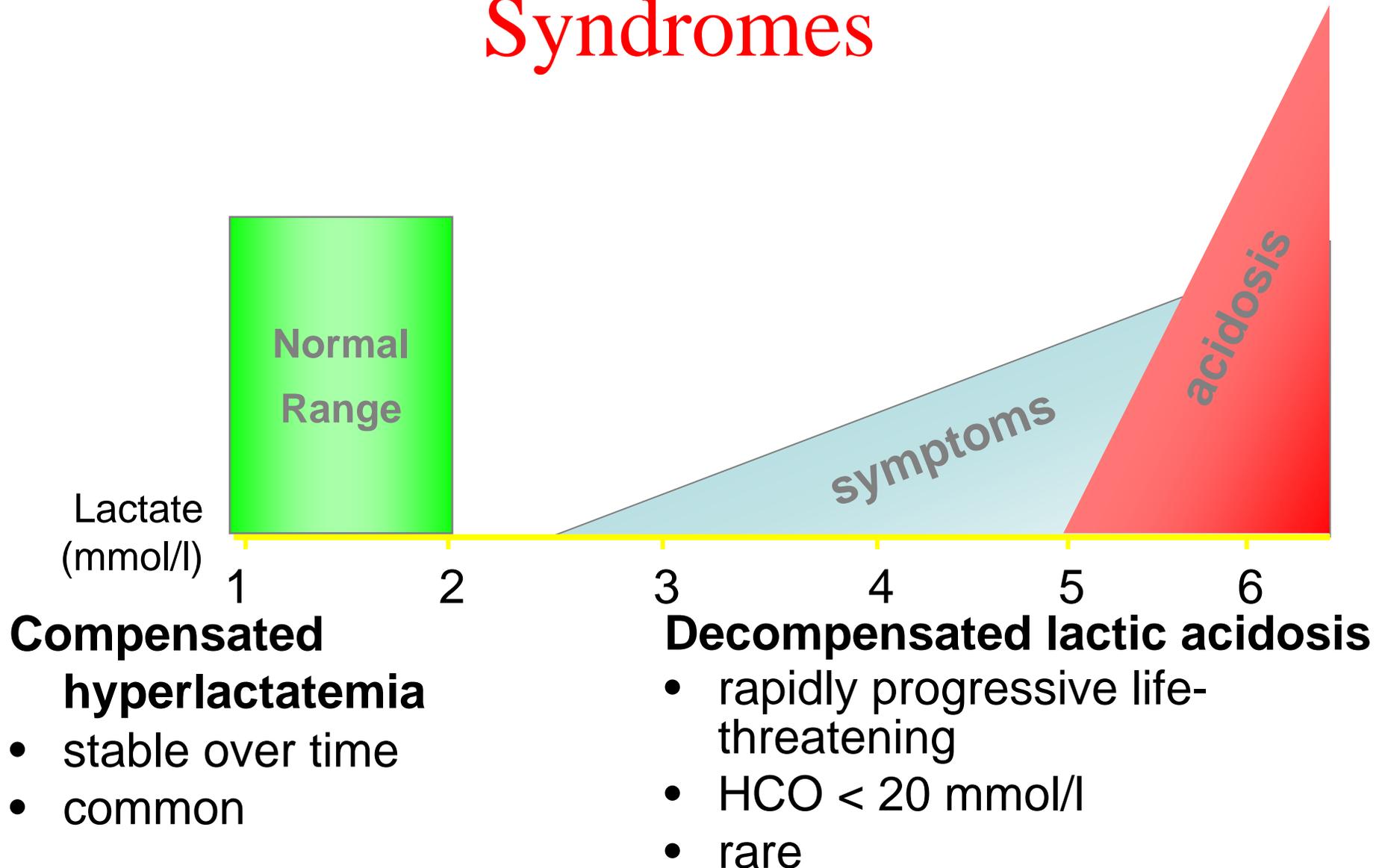
Risk factors

- 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



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 – 5mmol/l and bicarbonate > 20mmol
 - monitor regularly and check blood lactate again in 3 days, then weekly till normalised
 - change stavudine to zidovudine

may take up to 3 months
average 51 days

WC – switch d4T to tenofovir

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
- nevirapine or efavirenz

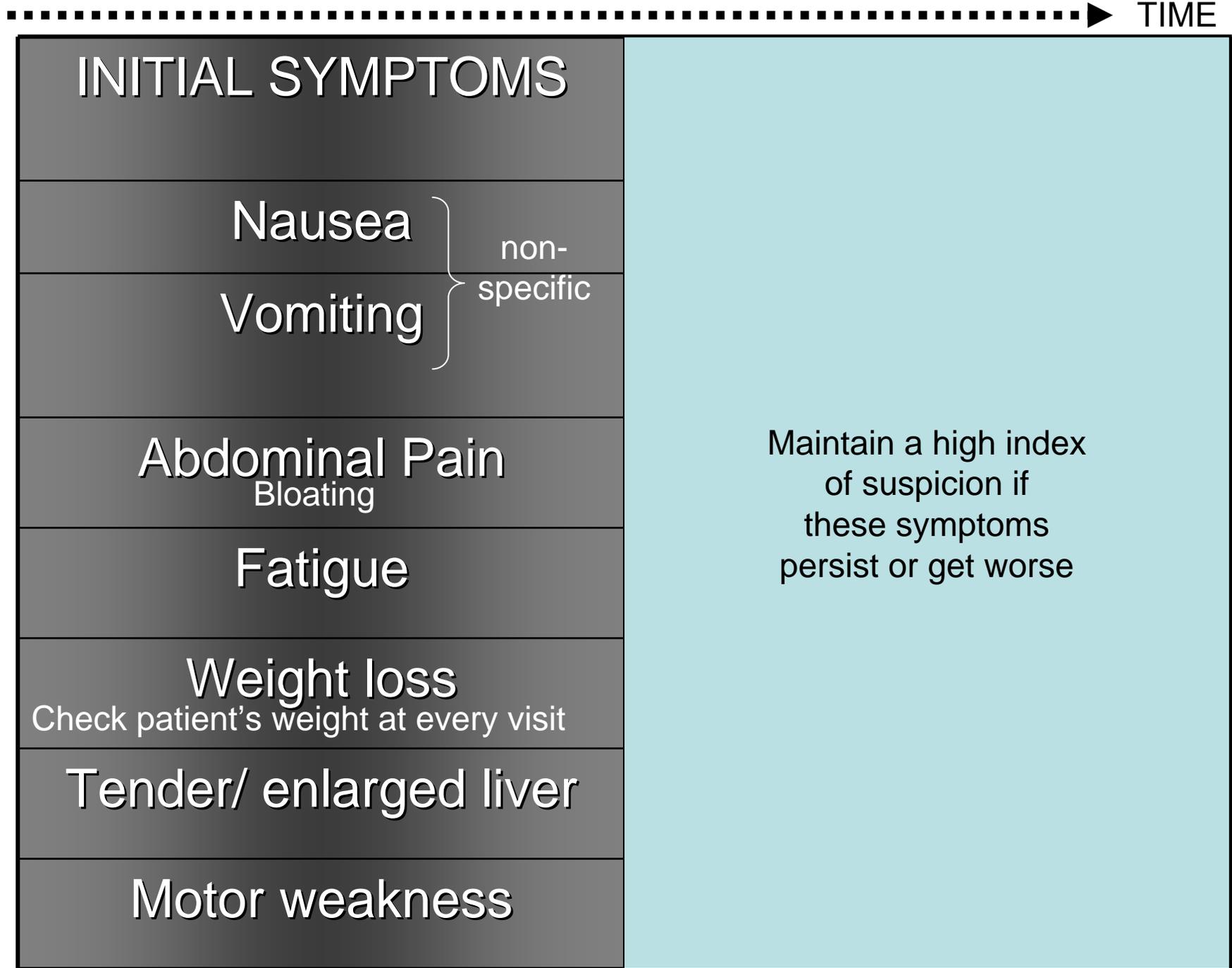
Lactic Acid Management

- 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

NEVER
rechallenge
with d4T

Boosted *Kaletra*[®]

WC - Do NOT use tenofovir



INITIAL SYMPTOMS

Nausea

Vomiting

non-specific

Abdominal Pain
Bloating

Fatigue

Weight loss
Check patient's weight at every visit

Tender/ enlarged liver

Motor weakness

Maintain a high index of suspicion if these symptoms persist or get worse

INITIAL SYMPTOMS	SUBSEQUENT SYMPTOMS
Nausea	Shortness of breath
Vomiting	Tachypnoea and Hyperventilation
Abdominal Pain Bloating	Liver or renal failure
Fatigue	Clotting abnormalities
Weight loss Check patient's weight at every visit	Seizures
Tender/ enlarged liver	Cardiac Dysrhythmias
Motor weakness	Death

} non-specific

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

Suspicious symptoms and signs

Risk factors:

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

- 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

Repeat lactate in 3 days, then weekly until normal

Rather stop HAART and get expert advice if:

1. lactate cannot be monitored
2. symptoms severe
3. NRTI other than D4T causative
4. symptoms worsen or lactate continues 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

See guidelines for drug choices for restarting HAART once lactate has normalised. Consult expert. Never use d4T or ddI again.

Brought to you in the interest of continuing education

Cipla Medpro

THE ETHICAL GENERIC COMPANY



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

APPROPRIATE DIAGNOSIS	INAPPROPRIATE DIAGNOSIS
Pain, numbness, paraesthesia	Weakness
Lower > upper extremities	Upper > lower extremities
Bilateral, symmetrical	Unilateral, asymmetrical
Distal	Proximal
No other causes	Other causes

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

TOXICITY	TB DRUG/S	ART/HAART
Peripheral neuropathy	INH isoniazid	Stavudine (d4T) Didanosine (ddl)
Rash	Rif rifampicin INH PZA pyrazinamide	NNRTI's
Nausea	PZA Rif	Didanosine (ddl) Zidovudine (AZT) PI
Hepatitis (42 days*)	Rif INH PZA	NNRTI's*

Common minor side effects of TB treatment

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

TB drug
reaction



NNRTI Dosage & Side Effects

Chemical Name	Brand Name	Generic (SA)	Suggested Dosage	Common Side Effects
Efavirenz (EFV)	Stocrin (MSD)		>40kg = 600mg at night <40kg = 400mg at night	<p><u>TERATOGENICITY</u>- Grade D – use injectable contraceptive</p> <p><u>Exacerbation of underlying CNS problems</u></p> <p>vivid dreams; dizziness; insomnia; psychosis – NB warn patient</p> <p>Maculopapular rash</p> <p>Hepatotoxicity (8% - although more recent evidence that Nevirapine and Efavirenz don't differ much)</p>
Nevirapine (NVP)	Viramune (BI)	Aspen	200mg once daily for 2 weeks, thereafter 200mg bid	<p>Rash (17% of patients)</p> <p>Hepatitis (15 %) : including necrotising hepatitis</p>

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
- HAART: 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:

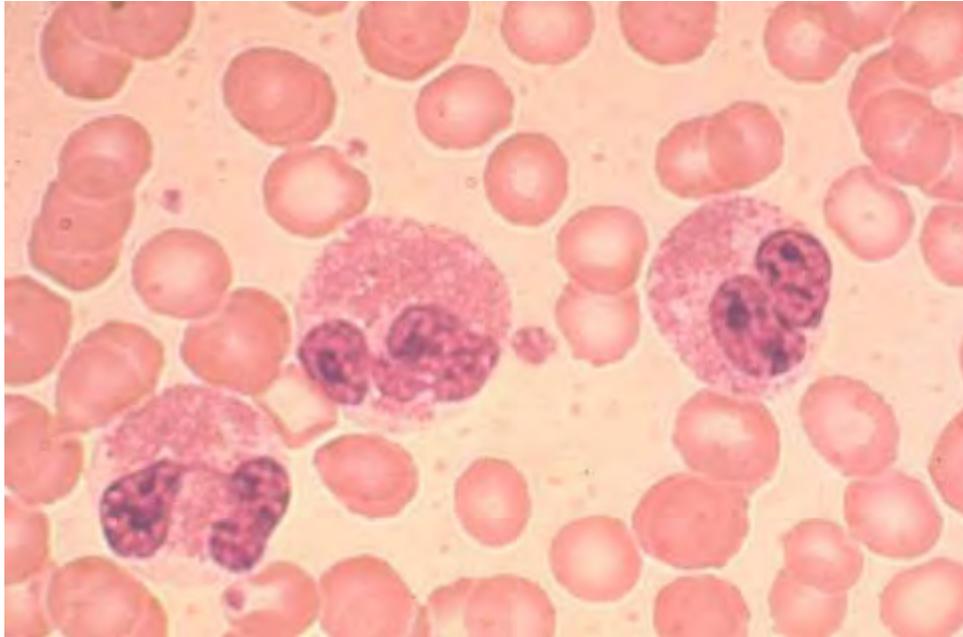
- malaise
- nausea/vomiting
- jaundice
- right upper quadrant pain or tenderness

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 cause 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”

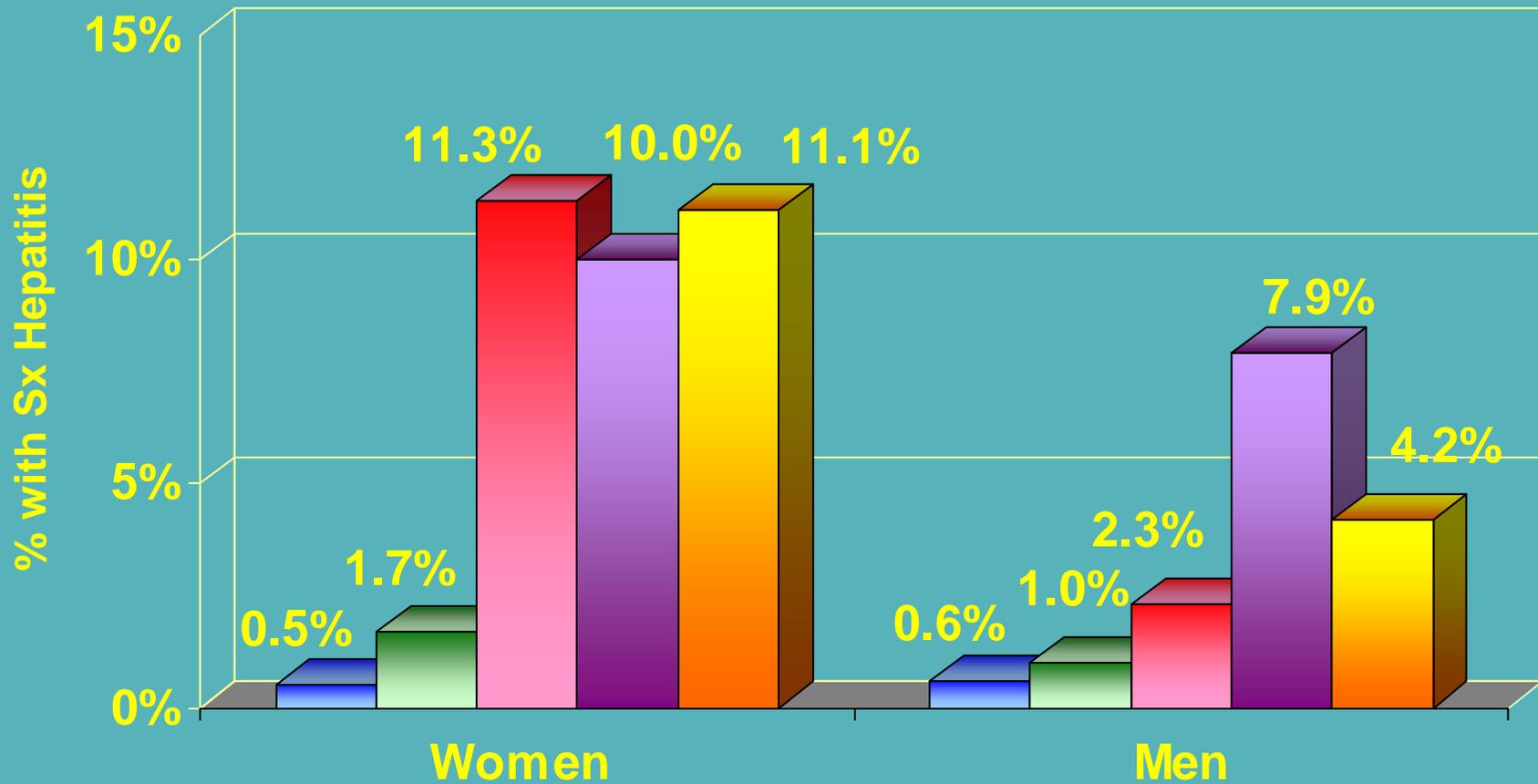
46% of symptomatic hepatitis is rash-associated

Public Health Service Task Force. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States June 23, 2004

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)

Baseline CD4 ■ <150 ■ 150-249 ■ 250-399 ■ 400-499 ■ ≥500



Prof James McIntyre Perinatal Research Unit, Bara

Changing ARVs

No need to introduce NVP
stepwise when switching
from EFV

- 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)

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

d1

d2

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

Slide 67

d1 dsolomon, 2008/06/27

d2 dsolomon, 2008/06/27

Table VI. ART toxicities and reasons for specialist referral

	Toxicity	Main causative drug(s)	When to refer
severe & rare	1. Hyperlactataemia/lactic acidosis	d4T>ddI>AZT	All suspected cases (see Fig. 3)
	2. Hepatotoxicity	NVP>EFZ>others (TB medication also an important cause)	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
	3. Drug rash	NVP>EFZ>others	Severe rash – extensive involvement, mucosal involvement, blistering, desquamation or significant systemic symptoms
mild and common	4. Myelosuppression (anaemia and neutropenia)	AZT	Symptomatic anaemia Neutropenia (neutrophil count <1) with fever
	5. Neuropathy	d4T >ddI	Atypical and rapidly progressive presentations
	6. Pancreatitis	ddI>d4T (also protease inhibitors via hypertriglyceridaemia)	All cases and suspected cases
chronic	7. Metabolic complications	Protease inhibitors (D4T can also cause impaired glucose tolerance and diabetes mellitus)	Hypertriglyceridaemia >15

PI Dosage & Side Effects

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

Lipodystrophy

from "Informed HAART" Issue 3, 2006

- 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

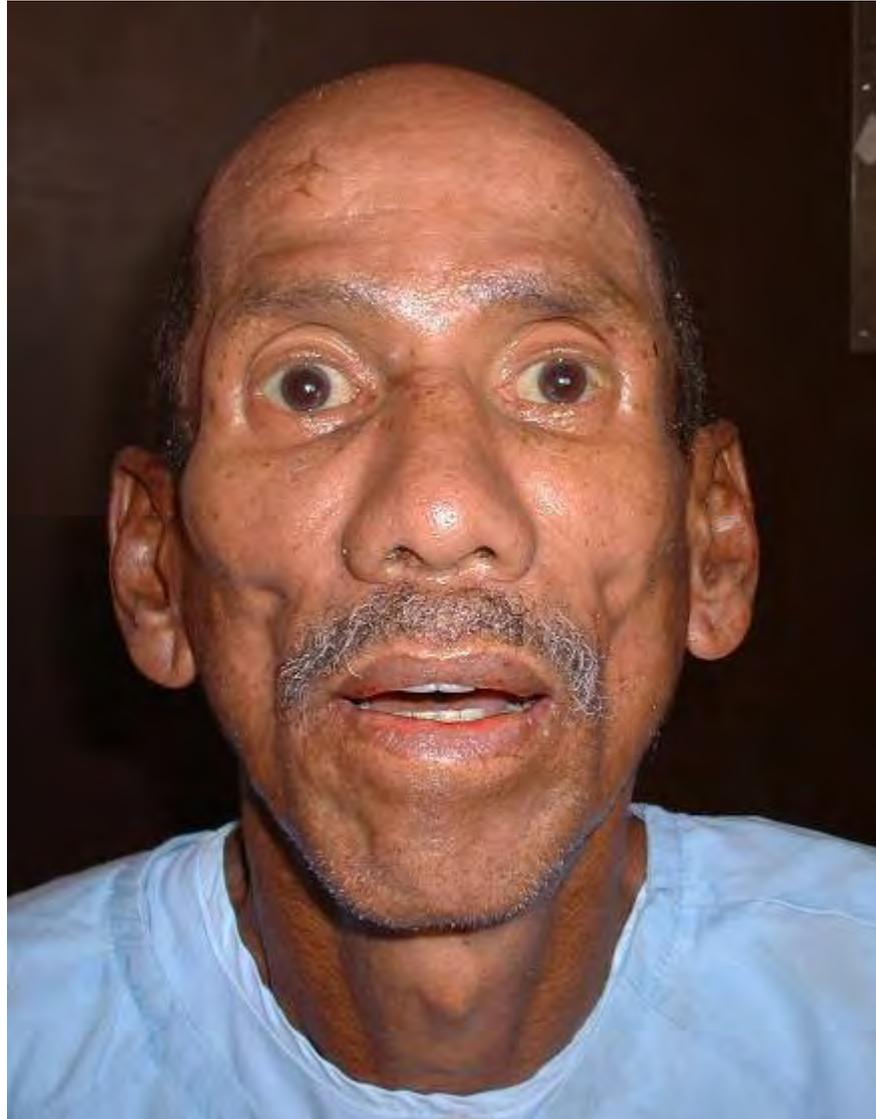
Affects

- 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

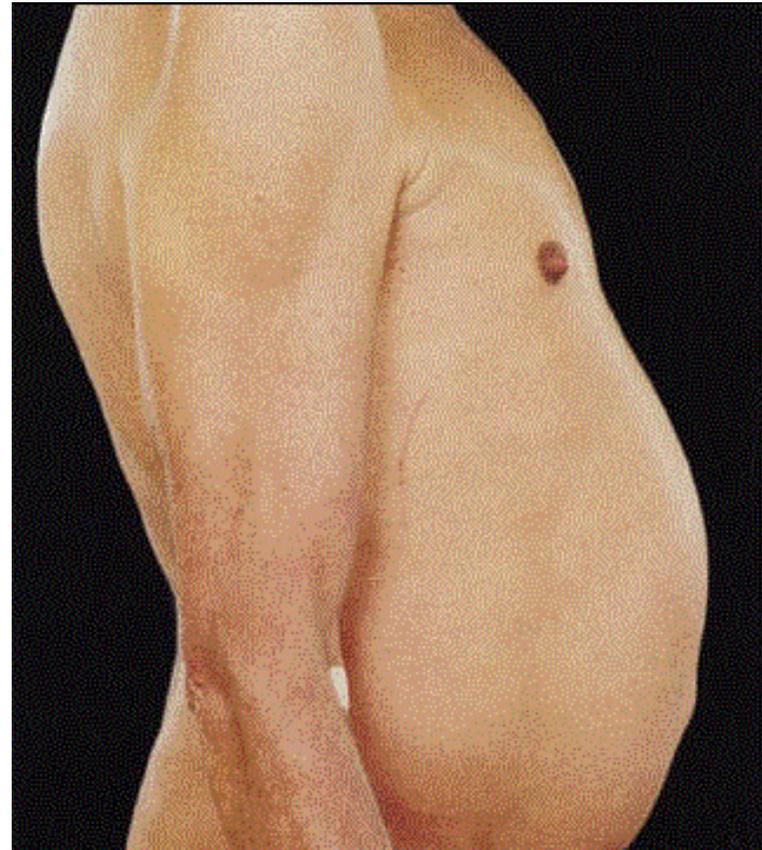
Causes

- 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

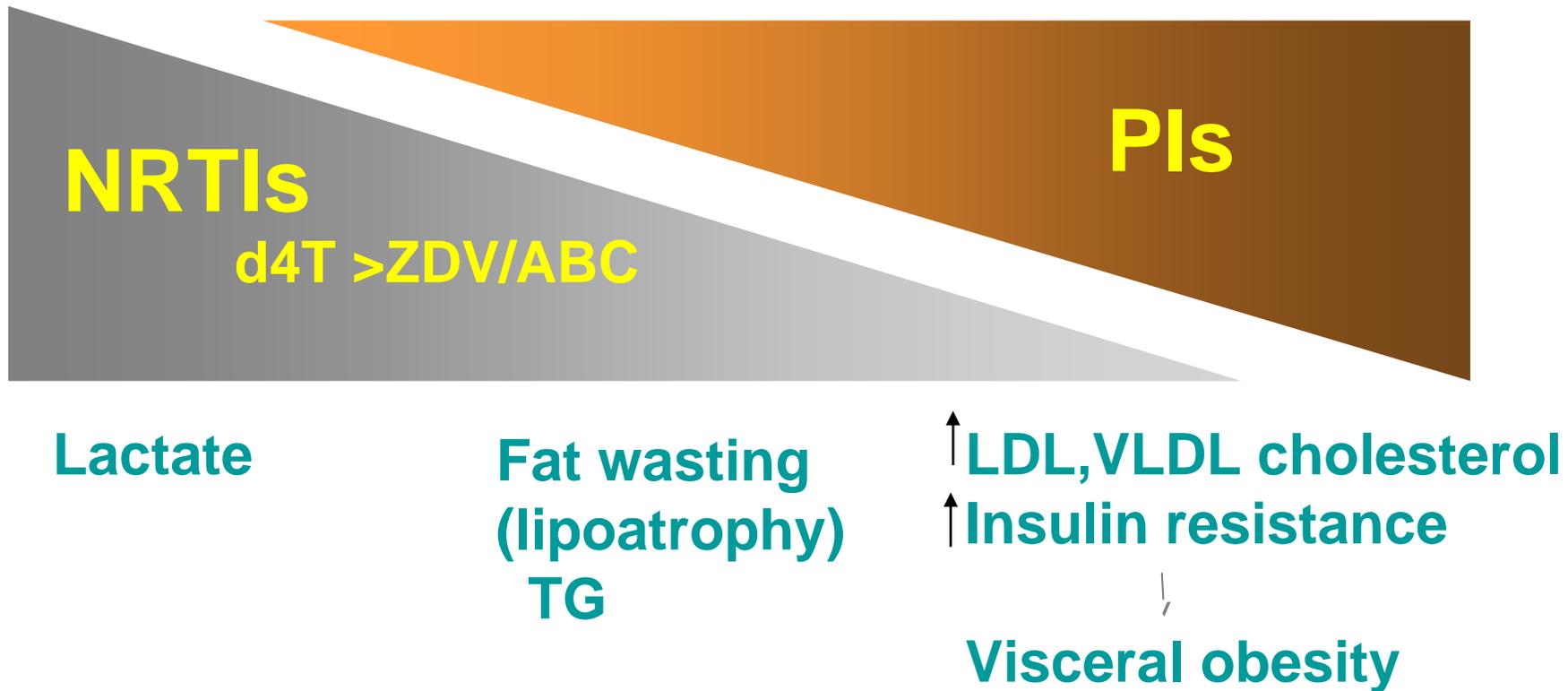
- increased risk for dyslipidaemia and insulin resistance
- remember to do a fasting lipogram & glucose in affected patients

HYPERLIPIDAEMIA

- PI's can cause fasting hypertriglyceridaemia and elevated LDL cholesterol.
- ↑↑Trigs → Pancreatitis

Triglyceride	2-5.5 mmol/l Diet	>5.5 mmol/l Diet + fibrate
LDL-cholesterol Low IHD risk	3-4.8 mmol/l Diet	>4.8 mmol/l Diet + fibrate/statin*
LDL-cholesterol High IHD risk	3-3.3 mmol/l Diet	>3.3 mmol/l Diet + fibrate/statin*

Lipodystrophy syndrome(s): overlapping NRTI & PI toxicities



John M, et al. *Antiviral Therapy* 2001; 6:9–20.



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

>5.6 Diet + fibrate

LDL-chol Lifestyle for all elevations

>4.9 (IHD > 3.4) consider fibrate/statin

Beware drug interactions statins & PI

SA guidelines?

- Primary prevention not part of Essential Drug List [EDL]
- Secondary prevention in EDL
- Need to protect against severe \uparrow TG
 - TG >10 give fibrate?

Statins & PI interactions

- Atorvastatin ↑ level - low dose (5-10mg)
- Pravastatin ↓ levels modest
- Simvastatin & lovastatin ↑↑ levels **toxic**

– **AVOID**

Insulin resistance

- Up to 40% abnormal GTT on PIs
- Overt diabetes uncommon
- Insulin resistance mechanisms
 - Impaired glucose uptake
 - Central obesity & lipodystrophy 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)

Antiretroviral Pharmacology 2007

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

Vincent C. Understanding and Responding to Averse Events. *N Engl J Med* 2003;348:1051-56

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

Cause ?

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

Grade 1	Grade 2	Grade 3	Grade 4
40 -100	100 -200	200 - 400	More than 400

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

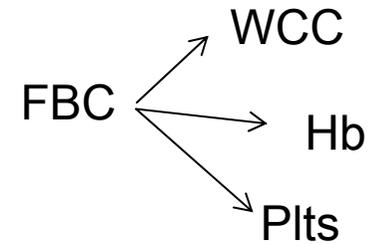
LABORATORY TEST ABNORMALITIES				
ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
Haemoglobin	8.0-9.4 g/dL	7.0-7.9 g/dL	6.5-6.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1.0-1.5 X 10 ⁹ /L	0.75-0.99 X 10 ⁹ /L	0.5-0.749 X 10 ⁹ /L	<0.5 X 10 ⁹ /L
ALT (SGPT)	1.25-2.5 X upper normal limit	>2.5-5 X upper normal limit	>5-10 X upper normal limit	>10 X upper normal limit
Triglycerides	3.0-4.51 mmol/L	4.52-8.48 mmol/L	8.49-13.56 mmol/L	>13.56 mmol/L
Cholesterol	>1-1.3 X upper normal limit	>1.3-1.6 X upper normal limit	>1.6-2 X upper normal limit	>2 X upper normal limit

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 = $2.3 \times 10^9 /L$ (2300)
- neutrophil percentage = 12%



- absolute neutrophil count = $2300 \times 12/100 = 276$

Grade 1	Grade 2	Grade 3	Grade 4
1000 to 1500	750 to 1000	500 to 750	Less than 500

Clinical abnormalities

CLINICAL ADVERSE EVENTS				
ITEM	GRADE 1 TOXICITY	GRADE 2 TOXICITY	GRADE 3 TOXICITY	GRADE 4 TOXICITY
Paraesthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; OR narcotic analgesia required with symptomatic improvement	incapacitating; OR not responsive to narcotic analgesia
Neuro-sensory	mild impairment (decreased sensation, e.g. vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution	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	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)	sensory loss involves limbs and trunk.
Cutaneous / Rash / Dermatitis*	erythema, pruritus	diffuse, maculopapular rash OR dry desquamation	vesiculation OR moist desquamation OR ulceration	exfoliative dermatitis OR mucous membrane involvement OR erythema multiforme OR suspected Stevens-Johnson syndrome OR necrosis requiring surgery

Table 10: Summary of Adult ARV Regimens and routine monitoring during treatment

Regimen	Test	Frequency
d4T / 3TC / NVP	<ul style="list-style-type: none"> • CD4 • VL • ALT 	<ul style="list-style-type: none"> • Staging, 6 monthly • Baseline, 6 monthly • Baseline, week 2, 4 and 8, thereafter 6 monthly
d4T / 3TC / efavirenz	<ul style="list-style-type: none"> • CD4 • VL 	<ul style="list-style-type: none"> • Staging, 6 monthly • Baseline, 6 monthly
AZT / 3TC / NVP (during pregnancy)	<ul style="list-style-type: none"> • CD4 • VL • FBC and white cell diff • ALT 	<ul style="list-style-type: none"> • Staging, 6 monthly • 6 monthly • baseline and monthly until delivery • Baseline, week 2, 4, thereafter monthly until delivery
AZT / ddi / lopinavir / ritonavir	<ul style="list-style-type: none"> • CD4 • VL • FBC and white cell diff • Fasting cholesterol and triglyceride • Fasting glucose 	<ul style="list-style-type: none"> • Staging, 6 monthly • 6 monthly • baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) thereafter.(Monthly during pregnancy) • baseline, 6 months and thereafter every 12 months. • Every 12 months

- **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

(Identities of reporter and patient will remain strictly confidential)

NATIONAL ADVERSE DRUG EVENT MONITORING CENTRE

Medicines Control Council,
The Registrar of Medicines,
Department of Health

Tel: (021) 447-1618
Fax: (021) 448-6181

In collaboration with the WHO International Drug Monitoring Programme

PATIENT INFORMATION

Name (or initials) Age Weight (kg)
 Gender M F DOB...../...../..... Height (cm)

ADVERSE REACTION/PRODUCT QUALITY PROBLEM

Adverse reaction¹ and/or Product Quality problem² Date of onset of reaction...../...../.....
 Time of onset of reaction.....h.....min

Description of reaction or problem (Include relevant tests/lab data, including dates):

1. MEDICINES/VACCINES/DEVICES (include all concomitant medicines)

Trade name and batch No. (Asterisk suspected product)	Daily dosage	Route	Date started	Date stopped	Reasons for use

ADVERSE REACTION OUTCOME (Check all that apply)

<input type="checkbox"/> death <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage	<input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalisation <input type="checkbox"/> Other	Event reappeared on rechallenge: <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> Rechallenge not done Treatment (of reaction).....	Recovered <input type="checkbox"/> Y <input type="checkbox"/> N Sequelae <input type="checkbox"/> Y <input type="checkbox"/> N Describe Sequelae.....
---	---	---	---

COMMENTS: (e.g. Relevant history, Allergies, Previous exposure, Baseline test results/lab data)

2. 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

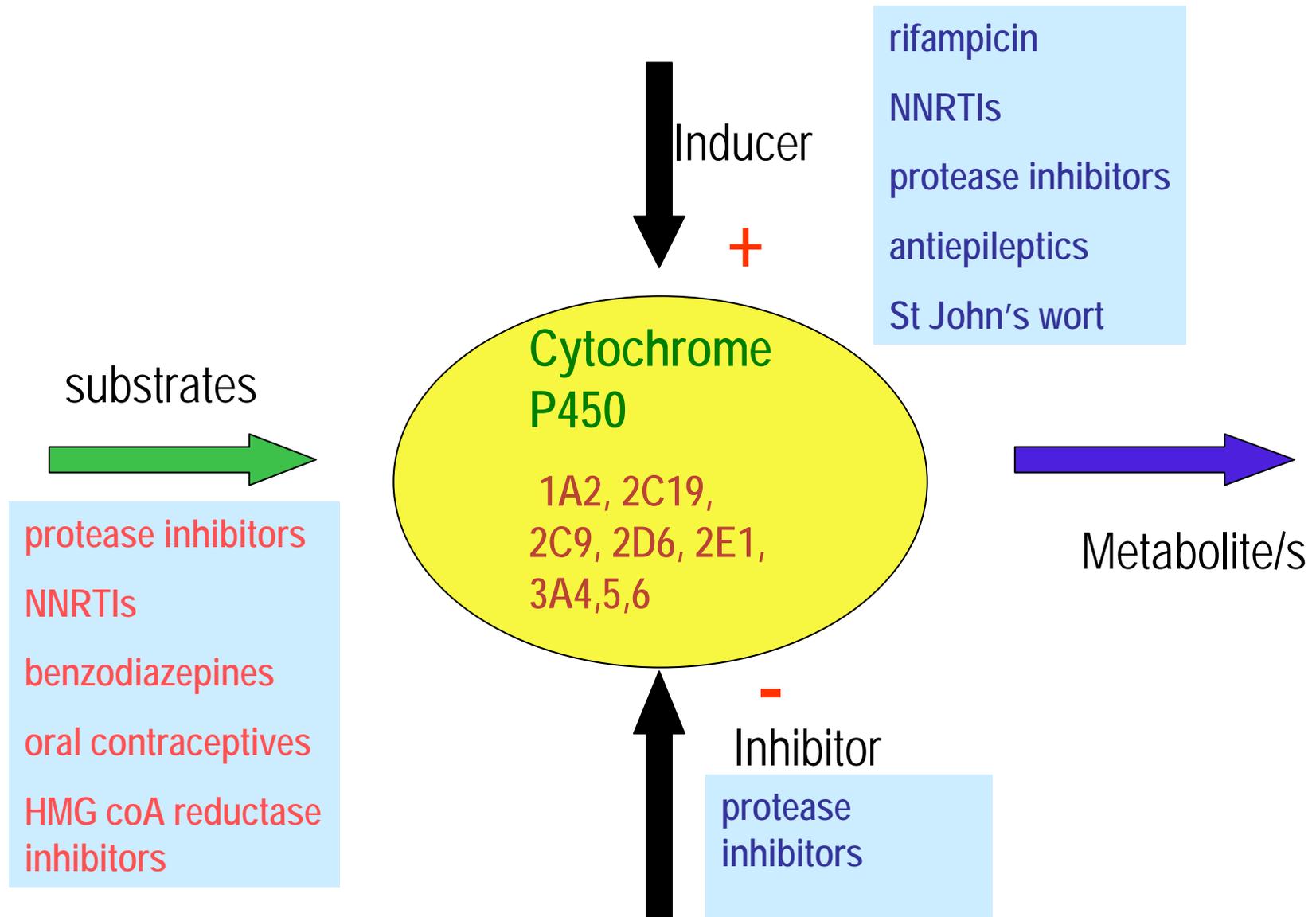
REPORTING DOCTOR/PHARMACIST etc:

Name Qualifications
 Address.....

 Tel: (.....).....
 Signature Date

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



Remember – dosage adjustment in renal failure

- formula to estimate creatinine clearance (CrCl) in ml/min:

$$\frac{(140 - \text{age}) \times \text{weight (Kg)}^*}{0.82 \times \text{serum creatinine } (\mu\text{mol/L})} \rightarrow \text{GFR} \quad \text{♂}$$

For women, multiply the GFR by 0.85

* Modified formula of Cockcroft and Gault

Adult dosages in renal impairment

bd = 12 hourly

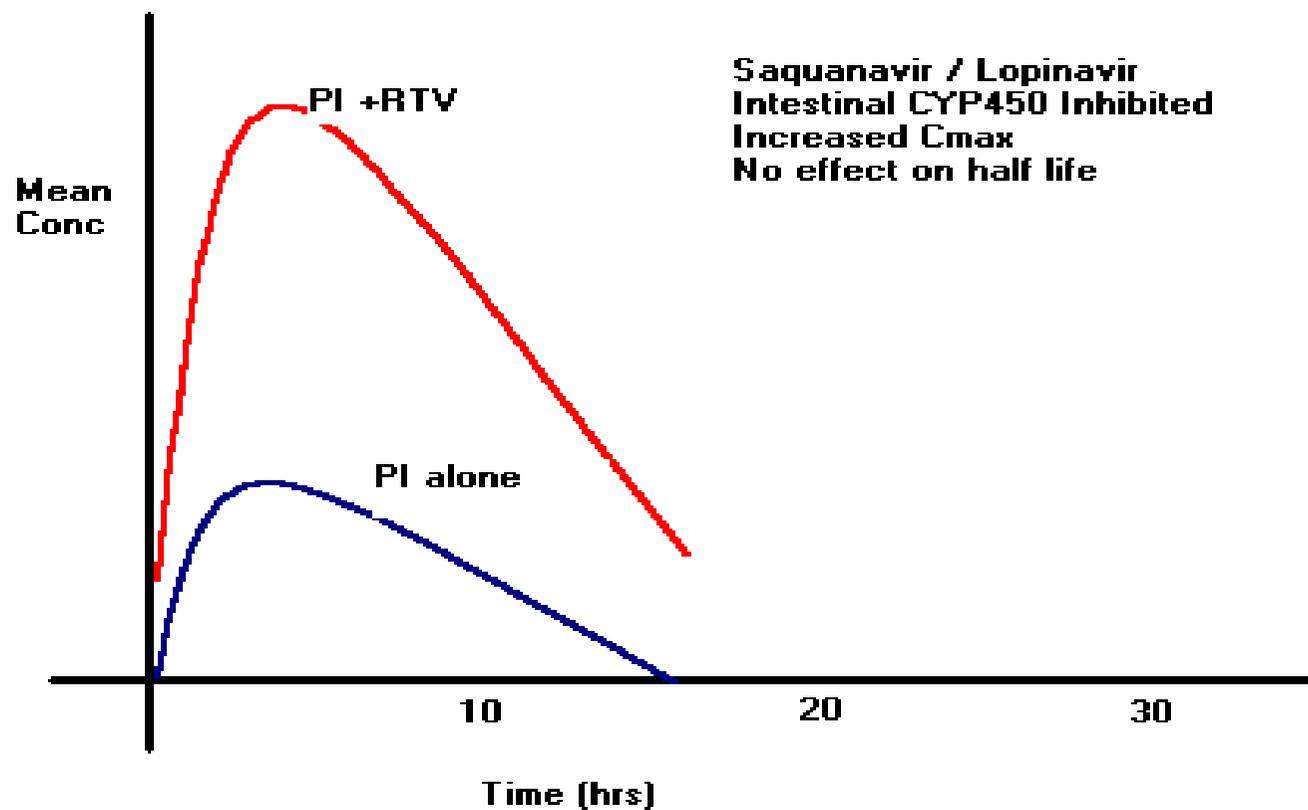
Drug NRTI's	Cr Cl 10 – 50	Cr Cl < 10
Stavudine d4T	>60kg 20mg bd <60kg 15mg bd	>60kg 20mg daily <60kg 15mg daily
Lamivudine 3TC	150mg daily	50mg daily
Zidovudine AZT	unchanged	300mg daily
Didanosine ddl	>60kg 200mg daily <60kg 150mg daily	>60kg 100mg daily <60kg 75mg daily

Adult dosages in renal impairment

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

Drug	Cr Cl 10 - 50	Cr Cl < 10
Tenofovir (TDF)	AVOID	AVOID
PI's	unchanged	unchanged
Nevirapine	unchanged	unchanged
Efavirenz	unchanged	unchanged

Saquinavir + ritonavir



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.

ART interactions with Rifampicin

NRTI's	No interactions
Efavirenz	Mild reduction in EFV levels, some experts ↑ dose to 800mg
Nevirapine	Moderate reduction in NVP levels - limited experience
Kaletra + Ritonavir (400/400mg bid)	No significant interactions
Ritonavir + Saquinavir (both 400mg bid)	No significant interaction
All the other PI's	Marked reduction in PI levels - AVOID!!

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

Deep salvage – keep going as long as the pt. tolerates 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 \pm 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

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 is 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 Campaign [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.sahivcliniciansociety.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)

TEST	If patient declines VCT, he/she may be putting his/her health at risk and other (include unborn)
TEST EARLY	Testing LATE means patient will present with a lower CD4 result and may be more susceptible to IRIS
START TREATMENT EARLY	Starting ARV's when patient is very ill slows recovery time, ↑ likelihood of SE and IRIS

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

Reg		d4T 30mg bd	3TC 150 mg bd	3TC 300 mg daily	EFV	NVP	AZT	TDF	ddl	<i>Kaletra Aluvia</i>	TOTAL Price (R)
	P R I C E	17.65	29.91	42.50	108.03	32.11	71.09	159.49	67.83	319.07	
1a		1	1		1						155.59
1b		1	1			1					79.67
1a TDF				1	1			1			310.02
1a AZT			1		1		1				209.03
2							1		1	1	457.99

TDF = tenofovir

1a per year = R1867.08

1b per year = R 956.04