Clinical guidelines for the management of HIV/AIDS in adults and adolescents ≥15 years

SAHIVCS - CME

13/06/15

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Introduction

- What is new?
- Goals and objectives
- Guiding principles
- HIV continuum of care

What is new in these guidelines?

Eligibility	• Earlier initiation: CD4 ≤500 cells/mm^3 • Option B+ • HIV+ partner in serodiscordant couple • HBV coinfection • All HIV/TB coinfected patients
Regimens	• Use of FDCs for simplification • Harmonised ART regimens • Alternatives in second line for AEs • Third line drugs
Labs	• Routine CrAg screening in CD4 <100 cells/mm^3 • Use of VL for monitoring treatment • TST for IPT eligibility and duration

ART eligibility and timing

CD4 count ≤500 cells/mm^3 irrespective of clinical stage

- (prioritise CD4 <350 cells/mm^3)

OR

Severe or advanced HIV disease (WHO clinical stage 3 or 4), regardless of CD4 count

OR

Irrespective of CD4 or clinical stage

- Active TB disease
- HIV-positive pregnant and breastfeeding women
- HIV-positive partner in serodiscordant couple
- Known HBV co-infection

ART should be started within 2 weeks after the CD4 count is done

In TB co-infection: TB treatment first, then ART ASAP, within 8 weeks

- CD4 <50 cells/mm^3 start ART within 2 weeks TB treatment, when symptoms improving and TB treatment tolerated
- Defer ART 4-6 weeks in TBM or cryptococcal meningitis

Immediate initiation: All HIV-positive pregnant or breastfeeding women

Within 7 days:

- Patients with low CD4 <200 cells/mm^3
- HIV stage 4, even if CD4 not available

First line regimens

Who?	What?	Comments
• Adults • Pregnant and breastfeeding women • TB co-infection • HBV co-infection • HIV-positive partner in serodiscordant couple • Adolescents >15 years and weighing >40kg	TDF + FTC (or 3TC) + EFV (FDC preferred)	Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. . Remember CD4 count restrictions for NVP Evidence supports the efficacy and safety equivalence of 3TC and FTC
• Adolescents <40kg	ABC + 3TC + EFV	If adolescent's weight <40kg, align with paediatric regimen

Substituting contraindicated drugs in first line

Contraindicated drug	Substitute	Comments
EFV	TDF + FTC (or 3TC) + NVP	Replace EFV with NVP if significant psychiatric comorbidity or intolerance to EFV and where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers. Remember CD4 count restrictions for NVP
NVP	TDF + FTC (or 3TC) + LPV/r	Avoid NVP in women if CD4 count >250 cells/mm^3, and men with CD4 count >400 cells/mm^3
TDF	ABC + 3TC + EFV (or NVP)	Renal disease or the use of other nephrotoxic drugs, e.g. aminoglycosides MDR treatment
Currently on d4T	TDF + FTC (or 3TC) + EFV FDC preferred	d4T to be discontinued in all patients, even if well tolerated. If patient is not virally suppressed, consider switching to second line

Monitoring at diagnosis/baseline

What?	Why?
Confirm HIV result with rapid antibody test if no test results are available	To confirm HIV-positive status in patients who present without proof of status
WHO clinical staging if HIV-positive	To assess eligibility and timing of ART initiation
Screen for TB symptoms using the TB screening tool	To identify TB suspects and refer for investigation; assess IPT eligibility
Screen for pregnancy or ask if planning to conceive	To identify women who need ART for PMTCT and offer family planning services
Screening for STIs	To identify and treat STIs
Blood pressure and glycosuria	Screen for comorbidities
Weight and height in adolescents	To determine which ARVs to use

Monitoring at diagnosis/baseline

What?	Why?
CD4 count	Identify ART (CD4 <500 cells/mm^3) eligibility Identify prioritisation (CD4 <350 cells/mm^3) eligibility Identify cotrimoxazole (CD4 <200 cells/mm^3) eligibility Identify CrAg eligibility (CD4 <100 cells/mm^3)
Screen for HBV (HBsAg)	Identify those co-infected with HBV to initiate ART
CrAg test if CD4 <100 cells/mm^3	Assess if there is disseminated cryptococcal infection and fluconazole therapy is indicated
Creatinine if pt requires TDF ALT if pt requires NVP FBC if patient requires AZT	Assess renal sufficiency Exclude liver disease Detect anaemia or neutropenia
Fasting cholesterol and triglycerides if LPV/r required	Identify patients at risk of LPV/r related hyperlipidaemia. If >6 mmol/L, give ATV/r instead of LPV/r

Monitoring on ART

What?	When?	Why?
TB screen	Every visit	TB infection / IPT eligibility
WHO staging		New OIs
Ask about SEs		ARV toxicity
CD4 count	At 12 months on ART	Immune response
Viral load	Months 6 and 12 on ART; then 12 monthly	Treatment failure / adherence problems
Creatinine	Months 3, 6 and 12 if on TDF; then 12 monthly	TDF toxicity / renal impairment
FBC	Months 3 and 6 if on AZT; then 12 monthly	AZT toxicity
ALT	If on NVP and develops rash or symptoms of hepatitis	NVP toxicity
Fasting TC and TG	At month 3 if on LPV/r	LPV/r toxicity

When should you check a viral load?

	SA Dept. Health	SA HIV Clin. Soc.	DHHS (USA)
At initiation	✗	✓	✓
Before 6 months	✗	3 months	At 2-8 weeks, then every 4-8 weeks until suppressed
6 months	✓	✓	✓
12 months	✓	✓	✓
Thereafter	Every 12 months	Every 6-12 months	Every 3-6 months

Why check viral loads before 6 months?

- Enables early detection of virological failure (usually due to poor adherence), before resistance develops, or worsens.
- At 3 months, most patients will be virally suppressed, but a small group of people who started with a very high viral load may still have detectable viraemia… although they'll still show at least a 2 $\log_{10}$ drop from their initiation viral loads.

What should you do if you find a high viral load?

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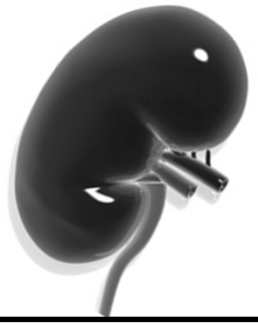
- < 400: no specific action
- 400-1000: adherence counselling & repeat VL 6 monthly
- > 1000: adherence counselling, repeat VL 2-3 months
  - If repeat < 1000, repeat VL in 6 months
  - If repeat > 1000, switch therapy

SA HIV Clinicians Society

- > 50: adherence counselling & repeat VL in 2-3 months
- > 1000 on 2 occasions 2-3 months apart: switch therapy
- > 200 for more than 1 year: switch therapy



General management: Creatinine clearance

TDF can only be used in patients with creatinine clearance >50 mL/min and creatinine <100 umol/L

Serum creatinine gives indication of renal function, but poor indicator in some cases:

- Elderly
- Low body weight
- Acute illness

Calculate creatinine clearance:

- Age >50 years
- Weight <50 kg
- Serum creatinine >100 umol/L
- Comorbidities that affect renal function (HPT; DM)
- Medications that may impair renal function

Don't forget dose adjustment of certain ARVs when used in renal impairment

Don't forget to readjust doses as renal impairment improves!

PREVENTION AND MANAGEMENT OF OPPORTUNISTIC INFECTIONS

Cotrimoxazole preventive therapy (CPT)

When to start

CD4 count <200 cells/mm^3

WHO stage 2, 3 and 4

HIV/TB coinfection

Reduces hospitalisation and morbidity

Protects against PCP, toxoplasmosis, malaria and bacterial infections

Benefit outweighs risk in pregnancy therefore continue in pregnant women

Maculopapular rash most common SE. Continue or stop and restart for mild rash

When to stop?

When to restart

CD4 drops <200

ART fails

New OI

160/800 mg daily

Monitor clinically at 3 monthly intervals

Safety of CPT

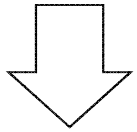
Neutropenia is rare SE. Routine FBC monitoring not required

Can use dapsone 100 mg unless severe reaction (cross reactivity) Less cover

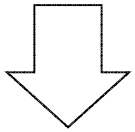
Do not delay ART in favour of cotrimoxazole initiation

Isoniazid Preventive Therapy (IPT)

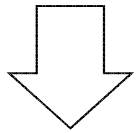
Exclude active TB



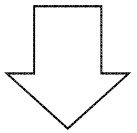
Confirm IPT eligibility



TST to determine duration



Start IPT and pyridoxine



Monitor adherence and SEs
Screen for TB at every visit

Exclude active TB

TB symptom screen

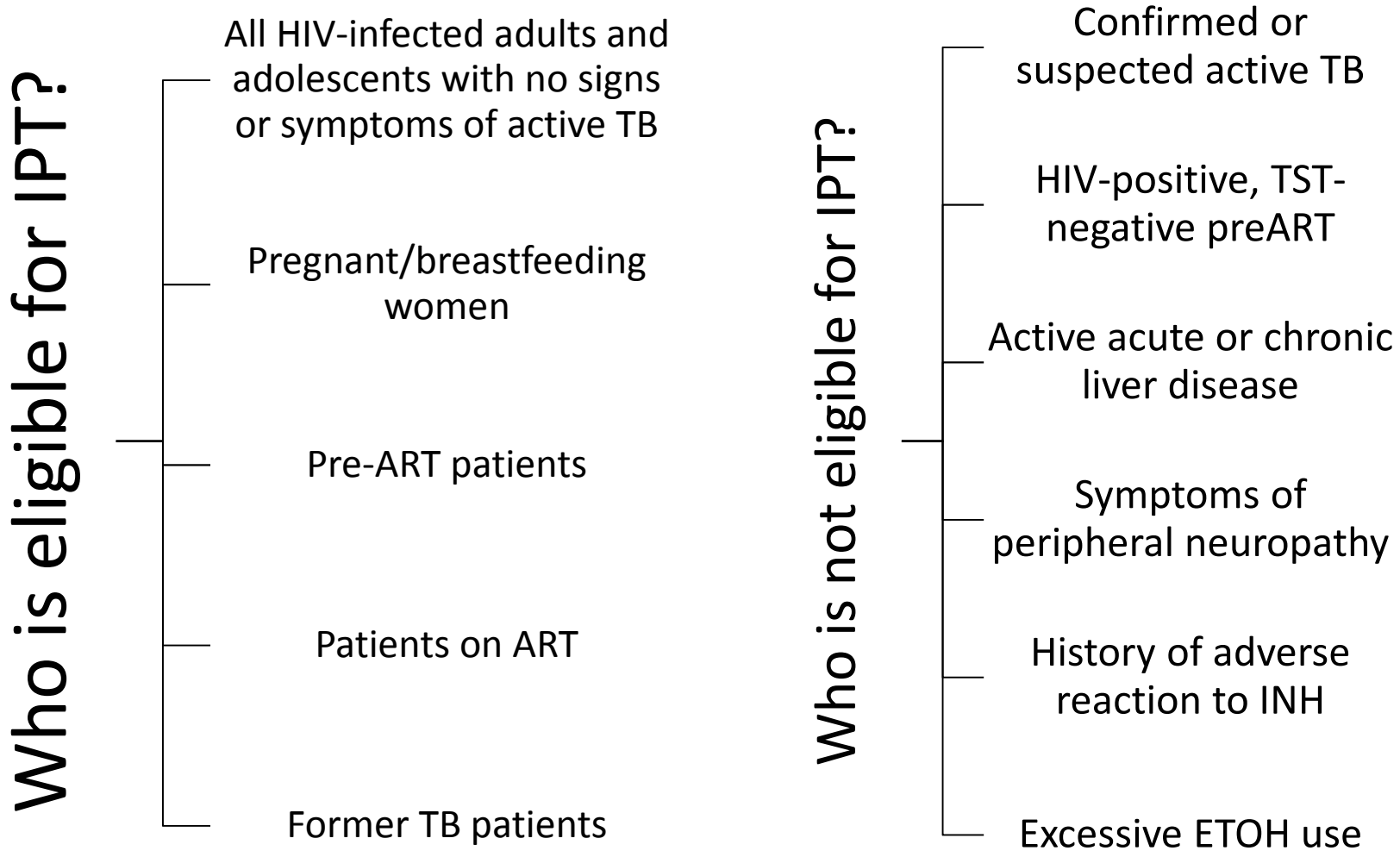
Investigate for TB if ≥1 symptoms

No TB, do not give IPT

Reassess for IPT eligibility after 3 months

TB symptom screen
Current cough, any duration
Persistent fever >2 weeks
Unexplained weight loss
Drenching night sweats

IPT eligibility



IPT provision

TST result	IPT duration	
	PreART	On ART
TST not available*	6 months	6 months [12]
TST negative	No IPT	12 months
TST positive	36 months	36 months
*Where TST not available at IPT initiation, must be performed as soon as possible after IPT initiation (within 1 month)		

- TST relies on competent immune response
  - Severely immunocompromised may not have reactive TST despite TB exposure
- Mantoux is recommended test
  - Inject a known amount of PPD between layers of skin
  - Measure reaction at injection site 48-72 hours later
- If TST negative, re-assess annually until it becomes positive

IPT regimen and monitoring

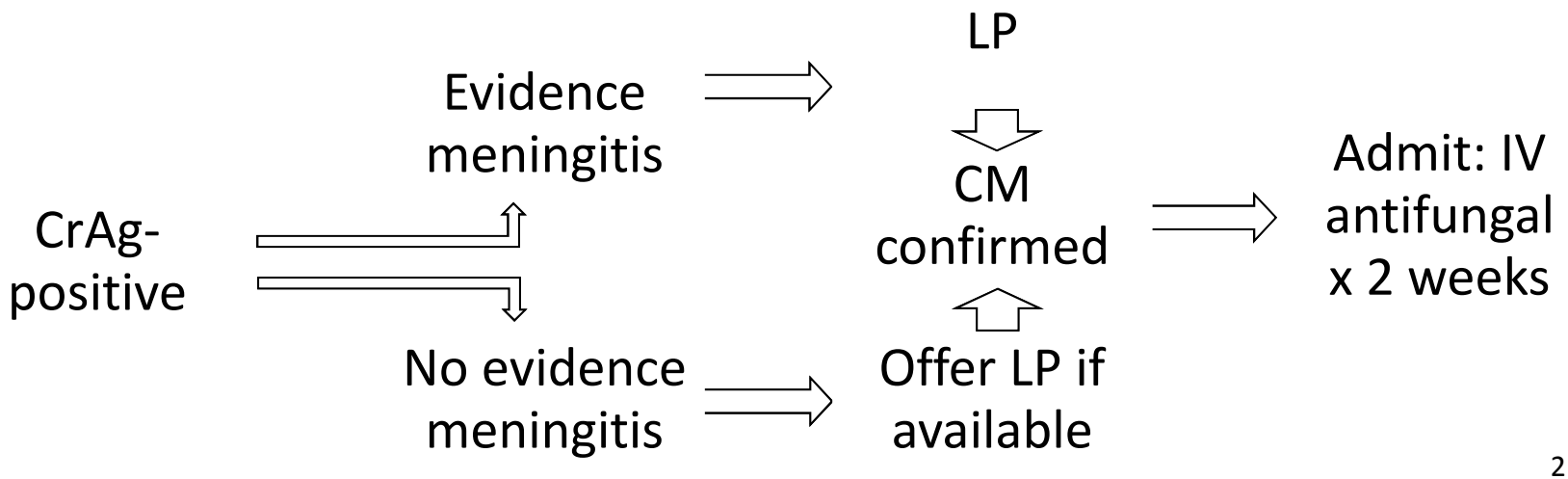
Dosage	Comments
INH 5mg/kg/day (max 300mg/day)	1 month supply for 3 months; then 3 month supply for remaining time
Pyridoxine 25mg/day	Prevent peripheral neuropathy
Clinical monitoring	
Ongoing counselling and patient education Adherence monitoring and social support and care Early identification and management of AEs TB symptom screening	Ensure IPT visits coincide with preART or ART visits

Isoniazid side effects

Side effect	Management
Peripheral neuropathy	Increase vitamin B6 (pyridoxine) to 100 mg daily; keep patient on that dose until the symptoms disappear If peripheral neuropathy is severe, discontinue INH immediately and refer If patient needs to take d4T for medical indication, discontinue INH
Hepatotoxicity	Stop INH immediately and refer patient to hospital
GI effects	Rule out other causes of nausea and vomiting. Consider LFTs Treat symptomatically (if no other cause is found)
Flushing reaction	Reassure patients and advise that they avoid tyramine and histamine containing foods while on INH Flushing is usually mild and resolves without therapy
Hypersensitivity	Discontinue until the reaction resolves Re-challenge after resolution of reaction • begin with INH 50mg on day 1 • if the original reaction was severe, begin with INH 5mg on day 1 • if a reaction does not occur after day 1 dose, increase to 300mg on day 2 • if a reaction does not occur after the day 2 dose, continue INH 300mg daily • if a reaction occurs during drug re-challenge, stop INH Treat with antihistamines and follow up

Cryptococcus

- Screen patients with CD4 count <100 cells/mm^3 for cryptococcal disease BEFORE initiating ART (CrAg)
  - Currently clinician initiated
- CrAg-positive indicates disseminated cryptococcal disease
  - Evaluate for symptoms/signs of meningitis



Cryptococcus

Summary recommendations		
Clinical picture	**Antifungal treatment**	**ART**
CrAg-positive but no evidence of meningitis	Oral fluconazole (800mg/day x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 2 weeks antifungal treatment
CrAg-positive with evidence of meningitis	IV antifungal treatment x 2 weeks; standard consolidation and maintenance antifungal treatment	Start after 4-6 weeks antifungal treatment

- WOCBA: if CrAg-positive, do pregnancy test before starting fluconazole (teratogenic)
- All CrAg-positive PREGNANT women should be offered LP
  - Discuss with expert before deciding management
- Fluconazole may cause liver injury
  - Monitor patients with evidence of liver disease carefully

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TB and ART – problematic combinations

ART drug	TB drug	ARV change	Reason
NVP	Rifampicin	Start NVP at 200mg BD No lead in dose	Rifampicin reduces NVP levels. Prefer to use EFV. If NVP needed , monitor ALT as higher risk of hepatotoxicity
EFV	Cycloserine Terizidone	-	Watch for increased CNS toxicity/ psychosis
TDF	Amikacin Kanamycin Capreomycin	**Avoid** Can only use if can monitor Renal function **very closely**	High risk of renal toxicity If Hb> 8g/dl: use AZT If Hb < 8g/dl : use ABC Can change back to TDF after injectable completed if CrCl> 50ml/min and VL LDL
ETV	Rifampicin	**Avoid**	Reduces ETV drug levels

TB and ART – problematic combinations

ART drug	TB drug	ARV change	Reason
LPV/r	Rifampicin	Increase drug dosage Adults : increased to 4 tablets BD Paeds : boost with RTV (see dosing table)	Rifampicin reduces LPV/r drug levels. Can go back to std doses 2 weeks after completed TB meds
ATV	Rifampicin	**Avoid**	Rifampicin reduces ATV drug levels. Rather use **Rifabutin for TB treatment ***
DRV	Rifampicin	Double dose of DRV (800mg BD) NB: boost with RTV 100mg	Rifampicin reduces DRV levels. **Can also motivate for Rifabutin as TB alternative ***
*With DRV and ATV – reduce Rifabutin dose to 150mg every 2nd day			

ART toxicity

- Currently recommended ART is well tolerated
- Many adverse events are mild
- If the toxicity is severe or does not resolve , the suspected offending ARV must be substituted
- **If on ART ≥ 6 months, ensure the VIRAL LOAD is < 50 before a single drug switch so as not cause resistance to the new drug**

ART toxicity

- Mostly can switch out the offending single drug
- **BUT if life threatening reaction** (severe liver dysfunction or lactic acidosis), **ALL ARVS may be stopped until full recovery**

Severe ART side effects

- **N**ephrotoxicity
- **H**epatotoxicity
- **H**aematological toxicity
- **H**yperlactaemia
- **H**ypersensitivity
- **These patients should always be discussed treatment expert**

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Nephrotoxicity

- NRTI's need dose adjustment in renal failure
- TENOFOVIR can cause tubular wasting syndrome with wasting of phosphate and potassium or acute renal failure
- Must know baseline renal function and monitor : CrCl
- If CrCl < 50 ml/min : USE ABACAVIR

Creatinine clearance calculation (GFR)

- Modified Cockroft-Gault equation :

- $$CrCl = \frac{(140 - age) \times weight}{Serum\ Creatinine}$$

For women : then multiply by 0.85

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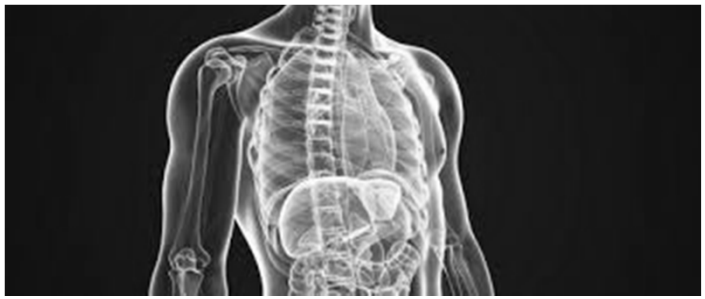
Nephrotoxicity

- If got renal impairment + HepBsAg – will need to be discussed with a ART specialist
- Watch TDF when with PI's as increased risk
- Caution in patients with comorbidities : DM and Hypertension and other nephrotoxic drugs (NB injectables with MDR intensive phase)

ARV dosage adjustments in renal failure

Drug	CrCl 10-50	CrCl < 10
TDF	Avoid	Avoid
ABC	No change	No change
3TC	150mg daily	50mg daily
AZT	No change	300mg daily
D4T	15mg BD	15mg daily
NNRTI PI InSTI	No change	No change

Hepatotoxicity



- Full LFT is expensive .Not routine unless abn ALT / symptoms of hepatitis
- ALT is most sensitive indicator of drug – induced liver injury
- All ARV classes can be associated with hepatotoxicity- Most commonly NNRTI's
- Mild ALT elevations are common. NO action needed

Hepatotoxicity

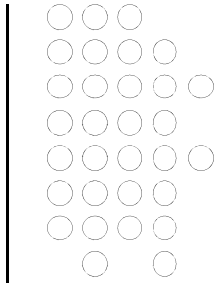
- Remember other drugs that the patient could be taking
- TB medication

- Can be tricky to isolate the problem drug – referral is needed

Management of hepatotoxicity

	<2,5 ULN	2.5-5X ULN	>5xULN
ALT	Monitor	Repeat in 1 week	Discontinue relevant drugs
ALP	Monitor	Repeat in 2 weeks	Ultrasound Biopsy
Bilirubin	Repeat in 1 week	Discontinue relevant drugs	Discontinue Relevant drugs
Any elevations with symptoms of hepatitis (nausea, vomiting,RUQ pain) should be regarded as indication to stop relevant drugs ULN= upper limit of normal			

Hepatic side effects with Atazanavir



- Causes isolated unconjugated hyperbilirubinaemia (drug induced Gilbert's syndrome)
- Elevated unconjugated bilirubin , rest of LFT is normal
- Benign condition but is cosmetically unacceptable to patients – as skin and eyes appear yellow
- No drug switch but refer to ARV treatment expert

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Hyperlactaemia

- Less common now as using less D4T.
- Can occur with all NRTI's
- Most likely D4T/DDI– AZT – least likely TDF/FTC/3TC/ABC
- Drug induced mitochondrial damage
- Mildly elevated lactate is common. No action needed if asymptomatic
- No good screening tests. Always have a high index of clinical suspicion

Lactic acidosis

- Lactic acidosis (LA)is serious and potentially fatal
- LA= Lactate >5mmol/l + metabolic acidosis
- Symptoms – non specific (watch females with high BMI) : nausea/vomiting/ abdominal pain/fatigue/ LOW/ dyspnoea
- Lactate: grey tube, non cuffed, on ice

Management of Lactic acidosis

Lactate levels (mmol/l)	Bicarbonate levels (mmol/l)	Action
2.5-5	> 20	NRTI should be switched to one with less potential for Hyperlactaemia. Monitor Lactate till level drops < 2,5
≥5	>15	Admit All ARVs stopped Start TDF once lactate < 2.5
≥5	<15	Admit, High care /ICU preferable All ARVS stopped Start TDF once lactate < 2.5 Monitor lactate closely once back on ART

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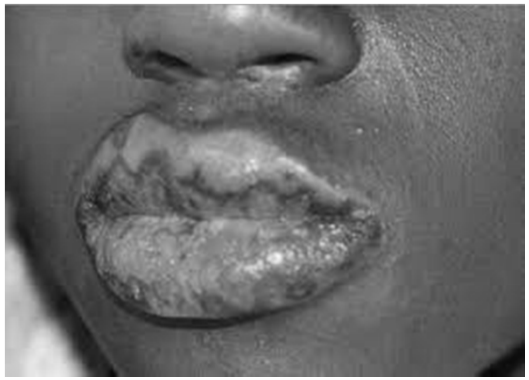
Hypersensitivity -NNRTI

- Rash with all NNRTI's is common .
- Mostly in first 6 weeks on ARV
- But severe and more frequent with Nevirapine
- If mild rash develops during NVP lead in phase , DO NOT increase to BD until the rash resolves . Only if can monitor patient otherwise substitute NVP .
- Can get EFV and NVP cross- reaction
- **NB : Other drugs** – Cotrimoxazole



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Management of NNRTI skin reaction

- If mild- continue same ARV , antihistamine and topical steroids (symptomatic treatment)
- NOT use systemic steroids
- If severe(Steven Johnson reaction) – stop ARV immediately . NEVER rechallenge
- Systemic features – fever/ hepatitis / increased ALT +
- Skin – blistering or mucosal involvement

Hypersensitivity – Abacavir

- VERY rare in Black Africans . 5% risk in Caucasians
- Mostly in first 6-8 weeks
- Linked to HLA typing : B 5701
- Never rechallenge
- Must be sure that it is ABC hypersensitivity before stopping the drug

Hypersensitivity – Abacavir

- Constitutional: fever , fatigue, malaise
- Rash : worsens with dose . 30% can have rash without ABC HSR
- Respiratory: range from mild pharyngitis, cough to dyspnoea
- Abdominal : pain , hepatitis, nausea, vomiting
- **Only suspect if got symptoms from ≥ 2 systems**

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Haematological toxicity

- **ART**
  - Zidovudine – anaemia/neutropenia
  - Lamivudine – Pure red cell aplasia

- **Other drugs** – Cotrimoxazole (mostly at higher doses)

Management of haematological toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Hb (g/dl)	>8 Monitor	7.0-7.9 Repeat in 2 weeks – if dropping switch off AZT	6.5-6.9 Repeat in 2 weeks .If dropping – switch off AZT	< 6.6 Switch from AZT
Neutrophils (10^{9} /L	1.0-1.5 Repeat in 4 weeks	0.75-0.99 Repeat in 2 weeks	0.50-0.74 Repeat in 2 weeks. Consider changing AZT	< 0.5 Switch from AZT

Dyslipidaemia

- Occurs mostly on PI regimens with LPV/r
- Can get increased Triglycerides on D4T
- If on LPV/r and fasting cholesterol > 6- change to Atazanavir
- Diet and lifestyle modification always
- Assess cardiovascular risk

Gynaecomastia

- Involves the development of breast tissue in adult and adolescent men
- May be unilateral or bilateral
- Watch in adolescent as can be related to hormonal change
- Also exclude other medical causes- chronic renal failure / low testosterone – always refer for investigation

Gynaecomastia

- Can be caused by EFAVIRENZ
- If no other cause : switch off EFV
- If severe and disfiguring please refer for surgery and or hormonal therapy

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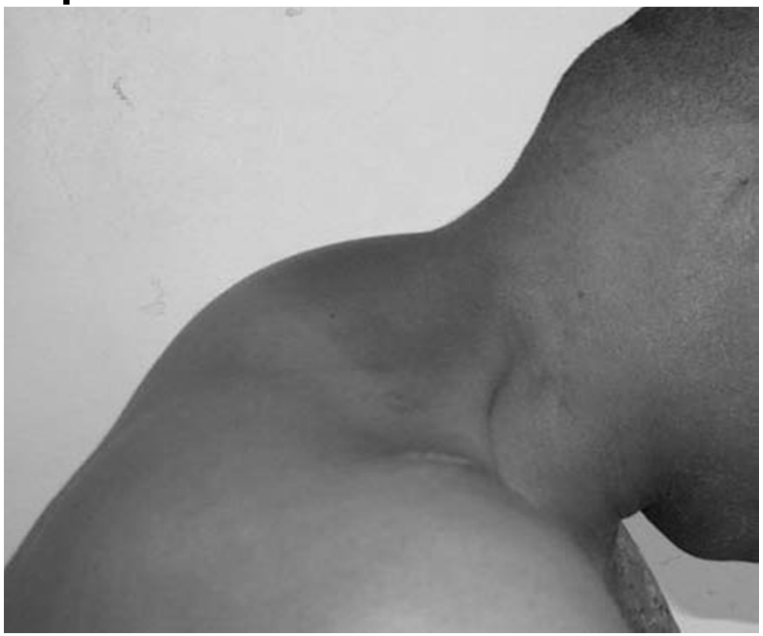
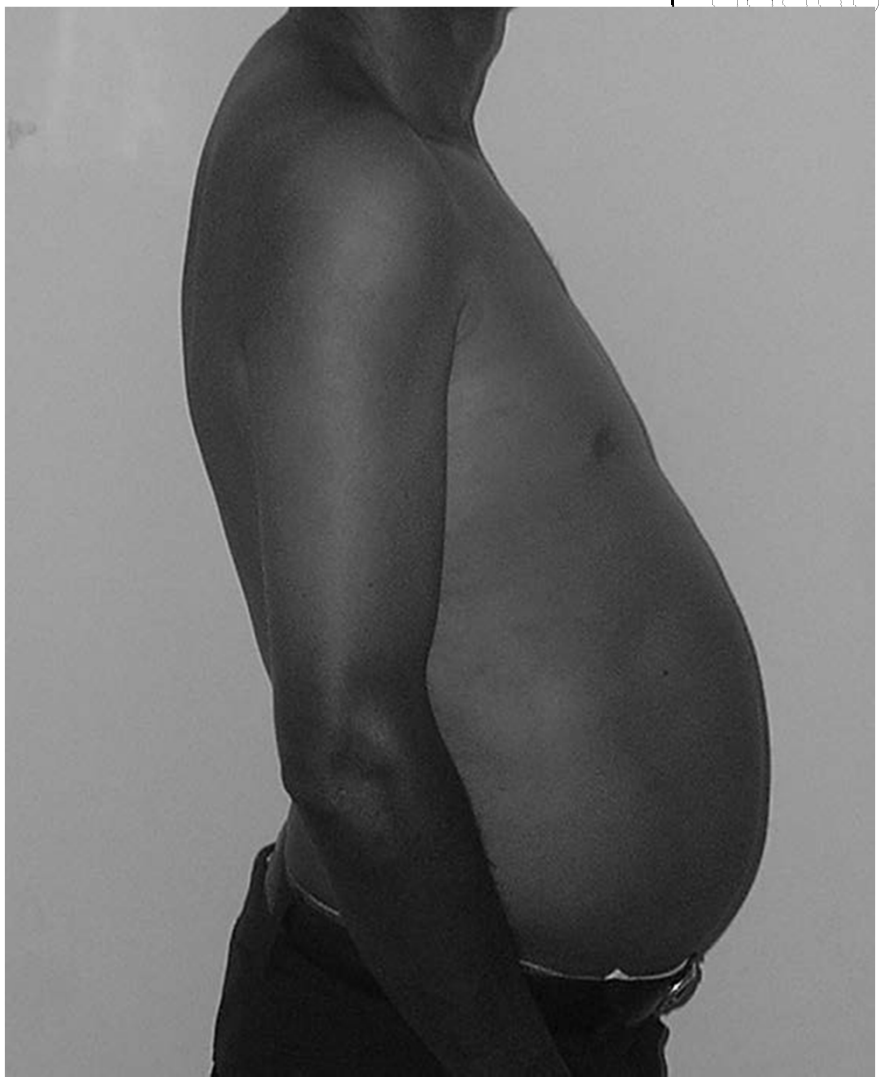
Fat redistribution syndrome

- Associated with thymidine analogue NRTI's- mostly D4T but also with AZT
- Get changes in body fat distribution
- Can present with fat accumulation or fat loss or both
- Change early to TDF if adult or ABC if child
- As late change can cause disfigurement as resolution is slow and often incomplete

Clinical picture of fat accumulation

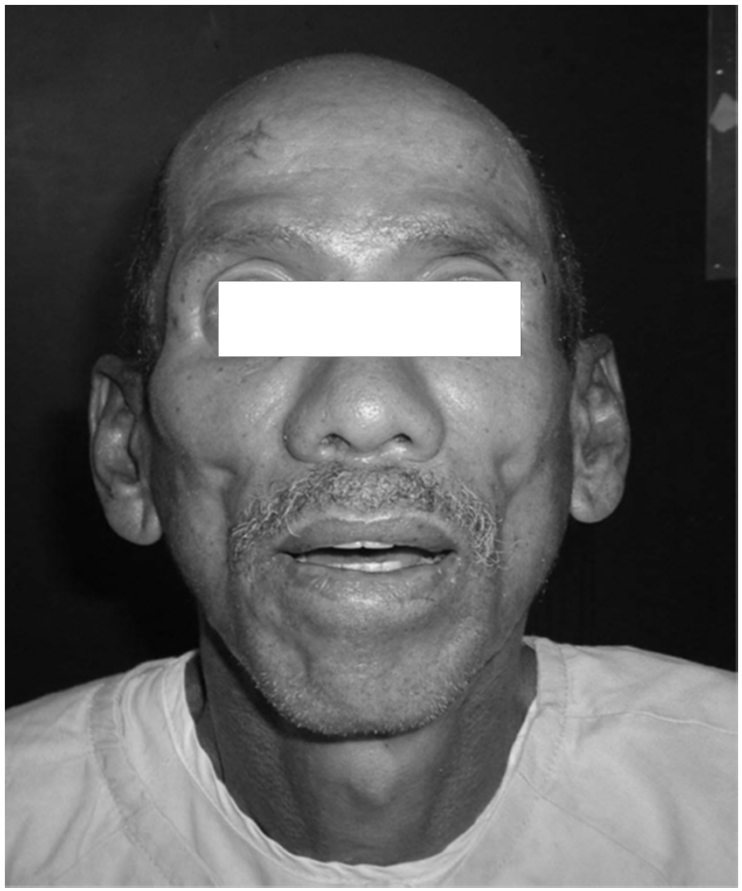
- Visceral obesity
- ‘Buffalo’ hump
- Breast enlargement
- Lipomata





Clinical picture of fat loss

- Loss of subcutaneous fat
- Mostly on face, limbs and buttocks



ARV drug substitutions – adults

ARV drug	Replacement ARV
Tenofovir	Abacavir
Stavudine	Adult- Tenofovir Paed- Abacavir
Nevirapine	Efavirenz Lopinavir / ritonavir if EFV contraindicated
Efavirenz	Nevirapine If rash or high CD4 (male > 400 , female > 250)– use Lopinavir / ritonavir
Zidovudine	Abacavir
Lopinavir/ ritonavir	Atazanavir

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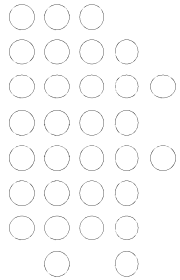

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Questions