ANTIRETROVIRAL THERAPY IN ADULTS

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Southern African HIV Clinicians Society

Sub-Saharan Africa has just over 10% of the world's population but is home to more than 60% of all people living with HIV (approximately 25.4 million people). Prevalence rates in southern Africa's antenatal clinics surpass 25%, the highest in the world.

South Africa is host to the highest number of HIV-infected people in the world (5.3 million, UNAIDS/WHO AIDS epidemic update, December 2004) with considerable regional variation and an annual increase in all but two provinces (Free State and Gauteng). The Free State, Mpumalanga and KwaZulu-Natal have prevalence rates among pregnant women attending public sector antenatal clinics of > 30% while the remaining provinces have a range of between 15% and 17.5%.

Four other countries in the region have very high antenatal prevalence rates, often exceeding 40%: Botswana, Lesotho, Namibia and Swaziland (39%). Elsewhere in the sub-region HIV infections in pregnant women appear to be stabilising at lower levels, e.g. Malawi (18%), Zambia (16%) and Zimbabwe (25%). Uganda's prevalence, though still high, has dropped in the last decade to 5 - 6%. Angola is the exception in the region, having had very low prevalence levels for some years, possibly owing to the war which restricted civilian movement. Prevalence remains at about 3% at Luanda's antenatal clinics; however, sex workers have an incidence of 33%, fuelling fears of a widespread and rapid spread in this country.

Most sub-Saharan countries have antiretroviral roll-outs, albeit at different stages and levels of delivery.

In July 2004, the Health Systems Trust, reported in the first *South African Health Review* (*SAHR*) that AIDS was responsible for 39% of deaths in South Africa in 2000. Gearing up for the national antiretroviral (ARV) roll-out in early 2003, the South African government estimated that about half a million South Africans with AIDS were in urgent need of ARV treatment (ART). In March 2003 the Department of Health commenced the national roll-out at a handful of pre-selected, designated pilot sites, aiming to treat 53 000 HIV-infected South Africans (CD4+ counts of < 200/µl) with ARVs by March 2004, and expanding the number of sites over time. To date progress has been slower than planned. National ART guideline regimens are advised in these guidelines.

1. GOALS OF THERAPY

The primary goals of ARV therapy are:

- improvement of quality of life
- reduction of HIV-related morbidity and mortality
- maximal and durable suppression of viral load, and
- restoration and/or preservation of immunological function.

This is achieved by suppressing viral replication as intensely as possible for as long as possible by using tolerable and sustainable treatment for an indefinite period of time. By doing so, the impact of HIV on the immune system may be minimised and the morbidity and mortality associated with HIV infection can be improved.

Effective combination ARV therapy has been shown to reduce the number of new cells infected by HIV and to impede the ability of the virus to evolve drug resistance.

2. STANDARD OF CARE

Maximally suppressive ARV regimens should be used in order to obtain the best clinical results and to prevent resistance. In the region there is still widespread use of non-suppressive regimens such as dual nucleoside reverse transcriptase inhibitor (NRTI) therapy. Initiation of such therapy should be strongly discouraged.

REGIMENS TO PREVENT TRANSMISSION OF HIV

Non-suppressive regimens are effective in preventing HIV transmission in prevention of mother-to-child trans-

mission (PMTCT), post-exposure prophylaxis for health care workers following occupational exposure, and following sexual exposure. Refer to appropriate guidelines.

3. CLASSES OF ARV AGENTS AND THEIR MECHANISMS OF ACTION

Currently available ARV agents inhibit one of two key viral enzymes required by HIV for intracellular viral replication (Table I, below):

- reverse transcriptase, which is essential for completion of the early stages of HIV replication, and
- protease, which is required for the assembly and maturation of fully-infectious viral progeny.

4. ARV AGENTS CURRENTLY AVAILABLE IN SOUTHERN AFRICA AND COMMON ADVERSE EVENTS (TABLE II, p. 21)

Notes on currently available ARVs:

- Always refer to the most current version of the guidelines as new treatments regularly become available for clinical use.
  Different fixed-dose combinations are increasingly being made available. The oldest combination is AZT/3TC, but 2- and 3-drug fixed combinations are now available throughout southern Africa. Side-effects remain as described above.
- Increasingly, low-dose ritonavir is being used to 'boost' the blood levels of certain PIs, routinely with lopinavir, and usually with indinavir and saquinavir; it is not used in combination with nelfinavir, where boosting has little impact on blood levels.

DOSAGES, RISK FACTORS AND SPECIAL PRECAUTIONS IN PREGNANCY, RENAL FAILURE, AND LIVER FAILURE

Risk factors in pregnancy are set out in Table III (p. 22).

ART dosages in renal failure are set out in Table IV (p. 22). For peritoneal dialysis the dose given under creatinine clearance < 10 should be given daily. For haemodialysis the dose given under creatinine clearance < 10 should be given daily, but it must be given *after* dialysis on dialysis days or else the drug will be dialysed out.

ART dosages in liver impairment are set out in Table V (p. 23).

5. READINESS FOR THERAPY

Patient readiness for therapy is as important as the medical indications for commencing therapy.

- Patient must demonstrate insight.
- Patient must be informed that lifelong therapy is essential.
- Patient must be aware of importance of adherence.
- Patient must have been adequately informed about side-effects.
- Patient must have established the ability to attend reliably and have attended at least two or three visits before commencing therapy.
- Active depression or substance abuse should be dealt with.
- Support, e.g. disclosure, support groups, treatment 'buddies'.
- Personal treatment plan including drug storage and strategies for missed doses.

6. SUPPORT AND COUNSELLING

LIFE-SKILLS, CRISIS INTERVENTION AND FAMILY PLANNING COUNSELLING

Life-skills and crisis counselling should take place in a locale where privacy and time are available to the counsellor and the patient. Where time and opportunity do not permit, the physician should refer to an appropriately skilled caregiver.

TREATMENT/MANAGEMENT-RELATED COUNSELLING

Many patients are afraid of starting ART. Reassure the patient that the drugs work and that side-effects are usually minor and manageable. The commencement of ART

TABLE I. CLASSES OF ARV AGENTS AND THEIR MECHANISM OF ACTION

Classification of antiretroviral agent	Abr.	Mechanism of action	Specific action
Nucleoside & nucleotide* reverse transcriptase inhibitors	NRTIs / NtRTI	Reverse transcriptase inhibition	Mimics the normal building blocks of HIV DNA
Non-nucleoside reverse transcriptase inhibitors	NNRTIs	Reverse transcriptase inhibition	Directly inhibits reverse transcriptase
Protease inhibitors	PIs	Protease inhibition	Inhibits late stages of HIV replication
Fusion inhibitors†		Entry inhibition	Binds to gp41

*Tenofovir – not yet registered in South Africa.
†Not yet available in the region and prohibitively expensive.

TABLE II. ARV AGENTS CURRENTLY AVAILABLE IN SOUTHERN AFRICA AND COMMON ADVERSE EVENTS

Generic name	Class of drug	Dosage (and pill burden)	Common adverse events
Zidovudine (AZT)*	NRTI	300 mg bid (2 tabs daily)	Bone marrow suppression, gastrointestinal (GI) upset, headache, myopathy, hyperlactataemia/ steatohepatitis (medium potential)
Didanosine (ddI)	NRTI	200 mg bid (125 mg bid if < 60 kg) or 300 - 400 mg qd (4 tabs daily)	Peripheral neuropathy, pancreatitis, nausea, diarrhoea (take on empty stomach), hyperlactataemia/steatohepatitis (high potential)
Zalcitabine (ddC)	NRTI	0.75 mg tid (3 tabs daily)	Peripheral neuropathy, pancreatitis, oral ulcers, hyperlactataemia/steatohepatitis (high potential),
Lamivudine (3TC)	NRTI	150 mg bid (2 tabs daily)	Anaemia, GI upset, myalgia, pancreatitis (rarely), hyperlactataemia/steatohepatitis (low potential)
Stavudine (d4T)	NRTI	40 mg bid (30 mg bid if < 60 kg) (2 caps daily)	Peripheral neuropathy, lipo-atrophy, hyperlactataemia/steatohepatitis (high potential)
Abacavir	NRTI	300 mg bid (2 tabs daily)	GI upset, hypersensitivity reaction 5%, hyperlactataemia/steatohepatitis (low potential)
Tenofovir*	Nucleotide RTI (NtRTI)	300 mg qd (1 tab daily)	Asthenia, headache, GI upset and tubular nephropathy, ddI concentrations increased 30 - 60%
Nevirapine (NVP)	NNRTI	200 mg qd for 14 days then 200 mg bid (2 tabs daily) or 400 mg od	Rash, hepatitis
Efavirenz (EFV)	NNRTI	600 mg od (3 tabs daily, new single tablet now available)	Rash, central nervous system symptoms, elevated transaminases
Nelfinavir	PI	750 mg tid or 1 250 mg bid 9 (tid)/10 (bid) caps daily	Diarrhoea (take with food), hyperglycaemia, dyslipidaemia
Indinavir	PI	800 mg q 8 h (6 caps daily) take on an empty stomach; now commonly used with decreased dosage, combined with ritonavir – recommended 800 mg bid with100 - 200 mg ritonavir bid, no food restrictions	Kidney stones, unconjugated hyperbilirubinaemia, GI disturbances, hair loss, hyperglycaemia, headache, dyslipidaemia
Ritonavir	PI	600 mg bid (12 caps daily) – very rarely used as sole PI in adults	GI upset, circumoral and extremities paraesthesias, diarrhoea, fatigue, hepatitis, taste perversion, hyperglycaemia, dyslipidaemia
Saquinavir (hard and soft gel formulations)	PI	600 mg bid, 1 200 mg tid (9 caps daily); when combined with ritonavir, dose at 400 mg combined with ritonavir 400 mg, both bid	GI disturbances (mild) (take with a fatty meal, or up to 2 hours after meal), headache, elevated transaminases, hyperglycaemia, dyslipidaemia
Atazanavir	PI	400 mg qd (2 tabs daily); combinations with ritonavir being explored	Unconjugated hyperbilirubinaemia, hyperglycaemia, dyslipidaemia (low potential)
Amprenavir*	PI	1 200 mg bid (16 tabs daily)	Rash, headache, GI upset, hyperglycaemia, dyslipidaemia
Lopinavir/ritonavir	Boosted PI	400/100 mg bid (6 caps daily)	Asthenia, headache, GI upset, hyperglycaemia, dyslipidaemia

*Not yet registered in South Africa.

TABLE III. RISK FACTORS IN PREGNANCY

Class, drugs	FDA category*
NRTIs	
Abacavir	C
Didanosine	B
Lamivudine	C
Stavudine	C
Tenofovir	B
Zalcitabine	C
Zidovudine	C
NNRTIs	
Efavirenz	D†
Nevirapine	C
PIs	
Amprenavir	C
Indinavir	C
Lopinavir-ritonavir (in combination)	C
Nelfinavir	B
Ritonavir	B
Saquinavir	B

Notes:

* The **FDA codes for A B, C and D** are listed below. The coding assigned to the drugs is based on package inserts; FDA, Briggs GG, Freeman RK, Yaffe SJ, *Drugs in Pregnancy and Lactation* 6th edition 2002; or expert opinion.

†**Efavirenz has been shown to be teratogenic in primates, causing craniofacial abnormalities. There have been three human case reports of myelomeningocele in infants following intrauterine exposure to efavirenz.**

FDA codes

A: Controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters), and the possibility of harm appears remote.

B: Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).

C: Either animal studies have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is evidence of fetal risk based on human experience, and the risk of use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

is never a medical emergency: let the patient voice a desire to start therapy and indicate their commitment to take medication and to follow up as instructed. Never coerce the patient into starting the treatment.

Give the patient a treatment plan. This should include the reasons for commencing therapy and which drugs are to be used. The names of the drugs must be mentioned and specific detail given including the appearance of each drug, when and how they are to be taken, and a brief indication of anticipated side-effects and toxicity.

The medication requires adherence of the order of 95 - 100%. Poor adherence and non-compliance result in the development of drug resistance. The desire to stop therapy or alter the number or timing of the drugs must be avoided. The patient must be encouraged to discuss drug-related issues with his/her doctor before any changes are made.

Drug	Creat. clearance 10 - 50	Creat. clearance < 10
Zidovudine	Unchanged	300 mg daily
Didanosine	> 60 kg 200 mg daily < 60 kg 150 mg daily	>60 kg 100 mg daily < 60 kg 75 mg daily
Lamivudine	150 mg daily	50 mg daily
Stavudine	> 60 kg 20 mg 12-hourly, < 60 kg 15 mg 12-hourly	> 60 kg 20 mg daily < 60 kg 15 mg daily
Abacavir	Unchanged	Unchanged
Tenofovir	AVOID	AVOID
Zalcitabine	0.75 mg 12-hourly	0.75 mg daily
PIs	Unchanged	Unchanged
NNRTIs	Unchanged	Unchanged

Sources: Bartlett JG. *Medical Care of Patients with HIV Infection* 2003, and *The Sanford Guide to Antimicrobial Therapy* 2003.

Formula to estimate creatinine clearance:

$$\frac{140 - \text{age} \times \text{ideal weight}}{0.82 \times \text{serum creatinine}}$$

Women: multiply total by 0.85

LIFESTYLE, NUTRITION, TRADITIONAL MEDICATION AND SUPPLEMENTS IN HIV

Various adjuncts to therapy are widely used in the community. These include specific diets, food/nutritional supplements, vitamins and so-called immune 'boosters'. Scientific evidence to support the use of these is largely absent. Some herbs, trace elements and the excessive dosing of certain vitamins may cause harm and ought to be discouraged. Fawzi *et al.* have recently shown survival benefit in Tanzanian women given a supplement of vitamins B, C and E over a period of 5 years. This study needs further confirmation but does form the basis of a general view that these vitamins can be used safely in patients who are HIV infected. A healthy lifestyle is recommended, including a balanced diet, plenty of exercise, regular clinic follow-up and a positive outlook on the future.

MALARIA, TRAVEL AND HIV

Travellers to areas endemic for malaria and yellow fever need to be cautioned. The forested regions where contact with the mosquito vector and the virus is possible must be avoided.

Drug interactions between antimalarials and anti-retrovirals:

- Among drugs used for chemoprophylaxis, there are no clinically significant pharmacokinetic interactions between antiretrovirals and mefloquine or doxycycline. However, mefloquine and efavirenz both cause frequent neuropsychiatric side-effects.

TABLE V. ART DOSAGES IN LIVER IMPAIRMENT

Drug	Prescribing with liver impairment
NRTIs	
Abacavir	Reduce adult dose to 200 mg bd for mild to moderate liver impairment. Contraindicated in severe hepatic impairment
Didanosine	Use with caution. Recent reports implicate ddI use as a risk factor for the development of hepatic decompensation in patients being treated for cirrhosis due to hepatitis C. Avoid co-administration of ddI with d4T in patients with liver disease in view of increased risk of lactic acidosis
Lamivudine	3TC should be used with caution in patients with chronic hepatitis B infection as there is a risk of rebound hepatitis after treatment
Stavudine	Avoid co-administration of ddI with d4T in patients with liver disease in view of the risk of lactic acidosis
Tenofovir	Acute exacerbations of hepatitis B have been reported in patients who are co-infected with HIV and have discontinued tenofovir
Zalcitabine	May be associated with exacerbation of hepatic dysfunction, especially in individuals with pre-existing liver disease or with a history of alcohol abuse. Such patients should be closely monitored and dose reduction or interruption of drug therapy should be considered if necessary. Avoid co-administration with either ddI or d4T in patients with liver disease in view of the likely increased risk of lactic acidosis
Zidovudine	Decrease dose by 50% or double dosage interval
NNRTIs	
Efavirenz	Caution should be exercised in administering efavirenz to patients with liver disease
Nevirapine	Contraindicated in severe hepatic impairment; accumulation may occur with moderate hepatic impairment but no specific recommendations on dose reductions can be made owing to limited data
PIs	
Indinavir	Reduce adult dose to 600 mg 8-hourly in mild to moderate hepatic impairment
Lopinavir/ ritonavir	Lopinavir is highly metabolised in the liver and concentrations may be increased in patients with hepatic impairment. Pharmacokinetic studies have not been done, but reduced adult dose to 2 tablets bd should be considered in severe liver disease
Nelfinavir	Dose reduction advised – limited data suggest doses of 500 mg bd to 750 mg bd
Ritonavir	No adjustment for mild hepatic impairment or moderate impairment (monitor closely). No data on severe impairment
Saquinavir	Avoid. There have been reports of worsening liver disease and development of portal hypertension after starting saquinavir in patients with severe liver disease

Doxycycline is therefore the preferred chemoprophylactic agent for patients on efavirenz.

- Levels of atovaquone, used in a fixed-dose combination with proguanil (Malanil), are reduced by PIs, the significance of which is uncertain. However, it would be prudent to avoid Malanil use in patients on PIs.
- Quinine levels are increased by PIs. Quinine is the drug of choice for severe malaria, but is a toxic drug with potential for life-threatening adverse effects. PIs should therefore be discontinued until the course of quinine has been completed, and monitoring for quinine adverse effects (hypoglycaemia and arrhythmias) is essential.

Yellow fever vaccination poses a risk to the HIV traveller whose CD4 level is below 200 cells/µl. Encourage the traveller to make alternative arrangements or to travel with documentation that permits travel without prior vaccination.

IMMUNISATIONS

HIV infection is associated with a suppression of both humoral and cell-mediated immune response, which may impair the response to vaccinations, reducing their efficacy especially if the CD4 count is < 200 cells/µl. The safety of live attenuated vaccination is also modified by HIV infection and live vaccines are contraindicated in symptomatic HIV disease or if the CD4 count is < 200 cells/µl. The decision to use a vaccine must be based on best assessment of risks and benefits.

It is mandatory to report all suspected vaccine-related adverse events and vaccine failures.

OPPORTUNISTIC INFECTIONS (OIs)

OIs must be avoided through the use of appropriate prophylaxis. Local and international guidelines should be consulted, e.g. the Southern African HIV Clinicians Society's OI guidelines.

7. INDICATIONS FOR STARTING ART (TABLE VI, p.24)

Initiation of highly active antiretroviral therapy (HAART) is never an emergency unless used as post-exposure prophylaxis.

ART should be deferred until patients are prepared to commit themselves to long-term treatment and to maintaining good adherence to treatment.

All infected individuals, including those on effective ART, should be viewed as potentially infectious. Adequate counselling about safer sex practices must be provided to encourage prevention of new infections and re-infection.

TABLE VI. INDICATIONS FOR STARTING ART

Symptomatic patient	Treatment
Presence of severe HIV-related symptoms (WHO clinical stage 3 or 4)*	ART recommended
Asymptomatic patient	**Treatment**
CD4+ count < 200	ART recommended
CD4+ count 200 - 350	ART should be considered on an individual basis†
CD4+ count > 350	Defer treatment

* WHO clinical staging is currently being revised. Initiation of tuberculosis therapy and HAART should not be commenced simultaneously (see below).
† Two CD4+ counts in this stratum should be done before a decision is made. Individuals with high viral loads (> 100 000) *or* with rapidly declining CD4+ counts *or* troublesome HIV-related symptoms that are not covered in the staging system should commence ART without delay, while others can wait until their CD4+ count approaches 200.

PRIMARY INFECTION

The recommendation to treat primary infection has been removed owing to lack of evidence, and primary infection should only be treated in a carefully monitored research environment, or in the presence of significant acute symptoms, in careful consultation with an expert and with a fully informed patient. There are compelling reasons to defer therapy, including lack of proven efficacy, drug toxicity, and the potential for drug resistance. Patients with severe primary infection progress more rapidly, and this is an indication for careful follow-up.

TUBERCULOSIS AND HAART

The following should be kept in mind when a patient presents with tuberculosis (TB) before commencing HAART:

- TB should always be managed by public sector TB clinics.
- If the patient is already on ART the regimen should be changed, if possible, to be compatible with rifampicin.
- When ART is commenced the patient's symptoms may *temporarily* worsen as part of immune reconstitution.
- If the patient's CD4+ count is > 200 cells/µl commence ART *after* completing TB therapy (providing the patient fulfils the criteria above). In other words, the CD4 count must be < 350.
- If the CD4+ count is < 200 cells/µl delay ART until after the intensive phase of TB therapy (2 months) *unless* the patient has other serious HIV-related illness or has a very low CD4+ count (< 50 cells/µl), in which case ART should be introduced only once the patient is stabilised on TB therapy.

Interactions of ARV agents with rifampicin are set out in Table VII.

TABLE VII. ART INTERACTIONS WITH RIFAMPICIN

ARV	Interaction
NRTIs	No significant interactions
Efavirenz (NNRTI)	Mild reduction in efavirenz levels; recommended to use conventional dose
Nevirapine (NNRTI)	Moderate reduction in nevirapine levels – limited experience – concern about shared hepatotoxicity; recommended to use conventional dose, but with close monitoring
Ritonavir (PI) (full dose, rarely used)	No significant interaction
Lopinavir/ritonavir (boosted PI) 400 mg/100 mg bid (Kaletra)	Add ritonavir 300 mg bid (3 tablets bid)
Ritonavir + saquinavir both 400 mg bid*	No significant interaction; do not use saquinavir without ritonavir
All other PIs	Marked reduction in PI levels – avoid

* A recent study of ritonavir 100 mg plus saquinavir 1 000 mg bid was associated with a high incidence of hepatotoxicity. Caution is advised when using the combination of ritonavir + saquinavir both 400 mg bid, with frequent monitoring of liver function tests.

Shared side-effects of TB and ART are set out in Table VIII.

TABLE VIII. SHARED SIDE-EFFECTS OF TB AND ART

Side-effects	ART	Tuberculosis treatment
Nausea	Didanosine, zidovudine, PIs	Pyrazinamide
Hepatitis	Nevirapine, efavirenz	Rifampicin, isoniazid, pyrazinamide
Peripheral neuropathy	Stavudine, didanosine	Isoniazid
Rash	Nevirapine, efavirenz	Rifampicin, isoniazid, pyrazinamide

Modified from 2004 National Antiretroviral Treatment Guidelines, 1st ed; Table VII; page 18.

Patients should be counselled before therapy about the following:

- Treatment for TB together with ART involves taking a large number of tablets. Patients may struggle with adherence.
- When ART is commenced, the patient's TB symptoms may temporarily worsen as part of immune reconstitution.

8. LABORATORY MONITORING

Viral loads are expensive and are not always available in resource-poor settings. However, viral loads are strongly recommended to monitor therapy. We recommend that they be done at the following times:

- baseline
- 6 - 8 weeks after commencement of therapy
- thereafter every 4 - 6 months.

CD4+ counts should be done at the time of viral load testing.

9. TOXICITY MONITORING

HAEMATOLOGICAL TOXICITY (TABLE IX)

Patients on zidovudine, stavudine or co-trimoxazole may experience abnormalities in their full blood counts. Significant bone marrow toxicity from co-trimoxazole generally only occurs with high doses used for treating opportunistic infections – it is reversible with folinic acid (not folate). Long-term monitoring of full blood counts is only necessary with zidovudine – this should be monitored monthly for the first 3 months of therapy and thereafter 3-monthly. The main problem is anaemia and neutropenia – platelet counts generally rise with zidovudine.

TABLE IX. GUIDELINES FOR MANAGING HAEMATOLOGICAL TOXICITY (MAINLY ZIDOVUDINE-INDUCED)

Hb	**> 8 g/dl**	**7 – 7.9**	**6.5 – 6.9**	**< 6.5**
	Monitor	Repeat 4 weeks Reduce AZT: 200 mg bd	Repeat 2 weeks Reduce AZT: 200 mg bd	Stop AZT
Neutrophils	**1 – 1.5 x 10^9/l**	**0.75 – 1**	**0.5 – 0.75**	**< 0.5**
	Repeat 4 weeks	Repeat 2 weeks	Repeat 2 weeks Reduce AZT: 200 mg bd	Stop AZT

HEPATOTOXICITY (TABLE X)

- Liver function tests (LFTs) should be done at ART initiation and thereafter tailored to individual drug regimens. All ARV agents may cause hepatotoxicity, but the most common is nevirapine (laboratory monitoring shows 10 - 15% of patients to be affected but only 1% present with clinical hepatitis). Hepatotoxic drugs should be discontinued at high levels of LFT abnormality (Table X) or at low levels if any symptoms of hepatitis appear.
- A common cause of fatty liver is NRTI use, especially stavudine.
- There is divided opinion that routine monitoring of ALTs is necessary but a full LFT is recommended for patients on nevirapine at baseline, and thereafter only the ALT need be monitored: at 2 weeks; 4 weeks; 2 months; and then 3-monthly *(National Guidelines say 6 months)* if no problems are detected.
- If GGT, alkaline phosphatase or conjugated bilirubin is elevated, a liver ultrasound scan should be done to exclude biliary obstruction. An ultrasound or CT scan may suggest fatty infiltration, but a liver biopsy may be necessary for a definitive diagnosis and assessment of the severity of the condition.
- Isolated unconjugated hyperbilirubinaemia (drug-induced Gilbert's syndrome) is generally benign and associated with some PIs (indinavir and atazanavir) and is more marked after fasting.
- **Note: Patients with underlying hepatitis B and C infection frequently experience a 'flare-up' of hepatitis when ART is commenced, as part of the *immune reconstitution syndrome*. Hepatitis B can also flare when ARVs that have activity against hepatitis B (lamivudine and tenofovir) are discontinued.**
- Many other drugs can cause hepatotoxicity, notably anti-tuberculosis therapy (including prophylactic isoniazid) and azoles.

HYPERLACTATAEMIA

- Elevated lactate is common in patients treated with NRTIs (up to 20%) but is generally asymptomatic.
- If asymptomatic, elevated lactate does not appear to predict the development of lactic acidosis and it is therefore unnecessary to monitor levels in asymptomatic patients.
- Lactic acidosis is a serious, rare but potentially fatal side-effect of NRTIs (most commonly associated with d4T, particularly when combined with ddI). It occurs in about 0.1% of patients, when it presents as a life-threatening acute illness with acidosis.
- Symptomatic hyperlactataemia without acidosis occurs in 1 – 2% of patients per annum.

The potential of NRTIs to cause elevated lactate is: zalcitabine/stavudine/didanosine > zidovudine > lamivudine/abacavir

- The combination of didanosine and stavudine is associated with a high risk of symptomatic hyperlactataemia or lactic acidosis, particularly in pregnancy (when the combination should be avoided).
- Risk factors for hyperlactataemia include:
  - female gender
  - obesity

TABLE X. GUIDELINES FOR MANAGING HEPATOTOXICITY

	< 2.5 × ULN	**2.5 – 5 × ULN**	**5 – 10 × ULN**	**>10 × ULN**
ALT	Monitor	Repeat 1 week	Discontinue relevant drug(s)	Discontinue all drugs
GGT/alk. phos.	Monitor	Repeat 2 weeks	Ultrasound, ? biopsy	Ultrasound, ? biopsy
Bilirubin	Repeat 4 weeks	Repeat 2 weeks	Discontinue relevant drug(s)	Discontinue all drugs

ULN = upper limit of normal.

- prolonged use of NRTIs
- development of NRTI-induced peripheral neuropathy or fatty liver.

- Hyperlactataemia and lactic acidosis generally occur after months of NRTI treatment.
- Symptoms include: nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
- A raised lactate level* of > 5 mmol/l, increased anion gap and metabolic acidosis confirm the diagnosis of lactic acidosis. Associated abnormalities include elevated AST and ALT, lactate dehydrogenase and creatinine kinase.
- If there is hyperlactataemia *without* acidosis and lactate levels < 5 mmol/l, it may be possible to manage the patient as an outpatient. Therapy should be adjusted in symptomatic patients to NRTIs that are less associated with elevated lactate (see box on previous page). Symptoms and serial lactate levels should be done for several months (note that lactate levels decrease slowly over weeks).
- If there is hyperlactataemia (> 5 mmol/l) *with* acidosis, ART must be discontinued and the patient should be admitted, preferably to an intensive care unit. The following signs may be present:
  - hypotension
  - respiratory failure
  - stupor/coma.
- Treatment is supportive. Bicarbonate replacement is controversial, but most experts would partially correct severe acidosis with bicarbonate. High-dose riboflavin (50 mg) and L-carnitine may be useful (no evidence for either intervention).
- In lactic acidosis NRTIs should be discontinued and not used again.

HYPERLIPIDAEMIA

- PIs can cause fasting hypertriglyceridaemia and elevated LDL cholesterol. Diet and lifestyle modification should always be advised.
- Marked hypertriglyceridaemia can cause pancreatitis.
- When treating hypertriglyceridaemia with lipid-lowering drugs, the fibrates should be considered the drugs of choice as they are more effective than the statins for hypertriglyceridaemia, do not interact with PIs and are effective against hypercholesterolaemia as well.
- Many statins have interactions with PIs which can lead to potentially toxic levels of statin, with the exception of pravastatin (levels of which are unaffected by PIs). Atorvastatin levels are significantly raised by PIs but lower doses (5 – 20 mg) can be used. Of the statins, only pravastatin or low-dose atorvastatin (10 mg) are recommended. See Table XI for management of hyperlipidaemia in patients on PIs.

* A lactate level is performed on venous blood collected after the tourniquet has been released and placed in a tube containing sodium fluoride (grey top). Bloods should be sent on ice and processed as quickly as possible.

TABLE XI. MANAGEMENT OF HYPERLIPIDAEMIA IN PATIENTS ON PIs

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

Schambelan M *et al.* Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society–USA Panel. *J AIDS* 2002; **31**: 257-275

LIPODYSTROPHY

- Long-term use of PIs and some NRTIs may cause chronic lipodystrophic changes including raised cholesterol and triglyceride levels and a change in body fat distribution (central obesity, peripheral and facial wasting or lipo-atrophy).
- The redistribution of body fat may cause distress on a cosmetic level.
- Lipo-atrophy may improve when stavudine is substituted with an NRTI less associated with such adverse effects, e.g. abacavir. Exercise is of some assistance in reducing abdominal fat.
- There may be some reversal on cessation of therapy but changes are very slow, and rarely complete. Ideally, substitution should be considered at the earliest onset of symptoms.

HYPERSENSITIVITY

- Rash with NNRTIs is common (more severe and frequent with nevirapine) in the first 6 weeks of therapy. If the rash is accompanied by systemic features (especially fever), elevated liver enzymes/hepatitis, or mucosal involvement/blistering discontinue the NNRTI immediately and do not rechallenge.
- If the rash occurs without these features, the NNRTI can be continued and the rash treated symptomatically with antihistamines and possibly also topical steroids, although the latter is controversial. Systemic steroids should not be used.
- Patients who develop rashes during the low dose nevirapine 'lead in' phase (200 mg daily) must not have the dosage increased to 200 mg bd until the reaction has completely resolved. This 'treat-through' approach is only acceptable if the patient can be carefully observed; otherwise substitute with a drug from a different class. Patients who develop nevirapine rashes at the higher dosage should have their nevirapine dose lowered to 200 mg daily until the rash resolves.
- There is an approximately 50% cross-reaction between nevirapine and efavirenz and they are therefore not recommended as substitutes for one another in cases of severe hypersensitivity.

- Abacavir hypersensitivity is primarily a systemic reaction occurring within the first 8 weeks of therapy in 3% of cases. Fatalities may occur. Therapy must be discontinued, and *never* rechallenge as fatalities may occur. The manifestations of hypersensitivity include fever, rash, fatigue and abdominal or respiratory symptoms. If there is any doubt about the diagnosis, e.g. if the patient has a cough with fever, then the patient should be admitted for observation. Symptoms progress if hypersensitivity is present.

9. OUTCOMES OF ART

CRITERIA FOR TREATMENT SUCCESS

- A decline in viral load of at least 1 log from pre-treatment levels by 6 - 8 weeks after initiating ART.
- A decline in viral load to < 400 RNA copies/ml by 24 weeks after commencement of therapy.

Note: *A sustained viral load of < 50 RNA copies/ml (or undetectable viral load) is associated with the most durable virological benefit.*

CRITERIA INDICATIVE OF TREATMENT FAILURE

Several factors can influence the measurement of HIV viral load. It is strongly recommended that the decision to alter therapy should be based on the results of repeat testing after 1 - 3 months following intensive adherence counselling. Inadequate patient adherence to the prescribed regimen remains one of the most common reasons for treatment failure.

Virological failure (as defined in these guidelines):
Primary virological failure. A decline in viral load of less than 1 log (10-fold) 6 - 8 weeks after commencing ART.
Secondary virological failure. A sustained increase in viral load > 5 000 copies/ml.

Immunological failure is defined as a 30% drop in CD4+ count from peak value or a return to pre-ART baseline or lower. A significant minority of patients on ART fail to achieve a significant rise in CD4+ count despite viral suppression, particularly if the CD4+ count is very low at baseline. Good viral load suppression should be seen as a good response in this percentile even if CD4+ counts remain low.

Clinical failure is defined as progression of disease with the development of OIs or malignancy occurring 3 months or more after initiation of ART.

Note that CD4 counts may rise, even in the presence of incomplete viral suppression and drug resistance. Similarly, OIs may occur despite excellent viral suppression and immunological recovery. All three parameters need to be closely monitored.

10. INITIAL ARV REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT

Initial regimens for treatment-naïve patients should consist of combinations of drugs that are expected to achieve the abovementioned treatment goals.

INDIVIDUALISED VS. STANDARDISED REGIMENS

The traditional approach in choosing drug regimens in countries where ART has been widely used has been to select a combination of appropriate drugs that suits a patient's individual requirements and preferences. The World Health Organization (WHO) advocates an approach to *'standardise and simplify ART, much like TB treatment in National TB control programmes, while acknowledging the relative complexity of HIV treatment, bearing in mind the needs of health systems that often lack sophisticated manpower and monitoring facilities, without compromising the quality and outcomes of the treatments offered.'*

Advantages of standardised regimens:
- Simplified training and education of providers and patients
- Simplified monitoring for toxicity
- Predictable patterns of resistance
- Predictable and standardised sequence of drug combinations, assisting mass procurement and prescribing
- Limited number of drugs to procure and manage

DEPARTMENT OF HEALTH GUIDELINES (DoH, SOUTH AFRICA)

Two ART regimens are recommended in the South African public sector (Table XII, p. 30). Patients failing both regimens are referred to ART specialists for individual evaluation. New developments in ART will determine options for salvage therapy. Substitution of drugs for toxicities can be made. Drug swaps between regimens can be made for toxicity.

In general, private sectors should tailor their programmes to the public sector guidelines if possible. Botswana, Lesotho, Zambia, Zimbabwe and Swaziland all follow WHO guidelines.

Optimal use should be made of available drugs.

Particular consideration should be given to those factors which may affect patient adherence, such as the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity and drug interaction profile.

The importance of adherence must be clearly explained to the patient and reinforced at every visit. Practitioners should take sufficient time and care to prepare themselves and the patient for an intervention that may be life-long.

In accordance with WHO and UNAIDS recommendations, these guidelines endorse the use of NRTIs and NNRTIs as first-line therapy.

TABLE XII. ART REGIMENS IN THE SOUTH AFRICAN PUBLIC SECTOR

Regimen	Drugs	Indications
Regimen 1		
Regimen 1a	d4T/3TC/EFV	Men, and women who are not of child-bearing potential *or* are using injectable contraception *plus* condoms
Regimen 1b	d4T/3TC/NVP	Women who are unable to guarantee reliable contraception while on therapy
Regimen 2	AZT/ddI and lopinavir-ritonavir	For patients virologically failing regimen 1 despite demonstrating adherence

The use of d4T in first-line therapy makes the choice of second line easier and less toxic (the combination of ddI and d4T should in general be avoided because of the risk of peripheral neuropathy and symptomatic hyperlactataemia).

11. INDICATIONS FOR CHANGING THERAPY

Treatment should only be changed as soon as possible in the following situations:

- patient intolerance despite adequate and appropriate intervention
- significant side-effects
- treatment failure, as defined in 9 on previous page.

12. OPTIONS FOR CHANGING THERAPY

Careful consideration should be taken before changing therapy because of limited number of drugs. Indications for changing regimens should be limited to *toxicity* (the offending drug should be substituted), *intolerance* or *failure* (the entire regimen should be changed). Table XIII contains recommendations for changing therapy in drug intolerance, and Table XIV (p. 31) recommendations for changing NRTIs when drug resistance emerges; the caveats listed above apply.

CHANGING NNRTIs IN THE PRESENCE OF RESISTANCE

There is broad cross-resistance between nevirapine and efavirenz. Resistance to one precludes the use of the other, unless resistance test data indicate the contrary (very rare).

TABLE XIII. RECOMMENDATIONS FOR CHANGING THERAPY IN DRUG INTOLERANCE

Regimen	Toxicity	Drug substitution
d4T/3TC/EFV	d4T-related neuropathy or pancreatitis	Switch d4T to AZT
	EFV-related persistent CNS toxicity	Switch EFV to NVP
	Lactic acidosis	Consult expert
d4T/3TC/NVP	d4T-related neuropathy or pancreatitis	Switch d4T to AZT
	NVP related severe hepatotoxicity	Switch NVP to EFV (except early pregnancy)
	NVP-related severe rash (but not life-threatening)	Switch NVP to EFV
	NVP-related life-threatening rash	Switch NVP to EFV or lopinavir/ritonavir
	Stevens-Johnson syndrome	Switch NVP to lopinavir/ritonavir
	Lactic acidosis	Consult expert
AZT/ddI/lopinavir/ritonavir	AZT-related anaemia or neutropenia	Switch AZT to d4T
	ddI-related GIT side-effects	Switch ddI for enteric-coated ddI
	ddI-related pancreatitis or hepatitis	Consult expert
	Lactic acidosis	Consult expert
	LPV/r-related GIT symptoms	Symptomatic management
	LPV/r-related hyperlipidaemia	See section 9
	Lipodystropy	Consult expert
	Impaired glucose tolerance	Antidiabetic agents (warning: metformin increases risk of acidosis)

Note:

- In the event of virological failure a change of regimen is advised.
- The clinician may choose to be guided by genotypic or phenotypic resistance testing. This must be done in close consultation with a specialist.

TABLE XIV. CHANGING NRTIs IN THE PRESENCE OF RESISTANCE

Initial agent	New agent
Zidovudine	Stavudine*
Stavudine	Zidovudine*
Didanosine	Lamivudine
Lamivudine	Didanosine*
Zalcitabine	Abacavir, stavudine or zidovudine or other as determined by resistance testing
Abacavir	Determined by resistance testing

*May exhibit cross-resistance.

Individuals who fail an NNRTI-containing regimen are candidates for a PI-containing regimen, or a triple-nucleoside NNRTI combination (there is serious concern, however, that triple NNRTI combinations are more likely to fail).

CHANGING PIs IN THE PRESENCE OF RESISTANCE

A major reason for regimens that contain PIs failing is sub-optimal pharmacokinetics and inadequate drug exposure as a result of poor adherence (often due to intolerance). This needs to be considered carefully before deciding to introduce an alternative PI-containing regimen. Second-line PI alternatives may exhibit reduced activity owing to extensive cross-resistance within this class of drugs.

Ritonavir-boosted PIs are preferred because they are more potent, have less frequent dosage intervals, are less susceptible to food-related changes in absorption, and are durable. Exceptions are unboosted nelfinavir in pregnancy and atazanavir, which has a more favourable metabolic side-effect profile.

If a patient fails a PI-containing regimen: If no NNRTI has been used previously, replace with an NNRTI. If this is not an option, if the PI is 'unboosted', consider using another PI with ritonavir boosting. If failing a boosted PI, consider resistance testing. If not available, use a different PI, also with boosting. Some clinicians use two PIs, and then boost both with ritonavir (e.g. lopinavir/saquinavir). There is some evidence that amprenavir may be useful after failure of PIs. Obtain expert help in all these cases.

Avoid triple NRTI regimens in patients who have failed PI-containing regimens – it is likely that significant NRTI resistance mutations will be present, and it is unlikely that these combinations will be effective.

13. THIRD AND FOURTH REGIMENS

Because of limited availability of drugs third and fourth regimens should only be prescribed by a specialist treater. In South Africa we think that genotyping should be done by a specialist because of cost. Indications would be failed second-line therapy and good adherence. Rational definition of a third-line regimen is difficult without genotyping.

Newer drugs we would like to see are tenofovir and tipranavir.

14. PSYCHOLOGICAL SUPPORT FOR PATIENTS AND CAREGIVERS

Severe depression, suicidal talk, domestic violence and psychotic and irrational behaviour, must be regarded seriously. Patients and their families must be assisted with obtaining the help they need.

If a patient is planning to fall pregnant and is taking ART, her ART may need to be changed. Efavirenz, indinavir and the combination of stavudine and didanosine are contraindicated in pregnancy.

Where ART has failed repeatedly or there is no access to such therapy, and death becomes a looming and unavoidable issue, living with grief and loss needs to be addressed by qualified individuals, with sensitivity and without time constraints. Patients are frightened by the prospect of losing control and the constellation of disabling symptoms of advanced AIDS. Palliative symptom control should be aggressively pursued, as it is rare that significant relief is unobtainable. Both the caregiver and the recipient may need help. Support groups and a long-term relationship with the patient and his/her family may make this time easier. Religious workers, palliative care nurses and doctors, and supportive members of the patient's community may need to be called in.

15. TREATMENT DECISION SUPPORT

For specific advice and assistance in using these guidelines, please contact the Southern African HIV Clinicians Society by e-mail: **sahivsoc@sahivsoc.org**

Disclaimer: Specific recommendations provided in this document are intended only as a guide to clinical therapy, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

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