GUIDELINES

ANTIRETROVIRAL THERAPY IN ADULTS

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Southern African HIV Clinicians Society

These guidelines are intended as an update to those published in the *Southern African Journal of HIV Medicine* of March 2005 (issue 18, pp.18 - 31). Since the previous guidelines, the scale-up of antiretroviral therapy (ART) in the region has expanded considerably. Cohort studies from the region show excellent clinical outcomes, but ART is still being started in advanced disease and early death rates remain high. New data have become available on antiretroviral (ARV) tolerability in the region and several new ARV drugs have become available. Important new sections have been added on ART use in special populations, including pregnancy and hepatitis B co-infection.

1. GOALS OF THERAPY

The primary goals of ART are:

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

These goals are achieved by suppressing viral replication for as long as possible by using tolerable and sustainable treatment for an indefinite period of time. With prolonged viral suppression the CD4 lymphocyte count usually progressively increases with partial restoration of pathogen-specific immune function, dramatically reducing the morbidity and mortality associated with HIV infection.

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 some use of non-suppressive regimens such as dual nucleoside reverse transcriptase inhibitor (NRTI) therapy. Initiating such therapy should be strongly discouraged.

However, non-suppressive regimens are effective in preventing HIV transmission in prevention of mother-to-child transmission (PMTCT), post-exposure prophylaxis for healthcare workers following occupational exposure and probably effective following sexual exposure. Refer to appropriate guidelines.

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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3. CLASSES OF ARV AGENTS AND THEIR MECHANISMS OF ACTION

Currently available ARV agents in the southern African region inhibit one of two key viral enzymes required by HIV for intracellular viral replication (Table I):

- 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 (TABLE II)

4.1 NOTES ON ARVs CURRENTLY AVAILABLE IN SOUTHERN AFRICA

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 a number of other 2- and 3-drug fixed combinations are now available throughout southern Africa. These are encouraged as they reduce the pill burden and have the potential to improve adherence. Side-effects remain as described above.
- Low-dose ritonavir is used to 'boost' the concentrations of other PIs. It is always used with lopinavir (fixed-dose combination) and saquinavir; and is strongly encouraged with other PIs (except nelfinavir).

5. INDICATIONS FOR STARTING ARV THERAPY (TABLE III)

Initiation of highly active antiretroviral therapy (HAART) is never an emergency unless used as post-exposure prophylaxis. However, patients with profound immunosuppression are at significant risk of opportunistic illnesses, and should be

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

Classification of ARV agent	Abbreviation	Mechanism of action	Specific action
Nucleoside & nucleotide reverse transcriptase inhibitors	NRTIs	Reverse transcriptase inhibition	Mimics the normal building blocks of 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
Entry inhibitors*		Entry inhibition	Bind to gp41 or chemokine receptors
Integrase inhibitors*		Inhibit integrase	Prevent integration of HIV DNA into the nucleus

*Not yet available in the region.

rapidly assessed and initiated as soon as adherence is assured. The following baseline investigations are recommended in all patients prior to initiating ART:

- liver function tests (LFTs) (alanine transaminase (ALT) measurement may be sufficient)
- full blood count
- serum creatinine (creatinine clearance must be estimated for all patients starting on tenofovir - see section 10 (iii) for the formula) and urinalysis for proteinuria
- hepatitis B surface antigen.

ART should be deferred until patients are prepared to commit themselves to long-term treatment and to maintaining good adherence to treatment (see 'Patient readiness for ART' below).

5.1 INDICATIONS FOR ART IN PATIENTS WITH TUBERCULOSIS

- Although extrapulmonary or disseminated tuberculosis (TB) are World Health Organization (WHO) stage 4 conditions, the spectrum of immune deficiency seen is very wide. Many patients with limited extrapulmonary TB have high CD4 counts.
- Therefore the decision to commence ART in patients with all forms of TB should be made on the basis of the CD4 count:
  - CD4 count <200 cells/µl: commence ART *after* it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated. The suggested time period to commence ART is between 2 and 8 weeks after starting TB therapy.
  - CD4 count 200 - 350 cells/µl: delay ART until after the intensive phase of TB therapy (2 months) *unless* the patient has other serious HIV-related illness. The longer delay before commencing ART in this group is recommended to reduce the risk of shared toxicity (as the patient will then only be on fewer TB drugs) and to reduce the risk of the immune reconstitution inflammatory syndrome (see below).
  - CD4 count >350 cells/µl: defer ART.
- There are important drug interactions and shared side-effects when ART is co-administered with TB therapy (see section 10 on ART in special populations).
- When ART is commenced patients should be warned that their symptoms or signs of TB may temporarily worsen or new features may occur in the first 3 months as a result of the immune reconstitution inflammatory syndrome.

5.2 PATIENT READINESS FOR ART

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.
- Patients should be provided with information on the following:
  - ART as lifelong therapy
  - the importance of adherence
  - side-effects of ART, and what to do if side-effects occur.
- Active depression or substance abuse should be dealt with.
- Formulate a personal treatment plan, including drug storage and strategies for missed doses, with your patient.
- Disclosure of HIV status should be strongly encouraged as this has been shown to be an important determinant of adherence.
- Patient should be encouraged to join a support group or identify a treatment 'buddy'.
- Personal treatment plan including drug storage and strategies for missed doses.
- Adequate counselling about safer sex practices must be provided to prevent transmitting to other or reinfection with a different strain.

5.3 PRIMARY INFECTION

There is insufficient evidence to recommend ART for primary infection. 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

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

Generic name	Class of drug	Recommended dosage	Common adverse drug reactions*
Zidovudine (AZT)	NRTI	300 mg 12-hrly	**Bone marrow suppression,** gastro-intestinal (GI) upset, headache, myopathy, **hyperlactataemia**/steatohepatitis (medium potential)
Didanosine (ddI)	NRTI	400 mg/d (250 mg/d if <60 kg) taken on an empty stomach (enteric-coated formulation preferred)	Peripheral neuropathy, **pancreatitis,** nausea, diarrhoea, **hyperlactataemia**/steatohepatitis (high potential)
Lamivudine (3TC)	NRTI	150 mg 12-hrly or 300 mg/d	Anaemia, GI upset, myalgia, **hyperlactataemia**/steatohepatitis (low potential)
Stavudine (d4T)	NRTI	30 mg 12-hrly (note - higher doses for >60 kg no longer recommended owing to toxicity)	Peripheral neuropathy, lipo-atrophy, **hyperlactataemia**/steatohepatitis (high potential), **pancreatitis**
Abacavir	NRTI	300 mg 12-hrly or 600 mg/d	GI upset, **hypersensitivity reaction** 3%, **hyperlactataemia**/steatohepatitis (low potential)
Tenofovir (TDF)	NRTI	300 mg/d	Asthenia, headache, GI upset, **renal failure**, ddI concentrations increased 30 - 60%, reduced bone mineral density, **hyperlactataemia**/steatohepatitis (low potential)
Emtricitabine (FTC)	NRTI	200 mg/d	Headache, nausea, **hyperpigmentation**, hyperlactataemia/steatohepatitis (low potential)
Nevirapine (NVP)	NNRTI	200 mg/d for 14 days then 200 mg 12-hrly	**Rash, hepatitis**
Efavirenz (EFV)	NNRTI	600 mg at night	Rash, central nervous system symptoms, elevated transaminases
Nelfinavir†	PI	750 mg 8-hrly or 1 250 mg 12-hrly (take with food)	Diarrhoea, hyperglycaemia, dyslipidaemia
Indinavir	PI	800 mg 12-hrly with 100 mg ritonavir 12-hrly, no food restrictions	Kidney stones, unconjugated hyperbilirubinaemia, GI disturbances, hair loss, hyperglycaemia, headache, dyslipidaemia
Ritonavir	PI	600 mg 12-hrly - very rarely used as sole PI in adults	GI upset, circumoral and extremities paraesthesiae, diarrhoea, fatigue, hepatitis, taste perversion, hyperglycaemia, dyslipidaemia
Saquinavir (hard gel formulation)	PI	1 000 mg with ritonavir 100 mg 12-hrly (take with a fatty meal, or up to 2 hours after meal) or 1 600 mg with ritonavir 100 mg/d (only if PI naïve)	GI disturbances (mild) (take with a fatty meal, or up to 2 h after meal), headache, elevated transaminases, hyperglycaemia, dyslipidaemia
Atazanavir	PI	400 mg/d (only if PI naïve); or 300 mg with ritonavir 100 mg/d	Unconjugated hyperbilirubinaemia, hyperglycaemia, dyslipidaemia (low potential)
Fosamprenavir‡	PI	1 400 mg 12-hrly or 1 400 mg with ritonavir 200 mg/d	Rash, headache, GI upset, hyperglycaemia, dyslipidaemia
lopinavir/ritonavir	Boosted PI	400/100 mg 12-hrly or 800/200 mg/d (only if PI naïve)	Asthenia, headache, GI upset, hyperglycaemia, dyslipidaemia

*Life-threatening reactions in bold type.

†Currently unavailable owing to contamination of manufacturing plant.

‡Limited availability in South Africa.

TABLE III. INDICATIONS FOR ART (NOTE THAT *EITHER* LISTED SYMPTOMS *OR* CD4 STRATA WOULD BE AN INDICATION FOR ART)

Symptoms (irrespective of CD4 count)	
WHO clinical stage 4*	ART recommended
Other severe HIV-related disorders,† e.g.: Immune thrombocytopenia Thrombotic thrombocytopenia Polymyositis Lymphocytic interstitial pneumonitis	ART recommended
Non HIV-related disorders,‡ e.g.: Malignancies Hepatitis B§ Hepatitis C	ART recommended
CD4+ counts	
<200/µl	ART recommended
200 - 350/µl	ART recommended¶
>350/µl	Defer ART

*Except for tuberculosis (see below). Note that the World Health Organization has recently expanded conditions in stage 4 - see Appendix 1.

†Specialist input required. Note that this list is not exclusive - any other severe HIV-related disorders should be considered an indication for ART.

‡Specialist input required. Other disorders that may benefit from an improved immune system should also be considered as an indication to start ART.

§Hepatitis B that qualifies for specific anti-hepatitis B therapy (see section 10 on ART in special populations for criteria and recommended ART regimens).

¶Two CD4+ counts in this stratum should be done before a decision is made.

for careful follow-up. ART in primary infection should only be considered in a properly conducted research study, or in the presence of very severe symptoms. Consultation with an expert treater is strongly advised.

6. INITIAL ARV REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT

In accordance with international recommendations, we recommend the use of NNRTIs and safe dual NRTI combinations in the first-line ART regimen. In comparison with PIs, NNRTIs are better tolerated in the long term and at least as potent when combined with an appropriate dual NRTI combination.

Either nevirapine or efavirenz may be selected as the NNRTI. Nevirapine should be selected for women of childbearing potential as efavirenz is teratogenic (local experience has been that pregnancy rates are high in women who initially indicate that they do not wish to fall pregnant).

The following dual NRTI combinations are recommended to be used with the NNRTI: lamivudine (or, in the case of tenofovir, emtricitabine) together with one of abacavir, tenofovir or zidovudine. Selection will depend on affordability and co-morbidity (e.g. patients with a creatinine clearance rate of <50 ml/min should not use tenofovir). We recognise that stavudine is a much cheaper option than abacavir, tenofovir or zidovudine, but it is considerably more toxic. Public sector programmes are urged to consider dropping stavudine from first-line ART, or at least to make alternative NRTIs available in the event of toxicity.

Refer to section 4 for doses and common side-effects.

7. LABORATORY MONITORING FOR ART EFFICACY

Viral loads should be measured at the following times:

- baseline (before commencing ART)
- 4 - 8 weeks after commencement of therapy
- thereafter every 6 months.

CD4+ counts: every 6 months.

8. DEFINING ART FAILURE

In resource-limited settings where viral loads are unavailable, the WHO has devised criteria for defining ART failure on the basis of CD4 count responses or clinical disease progression. There is currently no good evidence supporting these criteria. There is considerable concern that switching ART regimens using these criteria will result in both switching very late (with progressive accumulation of resistant mutations) and switching inappropriately (as the CD4 count response is not infrequently poor despite optimal virological suppression).

We recommend defining failure of ART on the basis of the viral load, irrespective of the CD4 response (see below) or the development of new HIV-related clinical features. If the viral load is undetectable, the virus cannot mutate and develop resistance.

8.1 VIROLOGICAL CRITERIA FOR TREATMENT SUCCESS

- A decline in viral load of at least 1 log from pretreatment levels 4 - 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.

8.2 VIROLOGICAL CRITERIA FOR TREATMENT FAILURE

A confirmed increase in viral load >1 000 copies/ml. Several factors can influence the measurement of HIV viral load. The decision to alter ART 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 the most common reason for treatment failure.

8.3 CD4 RESPONSE

Typically the CD4+ count increases rapidly in the first month. In the first year the count typically increases by 100 - 150 cells/µl and about 80 cells/µl per annum thereafter until the normal range is reached, provided the viral load is suppressed. However, CD4 responses are highly variable and about 10 - 20% of patients may fail to respond despite virological suppression. CD4 counts often continue to rise in the presence of incomplete viral suppression (which will

result in the emergence of drug resistance) until the viral load is high (approximately 10 000 copies/ml).

9. INDICATIONS FOR CHANGING ART

Individual ARVs may be substituted in the event of toxicity (see section 11 below for guideline).

Changing the first-line ART regimen to a second-line regimen is a major step. The drugs used in second-line regimens are not as well tolerated, and options for salvage therapy (see section 12 below) are currently limited in our region. For this reason clinicians tend to switch to second-line ART after a prolonged period of virological failure, which will cause a progressive increase in the accumulation of resistant mutations. This will reduce the efficacy of the second-line regimen. If the viral load is >1 000 copies/ml it is essential to step up adherence interventions, as discussed above. Once the viral load is confirmed on a second specimen to be >1 000 copies/ml, the patient should be switched to second line without undue delay.

9.1 SECOND-LINE ART

The following ritonavir-boosted PIs are recommended in conjunction with 2 NRTIs (see Table II for doses):

- atazanavir
- lopinavir
- saquinavir.

Indinavir is no longer recommended because it is significantly more toxic than other PIs, and other options have limited availability in the region.

If a patient has been on a first-line combination of 2 NRTIs and a PI (boosted or unboosted), it is best to discuss the choice of second-line regimen with an experienced treater and consider a genotype resistance test. NNRTI-based second-line options do not offer the same potency as boosted PI second-line options, making the choice of regimen more difficult.

9.2 SELECTING SECOND-LINE DUAL NRTIs

Because boosted PIs are robust drugs (i.e. resistance develops slowly), in someone who is PI naïve it is very likely that virological suppression will be achieved with good adherence, even if the 2 NRTIs used in second line are partially compromised by NRTI resistance mutations that have developed during first line. All first-line NRTI combinations can potentially select for mutations that compromise multiple drugs in the NRTI class, as illustrated in Table IV.

Certain NRTI combinations are contraindicated for toxicity reasons (e.g. D4T + ddI or TDF + ddI). TDF and ABC are not recommended for second line as they share several resistance mutations. The NRTI combinations advised for second line are either AZT + ddI or TDF + 3TC (FTC can be substituted in place of 3TC). The choice between these two options depends on the likely mutational profile that has been selected on the patient's first-line NRTI combination (Table V).

In some settings even when 3TC (or FTC) has been used in a failed first-line regimen (and therefore has probably selected for the M184V mutation which confers resistance to it) it is re-used in second line because of the capacity of the M184V mutation to partially resensitise HIV to AZT, d4T and TDF in the presence of thymidine analogue mutations (TAMs) (and to partially resensitise HIV to TDF in the presence of the K65R mutation). The M184V mutation also reduces the replicative capacity of the virus.

TABLE IV. MUTATIONS SELECTED BY FIRST-LINE NRTI COMBINATIONS (THESE ACCUMULATE WITH TIME – THE LONGER THE PATIENT IS VIROLOGICALLY FAILING FIRST LINE, THE MORE OF THESE MUTATIONS ARE LIKELY TO BE SELECTED)

NRTIs used in 1st line	NRTI mutations selected
3TC or FTC	Select for M184V, which compromises both 3TC and FTC and slightly impairs activity of ABC and ddI, but increase susceptibility to AZT, d4T and TDF
AZT	Selects for TAMs, which may compromise all NRTIs
d4T	Selects for TAMs, which may compromise all NRTIs In a minority of patients, d4T may select for K65R which compromises TDF, ABC and ddI but hypersensitises AZT
TDF	Selects for K65R, which compromises TDF, ABC and ddI, but hypersensitises AZT
ABC	ABC selects for L74V, which compromises ABC and ddI, but hypersensitises AZT and TDF ABC may also select for K65R, which compromises TDF, ABC and ddI, but hypersensitises AZT. ABC selects for Y115F, which decreases its susceptibility

TAMs = thymidine analogue mutations.

TABLE V. CHOICE OF SECOND-LINE NRTIs IN RELATION TO FIRST-LINE NRTIs USED

NRTIs used in 1st line	2nd-line NRTI combination advised
AZT + 3TC*	TDF + 3TC*
D4T + 3TC*	AZT + ddI (or TDF + 3TC*)
TDF + 3TC*	AZT + ddI
ABC + 3TC*	AZT + ddI

*3TC interchangeable with FTC.

10. ART IN SPECIAL POPULATIONS

10.1 TUBERCULOSIS

- TB should be managed by public sector TB clinics.
- The ARV regimen should be modified if necessary to make it compatible with rifampicin.
- Efavirenz is the preferred NNRTI for use together with rifampicin (Table VI). Nevirapine is an alternative in pa-

tients in whom efavirenz is contraindicated (e.g. first trimester of pregnancy).

- Rifabutin-based TB treatment is expensive. It may be considered in patients not tolerating concomitant ART and rifampicin-based antituberculosis therapy (for example patients unable to tolerate the increased lopinavir/ritonavir dose) or in ARV treatment-experienced patients with no rifampicin-compatible ART regimen. Both ARV and rifabutin doses may require adjustment (Table VII). Rifabutin is not currently available at public sector TB clinics.
- Shared side-effects of TB and ART are set out in Table VIII.

10.2 PREGNANCY

The US Federal Drug Administration (FDA) uses standard risk categories for teratogenic potential of drugs - see Table IX for pregnancy risk categories of antiretrovirals. Note that some drugs that are strongly recommended in pregnancy are in category C (e.g. zidovudine), while others in category B (e.g. didanosine) would be regarded as second-line agents.
In many southern African countries AIDS is the commonest cause of death in pregnant women, and a significant cause of morbidity and mortality in children born to women with HIV. Even where children are born HIV negative, their mortality is significantly increased. Traditionally, the focus on HIV and pregnancy has centred on the transmission of HIV to children. This has led to complex regimens to address concerns about efficacy and resistance. These guidelines attempt to simplify this approach where possible, decrease transmission in both pregnant and breastfeeding mothers, and facilitate the continuum of care.

TABLE VI. ARV INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR CO-ADMINISTRATION

Class	ARV agent	Interaction	Dose of ARV with rifampicin
NRTIs	All in class	No significant pharmacokinetic interactions	No dose adjustment required
NNRTIs	Efavirenz	Mild reduction in efavirenz concentrations	No dose adjustment required. 600 mg daily
	Nevirapine	Moderate reduction in nevirapine concentrations	Use standard dosing, but consider omitting the lead-in dose phase (limited safety data)
PIs	Ritonavir	No significant interaction	No dose adjustment required. Rarely prescribed because poorly tolerated
	Lopinavir/ritonavir	Lopinavir plasma concentrations significantly decreased	Double the dose of lopinavir/ritonavir to 800/200 mg 2-hrly or add ritonavir 300 mg 12-hrly (3 tablets 12-hrly) to Kaletra 400/100 mg 12-hrly*
	Saquinavir + ritonavir	Saquinavir concentrations are significantly decreased. Risk of severe hepatotoxicity if additional ritonavir is prescribed	Do not prescribe concomitantly
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly

*The double dosing regimen is preferred as it is better tolerated. Both dose adjustments should be made gradually over a week or so.

TABLE VII. DOSING OF ARVs AND RIFABUTIN WHEN PRESCRIBED CONCOMITANTLY

ARV	ARV dose change	Rifabutin dose
Efavirenz	None	↑450 mg/d
Nevirapine	None	300 mg/d
Fosamprenavir	None	↓150 mg/d
Indinavir, nelfinavir	↑1 000 mg 8-hrly	↓150 mg/d
Atazanavir or ritonavir-boosted PIs	None	↓150 mg every 2nd d

TABLE VIII. SHARED SIDE-EFFECTS OF TB THERAPY AND ART

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

General points

- Fertility choices in the context of HIV treatment are complex and clinicians should check fertility choices at every visit to minimise risks.
- In general, far too few women in the southern African region receive prophylaxis for PMTCT. Every effort must be made to ensure rapid ascertainment of HIV status, and rapid access to appropriate PMTCT and ART.
- South African data suggest that most transmissions to babies occur from HIV-positive mothers with CD4 counts below 350 cells/µl; rapid staging and ART initiation for the mother will have a large impact on both maternal and child health.
- All pregnant women of unknown HIV status or who were previously HIV negative should be offered an HIV test, irrespective of marital status, social group or perceived HIV risk status. Ideally, testing should be repeated in the last trimester, as some studies have suggested a greater HIV acquisition risk during pregnancy.
- Nevirapine-based ART is the preferred regimen in pregnant women. However, initiating nevirapine with a CD4 count above 250 cells/µl is associated with a much higher risk of rash-associated hepatitis. In this setting it is recommended that a boosted PI (together with 2 NRTIs) be used instead. However, it should be noted that switch-

TABLE IX. ARV TERATOGENIC RISK

Class	Drug	FDA category*
NRTIs	Abacavir	C
	Didanosine	B
	Emtricitabine	B
	Lamivudine	C
	Stavudine	C
	Tenofovir	B
	Zidovudine	C
NNRTIs	Nevirapine	C
	Efavirenz	D†
PIs	Atazanavir	B
	Fosamprenavir	C
	Indinavir	C
	Lopinavir-ritonavir (in combination)	C
	Nelfinavir	B
	Ritonavir	B
	Saquinavir	B

*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).

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

ing to nevirapine in women who plan to fall pregnant with CD4 counts that have increased to above 250 cells/µl on ART is NOT associated with this increased risk, provided the nadir was <250.

- If CD4 count >250, or if there is intolerance to nevirapine or NNRTI resistance, it is recommended that a boosted protease inhibitor regimen be used instead. Studies have shown that concentrations of lopinavir are significantly reduced in pregnancy. The limited efficacy data available indicate that outcomes have been good without increasing the dose, but some experts recommend a dose increase. Once-daily lopinavir/ritonavir should not be used in pregnancy.
- Efavirenz has been labelled as a human teratogen, but it should be noted that data supporting this are not definitive and the incidence is unknown. Most experts would be willing to use efavirenz in the third trimester if, for instance, nevirapine is not tolerated.
- Mother-to-child transmission is a rapidly evolving field, and international guidelines should be monitored for major changes.

Recommendations

The following is recommended as best standard of care, in situations where resources are available:

Women who are pregnant and who are NOT on ART:

- All pregnant women should be initiated on ART, if adequately prepared, irrespective of CD4 cell count and viral load.
- HIV testing and staging must be done quickly and ART adherence counselling should be accelerated, with the aim to put women on treatment within 2 weeks of the first visit. Women who are being initiated onto ART for PMTCT should ideally be initiated after their first trimester, but women with a CD4 count <200 cells/µl or with severe HIV morbidity should be started in first trimester.
- Women with baseline CD4 counts below 350 cells/µl should continue on ART indefinitely.
- Women who elect to breastfeed and have baseline CD4 counts above 350 cells/µl should continue ART until weaning has occurred.
- ART should be stopped after delivery in women with baseline CD4 counts above 350 cells/µl provided they are formula feeding.
- If a woman presents during labour and is not on ART, single-dose nevirapine should be given to mother and baby, with additional zidovudine and lamivudine to the mother for a week to reduce the risk of NNRTI resistance developing (nevirapine has a very long half-life). Refer to PMTCT guidelines for recommended regimens for the baby.

10.3 ARV DOSAGES IN RENAL FAILURE

For peritoneal dialysis the dose given under creatinine clearance <10 ml/min in Table X should be given daily. For haemodialysis the dose given under creatinine clearance <10 ml/min should be given daily, but it must be given after dialysis on dialysis days or else the drug will be dialysed out.

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

10.4 ARV DOSAGES IN LIVER IMPAIRMENT

Unlike with renal failure, there is no blood test that can quantify liver impairment. Child Pugh class C may require dose adjustment for the relevant ARVs listed in Table XI. In general, the combination of TDF with 3TC (or FTC) and efavirenz is regarded as the least hepatotoxic. If the patient has active hepatitis B, discontinuation of ARVs that have activity against hepatitis B can cause flares of hepatitis - see section on hepatitis B co-infection.

TABLE X. ARV DOSAGES IN RENAL FAILURE

Drug	Creat. clearance 10 – 50 ml/min	Creat. clearance <10 ml/min
Zidovudine	Unchanged	300 mg daily
Didanosine	>60 kg 200 mg/d	>60 kg 100 mg/d
	<60 kg 150 mg/d	<60 kg 75 mg/d
Lamivudine	150 mg/d	50 mg/d
Stavudine	15 mg 12-hrly	15 mg/d
Abacavir	Unchanged	Unchanged
Tenofovir	AVOID	AVOID
PIs	Unchanged	Unchanged
NNRTIs	Unchanged	Unchanged

Adapted from:

Bartlett JG. *Medical Management of Patients with HIV Infection.* 2007 edition. Baltimore, Md.: Johns Hopkins Medicine Health Publishing Business Group, 2007.

Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA. *The Sanford Guide to Antimicrobial Therapy.* 35th ed. Hyde Park, USA: Antimicrobial Therapy, Inc., 2005.

10.5 HEPATITIS B CO-INFECTION

Hepatitis B is a common co-infection with HIV in southern Africa, with significant implications for progression to cirrhosis, as well as for treatment options. Clinicians are encouraged to support current efforts in the region to vaccinate all children for hepatitis B, and to extend coverage to eligible adults. Access to vaccination, laboratory resources and treatment options are all limited to some extent in southern African countries, and the recommendations below should each be considered in the light of the local context.

All HIV-infected patients should be screened for active hepatitis B (limiting screening to those with liver function abnormalities will miss many cases, as liver enzymes are often normal in hepatitis B infection). Hepatitis B surface antigen is an appropriate screening test. Active hepatitis B that is surface antigen negative but anti-hepatitis B core antibody positive with detectable hepatitis B DNA has been described and may be more common in advanced HIV cases. It is unclear how prevalent this is in our region, but it should be considered in the differential of any unexplained liver dysfunction. It is too expensive to screen routinely with these tests. Hepatitis B DNA viral load correlates with disease progression and may be used to monitor anti-hepatitis B therapy, but it is expensive and availability is limited.

Vaccination should be undertaken in unexposed patients (hepatitis B surface antigen and antibody negative). Hepatitis B vaccine is less effective in cases of advanced immu-

TABLE XI. ARV 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
Emtricitabine	In patients with chronic hepatitis B there is a risk of rebound hepatitis when FTC is discontinued or if hepatitis B resistance to FTC develops
Lamivudine	In patients with chronic hepatitis B there is a risk of rebound hepatitis when 3TC is discontinued or if hepatitis B resistance to 3TC develops
Stavudine	Avoid co-administration of ddI with d4T in patients with liver disease in view of the risk of lactic acidosis
Tenofovir	In patients with chronic hepatitis B there is a risk of rebound hepatitis when TDF is discontinued or if hepatitis B resistance to TDF develops
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	
Atazanavir	Avoid in severe hepatic impairment
Indinavir	Reduce adult dose to 600 mg 8-hrly 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 reducing the adult dose to 2 capsules 12-hrly should be considered in severe liver disease
Nelfinavir	Dose reduction advised - limited data suggest doses of 500 mg bd to 750 mg 12-hrly
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

nosuppression, and should be deferred until immune reconstitution on ART has occurred (>200 cells/µl). Babies of pregnant women who have active/acute hepatitis B should receive hepatitis B immunoglobulin and subsequently be vaccinated.

Hepatitis B/HIV co-infection is associated with:

- increased risk of chronic liver disease
- higher hepatitis B viral load
- diminished responses to hepatitis B vaccine
- poorer responses to interferon
- increased incidence of drug-induced hepatotoxicity (particularly with nevirapine)
- flare of hepatitis within 3 months of commencing ART (owing to immune reconstitution syndrome, often misinterpreted as drug hepatotoxicity).

In our region drugs directed against hepatitis B that have no or minimal anti-HIV activity are largely unavailable or extremely expensive. Interferon therapy is poorly tolerated and has a low cure rate in HIV. So for practical purposes the only available therapy is to use ARVs that also have anti-hepatitis B activity. As with HIV, these drugs suppress hepatitis B, but do not eradicate it. Effective treatment prevents or slows progression to cirrhosis.

Indications for specific hepatitis B treatments (from Soriano V, Puoti M, Bonacini M, *et al.* Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005, 19: 221-240) are any one of:

- hepatitis B e antigen positive
- raised ALT (more than twice upper limit of normal)
- evidence of fibrosis on biopsy or on appropriate imaging
- hepatitis B viral load >10 000 copies/ml.

If any of the above criteria are met, ART (see below for recommended regimens) should be commenced irrespective of the CD4 count.

The ART regimen should include tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC). Using 3TC without including tenofovir leads to hepatitis B resistance in 80% of patients after 5 years of treatment. If patients meet criteria for switching to a second-line ART regimen (to treat their HIV), this combination (TDF and 3TC/FTC) should be continued in order to suppress HBV infection, as interruption of TDF and/or FTC/3TC has been associated with life-threatening hepatitis flares. The second-line ART regimen should be shaped around these two drugs in discussion with an experienced treater. Nevirapine should be avoided in patients with hepatitis B co-infection.

10.6 MALARIA

Several drug interactions between antimalarials and ARVs are predicted, but there are minimal data:

- Among drugs used for chemoprophylaxis, there are no clinically significant pharmacokinetic interactions between ARVs and mefloquine or doxycycline. However, mefloquine and efavirenz both cause frequent neuropsychiatric side-effects. Doxycycline is therefore the preferred chemoprophylactic agent for patients on efavirenz.
- Concentrations of atovaquone, which is used in a fixed-dose combination with proguanil (Malanil), are reduced by PIs. The significance of this is uncertain, but it would be prudent to avoid Malanil use in patients on PIs.
- Quinine concentrations will probably be 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. NNRTIs are likely to reduce quinine concentrations. Close monitoring for efficacy is recommended.
- Artemether-lumefantrine (Coartem) should be avoided as PIs, and NNRTIs are likely to reduce the concentrations of both antimalarials. Close monitoring for efficacy is recommended.

11. ARV TOXICITY MONITORING AND MANAGEMENT

11.1 HAEMATOLOGICAL TOXICITY (TABLE XII)

Anaemia, thrombocytopenia and neutropenia all occur commonly in HIV infection without exposure to drugs. However, this section is limited to drug-induced haematological toxicity. 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. Monitoring of full blood counts is only necessary with zidovudine - this should be monitored for the first 6 months of therapy and thereafter if clinically indicated (it is very unusual to see haematological toxicity occurring after 6 months). The main problem is anaemia

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

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

*Many experts would switch to alternative agents rather than reduce doses.

and neutropenia - platelet counts generally rise with zidovudine. Macrocytosis is usual with both stavudine and zidovudine therapy. This is due to a direct effect on the red cells and not to vitamin B_{12} or folate deficiency.

11.2 HEPATOTOXICITY

- LFTs should be done at ART initiation and thereafter tailored to individual drug regimens. The full panel of LFTs is expensive, so it is recommended that only ALT is monitored as this is the most sensitive indicator of drug-induced hepatitis. The full LFT profile should be requested at baseline (if affordable) and in patients with symptoms suggestive of hepatitis.
- All ARV agents may cause hepatotoxicity, but the most common is nevirapine (10 - 15% of patients by laboratory monitoring, but only about 2% present with clinical hepatitis). Mild elevations of ALT occur very commonly and usually transiently with many drugs.
- Hepatotoxic drugs should be discontinued at high levels of LFT abnormality (Table XIII) or at low levels if any symptoms of hepatitis appear. Rechallenge may be considered in selected cases - consult a specialist. If hepatitis occurred together with a rash or fever or other system involvement rechallenge should NOT be attempted.
- NRTIs may cause fatty liver with prolonged use, especially stavudine and didanosine.
- For patients on nevirapine the ALT should be monitored at 2 weeks, 4 weeks, 2 months, and then 3 months. Many experts stop monitoring LFTs after 3 months in patients on nevirapine as hepatitis is rare after this period (unless there is concomitant hepatitis B/C).
- If gamma-glutamyl transferase (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).
- **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 antituberculosis therapy (including prophylactic isoniazid) and azoles.

11.3 HYPERLACTATAEMIA

- Elevated lactate is common in patients treated with NRTIs (up to 20%), but is generally asymptomatic.
- Asymptomatic elevated lactate does not 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, presenting 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 varies: stavudine/didanosine > zidovudine > tenofovir/emtricitabine/lamivudine/abacavir

- The combination of didanosine and stavudine is associated with a high risk of symptomatic hyperlactataemia or lactic acidosis (particularly in pregnancy), and this combination should be avoided.
- Risk factors for hyperlactataemia include:
  - emale gender
  - obesity
  - >6 months' use of NRTIs
  - development of NRTI-induced peripheral neuropathy or fatty liver.
- Symptoms are nonspecific and include: nausea and vomiting, abdominal pain, dyspnoea, fatigue and weight loss.
- A raised lactate level of >5 mmol/l together with metabolic acidosis confirms the diagnosis of lactic acidosis. Low serum bicarbonate (<20 mmol/l) is the most sensitive marker of acidosis. Associated abnormalities include elevated aspartate aminotransferase (AST) and ALT, lactate dehydrogenase and creatine kinase.
- Treatment is supportive. High-dose riboflavin (50 mg) and L-carnitine may be useful (no evidence for either intervention).
- Management depends on the lactate and bicarbonate concentrations:
  - **Lactate <5 mmol/l and bicarbonate >20 mmol/l and minor symptoms.** NRTIs should be changed to agents less associated with hyperlactataemia: tenofovir or abacavir (if these are unavailable then zidovudine could be used) plus emtricitabine or lamivudine. Symptoms and serial lactate should be done for sev-

TABLE XIII. GUIDELINES FOR MANAGING HEPATOTOXICITY

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

*Any elevations with symptoms of hepatitis (nausea, vomiting, right upper quadrant pain) should be regarded as an indication to stop the relevant drugs.

ULN = upper limit of normal.

eral months (note that lactate levels decrease slowly over weeks).

- **Lactate >5 mmol/l and bicarbonate >15 mmol/l.** ART must be discontinued and the patient should be admitted. If the patient was on an NNRTI regimen, consider treating with a boosted PI for 2 weeks to protect against NNRTI resistance (NNRTIs have much longer half-lives than NRTIs, leaving patients on what is in effect monotherapy if all drugs are stopped simultaneously). Restart ART when lactate normalises. Stavudine and didanosine must never be used in future regimens.
- **Lactate >5 mmol/l and bicarbonate <15 mmol/l.** ART must be discontinued and the patient should be admitted, preferably to an intensive care unit. Bicarbonate replacement is controversial, but most experts would partially correct severe acidosis with bicarbonate. Cover with broad-spectrum antibiotic as sepsis can mimic NRTI-induced lactic acidosis. On recovery, all NRTIs should be avoided in future regimens (some experts would be prepared to use safer NRTIs as above if there were no other options).

11.4 HYPERLIPIDAEMIA (TABLE XIV)

- PIs, with the exception of unboosted atazanavir, can cause fasting hypertriglyceridaemia and elevated low-density lipoprotein (LDL) cholesterol. Stavudine can cause hypertriglyceridaemia. Efavirenz can cause elevated total cholesterol.
- Diet and lifestyle modification should always be advised. Diet is much more effective for hypertriglyceridaemia than hypercholesterolaemia.
- Marked hypertriglyceridaemia (>10 mmol/l) can cause pancreatitis.
- When treating hypertriglyceridaemia (with or without elevated cholesterol) with lipid-lowering drugs, the fibrates should be considered the drugs of choice as they are more effective than the statins for hypertriglyceridaemia, they do not interact with PIs (unlike most statins), and they are effective against hypercholesterolaemia as well.
- Many statins have interactions with PIs that can lead to potentially toxic concentrations of statins; the exceptions are pravastatin and fluvastatin, both of which can be used without dose adjustment. Concentrations of atorvastatin and rosuvastatin are significantly raised by PIs, but lower doses (e.g. 10 mg for either drug) can be used. Lovastatin and simvastatin should not be co-administered with PIs as their concentrations are dramatically increased.

TABLE XIV. MANAGEMENT OF HYPERLIPIDAEMIA IN PATIENTS ON PIs

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

*See text for which statins can be used with PIs.

IHD = ischaemic heart disease.

Source: Schambelan M, Benson CA, Carr A, *et al.* Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: Recommendations of an International AIDS Society-USA Panel. *J Acquir Immune Defic Syndr* 2002; 31: 257-275.

11.5 LIPODYSTROPHY

- Long-term use of ART may cause chronic lipodystrophic changes with a change in body fat distribution. This can present either with fat accumulation (visceral obesity, breast enlargement, 'buffalo hump', lipomas) or with fat loss (lipo-atrophy, presenting as facial, limb and buttock wasting) or with both fat loss and accumulation. The thymidine analogue NRTIs (zidovudine and especially stavudine) are associated with fat loss. Although the PIs are often implicated in the case of lipodystrophy, NNRTI-based regimens can also cause lipodystrophy.
- The redistribution of body fat may be cosmetically unacceptable to the patient, resulting in discontinuing ART.
- There is currently no effective therapy. Lipoatrophy may improve when stavudine/zidovudine is substituted with an NRTI less associated with such adverse effects, e.g. tenofovir or abacavir, but resolution is very slow and incomplete, so lipoatrophy is best avoided by early recognition or use of less toxic NRTIs. Exercise is of some assistance in reducing abdominal fat. Surgery should be considered in selected cases (e.g. those with prominent 'buffalo humps').
- Visceral fat accumulation is associated with insulin resistance and dyslipidaemia.

11.6 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 for 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 a possible cross-reaction between nevirapine and efavirenz, although most studies report no evidence of this. It is acceptable to substitute for one another in the event of hypersensitivity, unless the reaction was severe.
- Abacavir hypersensitivity is primarily a systemic reaction occurring within the first 8 weeks of therapy in about 3% of cases. Fatalities may occur, especially on rechallenge.

Therapy must be discontinued and never rechallenge. 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, the patient should be admitted for observation. Symptoms progress if hypersensitivity is present. The hypersensitivity reaction has been shown to be on a genetic basis, being virtually confined to the HLA-B*5701 allele, which is very uncommon in black Africans. If affordable, this allele should be excluded prior to using abacavir in populations where the allele occurs.

11.7 RENAL FAILURE

Measurement of the serum creatinine level and urinalysis for proteinuria must be done at baseline in all patients to detect sub-clinical renal disease, as there is an increased risk of renal failure in HIV infection due to a variety of causes. The dosage of NRTIs needs to be adjusted in renal failure (see section 10 on ART in special populations).

It is essential to estimate the creatinine clearance before commencing tenofovir, which should not be used if the clearance is <50 ml/min. For patients on tenofovir creatinine should be monitored monthly for 3 months, then 6-monthly.

12. SALVAGE ART

The term salvage therapy is used when the patient has experienced virological failure to NRTIs, NNRTIs and PIs. The implication is that these patients have multiple-drug-resistant HIV, although this is not always the case (e.g. if adherence has been poor). A resistance test can be done to confirm the presence of these mutations, but the test is very expensive and the patient must be on the failing ART at the time, as 'wild type' HIV is more fit and outgrows the resistant mutant population which cannot be detected after some weeks/months. If resistance tests are affordable, it is essential that these are interpreted in conjunction with a full ART history by an expert. Randomised controlled trials show only a modest benefit if treatment is guided by resistance tests.

Current international guidelines promote the idea that virological suppression is a realistic goal for salvage therapy. This is certainly true with the availability of several new classes of ARV agents (entry inhibitors and integrase inhibitors) together with newer PIs (darunavir and tipranavir) and NNRTIs (etravirine). However, these drugs are not yet available in the region. Provided the viral load can be maintained at <10 000 copies/ml the CD4 count will usually be maintained or even increase. No firm recommendations can be made about salvage ART. An expert treater should always be consulted. Here are a few guidelines on ART regimens:

- Currently available NNRTIs (nevirapine and efavirenz) have no place as they do not impair viral fitness.
- A boosted PI with the broadest resistance profile should be selected - this is currently lopinavir in our region.
- 3TC (or FTC) should be added, together with other NRTIs, as the M184V mutation that it selects for impairs viral replication.

13. SUPPORT AND COUNSELLING

13.1 ART-RELATED COUNSELLING

Many patients are afraid of starting ART. Reassure the patient that the drugs work and that side-effects are usually minor and transient or manageable. 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 given together with specific details including the appearance of each drug, when and how they are to be taken, and a brief indication of anticipated side-effects and toxicity.

Adherence of the order of 95 - 100% is required for virological suppression. Poor adherence results 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.

13.2 LIFESTYLE, NUTRITION, TRADITIONAL MEDICATION AND SUPPLEMENTS

A healthy lifestyle is recommended: a balanced diet, plenty of exercise, giving up smoking, moderating alcohol intake and a positive outlook on the future.

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, and high doses of trace elements and fat-soluble vitamins, may cause harm and ought to be discouraged. There are also potentially important drug interactions between some herbal remedies and ARVs. Refer to nutrition guidelines for further information.

13.3 IMMUNISATIONS

General

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.

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

13.4 OPPORTUNISTIC INFECTIONS

The use of appropriate prophylaxis, primary or secondary, is essential in patients initiating ART. In general prophylaxis

can be discontinued once the CD4 count has increased to 200 cells/µl, but certain minimal durations of prophylaxis apply for secondary prophylaxis - local and international guidelines should be consulted.

Appendix 1. WHO stage 4 conditions (2006 revision)

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site)

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Extrapulmonary tuberculosis

Kaposi's sarcoma

Cytomegalovirus infection (retinitis or infection of other organs)

Central nervous system toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacteria infection

Progressive multifocal leucoencephalopathy

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Recurrent septicaemia (including non-typhoidal salmonella)

Lymphoma (cerebral or B-cell non-Hodgkin's)

Invasive cervical carcinoma

Atypical disseminated leishmaniasis

Symptomatic HIV-associated nephropathy

Symptomatic HIV-associated cardiomyopathy

Conflict of interest

Gary Maartens has received research support from MSD, honoraria from MSD and Gilead, and consults for Aid for AIDS. Steve Andrews attended a Roche conference, received research support from MSD and honoraria from MSD, Gilead, Aspen and Pharmacare, and consults for Aid for AIDS. Karen Cohen consulted for QUALSA. Flavia Mugala-Mukungu attended the Abbott and Gilead conferences and received honoraria from GSK and Pfizer. Eric Hefer owns shares with Calibre Clinical Consultants, a managed care organisation, received honoraria from Aspen Pharmacare and consulted for Commed (Medical Schemes), CAMAF, AURUM, Southern Sun, Attran and some employer groups. David Spencer received research support from Tibotec and received honoraria from MSD, GlaxoSmithKline, Aspen and Adcock-Ingram. Ian Sanne attended the Pfizer conference and consulted for Pfizer, Bristol Myer-Squibb and GSK. Francesca Conradie received research support from BMS, Pfizer, Schering-Plough, Gilead, GlaxoSmithKline, Tibotec and Abbott, and consulted for Right-To-Care - Direct AIDS Intervention. Fred van der Veen, Ahsraf Grimwood, Francois Venter and Lulamile Jamjam have no conflicts to declare.