

Southern African HIV Clinicians Society

Clinical Guidelines

Antiretroviral therapy in adults

Introduction

The magnitude of HIV infection in Southern African and the number of impoverished people who desperately need antiretroviral therapy (ART) but who will never receive this, is overwhelming, and unparalleled in the history of infectious diseases. Lifetime costs associated with antiretroviral therapy and political intransigence remain the most important obstacles to adequate management of HIV infection in many countries including South Africa, where the availability of finance determines access to therapy. While the Southern African HIV Clinicians Society endorses the right of all HIV-infected adults and children to receive standard of care, it also acknowledges the serious constraints influencing individual's access to effective therapy.

The Southern African HIV Clinicians Society endorses the right of all HIV-infected adults and children to receive an optimal standard of care and supports all initiatives that improve access to effective therapy.

As knowledge and understanding of the use of antiretroviral therapies is still evolving and new therapeutic agents become available guidelines are reviewed and updated regularly. The most current version should always be consulted.

1. Goals of Therapy

The primary goals of antiretroviral therapy are:

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

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 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 antiretroviral regimens (Highly Active Antiretroviral Therapy – HAART) should be used whenever possible in order to obtain the best clinical results and to prevent resistance.

- **Single drug regimens (monotherapy)**
Monotherapy should not be used in the *treatment* of HIV-infection, however, it continues to play a very important role in the prevention of mother to child transmission (MTCT).
- **Dual drug regimens**
Dual therapy is moderately effective, but is unlikely to produce long term durable benefit in most patients. It is not the standard of care, but is considerably better than no therapy and should be considered in patients unable to afford HAART. This should only be applied to patients who have already developed AIDS. In this setting, dual therapy is better than no therapy otherwise resistance is a major concern if dual nucleoside therapy is prescribed to asymptomatic patients. The efficacy of two drug combinations (dual therapy is greater than monotherapy potentially achieving a 1.5 – 1.8 log reduction in viral load). Note that triple combinations are the standard of care.
- **Triple combinations**
The combination of three synergistic antiretroviral agents remains the standard of care; substantial reductions in medication prices continue to make triple-drug regimens more affordable.

3. Classes of antiretroviral agents and their mechanisms of action

Currently available antiretroviral agents inhibit one of two key viral enzymes required by HIV for intracellular viral replication:

- *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*

Classification of antiretroviral agent	Abr.	Enzyme Inhibited	Specific action
Nucleoside reverse transcriptase inhibitors	NRTIs	Reverse transcriptase	mimics the normal building blocks of HIV DNA
Non-nucleoside reverse transcriptase inhibitors	NNRTIs	Reverse transcriptase	directly inhibits reverse transcriptase
Protease inhibitors	PIs	Protease	inhibits late stages of HIV replication.

4. Antiretroviral agents currently available in South Africa

Note: Always refer to the most current version of the guidelines as new treatments regularly become available for clinical use (see below).

GENERIC NAME	TRADE NAME	CLASS OF DRUG
zidovudine (AZT)	Retrovir®*	NRTI
didanosine (ddl)	Videx®*	NRTI
zalcitabine (ddC)	Hivid®	NRTI
lamivudine (3TC)	3TC®*	NRTI
stavudine (d4T)	Zerit®*	NRTI
abacavir	Ziagen®*	NRTI
nevirapine	Viramune®*	NNRTI
efavirenz	Stocrin®	NNRTI
nelfinavir	Vira-cept®*	PI
indinavir	Crixivan®	PI
ritonavir	Norvir®*	PI
saquinavir (hard gel formulation)	Invi-rase®	PI
saquinavir (soft gel formulation)	Forto-vase®	PI
amprenavir	Preclir®*	PI
Lopinavir/ritonavir	Kaletra®	PI

* Available in paediatric formulations

5. Major side effects and complications of classes of antiretroviral agents

The tolerability of antiretroviral regimens remains one of the important determinants of treatment success. Some of the more common currently recognised side effects and complications of these agents are listed below. The consequences of changing antiretroviral therapy need to be carefully considered before substituting or stopping specific agents.

SIDE EFFECT / COMPLICATION	NRTI	NNRTI	PROTEASE INHIBITORS
Myelosuppression	Yes	No	No
GI Intolerance	Yes	Yes	Yes
Pancreatitis	Yes	No	No
Peripheral Neuropathy	Yes	No	No
Allergic Reaction	Rare potential for hypersensitivity reaction with abacavir	Yes	Rare
Lipoatrophy	Yes	Unknown*	Unknown*
Lactic acidosis	Yes	No	No
Lipodystrophy	Yes	Unknown*	Yes
Raised cholesterol & triglyceride	Unknown*	Yes: efavirenz	Yes
Insulin resistance	No	No	Yes
Neuropsychiatric manifestations	No	Yes: efavirenz	Yes

* More data required.

Efavirenz (Stocrin®) is teratogenic and should be avoided in women of childbearing potential unless using adequate intramuscular progestogens and barrier contraceptives, and only where no other antiretrovirals are available.

Stavudine (Zerit®) and didanosine (Videx®) are contraindicated in pregnancy and lactation. Fatalities due to lactic acidosis have been reported.

6. Standard of Care

Effective combination therapy should enable the following:

- Additive or synergistic antiviral activity
- The delay in, or prevention of, emerging drug-resistant viruses.
- Attack the virus at multiple anatomical sites using drugs that can penetrate different cellular and body compartments.

Drug therapies that do not sufficiently suppress viral replication invariably allow the emergence of resistant viral strains. Resistant virus compromises future therapy for the patient and poses a significant public health challenge as it may be disseminated into the community.

7. Indications for starting antiretroviral therapy

Antiretroviral therapy should be deferred until patients are prepared to commit themselves to long-term treatment and to maintaining good adherence to the therapy. All infected individuals, including those on effective ART therapy, should be viewed as potentially infectious. Adequate counselling about safer sex practices must be provided to encourage prevention of new infections and re-infection.

Symptomatic Patient	Treatment
Presence of HIV-related symptoms, current or previous HIV-associated disease *	Treatment recommended
Primary Infection**	Treatment recommended
Asymptomatic Patient	Treatment
CD4+ count <200	Treatment recommended
CD4+ count 200 - 350	Monitor CD4+ count and commence treatment if the CD4 annual decline is in excess of the expected 20 – 80 cells/year, or if the CD4 count approaches 200
CD4+ count >350	Defer treatment

* These include AIDS-defining illnesses (except tuberculosis – see section below), unexplained weight loss >10% of body weight, unexplained diarrhoea lasting > 1 month, oral candidiasis or oral hairy leukoplakia

** Primary Infection

HAART started early in primary infection leads to viral suppression which appears to maintain HIV-specific immunity in a significant proportion of cases who become slow progressors with a low viral load after discontinuing HAART. The duration of treatment is uncertain at the present time.

Notes on concomitant tuberculosis

- TB should always be managed by public sector TB Clinics.
- If the patient is already on antiretroviral therapy the regimen should be changed, if possible, to be compatible with rifampicin
- If the patient's CD4+ count is >200 commence antiretroviral therapy after completing tuberculosis therapy (providing the patient fulfils the criteria above)
- If the CD4+ count is < 200 delay antiretroviral therapy until after the intensive phase of tuberculosis therapy (2 months) unless the patient has other serious HIV-related illness or has a very low CD4+ count in which case antiretroviral therapy should be introduced only once the patient is stabilised on tuberculosis therapy

ART Interactions with rifampicin

NRTIs	No interactions
Efavirenz	Mild reduction in efavirenz levels – some experts increase the dose to 800 mg
Nevirapine	Moderate reduction in nevirapine levels – limited experience
Ritonavir (full dose)	No significant interaction
Ritonavir + saquinavir (both 400 mg bid)	No significant interaction
All other PI's	Marked reduction in PI levels - avoid

8. Laboratory Monitoring

Four laboratory methods are available for determining viral load:

AMPLICOR® PCR

Branched DNA

NucliSens, and

LCx

Comparable results are obtained with the first three methods; experience is currently more limited with the LCx assay. It is recommended that the same method be used for sequential testing in an individual patient.

Assay Tubes

Assay	Dynamic Range	Volume Required
Quantiplex HIV-1 RNA 3.) bDNA	<50 - >500 000	5ml EDTA tube (purple top)
AMPLICOR® PCR HIV-1 v1.5	<400 - >750 000 <50 - >100 000	200ul EDTA plasma 500ul EDTA plasma
LCx HIV RNA QT	50 – 1 000 000 178 – 5 000 000	“
NucliSens QT	400 - 10 000 000 40 – 10 000 000	“

Monitoring of Viral Load (VL) and CD4+ cell count is covered in full in the article on page.....

9. Outcomes of ART

(a) 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 is associated with the most durable virological benefit.

The article on page..... covers anomalies.

(b) Criteria indicative of treatment failure

Note: Inadequate patient adherence to the prescribed regimen remains one of the most common reasons for treatment failure.

These guidelines define virological failure as:

- A sustained increase in VL >5 000 copies/mL.
- A decline in VL of less than 1log within 6-8 weeks after commencing antiretroviral therapy.
- A sustained increase in VL of > 0,6 log from its lowest point or a return to 50% of pre-treatment value.

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 at least two consecutive viral load measurements performed at least one week apart.

10. Initial antiretroviral regimens for the previously untreated patient.

Initial regimens for treatment-naïve patients should be comprised of combinations of drugs that are expected to achieve the above-mentioned treatment goals. These are shown in the table below.

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. Institution of antiretroviral therapy is never an emergency in the setting of established infection. 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.

For initiation of ART therapy prescribe 2 NRTIs and an NNRTI (one drug from Category 1, one from Category 11, and one from Category 1V). If the viral load is <55 000 a third NRTI (Category 111) may be considered as part of a triple NRTI regimen.

Category 1	Category 11	Category 111	Category 1V	Category V
stavudine (d4T) zidovudine (AZT)	didanosine (ddl) zalcitabine (ddc) lamivudine (3TC)	<u>abacavir (abc)</u>	nevirapine (nvp) efavirenz* (efv) *teratogenic - should be avoided in women of childbearing potential unless using adequate intramuscular progestogens and barrier contraceptives, and only where no other antiretrovirals are available.	nelfinavir (nfv) indinavir (idv) ritonavir (rtv) saquinavir (sqv) (soft gel formulation) lopinavir/ritonavir combination

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 (b) above.

12. Options for changing therapy

The following table contains recommendations for changing therapy when drug resistance emerges; the caveats listed above apply.

When virological failure occurs it is essential to change at least two of the drugs in the patient's regimen when possible. The clinician may choose to be guided by genotypic or phenotypic resistance testing.

(a) Changing Nucleoside Reverse Transcriptase Inhibitors (Categories 1, 11 and 111)

INITIAL AGENT	NEW AGENT
zidovudine	stavudine**
stavudine	zidovudine**
didanosine	lamivudine or zalcitabine
lamivudine	didanosine*or zalcitabine*
zalcitabine	abacavir, stavudine or zidovudine or other as determined by resistance testing
abacavir	determined by resistance testing

*May exhibit reduced activity due to cross-resistance with lamivudine (3TC)

**May exhibit cross resistance

(b) Changing Non- Nucleoside Reverse Transcriptase Inhibitors (Category 1V)

There is broad cross-resistance between the currently available NNRTIs. Resistance to one NNRTI precludes the use of another, unless there is resistance test data to the contrary. Individuals who fail an NNRTI-containing regimen may be candidates for an abacavir-containing triple-nucleoside combination (if the viral load is <55 000 RNA copies/mL) or a protease-inhibitor containing regimen. Resistance to one agent of this class effectively results in cross-resistance to all members of drugs in this category (that are currently available in South Africa). Sequential use of these drugs is not recommended.

(c) Changing Protease Inhibitors (Category V)

A major reason for regimens that contain protease inhibitors 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 protease inhibitor alternatives may exhibit reduced activity due to extensive cross-resistance within this class of drugs. Pharmacologic boosting of protease blood levels can be achieved by combining amprenavir, saquinavir and indinavir with low doses of ritonavir. Experience with these combinations is limited and advice on dosing should be sought.

13. Treatment decision support

For specific advice and assistance in using these guidelines, please

contact The Southern African HIV Clinicians Society by e-mail:
sahivsoc@iafrica.com.

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.

GUIDELINES FOR ANTIRETROVIRAL THERPAY IN ADULTS

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