

AntiRetroViral therapy in adults

Southern African HIV Clinicians Society Clinical Guidelines



**Affordable ARV's
to treat 150 000 people
with AIDS by 2005!**

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.

Printed by the Treatment Action Campaign and Southern African HIV Clinicians society.

GUIDELINES FOR ANTIRETROVIRAL THERPAY IN ADULTS

JUNE 2002 VERSION

Chairperson of Adult Guidelines Committee

Dr Steven Millera

Expert Panel Members

Steven Andrews, Mark Cotton, Gary Maartens, Des Martin,

Steven Miller, Robin Wood, Dave Spencer, Francois Venter

International Reviewers

Pedro Cahn, David Cooper, Brian Gazzard, Stefano Vella

These guidelines are produced by local experts of the Southern Africa HIV Clinicians Society (SAMA's largest Special Interest Group) and are locally and internationally reviewed in accordance with new developments in therapeutic technologies.

Cover, back page and Bredell Consensus Statement by Treatment Action Campaign.

The Southern African HIV Clinicians Society takes no responsibility for flaws in these parts of the text in this booklet.

Reprinted by Treatment Action Campaign (TAC) and Southern African HIV Clinicians Society.

CONTENTS

1	INTRODUCTION	page 1
2	GOALS OF THERAPY	page 1
3	STANDARD OF CARE	page 2
4	CLASSES OF ARV AGENTS AND THEIR MECHANISMS OF ACTION	page 3
5	ARV AGENTS CURRENTLY AVAILABLE IN SOUTH AFRICA	page 3
6	MAJOR SIDE EFFECTS AND COMPLICATIONS OF CLASSES OF ARV AGENTS	page 4
7	STANDARD OF CARE	page 5
8	INDICATIONS FOR STARTING ARV THERAPY	page 6
9	LABORATORY MONITORING	page 8
10	OUTCOMES OF ARV THERAPY	page 8
11	INITIAL ARV REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT	page 9
12	INDICATIONS FOR CHANGING THERAPY	page 10
13	OPTIONS FOR CHANGING THERAPY	page 11
14	TREATMENT DECISION SUPPORT	page 12
	ANNEXURE: The Bredell Consensus	page 13

1 INTRODUCTION

The magnitude of HIV infection in Southern Africa 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 an optimal standard of care, it also acknowledges the serious constraints influencing individual's 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.

2 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,
- 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.

3 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.

4 CLASSES OF ARV 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 ARV 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.

5 ARV 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 (ddI)	Videx [®] *	NRTI
zalcitabine (ddC)	Hivid [®]	NRTI
lamivudine (3TC)	3TC [®] *	NRTI
stavudine (d4T)	Zerit [®] *	NRT
abacavir	Ziagen [®] *	NRTI
nevirapine	Viramune [®] *	NNRTI

GENERIC NAME	TRADE NAME	CLASS OF DRUG
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

6 MAJOR SIDE EFFECTS AND COMPLICATIONS OF CLASSES OF ARV 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.

7 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 compromise future therapy for the patient and pose a significant public health challenge as it may be disseminated into the community.

8

INDICATIONS FOR STARTING ARV 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	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 PIs	Marked reduction in PI levels - avoid