ANTIRETROVIRAL THERAPY IN ADULTS

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Southern African HIV Clinicians Society

The magnitude of HIV infection in southern Africa and the number of impoverished people who desperately need antiretroviral therapy (ART) but will never receive it 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 limitations influencing the 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 are becoming 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 that of 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 (Table I) 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.

TABLE I. CLASSES AND MECHANISMS OF ACTION OF ANTIRETROVIRAL AGENTS

Classification of antiretroviral agent	Abrev.	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 Table II).*

TABLE II. ANTIRETROVIRAL AGENTS CURRENTLY AVAILABLE IN SOUTH AFRICA

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*	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 in Table III. The consequences of changing antiretroviral therapy need to be carefully considered before substituting or stopping specific agents.

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.

TABLE III. SIDE-EFFECTS AND COMPLICATIONS OF ANTIRETROVIRAL 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, but potential for anaphylaxis with abacavir	Yes	Rare
Lipoatrophy	Yes	Unknown*	Unknown*
Lactic acidosis	Yes	No	No
Lipodystrophy	Unknown*	Yes	Yes
Raised cholesterol and 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 they are 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.

- 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 antiretroviral therapy, should be viewed as potentially infectious. Adequate counselling about safer sex practices must be provided to encourage prevention of new infections and reinfection.

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/µl	Treatment recommended
CD4+ count 200 - 350/µl	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/µl
CD4+ count > 350/µl	Defer treatment

*These include AIDS-defining illnesses (except tuberculosis – see box 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 if possible be changed to be compatible with rifampicin.
- If the patient's CD4+ count is > 200/µl, commence antiretroviral therapy after completing tuberculosis therapy (provided the patient fulfils the criteria above).
- If the CD4+ count is < 200/µl 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 PIs	Marked reduction in PI levels – avoid

8. LABORATORY MONITORING

Four laboratory methods are available for determining viral load:

- AMPICLOR 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	5 ml EDTA tube (purple top)
AMPICLOR PCR	< 400 - > 750 000	200 µl EDTA plasma
HIV-1 v1.5	< 50 - > 75 000	500 µl EDTA plasma
LCx HIV RNA QT	50 - 1 000 000	200 µl EDTA plasma
	178 - 5 000 000	500 µl EDTA plasma
NucliSens QT	400 - 10 000 000	200 µl EDTA plasma
	40 - 10 000 000	500 µl EDTA plasma

Monitoring of viral load and CD4+ cell count is covered in full in the article on p. 38.

9. OUTCOMES OF ART

9.1 Criteria for treatment success

- A decline in viral load of at least 1 log from pretreatment 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 p. 38 covers anomalies.

9.2 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 viral load > 5 000 copies/ml.
- A decline in viral load of less than 1 log within 6 - 8 weeks after commencing antiretroviral therapy.
- A sustained increase in viral load of > 0.6 log from its lowest point or a return to 50% of pretreatment 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 1 week apart.

10. INITIAL ANTIRETROVIRAL REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT

Initial regimens for treatment-naïve patients should comprise combinations of drugs that are expected to

TABLE IV. ANTIVIRAL REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT				
Category I	**Category II**	**Category III**	**Category IV**	**Category V**
Stavudine (d4T) Zidovudine (AZT)	Didanosine (ddI) Zalcitabine (ddC) Lamivudine (3TC)	Abacavir (ABC)	Nevirapine (NVP) Efavirenz (EFV)*	Nelfinavir (NFV) Indinavir (IDV) Ritonavir (RIV) Saquinavir (SQV) (softgel formulation) Lopinavir/ritonavir combination

*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.

achieve the abovementioned treatment goals. These are shown in Table IV.

Particular consideration should be given to those factors that 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 lifelong.

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 two NRTIs and an NNRTI (one drug from category I, one from category II, and one from category IV). If the viral load is < 55 000 copies/ml a third NRTI (from category III) may be considered as part of a triple NRTI regimen.

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 9.2 above.

12. OPTIONS FOR CHANGING THERAPY

Table V 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.

TABLE V. CHANGING NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS	
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.

9.1 Changing nucleoside reverse inhibitors (categories I, II and III) (Table V))

9.2 Changing non-nucleoside reverse transcriptase inhibitors (category IV)

There is broad cross-resistance between the currently available NNRTIs. Resistance to one NNRTI precludes the use of another, unless there are resistance test data to the contrary. Individuals in whom an NNRTI-containing regimen fails 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.

Changing protease inhibitors (category V)

A major reason for failure of regimens that contain protease inhibitors is suboptimal 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. Pharmacological 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.

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