SOUTHERN AFRICAN HIV CLINICIANS SOCIETY

GUIDELINES FOR ANTIRETROVIRAL THERAPY IN ADULTS

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. High costs associated with antiretroviral therapy remain the most prohibitive factor influencing the way that HIV is managed in countries such as 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 limitations influencing individual access to effective therapy.

As a result of the constraints within the Southern African context, treatment cannot always be optimal and this has resulted in serious contemplation of acceptable, yet not always optimal, therapeutic alternatives that may currently be more affordable and realistic. Certain recommendations in this document are therefore presented as unavoidable compromises that might not meet internationally established standards of care, and where these occur, they have been **indicated by a grey-shaded background.**

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

1. VIRAL DYNAMICS IN HIV INFECTION

HIV replicates at an extraordinarily high rate from the onset of infection. The level of virus in the plasma ('viral load') often increases to values between 100 000 RNA copies/mL and several million RNA copies/mL within a week of primary infection. This is thought to contribute significantly to seeding of distant tissues such as the brain, lymphoid tissue, thymus gland, etc.

Within 6 to 12 months of infection, equilibrium is usually reached between the host's defences and the replicating virus, which is termed the 'viral set point'.

The set point, or viral load, is the strongest predictor of the patient's rate of disease progression and duration to death, if the natural history of the infection is not influenced by therapy.

- Although the viral load ultimately rises in the majority of patients over time, the steady state or 'set point' can be maintained for several years.

  HIV infection nevertheless always causes progressive damage to the immune system and this is reflected by a gradual decline in the CD4 lymphocyte cell count.
- Untreated, those patients with set points in the range of 10 000 – 100 000 RNA copies/mL progress to AIDS within an average of 8 – 10 years.
- Patients with higher set points generally progress more rapidly, while those with lower viral burdens progress to HIV disease more slowly.
- A small group of untreated individuals appear to remain long-term non-progressors; they typically have viral loads < 5 000 RNA copies/mL and CD4 lymphocyte cell counts consistently above 500 cells/μL.

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, and reduction of HIV-related morbidity and mortality.

This is achieved by suppressing viral replication as intensely as possible for as long as possible using tolerable and sustainable treatment for an indefinite period of time. By doing this, 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. CLASSES OF ANTIRETROVIRAL AGENTS AND THEIR MECHANISMS OF ACTION

Antiretroviral agents that are currently available inhibit one of two key viral enzymes required by HIV for intracellular viral replication:

- Agents that inhibit the enzyme *reverse transcriptase* are termed **reverse transcriptase inhibitors (RTIs)** and act upon the early stages of HIV replication. RTIs that mimic the normal building blocks of HIV DNA are termed **nucleoside RTIs (NRTIs)**; the chemically diverse group of drugs that directly inhibit the reverse transcriptase enzyme at a common site of action are termed **non-nucleoside RTIs (NNRTIs)**.
- A second group of antiretroviral agents, the **protease inhibitors (PIs)**, inhibit the functioning of an enzyme known as *protease*, that is required for the late stages of HIV replication.

Hydroxyurea (HU) is used as an adjunct to antiretroviral therapy and has a dual mechanism of action: The predominant effect of HU is to inhibit the cellular enzyme *dideoxynucleotide reductase*, which leads to lower intracellular adenine triphosphate levels and enables preferential uptake of the antiretroviral drug didanosine into infected cells. This enhances antiviral activity; HU also increases the activity of cellular kinases, thereby promoting the activity of several other NRTIs - particularly stavudine.

No currently available antiretroviral agent is sufficiently potent to provide sustained benefit if used alone.

At best, monotherapy yields incomplete viral suppression (bringing about a 0.6 to 0.8 log reduction in the viral load) for 6 – 12 months. Thereafter, drug-resistant virus may emerge and cross-resistance to other antiretroviral agents is inevitable.

TREATMENT WITH SINGLE DRUG REGIMENS SHOULD THEREFORE NOT BE USED

The efficacy of two-drug combinations is relatively greater (potentially achieving a 1.5 – 1.8 log reduction in viral load) and this may be suitable for treating people with lower viral loads (where better regimens are not available).

The synergistic use of combinations of three agents remains the standard of care, and produces a potent and sustained reduction of viral load that should exceed a 2 log decline.

4. ANTIRETROVIRAL AGENTS CURRENTLY AVAILABLE IN SOUTH AFRICA

Note that new treatments will be made available, which requires reference to the most current version of these guidelines.

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
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

*available in paediatric formulations

ADJUNCTIVE AGENTS

GENERIC NAME	TRADE NAME	CLASS OF DRUG
hydroxyurea	Hydrea®	dideoxynucleotide reductase inhibitor

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	HYDROXYUREA
Myelosuppression	Yes	No	No	Yes
GI Intolerance	Yes	Yes	Yes	Yes
Pancreatitis	Yes	No	No	No
Peripheral neuropathy	Yes	No	No	No
Allergic reaction	Rare	Yes	No	No
Lipoatrophy	Yes	No	No	No
Lactic acidosis	Yes	No	No	No
Lipodystrophy	No	No	Yes	No
Raised cholesterol & triglyceride	No	No	Yes	No
Insulin resistance	No	No	Yes	No
Neuropsychiatric manifestations	Yes	Yes	Yes	No

Hydroxyurea and efavirenz (Stocrin®) may be teratogenic and their use is contraindicated in pregnancy.

6. COMBINATION THERAPY IS THE STANDARD OF CARE

Monotherapy is **not** recommended treatment for HIV infection, although it continues to have an important short-term role in specific situations, such as the prevention of mother to child HIV transmission.

Effective combination therapy should enable the following:

- Additive or synergistic impact on antiviral activity.
- The delay in, or prevention of, emerging drug-resistant viruses.
- Action on the virus at multiple anatomical sites by drugs that reach different cellular and body compartments.

Drug therapies that do not sufficiently suppress viral replication invariably promote 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. SAFER SEX

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

8. MONITORING VIRAL LOAD

Viral load measurements should be undertaken:

- At the initial clinical assessment.
- Four-monthly thereafter, if the patient does not require antiretroviral therapy.†
- Prior to commencing antiretroviral therapy.
- Six to eight weeks after commencing antiretroviral therapy, and 4 - 6 monthly thereafter.
- A repeat test is recommended whenever a routine measurement yields an unexpected result.
- Additional non-routine testing may be indicated if the individual's clinical condition changes.

† Patients not on antiretroviral therapy with low risk of disease progression may be monitored 6 monthly; those at higher risk of disease progression (see below) require more frequent (4-monthly) monitoring.

Three laboratory methods are available for determining viral load. These are:

- Amplicor® PCR
- Branched DNA
- NASBA which also allows measurement of viral load in non-plasma samples, e.g. semen, vaginal fluid, CSF.

The current versions of all three methods give acceptably comparable results; however, it is strongly advised that patients should be sequentially tested using the same method.

The appropriate sample to submit for determination of viral load is a well-filled EDTA (purple topped) blood tube.

9. MONITORING THE CD4 LYMPHOCYTE CELL COUNT

The CD4 lymphocyte cell count is a measure of the cumulative damage caused to the immune system by infection with HIV. It is the best predictor of the risk of developing an AIDS-related complication and, in advanced disease, of prognosis. The CD4 lymphocyte cell count is, however, a much poorer predictor of the rate of progression of HIV infection or risk of death than the viral load in the earlier stages of HIV infection.

It is recommended that the CD4 lymphocyte cell count should be measured whenever the viral load is determined, with the exception of those occasions on which the viral load is being repeated to verify an unexpected result.

A sustained decline in viral load is usually accompanied by improvement in the CD4 lymphocyte cell count. Recovery of the CD4 lymphocyte cell count may be less than anticipated if the treatment combination includes hydroxyurea, or if the pre-treatment CD4 lymphocyte cell count is lower than 50 cells/μL.

Patients with a low CD4 lymphocyte cell count should not be excluded from antiretroviral therapy.

As there is a strong association between CD4 lymphocyte cell count and the risk of developing opportunistic diseases, the CD4 lymphocyte cell count should be used as a guide to introducing appropriate prophylactic agents according to established Guide-lines for Prophylaxis of OIs (available from the Southern African HIV Clinicians' Society).

10. 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.

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

Since antiretroviral therapy reduces the risk of HIV progression and consequent development of disease complications, treatment can be initiated in patients at all levels of risk (low, moderate or high - as defined by virological, immunological and clinical parameters).

Where resources are constrained, antiretroviral therapy should still be initiated in all high-risk patients.

Patients in the moderate-risk category should be carefully considered for therapy, but treatment can be deferred for low-risk patients, provided these individuals continue to receive regular follow-up and monitoring.

DEGREE OF RISK	VIRAL LOAD & CD4 LYMPHOCYTE CELL COUNT
HIGH	Viral Load > 100 000 copies/mL CD4+ count < 350/μL **OR** Two consecutive CD4+ cell counts < 200/uL, irrespective of viral load **OR** SIGNIFICANT CLINICAL FEATURES * (see below)
MODERATE	Viral Load 10 000 - 100 000 copies/mL CD4+ count 350 - 500/μL
LOW	Viral Load < 10 000 copies/mL CD4+ count > 500/μL

* SIGNIFICANT CLINICAL FEATURES INCLUDE:

- The presence of any AIDS-defining condition (including current or recent active pulmonary tuberculosis)
  OR
- Significant symptoms, such as: oral thrush, with no other obvious cause; oral hairy leucoplakia; recurrent or refractory vulvovaginal candidiasis; recurrent herpes zoster; recurrent severe bacterial infections; chronic unexplained fever (lasting more than 1 month); involuntary weight loss (more than 10% of usual body weight); chronic unexplained diarrhoea > 1 month.

NOTE: The presence of any of the Significant Clinical Features listed in the table above categorises the patient as being at high risk for disease progression, irrespective of CD4 lymphocyte cell count and/or viral load.

Occasionally, results of the viral load test and CD4 lymphocyte cell count could make it difficult to allocate the patient to one of the above risk categories (e.g. viral load of 30 000 RNA copies/mL and a CD4 lymphocyte cell count of 250/uL). In this situation, greater emphasis should be placed on the viral load result as a measure of risk.

11. OUTCOME OF ANTIRETROVIRAL THERAPY

A. DETERMINANTS OF TREATMENT SUCCESS

Viral load is the major determinant of disease progression. It is also a significant predictor of the durability of an effective treatment response.

The following criteria are used to determine treatment success when using triple-drug combinations:

- A decline in viral load of at least 1 log from pre-treatment levels after 6 to 8 weeks of initiating antiretroviral therapy.
- A decline in viral load to <5 000 RNA copies/mL by 12 weeks of starting antiretroviral therapy.
- A viral load of < 50 copies/mL is associated with the most durable antiviral response.

In the event that two-drug combinations are used, the above criteria should be modified as follows:

- An undetectable viral load may be regarded as < 400 copies/mL
- When using the combination of ddI & hydroxyurea, treatment need not be changed if the viral load fails to drop to undetectable levels, provided that it remains stable at < 5 000 copies/mL.

Significant short- to medium-term clinical benefit may be achieved with two-drug regimens that suppress viral load to < 5 000 copies/mL but do not reach undetectable levels; however disease progression is inevitable.

B. DETERMINANTS OF TREATMENT FAILURE

The inability of an individual to adhere to his or her prescribed drug regimen is probably the single most important factor associated with treatment failure and the development of resistance when using potent multi-drug combinations.

Virological failure is defined as:

- A decline in viral load of not more than 1 log within 6 - 8 weeks of starting therapy.
- A sustained increase in viral load of greater than 0.6 log from its lowest point or a return to 50% of the pre-treatment value.

Several factors may influence the interpretation of viral load results and viral load readings may fluctuate. It is therefore recommended that, whenever possible, the decision to start therapy and/or alter therapy should be based on the results of two viral load measurements performed at least one week apart.

12. INITIAL ANTIRETROVIRAL REGIMENS FOR THE PREVIOUSLY UNTREATED (TREATMENT-NAÏVE) PATIENT

Therapy for the patient who has never previously received antiretroviral drugs should be initiated with a regimen that is expected to achieve the treatment goals (above). Additional consideration should be given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

A. COMPLIANCE

The importance of compliance should be explained to the patient and understood by the prescriber. The implications of treatment failure and drug resistance must be emphasised.

B. PRINCIPLES

It is recommended that the initial regimen should comprise a potent combination that is most likely to achieve the viral load targets listed in 11A, above. This can best be achieved using a triple-drug combination, however it is acknowledged that inadequate resources may only permit the use of a two-drug treatment regimen.

The durability and efficacy of two-drug regimens is generally less than that of three-drug combinations and it is likely that patients treated with two-drug regimens will require a change in therapy, as the current regimen fails. In order to preserve subsequent therapeutic options it is essential to choose the initial therapy wisely to minimise the development of cross-resistance.

The sequence of agents used becomes an extremely important consideration when using two-drug regimens.

Combining ddI with HU can produce viral load reductions equivalent to dual NRTI therapy; however, this combination is more toxic.

The NNRTIs and PIs should not be used when prescribing two-drug regimens.

C. DRUG COMBINATIONS THAT ARE NOT RECOMMENDED

Caution must be exercised when using combinations of drugs with similar side-effect profiles. The following drug combinations are associated with a high risk of adverse effects and should be avoided, or used with extreme caution:

- ddI and ddC (due to the high risk of peripheral neuropathy)
- AZT and HU (as they have additive bone marrow toxicity)
- d4T and ddC (result in a higher risk of peripheral neuropathy)

Certain drug combinations are antagonistic and must be avoided altogether:

- AZT and d4T (antagonistic)
- 3TC and ddC (antagonistic)

D. PHARMACOLOGICALLY UNFAVOURABLE INTERACTIONS

Combining NNRTIs with PIs may result in sub-therapeutic plasma concentrations of the protease inhibitor. Dosage adjustment of the PI may be required. It is recommended that advice should be sought from experts within the Society prior to prescribing a regimen that includes these two classes of antiretroviral agents.

E. THYMIDINE AND NON-THYMIDINE NRTI ANALOGUES

AZT and d4T are chemical analogues of thymidine, a building block of DNA. Thymidine analogues are most active in rapidly dividing cells such as activated CD4 lymphocyte cells. The remaining NRTIs are analogues of other DNA building blocks and tend to be more active in cells that divide more slowly.

It is common practice to combine a thymidine analogue with a non-thymidine analogue in order to target as wide a cell population as possible.

13. RECOMMENDATIONS FOR INITIAL ANTIRETROVIRAL COMBINATION THERAPY

DRUGS REFERRED TO IN EACH CATEGORY APPEAR IN THE TABLE BELOW

When prescribing a triple-drug regimen, taking into account the principles stated in section 12 (A to E), above:

Combine **one** drug from Category I with **one** drug from Category II
and **one** option from Category III **or** IV **or** V

OR

Combine **one** drug from Category I **or one** drug from Category II
with **one** option from Category IV

OR - for patients who do not have the resources for optimal therapy:

Combine **one** drug from Category I with **one** drug from Category II

OR

Combine ritonavir 400 mg twice daily
(starting at 100 mg bid and escalating over ten to fourteen days to improve tolerability)
PLUS saquinavir 400 mg bid (hard gel or soft gel formulation)

OR

Combine didanosine with hydroxyurea

Note that the durability and efficacy of the combinations in this shaded area is uncertain, particularly when the pre-treatment viral load exceeds 100 000 copies/ml.

CATEGORY I	CATEGORY II	CATEGORY III	CATEGORY IV	CATEGORY V*
• stavudine (d4T) • zidovudine (AZT)	• didanosine (ddI) • zalcitabine (ddC) • lamivudine (3TC)	• nevirapine • efavirenz	• ritonavir *& either* • indinavir *or* • saquinavir (hard gel or soft gel formulation)	• nelfinavir • indinavir • ritonavir • saquinavir (soft gel formulation)

Dosing modifications are required when using PI combinations: Contact the Society for prescribing assistance.
Note that the long-term biochemical and metabolic complications of using options from Category IV are currently unknown.

14. INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY

Treatment should only be changed in the following situations:

- Failure to achieve at least a 1 log reduction at 6 to 8 weeks after initiating therapy. (Where the initial combination includes either d4T or ddI, or both, treatment may be intensified by the addition of HU).
- Failure to achieve any of the three objectives for successful treatment listed in 11, above; where inadequate drug potency will inevitably lead to the emergence of resistant virus.
- Treatment failure, as defined in 11B, above.

15. OPTIONS FOR CHANGING THERAPY

The following table contains recommendations for changing therapy when drug resistance emerges; the caveats listed in 12 A to E (above) apply.

When drug resistance is suspected/confirmed it is essential to change at least two of the drugs in the patient's regimen.

A. Substitutes for Nucleoside Reverse Trancriptase Inhibitors

INITIAL AGENT	NEW AGENT
zidovudine	stavudine
stavudine	zidovudine
didanosine	lamivudine or zalcitabine
lamivudine	didanosine* or zalcitabine*
zalcitabine	lamivudine or didanosine

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

B. Non-nucleoside Reverse Transctiptase Inhibitors

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. Substitutes for Protease Inhibitors

A major reason for regimens that contain protease inhibitors failing 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.

Resistance to PIs causes treatment failure and all second-line protease inhibitor alternatives may exhibit reduced activity due to extensive cross-resistance within this class of drugs.

INITIAL AGENT/S	NEW AGENT/S
ritonavir *plus* saquinavir (soft or hard gel)	indinavir*
nelfinavir	indinavir* *or* ritonavir plus sequinavir* (soft gel)
indinavir*	ritonavir *plus* sequinavir* (soft or hard gel)

* All may exhibit reduced activity due to extensive cross-resistance between protease inhibitors.

16. ADDITIONAL PRACTICE POINTS

A. HYDROXYUREA

HU is not registered for use in HIV infection in South Africa , but there is some evidence supporting its use in combination with antiretroviral drugs. HU is at present recommended for use in combination with ddI and/or d4T. When combined with these drugs, HU can reduce the viral load more than the nucleosides alone. Resistance mutations to HU do not occur, and there is no cross-resistance to other antiretroviral drugs. In addition, it may produce beneficial immunological effects. These unique properties make HU a potentially important and affordable adjunct to currently available therapies, based on existing research data.

Caution should be exercised to exclude pregnancy when commencing this therapy in women as HU is potentially teratogenic. Women should be counselled not to become pregnant while taking the drug.

In addition, hydroxyurea should be used with caution in individuals who have a pre-treatment absolute neutrophil count < 1 000/mL, as neutropenia could be aggravated. It is good clinical practice to monitor haemoglobin and full blood count twice monthly for the first month of HU therapy and monthly thereafter.

When used in combination with other drugs that are potentially neurotoxic, HU increases the risk of developing peripheral neuropathy. The toxic effects of HU (particularly myelosupression) are more evident when HU is given to patients in advanced stages of HIV infection.

The full extent to which HU potentiates the adverse effects of other drugs, or to which it can be implicated in adverse drug reactions, when used in combination therapy, is still under investigation.

B. PROTEASE INHIBITORS

Protease inhibitors are only effective if they achieve specific pharmacokinetic targets. Failure to do so leads to the development of drug-resistant virus. Although each PI has a unique initial pattern of resistance, in suboptimal treatment conditions the virus soon undergoes mutations that confer extensive cross-resistance to all other currently used members of this class.

Saquinavir

Two forms of the drug saquinavir are commercially available: a hard gel capsule preparation (Invi-rase®) and a soft gel formulation (Forto-vase®). Due to its extremely poor pharmacokinetics, Invi-rase® should only be used as a component of a dual PI combination therapy, together with ritonavir. Forto-vase® may be used either on its own or with ritonavir. Ritonavir may also be used with indinavir to provide more favourable plasma levels.

DRUG-DRUG INTERACTIONS

Protease inhibitors exhibit numerous unfavourable drug interactions with other drugs, including rifampicin, and potential interactions should always be evaluated when combining antiretroviral therapy with other treatments. (Refer to individual drug package inserts for specific details.)

C. NUCLEOSIDE ANALOGUES

Resistance to nucleoside analogues is slow to develop, with the exception of 3TC. 3TC resistance arises within weeks when the drug is used in a regimen that fails to suppress viral replication fully. In circumstances that limit the use of antiretrovirals to sequential dual nucleosides, some experts recommend reserving 3TC as a component of second or subsequent regimens. Lower cost combined formulations that include 3TC might become available in the future and this could allow more affordable 3-drug combination therapy to be offered. 3TC resistance sensitises HIV to the antiviral activity of AZT, but the durability of this effect is uncertain.

All nucleoside analogues have been associated with lactic acidosis, a rare but potentially life-threatening metabolic complication of treatment. The pathogenesis is believed to involve drug-induced mitochondrial damage. Published data suggest that African females who are overweight may be more at risk of this complication. Clinical features include progressively worsening nausea, vomiting and abdominal pain accompanied by clinical signs of acidosis. Routine laboratory tests reveal a low serum CO_2, liver enzyme abnormalities and elevation of serum amylase. Arterial blood gas analysis confirms a metabolic acidosis; lactate levels are elevated in venous and arterial blood. Treatment is supportive; administration of riboflavin and l-acetyl carnitine may occasionally be beneficial. Therapy with nucleoside analogues should immediately be stopped and alternative classes of antiretroviral agents should be selected once the patient has recovered.

D. ANTIRETROVIRAL RESISTANCE TESTING

As antiretroviral therapy becomes more widely used, the future role of antiretroviral resistance testing may become important in guiding therapeutic decisions

17. TREATMENT DECISION SUPPORT

For specific advice and assistance in using these guidelines, please contact the Southern African HIV Clinicians Society by E-mail: art@hivclinicians.co.za

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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JUNE 2000 VERSION
Corresponding Author
Dr Steven Miller
Expert Panel Members
Steven Andrews, Andrew Clark , Shaun Conway, Mark Cotton, David Johnson, Gary Maartens, Des Martin, Steven Miller, Koleka Mlisana, Robin Wood
International Reviewers
Pedro Cahn, David Cooper, Brian Gazzard, Stefano Vella