MECHANISMS OF ACTION OF ANTIRETROVIRAL AGENTS

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Antiretroviral agents (ARV) reduce the plasma and tissue-associated viral load. This results in significant benefits to the individual infected by HIV (Table I) and to the community.

TABLE I. BENEFITS OF ANTIRETROVIRAL THERAPY

Clinical	Improved quality and quantity of life Reduction in HIV encephalopathy Fewer/no opportunistic diseases
Immunological	Restoration of immune function
Virological	Reduction in viral-mediated damage Reduced viral diversity
Societal	Reduction in infectiousness
Economic	Maintenance of productivity Reduction in overall medical costs

The number of clinically effective ARV has steadily increased since the introduction of zidovudine (formerly known as azidothymidine) in 1987. Fourteen agents are available for general use in South Africa. Several newer compounds are in preclinical development or have entered clinical trials. These are expected to make a significant contribution to the antiretroviral armamentarium.

In principle, any step in the HIV life cycle or its interaction with host cells, can serve as a potential target for therapeutic intervention. The ARV in general use in South Africa target reverse transcription of viral RNA into cDNA, or virus assembly and maturation (see article on the HIV life cycle elsewhere in this issue).

TARGETING REVERSE TRANSCRIPTION

There are three groups of reverse transcriptase inhibitors (RTIs).

Nucleoside RTIs (NRTIs) are chemical analogues of DNA building blocks (Table II). The HIV RT enzyme cannot distinguish between natural DNA building blocks and their nucleoside analogues; incorporation of an analogue into the growing cDNA chain instead of a natural building block terminates cDNA synthesis. This results in incomplete and non-functional cDNA. Preferential uptake of NRTIs can be achieved by depleting the host cell of the building blocks that are the natural competitors of an analogue.

Thymidine analogues exert their activity preferentially in activated cells; conversely, non-thymidine analogues are more active in quiescent or slowly growing T lymphocytes and monocyte/macrophages. It is generally recommended that a combination of NRTIs be used as the 'backbone' of antiretroviral therapy; this should comprise at least one thymidine analogue, and one non-thymidine analogue.

In order to achieve synergism from NRTI combinations,

TABLE II. NRTIs AVAILABLE IN SOUTH AFRICA

Common name	Natural DNA building block	Generic name	Trade name	Site of action	CNS penetration
AZT	Thymidine	Zidovudine	Retrovir	Intracellularly; activated T cells	Good
d4T	Thymidine	Stavudine	Zerit	Intracellularly; activated T cells	Good
ddI	Adenine	Didanosine	Videx	Intracellularly; slower-growing cells	Moderate
ddC	Cytosine	Zalcitabine	Hivid	Intracellularly; slower-growing cells	Poor
3TC	Cytosine	Lamivudine	3TC*	Intracellularly; slower-growing cells	Good
-	Guanine	Abacavir	Ziagen	Intracellularly; slower-growing cells	Good

* Trade name Epivir used in other countries.

TABLE III. ANTAGONISTIC NRTI COMBINATIONS	
Thymidine analogues	AZT + d4T
Non-thymidine analogues	ddC + 3TC

each drug should be the analogue of a different DNA building block. Combinations of NRTIs that are analogues of the same DNA building block are antagonistc and clinically ineffective (Table III).

All NRTIs require intracellular phosphorylation to exert antiretroviral activity. They therefore have a relatively slow onset of action and lack activity against free virus extracellularly and in plasma.

Nucleotide RTIs are DNA chain terminators that require fewer intracellular phosphorylation steps than NRTIs and are active in both activated and slowly growing cells. Nucleotide RTIs can be synergistically combined with NRTIs, as well as other ARV. They retain activity against many NRTI-resistant strains of HIV. Adefovir dipivoxacil (trade name Viread) is the first agent in this category to enter general clinical use.

Non-nucleoside RTIs (NNRTIs) are a structurally diverse group of compounds that nevertheless bind to the same, unique site on the RT molecule and inactivate it. This mechanism is distinct from that of NRTIs. Two NNRTIs are currently available in South Africa: nevirapine (trade name Viramune), and efavirenz (trade names Stocrin and Sustiva).

NNRTIs are rapidly absorbed after oral administration and display potent activity against cell-associated and free virions of HIV. Their long half-life makes them suitable for once-daily dosing. Nevirapine has better CNS penetration than efavirenz. NNRTIs have clinically significant interactions with rifampicin and the oral contraceptive pill.

Resistance to NNRTIs emerges rapidly if the viral load is not fully suppressed. These agents should therefore be used only in combinations of three, or more, antiretroviral agents. NNRTIs are synergistic with NRTIs and/or protease inhibitors (PIs); there is currently no evidence to support the use of two NNRTIs in a treatment combination.

TABLE IV. PIs AVAILABLE IN SOUTH AFRICA	
Generic name	**Trade name**
Nelfinavir	Vira-cept
Indinavir	Crixivan
Ritonavir	Norvir
Saquinavir (hard gel capsule)*	Invi-rase*
Saquinavir (soft gel capsule)	Forto-vase
Amprenavir	Preclir (also known as Agenerase)
Lopinovir/ritonavir	Kaletra

* In view of poor pharmacokinetics, only recommended for use when pharmacologically boosted by concomitant ritonavir.

TARGETING VIRUS ASSEMBLY AND MATURATION

HIV protease (PR) is responsible for the processing of viral components, as well as assembly and maturation of the virion. A wide variety of PIs are available that disrupt this process, by perturbing the structure of the enzyme, interfering with its function, or both. PIs are highly effective antiretroviral agents, displaying potent activity against both cell-associated and free virions of HIV. Unfortunately, they have a number of drawbacks including unpredictable oral absorption, complex pharmacokinetics, liver enzyme metabolism, drug-drug interactions, and significant adverse effects. CNS penetration of PIs is extremely poor.

The PIs available in South Africa are shown in Table IV. PIs can be incorporated into a wide variety of antiretroviral regimens. They are most commonly used in the following ways: for initial treatment regimens: 2 NRTIs + 1 PI, and for patients who have experienced one or more episodes of treatment failure: 1 or 2 NRTIs + 1 NNRTI + 1 or 2 PIs, or 1 NNRTI + 2 PIs, or 3 PIs. In view of the complexity of multiple-PI-containing regimens, a practitioner skilled in HIV medicine should manage these patients.