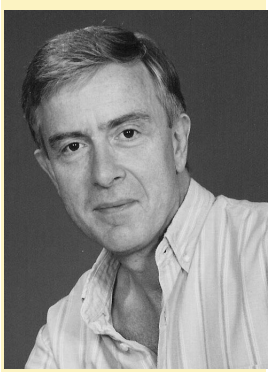
NEW ANTIRETROVIRALS: WHAT IS ON THE WAY?

Despite the present number of available antiretrovirals, there continues to be a need for new medications with improved tolerability and activity against resistant HIV strains.



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This article reviews antiretrovirals available in North America and Europe, not yet registered in South Africa, as well as promising new compounds in clinical development.

NEW NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Tenofovir	Once daily with unique NRTI-resistance profile
FTC	Once daily cytidine analogue
SPD 754	Cytidine analogue with activity against M184V mutation
D-D4FC	Cytidine analogue with activity against NRTI-resistance strains
Amdoxovir	Guanidine analogue with activity against NRTI-resistance strains

Tenofovir disoproxil fumarate is a nucleotide analogue of adenosine 5′-monophosphate. It was registered in the USA in 2001, initially for patients failing previous therapies and more recently extended to first-line therapy. The major route of elimination is renal and it is dosed once daily. When co-administered with didanosine it is recommended that the dose of didanosine be reduced from 400 mg to 250 mg per day. When combined with lamivudine (3TC) or FTC, tenofovir has shown ARV efficacy in both ARV-experienced and -naïve patients. Resistance is associated with a K65R mutation, which occurs infrequently in patients receiving tenofovir. Tenofovir has the least mitochondrial toxicity of the presently registered NRTIs.

FTC is a cytidine analogue closely related to 3TC but is administered once daily. The potency and resistance profiles of FTC and 3TC are similar.

SPD 754 is a de-oxycytidine analogue that has *in vitro* activity against HIV strains with the 3TC resistance-associated M184V mutation. In treatment-naïve patients, a dose-dependent antiviral activity was shown, with no development of new RT mutations. SPD 754 has the least mitochondrial toxicity when compared with 9 other NRTIs.

D-D4FC is another de-oxycytidine analogue with *in vitro* activity against NRTI-resistant HIV strains. *In vivo* activity was demonstrated in both treatment-naïve and treatment-experienced patients with virus highly resistant to other NRTIs.

Amdoxovir (DAPD) is a guanine analogue with a potentially attractive resistance profile. The addition of DAPD to optimised therapy in heavily pre-treated patients achieved a 0.5 log decline in 58% of subjects.

When combined with lamivudine (3TC) or FTC, tenofovir has shown ARV efficacy in both ARV-experienced and -naïve patients.

There is considerable interest in second-generation NNRTIs with activity against nevirapine- and efavirenz-resistant HIV strains.

PIs are associated with deranged lipid and glucose metabolism, which has motivated development of 'metabolic friendly' PIs.

NEW NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Capravirine	2nd generation NNRTI with extended resistance profile
TMC-125	Active against highly NNRTI-resistant virus

There is considerable interest in second-generation NNRTIs with activity against nevirapine- and efavirenz-resistant HIV strains.

Capravirine is a second-generation NNRTI that requires multiple mutations to develop *in vitro* high-level resistance. In patients failing NNRTI therapy, capravirine in combination with nelfinavir and 2 NRTIs was superior to placebo, nelfinavir and 2 NRTIs.

TMC-125 is a di-aminopyrimidine NNRTI with potent *in vitro* activity against HIV, including clinical isolates with high-level resistance to current NNRTIs. *In vivo* activity has been shown in both treatment-naïve and NNRTI-experienced patients.

NEW PROTEASE INHIBITORS (PIs)

Atazanavir	Once daily PI with 'lipid-friendly' profile
A-681799	Extended PI-resistance profile
Fosamprenavir	Pro-drug of amprenavir with lower pill burden
Tipranavir	Extended PI-resistance profile
TMC-114	Extended PI-resistance profile

There is a need for new PIs with distinct resistance profiles and activity against highly PI-resistant HIV strains. PIs are associated with deranged lipid and glucose metabolism, which has motivated development of 'metabolic friendly' PIs.

Atazanavir is an azopeptide PI free of cholesterol and triglyceride abnormalities. The main side-effect is an increase in unconjugated bilirubin, which is related to serum drug level and glucoronidation enzyme genotype (Gilbert's trait). Once-daily dosing and a benign metabolic profile make this an attractive first-line PI, particularly in patients with increased cardiovascular risk factors.

A-681799 is structurally related to atazanavir, with *in vitro* activity against lopinavir-resistant virus.

Fosamprenavir is a pro-drug of amprenavir and is formulated into 476 mg tablets. Its side-effect profile is similar to that of the parent drug. There is a considerably decreased pill burden (6 - 8 tablets) compared with amprenavir (16 tablets). Once-daily dosing is possible when fosamprenavir is combined with ritonavir.

Tipranavir is a non-peptidic HIV protease inhibitor, with interest driven by *in vitro* data indicating activity against highly PI-resistant strains of HIV. The dosing and formulation have been problematical and therapeutic boosting with ritonavir is necessary. A study of 3 doses of tipranavir/ritonavir (500/100 mg, 500/200 mg and 750/200 mg) in heavily pre-treated patients achieved a 1.0 log reduction in viral load in those receiving the 2 higher dosages; however, the 500/100 mg dose was safer and better tolerated.

TMC-114 has potent *in vitro* and *in vivo* activity against PI-resistant strains. A study of 3 regimens of TMC-114, with ritonavir substituted in heavily pre-treated patients for a currently failing PI, showed a 1.2 - 1.5 log decrease in viral load at 14 days.

NEW CLASSES OF ARVs

Fusion inhibitors	
T-20	Peptide binding to viral gp41-blocking membrane fusion
T-1249	Activity against T-20-resistant virus
CCR5 Inhibitors	
GW87314	Blocker of a human co-receptor for HIV binding
SCH-C/SCH-D	Blocker of a human co-receptor for HIV binding
UK-427857	Blocker of a human co-receptor for HIV binding
Integrase inhibitor	
S-1360	First-generation blocker of third HIV-encoded enzyme

New classes of ARVs include fusion inhibitors, chemokine co-receptor blockers and integrase inhibitors. While there is considerable clinical experience with the fusion inhibitor T-20, which was registered for use in the USA and Europe in 2003, co-receptor blockers and integrase inhibitors are entering phase III trials and phase I/II clinical studies, respectively.

Fusion inhibitors

T-20 or enfuvirtide is a large polypeptide molecule that inhibits HIV

fusion with T-cells. Membrane fusion requires conformational changes in viral gp41, which T-20 blocks by binding to this 'spring-like' molecule. The usual dosage of T-20 is 90 mg (1 ml) administered by subcutaneous injection twice daily; it should be augmented with other potent drugs. Manufacture of T-20 is complex, requiring multiple steps, and it is likely to remain a costly drug.

T-1249 is a second-generation fusion inhibitor with greater *in vitro* potency than T-20 and activity against viral strains that are resistant to T-20. Monotherapy studies in heavily pre-treated patients demonstrated a 1.3 log decline in viral load after 14 days with a 25 mg twice-daily dose. Unfortunately T-1249 development has been discontinued.

Chemokine receptor inhibitors

GSK-873140 is a spirodiketo-piperizine CCR5 antagonist with potent *in vitro* activity. In HIV-infected individuals with a CD4 > 200 and predominantly CCR5-tropic virus at baseline, a dose-related antiviral effect was shown.

SCH-C is a small-molecule CCR5 inhibitor with *in vitro* activity against CCR5 and CCX4/R5 duotropic strains. A dose-dependent response has been shown in HIV-infected patients.

UK427857 has also shown dose-related antiviral activity in antiretroviral therapy (ART)-naïve individuals, with predominately CCR5-tropic HIV. Receptor-binding modelling studies indicate a dose of 100 mg bd or equivalent daily dose for long-term treatment.

Integrase inhibitors

Integrase, the third enzyme encoded in the HIV genome, has remained an elusive target of drug development. A number of compounds have been shown to inhibit this enzyme *in vitro* but many of them have shown high toxicity. **S-1360**, a diketo-acid derivative, is a DNA strand transfer integrase inhibitor and was generally well tolerated in healthy volunteers. Dipyrimidine derivatives have also been shown to inhibit the binding of integrase with viral DNA and constitute a second class of integrase inhibitors. The use of combinations of integrase inhibitors offers the prospect of robust inhibition of the third HIV enzyme target.

CONCLUSION

ART continues to evolve rapidly, with increasing survival of patients. Chronic management not only requires potent antiviral effect but also user-friendly and less toxic regimens. The number of new compounds being developed and particularly the increase in drug targets increases options to fight this highly mutable virus.

Further reading

Guidelines for use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/guidelines/adult/aa102904.pdf

New therapies. British HIV Association guidelines for the treatment of HIV-infected adults with antiretroviral therapy. http://www.bhiva.org/guidelines/2003/hiv/new-therapies.html

IN A NUTSHELL

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