NEW NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

There are 7 compounds within this class available for therapy; however, cross-resistance, mitochondrial toxicity, overlapping side-effect profiles and the use of dual NRTIs as a backbone of many triple therapy regimens all combine to limit NRTI-therapeutic options. Members of this class under development include both new molecules and new formulations of existing approved drugs.

Tenofovir disoproxil fumarate is a diester pro-drug of the nucleotide analogue of adenosine 5’-monophosphate. It was registered in the USA in October 2001, initially for patients failing previous therapies and recently extended to use in first-line therapy.1 It also has activity against hepatitis B virus. Bioavailability is improved when administered with food (40%), and it is generally well tolerated. The prolonged elimination half-life allows once-daily administration, with the major route of elimination being both renal glomerular filtration and active tubular secretion. The recommended dosage is one 300 mg tablet daily, if creatinine clearance > 50 ml/min. Co-administration with didanosine results in significantly raised didanosine levels. It is therefore recommended that the dose of co-administered didanosine be reduced from 400 mg to 250 mg per day. New data suggest that this combination should be used with caution, as it is associated with increased early virological failures and CD4 declines even in those achieving viral suppression. It has been postulated that the combination of these adenosine derivatives may be antagonistic in vivo. Co-administration with the protease inhibitors (PIs), atazanavir, indinavir and lopinavir also results in increased tenofovir levels and should prompt increased surveillance for renal toxicity. Atazanavir levels are decreased by tenofovir and ritonavir boosting should be used when co-administered. However, when combined with 3TC (lamivudine) or FTC (emtricitabine), tenofovir has shown antiretroviral efficacy in both

NEW ANTIRETROVIRAL DRUGS: WHAT’S ON THE HORIZON IN 2005?

Despite the present number of available antiretrovirals (ARVs), there continues to be a need for new medications with improved tolerability, and activity against resistant virus. This article will review three groups of ARVs: those available in North America and Europe but not yet registered in South Africa; new formulations of drugs for which the parent formulations are already available in South Africa; and promising new compounds in early clinical stages of development. Table I shows the year of approval of ARVs available for treatment of HIV-infected individuals, in both the USA and South Africa and Table II summarises the characteristics and rationale for new ARVs.

<table>
<thead>
<tr>
<th>Year of registration</th>
<th>USA</th>
<th>RSA</th>
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<tbody>
<tr>
<td>Tenofovir (TFV)</td>
<td>2001</td>
<td>N/R</td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
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<tr>
<td>Nevirapine (NVP)</td>
<td>1996</td>
<td>1998</td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>1997</td>
<td>N/R</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>1998</td>
<td>1999</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td></td>
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<tr>
<td>Saquinavir (SQV)</td>
<td>1995</td>
<td>1997</td>
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<tr>
<td>Ritonavir (RTV)</td>
<td>1996</td>
<td>1997</td>
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<td>Indinavir (IND)</td>
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<td>1996</td>
</tr>
<tr>
<td>Nelfinavir (NLF)</td>
<td>1997</td>
<td>1999</td>
</tr>
<tr>
<td>Amprenavir (AMP)</td>
<td>1999</td>
<td>2001</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>2000</td>
<td>2001</td>
</tr>
<tr>
<td>Atazanavir (ATZ)</td>
<td>2003</td>
<td>N/R</td>
</tr>
<tr>
<td>fosamprenavir</td>
<td>2003</td>
<td>N/R</td>
</tr>
<tr>
<td>Entry inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>2003</td>
<td>N/R</td>
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N/R = not registered as of December 2004.
antiretroviral-experienced and naïve patients. Resistance is associated with the K65R mutation, which occurs infrequently in patients receiving tenofovir. Adverse events associated with tenofovir use include asthenia, headache and gastrointestinal upset. Tenofovir has the least propensity for mitochondrial toxicity of all the currently approved NRTIs. Nephrotoxicity, particularly tubular dysfunction, is less common than reported with use of the earlier nucleotide compound adefovir.

FTC is a fluorinated cytidine analogue approved by the Food and Drug Administration (FDA) in July 2004 for use in combination therapy of adult HIV infection.1,2 It is closely related to 3TC but has a longer elimination half-life, allowing once-daily administration. Potency and resistance profile are similar to 3TC, although it appears that the M184V mutation emerges more slowly under FTC than 3TC selective pressure. The dose of FTC is a single 200 mg capsule once a day.

Racivir is a mixture of FTC and its positive enantiomer with potent anti-HIV and anti-HBV activity. It is well tolerated and dosed once daily. In a phase II dosing study of 200, 400 and 600 mg o.d. in treatment-naïve volunteers, there was a rapid decline in viral load, which remained suppressed for 14 days after cessation of therapy.3

SPD 754 is a deoxycytidine analogue that has in vitro activity against HIV strains with the 3TC resistance-associated M184V mutation. SPD 754, however, has reduced activity against mutations associated with broad resistance to NRTIs (69 insertions and Q151M). The molecule is the negative enantiomer of dOTC, a mixture of both positive and negative enantiomers. The development of dOTC was discontinued because of toxicity observed in primates, which was attributed to the positive enantiomer. A 10-day phase I study of SPD 754 in treatment-naïve patients receiving one of 5 dosages showed dose-dependent antiviral activity with no development of new RT mutations.4 SPD 754 had the least mitochondrial toxicity in a tissue culture assay when compared with 9 other NRTIs including 3TC.

D-D4FC is another deoxycytidine analogue with in vitro activity against NRTI-resistant HIV strains. When dosed at 200 mg once daily for 10 days in vivo activity was demonstrated in both treatment-naïve and treatment-experienced patients harbouring HIV mutations associated with high-level resistance to other NRTIs including 3TC.

Amdoxovir (DAPD) is a guanine analogue, with a potentially attractive resistance profile. In vitro activity has been demonstrated against HIV strains resistant to AZT and 3TC, ddI, ddC and ABC and strains with the multiple NRTI-resistant SS insertions at codons 68 and 69. Virus containing L74V and the double mutations K65R and Q151M are fully resistant to DAPD. Excretion is predominantly renal and because of its low
Currently available NNRTIs cannot be used sequentially following initial NNRTI failure because resistance to any one individual drug usually results in high-level resistance to all members of the NNRTI class. There is therefore considerable interest in second-generation NNRTIs, which have demonstrated in vitro activity against HIV strains with resistance to nevirapine and efavirenz. Reverse transcriptase mutations such as K103N and Y181C, conferring resistance against NNRTIs, result in substitution of large amino acids around the NNRTI-binding pocket, thereby decreasing RT-NNRTI contact. Second-generation NNRTIs molecules retain the ability to attach to the RT-NNRTI binding pocket even when the conformational three-dimensional structure is altered by the presence of these amino acids.

Capravirine is a second-generation NNRTI, which requires 2 or 3 key mutations to develop high-level resistance, in contrast to currently approved NNRTIs that have high-level resistance associated with a single mutation of the pol gene. In patients who had previously failed NNRTI therapy, capravirine 400 mg b.d. in combination with nelfinavir and 2 NRTIs was superior to either 2 100 mg of capravirine or placebo with nelfinavir and 2 NRTIs, but results did not reach statistical significance. Clinical trials were suspended following the discovery that the drug caused vasculitis in dogs; development was resumed following safety assessment.

TMC-125 is a diaminopyrimidine NNRTI with potent in vitro activity against HIV, including clinical isolates with high-level resistance to current NNRTIs including K103N and Y181C mutations. A 1-week monotherapy study of 900 mg twice daily, in treatment-naive subjects, produced a 2 log decline in viral load. In NNRTI-experienced patients, substitution of the existing NNRTI of the treatment regimen with TMC-125 resulted in a 1.0 log decline in viral load at 7 days.

**NEW NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)**

Videx EC is a calcium phosphate ester pro-drug of ddI, which was approved for ARV use by the FDA in October 2001. Videx EC is taken once daily on an empty stomach, but the absence of antacid allows other medications to be taken at the same time. The removal of the calcium- and magnesium-based pH buffers results in fewer gastrointestinal side-effects. Videx EC is now the predominant formulation of ddI used in North America and Europe.

Extended-release stavudine (d4T XR) was approved for ARV use by the FDA in December 2002, and can be taken once a day. A randomised double-blind placebo-controlled trial compared d4T XR with the standard twice-daily immediate-release (IR) capsules and showed similar antiviral and immunological profiles in both arms. Discontinuations due to adverse events were similar in both.

Atazanavir, approved in July 2003 for use in the USA, is an azopeptide PI with freedom from the cholesterol and triglyceride abnormalities that are associated with other members of the PI class. Oral bioavailability is variable but is improved when taken with food. There is a low pill burden and the recommended dosage is 400 mg (2 tablets) taken once daily. An ISOL substitution appears to be a unique signature mutation of this PI, which is associated with increased in vitro susceptibility to other PIs. Atazanavir is extensively heptatically metabolised and largely excreted in faeces. An increase in unconjugated bilirubin can occur which is related to serum drug level and patients’ glucoronidation enzyme genotype (Gilbert’s trait). Elimination half-life is 7 hours and bioavailability is increased by 70% with light meals. Atazanavir blood levels are boosted by co-administration with ritonavir, a CYP3A4 hepatic enzyme inhibitor, but the role of this combination in salvage therapy continues to be delineated. Important ARV interactions requiring ritonavir boosting of atazanavir include the NNRTIs, efavirenz and nevirapine CYP3A4 inducers, and the NRTI tenofovir. Dual PI combination of atazanavir and saquinavir (600/1 200 mg q.d.) in combination with 2 NRTIs has been explored but was not inferior to ritonavir and saquinavir (400/400 mg q.d.). Once-daily dosing and a benign metabolic profile make this an attractive first-line PI, particularly in those with increased cardiovascular risk factors.

Fosamprenavir is a calcium phosphate ester pro-drug of amprenavir, approved for ARV use in the USA in October 2003. It is almost completely hydrolysed to amprenavir and caused vasculitis in dogs; development was resumed following safety assessment.
phosphate by cellular phosphatases in the gut epithelium. It is formulated in 476 mg tablets with a side-effect profile that is similar to the parent drug. The adult dosage of 3 - 4 tablets twice daily results in a considerably decreased pill burden compared with amprenavir (16 tablets). Once-a-day dosing is possible if fosamprenavir is combined with ritonavir. Unboosted fosamprenavir is associated with moderate elevations of total cholesterol but an increased HDL component.

Tipranavir is a non-peptidic HIV PI, with interest in the compound driven by in vitro data indicating that it has activity against strains of HIV that are multiply resistant to other current PIs. The dosing and formulation have been problematic and therapeutic boosting with ritonavir is necessary. The BI 118252 study of 3 doses of tipranavir/ritonavir (500/100 mg, 500/200 mg and 750/200 mg) in 216 heavily pretreated patients, with at least one PI resistance-associated mutation at baseline (not > 1 of 82U/T, 84V or 90M), achieved target plasma concentrations of tipranavir in 77% of the medium- and high-dose groups. A 1.0 log reduction in viral load was seen in those receiving the 2 higher doses; however, the medium dose (500/100 mg) was safer and better tolerated. The presence of > 2 PI resistance-associated mutations at baseline resulted in loss of tipranavir efficacy. Currently the 500/100 mg dosage has been selected for phase III development. Resist 1, an ongoing study of 620 heavily pretreated patients (median 12 ARVs), demonstrated that tipranavir had significant activity against highly resistant virus but outcomes were improved when used with another novel agent such as T-20.

TMC-114 has potential in vitro and in vivo activity against PI-resistant strains. The compound is mainly metabolised by the CYP3A4 heptatic enzyme system and is co-administered with ritonavir. A phase I/II study of 3 regimens of TMC-114 with ritonavir (300/100 mg b.i.d., 600/100 mg b.i.d. and 900/100 mg q.d.) substituted for a currently failing PI in heavily pretreated ritonavir. A phase I/II study of 3 regimens of TMC-114 with resistant strains. The compound is mainly metabolised by the heptad repeat regions (HR1 and HR2) of gp41, which triggers a membrane fusion process: viral-cell attachment; chemokine co-receptor binding; and gp41 conformational change resulting in gp41 heterodimerisation with other potent drugs. The formulation is a lyophilised reconstituted solution should be refrigerated and used within 24 hours. Irritation at the injection site is the commonest adverse event and hypersensitivity reactions are rare. An increase in bacterial pneumonia was observed in trial patients receiving T-20 compared with those receiving placebo, but the cause is uncertain. T-20 has a role in salvage therapy of heavily pretreated individuals, but its manufacture is complex, requiring multiple steps, and it is likely to remain a costly drug.

**SUMMARY**

ARV therapy remains a rapidly evolving field allowing prolonged survival of our patients. Chronic management not only requires potent antiviral effect but also less demanding and less toxic regimens. The number of new compounds in the production pipeline and the increase in drug targets will increase our ability to fight this highly mutable virus.

**REFERENCES**

12. Wood R, Arasteh K, Stellbrink H-J, et al. A six-week randomised controlled trial to compare the tolerability, pharmacokinetics, and antiviral activity of...


Medical Doctors

The award winning PHRU, a large research unit dedicated to finding ways to mitigate the impact of the HIV epidemic, has vacancies for Doctors, including Specialists with an interest in Paediatrics and Adults. The incumbents must be willing to learn and be part of a highly motivated team. There is opportunity for exposure to clinical research methods including GCP, computer literacy and HIV treatment and care. The Unit is located at Chris Hani Baragwanath Hospital where it has a primary care clinic. The positions may include travel to clinics in Soweto. Other attractions include good working hours, mentoring and support for your own research, and an excellent working environment. These positions would suit people who either want to embark on a career in clinical research, or are established researchers.

Experience and skills required: • Registered as a Medical Practitioner with the Health Professions Council of South Africa • Experience in HIV treatment in paediatric and adults • An interest in working with HIV-infected/affected children and adults • Ability to communicate in local languages would be an advantage • Computer literacy or a willingness to become computer literate • Meticulous attention to detail following study protocols and recording symptoms and clinical signs • Good writing and verbal communication skills.

Duties will include: • Participating in all phases of the research process • Assisting in conducting HIV research studies in accordance with ICH GCP and the specifics of the protocol • Providing clinical support for research studies • Providing comprehensive medical care to patients enrolled in studies • Taking histories and examining patients on their follow up visits • Ensuring timely recruitment for all research studies and protocols • Working together with the study team in order to optimise research strategies • Be accountable for study planning and logistics • Being part of the research team making recommendations on how to make studies run efficiently, suggestions for future research and being involved in report findings.

The positions are offered on a 1-year contract basis with the possibility of extension, subject to funding availability and individual performance.

Please send an application letter with an updated CV, including the names and contact information of at least 2 professional references, to Nthabiseng Thabethe by fax on 011 989-9798 or e-mail to nthabethe@witshealth.co.za Initial closing date: 30 April 2005, BUT we will accept applications on an ongoing basis until end of Nov 2005.

SECOND NATIONAL AIDS CONFERENCE

The second South African AIDS Conference will be held in Durban in June 2005.

The theme of this year’s conference is Unity and Accountability, reflecting the feeling of optimism and hope and the many new challenges brought about by the antiretroviral treatment programme.

The formal conference programme will be structured around four tracks: Basic and Clinical Sciences; Epidemiology, Prevention and Public Health; Social and Economic Sciences, Human Rights and Ethics; and Best Practices.

The 2nd South African AIDS Conference will be held at the International Convention Centre in Durban on 7 - 10 June 2005. More information may be obtained from www.sa-aidsconference.com