NEW CLINICAL PERSPECTIVES ON NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Dr Steven Miller, MB BCh, DTMH, FFFpath, MMed, MRCPath, Dip HIV Med (UK), delivered a presentation on the non-nucleoside reverse transcriptase inhibitors (NNRTIs) to the HIV Clinicians Society in Johannesburg on 31 July 2003. He confirmed the clinical usefulness of nevirapine and efavirenz and provided data that demonstrated comparable potency and efficacy of these agents. He highlighted the results of the recent 2NN study, which confirm the clinical equivalence of nevirapine and efavirenz. This prospective, randomised clinical trial is the first head-to-head comparison of nevirapine and efavirenz and included 1 216 patients in 17 countries (including South Africa) on 6 continents. The study showed that, after 48 weeks of treatment, there was no significant difference in the percentage of people who achieved virological success between the nevirapine and efavirenz arms. Serious drug toxicities were rare and were generally encountered at similar, low rates.

Both nevirapine and efavirenz possess excellent bioavailability and rapidly attain high plasma concentrations with recommended dosing schedules. All NNRTIs are biologically active in the form in which they are administered. They therefore inhibit free virions in the plasma and tissue fluids, as well as virus within cells. This mode of action is different from the nucleoside drugs, which are ingested as pro-drugs, require intracellular activation and inhibit only cell-associated virus. Tissue penetration of the NNRTIs is good and their ability to cross the placenta is one of the rationales for the much-publicised use of nevirapine in prevention of mother-to-child HIV transmission (PMTCT). Although nevirapine is only one of several regimens that are safe and effective in PMTCT, the low cost and simplicity of the regimen have made it an attractive strategy in resource-constrained settings. Nevirapine crosses the blood/brain barrier with ease and penetrates well into brain tissue, while efavirenz achieves far lower concentrations in the central nervous system. Paradoxically, efavirenz is associated with significant neuropsychiatric adverse effects while nevirapine is not.

Both nevirapine and efavirenz are highly protein-bound, which results in a long half-life that permits simple dosing regimens and once-daily administration. Both drugs are metabolised in the liver via the P450 cytochrome system, a pathway shared with many other compounds. This creates a risk for drug/drug interactions and the potential to modify the efficacy and/or toxicity of the agents involved. Particular attention should be given to the concomitant use of NNRTIs and rifampicin, oral contraceptives and the protease inhibitor family of antiretrovirals. Rifampicin reduces NNRTI concentrations by approximately 30%. While the clinical significance of this interaction remains uncertain, some authorities recommend increasing the dose of efavirenz to 800 mg at night in patients with a mass of > 60 kg. There are no clear recommendations for adjusting the dose of nevirapine. All NNRTIs reduce the plasma concentrations of oestrogen-containing oral contraceptives, so women of childbearing potential should be advised to switch to an injectable contraceptive or one of the newer progestogenic oral preparations. NNRTIs reduce the plasma concentrations of protease inhibitors to potentially subtherapeutic levels that can be corrected by dosage adjustments or the addition of a boosting dose of ritonavir.

Certain drug-related toxicities are common to both nevirapine and efavirenz, including hypersensitivity syndromes of varying severity, the most common manifestations being erythema multiforme and hepatitis. A critical evaluation of published literature confirms that skin eruptions—including the very rare Stevens-Johnson syndrome—occur with the use of either compound. Induction of hepatic transaminases is a common finding.
among people using nevirapine and efavirenz. On its own, this does not necessarily constitute hepatitis. True hepatitis is a clinical illness that comprises constitutional manifestations, jaundice and elevation of hepatic transaminases to greater than 3 - 5 times the upper limit of normal. Individuals who abuse alcohol and/or are positive for hepatitis B surface antigen and/or hepatitis C appear to be most at risk. Since the risk of hepatitis in these specific at-risk groups appears to be greater with nevirapine, many experts prefer efavirenz in this particular setting provided there are no contraindications to the use of the agent, e.g. pregnancy.

Dyslipidaemia has recently emerged as a major metabolic problem among individuals taking antiretroviral therapy. The nucleoside drugs and protease inhibitors are the most commonly implicated agents. Clinical studies in this setting confirm that switching from a protease inhibitor to nevirapine generally proves beneficial providing viral susceptibility to nevirapine has been assured. Switching from a protease inhibitor to efavirenz does not ameliorate dyslipidaemia. Among individuals receiving long-term NNRTI-based therapy, efavirenz has been demonstrated to reduce high-density lipoprotein (HDL) cholesterol, a pattern that is potentially atherogenic. Conversely, nevirapine consistently raises HDL cholesterol, which has the potential to confer protection against cardiovascular disease.

The Achilles heel of the currently available NNRTIs, Dr Miller said, is the rapidity with which HIV may develop resistance to these agents. Strict adherence is therefore essential for long-term success of an NNRTI-containing regimen as even single-dose nevirapine used to prevent perinatal HIV transmission has been associated with significant rates of resistance. Since resistance to one NNRTI generally confers full cross-resistance to other drugs in the same class, it is generally not possible to change from one NNRTI to another when a patient fails therapy. Recently, new NNRTI resistance mutations have been described in non-subtype B HIV 'African strains' and it is thought that this may confer additional virulence to the virus.

There is currently much debate about the appropriate use of NNRTIs. Although these agents are most widely used as first-line therapy, some opinion leaders prefer initiating treatment with protease inhibitor-based HAART, reserving NNRTIs as potent elements of a salvage regimen. Provided the virus remains NNRTI-susceptible, both approaches yield favourable clinical, virological and immunological outcomes.

In closing, Dr Miller presented preliminary data on a range of new third-generation NNRTIs that are 'resistance repellent'. Early laboratory and clinical studies confirm that these drugs possess potent activity against a broad range of HIV isolates, including many that are resistant to nevirapine and efavirenz. They offer the tantalising promise of being able to prescribe a new NNRTI despite resistance to older compounds. In addition, they have properties that allow them to be adapted for use in unique situations, such as topical microbicides or 'chemical condoms' within the female genital tract.