CONFERENCE REPORT

ANTIRETROVIRAL RESISTANCE

Highlights from the XV International AIDS Conference, Bangkok, 11 - 16 July 2004

Steven Miller, *MB BCh, DTM&H, FFPath, MMed, MRCPath, DipHIVMed (UK)*
Medical Director, innovirInstitute, Johannesburg

Over the past decade, the International AIDS Conference has evolved from a purely scientific event into a reunion of the international family of HIV researchers, policymakers and care providers. The recent meeting in Bangkok boasted a wide-ranging programme that attempted to cater for the diverse interests of around 19 000 delegates. Achieving this objective in the limited time available is a daunting challenge for even the most skilled conference organiser. This year it meant that delegates had to be satisfied with small amounts of new information on a multitude of topics.

The worldwide increase in the prevalence of antiretroviral resistance is of particular concern to researchers and practitioners. Since resistance remains one of the most significant threats to the long-term success of any highly active antiretroviral therapy (HAART) regimen, practitioners are anxious to learn from past mistakes, translate new knowledge into appropriate treatment strategies and develop new drugs that retain useful activity in the face of established resistance.

The conference programme emphasised three major areas related to resistance: *(i)* concerns regarding non-nucleoside reverse transcriptase inhibitors (NNRTIs), *(ii)* reassuring data on certain protease inhibitors (PIs), and *(iii)* development of new agents with potential clinical utility for treating resistant virus.

NNRTI RESISTANCE

Considerable emphasis was placed on the selection of resistant virus when using an NNRTI to prevent mother-to-child transmission (MTCT) of HIV. Since nevirapine (Viramune) is the current agent of choice in this setting, the spotlight was brightly focused on this compound. It is important to emphasise three important facts in this regard. Most MTCT prevention strategies currently used in resource-constrained environments employ regimens that are known to have suboptimal virological efficacy. The selection of NNRTI-resistant virus should therefore come as no surprise. The consequences of suboptimal nevirapine use are probably not unique to this agent, and are very likely to emerge with the suboptimal use of any other NNRTI.

Researchers from the conference's host country[1] presented data on the emergence of resistance among Thai women given zidovudine (AZT) monotherapy from the 28th week of pregnancy followed by single-dose nevirapine during labour. AZT resistance was subsequently documented in 5% and NNRTI resistance in 41%. HIV subtype AE accounted for the majority of infections; the G190A and the K103N mutations were most commonly identified. G190A mediates high-level phenotypic resistance to delavirdine (Rescriptor) and nevirapine, whereas K103N confers high-level phenotypic resistance to all currently available NNRTIs. Of interest was the high proportion of NNRTI-resistant viruses (28%) with multiple resistance mutations.

Until recently, opinion has varied on the long-term consequences of selecting NNRTI-resistant virus by single-dose, or short-course MTCT interventions. Dr Marc Lallement provided sobering information in this regard.[2] He described the outcome of HAART among 221 women who had participated in the Thai Perinatal HIV Prevention Trial (PHPT). All had previously received nevirapine and were allocated to a regimen of stavudine (d4T), lamivudine (3TC) and nevirapine. After 6 months of medication only 47% had achieved full virological suppression (viral load < 50 copies/ml). Thirty-two per cent of women had nevirapine-resistant virus.

A novel strategy to avoid maternal exposure to nevirapine might be administering the drug to the newborn as post-exposure prophylaxis (PEP). Researchers from South Africa[3] reported on the outcome of administering nevirapine as PEP to 23 HIV-infected infants (PEP group); they compared this with the outcome among 30 infants who were given single-dose nevirapine at birth and whose mothers received single-dose nevirapine during labour (standard group). In the standard group, 11/30 (37%) of infants

developed NNRTI resistance (all with the Y181C mutation that causes high-level resistance to nevirapine and delavirdine, and low-level resistance to efavirenz) compared with only 3/23 (13%) in the PEP group. Curiously, only the Y188C mutation (that mediates high-level resistance to nevirapine and delavirdine) was found in the latter group. These results require confirmation in larger studies but suggest that innovative strategies for using nevirapine in a non-HAART setting may result in significantly lower rates of NNRTI resistance, perhaps with different genotypic resistance profiles.

A final aspect of NNRTI resistance is the question of how this phenomenon might affect the success of programmes currently being rolled out in developing countries. HAART regimens comprising AZT or d4T, plus 3TC, plus nevirapine or efavirenz (Stocrin) are recommended as the preferred first-line regimens in many guidelines. These combinations are purported to be safe, effective and affordable, and are often prescribed as fixed-dose, generic drug combinations. The potential weakness of this approach is that both 3TC and the NNRTIs have a low genetic barrier to resistance. Data from our own centre[4] documented a treatment failure rate (viral load > 1 000 cp/ml) of over 20% within the first 12 months of therapy, despite apparently good treatment adherence. Genotype analysis of these predominantly clade C viruses showed that single-drug resistance was rare. Over 90% of patients failing therapy harboured virus with resistance to multiple drugs including both nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs. Since a patient's initial HAART regimen is the one associated with the greatest chance of treatment success, the universal use of NNRTI-based regimens as first-line therapy warrants in-depth evaluation and wider debate.

PIs AND RESISTANCE

Lopinavir/ritonavir (Kaletra) received the lion's share of the scant information on this important topic.

One of the benefits of PIs is their higher genetic barrier to resistance. Long-term follow-up data on patients from several sites in the USA[5] confirmed the impressive durability of treatment response to lopinavir/r and a remarkably low rate of resistance among patients followed up for over 5 years. Of an original group of 100 patients enrolled in the 720 Study (stavudine, plus lamivudine, plus lopinavir/r) 68 have remained on their allocated therapy for a median of 5.4 years. Thirty-two have discontinued therapy, 13 because of adverse events and 19 for other reasons; none have stopped treatment because of lopinavir/r resistance. Sixty-four of the 68 patients who remain on treatment have viral loads < 50 copies/ml, 3 have viral loads of 50 - 400 copies/ml and only 1 has a viral load of > 400 copies/ml. Resistance testing has confirmed the presence of the M184V mutation in 3 of these individuals (i.e. 3TC resistance). Minor mutations have been documented in the protease gene sequence of 6 individuals. None of the mutations detected are recognised as causing lopinavir resistance.

Because of the dominance of clade B virus in the developed world, considerable attention has been devoted to studying this subtype. Globally, however, the majority of HIV infections occur in the developing world and these are due to viruses belonging to other subtypes. Recently evidence has emerged suggesting that resistance to certain antiretroviral agents might evolve along different pathways among clade B versus non-clade B virus. This is particularly relevant to the clinical use of PIs. Information from Brazil[6] added to the growing body of knowledge on this important aspect of antiretroviral resistance. Subtype C virus (which is also the most prevalent subtype in southern Africa) frequently has a natural polymorphism at codon 93 in the protease gene known as I93L. This appears to render the virus more susceptible to lopinavir/r. In addition, subtype C virus is unusual with regard to nelfinavir (Viracept) resistance. Among clade B virus, nelfinavir resistance is due to the selection of the D30N mutation; this confers little cross-resistance to other PIs, permitting the practitioner and patient to use PIs in a specific sequence. For this reason, nelfinavir has been widely advocated as the preferred initial PI in Europe, North America and Australia. Clade C virus, however, is much more likely to develop nelfinavir resistance via the L90M mutation. In contrast to D30N, L90M mediates extensive cross-resistance among the PIs. For treating clade C virus nelfinavir is ranked equally with other, older unboosted PIs with regard to its resistance profile.

A disappointing omission from the conference programme was the lack of new data on the novel, once-daily PI atazanavir (Reyetaz). Atazanavir has been approved for use in many parts of the world. Registration in South Africa is anticipated later this year, or early in 2005. In treatment-naïve patients, atazanavir resistance has been associated with a distinctive mutation known as I50L. This confers no cross-resistance to other PIs, suggesting that atazanavir could have an important role as first-line PI therapy. To date, however, clinical trial data suggest that atazanavir is less potent than lopinavir/r. Many authorities therefore recommend combining atazanavir with another PI such as saquinavir, or boosting its pharmacological activity by the concomitant administration of low-dose ritonavir. Information is eagerly awaited on the impact that these strategies will have on the evolution of PI resistance.

NEW AGENTS FOR TREATING RESISTANT HIV-1

Data on two new agents, enfuvirtide and F-ddC, brought bad news and good. Enfuvirtide (Fuzeon) is the first entry inhibitor to enter general clinical use. Because of limited manufacturing capacity and cost, enfuvirtide has generally been reserved for treating patients with multi-drug-resistant virus. Data from Canada showed that virus from 40 of 41 patients under treatment with this agent developed a recognised enfuvirtide resistance mutation after as little as 8 weeks of therapy. Several patients had virus with multiple enfuvirtide mutations and/or novel mutations affecting the drug's site of action. This disappointing information suggests that enfuvirtide may be useful only when used as part of a maximally suppressive HAART regimen. The current practice of reserving its use for deep-salvage therapy may need to be revised. By the time the next International Conference on AIDS comes around, there should be early clinical data available on the new oral fusion inhibitors, particularly the novel CCR5-receptor blocker from Pfizer.

F-ddC (Reverset), a new cytidine analogue that inhibits HIV-1 reverse transcriptase, was reported to be effective in early phase II studies that recruited both treatment-naïve and experienced patients.[7] On average, viral loads dropped by >1 log in the treatment-naïve group and 0.8 log in the treatment-experienced group. Larger studies have been initiated in the USA and Europe. Preliminary results will be released early next year.

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