

Novel therapeutic approaches for existing drug treatments in HIV/AIDS

Elizabeth Davies reports highlights of the clinical research, treatment and care component of the recent international AIDS conference

Much of the research presented at the conference focused on novel therapeutic approaches to existing drugs. This report concentrates primarily on data that are relevant to the treatment of HIV in the UK and in the rest of the developed world.

Standard HIV treatment in the developed world is to use a combination of at least three drugs to which the virus is sensitive. This has become known as “highly active antiretroviral therapy” (HAART). Guidelines from the British HIV Association (BHIVA) advocate initiation of treatment when the CD4 lymphocyte count is between 200–350 cells/mm³. There were two abstracts at the conference which presented data on the use of Kaletra (lopinavir/ritonavir) monotherapy. Kaletra is available as a co-formulated capsule containing a combination of two protease inhibitors, lopinavir and a small dose of ritonavir, which is used as a pharmacokinetic enhancer to increase the bioavailability of lopinavir. Ritonavir-boosted protease inhibitors are advocated for use over single protease inhibitors nowadays due to their improved pharmacokinetics, which reduces dosing frequency and leads to optimal plasma drug levels required for inhibition of viral replication. Kaletra has proven potency and is commonly prescribed as a component of triple HAART in the UK. Single drug therapy could decrease costs, help reduce toxicity, preserve future treatment options and improve adherence to treatment, but is it potent enough? Early treatment of HIV involved administration of single agents such as zidovudine which we now know to be ineffective as well as encouraging the development of resistance. However, could this strategy be used now that we have access to more potent drugs such as Kaletra?

Kaletra monotherapy

Gathe and colleagues,¹ from Houston, Texas, presented the results of a 48-week open label single site, pilot study of Kaletra monotherapy. The study included 30 patients who were naive to antiretroviral therapy. The inclusion criteria for the study was a viral load (VL) above 2,000 RNA copies per ml (cpm) and there was no limitation on CD4 lymphocyte

Studies on preventing mother-to-child transmission of HIV in developing countries were presented (see p164)

count. The mean CD4 count was 164 cells/mm³ at baseline and the mean VL was 262,000 cpm (over 50 per cent of patients had a VL > 100,000 cpm at baseline, a cut off figure commonly used as a marker of high VL). The primary end points for the study were the percentage of patients who had a VL < 400 cpm at week 48 and the presence of adverse events. Secondary endpoints were the percentage of patients who had a VL < 50 cpm (commonly referred to as below the level of detection) at week 48 and the change in CD4 lymphocyte count. Using an intention to treat (ITT) analysis, 19/30 patients (63 per cent) had a VL < 400 cpm at week 48, and 18/30 (60 per cent) were < 50 cpm. A mean increase in CD4 count of 228 cells/mm³ was demonstrated. Of those remaining on treatment at week 48, 18/20 (90 per cent) had a VL < 50 cpm. There was a large drop out of 10 patients; two were lost to follow up, two were non-adherent to medication, two had adverse events, one was deported, one developed hepatitis B therefore lamivudine was added to the drug regimen, but only two patients experienced virological failure. One point to note within the study was that the dose of Kaletra was modified to four capsules twice daily for those patients weighing over 70kg,

whereas the current licensed dose is three capsules twice daily irrespective of weight. No significant adverse events were seen. The results of this pilot study warrant further investigation in the form of a randomised controlled clinical trial using standard HAART as a comparator.

Arribas *et al*² presented data on 42 patients in a 24-week, randomised open label pilot trial, on simplification to single agent Kaletra in an induction-maintenance strategy. Patients were eligible if they were taking HAART consisting of Kaletra and two nucleoside reverse transcriptase inhibitors for at least one month and had had an undetectable VL (< 50 cpm) for at least six months prior to enrolment. Patients were randomised on a 1:1 basis either to continue with their present three drug regimen or reduce to single agent Kaletra. At week 24, of those patients still on therapy (on treatment analysis), 100 per cent in the triple drug arm remained undetectable with a VL < 50 cpm versus 95 per cent of patients in the simplification arm. In the ITT analysis (non completer = failure), 81 per cent in the simplification arm remained undetectable versus 100 per cent in the triple drug arm. The three failures, which were all in the simplification arm, each had genotypic resistance testing performed, none of which demonstrated the development of resistance mutations in the protease genome to Kaletra. This study demonstrated that a large proportion of patients simplified to single agent Kaletra remain with an undetectable VL after 24 weeks of therapy and preliminary data show that failures are not associated with the development of resistance mutations, which means that future treatment options are not jeopardised.

Intermittent treatment

Treatment of HIV to date has generally been considered to be long-term and possibly life-long. With the ever increasing costs of HIV antiretroviral therapy and a growing population of newly diagnosed cases requiring treatment, there was much interest in Bangkok in looking at strategies of intermittent treatment, which has the potential not only to reduce expenditure on drug therapy but also provide perceived benefit to patients by improvement to quality of life.

Ananworanich³ presented the results of a Thai study investigating three therapeutic approaches to antiretroviral therapy in 74 patients. The study involved three arms: continuous antiretroviral therapy, CD4-guided treatment and one week on-one week

Details The XV International AIDS Conference took place in Bangkok, Thailand, from 11 to 16 July. The theme of the conference was “Access for all”. Elizabeth Davies is principal pharmacist, HIV and genitourinary medicine at Chelsea and Westminster Hospital, London

SMART study due to start

The SMART study, which was discussed during the meeting, is about to start. It is a large scale multinational trial involving the UK to compare the long-term clinical consequences of two treatment strategies: drug conservation (DC) versus viral suppression (VS) strategy. DC is a strategy aimed at conserving antiretroviral treatment for the minimum time required to maintain the CD4 cell count between 250 and 350cells/mm³ then episodic treatment will be used guided by the CD4 cell count. The VS strategy is the conventional method of treatment that we currently follow according to the BHIVA guidelines, whereby we aim to suppress the VL to as low a level as possible on a continual basis, changing treatment components when required, to maintain viral suppression.

off treatment. All patients had previously been exposed to nucleoside reverse transcriptase inhibitors (NRTIs). All patients were initially prescribed two NRTIs plus saquinavir (boosted with low dose ritonavir) until they reached a VL<50cpm and had a CD4 response to above 350cells/mm³, at which point they were then randomised to one of the three treatment arms for 96 weeks. After 96 weeks of randomised therapy all patients then took continuous HAART for 12 weeks. The CD4-guided therapy was based on a CD4 cut off of 350cells/mm³ (ie, treatment when the CD4 count falls below this level and discontinuation once the CD4 count recovers) or CD4 count rise or fall of 30 per cent. The one week on-one week off strategy had high rates of virological failure and was prematurely stopped. After 12 weeks of HAART retreatment, patients in the CD4-guided arm for 96 weeks achieved similar CD4 and VL outcomes as continuous arm patients but used 46 per cent less HAART. In summary, this study demonstrates that CD4-guided treatment may be a safe, effective and cost saving approach to therapy.

Two progress reports on intermittent therapy studies were presented and the results are pending. One is looking at eight weeks on-eight weeks off therapy compared with continuous treatment and the other is a three-arm randomisation: continuous treatment versus two months interruption-four months treatment versus CD4-guided treatment. We eagerly await the results of both these studies.

Mother-to-child transmission

There were several presentations on the topic of mother to child transmission (MTCT). One of the strategies adopted within the developing world has been to administer a single dose of nevirapine to the mother during labour, due to its simplicity, availability and low cost. However, this has been demonstrated in a large scale study, the HIV-NET 012 trial, to give rise to high risk of nevirapine resistance, even following a single dose, which can compromise future treatment options for the

mother and the newborn. This is because nevirapine has a long half life and only one mutation in the genome needs to emerge for high-level resistance to develop. One approach to resolving this problem could be to add Combivir (lamivudine plus zidovudine) to avoid single drug exposure. A prospective, randomised study is being conducted in South Africa, the results of which to date were presented by McIntyre.⁴ Women are assigned to receive single-dose nevirapine in labour (group 1, the current standard) or Combivir supplementation for four (group 2) or seven (group 3) days. Genotypic resistance testing is performed at weeks 2 and 6 post partum. To date, 61 mothers have been evaluated with a median CD4 cell count and HIV plasma VL of 318cells/mm³ and 32,600cpm, respectively. Despite the fact that no mothers exhibited resistance to nevirapine before entry to the study, nevirapine resistance was present in isolates from nine of 18 women (50 per cent) who received nevirapine alone, compared to four of 43 women (9 per cent) who also received Combivir. This difference was significant and the nevirapine-only arm has now been discontinued. The presence of resistance was 5 per cent in the four-day Combivir arm versus 13 per cent in the seven-day arm. This difference was not significant. There was no resistance to either zidovudine or lamivudine. Of 68 evaluable infants, five (7 per cent) were infected, a figure that is slightly higher than expected. Four of these were infected *in utero* and one after delivery. Nonetheless, the use of zidovudine/lamivudine significantly reduced the development of resistance, suggesting that this may be a viable addition to current MTCT programmes. Further research will be required to establish the optimal duration of Combivir therapy that will be required. It would be prudent to use the shortest duration possible that protects against nevirapine resistance, yet reduces MTCT effectively, since the consequence of prolonged treatment is the risk of developing NRTI resistance, most likely to lamivudine.

Within the developed world, protease inhibitors are widely used during pregnancy to prevent MTCT. Optimal antiretroviral exposure during pregnancy is critical for prevention of MTCT and for maternal health. Pregnancy can alter the pharmacokinetics of certain drugs and Stek and colleagues⁵ reported on 12 pregnant women who received Kaletra in pregnancy. Extensive 12-hour pharmacokinetic profiles were completed at 30–36 weeks of gestation and were compared with historical controls as well as postpartum measures (completed in four cases). During the third trimester, 10 of 12 women had inadequate total drug exposure. These data are worrisome, and suggest that therapeutic drug monitoring and dose adjustment will need to be performed if Kaletra is used during pregnancy. The safety, pharmacokinetics and efficacy of increased dosing regimens of Kaletra during pregnancy should be investigated.

In contrast to this, data on the use of saquinavir boosted with ritonavir in preg-

nancy was presented by Hawkins *et al*⁶ from Chelsea and Westminster Hospital in London. They showed that in 10/11 patients, plasma drug trough levels were greater than the target required for saquinavir. This indicates that effective saquinavir exposures are delivered during pregnancy when administered with ritonavir at a dose of 1,000mg saquinavir plus 100mg ritonavir twice daily.

Tipranavir

Tipranavir is a new protease inhibitor manufactured by Boehringer Ingelheim with activity against HIV which has become resistant to other protease inhibitors. Until recently it has been restricted to use within clinical trials. In order to make it available to those patients who cannot enter the phase III trials, a multinational, open-label programme has been initiated, and was announced in a poster presentation.⁷ This is currently operating within the UK in order to provide early access to tipranavir to those patients with advanced HIV-1 infection who have limited treatment options. There is now no restriction on CD4 count and VL for entry into the programme. It is taken twice daily in combination with ritonavir. One of the phase III trials of tipranavir looked at combining it with other protease inhibitors, a concept referred to as double boosting. Interim results demonstrate that this is not feasible due to negative pharmacokinetic drug interactions between tipranavir and the protease inhibitors lopinavir, amprenavir and saquinavir. The plasma levels of these drugs were significantly decreased.

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Presentations sourced

1. IMANI-1 TC3WP Single drug HAART-proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV + ARV-naive patients — interim analysis of subjects completing final 48 week data (J.C. Gathe *et al*) — Abstract number MoOrB1057.
2. Simplification to lopinavir/r single-drug HAART: 24 weeks results of a randomized, controlled, open label, pilot clinical trial (OK Study) (J. R. Arribas *et al*) — Abstract number TuPeB4486.
3. A randomized trial of continuous, CD4-guided and one week on-one week off HAART in 74 patients with chronic HIV infection: week 108 results (J. Ananworanich *et al*) — Abstract number WeOrB1283.
4. Addition of short course Combivir to single dose Viramune for prevention of mother-to-child transmission of HIV-1 can significantly decrease the subsequent development of maternal NNRTI resistant virus (J. McIntyre *et al*) — Abstract number LbOrB09.
5. Reduced lopinavir exposure during pregnancy: preliminary pharmacokinetic results from PACTG 1026 (A. Stek *et al*) — Abstract number LbOrB08.
6. Pharmacokinetics, safety, tolerability and efficacy of saquinavir hard-gel capsules/ritonavir (SQV/r) plus 2 nucleosides in HIV-1-infected pregnant women. (D. A. Hawkins *et al*) — Abstract number ThPeB7064.
7. An open-label Expanded Access Program (EAP) to assess the safety of tipranavir co-administered with low-dose ritonavir (TPV/r) in patients with advanced HIV-1 infection and limited treatment options (M. Taton *et al*) — Abstract number ThPeB7178.