

IAS 2007: Promising signs

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A major HIV/AIDS medical conference in Sydney has generated lots of news on the treatments front. Several of the big guns of recent HIV drug development have continued to perform well in clinical trials, and there are promising signs in dealing with toxicities, neurological complications and more.

The International AIDS Society conference on HIV Pathogenesis, Treatment and Prevention is held every second year. It's one of the major events on the HIV calendar, and regularly delivers significant news. This year's IAS conference was held right here in Australia, at the Sydney Convention Centre from 22-25 July. This was the biggest HIV-related conference ever held in Australia, attracting more than 5000 clinicians, activists and government representatives from around the world.

At the opening session, speakers repeatedly referred to the contentious plans by the federal government to place new restrictions on HIV-positive immigrants. While Australia's long-standing partnership between government, researchers and affected communities was applauded, speakers warned that the partnership was threatened by recent political developments.

"Recent comments by high governmental authorities have cast doubt on Australia's commitment to reduce stigma and discrimination for people living with HIV," said IAS president Pedro Cahn. "Fortunately, neither the scientific community nor the Australian people support these statements. We stand united with local and global AIDS community to ensure that people living with HIV have the right to travel without harassment or the requirement to disclose their HIV status."

Professor David Cooper, of Australia's National Centre in HIV [Epidemiology](#) [1]The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population. and [Clinical](#) [2]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. Research, said Australia's partnership is "worth not just saving, but actively nurturing." But he warned that recent rises in HIV infections meant the partnership was in danger of fragmenting as the issue becomes increasingly politicised.

"Pointing fingers of blame will do nothing to curtail infections," he told the crowd. "Threatening to demonise people living with HIV infection will not help. Making recent immigrants from developing countries the alleged culprits will not help."

Federal health minister Tony Abbott, representing the Australian government, noted that there are no restrictions on HIV-positive people coming to Australia on tourist visas, and there was no intent to change this. But for people seeking permanent residency, he confirmed the government's intention to implement new restrictions.

Australia is a "big-hearted and compassionate country," Abbott said, however applicants for permanent residency will have to give "enforceable undertakings" to seek treatment. But he stressed that the measures were being introduced "because we want to help people, not judge them."

Maura Mea, an HIV-positive woman from Papua New Guinea, reminded the audience of the importance of maintaining a strong involvement by people living with HIV/AIDS in the response to the epidemic, in our region and globally. "One of the keys to addressing the HIV epidemic is to address stigma and discrimination," she said. "An important way of doing this is to put a real human face to the epidemic and embrace the principles of Greater Involvement of Positive People (GIPA) in decisions that affect their lives. Those principles are as important today as they were when they were first developed in 1994."

New drugs

There is a lot of excitement about new treatments at the moment, with several new agents, many from entirely new

Integrase inhibitor

Raltegravir (Isentress, formerly MK-0518) is an [experimental](#) [5] (Of a drug) Not licensed for use in humans, or as a treatment for a particular condition. Experimental drugs are studied in clinical trials to determine their safety and efficacy, and are sometimes made available via Special Access Schemes prior to their approval. integrase inhibitor being developed by Merck. Integrase inhibitors target a different part of the HIV life cycle to existing treatments – by interfering with the integrase enzyme, which HIV uses to insert its viral DNA into human cells. As they represent an entirely new class of HIV drugs, the development of effective integrase inhibitors has the potential to radically improve treatment options.

Forty-eight week data from a major phase-2 trial of raltegravir was presented to the conference, with the drug showing similar efficacy to efavirenz in people who had not previously taken HIV treatments. The 189 people participating in this study were randomly assigned to one of five groups, four of which took different doses of raltegravir; the fifth group received efavirenz at the standard dose. All participants also took Truvada (FTC plus tenofovir). The objective was both to see whether raltegravir was as effective as efavirenz, and to find the most appropriate dose of the new drug.

The rate of virologic failure (defined in this study as having a [viral load](#) [6] A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma. over 400 at the 24-week mark) was similar in both the raltegravir and efavirenz groups at about 3 percent. Only one person taking raltegravir had no response to it, while four others had an initial response followed by a viral rebound.

At 48 weeks, more than 83 percent of people taking raltegravir had viral load below 50 copies/ml. There were very few cases of people discontinuing treatment due to side effects or toxicity problems, a sign that the drug is well tolerated. Diarrhoea was somewhat more common among people taking higher doses of raltegravir compared with efavirenz, while CNS side effects such as abnormal dreams, and increases in [cholesterol](#) [7] An essential component of cell membranes and nerve fibre insulation, cholesterol is important for the metabolism and transport of fatty acids and the production of hormones and Vitamin D. Cholesterol is manufactured by the liver, and is also present in certain foods. High blood cholesterol levels have been linked to heart disease and may be a side effect of some anti-HIV medications. and triglycerides were significantly more common in those taking efavirenz.

These are impressive results and show that this new treatment is very effective in treatment-naïve people and relatively easy to tolerate. There are also signs that raltegravir is capable of producing much faster reductions in viral load compared to efavirenz, and while the clinical significance of this is not yet understood, it does suggest that, assuming further trials continue to report good results, this drug will have a big role to play in HIV therapy in the future.

CCR5 inhibitors

Maraviroc (Celsentri) is a CCR5 inhibitor being developed by Pfizer. This is another drug from an entirely new class, and again 48-week results from a clinical trial were presented in Sydney.

CCR5 inhibitors work by blocking one of the co-receptors used by HIV to gain entry to human cells. There has been some concern about them because HIV is able to use an alternative co-receptor (CXCR4) in some people, and so the participants in this trial had been pre-screened to ensure they had 'R5-tropic' [virus](#) [8] A small infective organism which is incapable of reproducing outside a host cell., which uses the CCR5 co-receptor. People with 'X4-tropic' or mixed virus were excluded from this trial and are unable to use this treatment.

The MERIT trial is a phase-3 study involving 721 treatment-naïve participants, who were randomly assigned to receive either maraviroc or efavirenz, plus Combivir (AZT plus 3TC). The study is looking to see the proportion of people who achieve undetectable viral loads (below 400 copies/ml and below 50 copies/ml) at week 48.

The results showed that in this trial, maraviroc was 'statistically non-inferior' to efavirenz in the number of patients below 400 copies, but performed slightly less well in achieving viral load below 50 copies: 65.3 percent of participants taking maraviroc had viral load below 50, compared with 69.3 percent of those taking efavirenz. The drug was however well tolerated, with similar rates of discontinuation in both study arms, and importantly there were no signs of increased rates of malignancies in patients taking maraviroc.

The issue of increased malignancies has led to the abandonment of other drugs in this class, and continues to

cloud another CCR5 inhibitor being developed by Schering-Plough, vicriviroc, which was the subject of a separate presentation in Sydney. Week 48 data from a study involving 188 treatment-experienced people were presented, updating earlier results unveiled at last year's International AIDS Conference in Toronto.

Vicriviroc produces very pronounced drops in viral load (about 2 logs) at both the 10mg and 15 mg doses, however a 5mg arm in this trial was discontinued due to lack of efficacy. At week 48, the proportion of participants with undetectable viral load was 27–37 percent, much higher than in the [placebo](#) [9]A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial. arm (11 percent). But two additional cases of cancer among those taking the drug, adding to six malignancies at the 24-week stage, mean that the question of any causal relationship between vicriviroc and increased incidence of cancer will need to be investigated.

Encouraging early results for another drug in the CCR5 inhibitor class, INC9471, were also presented in Sydney. This is a drug which has shown good activity against HIV in test-tube studies and has a long half-life, making it suitable for once-daily dosing.

In a [randomised trial](#) [10]A clinical trial in which participants are [randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. involving 23 people, INC9471 was given as monotherapy for 14 days to 19 patients, while a further four received a placebo. Of the 19 participants taking the active drug, 18 had a viral load reduction of at least one log, and 16 had greater than 1.5 log reduction, and there were no serious adverse effects. Two participants had a change in HIV tropism from R5-tropic to X4- tropic over the course of the study, a finding that will require further study.

Abacavir hypersensitivity screening

An Australian-developed genetic test for abacavir (Ziagen) hypersensitivity reduced the rate of allergic reactions to zero in a large [randomised](#) [11]A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant control, the conference heard.

About five percent of people taking abacavir develop a severe allergic reaction shortly after starting the drug, which can be life-threatening if abacavir is taken again in the future. The large international PREDICT trial was designed to measure the 'negative predictive value' of the genetic test – i.e. whether using this test, physicians could be confident that a hypersensitivity reaction would not occur. The results were very clear, with none of the 1956 participants who had a positive test having a clinically proven hypersensitivity reaction.

The availability of this test now means that doctors and patients can rule out the possibility of a dangerous allergic reaction to abacavir, reducing both the overdiagnosis of allergic reactions and patient anxiety when starting abacavir.

When to start treatment

The question of what is the best time to start [antiretroviral](#) [12]A medication or other substance which is active against retroviruses such as HIV. treatment was the subject of a number of presentations at the conference, and as previously reported in PL there seems to be a swing back towards earlier treatment initiation.

While the risks of developing long-term toxicities have for some years been used as an argument against earlier initiation of [HAART](#) [13]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together., improved tolerability and the emergence of new classes of drugs mean the question is very much back on the agenda. Scientists are also starting to understand better the mechanics of early infection, particularly the changes that happen to immune cells located inside the gut, and this suggests a benefit for starting treatment earlier rather than later.

A symposium session at the conference canvassed the issues, looking at the systemic immune activation that occurs immediately after infection, the loss of immune cells in the gut, and evidence from SMART and other studies which used specific CD4 thresholds to start treatment. A fascinating study from Canada also looked at the impact of earlier treatment of HIV prevention in a country with similar treatments access and a comparable epidemic to Australia's, concluding that an increased uptake of treatment would significantly reduce new HIV infections.

There still isn't any widespread consensus on what the 'magic number' – the right CD4 count at which to start treatment – is. Current UK, US and Australian guidelines suggest that treatment can be delayed until 250 or 200, however there seems to be little support for doing so, and indeed few clinicians now believe there is a benefit in delaying treatment once the CD4 count falls to 350.

We aren't back to 'hit early, hit hard' (the catchcry of a few years ago, before lipodystrophy and other long-term toxicities emerged) but the pendulum is certainly swinging back. From the perspective of a positive person, it's hard not to wonder when the clinicians will make up their minds and stop treating us like guinea pigs! The good news is that this question is now being actively explored and several studies are being planned which will shed some light on it in due course. Watch this space.

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Links:

- [1] <http://www.napwa.org.au/glossary/term/490>
- [2] <http://www.napwa.org.au/glossary/term/475>
- [3] <http://www.napwa.org.au/glossary/term/124>
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