

Global crisis: local action

Created 15 Dec 2003 - 6:00am

The annual conference of the Australasian Society for HIV Medicine ([ASHM](#) [1]Australasian Society for HIV Medicine. The peak Australasian organisation representing the medical and health sector in HIV/AIDS and related areas.) is Australia's only regular HIV medical conference. PAUL KIDD reports on the latest medical developments discussed at this year's conference in Cairns.

The theme of the 2003 ASHM Conference was 'Global Crisis: Local Action' and two major plenary speeches, by Professor Dennis Altman and Professor David Cooper, focused on the big picture and Australia's place in it.

HIV/AIDS is a greater threat to our regional stability than terrorism, Altman told the opening day of the conference. With predictions that Asia will soon surpass Africa as the main battleground of HIV/AIDS, Altman warned of the dangers posed by a rapidly escalating epidemic on our doorstep.

"The growing spread of HIV in the Asia-Pacific, in particular its rapid growth in major countries such as India, China and Indonesia, has major implications for the stability and cohesion of the region," Altman warned.

Altman told the conference that despite the predicted growth in infections in our region, the issue has been 'sidelined' in recent years due to international conflict.

"The impetus for recognising HIV as a first order threat — seems to have declined since the events of September 11 and the subsequent wars in Afghanistan and Iraq," he said. "Yet to ignore the lessons of the epidemic in Africa, where it is effectively destabilising most of the continent, because of current concerns with the threat of terrorism, is to risk a heightened emergency on a scale even greater than that currently affecting Southern Africa."

'Delivering [antiretrovirals](#) [2]A medication or other substance which is active against retroviruses such as HIV. to the world' was the topic of Professor Cooper's plenary speech a couple of days later.

"[HAART](#) [3]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. works," Cooper told the audience, and without it, at least 42 million people will die in the next few years. The mounting evidence of the [effectiveness](#) [4](Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of HAART, together with increasing treatments activism, low-cost generic antiretrovirals and increasing government commitments to fight AIDS mean that it's high time to act on treatments for poor countries.

Cooper's blunt, self-deprecating speaking style is as much a drawcard at these events as his international reputation, and he pulled no punches in dismissing the 'flawed assumptions' he said had prevented action on treatments to date.

Taking a line from the British immunologist Peter Medawar, Cooper told the crowd that science is "the act of the soluble," and that the global AIDS problem is soluble, not just for compassionate reasons, but because it must be solved if economic development is to occur.

Making treatments available in the developing world will have a dramatic impact on prevention efforts too, Cooper argued, pointing out that in the developed world, HAART has proven to be one of the most cost-effective treatment interventions.

"Even if antiretroviral agents were given out for free tomorrow, only a fraction of the HIV-infected population would benefit in the short term," Cooper said. "But that shouldn't hold us back. You have to start somewhere."

Lipodystrophy

In a departure from the traditional separation of social from medical research at AIDS conferences, the session on lipodystrophy opened with a presentation by Asha Persson of the National Centre in HIV Social Research.

Persson reported on the Side Effects Project, which has conducted interviews with 40 positive people, "mostly Anglo gay men," about their experience with lipo.

The participants had diverse responses to the physical changes brought on by lipo, including feeling unattractive and worrying that their appearance would disclose their HIV status.

The most common strategy to deal with lipo among this group was regular exercise, a strategy that participants acknowledged would not reverse their lipodystrophy, but which helped in another way, by increasing their self esteem and sense of general well-being.

Participants who had been treated with NewFill (polylactic acid) injections reported a dramatic improvement in their facial appearance, Persson said, but were concerned that the expensive treatment was only cosmetic and could not fix the underlying metabolic disorder.

Persson told the conference that lipodystrophy should be treated as more than merely a medical problem, and requires a broad approach with multiple strategies to both combat the physical changes and maintain mental health and self-esteem.

Dr Anne Mijch reported on a Victorian study examining the effect of NewFill injections on facial wasting in 27 heavily pre-treated patients, six of whom had completed the course of three injections. The doctors used both visual grading of the severity of facial wasting, and CT scans which precisely measured the volume of facial fat, to determine the effectiveness of the treatment.

Among the patients who had concluded the study, there was a significant visual improvement in the amount of facial fat loss, both on the patients' own assessment and that of an independent plastic surgeon; however there was only a very small, statistically insignificant change in the volume of facial fat measured by CT scan (from 133.9 to 140.2 cubic centimetres).

More than three-quarters of the patients in this study experienced side effects including pain, swelling and fluid accumulation at the injection site.

The ROSEY trial, which has been investigating the use of rosiglitazone as a potential treatment for lipoatrophy, was the subject of several different presentations.

Rosiglitazone is a drug that has proven useful in several types of non-HIV-related lipodystrophy. It is known to combat [insulin resistance](#) [5] A diabetes-like condition in which, while adequate amounts of insulin are produced by the pancreas, the body does not respond normally to the action of insulin. In the wider community, insulin is related to obesity, while in HIV it may be related to lipodystrophy., which is widely believed to be a possible cause of HIV lipodystrophy, especially the facial and limb fat loss known as lipoatrophy.

Unfortunately, the results of the ROSEY trial have been largely disappointing. The trial enrolled 108 participants, half of whom received rosiglitazone and half took a [placebo](#) [6] A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial..

At the end of the 48-week trial, there was no observable difference in the level of fat loss between the rosiglitazone and placebo groups, despite the fact that the rosiglitazone group showed clear signs of improved insulin sensitivity. The causes of lipoatrophy will need to be reconsidered, the researchers concluded, as this study doesn't support insulin resistance as the cause.

Heart disease

Matthew Law presented some findings from D:A:D ('Data Collection on Adverse Events of Anti- HIV Drugs'), a large international [cohort](#) [7] In epidemiology, a group of individuals with some characteristics in common. A cohort study is a special kind of clinical trial which looks at a treatment or treatment strategy in a cohort of people. study.

The D:A:D cohort has enrolled 23,468 participants in Europe, Australia and the US. Its purpose is to examine the rates of incidence of myocardial infarction (MI) — heart attacks — among people with HIV.

The study results to date, after an average follow-up of about 18 months, show a direct linear relationship between the amount of time a person has been on HAART and the risk of having an MI, and this risk is independent from other risk factors such as smoking, older age, and previous heart disease.

Law displayed a graph which, depressingly, showed the calculated risk of heart attack increasing — by 26 percent — for every year on treatment, up to five years: among people who had never taken HAART, the 'adjusted incidence rate' was 5.7 MIs per 1000 person years, rising to 8.4/1000py for people who had been treated for four or more years.

The D:A:D study will continue for at least a couple more years. The researchers will be looking at whether the trend continues past the five-year mark (or whether it levels off), and identifying specific risk factors, such as antiretroviral [drug classes](#) [8]A group of anti-HIV drugs with the same target of action. Anti-HIV drug classes include *nucleoside analogue reverse transcriptase inhibitors*, *protease inhibitors* and *non-nucleoside analogue reverse transcriptase inhibitors*, as well as several others. Combining drugs from three or more classes is the basis of Highly Active Antiretroviral Therapy (HAART)., which might contribute to the effect.

SMART

Fraser Drummond presented an update on the SMART ('Strategies for Management of Antiretroviral Therapy') study. This large and important cohort study is still [enrolling](#) [9]The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the informed consent process., and will eventually follow its planned 6000 participants for a whole decade.

SMART's objective is to determine which of two treatment strategies is most effective in preventing people from developing AIDS.

Participants need to have a CD4 count over 350 and have never taken antiretrovirals at the time they enter the study. The people in the study will be randomly divided into two groups: Those in one group will follow a 'drug conservation' strategy (treatment is not commenced until the CD4 count drops below 250 and treatment is stopped when CD4s rise above 350) while those in the second group will follow a 'viral suppression' strategy (treatment is used to keep the [viral load](#) [10]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. as low as possible).

Immune-based therapies

ESPRIT is a large [phase 3](#) [11]A large clinical trial designed to establish whether a drug is effective and safe enough for widespread use. Phase III studies include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling. trial looking at interleukin-2 (IL-2) as a therapy for stimulating reconstitution of the immune system. More than 4000 people are enrolled — half receive eight-weekly transfusions of IL-2 in addition to their antiretrovirals, the other half receive antiretrovirals but no IL-2.

Cate Carey presented an analysis of 1446 patients who had completed at least eight months in the trial, looking at the factors which best predicted response to the therapy. The vast majority of people receiving IL-2 have seen substantial increases in their CD4 count, with about two-thirds having rises of more than 200 cells. The treatment was most effective in people who were younger, who had higher nadir CD4 counts (the nadir is the lowest-ever CD4 count recorded for that person) and who had higher CD4 counts at the start of the trial.

While the results are impressive among those who completed the therapy, IL-2's side effects make it difficult to tolerate for many people.

Treatment interruptions

James Cox gave a presentation on the STACCATO trial, which is comparing two different types of structured treatment interruptions — ‘one week on, one week off’ and ‘CD4-guided’ (treatment is stopped and started when CD4 rises above or falls below 350).

Thirty-six people were assigned to the ‘week-on, week-off’ (WOWO) [arm](#) [12]Any of the treatment groups in a randomised trial. Most randomised trials have two "arms," but some have three "arms," or even more., 48 to the CD4-guided arm and 43 to receive continuous treatment. After just 12 weeks of treatment, the researchers were alarmed to discover 19 of the WOWO group (53 percent) had experienced treatment failure (two consecutive viral load counts over 500) and the WOWO arm of the trial was cancelled. By comparison, just two of the patients in the CD4-guided group, and none in the continuous treatment group, experienced treatment failure even after a much longer period.

The Thai HIVNAT 001.4 trial was the subject of a presentation by Chris Duncombe. This trial has the same three arms as STACCATO but is structured differently in that it is looking at progression to AIDS or death and changes in CD4 count rather than viral load.

The three arms all had similar results in terms of CD4 counts, adverse events and quality of life, and no one in any of the arms developed AIDS or died. But as in STACCATO, a large proportion (30 percent) of the patients in the WOWO arm experienced treatment failure.

More encouragingly, the CD4-guided group had similar viral load levels at the end of the trial to the continuous treatment group, and this approach proved more cost-effective than WOWO. But the continuous treatment group ended up with higher CD4 counts, suggesting that the cost savings may be illusory in the longer term.

“Structured treatment interruptions may not be dead yet,” Duncombe told the audience, “but they have at least one foot [week-on, week-off] in the grave.”

Further information

- Rapporteur reports from the ASHM conference are available on the [ASHM website](#) [13].
- [clinical trials](#)
- [IL-2](#)
- [immune-based therapies](#)
- [Lipodystrophy and lipoatrophy](#)
- [polylactic acid](#)
- [rosiglitazone](#)
- [The global HIV epidemic](#)
- [treatment interruption](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/382>
- [2] <http://www.napwa.org.au/glossary/term/122>
- [3] <http://www.napwa.org.au/glossary/term/96>
- [4] <http://www.napwa.org.au/glossary/term/486>
- [5] <http://www.napwa.org.au/glossary/term/99>
- [6] <http://www.napwa.org.au/glossary/term/106>
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