

Retro roundup

Created 1 Apr 2003 - 8:00am

The 10th Conference on Retroviruses and Opportunistic Infections took place in Boston in February. This annual conference is a very highly regarded event with a strong scientific focus, so it often produces a number of important advances in our understanding of HIV and its treatment, and this year was no exception. Here are some of the key developments.

Drug 'pipeline' fills

"This is an exciting, important year for therapy," Dr John Mellors of the University of Pittsburgh told a press conference after the opening ceremony. "The pipeline is fuller than it has been for a long time."

Conference-goers saw major presentations on at least ten [experimental](#) [1](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. drugs at various stages of development, including protease inhibitors designed to be effective against PI-[resistant](#) [2]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. virus, new non-nucleosides and a number of entry inhibitors, integrase inhibitors and the first "maturation inhibitor".

While most of these drugs are in very early development, there is great optimism about the prospects for new drugs, and new classes of drugs, in the years ahead. Most of the drugs currently available focus on inhibiting two HIV enzymes — protease and reverse transcriptase — but new drugs are being developed that attack HIV at eight different points in its life cycle.

This is especially important because of the disheartening reality that HIV almost inevitably develops resistance to whatever drugs we throw at it.

European and US approval of the new fusion inhibitor **T-20** is imminent, with Australia likely to follow in 2004. Because of its very high cost and the inconvenience for patients of twice-daily injections, T-20 is likely only ever to be used as [salvage](#) [3][salvage therapy] A treatment strategy for managing HIV in people who have developed resistance to existing therapies. therapy in heavily pre-treated people for whom there are few other options. A presentation at Boston looked at the evolution of resistance in 661 people taking T-20 as salvage therapy in phase

Anticipating this problem, the manufacturers designed their second fusion inhibitor, **T-1249**, to be effective against T-20 resistant virus. T-1249 has previously been shown to have good [antiviral](#) [4]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. activity in people who are treatment-naive, and is now being studied in a small group of 54 people who have developed resistance to T-20. An interim analysis of this study, based on 25 patients, was presented at Boston: 63 percent had a significant reduction in [viral load](#) [5]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. (??1 log10) after ten days of T-1249 monotherapy, although the response tended to be weaker in people who had been on T-20 for longer. Further clinical trials are planned.

The new protease inhibitor **atazanavir** has recently become available in Australia on a [Special Access Scheme](#) [6]

One interesting drug in the earliest stages of development is TNX-355, a 'monoclonal antibody' against HIV. This drug, which has shown promise in animal tests, works by binding to molecules on the surface of T-cells, blocking HIV from entering the cell. In Boston, researchers presented the results of a [Phase I](#) [10]A clinical trial designed to establish whether an experimental drug is safe for humans to take. Phase I studies determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and look for early evidence of effectiveness; these studies may include either people with HIV, HIV-negative volunteers, or both study

Tenofovir toxicity

The recently approved nucleotide analogue drug tenofovir is a close relative of two other drugs — cidofovir and adefovir — which we know can cause kidney problems. Although clinical trials of tenofovir have found that it is safe and effective, researchers have remained alert to the possibility that it may cause kidney problems with longer-term use.

In a study presented in Boston, researchers followed 81 people attending a single outpatient clinic in France who took tenofovir over a long period. Three of the patients (3.7 percent) developed Fanconi syndrome (a type of kidney dysfunction) after being on tenofovir for between eight and 11 months. Fanconi syndrome causes excess amounts of glucose, bicarbonate and phosphates to be excreted in the urine, and typically causes weakness and bone pain.

In all three patients, the syndrome resolved after stopping tenofovir.

In a separate study³ presented at the conference, researchers from the United States suggested that people who had previously taken adefovir (which is used to treat Hepatitis B) might be at greater risk of developing tenofovir-related kidney problems.

Because Fanconi syndrome can lead to bone disease and kidney failure, it is important that people taking tenofovir have regular blood and urine tests to screen for kidney problems, and see their doctor immediately if they experience unexplained weakness or bone pain.

Nevirapine and efavirenz

The results of the long-running “2NN” study⁴ were presented at Boston. This study compared the two most popular non-nucleoside drugs, efavirenz (Stocrin) and nevirapine (Viramune) to determine whether one or the other was preferable as first-line therapy — it’s the first big study to compare these two drugs directly.

More than 1200 treatment-naive patients in 17 countries were [enrolled](#) [11]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. in the study; they all received 3TC and d4T, plus either efavirenz, nevirapine, or both.

After 48 weeks, both the efavirenz and nevirapine groups had similar responses to treatment, both in terms of reductions in viral load (65-70 percent were below 50 copies/ml) and increases in CD4 count (ranging between +150 and +170 cells). The researchers concluded that both efavirenz and nevirapine are equally effective as first-line therapy. Interestingly, people who took both drugs were more likely to experience treatment failure than those taking one or the other, confirming that these two drugs should not be used together.

While there was no statistically significant difference in [effectiveness](#) [12](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. between the two drugs, there were differences in side effects, with the nevirapine group more likely to experience increased [liver](#) [13]A large organ, located in the upper right abdomen, which assists in digestion by metabolising carbohydrates, fats and proteins, stores vitamins and minerals, produces amino acids, bile and cholesterol, and removes toxins from the blood. enzymes and the efavirenz group more likely to experience central nervous system effects such as vivid dreams.

GBV-C coinfection

An apparently harmless virus carried by millions of people might help slow HIV disease progression. Discovered in 1995, GB virus C (GBV-C, previously known as the Hepatitis G virus) is related to the Hepatitis C virus but doesn’t appear to cause any disease.

A couple of years ago, researchers in the US noticed that people who are coinfecting with both HIV and GBV-C seemed to have slower HIV disease progression, lower rates of death from AIDS and better response to [HAART](#)

[14] Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. than people infected with HIV alone.

Several presentations in Boston looked at this intriguing phenomenon. In one study⁵, American researchers tested stored blood samples taken in 1985 from 271 newly HIV-positive men for GBV-C, then examined further blood samples from the same men from 1990. They discovered that the men who had persistent GBV-C infection through the period were the most likely to survive a further five years — 80 percent were still alive in 1995. Those who were never infected with GBV-C did less well — 36 percent survived to 1995 — and those who were infected with, then cleared, the GB virus fared worst of all: just 16 percent of this group were still alive in 1995.

Speaking at a press conference, Dr Carolyn Williams, one of the authors of the study, compared coinfection with GBV-C to having an extra 250 or 300 CD4 cells. “There is a high attributable benefit if this virus is present,” she said.

A Swedish study⁶ also found that clearing the GBV-C virus was associated with disease progression, but did not find the same protective effect with persistent infection.

The reason why GBV-C infection might have a protective effect against HIV is unclear. One possible explanation suggested by a study⁷ presented in Boston is that GBV-C could strip off one of the co-receptors that HIV needs in order to enter cells, or that infection with it could stimulate the production of chemokines, chemicals that mobilise the immune system against infection.

The possibility of deliberately infecting HIV-positive people with GBV-C was discussed, although at this stage we don't know enough about the long-term effects to countenance such a dramatic move. But there is a real possibility that this discovery could lead to a greater understanding of HIV and new treatments in the future.

References

¹ “Safety and Preliminary Anti- HIV Activity of an Anti-CD4 mAb (TNX-355; Formerly Hu5A8) in HIV-infected Patients” D. R. Kuritzkes et al, Abst. 13, CROI 2003.

² “Renal Tubular Injury and Severe Hypophosphoremia (Fanconi Syndrome) Associated with Tenofovir Therapy” J. Reynes et al. Abst. 717, CROI 2003.

³ “Tenofovir May Cause Severe Hypophosphatemia in HIV/ AIDS Patients With Prior Adefovir-induced Renal Tubular Acidosis” G. Blick et al. Abst. 718, CROI 2003.

⁴ “Results of the 2NN Study: A Randomized Comparative Trial of First-line [Antiretroviral](#) [15] A medication or other substance which is active against retroviruses such as HIV. Therapy with Regimens Containing Either Nevirapine Alone, Efavirenz Alone or Both Drugs Combined, Together with Stavudine and Lamivudine” F. van Leth et al, Abst. 176, CROI 2003.

⁵ “Persistent GBV-C virus Type C (GBV-C) Infection is Associated with Decreased Risk of Death in HIV-seroconvertors in the Multicenter AIDS [Cohort](#) [16] 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 (MACS)” C. Williams et al, Abst. 159lb, CROI 2003.

⁶ “GB Virus C Viremia During the Natural Course of [HIV-1](#) [17] One of two distinct HIV species, HIV-1 is the predominant type in Australia and around the world. Infection: Viremia at Diagnosis Does Not Predict Mortality” P. Bjorkman et al, Abst. 157, CROI 2003.

⁷ “GBV-C Infection Inhibits CCR5 and CXCR4 HIV Strains and Alters Chemokine and Cytokine Gene Expression in PBMC Cultures” J. Xiang et al, Abst. 156, CROI 2003.

- [atazanavir](#)
- [clinical trials](#)
- [efavirenz](#)
- [enfuvirtide \(T-20\)](#)
- [HIV treatments](#)
- [nevirapine](#)
- [tenofovir](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/491>
- [2] <http://www.napwa.org.au/glossary/term/109>
- [3] <http://www.napwa.org.au/glossary/term/111>
- [4] <http://www.napwa.org.au/glossary/term/123>
- [5] <http://www.napwa.org.au/glossary/term/416>
- [6] <http://www.napwa.org.au/glossary/term/112>
- [7] <http://www.napwa.org.au/glossary/term/88>
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