

## A tale of two cities

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With major medical conferences in the United States and Scotland, November was a busy month for HIV medicine. PAUL KIDD reviews some key findings.

### Tipranavir impresses

Boehringer-Ingelheim researchers presented 24-week data from major clinical trials of their new protease inhibitor, tipranavir. The RESIST-1 and RESIST-2 studies are looking at the drug in heavily pre-treated people.

Tipranavir is the first non-peptidic protease inhibitor to go through [clinical](#) [1]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials. Unlike existing PIs, which are based on short chains of amino acids called peptides, tipranavir's novel molecular structure is designed to make it effective against [virus](#) [2]A small infective organism which is incapable of reproducing outside a host cell. which has become PI [resistant](#) [3]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant.. Because of this, these clinical trials are specifically looking at tipranavir's utility as [salvage](#) [4][salvage therapy] A treatment strategy for managing HIV in people who have developed resistance to existing therapies. therapy.

The RESIST-1 study [enrolled](#) [5]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. 620 patients in the United States, Canada and Australia; RESIST-2 enrolled 863 patients in Europe and Latin America.

Participants in both trials were [randomised](#) [6]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 to receive either 500mg tipranavir boosted with 200mg ritonavir twice daily, or a different boosted PI, chosen on the basis of resistance testing. All patients also took a nucleoside backbone selected based on their resistance test, and some patients also took T-20 if they had already been on that drug when the trial started.

In the interim results of the RESIST-1 study, presented in Washington, 41.5 percent of people taking tipranavir responded to treatment, compared with 22.3 percent of those taking other PIs. The people in the tipranavir [arm](#) [7] were also significantly more likely to have undetectable [viral load](#) [8]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.

The results from the RESIST-2 study, which were unveiled in Glasgow, were similarly impressive: 41 percent of those on tipranavir had a treatment response, compared with 14.9 percent of the other arm.

The major [side effect](#) [9]An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time. noted in both studies was increased [liver](#) [10]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 ([ALT](#) [11]alanine transaminase or alanine aminotransferase, an enzyme involved in the metabolism of the amino acid alanine. Elevated ALT levels in the blood may indicate liver injury or disease such as hepatitis. Also called SGPT (serum glutamate pyruvate transaminase). and AST), but no patients had to stop taking the drug because of this. Like most other PIs, tipranavir seems to cause increases in [blood fats](#) [12]A type of fat in the blood. Elevated triglyceride levels may be a side effect of some anti-HIV drugs., and a significant number of people reported diarrhoea, stomach cramps and nausea.

Based on these two studies, Boehringer Ingelheim has now applied for marketing approval for tipranavir in the US and Europe, and is hopeful of gaining those approvals by mid-2005.

In Australia, it's unlikely we will see tipranavir on the [PBS](#) [13][Pharmaceutical Benefits Scheme] The federal government program which subsidises medication costs in Australia. Anti-HIV drugs are part of a special part of the PBS called Section 100 (S100) which is used for expensive, highly specialised drugs. before 2006, however in the meantime there is an Emergency Access Scheme available for people who need access to this drug. At present this small allocation is only open to people with fewer than 100 T-cells; NAPWA is currently negotiating with the manufacturer to ease that restriction.

## Kaletra keeps on keeping on

A long-term follow-up of participants in a clinical trial of Kaletra (lopinavir/ritonavir) showed that this protease inhibitor has substantial staying power<sup>1</sup>. The poster presentation looked at 100 patients from the M97-720 trial after six years on the combination of Kaletra, 3TC and d4T, finding that 62 percent had viral load levels below 50 copies/ml. The average increase in CD4 count over that period was 529 cells/mm<sup>3</sup>.

## Truvada vs Combivir

Patients in the Gilead 934 study took efavirenz (600mg once daily) in combination with either Gilead's tenofovir (Viread) and FTC (Emtriva) or Glaxo's AZT-plus-3TC (Combivir)[2]. Although the patients in this trial took tenofovir and FTC as separate tablets, the company also markets the two in a co-formulated, once daily, tablet (Truvada) in the US and Europe. This trial was widely seen then as comparing Combivir with Truvada.

The trial enrolled 517 people who had not taken treatment before, and randomly assigned them to one of the two arms. The 24-week results presented in Washington seemed to slightly favour the tenofovir/FTC arm, but mainly because a larger number of patients in the AZT/3TC arm stopped treatment due to tolerability problems. Among those who stayed on treatment, there was no significant difference between the two groups.

## T-20: better sooner than later

A new analysis of the TORO-1 and TORO-2 trials of T-20 (enfuvirtide, Fuzeon) presented in Washington suggests that people are likely to do better on T-20 if they don't delay starting the drug<sup>3</sup>. Because of the complexity and inconvenience of twice-daily injections, T-20 is used as a 'last resort' drug for people with multiple drug resistance and few other options.

A retrospective analysis of the TORO trials looked at those patients who were initially randomised not to receive T-20, but who later added it to their treatment. This group of patients got significantly less benefit from T-20 than those who were originally assigned to receive the drug, the researchers concluded, and they recommended that T-20 be actively considered in people who have multiple treatment failures, not saved as a last resort.

Another presentation in Washington will be of great interest to people taking T-20. A small study looked at the possibility of once-daily dosing of T-20, with encouraging results<sup>4</sup>. The 37 participants in this study had their blood levels of T-20 monitored during a two-week period when they took either the standard 90mg twice-daily dose of T-20, or a 180mg once-daily dose. The researchers concluded that the once-daily dose was acceptable and needed further investigation.

## [HAART](#) [14]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. associated with prem babies

A report from a large, long-term survey of antiretroviral use in UK women has found that pregnant women on HAART are more likely to give birth prematurely<sup>5</sup>. The study, based on voluntary reporting of pregnancies in positive women, looked at 3807 pregnancies which occurred between 1990 and 2003, 80 percent of which resulted in a live or still birth. While the rate of congenital abnormalities was the same as in the general population, the women in this study were about 1.5 times more likely to give birth before 37 weeks, and also had higher levels of spontaneous abortion.

## Keep Kaletra cool

Just in time for summer in Australia, researchers in the United States have been examining the effect of high temperatures on Kaletra capsules<sup>6</sup>. The researchers found that when kept at temperatures over 35 degrees C, the capsules eventually softened, became sticky, clumped together or broke apart.

While the objective of this study was to look at the storage issues for Kaletra in the hot climates of Africa, positive people living in the more tropical parts of this country will want to take heed of this warning, and perhaps keep their Kaletra capsules in the fridge during the warmer months.

## References

- <sup>1</sup> Gulick RM et al. *Lopinavir/ritonavir (LPV/r)-based therapy in antiretroviral (ARV) [15]A medication or other substance which is active against retroviruses such as HIV.-na??ve, HIV-infected patients: 6-year follow-up of study 720*. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract P28, 2004.
- <sup>2</sup> Gazzard B et al. *The combination of tenofovir DF (TDF), emtricitabine (FTC) and efavirenz (EFV) has significantly greater response vs fixed dose zidovudine/lamivudine (CBV) and EFV in antiretroviral na??ve patients: a 24 week preliminary analysis*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-1137C, 2004.
- <sup>3</sup> Cohen C et al. *Selection of non-enfuvirtide (ENF) versus ENF-containing regimens leads to higher failure rates and loss of future antiretroviral (ARV) treatment options*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-580, 2004.
- <sup>4</sup> Thompson M et al. *Pharmacokinetic (PK [16]Referring to the processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine. In clinical trials, measurements are made of the rate at which a drug is absorbed into the bloodstream and then excreted via the kidneys or liver, to determine the optimum dose of the drug.), pharmacodynamic and safety assessment of QD versus BID dosing with enfuvirtide (ENF) in HIV-infected subjects*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-866, 2004.
- <sup>5</sup> Tookey P et al. *Antiretroviral therapy and pregnancy outcome: UK/Ireland surveillance data 1990-2004*. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract PL11.3, 2004.
- <sup>6</sup> Capparelli E et al. *Stability of lopinavir/ritonavir (LPV/RTV) at elevated temperatures: relevance to HIV therapy in sub-Saharan Africa*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-868, 2004.

- [clinical trials](#)
- [Combivir](#)
- [conference reports](#)
- [enfuvirtide \(T-20\)](#)
- [HIV treatments](#)
- [lopinavir](#)
- [pregnancy and childbirth](#)
- [tipranavir](#)
- [treatment side effects](#)
- [Truvada](#)

## Links:

- [1] <http://www.napwa.org.au/glossary/term/475>
- [2] <http://www.napwa.org.au/glossary/term/125>
- [3] <http://www.napwa.org.au/glossary/term/109>
- [4] <http://www.napwa.org.au/glossary/term/111>
- [5] <http://www.napwa.org.au/glossary/term/489>
- [6] <http://www.napwa.org.au/glossary/term/513>
- [7] <http://www.napwa.org.au/glossary/term/470>
- [8] <http://www.napwa.org.au/glossary/term/416>
- [9] <http://www.napwa.org.au/glossary/term/469>
- [10] <http://www.napwa.org.au/glossary/term/102>
- [11] <http://www.napwa.org.au/glossary/term/80>
- [12] <http://www.napwa.org.au/glossary/term/114>
- [13] <http://www.napwa.org.au/glossary/term/121>
- [14] <http://www.napwa.org.au/glossary/term/96>
- [15] <http://www.napwa.org.au/glossary/term/122>
- [16] <http://www.napwa.org.au/glossary/term/505>