

## CROI 2007: A great leap forward

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A major scientific conference on HIV has wound up with promising news on treatments which could signal a significant improvement in HIV treatment for the first time in some years.

The 14th Conference on Retroviruses and Opportunistic Infections (CROI) was held in Los Angeles, USA, between 25 and 28 February, attracting high-level AIDS researchers and clinicians from around the world. The annual conference is widely seen as a highlight in the research calendar, and routinely includes significant presentations on HIV treatments research. This year was no exception.

### New treatments, new classes

The biggest news from the conference revolved around a trio of new drugs which, if they continue to perform well in [clinical](#) [1]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. studies, have the potential to transform HIV treatment.

#### Raltegravir

Formerly known by the code name MK-0518, raltegravir is an integrase inhibitor being developed by Merck. Integrase inhibitors target an enzyme (integrase) that HIV uses to insert its genetic code into the DNA of the host cell. There are currently no licensed integrase inhibitors, so the development of drugs in this class is being keenly anticipated.

We have previously reported on raltegravir in the December 2006 edition of [\\_PL\\_](#). The drug is currently available on a restricted Special Access Scheme ([SAS](#) [2]Before a drug has been approved, manufacturers often provide the drug free of charge to people who cannot participate in a clinical trial and who meet certain criteria under a Special Access Scheme (SAS). ) for people who urgently need it.

Interim results from two ongoing studies of raltegravir were presented at the conference by David Cooper, director of the National Centre in HIV [Epidemiology](#) [3]The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population. and Clinical Research in Sydney. BENCHMRK 1 and 2 are parallel Phase-3 studies examining 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 raltegravir in heavily pre-treated people (those who have taken many previous treatments).

Participants all had resistance to all three main HIV [drug classes](#) [5]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)., and viral loads of at least 1000 copies (the average viral load in the two studies was between 30,000 and 40,000). A total of 699 people were [enrolled](#) [6]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 two trials, which were designed to see if the drug could lower viral load, and to measure the proportion of participants who achieved viral loads below 400 copies and 50 copies.

Participants were [randomised](#) [7]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 400mg raltegravir twice daily, or a [placebo](#) [8]A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial., in addition to an 'optimised background regimen' of

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existing HIV drugs.

After 16 weeks, around twice as many patients in the raltegravir [arm](#) [9]Any of the treatment groups in a randomised trial. Most randomised trials have two "arms," but some have three "arms," or even more. achieved undetectable viral load, compared with those taking the placebo (the trial is scheduled to continue for 48 weeks). About 77 percent of patients taking raltegravir had viral load below 400 copies, and 61–62 percent were below 50 copies. In the placebo arm, the numbers were 41–43 and 33–36 percent respectively. Those taking raltegravir also had much better improvements in CD4 count.

A subgroup analysis showed even more impressive results when raltegravir was used in combination with other new therapies. Among those whose background regimen included T-20 (enfuvirtide/Fuzeon) and darunavir (TMC-114/Prezista), 98 percent of patients achieved viral load below 400, compared with 87 percent in the placebo group.

The drug appears to be well tolerated, with only mild side effects reported and few patients discontinuing due to toxicity problems.

The downside is that it appears that resistance to raltegravir and other integrase inhibitors is likely to be a concern. There appear to be two different pathways to development of resistance to raltegravir, Cooper reported, but he cautioned against drawing too many conclusions from the limited data available. There does not, fortunately, appear to be any cross-resistance between raltegravir and other available therapies.

Another integrase inhibitor which is at an earlier stage of development was also the subject of a presentation at CROI. Preliminary data from a phase-2/3 study of Gilead's \*elvitegravir\* (formerly known as GS-9137) in heavily pre-treated people showed that after 16 weeks of treatment, participants taking elvitegravir monotherapy had viral load reductions of up to 1.7 logs. A phase-3 trial of this drug is planned and we will report on this in PL when results are available.

### Maraviroc

Another eagerly-awaited new drug, maraviroc is a CCR5 antagonist in development by Pfizer. This class of drugs is designed to target the CCR5 molecule, one of the key 'co-receptors' used by HIV to enter and infect human cells. Like T-20, maraviroc is designed to stop HIV from entering cells, rather than interfering with it once it is inside, although it does so in a different way. We last reported on maraviroc in October 2006.

Interim results from the MOTIVATE 1 and 2 trials were presented at CROI. These are ongoing international [placebo-controlled](#) [10]A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition. Phase-2b/3 studies examining the safety and effectiveness of maraviroc in heavily pre-treated individuals. Like the raltegravir study described above, the MOTIVATE trials recruited people with triple-class resistance and reasonably high viral load (median 65,000 copies), who took the drug (or placebo) in combination with an optimised background regimen. The interim results presented in LA were based on 601 participants in the MOTIVATE 1 study, and 475 from MOTIVATE 2, who had completed 24 weeks on the trial.

At the 24 week mark, between 55 and 61 percent of those who took maraviroc had achieved viral loads below 400 copies, compared with 23–31 percent of those taking the placebo. A further analysis looked at the percentage of participants achieving viral loads less than 50 copies – between 41 and 48.5 percent of those taking maraviroc were able to do so, compared with 21–25 percent of those in the placebo arm. Increases in CD4 counts were also best in the maraviroc group.

At a press conference following the presentations for the two drugs, John Mellors, professor of medicine at the University of Pittsburgh, described the results of the two studies as "a really remarkable development."

"I would not be going out on a limb to say these results are as exciting for experienced patients as were the results of the original trials with combination highly active [antiretroviral](#) [11]A medication or other substance which is active against retroviruses such as HIV. therapy," he said.

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**TMC-278**

Another new drug which generated some excitement at CROI was TMC-278, an [experimental](#) [12](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. non-nucleoside being developed by Tibotec. Unlike maraviroc and raltegravir, TMC-278 doesn't come from an entirely new drug class, but it promises to be an important addition to the non-nuke class.

Non-nukes are a popular anti-HIV treatment choice – they are at least as powerful against HIV as protease inhibitors, and they have fewer side effects. But there are only three approved drugs in the class – nevirapine (Viramune), efavirenz (Stocrin) and the rarely-used delavirdine (Rescriptor) – and they all exhibit cross-resistance to each other. That means that once you've become [resistant](#) [13]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. to one of them, you are unlikely to get any benefit from taking another.

Like its sister drug etravirine (TMC-125), TMC-278 has been developed specifically to be effective in people who have become resistant to existing non-nukes. Test-tube studies have previously shown that TMC-125 appears to be highly active against both non-nuke resistant and 'wild type' virus, and a small previous study, reported two years ago, delivered encouraging results when the drug was used as monotherapy over a seven day period.

Researchers presented data from a 48-week phase-2 trial comparing TMC-278 with efavirenz. The 368 participants in this study, none of whom had taken treatment before, were randomised to receive one of three different doses of TMC-278 or efavirenz, in combination with a nucleoside backbone of either Combivir or Truvada.

After 48 weeks, similar numbers of participants in all four groups had viral load levels below 50 copies (around 80 percent in each arm). This suggests that TMC-278 has similar efficacy to efavirenz in people who have not taken treatment before. The rate of side effects was similar in all arms; however TMC-278 does not appear to cause the same central nervous system disturbances (sleeplessness, vivid dreams, etc) as efavirenz.

A phase-3 trial of TMC-278 in treatment-naive individuals is planned, after which (if successful) the company hopes to market the drug as a first-line treatment. Along with etravirine, also being developed by Tibotec but at a more advanced stage, these promise to significantly expand the range of options in the non-nuke class. Etravirine has recently become available in Australia under a Special Assistance Scheme, but TMC-278 is not yet available outside clinical trials.

## Lipodystrophy

A number of presentations looked at management of lipodystrophy (abnormal fat redistribution) and lipoatrophy (fat loss) in people with HIV.

A new analysis of the ACTG5142 study has suggested that the link between protease inhibitors and lipodystrophy is not as strong as was once thought. The association between protease inhibitors and lipo goes back a long way – there was a time when the fat belly associated with lipodystrophy was known as 'protease paunch' – however in recent years it has become clear that nucleoside drugs, especially d4T, are more strongly to be the cause.

This study compared a 'nucleoside-sparing' regimen of efavirenz plus Kaletra with standard regimens using either efavirenz or Kaletra in combination with nucleoside analogue drugs. The initial results, reported last year in Toronto, showed that efavirenz-containing regimens were more durable than Kaletra in suppressing HIV over a long period, and that the Kaletra/efavirenz combo was about equal to Kaletra plus nucleosides.

The follow-up analysis presented in LA looked at the gain or loss of limb fat in the three groups. After 96 weeks on treatment, those in the nuke-sparing arm had an average 18 percent gain in limb fat, compared to 9.8 percent among those taking Kaletra plus two nucleosides. The third arm, efavirenz plus two nukes, had the lowest gain in fat (1.4%), a finding which reinforces the view that some nucleosides, not protease inhibitors, are the major cause of lipoatrophy.

There was also encouraging news about TH-9507, a human growth hormone stimulant which is being studied as a treatment for lipodystrophy. Unlike growth hormone supplements, this drug stimulates the body's own release of its

own growth hormone. A 26-week phase-3 study found that the drug is effective in reducing abdominal visceral fat accumulation by about 20 percent. The drug was well tolerated and did not produce the elevated blood glucose levels which are seen with growth hormone supplements. Further studies are underway.

## SMART and DAD

Further reports from these two very big international trials focused on adverse events of HIV and HIV therapy.

A presentation from the DAD study reported on the prevalence of 'non-AIDS-defining' cancers in people with HIV. It is well established that the risk of certain 'AIDS-defining' cancers such as non-Hodgkin's lymphoma (NHL) and Kaposi's Sarcoma (KS) rises in people with severely impaired immune systems, but there has been little study of the risk of development of other cancers in people living with HIV. The DAD study, which has been going since 1999 and has enrolled 23,000 people internationally, is examining the prevalence of a range of adverse events in people living with HIV.

'Non-AIDS' cancers are now more prevalent in people living with HIV in the developed world than AIDS-defining cancers, the researchers reported. Out of the 1246 deaths so far in the study, 193 were due to non-AIDS-defining cancers, including lung, stomach and liver cancers, Hodgkin's lymphoma and anal cancer. There were 110 deaths from AIDS-defining cancers in the same period.

The researchers reported that the risk of developing either group of cancers increased as CD4 counts fell. For AIDS-defining cancers, the risk was ten times higher for a person with a CD4 count of 50 compared to a person with a CD4 count of 500; for non-AIDS-defining cancers the risk increased 200-fold. By contrast, there was no correlation between the risk of developing cancer and viral load.

A new analysis of the SMART study has found a slightly increased risk of developing heart disease in people who interrupt treatment. SMART was the large study comparing continuous treatment with CD4 count-guided treatment interruptions which was halted early last year after it became apparent that people taking treatment breaks were at increased risk of disease progression.

An unexpected finding of this study has been that people who took treatment breaks were at increased risk of medical problems thought to be unrelated to antiretroviral therapy, such as heart, liver and kidney problems. About 2.1 percent of those taking breaks had problems of this type, compared with 1.4 percent of those taking continuous treatment.

The study team reported on the prevalence of cardiovascular events (such as fatal and non-fatal heart attacks, strokes and [coronary artery](#) [14]One of the two arteries that supply the heart with oxygenated blood. disease) in the study. There were 48 such events in the intermittent treatment arm compared with 31 in the continuous therapy arm. The risk of experiencing one of these events was 1.5 times greater for people taking treatment breaks compared with those who stayed on treatment continuously.

While noting that the increased risk was only "marginally significant," and there was no evidence that interrupting treatment immediately increased the risk of developing a cardiovascular event, the study team cautioned against taking treatment breaks as a strategy to reduce the risk of heart and artery disease.

*This article was compiled from reports on Aidsmap.com and elsewhere.*

- [anal cancer](#)
- [efavirenz](#)
- [elvitegravir \(GS-9137\)](#)
- [etravirine \(TMC-125\)](#)
- [heart disease](#)
- [Lipodystrophy and lipoatrophy](#)
- [lopinavir](#)
- [maraviroc](#)
- [raltegravir](#)
- [rilpivirine \(TMC 278\)](#)

**Links:**

- [1] <http://www.napwa.org.au/glossary/term/475>
- [2] <http://www.napwa.org.au/glossary/term/112>
- [3] <http://www.napwa.org.au/glossary/term/490>
- [4] <http://www.napwa.org.au/glossary/term/486>
- [5] <http://www.napwa.org.au/glossary/term/124>
- [6] <http://www.napwa.org.au/glossary/term/489>
- [7] <http://www.napwa.org.au/glossary/term/513>
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