

Rocky Mountain CROI

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The 13th annual Conference on Retroviruses and Opportunistic Infections (CROI) took place in Denver, Colorado, from February 5 to 8. The major breaking news from this conference was the premature cancellation of the SMART

New antiretrovirals

With more than 20 different [antiviral](#) [1]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. medications approved in Australia, it's somewhat surprising that we still need new drugs to treat HIV. But, a decade after the turning point that was the introduction of HAART, factors such as treatment side effects and viral resistance continue to challenge HIV treatment, and the need for newer, better drugs is very real.

Frustratingly, the timeframe for development of new treatments is very long, and the incentives for drug companies to invest the millions of dollars it takes to bring a drug through clinical trials and to market are limited. But the 'drug pipeline' is far from empty and there are several compounds currently in development which show great promise.

Researchers from Tibotec Pharmaceuticals presented new data on **etravirine**, the non-nucleoside formerly known as TMC-125. This drug has been designed to overcome the cross-resistance which affects existing non-nucleosides, and which prevents people who have failed one non-nuke from using other drugs in the class.

Results from a 199-person study presented late last year demonstrated etravirine's [effectiveness](#) [2](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. in heavily pre-treated individuals, producing [viral load](#) [3]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. reductions of at least 1.04 logs after 24 weeks when used in combination with other drugs. The data presented in Denver looked at the resistance profiles of participants on that study, in order to assess effectiveness in people with pre-existing non-nucleoside resistance.[1]

Almost all patients in this study had previously used at least one other non-nuke and had at least partial resistance to this class of drugs, with resistance tests showing a median 40-fold resistance to efavirenz and 60-fold to nevirapine. In comparison, there was a median resistance of just 1.7-fold to etravirine, indicating good levels of effectiveness even in people with non-nucleoside resistance.

Tibotec also presented further impressive data on **darunavir**, previously called TMC-114, which is currently in [clinical](#) [4]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials internationally, including in Australia.[2]

An analysis of resistance profiles of participants in the POWER studies, which involved a total of about 600 people, was undertaken to determine the extent of cross-resistance with other PIs. The analysis identified a number of viral mutations which were associated with decreased efficacy of darunavir, suggesting that some level of cross-resistance with existing PIs does occur, however they found that, compared with the other drugs studied, darunavir maintains a significant clinical benefit. Tibotec has lodged applications with regulatory bodies in the US and Europe for approval of darunavir, and in Australia a [Special Access Scheme](#) [5]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). is now underway.

Integrase inhibitors: the next big thing?

Integrase inhibitors are designed to target the stage in the HIV life cycle where the virus integrates its own genetic material into human DNA, 'reprogramming' immune system cells to produce more virus.

One of the most keenly-watched drugs in development is the Merck integrase inhibitor **MK-0518**. Researchers presented preliminary data from a study involving 167 highly treatment-experienced people, all with viral loads over 5000 and documented triple-class resistance to existing treatments. Participants were individually assigned optimised background treatment regimens based on resistance test results, and were randomly assigned to receive one of three doses of MK-0518 or a [placebo](#) [6] A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial. [3]

After 16 weeks, at least 70 percent of participants receiving MK-0518 had viral loads below 400 copies/ml, compared with 24 percent of those in the placebo arm. Viral load reductions of at least 2 logs were seen in most patients after two weeks, compared with a 0.8 log reduction in the placebo group.

Describing the results as “phenomenal,” Associate Professor Paul Sax of Harvard Medical School told Medscape.com: “It was only a 16-week interim result, so we don’t know about the durability, and we can’t say much about safety, because there weren’t that many patients in the study. Nonetheless ... these are really exciting responses for an [investigational](#) [7] (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. agent.” [4]

The results are especially impressive considering the heavily pre-treated nature of the participants. Resistance tests conducted at the outset of the trial showed that, in about half the participants, resistance had developed to every current anti-HIV drug, and 98 percent were [resistant](#) [8] HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. to all protease inhibitors.

Integrase inhibitors have generated excitement before, but have been plagued by toxicity problems. So far, this new drug appears to have a manageable [side effect](#) [9] Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects. profile, with no real difference in side effects noted between the active treatment and placebo arms. The full results from this study will be presented at a later date.

Another integrase inhibitor, **GS-9137**, being developed by Gilead Sciences, was the subject of another study discussed at CROI. [5] The small study involved 40 participants, half of whom were treatment-experienced and half treatment-naïve, who were randomly assigned to receive one of five different doses of GS-9137, or a placebo, for ten days, with no other anti-HIV drugs. Viral load reductions of between 0.89 and 2.03 logs were recorded, compared with a 0.26 log drop in the placebo group. Further studies are planned to follow up on these encouraging results.

Monotherapy: the new-old thing

The use of a single anti-HIV drug as ‘maintenance’ treatment in people who have already achieved undetectable viral load on [combination therapy](#) [10] Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. has been the subject of several recent studies, notably the ‘OK’ study into Kaletra monotherapy which we reported on following last year’s IAS conference in Rio de Janeiro.

Preliminary data presented at CROI from a small study suggest that atazanavir/ritonavir also has a future in this ‘treatment simplification’ approach. The 36 participants in this US-based study had maintained continuous undetectable virus for at least 48 weeks. Participants were first switched to an atazanavir/ritonavir-based combination for six weeks, then the nucleoside drugs were stopped. Of the 34 participants who stayed in the trial, three (9 percent) experienced viral rebound, while the remainder stayed undetectable for up to a year. [6]

Cardiovascular risk

An analysis of a large international study has concluded that the increased risk of [heart attack](#) [11] A life-threatening emergency in which the blood supply to the heart is suddenly cut off, causing the heart muscle (myocardium) to die from lack of oxygen. in people taking antiretrovirals is related to protease inhibitors and not to non-nucleosides. [7]

The D:A:D study is a very large international project involving more than 23,000 people, which has previously reported an increased risk of heart attacks of about 17 percent for every year a positive person spends on treatment. While the incidence of heart attack remains low, the results of this study have caused considerable concern about the likely effects of long-term treatment.

The results presented in Denver show that 345 study participants have experienced at least one heart attack during the study. Of these, 83 percent had taken protease inhibitors, for a median period of three years. After adjusting for other risk factors such as tobacco smoking, the researchers have concluded that the risk of heart attack doubles for every five years on protease inhibitors. In contrast, for non-nucleosides, the risk of heart attack increased by an average of 5 percent for each year on treatment, which the researchers said was not 'statistically significant' – in other words, the increase was so small it could have arisen by chance.

The presenters speculated that increases in [blood fat](#) [12] A fat. ([cholesterol](#) [13] 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 [triglyceride](#) [14] A type of fat in the blood. Elevated triglyceride levels may be a side effect of some anti-HIV drugs.) levels associated with protease inhibitor therapy may be responsible for the correlation with heart attacks, but even after adjusting for blood fat levels, the D:A:D study data still shows an independent link between proteases and heart disease, suggesting that another mechanism is partly responsible.

While these figures may understandably alarm people taking protease inhibitors, it's important to take them in context. While an *increase* in risk of 17 percent seems huge, the *actual* risk of having a heart attack remains quite low, at less than 0.4 percent per year. Other risk factors – smoking, poor diet, lack of exercise, [high blood pressure](#) [15] Persistently high blood pressure, an outwardly symptomless condition which carries an increased risk of serious illnesses such as stroke, heart disease and heart attack. and increasing age – are much more likely to result in the development of cardiovascular illness, and these should be eliminated or managed wherever possible.

Sexual transmission of [hep](#) [16] Any inflammation of the liver. It is usually caused by viral infection, toxic agents or drugs but may be an autoimmune response. It is characterised by jaundice, abdominal pain, liver enlargement and sometimes fever. The different types of viral hepatitis include hepatitis A (formerly called infectious hepatitis), hep B (serum hepatitis), hep C (formerly called non-A, non-B hepatitis), and hepatitis D, E, F and G. C

Evidence of sexual transmission of hepatitis C among HIV-positive people continues to accumulate. Three presentations at CROI focused on this emerging issue.

A British study looked at the risk factors for sexual transmission among 111 HIV-positive gay men diagnosed with sexually-acquired hep C.[8] The men in this study had higher-than average numbers of sexual partners, and were more likely to practice unprotected receptive anal intercourse, to engage in 'mucosally traumatic practices' such as fisting or use of sex toys, group sex and use of party drugs such as crystal meth. A Dutch study had similar findings, with 50 percent of participants reporting receptive fisting, and 65 percent having also been diagnosed with sexually-transmissible infections including LGV or syphilis.[9]

A French study suggested that not only gay men, but HIV-positive heterosexual women, are at risk of acquiring hep C via sex. The poster presentation focused on three men and two women from a 605-member [cohort](#) [17] 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 who developed hep C with no other risk factors identified apart from unprotected sex.[10]

PrEP

Pre-exposure prophylaxis (PrEP) is the idea that giving HIV drugs to uninfected people might protect them from HIV infection. It's a subject that has caused a great deal of controversy over recent years, with activists successfully lobbying for the cancellation of several international clinical trials. Yet it remains an area which holds much promise for HIV prevention.

The conference heard about a successful animal study which used a combination of tenofovir and FTC as PrEP. In the study, 12 rhesus macaque monkeys were given daily injections of tenofovir and FTC, after which the researchers 'challenged' the monkeys with weekly rectal inoculations of SHIV, a virus very similar to HIV which is capable of infecting these animals. A 'control group' of a further six monkeys were also inoculated, but did not receive any drugs.

Four of the six monkeys in the control group became SHIV-positive within four weeks, and a fifth had seroconverted by the end of the 14-week study. In contrast, none of the monkeys who were given the study drugs became infected after 14 weekly inoculations with SHIV. The researchers then repeated the experiment using FTC

The positive results for tenofovir plus FTC were significantly superior to those seen in earlier trials which used tenofovir alone, suggesting as in HIV treatment, combinations of drugs give far better results than single agents.

The choice of rectal inoculation was chosen in order to mimic, as closely as possible, human sexual transmission of HIV, in order to determine whether antiretroviral medications could have a role in HIV prevention among high-risk groups, and this trial has understandably generated a great deal of interest. Concerned at reports of gay men self-medicating with tenofovir as a risk reduction strategy, the researchers stressed that this study is a 'proof-of-concept' only and that further trials in humans will be needed before we know whether PrEP works.

—Reports from Aidsmap.com, Medscape.com and NATAP.org formed the basis of this article.

References

¹ Vingerhoets J et al. *Effect of [baseline](#) [18]*1. Information gathered at the beginning of a study from which variations found in the study are measured. 2. A known value or quantity with which an unknown is compared when measured or assessed. 3. The initial time point in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values. resistance on the virologic response to a novel NNRTI, TMC125, in patients with extensive NNRTI and PI resistance: analysis of study TMC125-223. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 154, 2006.

² De Meyer S et al. *Effect of baseline susceptibility and on-treatment mutations on TMC114 and control PI efficacy: preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2*. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 157, 2006.

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⁴ <http://www.medscape.com/viewarticle/523393> [20]

⁵ DeJesus E et al. *The HIV integrase inhibitor GS-9137 (JTK-303) exhibits potent antiviral activity in treatment-naïve and experienced patients*. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract LB160, 2006.

⁶ Swindells S et al. *A prospective, [open-label](#) [21]*A clinical trial in which doctors and participants know which drug or vaccine is being administered., pilot trial of regimen simplification to atazanavir/ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression (ACTG 5201). Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 108LB, 2006.

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¹⁰ Ghosn J et al. *Increase in HCV Incidence in HIV-1-infected Women and Men Followed in the French PRIMO Cohort*. Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, abstract 843, 2006.

- [atazanavir](#)
- [darunavir](#)
- [elvitegravir \(GS-9137\)](#)
- [etravirine \(TMC-125\)](#)
- [heart disease](#)
- [hepatitis C](#)
- [Pre-exposure prophylaxis \(PrEP\)](#)
- [raltegravir](#)
- [Truvada](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/123>
- [2] <http://www.napwa.org.au/glossary/term/486>
- [3] <http://www.napwa.org.au/glossary/term/416>
- [4] <http://www.napwa.org.au/glossary/term/475>
- [5] <http://www.napwa.org.au/glossary/term/112>
- [6] <http://www.napwa.org.au/glossary/term/106>
- [7] <http://www.napwa.org.au/glossary/term/491>
- [8] <http://www.napwa.org.au/glossary/term/109>
- [9] <http://www.napwa.org.au/glossary/term/471>
- [10] <http://www.napwa.org.au/glossary/term/96>
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- [19] <http://www.napwa.org.au/glossary/term/191>
- [20] <http://www.medscape.com/viewarticle/523393>
- [21] <http://www.napwa.org.au/glossary/term/503>
- [22] <http://www.napwa.org.au/glossary/term/132>