

## Good news, bad news: report from CROI

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John Daye, NAPWA's Health, Treatments & Research Portfolio Co-Convenor reports from the 15th Conference on Retroviruses and Opportunistic Infections (CROI) held in Boston, USA from 3-6 February 2008

Every year, for the past fifteen years, the world's most dedicated and cutting edge scientists, [clinical](#) [1]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. investigators, researchers, educators and advocates get together in one place to figure out how we can better manage HIV and its opportunistic infections.

The Conference on Retroviruses and Opportunistic Infections is a four-day intensive meeting where the year's biggest findings are presented and fiercely debated. The focus is on translating research into practical ways to fight the global HIV/AIDS epidemic.

It's not difficult to understand why CROI is regarded as the premier scientific conference. This year, icy Boston, Massachusetts attracted a record 4200 delegates who examined an impressive 6644 posters, attended 657 oral presentations and witnessed 164 "late breaking" abstracts.

In the opening session, three big questions were posed by Constance Benson, Professor of Medicine at the University of California: When is the optimal time to start [antiretrovirals](#) [2]A medication or other substance which is active against retroviruses such as HIV.? What are the best first line regimens? And how do we deal with their serious toxicities, particularly [insulin resistance](#) [3]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., lipoatrophy and abnormal fat distribution and dyslipidemia? Her talk was a reminder that although intense work has been undertaken in these areas the answers still remain elusive.

### CCR5 Inhibitors – the new kids

#### Vicriviroc

CCR5 inhibitors are the new class of antiretroviral. Unlike the other drugs which focus on destroying already infected cells, this class prevents the virus from infecting the cell in the first place by blocking the chemical doorway the virus uses to enter. The first [FDA](#) [4]The U.S. Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, vaccines, and medical devices, including those used in the diagnosis, treatment, and prevention of HIV infection, AIDS, and AIDS-related opportunistic infections. The FDA also works with the blood banking industry to safeguard the nation's blood supply. The Australian equivalent is the Therapeutic Goods Administration (TGA). approved CCR5 inhibitor, maraviroc, is currently available in Australia only through restricted access sites and clinical studies, with a small number of doctors.

Vicriviroc is a new drug from this class and there are promising results about its safety and [effectiveness](#) [5](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.. After 48 weeks, 56% of the study participants taking vicriviroc plus an optimised background regimen had their virus reduced to undetectable levels, compared with only 14% of those taking the optimised background regimen alone. Reported side effects were no different between groups and the 30mg drug is administered once daily.

#### SCH532706

Phase One of a study into another new CCR5 inhibitor – SCH532706 or '706 – was presented by Australian ID physician, Sarah Pett, from the National Centre in HIV [Epidemiology](#) [6]The branch of medical science that deals

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with the study of incidence and distribution and control of a disease in a population.& Clinical Research. Sarah's findings revealed '706 to be a potent agent in both laboratory tests and amongst healthy volunteers.

In the Sydney pilot study, 12 HIV-positive individuals who were not on [combination therapy](#) [7] Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. received 10 days of '706 (twice-a-day) with ritonavir (once-a-day). The investigators then stopped all treatment for two weeks before commencing the volunteers on a combination that did not include '706.

Pett's findings showed that there was a [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. drop at day 10 of between 2,400 and 40,000 copies. Even further declines of 1000 copies were seen at day 15 – four days after stopping the '706. Because the drug stays in the body for up to 40 hours and then remains attached to the CCR5-receptor for several days, '706 could be dosed daily with ritonavir.

'706 was well tolerated with gastrointestinal discomfort reported as the most common [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.. One person did develop pericarditis, an inflammation of membranes around the heart, and this, Pett noted, could have been related to the drug.

Plans for further development of this drug, plus information on cross-resistance with other CCR5 inhibitors – maraviroc and vicriviroc – are not yet known.

## Nanoparticle technology – the future is now

### Rilpivirine

Nanoparticle technology made various appearances at CROI.

Pharmaceutical company, Tibotec, presented an exciting development in infrequent dosing with their new Non-Nucleoside Reverse Transcriptase Inhibitor rilpivirine (TMC278).

The drug only needs to be injected once a month because it has been encapsulated into tiny polymer particles that release the drug slowly into the body. These particles have an average diameter of 200 nanometres (one five-thousandth of a millimetre), which is comparable to the size of the HIV virus (120nm).

The presenter, Dr Gerben van t'Klooster said the next stage was to concentrate rilpivirine into the nanoparticles more efficiently so that injection volume could be reduced. He also hinted that Tibotec is interested in this slow-release formulation for use in pre-exposure prophylaxis or microbicides.

They are also actively looking for molecules to pair with rilpivirine so that a truly injectable combination therapy could be found. Drugs such as darunavir need daily doses too large for a slow-release formulation to be feasible.

### Slow release combinations

Another group based at Creighton University in Omaha, Nebraska, has succeeded in creating slow-release nanoparticles containing the drugs lopinavir, ritonavir and efavirenz.

So far they have only tested these particles' drug-releasing properties by suspending them in a medium in a laboratory dish. Maximum drug levels in the medium were reached by six days, but at 30 days drug concentration in the medium was still, even with regular changes of medium, over 30mg/ml of drug. They also did experiments to show that the nanoparticles were readily taken up by human monocyte derived macrophages, a kind of immune-system cell.

**Crossing the [blood-brain barrier](#) [10] A selective barrier (obstacle) between circulating blood and brain tissues that prevents damaging substances from reaching the brain. Certain compounds readily cross the blood-brain barrier; others are completely blocked.**

In another experiment from Creighton University, scientists succeeded in loading indinavir into nanoparticles then getting bone-marrow-derived macrophages (BMMs), another kind of immune cell, to absorb them. These were then injected into mice with induced HIV-related encephalitis. The BMMs migrated preferentially to sites in the brain where nerve cells were being destroyed due to HIV-related inflammation. Conversely, they were not found in brain areas without inflammation.

This model provides an exquisitely precise way of targeting drugs that normally cross the blood- brain barrier inefficiently to the sites in the brain that most need them.

### **The gold standard**

Finally, a team from the University of North Carolina attached a normally inactive CCR5 inhibitor to gold nanoparticles, and thereby restored its anti- HIV activity.

The point of doing this was to create large gold- drug complex molecules that would act like, and interact with, large viral proteins, and eventually to develop a mechanism to introduce agents into cellular spaces that have proved difficult to target with small- molecule drugs.

An example includes vif, the viral infectivity factor, an HIV accessory protein that has been a tantalising target for HIV drug delivery for years but which has so far eluded inhibition.

### **Old drugs – new tricks**

#### **Darunavir and lopinavir**

A significant poster abstract compared the development of drug resistance between lopinavir and darunavir in treatment-experienced individuals. This report suggested that darunavir has lower virological failure rates and was better at preventing the development of primary protease inhibitor mutations than lopinavir.

The majority of individuals experiencing virological failure to darunavir retained susceptibility to other protease inhibitors.

#### **Herpes drugs and HIV**

It had been hoped that daily treatment with the anti- herpes drug aciclovir might reduce the risk of being infected with HIV. But results from studies involving over 1800 gay men with genital herpes in the US and Peru and over 1300 heterosexual women with HSV-2 in Africa showed that aciclovir treatment did nothing to reduce their risk of HIV infection.

Whilst these results were disappointing, it has raised important issues, including the need to understand more about the link between HSV- 2 and HIV as well as whether the strategy of using 400 milligrams twice daily was the best dose for the purpose in Africa, as this appeared to suppress genital ulcers, but not HIV transmission.

#### **Starting treatment earlier**

Current HIV treatment guidelines recommend that treatment should be started when a person's CD4 cell count is around 350 cells/ mm<sup>3</sup>. But evidence presented at CROI by Andrew Phillips from London, suggests that HIV-positive individuals had a higher risk of death than the general population, even when CD4 cell counts were above 350.

Over 46,000 patients were included in this analysis, from a number of cohorts and large studies undertaken since the beginning of antiretroviral therapy. Gay men had only a slightly increased risk of death compared to the general population, but for heterosexual men and women the risk of death was three times greater and ten times greater for some injecting drug users.

Although the researchers do acknowledge that factors other than HIV may underlay the increased risk of death for some patients, they did find that HIV itself was causing non AIDS related death, even amongst patients with higher

CD4 cell counts.

Results from this study seem likely to contribute to the debate about the best time to start anti-HIV treatment, with Phillips concluding that “we need to be looking at whether ART should be initiated earlier in patients with CD4 counts above 500.”

### **Antiretrovirals and opportunistic infections**

A US study shows that introducing anti-HIV therapy while still treating an opportunistic infection reduces the risk of death or further disease progression and doesn't increase the risk of side effects.

Patients who deferred anti- HIV treatment were about 50% more likely to develop another AIDS-defining illness or die than those taking immediate treatment. And CD4 cell counts increased at a slower rate in those waiting to start treatment. There were no differences in rates of adherence between the two groups of patients nor was there any difference in the risk of developing an immune reconstitution inflammatory syndrome once treatment was started.

### **Treatment interruptions**

Patients who have treatment interruptions have indicators of increased inflammation as well as dysfunction in the lining of the blood vessels. This could explain the increased risk of illness and death due to diseases not usually associated with HIV, such as heart, kidney and liver disease, seen in the SMART study.

Researchers continue to look at the results of the SMART and STACCATO treatment interruption studies, and in presentations at CROI have shown that HIV replication during structured treatment breaks affected key biomarkers that indicate inflammation, increased blood clotting and endothelial dysfunction – reduced flexibility in the lining of blood vessels, an early sign of heart disease.

### **Circumcision**

Evidence from Uganda has revealed that men who are circumcised are less likely to become infected with HIV, providing the circumcision wound has healed. The wives of HIV-positive circumcised men whose circumcision wound had not thoroughly healed had an increased risk of contracting HIV.

### **Expert advice matters**

Results from the HAVANNA trial suggest that “expert advice” in interpreting results from resistance testing may be crucial to making treatment decisions. Basically interpreting the results from resistance testing takes expertise, otherwise the ability to select the best regimen based on the test results is limited. At week 24 of this study there was significant difference reported between the groups receiving genotyping and not receiving genotyping (57% vs. 42%), and the expert advice and non expert advice groups (59% vs. 41%). The study authors also concluded that expert advice may add to the benefit of genotyping in heavily pre-treated patients.

### **Predictive power of genetic profiles to responding better to antiretroviral treatment**

Variability of drug plasma levels amongst HIV infected patients on antiretroviral therapy can explain differences in how patients experience drug toxicities, drug failure, and the efficacy of the drug response. In a late breaker study presented by a Swiss group, variations of [genes](#) [11]The most basic unit of genetic information. coding that are involved in the metabolism of ART were described. The findings suggest that a genetic predisposition in the genes that process drugs in the human body may affect drug levels in blood which may be affecting an individual's response to therapy.

While this is early research, it is potentially critical for future research into therapeutic drug monitoring and adjustments for individualised therapy. For example, if it is possible to determine a person's predicted response to how the drugs will metabolise in their body, then drug dosing could be adjusted to improve initial response to therapy, and the durability of that response.

[darunavir](#)

[HIV treatments](#)

[lopinavir](#)

[rilpivirine \(TMC 278\)](#)

[SCH532706](#)

[starting treatments](#)

[vicriviroc](#)

[experimental treatments](#)

**Links:**

[1] <http://www.napwa.org.au/glossary/term/475>

[2] <http://www.napwa.org.au/glossary/term/122>

[3] <http://www.napwa.org.au/glossary/term/99>

[4] <http://www.napwa.org.au/glossary/term/492>

[5] <http://www.napwa.org.au/glossary/term/486>

[6] <http://www.napwa.org.au/glossary/term/490>

[7] <http://www.napwa.org.au/glossary/term/96>

[8] <http://www.napwa.org.au/glossary/term/416>

[9] <http://www.napwa.org.au/glossary/term/471>

[10] <http://www.napwa.org.au/glossary/term/415>

[11] <http://www.napwa.org.au/glossary/term/126>