

The bleeding edge

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The annual Retrovirus Conference is a key event on the HIV scientific calendar, and regularly highlights the most exciting 'bleeding edge' developments from the world of HIV science. NAPWA's treatments portfolio convenor JOHN DAYE was there.

Just two weeks after a report from New York City health officials that a new [strain](#) [1][HIV strain] Any subgroup of the HIV species. Because HIV mutates very easily, there are many different strains (and may be multiple strains within a single person). of highly drug-[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. HIV had been detected, the 12th Conference on Retroviruses and Opportunistic Infections took place in Boston. Amidst the hype, publicity and political posturing that surrounded the case, organisers considered the situation urgent enough to hastily arrange a special symposium one evening focused on the so-called 'super bug'.

Before an auditorium packed with delegates we heard a panel of experts explain that the phenomenon, although rare and serious, was not new and there was no evidence that transmission of this multi-resistant HIV had been detected elsewhere. We were informed that rapid progression to AIDS in newly infected people has been documented before and there is uncertainty over whether the virus detected is really a single highly resistant strain of HIV or possibly [subtypes](#) [3][HIV subtype or clade] A genetically distinct subtype of HIV within a defined HIV group. Group M has nine known subtypes -- A, B, C, D, F, G, H, J and K. of the virus in the same person. It was widely agreed the transmission of multi-drug resistance requires further research before we can be better understand what is happening.

A poster presentation of this case also attracted unprecedented attention with conference attendees lining up to scrutinise the detail¹. Many community advocates present were deeply concerned about the alarmist way this case was handled and the potential for fallout against New York City's gay men's population.

The annual Retroviruses Conference is one of the most significant scientific conferences to deal with HIV/AIDS. It's particularly important because of the depth of the research which is presented — research into HIV treatments, drug resistance, treatment failure, drug toxicities, and strategic [clinical](#) [4]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. approaches to manage HIV and opportunistic infections.

Close to 3800 delegates attended the conference. Presentations focusing on new antiretroviral drugs and mechanisms to treat HIV were particularly welcome after the fear-based discussions surrounding the New York 'super bug' in the mainstream press. The importance of developing new drugs with different mechanisms of action to control HIV is a huge challenge to scientists, researchers, clinicians and the HIV-positive people who take part in clinical trials so that we can stay one step ahead of drug resistance.

At the opening session Dr Jim Kim, the Director of HIV/AIDS for the World Health Organisation (WHO), called on governments and nations to support the WHO's 'three by five' strategy and implored people to stop speculating about whether the target of treating three million people by the end of this year will be met, but to do what they can to make it happen.

Dr Kim especially appealed to those attending the conference to promote treatment and open up research in poor countries and advocate for a wider public health approach to HIV/AIDS globally. He urged political leaders to take a greater stand in pushing for access to antiretroviral drugs, singling out South Africa, Nigeria and India as the countries which are lagging behind most.

Drugs in development

Encouraging preliminary results were presented from a proof-of-concept trial of the first drug in an entirely new class, a 'maturation inhibitor'. PA-457 inhibits a protein produced by HIV-infected cells which would normally

become a component of new HIV particles, thereby interfering with HIV replication.

In the small study, 24 HIV-positive men who were not on treatment were given a single dose of either 75, 150 or 220 milligrams or [placebo](#) [5] A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial. Those on the two higher doses had significant reductions in [viral load](#) [6] 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., lasting for up to nine days. The half-life of PA-457 is very long (2-3 days). Of particular interest, PA-457 was effective in two trial participants who had extensive resistance mutations. The drug was apparently well tolerated at all dose levels in this study².

One of the highlights of the conference was the research presented about the new protease inhibitor TMC 114, which promises to be effective against other protease inhibitor resistant HIV.

The potential usefulness of this drug, particularly for those who have reduced treatment options due to drug resistance, was demonstrated in a 24-week study involving 497 participants who had extensive past treatment from three different [drug classes](#) [7] 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 who had developed primary drug resistance from within the protease inhibitor class. The rapid and substantial reductions in viral load indicate that this drug may be a potent option for people with multi-class drug resistance. Based on the results of this study, TMC 114 (600mg boosted with 100mg ritonavir) has been selected for use in its forthcoming [phase 3](#) [8] A large clinical trial designed to establish whether a drug is effective and safe enough for widespread use. Phase III studies include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling. trial to examine in greater detail its [effectiveness](#) [9] (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. over a longer duration³.

TMC 278 is a potent new non-nucleoside reverse transcriptase inhibitor which has been shown in test-tube studies to be effective against HIV which has become resistant to existing non-nucleoside drugs and has an increased genetic barrier to the development of drug resistance⁴.

In a short seven-day monotherapy study involving people who had not previously taken treatments, major reductions in viral load were observed and participants were switched to standard treatment. TMC 278 was well tolerated — the most common adverse event observed was headache (8.4 percent).

Another trial is now underway to establish the correct dosage. In a phase 2a study (a type of clinical trial that establishes the dosage, safety and tolerability of a new drug), seven days of TMC278 monotherapy (25-150 mg once daily) produced a significant decrease in viral load for all doses studied, and four individuals achieved a viral load below 400 copies/ml during the treatment. No severe adverse effects were reported⁵.

The Belgian drug company Tibotec is developing a new class of HIV reverse transcriptase inhibitors called 'nucleoside-competitive RT inhibitors' (NcRTIs). The company presented data on a pre-clinical molecular modelling study of an agent referred to as 'compound X'. [Antiviral](#) [10] A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. assays and biochemical experiments showed that this compound could inhibit HIV by a mechanism of action that is clearly different from that of other drug classes⁶.

TAK-652 is a new drug which targets the CCR5 co-receptor and shows promise as an entry inhibitor. Preliminary test-tube studies suggest this drug will be effective against drug-resistant strains of HIV. TAK-642 was demonstrated to selectively inhibit CCR5 and to have no effect on CXCR4 replication. A single oral dose amongst HIV-negative men was well tolerated. In another laboratory study of TAK-652 it was shown to have favourable antiviral interactions between TAK-652 and AZT, 3TC, efavirenz, indinavir and T-20[7-8].

Another CCR5 inhibitor, 873140, appears to have a high rate and prolonged occupancy of the CCR5 receptor

following oral administration. It also appears to have synergistic effects with some other antiretrovirals (nevirapine, indinavir and T-20) and with the X4 inhibitors AMD3100 and TE14011. This compound is in a phase 2 clinical trial (to establish dosage, safety and tolerability)[9-10].

Data was also presented on Pfizer's CCR5 inhibitor, maraviroc (MVC, formerly UK-427,857) blood levels are reduced approximately 50 percent by efavirenz-containing drug combinations and increased approximately 100 percent by Kaletra-containing combinations. Nevirapine-containing drug combinations cause a small increase in blood concentration levels but do not reduce exposure to the drug. Preliminary laboratory data indicate that due to differences among the CCR5 inhibitors regarding the site at which they bind the CCR5 receptor, MVC resistance does not cause cross-resistance with the other CCR5 inhibitors[11-12].

Kidney problems

Chronic kidney disease appears to be more common in HIV-positive people compared with their HIV-negative counterparts¹³. Monitoring the gradual kidney damage that can lead to chronic kidney disease in people with HIV is particularly important as they live longer. Kidney damage can occur as a result of HIV disease, treatment toxicities, or other conditions such as [diabetes](#) [11][Diabetes mellitus] A disorder in which sugars in the diet cannot be metabolised into energy due to a lack of the enzyme insulin. Late-onset diabetes mellitus may be a long-term side effect of some anti-HIV drugs. or [high blood pressure](#) [12]Persistently high blood pressure, an outwardly symptomless condition which carries an increased risk of serious illnesses such as stroke, heart disease and heart attack.. Investigators reported on a potential marker for the early detection of kidney impairment. In a study of 1298 individuals, a test that estimates the kidney's ability to filter blood showed that kidney damage was more advanced and prevalent in HIV-positive individuals¹⁴.

Lymphogranuloma venereum

A poster presented the incidence in a retrospective study of this newly-recognised sexually transmitted infection in 123 French men. Rectal Lymphogranuloma venereum (LGV) among men who have sex with men has been mainly observed in HIV-positive men in Belgium, Germany, San Francisco and the UK and now appears to be more prevalent than first thought. Screening, treatment and prevention are especially important because treatment of this disease is particularly lengthy with antibiotics over several months¹⁵.

D:A:D study

This study has been collecting information about the adverse effects of antiretrovirals in a large international [cohort](#) [13]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. of 23,441 people with HIV/AIDS. It is of sufficient size to accurately detect the rate of [heart attack](#) [14]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. (myocardial infarction) in the HIV population who are on treatment. In this study 277 individuals experienced an adverse cardiac (heart) event of which 28.5 percent were fatal.

The risk of heart attack per additional year whilst on antiretrovirals was calculated at 1.17 percent. The study determined that the risk of heart attack is low and similar between men and women, and younger and older individuals. Irregular blood-fat levels explain some but not all of these events. Modifying risk factors such as cigarette smoking, physical fitness and diet was emphasised to further reduce risk¹⁶.

In another study of 5134 HIV-positive people, rates of coronary heart disease were examined, finding higher rates of coronary heart disease in HIV-positive people compared with HIV-negative people. No link with protease inhibitors was established. Despite advancing age and accumulating exposure to antiretrovirals rates of coronary heart disease have risen only modestly¹⁷.

MaxEPA

A study in 58 individuals demonstrated the efficacy of maxEPA, a fish oil supplement, to decrease [triglyceride](#) [15]A type of fat in the blood. Elevated triglyceride levels may be a side effect of some anti-HIV drugs. levels in antiretroviral-treated individuals with elevated triglycerides. The supplement proved equivalent to the conventional treatment of statin drugs. MaxEPA appears to be a promising option for people with high [blood fat](#) [16]A fat. levels — it has good tolerance and the advantage of an absence of drug interactions that can occur with the use of statin drugs¹⁸.

Metabolic challenges

A question frequently asked by many positive people is whether there are any medications that can be taken to prevent them from developing lipoatrophy (sunken cheeks and thinning of the limbs) while keeping HIV under control. This is a good question because these disfiguring side effects really can affect self esteem.

Investigators have been looking for an answer to this question and a number of studies that involved changing drugs have showed modest improvements. In a poster presentation, a study in 53 individuals with lipoatrophy who switched from d4T and AZT to tenofovir and abacavir showed a slow but significant increase of general fat mass and of cheek fat thickness at six, 12 and 18 month intervals¹⁹.



NAPWA Health & Treatments Portfolio

Convenor John Daye at the Retrovirus conference with Australian HIV specialists Andrew Carr, Jenny Hoy and Anne Mijch

Another study on this subject involved 101 individuals with fat wasting in the face, arms and legs. Changing from d4T and AZT-containing combinations to other drug classes which included Kaletra and nevirapine showed significant improvements in subcutaneous body fat after 24 weeks without losing control of HIV. The researchers did however note that longer-term follow-up is need to better understand the long term implications²⁰.

In another study on this subject, 105 individuals who switched from d4T and AZT to an abacavir or tenofovir-containing combination had significant increases in limb and subcutaneous fat after 48 weeks²¹.

In another study, researchers looked at 62 treatment-inexperienced individuals with advanced HIV and found that switching from nucleoside reverse transcriptase inhibitors (NRTIs, e.g. AZT, d4T, abacavir) to Kaletra and efavirenz-containing combinations was associated with significant improvement in body fat. The results of this study provided additional evidence that NRTIs are associated with the body fat loss that characterises HIV lipoatrophy. The switch to a 'NRTI sparing' drug combination represents an option for individuals with lipoatrophy

Polylactic acid

Subcutaneous injection of polylactic acid (the active ingredient in New-Fill) produced durable improvement over six

months in facial appearance in 74 percent of individuals with moderate to severe facial lipoatrophy. Few adverse events were recorded and patients' distress was markedly improved ²³.

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