

Time to deliver

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The [16th International AIDS Conference](#) [1], held in Toronto, Canada in August, brought together 26,000 scientists, activists, leaders and people living with HIV from around the world. This year's theme, "Time to Deliver", reflected on the hope that it is time to deliver the medicines that can save lives; time to deliver on promises made by governments and time to deliver on human rights. JOHN DAYE was there.

At the opening ceremony [UNAIDS](#) [2] Joint United Nations Programme on HIV/AIDS. UNAIDS is the main advocate for accelerated, comprehensive and coordinated global action on the epidemic. head Peter Piot said that money is not being spent well in some countries even though US\$8.3 billion was spent on AIDS in developing countries in 2005. His comments were echoed by the Indonesian HIV-positive activist Frika Iskandar who said, "We need a funding mechanism that is driven by the needs of the community. I wonder why most of the money doesn't reach communities".

US billionaire-turned-philanthropist Bill Gates and his wife, Melinda Gates, spoke about the need to put power to prevent HIV in the hands of women. "It is a priority to develop microbicides and oral prevention drugs that women could use to avoid infection without relying on their sexual partners," Melinda Gates told the audience. Her husband added, "No matter where she lives, who she is, or what she does, a woman should never need her partner's permission to save her own life."

The closing ceremony featured an emotional speech by Stephen Lewis, the UN special envoy for HIV/AIDS in Africa, in which he sharply criticised Canada's new Prime Minister, Stephen Harper, US President George Bush and South Africa's President, Thabo Mbeki, for negligence, a lack of accountability and for presiding over bloated bureaucracies.

Lewis attacked aid agencies for spending too much money and time on bureaucratic activities rather than on work that directly helps HIV-positive people. He condemned Harper for not even attending the International AIDS Conference for his government's delay in addressing fears about the future of the highly successful safe injecting sites in Vancouver. The Bush administration came under attack for its insistence that a third of the US AIDS prevention budget be spent on abstinence-only programs.

But Lewis's greatest criticism was reserved for Mbeki and his government for their state of denial about HIV/ AIDS treatment and for ignoring medical and scientific evidence in treating the [virus](#) [3] A small infective organism which is incapable of reproducing outside a host cell., and instead pushing vegetables and herbs. South Africa is "the only country in Africa whose government continues to propound theories more worthy of a lunatic fringe than of a concerned and compassionate state," he said.

The scientific content was stronger at Toronto than at other recent world AIDS conferences. While the focus of the conference was mainly on access to drugs and prevention technologies there was some news about [investigational](#) [4] (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. drugs and new target mechanisms to treat HIV.

Integrase inhibitor – MK-0518

The success of the most recent trials of a new anti-HIV drug called MK-0518 in a new class called integrase inhibitors was detailed by leading [investigator](#) [5] A medical researcher in charge of carrying out a clinical trial's protocol. Marty Markowitz in one of the most important treatment presentations¹. Researchers have been looking for better ways to slow down replication of the virus, and this drug targets an entirely different point in the HIV replication cycle to existing treatments.

MK-0518 works by blocking integrase, the enzyme the virus uses to integrate its genetic material into the DNA of a host cell. Previous attempts to design a drug to inhibit integrase have proved unsuccessful, but after 24 weeks of

data collected and analysed from 28 international sites, investigators have found that MK-0518, when used in combination with two other [antiretrovirals](#) [6]A medication or other substance which is active against retroviruses such as HIV., is able to suppress HIV just as effectively as any of the best HIV treatments currently available. The phase-2 (dose ranging, safety and efficacy data) end of this study is a significant step for those who are running out of treatment options and have some degree of drug-[resistant](#) [7]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. virus.

Only one person in the study of 198 people had to stop the medication due to side effects (which can include diarrhoea, headaches and insomnia), however, so far it seems to be a well-tolerated drug. This drug, which is currently in trials in Australia and overseas, has been eagerly awaited and the data presented at the conference gives good reason for cautious optimism about a major improvement in the treatment of HIV.

CCR5 inhibitors

Another new class of drugs, the CCR5 antagonists, are in active development. For HIV to bind and infect cells it gains entry through two 'doors' on the surface of the host cell – either the CCR5 or CXCR4 co-receptors. In newly infected people, HIV most commonly binds by entering cells with the CCR5 co-receptor. However over time, possibly as infected cells are destroyed, the virus may switch to using the CXCR4 co-receptor. These different co-receptors (or doorways) offer scientists different points of the HIV replication cycle at which to intervene.

The way in which HIV replicates through either the CCR5 or CXCR4 co-receptor is known as tropism. The increased presence of CXCR4 co-receptors is associated with more advanced HIV infection and often, faster disease progression. The types of HIV co-receptor that predominate can be measured.

The results from a phase-2b (safety and efficacy) study of maraviroc², a CCR5 antagonist, were presented at the conference. This study measured the safety, virologic and immunologic effects of maraviroc in 186 treatment-experienced patients with advanced infection. This study is important because it examined whether it was safe to use maraviroc. The early findings suggest that administration of maraviroc does not lead to the development of the potentially more virulent, CXCR4-tropic, form of HIV. Maraviroc was found to be safe and well tolerated in an advanced group of people with dual-tropic (both CCR5 & CXCR4) virus. There was no virological or immunological decline in the people studied. Maraviroc is now in phase-3 studies, the final stage of [clinical](#) [8] Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. development, including sites here in Australia.

Another investigational CCR5 inhibitor that was presented was vicriviroc³. In this phase-2 study of 118 treatment-experienced people, vicriviroc demonstrated potent and sustained viral suppression after 24 weeks of therapy, when taken with antiretroviral regimens that included a ritonavir-boosted protease inhibitor. Roy Gulick, who presented this data, said new resistance profiles are particularly important for patients who need new treatment options. Among vicriviroc patients who took part in this [clinical trial](#) [9]A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed. , two developed Hodgkin's disease (one with a prior history of Hodgkin's disease); two developed non-Hodgkin's lymphoma (one with prior Hodgkin's disease) and one developed gastric adenocarcinoma. The relationship of vicriviroc to these cancers is uncertain. The AIDS Clinical Trials Group (including an independent safety monitoring committee) concluded causal association between vicriviroc and the malignancies could not be determined by this study. Further clinical trials of this agent are underway.

TNX-355

TNX-355 is another new drug in which works in a different way to existing treatments – a monoclonal antibody attachment inhibitor⁴. It works by blocking the entry of HIV into cells, like T-20, but does so in a novel way. A 24-week interim assessment of an ongoing 48-week trial in treatment-experienced patients showed greater [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. activity when this agent is used with a standard antiretroviral combination than using a standard antiretroviral combination alone. This is a distinct benefit to people who are highly treatment-experienced and who have limited therapy options. This phase-2 (safety & efficacy) trial in 82 patients found TNX-355 be active against CCR5- and CXCR4-tropic HIV. The drawback of this drug is that it has to be administered intravenously at fortnightly intervals. Of interest was also data presented on this agent that showed that it was not cross-resistant to T-20⁵.

Darunavir

Darunavir (formerly known as TMC-114) is a protease inhibitor already approved for use in the United States and available through a [Special Access Scheme](#) [11] 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). in Australia. Data presented at the conference demonstrated sustained efficacy in a treatment-experienced population. Its tolerability was similar to other protease inhibitors but with a lower incidence of diarrhoea⁶. In another, larger, study, darunavir boosted with a low dose of ritonavir provided substantial [viral load](#) [12] 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 and CD4 increases and was generally safe and well-tolerated⁷. In another study darunavir/ritonavir was found to be generally well-tolerated by treatment-experienced patients. The incidence of diarrhoea was lower than other protease inhibitors⁸. This new protease inhibitor is proving a valuable HIV therapy option and its availability on the [Pharmaceutical Benefits Scheme](#) [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. is eagerly awaited by positive people here in Australia.

TMC-125

TMC125 is an experimental non-nucleoside reverse transcriptase inhibitor (NNRTI). Existing drugs in this class are plagued by cross-resistance – if HIV develops resistance to one you become resistant to the other. For this reason, the development of a new drug in this class with a better barrier to resistance has been much-awaited. Week-24 results were presented from a trial at 800mg twice a day which showed benefit in raising CD4 counts and suppressing viral load⁹. In another study of 199 patients, TMC-125 showed high rates of sustained efficacy at 48 weeks in heavily pre-treated patients. The trial showed that TMC-125 retains activity in the presence of multiple NNRTI mutations where current NNRTIs are not expected to be effective¹⁰.

Brecaonavir

Brecaonavir is a new protease inhibitor which is in phase-2 (safety & efficacy) clinical trials. It has potent activity against protease inhibitor resistant HIV when boosted with ritonavir. The data presented at the conference demonstrated highly potent activity against resistant virus and support further development of this drug. In laboratory tests it has shown greater antiviral potency than many other protease inhibitors¹¹.

Discovery of a new HIV fusion inhibitor

The fusion inhibitor T-20 is an important and effective drug, but the inconvenience of twice-daily injections has restricted its use to [salvage](#) [14] [salvage therapy] A treatment strategy for managing HIV in people who have developed resistance to existing therapies. therapy – so the development of a fusion inhibitor which could be given in tablet form would be an important breakthrough. Data presented in a poster at the conference showed a novel approach for the discovery of small molecule HIV fusion inhibitors with unique mechanisms of action. Finnegan et al have identified distinct families of drug-like small molecules that specifically inhibit HIV infection. This approach interferes in the replicative cycle by blocking proteins in the HIV envelope fusing with human cell membranes. The compounds identified in this study are currently being optimised for drug development and may lead to attractive therapeutic alternatives in the future¹².

Enfuvirtide (T-20)

A poster presentation examined the role of doctor and patient attitudes to injectable HIV treatment¹³. It suggested that there is a 'disconnect' between doctor and patient beliefs, with patients having more positive attitudes towards injectable antiretrovirals than anticipated by doctors. The study indicated that patients may be more receptive to initiating self-injectable therapy than their doctors believe. Another study compared the use of alternative injecting mechanism against the current standard needle and syringes. Called Bioject, this 'needle-less' gas-powered injecting device demonstrated high levels of tolerability and acceptability to people using it. Improvements in tolerability and patient acceptability were significant and most pronounced in patients who switched from other injection methods to the Bioject device. People who switched to the Bioject reported significantly less pain and fewer skin reactions at the injecting sites¹⁴.

Depression and peripheral neuropathy

A number of papers at the conference suggested that neurocognitive impairment (problems with thinking, concentration or memory), peripheral neuropathy (tingling, itching or pain in the feet and hands) and depression are commonly under-diagnosed among HIV-positive outpatients from Asia Pacific sites in Thailand, Indonesia, China and Malaysia, pointing to the need for improved clinical services to recognise and treat depression¹⁵.

Another study from the United States reported that depression, insomnia, peripheral neuropathy and fatigue are among the most frequent and bothersome symptoms of HIV disease. The objective of the study was to see if these four symptoms form a 'cluster' in HIV disease and test the relationship of this cluster of symptoms with quality of life. The results suggest that they do, and interventions that address these symptoms simultaneously may be beneficial¹⁶.

In yet another study of 3431 patients it was found that untreated depression was associated with significantly reduced adherence to antiretroviral therapy¹⁷. Another study looked at the cultural differences in predictors of depression amongst different countries and found that depression was high in all countries amongst HIV-positive people but required culturally-based interventions, adding that targeted interventions may improve adherence, reduce risky behaviours and improve health outcomes in people living with HIV/AIDS¹⁸.

Dedicated lipodystrophy clinic

A lipodystrophy clinic established in Manchester, United Kingdom, was the subject of an interesting poster presentation¹⁹. This clinic was a new approach to dealing with the metabolic problems that can be associated with antiretroviral therapy. The majority of patients were referred because of facial lipoatrophy for consideration of treatment with poly-lactic acid (Sculptra, formerly New-Fill). In addition to managing lipoatrophy, the clinic also ran diet and exercise programs and managed abnormal [blood fat](#) [15]A fat. and glucose levels and provided advice on antiretroviral switching to diminish the development of lipoatrophy. This presentation was particularly interesting because it looked at building expertise and enhancing care in the management of metabolic disorders associated with treatment.

In another poster presentation about lipodystrophy, quality of life associated with changes in weight and body appearance among HIV-positive individuals was explored²⁰. It concluded that weight and body changes are common and bothersome symptoms among people with HIV and have significant and measurable quality-of-life effects. Scoring by HIV-positive people sadly indicated that they are willing to forego 10 to 15 percent of future life expectancy to alleviate symptoms.

Uridine

A German study, presenting data on the effect of uridine (a supplement extracted from sugar cane) on symptoms of

lipodystrophy and peripheral neuropathy at a dosage of 500mg twice a day in 31 patients, showed improvements of these symptoms according to subjective patient scores. This was reported to be the first clinical trial evaluating tri-acetyl-uridine as a new treatment strategy in HIV-infected patients with lipodystrophy and polyneuropathy²¹.

Transmission of HIV Drug Resistance

The SPREAD program provides the first representative data on transmission of HIV drug resistance across Europe. The prevalence of 9 percent [baseline](#) [16]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 in prospectively-identified, newly-diagnosed, patients warrants continuous surveillance²². This study is particularly important because it begins to examine the extent of drug resistance occurring in new HIV transmissions.

- **John Daye** is NAPWA's National Health and Treatments Portfolio Convenor.

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