Advances at *AIDS 2014*. What does for future look like and how can we better use the tools we have now?

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During July 2014 the International AIDS Conference, AIDS 2014 was held in Melbourne, Australia. Approximately 13,600 delegates took part, and this brief report from an Australian pharmacist who attended, outlines some of the drug-related developments discussed during the six-day meeting. There is also an AIDS 2014 *YouTube* channel through which many sessions from the conference can be accessed without charge.

Background on HIV in Australia

At the end of 2013 there were approximately 27,000 people living with Human Immunodefiency Virus (HIV) infection in Australia (1). There were 1,236 new cases reported in 2013 and 70% of newly diagnosed cases were sexually transmitted between men who have sex with men (MSM). Nearly half of the 313 newly diagnosed cases acquired through heterosexual transmission were in people from high-prevalence countries or their partners. Thirty percent were late presentations, defined as a CD4 cell count of less than 350 cells/µL at the time of diagnosis. After a marked downward trend in new diagnoses during the 1990's, there has been a steady increase from 1999 when 724 new cases in Australia were diagnosed. An estimated 49-73% of those living with HIV (whether diagnosed or not) and 57-84% of those who have been diagnosed were on effective antiretroviral therapy (ART) at the end of 2013. These numbers demonstrate that while Australia remains a low HIV prevalence country, some barriers to diagnosis and treatment remain.

At a special 'Australia session' during the conference the nation's Chief Medical Officer discussed the Seventh National HIV Strategy 2014-2017 (2). One of the

goals of the strategy is to “work towards achieving the virtual elimination of HIV transmission in Australia by 2020” and several presentations explored ways of achieving this ambitious goal. One presentation was provided by Cameron Cox, a sex worker who described his outreach role at the Sex Workers Outreach Project (SWOP) in New South Wales (3). He discussed the use of social media, including through popular “hook-up” sites, as an effective means of reaching male sex workers, a population who describe that they do not always feel they want to be the recipients of outreach services.

In the lead up to the conference, changes to prescribing and dispensing of antiretrovirals (ARVs) were announced by the Australian Government Department of Health (4). These changes will allow for the dispensing of ARVs from community pharmacies as well as hospitals from 1 July 2015. From the same date, prescribers will no longer have to demonstrate an affiliation with a hospital to prescribe ARVs, though all other requirements for Section 100 prescribing under the auspices of the Pharmaceutical Benefits Scheme will remain the same. Restrictions on home-testing kits for HIV have also been lifted so that companies producing these can now apply to the Australian Therapeutic Goods Administration for registration to allow sale directly to the public.

New developments with ARVs

ARVs are well-established as an effective treatment for HIV and the wide availability of fixed-dose combinations (e.g. Atripla ® - efavirenz 600 mg/ emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg), rendering the dosing regimens in current use

considerably less complex than was the case during earlier stages of the pandemic. Most of the discussion of ART at the conference related to increasing testing and subsequent access to these drugs by effecting society-level cultural and legislative change to reduce stigma around HIV, especially in high-prevalence countries. Another major theme of the conference related to the ways that ARVs can be used to prevent infection with HIV – a summary is provided in table 1.

In recent times, another strategy referred to as oral Pre-Exposure Prophylaxis (PrEP) has been evaluated to determine if ARVs can reduce transmission of HIV if people who are HIV-negative, but who are at a high risk of infection, take them prophylactically. There is a growing number of randomised controlled trials (RCTs) that have assessed the efficacy of PrEP as part of a HIV prevention strategy. Results of trials where PrEP has been evaluated in heterosexual participants at high risk of HIV infection have been mixed, and outcomes appear to be closely linked with adherence to therapy. The phase 3, multi-country, placebo-controlled iPrEx trial (N = 2,499) found a 44% reduction in HIV incidence with tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) PrEP versus placebo ($p = 0.005$) amongst MSM and transgender women who have sex with men, with efficacy again linked with adherence (8). Both active and placebo arms of the iPrEx trial were offered a package of HIV reduction strategies (condoms, HIV testing and so on). The available trial data for PrEP use with TDF/FTC and TDF alone in heterosexual, MSM and transgender populations are summarised in recently published clinical practice guidelines from the USA (9). Currently only combination TDF/FTC (Truvada ®) is approved by the US Food and Drug Administration for PrEP use.

At the AIDS 2014 conference, data from the iPrEx open label extension (OLE) trial were presented and simultaneously published in the Lancet Infectious Diseases (10, 11). Previous iPrEx participants were invited to be involved, resulting in the recruitment of 1,603 participants from 11 study sites. The study was of 72 weeks duration and 76% of participants elected to take daily TDF/FTC PrEP. This study aimed to assess the efficacy of PrEP when provided to participants who knew that the intervention was TDF/FTC and not a random chance of active or placebo, as was the case in the original iPrEx trial. As with previous PrEP RCTs, efficacy was correlated with adherence to treatment. Notably, dried blood spot analysis of TDF levels showed that no participants taking four or more tablets per week became infected with HIV during the study period. In a presentation of a qualitative sub-study of the iPrEx OLE by Kimberly Koester, it was reported that use of PrEP did not lead to 'risk compensation' such as the lower use of other preventative strategies such as condoms (12). Instead, these researchers found that the use of PrEP was associated with less anxiety about being infected with HIV during sex.

Preliminary adherence results from pilot sites of the IPERGAY study being conducted in France and Canada were also presented, assessing a strategy of 'on demand' rather than regular PrEP dosing (13). Participants are randomised to receive TDF/FTC PrEP or placebo and are asked to take two tablets, two to 24 hours prior to sex and another tablet once daily for two days following. Participants are also offered a treatment package to reduce HIV infection risk as part of their involvement. Early data indicates a high adherence rate to this approach, though not always taken exactly as directed. Adherence was measured through computer-assisted self-interviews, tablet counts, plasma and scalp hair (when this was available)

concentrations of TDF and FTC. This trial is ongoing with planned completion in late 2016 (14).

The World Health Organization has this year released a revised strong recommendation that PrEP should be offered to MSM as part of a range of options to reduce risk of being infected with HIV (15). Other options include the use of condoms and lubricants, routine HIV testing, risk-reduction counselling and adherence counselling if PrEP is offered. In Australia, the Victorian PrEP HIV Demonstration Project (VicPrEP study) is being led by Associate Professor Edwina Wright of Monash University to assess the efficacy and acceptability of PrEP in Australia, when combined with other risk reduction strategies (16). Researchers plan to enroll 100 participants at risk of HIV infection who elect to use PrEP, and to compare outcomes to another 100 participants who do not wish to receive PrEP, following both groups for 12 months. It is noteworthy that no ARVs are currently licensed for use in a PrEP context in Australia (outside of demonstration projects). The VicPrEP study, along with others planned in Queensland and New South Wales (17), should yield important data to support future policy decisions around PrEP, as it is still a very new approach to HIV prevention.

HIV doesn't exist in isolation: viral hepatitis and tuberculosis advances

At the conference, the results from trials focusing on the drug treatment of viral hepatitis and tuberculosis (TB) treatment were also presented. Viral hepatitis and HIV share common risk factors for transmission, especially for those people who

inject drugs (10). TB is the leading cause of HIV-associated deaths globally, and naturally was also an important focus for the conference (15).

Trial data assessing the efficacy of newer, direct-acting antiviral regimens for patients co-infected with viral hepatitis C (HCV) and HIV showed similar treatment outcomes to those seen with HCV mono-infected patients. These findings support the 2014 European Association for the Study of the Liver (EASL) recommendation that for chronic HCV “the same treatment regimens can be used in HIV co-infected patients as in patients without HIV infection, as the virologic results of therapy are identical” (18, p. 5).

Phase 2B trial results were presented for PaMZ, an anti-TB regimen containing a new nitroimidazole currently referred to as PA-824 (used at a dose of 100 mg or 200 mg daily), plus Moxifloxacin (M - 400 mg daily) and pyrazinamide (Z - 1,500 mg daily) (19, 20). Patients with drug-sensitive and multi-drug resistant (MDR) TB, defined as resistance to rifampicin and isoniazid, were enrolled from study sites in South Africa and Tanzania. In all, 207 patients were enrolled (20% with HIV co-infection) and 173 were included in the final analysis: 164 with drug-sensitive TB and 9 with MDR-TB. Patients with drug-sensitive TB were randomly assigned to receive either PaMZ or a standard, weight-based, anti-TB regimen containing rifampicin, isoniazid, pyrazinamide and ethambutol (RHZE). There was no comparator for the MDR-TB patient group and these patients all received the higher dose of PA-824. PaMZ yielded good results, with a primary endpoint of reduction in colony forming units of *Mycobacterium tuberculosis* from sputum samples taken over eight weeks (at day 0, 3, 7 and then weekly thereafter). The log reduction per day was greater

than the RHZE regimen (N=54) for each of the PaMZ groups and this difference was statistically significant ($p < 0.05$) for the Pa (200mg) MZ drug-sensitive TB group (N = 56). These results were unchanged when adjusted for HIV status. The follow on Phase 3 study is planned to commence this year, aiming to assess the efficacy of PaMZ over a full treatment course. The researchers plan to enroll 1,500 patients; drug-sensitive TB treatment duration will be for four or six months and MDR-TB treatment will be for six months. With current regimens for MDR-TB treatment taking 18 - 24 months to complete, the results of this trial will be watched for closely. Other clinical trials assessing the efficacy of shorter MDR-TB treatment regimens are also underway.

Future directions in HIV

A lot of discussion during the AIDS 2014 conference focused on advances in basic science. Rather than the term cure, most of the sessions referred to achieving sustained HIV remission. Presentations focused on areas such as the anatomical distribution of enduring HIV viral reservoirs, HIV viral latency and studying the natural immune response to HIV infection, particularly through the production of broadly neutralising antibodies. The cases of the ‘Mississippi baby’ (born with HIV to a HIV-positive mother, with undetectable viral load after early ART - 18 months of treatment commencing 30 hours after delivery - but recently relapsed after 27 months testing HIV-negative without ART), the two ‘Boston patients’ (initially thought to cleared of HIV infection following bone marrow transplants but later relapsing), Timothy Ray Brown (the ‘Berlin patient’ - who no longer requires ART following bone marrow transplantation in 2007 and 2008 with donor cells deficient in a co-receptor

called CCR5) and the VISCONTI cohort (14 French patients given ART soon after becoming infected with HIV and achieving a sustained “functional cure”, with no HIV viral rebound despite ARVs no longer being taken), were frequently mentioned. These seminal cases present opportunities to advance our understanding of potential ways to access the small amount of HIV retrovirus that remains integrated with host cell DNA, even in patients that are well-controlled on ART.

Focus on the here and now

There are many tools available for the prevention and treatment of HIV available now. This is especially the case in Australia, where many of the legislative, logistics and cultural barriers to effective HIV control that exist elsewhere are absent, or at least far less significant than in other parts of the world. Through working with sectors outside of health and using a pragmatic approach to provide information to those most at risk of acquiring HIV without prejudice, the incidence of HIV in Australia can be reduced with the array of scientific strategies that are currently available.

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285 **Table 1: Approaches using ARVs to reduce the risk of HIV infection.**

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Preventative strategy	**Currently available in Australia?**	**Description**	**Suggested further reading (accessible by typing title into web browser).**
Treatment as prevention (TasP)	Yes	Early treatment of HIV-positive patients with ART was shown to reduce the risk of sexually transmitting HIV to a seronegative partner by 96% amongst an almost exclusively heterosexual cohort, in early results of the HPTN-052 trial (5). The two arms of this study compared; 1) the HIV-positive partner starting ART with a CD4 count between 350-550 cells/mm^3, and 2) the HIV-positive partner starting treatment when the CD4 count fell	Australasian Society for HIV Medicine. 2014 DHHS guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents with Australian commentary. Darlinghurt, NSW: 2014.

		below 250 cells/mm^3 or if AIDS-related illness developed. The ongoing PARTNER study has also shown the potential of TasP, this time looking and serodiscordant heterosexual and homosexual couples where the HIV-positive partner is already virally suppressed on ART (6). Promising preliminary results for this study were presented at the Conference on Retroviruses and Other Infections (CROI) 2014 (7). There remains uncertainty regarding when exactly to start ART for HIV-positive patients and recent Australian-adapted guidance on this is provided in the further reading column. TasP reduces but does not eliminate the risk of HIV transmission and should be combined with other HIV prevention strategies such as correct	

		and consistent condom use and safe injecting practices. The Australian, “Opposites Attract” study aims to test the efficacy of TasP amongst serodiscordant homosexual couples and is currently recruiting in Sydney, Melbourne, Brisbane, Cairns and Canberra.	
Post-exposure prophylaxis (PEP)	Yes	People that have potentially been exposed to HIV (through sexual contact, needle-stick injury etc.) can be offered a 28-day course of ARVs. The decision to offer PEP and regimen prescribed is based on the type of exposure and the risk of the source being HIV-positive, if the HIV status of the source is unknown. PEP must be commenced within 72 hours of exposure.	Australasian Society for HIV Medicine. Post-exposure prophylaxis after non-occupational and occupational exposure to HIV: national guidelines. Darlinghurt, NSW: 2013.
Prevention of	Yes	ART can significantly reduce the likelihood of	State Government of Victoria, Better Health

mother-to-child transmission (PMTCT)		HIV transmission to a baby from a HIV-positive mother. Not all ARVs are safe in pregnancy and dosing regimens can vary depending on the situation, specialist advice should be sought. Mother-to-child HIV transmission is very rare in Australia, with an average of one case per year over the past decade (1). The further reading references material aimed at consumers with links to other resources.	Channel. HIV and women - having children [web resource]. Melbourne, Victoria: 2014.
Oral pre-exposure prophylaxis (PrEP)	No	Refer to main text for more in-depth discussion.	

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