Highlights of the International Congress on Drug Therapy in HIV Infection, 23–26 October 2016, Glasgow, UK

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Introduction

Jürgen Rockstroh

The 2016 International Congress on Drug Therapy in HIV Infection brought together HIV clinicians, patient advocates and further stakeholders in the HIV research space to address new developments and innovations in therapeutic strategies and research impacting on the management of HIV infection. Although significant progress has been made and, for most HIV patients, if combination antiretroviral therapy (cART) is started early enough normal life expectancy can be achieved, there are still a number of challenges that accompany lifelong drug therapy. Also, new tools for prevention of HIV remain a hot topic in order to further curb the epidemic. Therefore, clearly the HIV cure agenda remains of utmost importance and was the focus of the opening lecture delivered by Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases [1]. Cure research has accelerated greatly over the past few years in two areas. The first is the prospect of eradicating the HIV reservoir altogether, i.e. a classic cure, which might involve novel latency-reversing and immunotoxic regimens, and gene editing techniques to create a host cellular environment that does not allow HIV replication. The second approach is the possibility of controlling HIV after stopping cART without eradicating the virus, which more recently has turned into a popular new area of research. In this context, he presented results from a study of an antibody against the cell receptor alpha 4 beta 7 integrin, the homing receptor for CD4 T cells. In this study, monkeys infected with the simian version of HIV were treated using antiretroviral therapy. They were then given the antibody, and treatment was discontinued. Almost 2 years later, the monkeys still had replication-competent virus but they had no viraemia. Although the exact mechanism of these findings remains unknown, these exciting results clearly inspire further research in this area.

Further important topics were tools that are available for ending the HIV epidemic. Treatment as prevention was covered by Julio Montaner, and new technology-based service-delivery models by Tarandeep Anand [2,3]. A special focus was on pre-exposure prophylaxis (PrEP), as PrEP with TDF/FTC recently became registered in Europe, but is still not financed in most European countries. Feedback from France and the US shows an increasing uptake of PrEP with continued good efficacy. Whether the risk for other sexually transmitted infections (STI), such as syphilis or acute HCV infection, increases over time will need to be further investigated. Of note, there are considerable disparities in the uptake of PrEP between black and white men who have sex with men (MSM) in the US, suggesting that the most vulnerable patient groups still have restricted access to PrEP at present. Pharmacological studies in a population at high risk of STIs, who cannot yet access PrEP, from the NHS in the UK, demonstrated convincingly that concentrations of TFV and FTC in generic formulations purchased over the internet were similar to those on the original formulation by Gilead [4].

Various sessions were devoted to HIV and ageing. These included the transition from HIV-infected children and infants to adult care (see summary by Pablo Rojo), as well as the complexities of medical care in adult HIV patients with increased risks of age-related conditions, such as fractures, cardiovascular disease, high blood pressure and diabetes. Indeed, as it is estimated that 50% of HIV-infected patients in Europe and the US will be above 50 years old by 2020, this is of growing concern. In this context, development of a new tenofovir formulation (tenofovir alafenamide), which appears to be less likely to cause bone mineral density changes or tubular toxicity compared with the former tenofovir fumarate formulation, was of interest, and discussed in the context of switch studies, which were presented here at the Glasgow conference for the first time [5,6]. In addition, the new European Aids Clinical Society (EACS) Guidelines were presented and discussed, which offer the advantage of a large section on comorbidity management, which is extremely helpful in clinical practice [7]. Overall, the management of these complex comorbidities requires a multidisciplinary approach to best take care of ageing HIV-infected individuals.

Finally, a large number of presentations covered new treatment strategies as well as new antiretroviral drugs in development. This included simplification strategies that looked at maintenance strategies with just one nuclease reverse transcriptase inhibitor (NRTI) (mostly 3TC) and a boosted protease inhibitor (PI), which may allow for improved safety and reduced treatment costs, or monotherapy with dolutegravir, which so far is believed to have a higher genetic barrier than other integrase inhibitors and may allow for a one-drug-only treatment option [8,9]. Indeed, no significant difference in rate of virologically suppressed patients was noted for the 3TC/PI/r arm, whereas some virological failures were observed in the dolutegravir-only maintenance study, which clearly emphasises that this strategy should not be employed outside of clinical trials at present. New data on new drugs or formulations included a subgroup analysis from the ONCEMRK trial that compared a new once-daily formulation of raltegravir with the old, twice-daily formulation, demonstrating comparable efficacy results independent from baseline CD4 cell count or viral load [10], and a subgroup and safety analysis from the new HIV1 attachment inhibitor BMS-663068, which continues to be developed by ViiV [11,12]. At week 96, virological response was generally similar for BMS-663068 and ATV/r in treatment-experienced subjects, regardless of sex, age, race, baseline viral load (VL) or baseline CD4 T cell count. BMS-663068 was generally well tolerated, with no BMS-663068-related AEs leading to discontinuation. This new drug remains of interest particularly for patients with multiple prior virological failures and extensive drug resistance as it offers the benefit of a new mechanism of action.

In conclusion, the Glasgow congress succeeded once again in providing an open forum where the ongoing challenges in HIV care and research were presented in excellent state-of-the-art

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lectures, discussed in great detail and hopefully will help to further improve HIV care overall.

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Treatment as prevention (TasP): from a research hypothesis to a new global target and beyond

Julio Montaner

In 1996, combination antiretroviral therapy (cART) revolutionised the treatment of HIV/AIDS [13]. Within a year, marked decreases in HIV/AIDS-related morbidity and mortality in British Columbia (BC) were documented, with a concomitant decrease in new HIV infections, despite rapidly increasing syphilis rates. Subsequent studies led to the conclusion that cART was exerting a previously unrecognised effect on preventing HIV transmission. Treatment as Prevention (TasP) came to characterise the triple impact of cART on markedly decreasing: (1) progression to AIDS; (2) premature mortality; and (3) HIV transmission. In 2006, we proposed that expanding cART coverage to all individuals living with HIV could stop the HIV/AIDS pandemic [14]. Subsequently, we reported on the effectiveness of TasP® in BC [15]. In brief, between 1996 and 2012 we saw an 80% decrease in HIV morbidity, an 80% decrease in AIDS-related deaths, and a 66% decrease in new HIV diagnoses in association with a major increase in cART coverage.

More recently, HIV Prevention Trials Network 052 (HPTN 052) confirmed cART is over 95% effective in preventing sexual transmission among serodiscordant heterosexual couples [16], and this effect was sustained over 5 years [17]. Additionally, the PARTNER Study confirmed TasP was similarly effective in the context of hetero- and homosexual sex [18]. Separately, two large prospective studies (TEMPRANO and INSIGHT START) confirmed the clinical efficacy of immediate versus delayed cART in preventing disease progression to AIDS or premature death [19,20]. Taken together, these results have allowed a global consensus to emerge in support of TasP. In 2015, immediate initiation of cART regardless of CD4 cell counts became the new standard of care, globally [21].

In 2014, under the auspices of UNAIDS, we proposed a TasP-inspired 'Ambitious Global Target for HIV Treatment', currently known as the UN 90-90-90 Target [22], aimed to bring about the end of the AIDS pandemic. The UN 90-90-90 Target proposes that by 2020, at least 90% of HIV-infected people should know their status, at least 90% of them should be on cART, and at least 90% of them should achieve sustained plasma viral load suppression. Meeting the UN 90-90-90 Target by 2020 would lead to a 90% decrease in AIDS-related deaths by 2030 and a 90% decrease in new HIV infections by 2030. Earlier this year, the UN 90-90-90 Target was ratified by UN member countries [23].

Importantly, TasP has the potential to be highly cost-effective and cost-saving [24–27]. Specifically, the effect of TasP on decreasing HIV transmission acts as a multiplier of the return-on-investment. The success of HIV-TasP has generated substantial enthusiasm regarding the expansion of the strategy to other contagious diseases, such as hepatitis C [28]. Additionally, preliminary work is currently exploring the role of TasP in the management of non-infectious, contagious, high-burden diseases, where there is evidence of 'social contagion' (i.e. any condition where increased prevalence is associated with increased incidence through behavioural contagion [29], such as smoking, addiction, or obesity-related diseases) amenable to modification through optimised management. As such, HIV-TasP provides a road map for HIV/AIDS control, as well as the basis for a novel targeted disease elimination strategy aimed at controlling contagious (infectious and non-infectious) diseases to promote healthcare sustainability.

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Transition of HIV-positive children to adult care

Pablo Rojo

The paediatric HIV epidemic in Western Europe started in the early 1980s. In Spain, the epidemic peaked in the late 1980s and early 1990s because of the heroin wave in young adults that swept the country, which led to a large number of children being infected by mother-to-child transmission. Over 60% of those children died before reaching the age of 5 when no antiretrovirals were available, but those who survived were saved by the appearance first of AZT monotherapy, then dual therapy, and finally the combined antiretroviral therapy. These patients, and those who came afterwards, are now adults and have been, or continue to be, transferred to HIV adult units.

The decision about when to make the transition to adult units has to be taken by the paediatrician in collaboration with the adult physician, and with the agreement of the patient and the family. The age of the patient, but also the maturity and the personal independence of the adolescent or young adult, must be taken into account. Transition is a process that starts in the paediatric unit for the patient; steps towards becoming independent from their parents in the clinic include: taking care of their disease and their medication, being able to schedule or reschedule their medical appointments, maintaining punctuality and being responsible for the pharmacy refills.

HIV vertically infected adolescents are very different to those who were infected horizontally. The former have been living with the infection throughout their entire life and have probably had opportunistic infections, multiple antiretroviral therapies and medical side effects, whereas the latter, probably, have not.

However, it is also important to notice the difference between the individuals who were infected before or after the availability of combined antiretroviral therapy, because they may suffer from quite different diseases. A significant proportion of the former have suffered some, or many, opportunistic diseases, the most important being HIV encephalopathy, and these illnesses will have left long-term sequelae. Children who suffered HIV encephalopathy during childhood are now around, or just over, 20 years of age and suffer from spastic diplegia and from some stage of neurocognitive impairment. The children who had the infection before 1996–1998 also have a significantly higher proportion of resistance mutations or even triple-class resistance mutations mostly related to non-optimal therapies such as mono- or dual-antiretroviral regimens or the use of the non-boosted nelfinavir. Also, patients in Spain come mainly from socially limited families, with a significant proportion of those families having lost at least one parent.

In summary, transition to adult care is a process for the adolescent or young adult. The characteristics of that patient will mainly be driven not only by the method of infection but also by the year in which the infection occurred.

Technology-based service-delivery models

Tarandeep Anand

In Thailand, where almost half of new HIV infections occur in men who have sex with men (MSM) and transgender women (TGW), a mere 29% of these populations have received HIV testing [30]. Knowing that Thai MSM and TG women have the highest internet and technology utilisation [31], the Thai Red Cross AIDS Research Centre (TRCARC) launched 'Adam's Love' (www.adamslove.org), the first technology-based sexual health initiative in Asia for MSM and TGW [32] in 2011. It has gained over 3 million unique visitors since then and has e-counselled and referred more than 25,000 clients to relevant clinical services.

In December 2015, Adam's Love extended its function to provide 'online HIV testing' as part of amfAR GMT implementation science research. MSM and TGW can opt to receive conventional HIV testing and counselling, or receive online counselling and private clinic-based testing (Hybrid arm), or have a finger-prick HIV testing kit and receive online supervised self-testing support and counselling (eHTC arm) through secured and live video chats with counsellors. Preliminary data demonstrate that the technology-supported eHTC model has a high potential to engage less frequent and first-time testers, and demonstrates trends towards better reaching HIV-positive, discreet MSM and TGW groups [33].

Thailand is among the first countries to launch pre-exposure prophylaxis (PrEP) programmes for key populations. To support free PrEP access and optimise PrEP uptake among MSM and TG through TRCARC's Princess Soamsawali PrEP program, Adam's Love piloted its novel Online-to-Offline (O2O) model [34]. O2O uses targeted online PrEP promotions, e-counselling and real-time risk assessment, with linkage to offline PrEP services using an electronic booking system. From January to April 2016, 325 clients (76.5% of clients who made online bookings and received e-tickets) accessed offline services and 168 initiated PrEP. At enrolment, 105 (79.5%) participants believed they were likely or extremely likely to be adherent to daily PrEP, but only 13 (9.8%) reported daily adherence at 1-month follow-up. A technology-based reminder intervention personalised for content, timing and delivery platform was phased in to optimise the PrEP cascade and daily adherence increased to 83% post 1-month intervention. Personalised reminders are seen as engaging, non-intrusive, effective in achieving optimal PrEP adherence, and highly desirable to sustain future adherence (Figure 1). In addition, an electronic Directly Observed Therapy (e-DOT) study using live videos for supporting PrEP adherence is under way.

To facilitate early linkage, support adherence and retention among HIV-positive young MSM and TG, Adam's Love 'We Care' intervention allows users to get real-time online counselling through already popular platforms, sign up for personalised ART, clinic visit reminders, and report their daily medication-taking behaviour. Users earn points when they use these features, which they can redeem for incentives such as portable pillboxes and t-shirts.

The question is not whether technology can help, but whether we have harnessed technology to its potential. Technology-based approaches are plausible, scalable and desirable, and there is evidence to believe that they work. To end AIDS among arguably the most connected population, technology is to play a pivotal role and its integration in service delivery has to be one of the most fundamental global approaches.

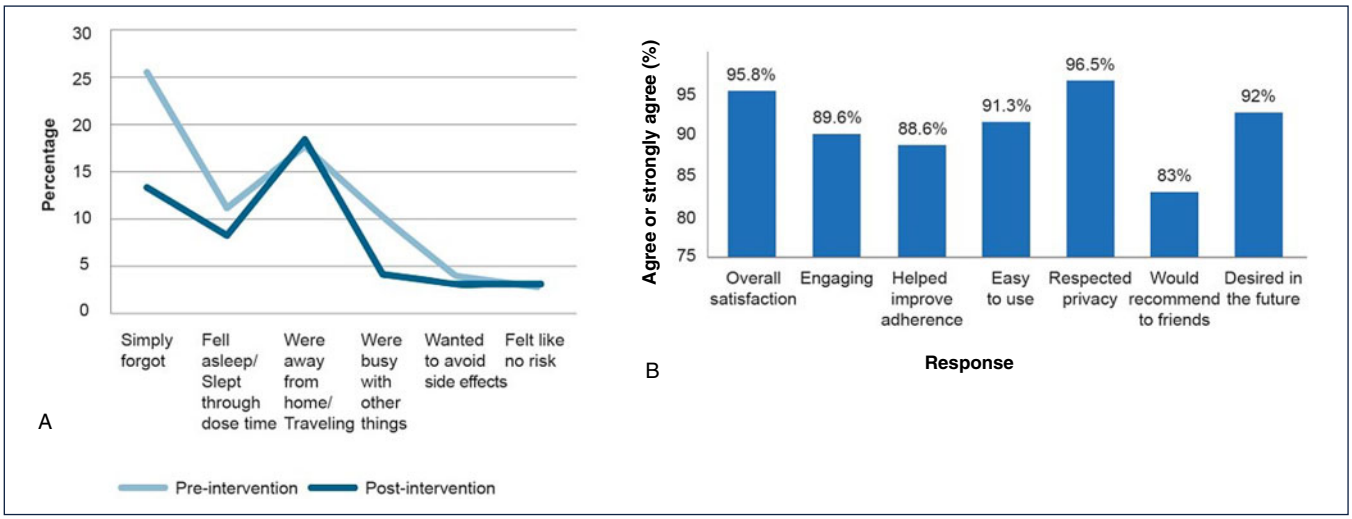

Figure 1. (A) Reasons for ever having missed PrEP dose pre- versus post-intervention. (B) Personalised PrEP adherence reminder intervention satisfaction: participants' ratings.

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