

Highlights from the 24th Conference on Retroviruses and Opportunistic Infections

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Abstract

From the 13th to 16th February 2017, researchers from around the world convened for the 24th annual *Conference on Retroviruses and Opportunistic Infections* (CROI) at the Washington State Convention Center in Seattle, Washington. The conference was organised by the International Antiviral Society-USA (IAS-USA) in partnership with the CROI Foundation. The conference included over 1000 oral and poster presentations of peer-reviewed original research as well as lectures and symposia featuring insights from leading basic, translational and clinical researchers. Highlighted here are key data presented at the conference.

Keywords: HIV, eradication, reservoirs, T cells, opportunistic infections, hepatitis C

Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) was established in 1993 and has grown to become the pre-eminent HIV research meeting, providing a forum for researchers from all disciplines and from around the world to share and discuss cutting-edge HIV research. This year, the conference featured 905 poster presentations and 96 oral presentations of peer-reviewed, original research. International experts presented lectures and participated in symposia addressing many aspects of HIV pathophysiology, prevention, management and eradication. This report summarises some of the major findings presented at the conference.

HIV prevention

Pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine continues to expand rapidly as an HIV prevention method for men who have sex with men (MSM) and other high-risk populations. This year's conference included the first report of transmission of wild-type HIV in a man with good PrEP adherence [1]. The research team from Amsterdam reported that the man had been taking PrEP with good adherence for 8 months when he experienced seroconversion with both an indeterminate HIV antibody test and Western blot, and negative HIV RNA. PrEP was stopped over concerns about inducing potential resistance, and within 3 weeks HIV RNA became positive with wild-type virus, demonstrating no genotypic evidence of drug resistance to tenofovir/emtricitabine or other antiretroviral therapy (ART). Tenofovir levels on dried blood spot were consistent with daily dosing. During the 8 months he was on PrEP, the man reported condomless anal sex with a median of three to five sex partners per day, and up to 75 different sex partners per month. He also reported frequent drug use, including amphetamine, cocaine, GHB/GBL, mephedrone and ketamine. The authors speculated that

HIV transmission might be attributable to an extremely high rate of sexual exposure with potential mucosal damage. They also hypothesised that lower levels of PrEP drugs in the rectal mucosa than in the blood could have contributed to the transmission.

Retail pharmacies as service delivery points were evaluated in two studies. In Seattle, a community pharmacy started by 245 individuals (84% MSM) on PrEP and had 75% retention at 1 year [2]. The model was cost-effective, recouping start-up costs within 9 months. In Virginia, HIV testing was added to existing laboratory services as part of a public/private partnership in a network of 32 retail pharmacies [3]. In 2 years, 3221 HIV tests were performed, of which 25 (0.8%) were positive. Many of those tested (46%) and most of those with positive results (64%) were first-time testers with the majority of testing (61%) being performed outside business hours.

Empirical evidence that combination HIV prevention can be effective at reversing generalised epidemics came from the well-studied Rakai region in Uganda, where, by 2016 scale-up of medical circumcision, ART and viral suppression among those on ART had all achieved levels of 60–75% [4]. From 2012 to 2016, HIV incidence declined by 41%.

Antiretroviral therapy

A few years ago, there was a feeling that ART development was slowly coming to an end. This was refuted once again at CROI with a rich pipeline of medications in development, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs), and capsid inhibitors, the latter of which represent a new class of drugs. HIV-specific broadly neutralising monoclonal antibodies were also highlighted this year for their potential roles in both prevention and treatment of HIV.

Long-acting (LA) preparations are one of the most exciting recent developments in ART and they were featured prominently at CROI. They have the potential to simplify regimens and facilitate adherence to therapy, thereby increasing virological suppression rates and

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potentially decreasing the development of drug resistance. Charles Flexner from Johns Hopkins University provided an extensive review of agents being developed for LA therapy, including novel agents as well as reformulations of existing antiretroviral medications in order to extend their half-life [5]. Agents discussed included, in Phase I: EFda-MK8591; in Phase II: ibalizumab, PRO-140, albuviride and broadly neutralising antibodies such as VRC01-LS, 3BNC117, and 10-1074; and in Phase III: cabotegravir-LA and rilpivirine-LA. Implants have been developed using tenofovir alafenamide (TAF), which allow the drug to be released very slowly over a prolonged period of several months. The implant with the new NRTI MK-8591 (EFda) also produces prolonged drug levels. These implants can be removed in case of toxicity.

Dr Flexner also described how nanoformulation can be used to extend drug half-life, and this approach has been taken in the development of LA versions of tenofovir (TDF), lopinavir (LPV), ritonavir (r) and also in the case of dolutegravir (DTG) with a mixed lineage kinase-3 inhibitor, URM-099. Additionally, oral nanoformulations of efavirenz (EFV) and LPV could potentially reduce the dose of drugs and lead to lower costs [6]. Uptake of drugs in lymph nodes is also enhanced by these nanoformulations.

At an early stage of development, researchers described a new class of compounds with an untouched target: the HIV capsid, which plays a role at several stages of the virus life cycle [7]. One compound, GS-CA1, looks particularly promising due to some of its characteristics such as high potency (EC₅₀ of 140 picomolar), stability, low clearance and good resistance profile and could be used as an extended-release parenteral formulation for LA treatment. A new PI, GS-PI1, with the potential for once-a-day administration with an absence of boosting, was described at an early stage of development [8]. This novel compound displayed potent inhibition of HIV replication *in vitro* with less than two-fold reduction in potency in the presence of major protease inhibitor resistance-associated mutations.

GS-9131, a monamide prodrug of the nucleotide analogue GS 9148 has activity against NRTI-resistant strains, in subtypes A, B, C, D, E, F, group O and N and also against HIV-2 and is not affected by reverse transcriptase mutations such as K65R, L74V, M184V or their combination, and has a potential for once-daily dosing [9]. Bictegravir (BIC) is a new potent and unboosted INSTI with *in vitro* activity against wild-type and most INSTI-resistant variants. It has shown more than a 2-log decrease in a 10-day study [10]. When comparing BIC to dolutegravir (DTG) with FTC/TAF for initial therapy in ART-naïve individuals (almost all male, median CD4 cell count around 450 cells/mm³), in a Phase IIb double-blind, randomised trial, this new integrase inhibitor has shown a high rate of viral suppression (<50 copies/mL=primary end-point) at 48 weeks, e.g. 97% vs 91% for BIC and DTG, respectively, with no emergence of resistance through week 48, and good safety and tolerability for both compounds. There are four Phase III, fully enrolled, ongoing clinical trials assessing safety, efficacy and tolerability of the compound.

Among the agents in a more advanced stage of development is doravirine (DOR), which is a next-generation NNRTI with *in vitro* activity against wild-type virus as well as virus with many common NNRTI-resistance mutations (K103N, Y181C, G190A, K103N/Y181C and E138K). It also demonstrated a superior neuropsychiatric profile when compared to efavirenz in a Phase IIb trial. Presented at CROI were the results of a Phase III treatment-naïve trial (DRIVE-FORWARD) with TDF-3TC/ABC-3TC background plus DOR or darunavir/ritonavir (DRV/r) [11]. This study showed non-inferiority of DOR at 100 mg as a once-daily regimen on the primary end-point (VL<50 copies/mL, 84% vs 80% for DOR and DRV/r, respectively). Side effects were similar between arms. Discontinuation rates were quite high (DOR of 15% and DVR/R of 19%), which authors speculated could have been caused by the high-pill burden of these

regimens. Doravirine showed a superior lipid profile as compared to DRV/r (fasting LDL-C and non-HDL-C) and a low rate of development of drug resistance.

Two Phase III, randomised, multicentre, open-label, parallel group and non-inferiority studies (SWORD 1 and 2) have demonstrated that the switch to a two-drug regimen, DTG and rilpivirine (RPV) in virologically controlled individuals on INSTI, NNRTI or PI + two NRTIs maintained virological suppression (<50 copies/mL) through 48 weeks with a neutral effect on lipids and was as effective as a 3–4 drug combination [12].

In the case of multi-resistance and limited treatment options, there was a very interesting presentation on ibalizumab, a humanised monoclonal antibody that blocks HIV entry into CD4 T lymphocytes [13]. It is a long-acting compound in Phase III development for the treatment of multi-drug resistant HIV infection by IV administration. The 24-week data from TMB-301, an open label study that recruited 40 individuals with very resistant virus and administered a loading dose of ibalizumab 2 g and then 800 mg every 2 weeks with an optimised background for 24 weeks, showed mean viral load change from baseline of $-1.6 \log_{10}$ copies/mL and virological suppression to below 50 copies/mL was achieved in 43% of individuals. More than a 1-log decrease in viral load was observed in the first 2 weeks while on monotherapy only. Interestingly, the pharmacokinetic profile of bi-weekly ibalizumab 800 mg administered IM was comparable to the profile of IV administration [14].

Recognising the anticipated expansion of INSTI use in sub-Saharan Africa, data from two observational cohort studies were presented that suggested an association between INSTI use and an increased risk of immune reconstitution inflammatory syndrome (IRIS). In the 144-week SINGLE trial, first-line DTG-based ART showed improved tolerability compared to efavirenz, but no benefit in terms of preventing virological failure [15]. Thousands of individuals in Botswana have already started DTG as part of their initial regimens for HIV infection. IRIS occurs most often during first-line ART initiation and, since INSTIs suppress HIV RNA levels more quickly than other antiretroviral drug classes, the resulting rapid recovery of immune function could cause immune reactions to existing infections, often with severe effects. In a Dutch cohort study, IRIS was either diagnosed by a clinician or classified by the French 2004 definition based on the observation of atypical tumour or opportunistic infection accompanied by viral load decline or CD4 increase [16]. Utilising these definitions, researchers found that 38% of those who started ART with an INSTI and 16% of those starting any other treatment regimen, developed IRIS. After adjusting for other factors, participants prescribed INSTIs were more likely to develop IRIS as compared to participants prescribed other ART (odds ratio 3.25, 95% confidence interval [CI] 1.83–5.80). In a French cohort study, severe IRIS leading to hospitalisation developed in 3% of individuals in the INSTI group versus 1.5% in the non-INSTI group, yielding a relative risk for IRIS of 1.99 (95% CI 1.09–3.47) with INSTI-based ART [17]. IRIS was most frequently related to tuberculosis, *Mycobacterium avium* complex, and progressive multifocal leukoencephalopathy.

HIV eradication

The most discussed mechanism of HIV-1 reservoir persistence in individuals on ART was the clonal proliferation of cells harbouring the replication-competent proviral HIV-1, addressed in the themed discussion 'HIV persistence: clones, clones, and more clones'. Guinevere Lee showed that only 7% of the HIV-1 DNA sequences were genome-intact, where the defective genomes had large deletions and APOBEC3G/3F-associated hypermutations [18]. Th1-polarised cells were found to harbour the highest proportion

of genome-intact HIV-1 sequences with indication of clonal expansion. Furthermore, Bonnie Hiener demonstrated clonal expansions of cells with intact proviruses and identified effector memory T cells (T_{EM}) as the reservoir containing the highest proportion of intact proviruses, demonstrating the importance of targeting these cells in future eradication strategies [19]. In addition, Zheng Wang proposed T cell activation and homeostatic cytokines as potential mechanisms that induce the proliferation of CD4 T cells carrying replication-competent HIV-1 [20].

Different research on HIV proteins and cellular RNAs was presented within the selected themed discussion 'Virus and cell RNA in HIV replication' and the symposium 'Creating and destroying HIV capsids'. First, Edmund Osei-Kuffour introduced a new host protein (USP18) to abrogate SAMHD1 functioning in Tamm-Horsfall Protein 1 (THP-1) macrophage-like cells and upon overexpression resulting in increased HIV infection [21]. Secondly, Wim Trypsteen highlighted the importance of long non-coding RNAs in HIV infection in transcriptome-wide screening during the different stages of the HIV replication cycle, advocating further study of these molecules [22]. Also, several structural imaging studies (Cryo-EM) were presented focusing on the mature and immature HIV capsid (CA) to understand the process of maturation. In this context, the completed structure of SP1-CA was elucidated by Hans-Georg Kräusslich and it was repeated that mature CA performs all of its functions after cell entry and acts as a transport module and reaction container for HIV genome replication [23]. Other work by Barbie Ganser-Pornillos visualised the mode-of-action of TRIM5 α in CA degradation. Upon viral entry, TRIM5 α forms a 2-D hexagonal net over the CA and signals it for ubiquitin-dependent downstream processes that lead to viral inhibition and interferon signalling [24].

The use of gene therapy was discussed by Carl June in the plenary 'Advances in cellular therapy in cancer and HIV' [25]. Chimeric antigen receptor (CAR) technology has diversified in the last decade from engineered T cells with CAR of CD4 linked to the CD3 ζ signalling chain to the use of broadly neutralising antibodies (bNAb) CAR, stem cells and HIV-resistant cells through CCR5 gene editing. These showed promises in cell line or murine models and the field awaits human data.

In the oral abstract session 'HIV persistence and reactivation', Jeffrey Murry demonstrated the potency of TLR7 agonist GS-9620 to increase the immune-mediated clearance of HIV-infected cells isolated from ART-suppressed individuals *in vitro*. GS-9620 stimulated both HIV production by infected CD4 T cells and their elimination by cytolytic CD8 T cell activation or improved killing by an effector antibody, indicating its potential within the therapeutic vaccines or bNAbs [26].

Clinical studies of HIV cure

The topic of HIV cure featured prominently at CROI 2017. Jintanat Ananworanich, in her plenary session outlined the major strategies that may potentially contribute to viral control and the reduction of the latent HIV reservoir, including the early initiation of ART, the use of latency-reversing agents (LRA), and immune and gene therapies [27]. She also presented data on the impact of early ART initiation in participants who initiated treatment during Fiebig I in Bangkok, Thailand [28]. In this study, eight participants (seven male, one female) who had been virologically suppressed for a median of 2.8 years underwent intensively monitored ART pause (IMAP). Despite undetectable total HIV DNA and inducible HIV RNA in all participants prior to IMAP, all experienced viral rebound with a median time to rebound of 26 days. A pre-IMAP CD4/CD8 ratio ≤ 1 predicted time to viral rebound ($P=0.004$). IMAP was safe, with no participants developing symptoms consistent with an acute retroviral syndrome, new resistance mutations or treatment failures after ART resumption.

Importantly, Beatriz Mothe shared results of a trial of therapeutic vaccination and administration of a latency-reversing agent in a rollover from the BCN01 study. Investigators showed a manipulation of the CTL immunodominance pattern and viral control in some of the participants in this study, in which 13 early-treated individuals stopped ART after immunisation with MVA.HIVconsv vaccine, followed by three, weekly doses of romidepsin and by a second MVA.HIVconsv vaccination. To date, five participants remain off ART after 7, 12, 14, 22 and 28 weeks, respectively [29]. In addition, the data presented by Julie Mitchell suggested that plasmacytoid dendritic cells (pDC) and non-classical monocytes were sensing viral replication after stopping ART and might represent biomarkers prior to viral rebound [30]. They observed increased levels of pDC, non-classical monocytes and surface expression of PD-L1 and CD69 on pDCs prior to viral rebound.

The use of bNAbs in inducing HIV remission was discussed by Michel Nussensweig [31]. Passive infusion of bNAb is associated with HIV viral load reduction [32,33] and delayed time to viral rebound [34,35], but also loss of efficacy due to the development of escape mutants. In data presented at CROI by Sharon Riddler, 40 participants with chronic HIV infection on ART with viral suppression were randomised to either two or four infusions of VRC01 at 40 mg/kg [36]. Although these were safe and well-tolerated, no significant impact was made on the HIV reservoir as measured by plasma single-copy HIV-RNA, cell-associated HIV RNA/DNA, or stimulated virus production from CD4 T cells. Postulated mechanisms for the lack of response included viral resistance to VRC01, poor penetration of VRC01 to sites of virus replication, or inherent inability of VRC01 to clear virus particles or virus-expressing cells.

Despite the single described case of HIV cure having occurred in the setting of bone marrow transplantation (BMT) over 10 years ago, this outcome has yet to be replicated [37]. In the Boston individuals, despite the disappearance of a measurable reservoir of latent HIV infection after BMT, HIV rebound was observed after ART was stopped [38]. At CROI, new studies were presented to improve our understanding of transplantation and HIV. Kobus Bosman presented findings from IciStem, the largest multinational collaborative study investigating the potential for HIV cure in HIV-infected individuals requiring allogeneic stem cell transplantation for haematological disorders [39]. Despite undetectable HIV-1 DNA in peripheral blood mononuclear cells (PBMCs) of 11 HIV-infected individuals who underwent transplantation with stem cells carrying the CCR5 $\Delta 32$ mutation, HIV-1 DNA persisted in tissues such as the ileum, liver, spleen, lung, bone marrow and lymph node.

It has been postulated that selecting donors who enable the establishment of full donor chimerism, and have the right natural killer (NK) cell genetics to kill donor haematopoietic cells infected with HIV, would eradicate HIV reservoirs formed post-transplant [40]. At CROI, Adam Capoferri described HIV persistence in a patient who achieved full donor chimerism in peripheral blood after allogeneic BMT, with HIV measurable in resting memory CD4 T cells by droplet digital PCR (ddPCR), quantitative PCR (qPCR) and viral outgrowth assay [41]. Similar findings were reported by Alyssa Martin, who described inducible HIV-1 latent reservoirs after HIV donor-positive and donor-negative solid organ transplantation [42]. Latent reservoirs were measured using a novel quantitative viral induction assay (QVIA) pre- and post-transplantation in 17 HIV-infected recipients who were maintained on ART. Further research is needed to determine the impact of immunosuppressive or conditioning regimens on HIV reservoirs, whether HIV reservoirs post-transplantation are being expanded via infection of donor cells and/or clonal expansion of donor/recipient-infected cells, and also to determine the optimal timing for ART cessation post-transplantation in order to potentially demonstrate HIV remission.

Hepatitis C virus

Whilst there are few new drugs coming through the pipeline for treating hepatitis C virus (HCV), the challenge of implementing HCV cure strategies is beginning to emerge with data from real-world cohorts of patients treated with directly acting antivirals (DAAs). Anne Boerkamps presented experience from the Netherlands of treating HCV in HIV co-infected patients [43]. DAAs with pegylated interferon (pegIFN) and ribavirin were made available for HIV/HCV co-infected patients with F3/F4 fibrosis in 2014. By 2016, there was a national decision to make DAA-based therapy available for all HIV/HCV co-infected patients regardless of fibrosis stage. The cohort studied included 98% of HIV-infected patients in care nationally, including 1400 HIV/HCV co-infected individuals, of whom 1100 had received HCV treatment by January 2017. Of those who had received treatment, 829 (59.3%) had successfully cleared the virus, 94 (6.7%) were still on treatment and 197 (14.1%) had failed therapy. Of the 300 individuals who had not received HCV treatment, most were either current injection-drug users, had poorly controlled HIV infection, or were refugee females poorly engaged in care.

Laurent Cotte presented similar data from the DatAIDS cohort, representing 25% of HIV-infected patients in France [44]. In this French cohort, treatment was reported for more than 65% of all HIV/HCV co-infected patients in care by the end of 2015, with successful viral clearance in more than 60%. For those not able to access DAAs via national programmes, Andrew Hill reported data on viral clearance for 1150 individuals accessing DAAs via 'buyers clubs' in Australia, China, Russia and southeast Asia [45]. Generic DAAs were sourced from manufacturers in Bangladesh, India, Egypt and China. Sustained virological response rates 12 weeks after therapy were greater than 95% across all genotypes and fibrosis stages. Further data from the German Hepatitis C and Co-infection (GECCO) cohort showed an 11% HCV re-infection rate in MSM successfully treated for HCV with DAAs [46].

An epidemiological study in the Netherlands provided evidence for the concept that treatment as prevention (TasP) may be effective at decreasing the incidence of HCV infection [47]. Within 2 years after the introduction of DAAs in the country in 2014, 65% of Dutch HIV-infected MSM had initiated treatment and the incidence of acute HCV infection in the group had declined by 53%. Moreover, the decline in HCV incidence continued throughout 2016, and was 42% lower in the second half of the year compared to the first half. In contrast, syphilis rates increased during this period, suggesting a biological link between HCV treatment and reduction in new infections rather than temporal changes in risk behaviours.

There were two further datasets that gave important clues to the continued drivers of the HCV epidemic amongst HIV-infected MSM populations in Europe despite increasing access to unrestricted DAAs. Elske Hoornenborg presented data from Amsterdam showing that 4.8% of HIV-negative MSM enrolled on to an HIV PrEP programme were infected with HCV [48]. Phylogenetic analyses of the HCV NS5b sequences showed clustering with viruses obtained from HIV/HCV co-infected MSM in the Netherlands, suggesting transmission between HIV-infected and HIV-uninfected MSM groups. This suggests a reversal of the previously described sero-sorting risk behaviours and perhaps risk-compensation with increasing availability of HIV PrEP. Dominique Braun presented data from the Swiss HIV Cohort that, in preparation for an HCV TasP project amongst HIV-infected MSM, prospectively screened 3722 individuals for HCV with RNA testing between December 2015 and May 2016 [49]. Incident HCV infection was diagnosed in 17% of this cohort; 21% of whom were anti-HCV negative at the time of diagnosis, suggesting that transmissions could easily occur before HCV is diagnosed in routine care.

In summary, whilst access to treatment for HIV/HCV co-infected individuals is increasing across Europe, treatment coverage is far from universal. TasP for HCV appears to have reduced the incidence among the HIV-infected MSM population in the Netherlands, but data suggest that eradication of HCV in this group of individuals is going to require a concerted effort to capture undiagnosed HCV among HIV-infected and uninfected MSM, address cross-border transmissions, and provide early treatment with DAAs for all newly diagnosed individuals with HCV, while continuing to promote risk-reduction strategies to prevent new infections.

Sexually transmitted infections

Challenges and opportunities in sexually transmitted infections (STI) control were highlighted in an early symposium at CROI. Scott McClelland discussed the vaginal microbiome and susceptibility to HIV, building upon several prospective studies that have explored this relationship [50]. Emphasis was placed on the vaginal microbiota and its potential to impact HIV susceptibility through pathways including inflammation, immune mediators, HIV-inducing factors and disruption of structural barriers. New interest in biomedical interventions for STIs was discussed in the setting of increasing prevalence and incidence of STIs in PrEP users [51]. Periodic presumptive treatment in female sex workers with azithromycin has shown reduction in gonorrhoea and chlamydia but not syphilis or HIV and studies using doxycycline prophylaxis for MSM are ongoing. Matthew Golden showed that rates of syphilis in high-income nations have been rising since 2000 [52]. This poses a challenge for clinicians but also presents an opportunity for capitalising on the diagnosis to promote frequent HIV testing, PrEP and condom use. Finally, Rebecca Guy described technological advances in clinician point-of-care tests and self-testing at home that could facilitate STI diagnosis for both routine clinical care and research purposes [53].

Data from an STI post-exposure prophylaxis (PEP) sub-study of the IPERGAY trial of PrEP were presented by Jean-Michel Molina [54]. This study showed that a single oral dose of doxycycline 200 mg taken within 72 hours of condomless sex resulted in a 47% decline in STI incidence, including a 70% decline in *Chlamydia trachomatis* infections and a 73% decrease in syphilis cases. There was no significant effect on new *Neisseria gonorrhoeae* infections.

Opportunistic infections

A symposium emphasising TB and other opportunistic infections discussed a broad array of recent developments. Results from a multicentre diagnostic accuracy study of the Xpert Ultra illustrated higher sensitivity than the Xpert in smear-negative and HIV-infected individuals and improved accuracy for the detection of rifampin (RIF) resistance [55]. However, a limitation included detection of TB-DNA in some individuals with prior TB disease, leading to reduced specificity of the assay overall. Results from a previously published study assessing benefits of early ART and 6-month isoniazid prophylaxis (IPT) among HIV-infected adults in Côte d'Ivoire were expanded to include results on the efficacy of IPT in reducing long-term mortality [56]. These results showed that, in adults with high CD4 cell counts, 6-month IPT led to a 39% decrease in mortality, independent of ART initiation and baseline CD4 cell count. Finally, results of a randomised controlled trial of prednisone for prevention of paradoxical TB-IRIS showed that, in individuals at high risk of IRIS, prednisone during the first 4 weeks of ART reduced the risk of TB-IRIS by 30% and also reduced the need for corticosteroids to treat TB-IRIS by 53% [57].

New data on HIV-related cryptococcal meningitis were also presented at the Conference. The prevalence of advanced HIV disease and cryptococcal infection (CI) in Botswana was highlighted, emphasising that almost one in five inpatients with

a CD4 cell count <100 cells/ μ L had CI [58]. A Phase II, randomised, non-inferiority trial examining early fungicidal activity (EFA) of three short-course high-dose liposomal amphotericin B (L-AmB) schedules showed that single doses of 10 mg/kg L-AmB were well tolerated and lead to non-inferior EFA as compared to 14-day courses of 3 mg/kg L-AmB in HIV-associated CM [59]. Results are being taken forward to a Phase III clinical endpoint trial.

Ageing and inflammation

Judith S Currier from Los Angeles highlighted new insights into long-term complications of HIV infection during the preconference session for new investigators and trainees, including cardiovascular disease (CVD), non-AIDS cancers, osteoporosis, diabetes mellitus, frailty, cognitive disorders, chronic liver diseases, COPD and chronic renal disease. These non-communicable diseases still remain a persistent threat because of different individual risk profiles and insufficient interventions on traditional risk factors of diseases.

Leah T Le presented neuropsychological outcomes in a retrospective longitudinal analysis of the PISCES cohort in San Francisco [60]. In a multivariate analysis, change in blood CD4 to CD8 cell ratio was the sole parameter independently associated with NPZ4 score. The investigators concluded that CD4/CD8 trajectory can be used as a predictor of neurocognitive impairment even during early infection. Sarah Beth Joseph described a cross-sectional analysis of the THINC cohort, in which the prevalence of asymptomatic CSF escape was found to be 6.6% [61]. During this state of escape, there was no evidence of neuronal damage or inflammation. Dominique Costagliola presented data showing a 52% prevalence of cerebral small vessel disease (CSVD) diagnosed by MRI in volunteers with well-controlled HIV on ART [62]. Classical risk factors associated with CSVD were age and hypertension. The only HIV-related risk factor associated with increased risk of CSVD was a CD4 cell count nadir <200 cells/mm³.

Vincent Marconi analysed associations between bilirubin levels and cardiovascular events in the Veterans Aging Cohort Study [63]. After adjusting for classical cardiovascular disease (CVD) risk factors, higher bilirubin seemed to be associated with a lower risk of heart failure and acute myocardial infarction. Using data from the D:A:D study, Lene Ryom analysed the risk of CVD with use of modern ritonavir-boosted PIs, darunavir and atazanavir (ATV) [64]. After adjustment for confounding factors, cumulative use of darunavir, but not atazanavir, was associated with a small but gradually increasing CVD risk. Rosan van Zoest presented an individual-based model of CVD from the national ATHENA cohort in order to predict CVD and evaluate interventions [65]. According to this model, intensified monitoring and drug treatment of hypertension and dyslipidaemia will have the greatest impact on averting CVD events, preventing 17.0–20.0% of CVD cases annually. The next most impactful intervention was smoking cessation.

Leah Shepherd estimated cancer rates after smoking cessation in 39,701 HIV-infected participants in the D:A:D study [66]. Incidence of smoking-related cancers other than lung cancer rapidly declined following 1-year cessation. Lung cancer incidence appears to remain elevated in HIV-infected individuals even more than 5 years after smoking cessation.

Priscilla Hsue described IL-1beta inhibition using canakinumab (a human monoclonal antibody) in 10 HIV-infected and virologically suppressed individuals [67]. In this pilot study, a single dose of canakinumab significantly reduced inflammatory markers (IL-6, hsCRP and sCD163) and seemed to show a reduction of both arterial inflammation and bone marrow activity in FDG-PET/CT.

Prevention of mother-to-child transmission of HIV (PMTCT) and paediatric HIV

Issues for children with HIV and women who want to prevent their children from being infected with HIV were at the forefront of discussion (see CROI webcasts). There were two plenary presentations: 'The Emerging Potential for HIV Cure for Infants, Children, and Adults' by Jintanat Ananworanich [27], and '(Preventing) the Coming Epidemic: HIV in Youth' by Shannon Hader [68]. A highlight symposium presented on issues for infants 'The First Age: Infants on the World Stage' with four excellent talks by Roger Shapiro – 'MTCT: Evolving Epidemiology and Outcomes' [69]; Martina Penazzato – 'The ART and Science of Infant Diagnosis' [70]; Claire Thorne – 'The HIV-Exposed and Uninfected Child: What's to Worry?' [71] and Elizabeth Obimbo – 'Treatment of Newborns and Infants Living with HIV' [72]. A themed discussion: 'The Impossible Dream: Population Perspectives on 90-90-90 in Adolescents and Young Adults' addressed novel models and hurdles in how to keep young people with HIV in care [73–77].

Observational prevention of mother-to-child transmission studies

Birth outcomes from Botswana were described where 22% of pregnant women are HIV infected and over 90% of them receive ART in pregnancy (Tsepamo Study) [78]. Data was extracted from births at eight maternity wards, representing about 45% of all births in the country. Since 2012, Botswana adopted the WHO Option B, with all pregnant women with CD4 cell counts <350 cells/mm³ commencing life-long TDF/FTC/EFV. Of 47,124 births that occurred from August 2014 to August 2016, 25% were HIV-exposed and ART was started prior to conception in 5780 (48%), and 43% of women were on TDF/FTC/EFV. Compared to HIV-negative pregnancies, there was an increase in all adverse birth outcomes (preterm delivery, stillbirth and small for gestational age). Notably there were significantly fewer combined adverse birth outcomes among women on TDF/FTC/EFV than other ART regimens.

Do HIV-positive women on PI deliver preterm? Findings from a UK study were presented by Graziella Favarato [79] on over 6000 women from the national study of HIV in pregnancy, 2007–2015, which compared preterm delivery risk according to maternal ART such as NNRTI/2NRTI, LPV/r/2NRTI and other-PI/r/2NRTI regimens. More than 50% of women conceived on ART, and when compared to those on an NNRTI-based regimen, one based on LPV/r was associated with an increased risk of preterm delivery (aOR 1.48, 95% CI 1.16–1.88); however, this was not the case for other PI/r-based regimens (aOR 1.13 95% CI 0.89–1.43). Kathryn Rough presented data on TDF/FTC in pregnancy showing no increase in adverse infant birth outcomes in two large US cohorts [80]. In the PROMISE (Promoting Maternal and Infant Survival Everywhere) trial there was an unexpected increased risk of very preterm birth, very low birthweight and death in infants of women randomised to TDF/FTC/LPV/r as compared to ZDV/3TC/LPV/r. This study compared risk of adverse infant birth outcomes in 4646 women exposed to ZDV/3TC/LPV/r, TDF/FTC/LPV/r and TDF/FTC/ATV/r from two large prospective US-based cohorts. Results showed that in the US, TDF/FTC/LPV/r was not associated with an increased risk of adverse birth outcomes compared to ZDV/3TC/LPV/r or TDF/FTC/ATV/r. Indeed TDF/FTC/ATV/r appeared slightly protective for preterm birth, low birthweight and any adverse event.

A number of posters described further data from the PROMISE trial, a comprehensive, multi-faceted, international, randomised controlled trial of ART in pregnancy and postnatally. The antenatal

ART and adverse birth outcomes were described by Benjamin Chi [81]. Birth outcomes were available for 3423 HIV-infected women across 14 sites in Africa and Asia. Women were randomised at ≥ 14 weeks' gestation and not in labour into three arms: zidovudine (ZDV) only (Arm A), ZDV/3TC/LPV/r (Arm B) or TDF/FTC/LPV/r (Arm C). Antiretroviral regimens containing LPV/r were associated with an elevated risk of adverse birth outcomes after adjustment for multiple obstetrical and clinical factors. In women on LPV/r, there were more severe outcomes on TDF/FTC compared to ZDV/3TC. Further studies are needed to determine whether this is an independent effect of TDF/FTC, a result of drug–drug interactions with LPV/r, or of other factors.

The risk factors for low birthweight and preterm delivery in the PROMISE trial were presented by Dorothy Sebikari [82]. In the final multivariate models (adjusted for country and gestational age at entry) analysed for 3423 women, these risk factors included BMI, multiple gestation, prior preterm delivery, pregnancy or chronic hypertension, intrauterine growth restriction, placental abruption, preterm labour, oligohydramnios, premature rupture of membranes, and antenatal ART. The investigators concluded that public health interventions are needed to address modifiable-obstetrical risk factors and management of pregnancy complications, as well as optimising choice of ART regimen.

Subsequent pregnancy outcomes in women followed up in the PROMISE Trial [83] were described by Jose H Pilotto, in a post hoc comparison of subsequent pregnancy outcomes in asymptomatic women (pre-ART CD4 cell count ≥ 400 cells/mm³) who started ART during their first PROMISE pregnancy (2011–2014). Women were randomised to continue (cART) or discontinued (dART) ART after their first pregnancy, LPV/r+TDF/FTC or ZDV/3TC were the preferred regimens. Subsequently, 17% of women had a pregnancy with spontaneous abortions and stillbirths, more commonly in women who had continued ART (cART 23.6% vs dART 11.9%, $P=0.02$).

Alison Drake described a study of breast milk (BM) HIV viral load (VL) among women with a recently acquired infection [84]. Among pregnant/postpartum women with recent HIV infection, 25 women (14 diagnosed in pregnancy, 11 postpartum), with a median time to ART initiation of 13 days, BM VL and plasma VL were prospectively measured. The virus was detected in BM in all women, even those who had initiated ART during pregnancy. The BM VL was not associated with plasma VL or months since ART initiation. The authors importantly concluded that further analysis of BM viral dynamics in women on ART is warranted.

Prevention of mother-to-child transmission and the neonate

Extending the narrow range of ART available to the HIV-exposed neonates is very important. The pharmacokinetic (PK) studies presented demonstrated dosing and safety for raltegravir as presented by Diana Clarke [85], and for nevirapine for low birthweight infants by Adrie Bekker [86]. A triple ART regimen (NVP/ZDV/3TC) for high-risk infants was also shown to be safe [87]. Monoclonal antibodies against HIV treatment has exciting potential for prevention and treatment with reassuring safety and PK data for VRC01 in HIV-exposed neonates as presented by Coleen Cunningham [88].

Data presented at the Conference highlighted that a cost is attached to PMTCT. Although all ART regimens are highly effective in preventing MTCT through viral suppression, adverse outcomes of pregnancy, including stillbirth, premature delivery and small-for-gestation age infants are more common, and more so with certain regimens. These results are of particular importance for resource-poor settings. Adverse outcomes were demonstrated in

randomised controlled trials and observational cohorts. As Roger Shapiro concluded in his talk, there is a trade-off between using ART to maximise PMTCT and adverse birth outcomes: 'For the past two decades, the public health focus has been to expand ART availability in pregnancy and from a public health standpoint it has been difficult to address the growing evidence for adverse birth outcomes. We now need to move into a new era where we remain committed to using ART in pregnancy, but also work to understand and address its complications.'

Paediatric studies

Optimising early infant diagnosis (EID) of HIV

Owing to the need to detect the virus, delay in diagnosis and treatment for HIV-infected infants is an international issue. Ilesh Jani demonstrated the effective use of a point-of-care test on ART initiation rates in infected infants in Mozambique [89]. Nurses in eight intervention primary health clinics (PHC) implemented the Alere q HIV-1/2 Detect POC EID test at 4–6 weeks of age (POC arm) and eight control PHCs collected dried blood spots for EID testing at standard of care (SOC arm) reference laboratories. Access to POC significantly increased ART initiation and retention in care. Decentralisation of EID could accelerate ART initiation in challenging environments, thereby improving global paediatric ART treatment rates.

Treatment with ART that is initiated soon after primary infection influences the seeding of the viral reservoir with beneficial effects for virological control. Infants are an important group in whom HIV infection can be identified soon after infection. In this study of very early diagnosed and ART-treated infants, from the Rahima Moosa Mother and Child Hospital, Johannesburg, virological dynamics were described [90]. Of 68 infants, 50% started treatment within 2 days and 90% by day 15. Six months later, 11% had persistently high HIV RNA, 35% had a declining trajectory and 54% had declined to undetectable levels. Of those with full suppression by 6 months, 30% changed to a negative diagnostic HIV-1 DNA PCR during follow-up. The authors concluded that many clinical and social challenges may affect the variability in virological response in this high-risk group of infants.

Moherndran Archary addressed the issue of HIV-positive children with severe acute malnutrition (SAM) and initiation of ART in this clinically important randomised trial of 82 children [91]. Results showed no difference in mortality on early (<14 days) *versus* delayed ART (>14 days or until recovery). Although the response at 48 weeks was not different between the two groups in terms of CD4, VL and anthropometric parameters, the rates of CD4 increase, VL decrease, and WAZ and HAZ scores recovery favoured the delayed ART arm. The authors concluded that ART initiation in children with SAM should be delayed for at least 2 weeks after starting nutritional rehabilitation. This helps to simplify the early, complex management of these very sick children.

Long-term adherence to ART is demanding, particularly for young people. Anna Turkova presented extended data from the BREATHER study according to the original randomisation continuous therapy (CT) versus 5/7 days short cycle therapy (SCT) [92]. Non-inferiority of viral load suppression between the two arms was demonstrated over a median 3.6 years follow-up, thus demonstrating that EFV/2 NRTI first line may be used effectively and safely if taken 5 days a week, a forgiving option for young people.

A global analysis of the predictors of switch to second-line ART in HIV-positive children was presented by Kara Wools-Kalousitan [93]. The CIPHER cohort collaboration brings together data on more than 93,000 children with HIV, worldwide. In this analysis

of 12 cohort networks within this study, predictors of switch to second-line ART were assessed in 3883 children. The median age at ART switch was 8.6 years, the median first ART duration was 35 months with 85% of children switching from NNRTI to PI. The factors associated with a switch were male sex, older age, earlier calendar years, NNRTI, viral load monitoring and region. There was a marked difference by regions, with a faster time to switch with targeted and routine VL monitoring. There was delayed switch and under-recognised treatment failure with clinical or CD4 cell monitoring. These data are important when considering the scale-up of HIV-1 viral load testing in low- and middle-income countries, which will increase the more rapid detection of treatment failure and the need for second-line ART for children.

Looking at HIV detection and latent reservoirs in children, Shalena Naidoo described 10 children (post-CHER participants) who had initiated ART within 1 year of birth and remained undetectable until the age of 7–8 years. Median cell-associated DNA was 38 copies/million (M) cells (range 4.5–186). Inducible HIV-1 RNA could be detected in four children, with all virus outgrowth assay supernatants collected remaining negative for p24 antigen [94].

The impact of the HIV reservoir size was studied by Mark Pankau in 14 Kenyan infants who were randomised to treatment interruption after 24 months of ART (median age of 28.9 months) after early treatment initiation (median age of 4.8 months) in The Optimizing Pediatric HIV Treatment study. Those children who continued ART had a median of 168 copies of HIV-1 DNA/M PBMCs 24 months after ART initiation and of 50 copies 18 months later. Infants randomised to interruption had a median of 90 copies at 24 months and of 184 copies after 18 months of ART interruption showing a continuous decay in the viral reservoir while on ART and not a very substantial increase with ART interruption [95]. Leila Giron described an increased latent reservoir size in children with subtype D (mean duration of ART of 566 days) as compared to those with subtype A (PROMOTE paediatrics trial) [96].

Finally, Emily Adland described the restoration of anti-HIV-1 CD4 T cell activity in children treated with ART, even for those of only 12 months of age, with strong IL-2 gag specific CD4 T cell responses. The treatment duration was associated with CD4 and CD8 T cell polyfunctionality and decreased expression of immune activation and inhibitory receptors [97].

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