Highlights of the Conference on Retroviruses and Opportunistic Infections, 4–9 March 2019, Seattle, WA, USA

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Introduction

The 26th Conference on Retroviruses and Opportunistic Infections 2019 meeting (CROI 2019) took place on 4–9 March in Seattle, WA, USA. This meeting provides up-to-date information of outstanding quality on HIV prevention, treatment and cure research as well as comorbidities.

The case of viraemia remission over 18 months after antiretroviral therapy (ART) discontinuation in a patient who had received stem cell transplantation, otherwise known as the 'London Patient', was one of the highlights of the meeting and produced much excitement among attendees and the international press. There was ongoing new data regarding the issue of potential teratogenicity with integrase inhibitors as raised in May 2018 in a cohort in Botswana. Impressive novel preventative and therapeutic agents and options for HIV were also presented together with important issues in terms of clinical management, opportunistic infections, sexually transmitted infections and comorbidities such as ageing, cognitive dysfunction and weight gain.

HIV-1 cure

There were two reports of control of viraemia after stem cell transplantation, the so-called 'London Patient' and a Dusseldorf patient [1,2] with delayed viral rebound during analytic treatment interruption (ATI) after infusion of CCR5 ZFN–treated CD4 T cells [3]. A report of *ex vivo* and *in vivo* editing of SIV genome in non-human primates by CRISPR-Cas9 [4] and a study using multidose IV romidepsin with no increased HIV-1 expression in persons on antiretroviral therapy (ART) (ACTG A5315)[5] were also presented.

The two cases of control of viraemia after discontinuation of antiretroviral therapy (ART) were described and included viraemia control for 18 months in the 'London Patient' after lymphoma treated with chemotherapy and a stem cell transplant from a homozygous CCR5Δ32 donor and for 3 months in a patient similarly treated in Dusseldorf for leukaemia, both with relatively low-level conditioning before stem cell transplant [1,2]. These case-reports confirm the fact that the 'Berlin patient' who had remained the only patient cured with similar intervention was not an isolated case in terms of viral remission after such an intervention; however, a longer follow-up is needed to be able to conclude on a cure. Although this improves our understanding of the importance of the CCR5 receptor in viral rebound, the great limitation of this process is that it is not easily generalised.

The open-label, pilot three-arm study by Tebas and colleagues presented on zinc finger nuclease (ZFN) gene therapy with *ex vivo* treatment of CD4+ T cells with CCR5 ZFN using RNA-based transfection (RNA encoding ZFN SB 728) with or without a single dose cyclophosphamide [3]. Individuals were well controlled in terms of HIV infection. One infusion of modified cells resulted in about 25% of disrupted CCR5, with an impact on the percentage of cells with cyclophosphamide with a potential delay in viral rebound post-ART interruption.

A new approach aimed at integrated SIV at *LTR* and *gag* was presented by Burdo and colleagues using CRISPR-Cas9 *ex vivo* and *in vivo* SIV genome editing in non-human primates. Results showed SIV cleavage *in vitro* in PBMCs and excellent biodistribution of these edited SIV genomes in tissues [4].

The ACTG trial A5315 reported by McMahon and colleagues was disappointing as it showed no increase in plasma viraemia after multi doses of romidepsin, an HDAC inhibitor, given intravenously [5]. There were no changes when either using a single-copy assay or cell-associated DNA or RNA measurements. This is part of the' kick and kill' strategy, which has also used other HDAC inhibitors. The use of romidepsin in this study did not raise safety concerns.

Broadly neutralising antibodies and their potential use in cure research use is reviewed below.

Antiretroviral agents against HIV-1 in development

There is continuing drug development with exciting new compounds active against multi-resistant viruses, long-acting activity and a potential broadening of their impact on the immune system.

The novel nucleoside produced by Merck, MK8591 (EFdA) inhibits reverse transcription and translocation. It is potent and active against multiple resistant strains. Its long half-life may allow weekly dosing [6]. It is currently in a Phase 2 clinical trial (NCT03272347) for the treatment of HIV-1 infection with once-daily administration of 0.25, 0.75, or 2.25 mg in combination with doravirine.

The first in class HIV-1 capsid function inhibitor, GS-6207, developed by Gilead has potent antiviral activity also in multiclass resistant virus and low predicted human clearance and aqueous solubility. It is of great interest due to the fact that parenteral administration could be given infrequently. It was reported at this meeting that this agent acts early but also late in the virus life cycle [7]. This Phase I study evaluated safety, tolerability and pharmacokinetics. Data in healthy volunteers (four cohorts) receiving different dosing such 30, 100, 300 and 450 mg subcutaneously shows that with a single dose of at least 100 mg levels above EC95 are maintained for more than 12 weeks. There were no serious side-effects reported. Based on interim data it was well-tolerated as a single dose administered subcutaneously in healthy subjects and supported a dosing interval of at least 3 months. [8].

DeJesus and colleagues presented results from a 10-day Phase 2a, dose-finding study for the GSK maturation inhibitor, GSK2838232, in 33 participants. Binding to *gag*, it targets

late-stage viral life-cycle. This new compound, which follows the discontinuation of two previous maturation inhibitors, has good potency and broad activity. It has shown good tolerability. The two-part study presented used 150-mg cobicistat boosting. Doses tested were 20, 50, 100 and 200 mg once daily in participants with mean CD4 cell counts of 540 cells/mm^3 and 58,000 HIV-1 copies/mL. Mean viral load decrease was 1.5 log$_{10}$ for the 200-mg dose at 10 days and 1.2 log$_{10}$ in the 50- and 100-mg doses. The available resistance data show genotypic changes at A364A/W in *gag* [9].

There is a need for the development of new compound with activity against NRTI resistance. The NRTI candidate GS-9131, with potent activity against HIV-1 virus with NRTI resistance, has a broad activity against HIV-1 subtypes. It is a monoaminate prodrug of the nucleotide analogue GS-9148, which acts through chain termination, with low potential for mitochondrial and renal toxicity and activity against major NRTI resistance [10].

A long-acting (LA) combination is a very important development in HIV-1 treatment. At this meeting two studies, FLAIR and ATLAS, were presented on the LA combination of cabotegravir (CAB) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV), which were shown to maintain virological suppression [11,12].

The FLAIR study, a Phase 3, open-label, randomised controlled trial in ART-naïve adult participants aimed to establish whether virological suppression in participants on an integrase inhibitor single-tablet regimen abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) continued after participants switched to LA CAB/RPV by intramuscular administration every 4 weeks and its safety. The primary end-point was at 48 weeks and aimed at showing non-inferiority compared to the oral comparator. There were 566 naïve individuals to ART who started on ABC/DTG/3TC. Participants undetectable at 20 weeks were randomised to continue the regimen or switch to short-acting CAB/RPV followed by LA CAB/RPV [11].

The ATLAS study evaluated efficacy, safety and tolerability of switching to LA CAB/RPV from current antiretroviral regimen in virologically suppressed adults with HIV-1. There were 616 virologically suppressed individuals on PI, NNRTI and integrase inhibitors regimens. Participants either remained on their regimen or were switched to oral CAB/RPV for 4 weeks followed by LA CAB/RPV for 48 weeks. In both studies the combination was shown to be well-tolerated with few discontinuations and non-inferiority was demonstrated [11,12].

A new generation of potent, broadly neutralising antibodies (bNAbs) is being developed. bNAbs are of great interest as preventative, therapeutic and cure agents as they show antiviral potency coupled with the potential to activate immune responses that may also be of importance in cure strategies. However, development of resistance when they are used as single agents for treatment is leading to the combination of these agents along with testing with the addition with other immunomodulators such as the oral toll-like receptor 7 (TLR7) agonist GS-9620.

PGT121 is an IgG$_1$ monoclonal antibody (Ab) targeting the V3 envelope and has potent neutralising capacity against 60–70% of all HIV-1 strains. It had been tested in preventative and therapeutic studies in non-human primates showing in association with GS-9620 control of viraemia without ART initiation. At this conference the first human Phase I study was presented by Kathryn Stephenson. PGT121 was tested in individuals with HIV-1 and on ART and in individuals without HIV-1. The study had a dose-escalating first phase with PGT121 administered as a single

infusion at 3, 10, and 30 mg/kg and also subcutaneously at 3 mg/kg. This was followed by an open-label phase where PGT121 was given as a 30-mg/kg infusion to viraemic adults not on ART with either a high or low HIV-1 viral load in a small cohort of patients. A few participants in the low viral load arm showed long-term viral suppression. It was safe, with good tolerability and a good pharmacokinetic (PK) profile. Its impact on host immunity is under investigation [13].

The novel compound, GS-9722, is described as a first in-class, effector-enhanced bNab for HIV cure. It is targeted at eliminating latently infected cells. Compared with PGT121, it has been shown to have the same neutralisation breadth and potency but has improved drug-like properties, less risk of immunogenicity, enhanced effector function and optimised PK function. It is planned to use it in combination with other bNAbs [14].

The presentation by Pegu and colleagues of a trispecific broadly neutralising antibody compound with potent antiviral activity is a very exciting development. Combination of antibodies is aimed at preventing development of resistance to HIV-1. These antibodies interact with the CD4 binding site, membrane proximal external region (MPER) and V1V2 glycan which should lead to enhanced neutralisation. They have an intact IgG$_1$ backbone. Potent Fc effector functions in animal studies are promising for mediating ADCC and phagocytosis [15,16]. Trispecific HIV broadly neutralising antibodies demonstrate potent neutralisation and antibody-dependent cellular cytotoxicity (ADCC) *in vitro*, and mediate antiviral activity *in vivo*.

Second- and third-line antiretroviral therapy

With widespread use of integrase inhibitors and the presence of resistance, various studies were presented to clarify the efficacy of second-generation integrase inhibitors in this situation.

The DAWNING study is a non-inferiority, randomised, Phase 3b, open-label study conducted to evaluate the safety and efficacy of DTG and two NRTIs compared with lopinavir/ritonavir (LPV/r) and two NRTIs in participants whose first-line ART of an NNRTI plus two NRTIs was failing. Dolutegravir has been shown previously to be superior to LPV/r in a comparison of a DTG-based regimen versus the WHO-recommended second-line regimen [17]. The presentation showed that the advantage of the DTG-based regimen over that of the LPV/r-based regimens, where both included at least one fully active NRTI, persisted regardless of baseline NRTI resistance in a post hoc analysis. The M184V mutation was present in the majority of patients and in isolation in 25%, and when present in an individual, DTG outperformed LPV/r. The K65R mutation was present in 30% of participants while 24% had at least one thymidine-analogue mutation. TDF and zidovudine were included in the baseline regimens for some participants with these mutations and high responses were observed in the DTG arm although participant numbers were small [18].

The ongoing Phase 3 randomised, double-blinded GS 4030 study, which has enrolled 565 participants, is looking into well-controlled patients with documented baseline resistance to any drug classes except integrase inhibiters. Randomisation involved staying on a DTG with tenofovir or TAF/FTC regimen or a switch 1:1 to bictegravir (BIC)/FTC/TAF for 48 weeks. In total, 82% (462/565) of participants had pre-switch genotypic data available. Planned interim analysis (12 weeks of follow-up) showed a high rate of baseline NRTI resistance (24%) with 99% of participants with HIV-1 viral load <50 copies/mL. Primary NNRTI and protease inhibitor (PI) resistance mutations were present in 24% and 8%

of participants, respectively. Pre-existing integrase inhibitor mutations were found in 5% of participants [19].

Andreatta and colleagues from Gilead presented resistance and virological data on long-term BIC/FTC/TAF efficacy from studies 1844 and 1878 on 2 year-open-label BIC/FTC/TAF in patients with archived resistance [20]. Pre-existing primary NRTI (16%), NNRTI (21%) and a low level of integrase level resistance (1.9%) were detected. No further development of resistance was noted at the time of analysis with maintenance of virological control.

Santoro and colleagues looked into another aspect of pre-existing resistance with second-generation integrase inhibitors such as bictegravir. Their study aimed at defining the genotypic and phenotypic resistance profiles of BIC and other integrase inhibitors in highly treatment-experienced and multiresistant patients within the Italian PRESTIGIO registry whose treatment with twice-daily raltegravir (RAL)- or DTG-based regimens had failed [21]. GeneSeqIN and PhenoSenseIN assays were performed. Twenty-two samples from 17 patients were evaluated with a median time since diagnosis and duration of treatment of 20 years. Median viral load and CD4 T cell count were 4.5 $\log_{10}$ copies/mL and 168 cells/mm^3, respectively. Primary integrase resistance substitutions E138A/K, Y143C/H/R, Q148H, and N155H were present in 14/22 samples together with the G140S and Q148H mutations in 11/22 samples. All 14 samples showed resistance to elvitegravir and raltegravir and two to BIC and DTG, the latter two samples showing L74M, E138K, G140S, and Q148H or L74M, T97A, S119T, E138K, G140S, Y143R and Q148H substitutions. Intermediate resistance was reported for 8/14 isolates for BIC and 9/14 isolates for DTG. Median fold-change (range) values were: BIC 3.1 (0.6–66), DTG 6.1 (0.8–>186), elvitegravir >164 (2.6–>164), and raltegravir >188 (2.7–>197) in the 14 samples.

Data from another team of Italian investigators by Saladini and colleagues described the *in vitro* activity of DTG/BIC/elvitegravir/CAB on first-generation integrase inhibitor-resistant HIV-1 in plasma samples of 19 patients with major INSTI mutations [22]. The integrase inhibitors DTG, BIC and CAB showed comparable activity with the Q148H in addition to one or two mutations to integrase inhibitors associated with decreased susceptibility for all drugs tested. Data indicates that the Q148H mutation pathway in those in whom raltegravir was failing appeared more detrimental to the use of second generation INSTIs than when elvitegravir was failing.

Pregnancy

Since the report of a significant increase of neural tube defects (four cases) from the Botswana Tsepamo cohort in women exposed to the drug at conception but not later in pregnancy, there were several reports on the use of other integrase inhibitors during pregnancy and a review of several cohorts.

Further data from the Tsepamo cohort are awaited and should be available in 2019 with a report on 1400 pregnancies. Several databases have not clearly highlighted a relationship between the use of integrase inhibitors and neural tube defects. Two studies that have compared the use of efavirenz to integrase inhibitors during pregnancy, using raltegravir- and DTG-based ART regimens, have been shown to be both virologically superior to the efavirenz-based regimen in pregnant women [23-27].

Contraception

Issues of drug–drug interaction remain paramount in the case of contraception. Previous reports have highlighted that efavirenz

decreases levonorgestrel concentration in subdermal implants with unintended pregnancy as a consequence. It was disappointing to learn that doubling the levonorgestrel dose from 150 mg to 300 mg did not overcome this interaction [28-31]. Double-dose levonorgestrel implants do not fully overcome the interaction with efavirenz but it is not clear if this double-dose would be able to prevent pregnancies.

STIs

There was an impression of a déjà vu when Jeanne Marrazzo (University of Alabama, Birmingham, USA presented on 'Resurgent sexually transmitted infections (STIs) in HIV care and prevention' [32]. Dr Marrazzo started by talking about the dramatic explosion of STIs (www.cdc.gov/std; [33,34]. Indeed, it is not just the burden of these infections that is of concern, but also their characteristics, such as antimicrobial resistance to treatment for gonorrhoea (24% of countries reported decreased susceptibility to ceftriaxone, 81% to azithromycin [35]), the incidence of syphilis that is above the pre-AIDS era estimates (153% increase compared to 2013 [36]), the collision with methamphetamines using networks, the re-emergence of hepatitis C and the reappearance of classics such as LGV rectitis (TD 05). But what about the role of STIs in 'Getting to Zero'? For some, STI burden and scaling up PrEP is independent from HIV incidence [37,38], and for others, further drivers of HIV spread, including economic and gender inequality, have to be considered [39-42]. In this context, it would be useful to deploy rapid and accurate diagnostic tests particularly in high HIV incidence settings, to establish STI screening in asymptomatic people, and to recognise the pattern of STIs in the context of HIV.

Comorbidities

ART-associated comorbidities, such us weight gain also occupied a particular place in CROI. The TD-08 Themed Discussion Session was inaugurated by Jordan E Lake (University of Texas at Houston, Houston, TX, US) who presented weight gain assessment following switch to INSTI-based ART among 972 AIDS Clinical Trials Group (ACTG) participants in ACTG protocols A5001 and A5322 (68% from PI, 31% NNRTI, 2% other non-INSTI at median 7.8 years after parent trial entry) [43]. Median age at switch was 50 years, CD4+ T cell count 511 cells/mm^3 and BMI 26.4 kg/m^2; 539 switched to RAL, 222 to EVG and 211 to DTG. In adjusted models, white or black ethnicity, age ≥60 and BMI ≥30 kg/m^2 were associated with greater weight gain following switch among women, whereas age ≥60 was the greatest risk factor among men.

Kassem Bourgi (Vanderbilt University, Nashville, TN, USA) presented results of weight changes after initiating ART among treatment-naïve people living with HIV in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)[44]. Among 4112 individuals initiating INSTI-based regimens between 2007 and 2016 (2106 RAL, 1510 EVG and 477 DTG), weight gain was greatest among individuals starting INSTI. At 2 and 5 years, individuals on INSTI gained 4.4 and 5.8 kg, respectively, compared to 3.3 and 4.1 kg for those taking NNRTIs (*P*<0.001), and 4.3 and 5.0 kg for those on PIs (*P*=0.68), but the mechanisms of these differences are poorly understood.

Grace A McComsey (Case Western Reserve University, Cleveland, OH, USA) described the demographic, clinical and treatment characteristics of treatment-experienced adults with virally suppressed HIV who had ≥3% annual weight gain in recent years (2013–2018) and who were within an observational retrospective study of US clinical practice [45]. In total, 3468 patients were followed-up for a median time of 19 months. Among them, 1045

participants had ≥3% annualised weight gain and when compared to the other 2423 patients they had higher proportions of underweight and normal BMI at baseline, female, age <50, and psychiatric disorders and lower rates of comorbidities CKD, CVD, DM, hyperlipidaemia and hypogonadism. In this multivariable logistic regression analysis, the authors did not see that INSTI use was independently associated with weight gain, suggesting that, in this population, weight changes are primarily driven by other factors.

Anne Marie Kerchberger (Emory University, Atlanta, GA, USA) highlighted results of the Women's Interagency HIV Study (WIHS) that evaluated change in body weight, body measurements and blood pressure in virologically suppressed women living with HIV (WLHIV)[46]. Women who switched to or added an INSTI to ART (SWAD group) were compared to women who remained on non-INSTI ART (STAY group). In total, 1118 WIHS participants (884 STAY and 234 SWAD) were followed for an average of 2.0 (+/− 0.1) years. Mean baseline age was 48.8 (+/− 8.8) years. In this population INSTIs were associated with significant increases in body weight, body mass index, body circumference measurements and blood pressure over a short period time. No significant differences in outcomes were observed by INSTI type.

Raphael J Landovitz (University of California Los Angeles, CA, USA) presented the first results of cabotegravir studies regarding weight gain under a regimen containing this molecule [47]. HPTN 077, a Phase 2a randomised placebo-controlled study of two dose/dose-interval regimens of cabotegravir, enrolled 199 HIV-uninfected participants from eight sites in the US (4), Brazil (1) and sub-Saharan Africa (3). Median weight change over 41 weeks was +1.1 kg (IQR -0.9–3.0) in the CAB arm and +1.0 kg (IQR -1.2–3.2) in the placebo arm (*P*=0.66). In longitudinal statistical analyses, no statistically significant differences were found in change in weight from weeks 0 to 41 in CAB- versus placebo-treated participants in aggregate, by sex, dosing cohort, age, race/ethnicity, smoking status, BMI, nor by baseline BMI category. Changes in fasting glucose and fasting lipids from weeks 0 to 41 were not different between CAB and placebo. This analysis suggests that CAB may have different effects on weight/weight gain than dolutegravir.

Sara H Bares (University of Nebraska Medical Center, Omaha, NE, USA) explored changes in immune activation following ART initiation in two large randomised ACTG trials (A5202 and A5257)[48]. In total, 340 participants were selected with a median pre-ART age 42 years, CD4 cell count 273 cells/mm^3, HIV-1 RNA 4.7 log$_{10}$ copies/mL; 49% were women, 33% white, 42% black and 24% Hispanic. While pre-ART BMI was similar between gainers and maintainers (overall and within sex), gainers had significantly lower pre-ART CD4 cell counts versus maintainers. In adjusted models among those with normal pre-ART BMI, pre-ART IL-6, sTNF-RII, IP-10 and sCD163 were higher for gainers versus maintainers. Association of weight gain on week 96 changes of these four biomarkers differed by sex: women who gained weight had smaller declines in biomarkers compared to men who gained. In total, higher pre-treatment immune activation markers are significantly associated with weight gain following ART initiation even after controlling for pre-ART CD4 counts. Weight gain attenuates the decline in several immune activation markers following ART initiation among women; thus, women may be at increased risk for complications of weight gain.

Cardiac morbidity was at the heart of communications regarding 'Non-communicable Diseases in treated HIV'. Kristina Crothers (University of Washington, Seattle, WA, USA) assessed 25,509 people living with HIV of the CFAR Network of Integrated Clinical

Systems (CNICS) cohort for COPD and myocardial infarction (MI) risk [49]. COPD was associated with a significantly increased risk of MI (adjusted hazard ratio [aHR] 2.09, 95%CI 1.50–2.91) even after adding smoking (aHR 1.88, 95%CI 1.34–2.63). Matthew Freiberg (Vanderbilt University, Nashville, TN, USA) analysed data on 144,362 veterans (30% living with HIV) from the Veterans Aging Cohort Study (prospective study of veterans living with HIV and age, sex, race/ethnicity and clinical site matched veterans without HIV) in terms of risk of sudden cardiac death (SCD)[50]. In this analysis and after adjustment for confounders, veterans living with HIV had a 14% higher risk of SCD (hazard ratio=1.14, 95% CI 1.04–1.25) compared to veterans without HIV. The risk was highest among those with sustained high HIV viral loads or low CD4 cell counts.

Linda Ann Battalora (Colorado School of Mines, Golden, CO, USA) calculated mortality rates over 17 years in a longitudinal prospective observational cohort (HOPS, HIV OutPatients Study) currently conducted in six US cities, which is also evaluating the association of bone fractures with mortality [51]. Among 6826 HOPS participants followed for a median of 6.2 years, 502 (7%) had incident fracture recorded and 729 (10%) had died. Median age at fracture was 48 years (interquartile range 41–55 years). Of patients, 16.5% with major osteoporotic fractures died (crude mortality 1.5 per 100 person-years [py]), while 14.6% with fractures at other sites died (crude mortality 1.3 per 100 py). In multivariable analysis, incident fracture was significantly associated with all-cause mortality (Hazard ratio 1.5, 95% CI 1.2–1.9) as were multiple other factors, notably nadir CD4 cell count <200 cells/mm^3, non-AIDS cancer, hepatitis C infection and chronic liver, renal and cardiovascular disease comorbidity.

Prevention

Sharon L Hillier (Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA) gave an interesting update on HIV prevention during the Committee Workshop for New Investigators and Trainees [52]. She said that even if new HIV infections have declined by 51–76% since the start of PEPFAR, the success in HIV epidemic control is disproportionate by age group or belonging or not to a minority group, and rates of HIV in Africa still are eight times higher than in the US and 10 times higher than in Europe.

There is a terrible mismatch between people in real need for PrEP and people who finally get it. In terms of PrEP, the Phase-3 DISCOVER study [53] was a randomised (1:1), double-blind, active-controlled study conducted in North America, Canada and Europe in cis-men who have sex with men (MSM) and transgender women (TGW) who are at high risk of HIV acquisition. The objective was to describe the efficacy and safety of FTC/TAF versus FTC/TDF for PrEP. A total of 5387 adults was treated at 94 sites in 11 countries, with a mean age of 34 years, range 18–76 years, 9% black, 2% TGW, 25% had prior PrEP use and 41% had more than three receptive condomless anal sex partners in the 90 days before study entry. The HIV incidence rate on either FTC/TAF or FTC/TDF was very low and significantly less than the background rate in those at risk but not on PrEP in the US. In almost 2 years of follow up, both FTC/TAF and FTC/TDF, given daily, were tolerated and had low discontinuation rates. The primary endpoint analysis reported an HIV incidence of only 22 HIV infections across both arms diagnosed over 8756 py of follow-up. The incidence rate ratio was 0.47 (95% CI 0.19–1.15) establishing non-inferiority of FTC/TAF to FTC/TDF for HIV prevention.

Even though the effectiveness of PrEP in real life has been even better than in clinical trials [54], failures were reported in a context of increased and/or improper use [55,56]. Screening

difficulties for instance, may expose non-reactivity of the fourth-generation assay that can reach 18% in acute infection in some studies [57].

PrEP failures have many causes, such as ambiguous HIV screening test results. System failures refer to the lack or limited access to PrEP because of unavailability, lack of awareness among people at risk and healthcare providers and cost. Doctors' failures refer to insufficient knowledge of PrEP with the failure to rule out HIV infection when starting or renewing PrEP, or reluctance to prescribe PrEP. People failures are mostly due to the deferred or improper use of PrEP. Assay failures refer to the challenges of HIV diagnosis due to the low sensitivity of HIV tests during the first days/weeks following HIV acquisition. PrEP failures can lead to drug resistance when PrEP is started or maintained in a person who has acquired HIV. In clinical trials, most cases of HIV infection with resistance occurred when PrEP was started in someone with undiagnosed HIV infection. Overall, true biomedical failures of PrEP remain rare.

The much expected results of the HPTN 071 (PopART) trial were presented [58].

The primary result of the trial was presented by Professor Richard Hayes (London School of Hygiene and Tropical Medicine). The HPTN 071 (PopART) trial was designed to see whether delivering a door-to-door combination package including HIV testing, linkage to treatment and prevention could achieve high coverage of ART in people living with HIV such that the number of new HIV infections would be reduced compared with current standard of care approaches. The study design was as follows: one million people living in 21 urban communities in South Africa and Zambia agreed that their community would participate in this study. The 21 communities were randomly allocated to one of three approaches matched into triplets by the baseline levels of HIV prevalence. Seven communities allocated to arm A of the trial were offered community-wide HIV combination prevention approach, seven arm B communities were offered the same household-based HIV testing and education but, in these communities, antiretroviral treatment (ART) was offered in line with current national guidelines and seven arm C communities received the current standard-of-care approach to HIV testing prevention and treatment. ART was available through routine government HIV clinics in all 21 communities irrespective of study arm. The PopART intervention included all HIV care, ART and prevention was offered to every resident within all 21 communities involved in the trial by government partners at the local healthcare facilities. This continued in the standard-of–care arm C communities, and changes in national guidelines and policy for ART initiation changed through the lifetime of the trial and were implemented in accordance with local recommendations. ART initiation guidelines changed during the study period to the offer of universal ART irrespective of CD4 cell counts by 2016. In addition to the routine government healthcare facility provision of HIV testing, prevention and treatment, the PopART intervention employed a new cadre of staff: community HIV care providers, referred to as 'CHiPs'. CHiPs were lay counsellors specially trained to work through every household within a community on an annual basis offering HIV counselling, testing, prevention and treatment, provision of condoms, TB screening and testing, and sexual and reproductive health tests. In any cases requiring medical care and treatment, CHiPS teams encouraged and supported HIV-positive clients to attend and remain in care at government healthcare clinics.

In terms of the primary outcome, the number of new HIV infections in each community was measured over the study period (2014–2018) in a separately recruited randomly selected cohort of approximately 20,000 individuals per community who consented to have a blood test taken annually for HIV testing.

The main outcome of the trial was to compare HIV incidence by study arm over the time of the trial (between 2014 and 2018); arms A versus C and arms B versus C. This was done based on blood collected from the research cohort. Results show that the intervention overall reached the UNAIDS 90-90-90 targets, and viral suppression among people living with HIV increased in the intervention arms from a baseline of approximately 55% to over 70% by the end of the trial period. This resulted in a 30% decline in new HIV infections in communities where HIV prevention, including home-based HIV counselling and testing, was provided, as well as referral to HIV care and treatment for people testing positive for HIV according to country guidelines (arm B). This finding is highly statistically significant. There was a much lower reduction in HIV incidence (7%) comparing arm A communities with arm C that was not statistically significant. The lack of impact in arm A communities is difficult to explain at present. Ongoing analyses are exploring this further. A post hoc analysis combining the impact of arms A and B versus C demonstrated an overall statistically significant reduction in HIV incidence of 20%. Overall this trial showed that community-wide services can enhance the coverage of knowledge of HIV status and ART coverage to a level that leads to significant reductions in HIV incidence.

Hepatitis C

Jürgen K Rockstroh (University of Bonn, Germany) described dynamics of acute HCV in Western Europe [59]. With the advent of highly successful and well tolerated direct acting antiviral (DAA) combinations, HCV elimination appears to be a reachable goal. The Global Health Sector Strategy (GHSS) calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). Nevertheless, major obstacles have to be overcome in order to approach HCV elimination, namely underdiagnosis (only 20% of people with HCV worldwide having been diagnosed so far) and insufficient treatment uptake (among 71 million people that were thought to be infected with HCV in 2015, only 1.76 million people received HCV treatment in 2016). Additionally, although national studies from the Netherlands and Switzerland show a significant 50% reduction in the incidence of newly acquired acute HCV infections by increasing treatment uptake for MSM with HIV and HCV co-infection, current HCV outbreaks and the risk of HCV re-infections clearly weakens this success. Earlier HCV treatment initiation and earlier acute HCV diagnosis will be needed in order to impact HCV dynamics.

Lucy Garvey (Imperial College Healthcare NHS Trust, London, UK) described HCV incidence kinetics in MSM living with HIV in London following wider access to DAA therapy [60]. While BHIVA aims to cure HCV co-infections in 100% by 2021, modelling work predicts that significant scale-up of HCV treatment will be important [61]. Using real world experience, Sanjay Bhagani's group examined trends in incidence of acute HCV between 2013 and 2018 in three central London HIV clinics in MSM living with HIV, who constitute a potential target for microelimination. In total, 256 acute HCV diagnoses were identified, of which 45 were reinfections. The median age was 43 years and 85% were virologically suppressed. Incidence of first HCV episode peaked at 15/1000 (95%CI 10–19) person-years of follow upin 2015. Rates declined by 79% by 2018 with no change to screening

practices. Re-infection rates increased from 9% to 47% during the study period. Patients diagnosed with acute HCV during the study period most likely awaited chronic infection to receive DAAs via the NHS (for an average of 23 months following diagnoses), while the majority of individuals received treatment via a clinical trial in more recent years (average of 10 months). Time from diagnosis to starting any HCV treatment reduced from an average of 40.9 months (2013) to 3.1 months (2018).

Adeel A Butt (Pittsburgh Healthcare System, PA, USA) presented results about the impact of newer DAA regimens upon subsequent incidence and risk of diabetes comparatively to untreated and pegylated interferon/ribavirin (PEG/RBV)-treated controls within the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES)[62]. Researchers identified 4764 PEG/RBV-treated, 21,279 DAA-treated, and same number of untreated controls. Diabetes incidence rate (95% CI)/1000 person-years of follow up were 19.8 (18.3–21.4) among PEG/RBV- and 9.89 (8.7–11.1) among DAA-treated persons (*P*<0.001). Among the treated, rates were 13.3 (12.2–14.5) for those with sustained virological response (SVR) and 19.2 (17.4–21.1) for those without SVR (*P*<0.0001). Treatment was associated with a larger reduction in incident diabetes rate in persons with more advanced fibrosis/cirrhosis (absolute difference 2.9 for FIB-4 <1.25; 5.7 for FIB-4 1.26–3.25; 9.8 for FIB-4 >3.25). DAA treatment (HR 0.48, 95%CI 0.42–0.56) and SVR (HR 0.81, 95%CI 0.70–0.93) were associated with a significantly reduced risk of diabetes, and may therefore be useful in mitigating some of the extrahepatic complications of HCV.

In the context of growing incidence of hepatocellular carcinoma (HCC) in people living with HIV since 1996, Jessie Torgensen (University of Pennsylvania, Philadelphia, PA, USA) conducted a cohort study within the VACS in order to determine the impact of HIV and CD4 cell count on HCC risk [63]. They identified 278 incident cases of HCC, with a median age of 56 years, and what was striking is that 43% (95% CI 37–49%) of patients at the time of HCC diagnoses had no markers of advanced hepatic fibrosis/cirrhosis by FIB-4 (FIB-4 <3.25), which is in contrast with the general population where 13% of HCC occur without cirrhosis. Among these patients, there is a higher proportion of morbid obesity (BMI>30 kg/m^2) and diabetes and chronic hepatitis B were independently associated with incident HCC. In multivariable models, among patients with baseline FIB-4 >3.25, only chronic hepatitis B and C increased the risk of HCC development. In contrast, among patients with low baseline markers of hepatic fibrosis/cirrhosis (FIB-4 <3.25), HIV and CD4 cell count were also as significant as chronic hepatitis B and C. Specifically, there was a 24% increased risk of HCC for every one log increase in HIV viraemia, and a 57% increased risk of HCC for people with more than 11 months of detectable viraemia.

Catherine Anne Chappell (Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA) presented a pilot study about the safety of and virological response to ledipasvir 90 mg/sofosbuvir 200 mg (LDV/SOF) therapy in pregnancy [64] in the context of the ongoing hepatitis C virus epidemic among young people in the US, including pregnant women (200 women per year)[65,66]. Seven women were enrolled, all of whom were white, with a median age of 32 (range 25–38) years and a median HCV viral load at enrolment of 518,173 (range 103,457–3,757,923) copies/mL. All had a rapid response to therapy and all achieved SVR-12. All adverse events related to LDV/SOF were ≤grade 2. All seven participants delivered at term with undetectable HCV viral loads at delivery. One-year follow-up of infants is ongoing, but these results suggest that viral response is similar to non-pregnant individuals.

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