Highlights of the 10th International AIDS Society (IAS) Conference on HIV Science, 21–25 July 2019, Mexico City, Mexico

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Introduction

The IAS Conference and the pre-IAS HIV and HBV Cure Symposium were held in 21–25 July 2019 in Mexico City, Mexico. This report focuses on some selected presentations in the field of HIV treatment, cure and the prevention. The HBV/HIV Cure Symposium is comprehensively presented in a separate article in this issue with some overlap with the Conference summary.

Treatment of primary HIV-1 infection

In a plenary session John Frater (University of Oxford, Oxford UK), discussed the opportunities at individual and population levels offered by the identification of primary HIV infection (PHI) and immediate antiretroviral treatment (ART) initiation. He summarised the evidence supporting enhanced immune recovery by sharing data from the large, prospectively enrolled UK HEATHER cohort of over 350 participants diagnosed during PHI and showed the potential for CD4 T cell count and CD4/CD8 ratio normalisation between 1 to 3 years after ART initiation. Data from this cohort demonstrate that whilst ART initiated at PHI conferred a large reduction in HIV-1 reservoirs when using cell-associated RNA, total HIV-1 DNA/CD4 T cells and viral outgrowth assay measurements, the most important determinant of the reservoir size 1 year after ART initiation was its size at the time of HIV-1 acquisition. In terms of designing future cure intervention trials, the current accepted paradigm is to interrupt ART and report on the period of viremia control after treatment interruption. Novel data have illustrated that the expression of immune activation genes at the point of treatment interruption correlated with the time to plasma viral rebound. Dr Frater presented data to support a compelling case for testing novel curative interventions in proof-of-concept studies in treated PHI cohorts since immune function in terms of immune activation and exhaustion is optimal compared to chronic infection and with fewer opportunities for viral immune escape in a context of reduced viral reservoir size. The RIO trial which will use the long-acting broadly neutralising antibodies (bNAbs) 3BNC-117-LS and 10-1074-LS in treated PHI participants with viral envelope sequences sensitive to the two compounds is planned to start soon in the UK [1].

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Role of microbiome in HIV-1 transmission and pathogenesis

Adam Burgener (University of Manitoba, Canada) summarised the role of the microbiome in terms of susceptibility, pathogenesis and treatment of HIV-1 [2]. Many examples support the role of gut/vaginal microbial symbiosis in diseases. Despite being on ART, HIV-1 positive individuals are known to have gut epithelial barrier disruption, allowing microbial product translocation, which is associated with chronic immune activation and inflammation. The microbiome is important for gut mucosal homeostasis and compositional changes in HIV-1 positive individuals and has immune correlates and metabolic consequences. Furthermore, bacterial gene richness (total number of genes contained within the bacterial community) is important for gut health and is highly correlated with HIV-1 disease progression, in as so far as low bacterial gene richness is linked to a lower nadir CD4 T cell count. Several interventions (dietary, probiotics/prebiotics, faecal microbial transplantation) are being tested to improve gut microbial dysbiosis in human and non-human primates with HIV-1 infection showing results that are not yet conclusive. We also know that vaginal microbial composition affects mucosal homeostasis and that bacterial vaginosis is associated with a 60% increase in the risk for HIV-1 acquisition [3]. The vaginal microbiome also impacts on topical pre-exposure prophylaxis drug efficacy [4], but not oral PrEP [5].

Measuring the HIV-1 reservoir: insights from single cell analysis

At the IAS HIV/HBV cure meeting, Lillian Cohn (Chan Zuckerberg Biohub, USA) presented insights into single-cell analysis for assessing the HIV-1 reservoir, which is established by about 3 days post-infection. Its identification and accurate measurement remain difficult. Most of the reservoir is transcriptionally silent with unknown mechanisms of persistence and we do not have validated biomarkers to measure its size. The first assay introduced to quantify the resting CD4 T cell reservoir was the culture-based viral outgrowth assay (VOA), which underestimates its size because not all proviruses can be induced to replicate with each activation cycle. Other strategies include cell-based assays measuring surface protein expression, HIV-1 sort-sequencing (using fluorescent HIV-1 RNA probes to identify cells capable of generating virus), latency capture (where cells need to be activated, which may alter cells) and free HIV-1 RNA, provirus HIV-1 DNA and integration site measurement. When using any of these methods, distinguishing intact proviruses from the vast amount of defective proviruses remains challenging.

Dr Cohn introduced the novel quantitative intact proviral DNA assay (IPDA) assay. Following near full HIV-1 genome sequence evaluation, sequence information was used to design probes for a droplet digital PCR assay (ddPCR) that distinguished intact proviruses from those with deletions or extensive mutations. While this method identifies intact virus, it does not necessarily identify replication-competent virus.

A major challenge to the field remains the integration of sequencing data with analysis techniques to enable the identification of cells in steady state without reactivating them. Ninety-eight percent of CD4 T cells are not in circulation as most reside in lymphoid tissue (LT). An important point is that latent virus from circulating CD4 T cells are not the ones involved in plasma rebound. However, some rebound viral sequences were found probably to be viral recombinants identified in circulation. Single-cell analyses have revealed clonally expanded infected cells, most of which had defective virus, but cells with replication-competent virus were also identified. Some overlap between single-cell analyses comparing LT, blood and gut has been demonstrated, which is a future avenue to watch out for.

Stem cell and genome editing for HIV-1 cure

Paula Cannon (University of Southern California, USA) delivered a plenary lecture where she reviewed stem cell and genome editing-based strategies to achieve an HIV-1 cure. She summarised the three main roles for this technology: 1) to protect (gene engineering to render HIV-1 uninfected cells resistant to infection); 2) to attack (enhance anti-HIV-1 immune responses); and 3) to purge (remove reservoirs of latent HIV-1). Genome editing using CRISPR/Cas9 and zinc finger nuclease (ZFN) technologies recognise specific DNA sequences and allow precise changes to be made to cellular genetic information. The CCR5 gene was the first target used for editing and is currently undergoing clinical trials at several research centres in the USA (ClinicalTrials.gov Identifier: NCT01044654, NCT02500849) and China (ClinicalTrials.gov Identifier: NCT03164135).

Dr Cannon described the pilot study that her group is running, investigating the safety and feasibility of ZFN CCR5-modified hematopoietic stem cells (HSC) engraftment (ClinicalTrials.gov Identifier: NCT02500849). The theory behind this concept is that upon reintroduction into the host, engineered HSCs will give rise to differentiated cells that are resistant to HIV-1.

Dr Cannon's approach to HIV-1 cure through genome editing may face challenges, given the complexities and high costs of the procedure, its unknown safety profile for a treatable condition, public acceptance following the recent report of the 'CRISPR babies' in China [6] and potential recently reported negative impact of CCR5d32 deletion on life expectancy [7].

Broadly neutralising antibodies as components of an HIV-1 cure strategy

Compounds such as broadly neutralising antibodies (bNAbs) have the potential to cure HIV-1 infection via virus elimination by neutralising cell-free virus, clearance of infected cells through antibody-dependent cell-mediated virus inhibition, (ADCVI) and immunomodulation or an immunisation effect by improving host immune function [8]. Katharine Bar (University of Pennsylvania, USA) presented advances in bNAb formulation which now have enhanced breadth by engineered targeting of new epitopes, enhanced effector function and half-life (e.g. the LS mutation in the Fc component of the bNAb increases VRCO1 half-life by over four-fold). Clinical trials are currently underway using two or more long-acting bNAbs, multi-specific bNAbs (tri- and bi-specific, or dual affinity such as anti-*env* and anti-CD3), and combination immunotherapy (using bNAbs, latency reversing agents and immunomodulators).

Treatment and management of HIV-1 infection: a summary of highlights

The Conference included the report of many highly anticipated trials, some of which will change our guidelines and practice. If the conference findings were to be summarised in a single line, it must be 'two-drug regimens have really arrived' and this summary will primarily cover the key findings related to two-drug therapy, plus some new evidence for first-line therapy and new drugs.

Two-drug therapy

The 2018 International AIDS Conference in Amsterdam saw the first presentation of the since published, GEMINI trial. GEMINI is a large (1441 participants), randomised, double-blind trial comparing a 'standard' three-drug regimen (3DR) of tenofovir-DF/emtricitabine + dolutegravir (TDF/FTC/DTG) with a two-drug regimen (2DR) of DTG + lamivudine (DTG/3TC) in treatment-naïve individuals [9]. At week 48, DTG/3TC was non-inferior to TDF/FTC/DTG and, importantly, there was no resistance emergence in the small number of virological failures. While some clinicians had already been using DTG/3TC, or hurried to embrace it after GEMINI week 48 was presented, some were awaiting the week-96 results to assess the durability of this new paradigm. One concern was that one trial assessing dolutegravir monotherapy, a strategy we can now confidently say is sub-optimal, demonstrated reasonable efficacy up to week 24 but with late virological failure and resistance emergence after that time point [10]. Would the addition of lamivudine simply delay the emergence of resistance? We can now say no, it won't!

The week-96 results for GEMINI demonstrated continued, high rates of virological efficacy and no emergent nucleoside inhibitor of retrotranscriptase (NRTI) or integrase (INSTI) resistance [11]. Amongst the mainly white (67–69%), male (84–86%) participants with high baseline CD4 T cell count (around 660 cells/mm^3, <10% with <200 cells/mm^3), week-96 efficacy rates were 86% on 2DR and 89.5% on 3DR by a snapshot HIV-RNA <50 copies/mL analysis. Worthy of note is the slippage of the confidence interval for the difference between arms from week 48 to 96. By week 96, the difference between arms was –3.4% (95% confidence interval [CI] –6.7 to 0.0%) so statistically speaking DTG/3TC just scrapes non-inferiority. However, we must consider whether this is clinically important. Efficacy is high in both arms, the difference is numerically small and with no resistance consequences, arguable not clinically important. Additionally, by 'treatment-related discontinuation=failure' (TRDF) analysis, which considers only discontinuations for confirmed virological withdrawal, lack of efficacy, treatment-related adverse events (AE), or protocol-defined stopping criteria, the suppression rates were 96.6% on DTG/3TC and 96.4% on TDF/FTC/DTG, a difference 0.2% (95% CI –1.8 to 2.2%).

Efficacy was consistent and similar by baseline viral load (around 1 in 5 individuals had a baseline viral load >100,000 HIV-1 copies/mL) and the lower suppression rate on DTG/3TC amongst people with a baseline CD4 <200 cells/mm^3 (68% *vs* 87%), this was also attenuated in the TRDF analysis. Despite this, it may be sensible to avoid DTG/3TC first line in people with advanced HIV-1 infection until we have more evidence in this setting. People with a CDC-C event or an historical CD4 T cell count <200 cells/mm^3 were excluded from the trial, so this was not a population with advanced HIV-1 infection. Additionally, one must consider that treatment relatedness of adverse events is made by investigators,

so is often subjective. We should therefore employ caution when reviewing rates of any 'treatment-related' events.

There were numerically more drug-related adverse events in the DTG/3TC arm (20% *vs* 25%, though the caveat outlined above also applies here) but the only drug-related event affecting ≥1% in either arm was headache: eight individuals (1%) in each arm. It would be interesting to see whether the severity or duration of headache differed at all. Renal and bone biomarkers were as we would expect for any TDF-based *vs* non-TDF based trial and there was an expected increase in serum creatinine owing to inhibition of tubular creatinine secretion by DTG, and consequent small decline in estimated glomerular filtration rate (eGFR) by creatinine-based CKD-EPI, but not by cystatin-C-based CKD-EPI which improved in both arms but to a greater degree on 2DR (P<0.001). Finally, there were small, but significant differences in lipid markers (including total: HDL-cholesterol ratio) favouring 3DR, again consistent with other trials comparing TDF-based *vs* non-TDF based regimens.

The other keenly anticipated results of the trial investigating DTG/3TC was TANGO, which compared continued tenofovir-alafenamide (TAF/FTC)-based 3DR (or 4DR if you count a booster as a drug) with a switch to DTG/3TC [12]. All participants, of whom around 80% were of white ethnicity and >90% male, had been suppressed on treatment for at least 6 months with no history of virological failure (VF) or NRTI/INSTI resistance. About two-thirds were on elvitegravir/cobicistat at study entry, followed by rilpivirine and boosted-darunavir (around 12% and 7%, respectively). As a suppressed switch study, the primary endpoint was VF showing rates <1% in both arms and the confidence interval was within the 4% margins for a failure endpoint. Virological success was high at 93% in each arm with a confidence interval for the difference well within the pre-defined 8% margin. As expected for a switch study there were more drug-related adverse events on DTG/3TC but there were no serious adverse events considered to be drug-related. Lipids tended to remain unchanged on the continued TAF-based arm with small improvement in the 2DR arm, which may be related to switching away form a booster for most participants. Changes in creatinine, but not cystatin-C based eGFR, were consistent with a switch to DTG but there were some small but significant differences in bone turnover, favouring continued TAF; the clinical importance is unknown. ViiV also looked at the presence of the M184V/I mutation by baseline proviral HIV-1 DNA sequencing. This was post hoc but with Gilead data suggesting higher than expected rates of proviral 3/FTC resistance, an important analysis to undertake. Only 1% in each arm had a M184V/I mutation on DNA sequencing and, though numbers were very small, there was no impact on virological suppression. The clinical utility of DNA sequencing remains unknown with most DNA 'mutations' present in non-replicative virus.

Finally, DUALIS was a German randomised clinical trial recruiting people suppressed on two NRTI and boosted darunavir to continue their treatment or switch to a 2DR of DTG + DRV/COBI [13]. Virological efficacy was maintained, perhaps unsurprisingly in a population with no history of VF or resistance, but this study provides proof of efficacy and trials in in people with resistance are pending.

What was new in triple antiretroviral therapy?

The ADVANCE trial, a large, first-line study, undertaken in South Africa [14] is unlike the GEMINI and TANGO trials whereby almost all participants were black and around 60% female. It compared TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV with all arms yielding high efficacy rates (week 48 <50 HIV-1 copies/mL by ITT analysis of 84%, 85% and 79%, respectively) despite a lack of baseline resistance testing in a region where pre-treatment NNRTI resistance is estimated to be around 15%. Numbers with VF with paired baseline/failure genotypes were small: one in the TAF/FTC/DTG arm (no resistance), one in the TDF/FTC/DTG arm (emergent NRTI but not INSTI mutations) and six in the TDF/FTC/EFV arm (four and three with emergency NRTI and NNRTI mutations, respectively). Renal, lipid and bone markers were consistent with those of other trials, with no reported differences in sleep, anxiety or depression, and minimal immune reconstitution inflammatory syndrome, though rates of TB were low owing to a high use of isoniazid prophylaxis. The most striking endpoints were related to weight gain, particularly in women.

The Reflate TB2 [15] based on supportive pharmacokinetic and Phase 2 data, compared two first-line ART regimens in people on standard tuberculosis (TB) treatment: TDF/3TC with either raltegravir (RAL) 400 mg twice daily or efavirenz (EFV) 600 mg OD. Despite similar efficacy at week 24, by week 48 the 61% viral suppression rate on RAL, compared to 66% on EFV, left RAL failing to show non-inferiority; the lower cut-off for the 95% confidence interval of difference between arms was 13.9%, crossing the 12% pre-defined margin for non-inferiority. The VF rates were high for both treatment arms, e.g. 22% on EFV and 29% on RAL. The authors concluded that EFV 600mg should still be considered the third agent of choice in the context of TB co-infection but RAL still has a role to play, such as in those with a baseline viral load below 100,000 copies/mL where virological response was 75% and 73% on RAL and EFV, respectively.

Finally, the Gilead 4030 study investigated switch to TAF/FTC/bictegravir (BIC) *vs* TAF/FTC + DTG in individuals already suppressed on TDF/FTC or TDF/FTC + DTG therapy [16]. All individuals had to be suppressed for at least 3 months with no INSTI failure or resistance, but a history of NRTI, NNRTI and PI resistance was permitted (though individuals with resistance were required to have had an undetectable viral load for at least 6 months). What makes this study difficult (or impossible) to interpret, is that investigators lumped historical genotypic resistance and proviral DNA resistance together; with the aforementioned uncertainty around the meaning of detected 'mutations' in proviral HIV-1 DNA this limits meaningful conclusion. For what it is worth, 86% had no resistance and the remainder had some form of NRTI resistance including 7% with M184V/I mutations. Results showed that patients already suppressed on tenofovir/FTC + dolutegravir largely stay suppressed on the same regimen or on TAF/FTC/BIC, at 93% in the BIC arm and 91% in the DTG one at week 48. Choosing an already suppressed population really does not tell us if TAF/FTC/BIC is a good choice in people with 3TC/FTC resistance and we need to see this regimen challenged in people experiencing virological failure with genotypic resistance.

New antiretroviral drugs

The 96-week results of the BRIGHTE study showed impressively high rates of viral suppression in a highly treatment-experienced group of individuals, failing their current therapy at enrolment, treated with gp120 attachment inhibitor fostemsavir [17]. This study included two cohorts: the randomised cohort (the randomisation was addition of fostemsavir or placebo to the failing regimen for 8 days) were required to have 1 or 2 ARV classes remaining with ≥1 fully active approved agents per class and no reasonable, viable alternative regimen based on current agents; the second cohort had no fully active approved agents remaining. Despite this challenging starting point, week-96 viral suppression (<40 HIV-1 copies/mL) rates were 60% for the randomised cohort and 37% for the non-randomised one with on-treatment responses of 79% and 59%, respectively. At the time of writing, manufacturing

issues have led to a postponement of the fostemsavir compassionate access scheme in the US and limited its rollout elsewhere; however, those issues are reported to be resolved and we should hear more about compassionate access in late 2019.

Data for islatravir (ISL), previously known as MK-8591, the first nucleoside reverse transcriptase translocation inhibitor, was also presented, [18]. Its unique mechanism of action is associated with a high barrier to resistance and activity against many NRTI resistance mutations. In the Phase 2b, double-blind, placebo-controlled Protocol 011, 120 treatment-naïve individuals were randomised to one of three ISL doses with doravirine (DOR) and 3TC or to TDF/3TC/DOR for 24 weeks. At week 24, participants virally suppressed on ISL-based therapy dropped 3TC, remaining on ISL + DOR. After a further 24 weeks viral suppression rates remained high and similar to those observed in the group who stayed on TDF/3TC/DOR (89–96%). There were no protocol-defined virological failures meeting criteria for resistance testing (all viral loads were <80 HIV-1 copies/mL) and ISL + DOR was well tolerated. Phase 3 studies are planned.

Finally, we saw the first virological efficacy results for GS-6207, a capsid inhibitor, in an ongoing double-blind, placebo-controlled, dose-finding Phase 1b study in 24 ART-naive individuals [19]. After a single, subcutaneous dose, the average viral load reduction in the three active arms was 1.8–2.2 log HIV-1 copies/mL with no serious adverse events and no grade 3/4 side-effects or laboratory abnormalities. This compound is under further study as a long-acting antiretroviral.

Novel implant delivery of ART

Randolph Matthews (MSD, USA) introduced a prototype of an islatravir (ISL) subdermal implant, its pharmacokinetic and pharmacodynamic data with regards to pre-exposure prophylaxis, along with its safety data. In this placebo-controlled, double-blinded trial among 10 healthy individuals, two ISL subdermal implant prototypes containing 54mg and 62mg of ISL respectively were investigated. At week 12, participants in both study arms demonstrated ISL concentrations above the pre-exposure prophylaxis pharmacokinetic thresholds. Additionally, the ISL implant containing 62mg was projected to maintain ISL concentrations well above this threshold level for >12 months. Both implants were generally well tolerated through to 12 weeks, with only mild to moderate drug-associated side effects reported.

Dolutegravir safety update at conception and risk of neural tube defects

Rebecca Zash (Beth Israel Deaconess Medical Centre, Boston, USA) presented an updated analysis report from the Tsepamo birth outcomes surveillance, which showed that as of March 2019, the incidence of neural tube defects (NTD) amongst 1683 females who conceived on DTG in Botswana had reduced from 0.94% (95% CI 0.37 to 2.4) to 0.30% (CI 0.13 to 0.69), since the initial analysis in May 2018. She also reported that the NTD incidence among females who were exposed to an ART regimen that did not include DTG at conception had reduced from 0.12% to 0.10%.

The World Health Organization (WHO) have updated their guidelines on preferred first- and second-line therapy for adults and adolescents, including females of child-bearing age, due to the benefits of DTG over efavirenz (EFV), though they recognise the declining but still significantly higher risk of NTD incidence in females who conceived on DTG. WHO also recommends that all females of childbearing age who wish to become pregnant or are not on effective contraception should be fully informed regarding the potential risk of NTDs, and that birth surveillance should continue.

Dolutegravir and weight gain

Michelle Moorhouse (University of the Witwatersrand, Johannesburg, South Africa) presented new data on DTG and weight gain (WG) from the NAMSAL (ClinicalTrials.gov Identifier: NCT02777229) and ADVANCE trials (ClinicalTrials.gov Identifier: NCT03122262) studies [14].

The NAMSAL study compared weight gain and body mass index (BMI) amongst HIV-1 positive participants who received TDF + FTC + DTG (n=293) and TDF + FTC + 400 mg EFV (n=278) in Cameroon. At week 48, both arms demonstrated in participants increase in weight (5 and 3kg, respectively) and BMI, with significantly higher body weight (BW) gain noted in the DTG arm compared to the EFV one.

The ADVANCE randomised study compared F/TAF + DTG, TDF + FTC + DTG and TDF + FTC+ EFV with nearly 350 HIV-1 positive participants in each arm. The 96-week data showed that there was a mean BW increase of 8 kg, 5 kg and 2 kg, respectively in each arm, and significantly higher increase in the DTG arms, compared to EFV. Increases in BMI and treatment-emergent obesity were also observed across all three arms. Participants in the F/TAF+ DTG arm showed greatest increases in all three parameters compared to the other two arms.

Both studies highlighted previously unreported findings of dramatic WG observed particularly in African women, with many participants entering the 'obese' BMI range. Weight gain amongst females were higher than males in all three arms in the ADVANCE trial, the highest mean WG being seen in women in the F/TAF+ DTG arm, at 10 kg with a progressive upward trend at 96 weeks. This phenomenon was not reported in the previous licensing studies, which were conducted predominantly amongst white ethnicity men. The WG seen in these studies was deemed to be significant and could not solely be accounted for by a 'return to health' for participants with previously advanced HIV disease.

The second generation of integrase inhibitors (INSTI) provides an option with a high genetic barrier without the complications of pharmacokinetic boosting. Dolutegravir with lamivudine offers a real alternative to triple therapy, both first-line and in suppressed switch, and has now become one of the options considered as 'standard of care'. Bictegravir (BIC) certainly maintains efficacy when substituted to DTG in suppressed patients, including in some with historical resistance, but is available only as co-formulated with TAF/FTC. The lack of BIC data in people experiencing virological failure and our inability to use it in novel ways are some of the present limitations. Whether the successful results of the GEMINI and TANGO studies will trigger the release of BIC from its fixed-dose combination remains uncertain. The ADVANCE study demonstrated again the high barrier of DTG-based first-line therapy but also supports the continued use of EFV where options are limited.

Despite the excellent success rates for our modern therapy, we will always need new options for some patients. Fostemsavir may be a lifesaver for individuals with limited treatment options. The hopefully imminent compassionate release programme is welcomed. In earlier development, islatravir and GS-6207 offer new mechanisms of action, and in the case of GS-6207, another option for long-acting therapy that will undoubtedly play a part in HIV-1 treatment in the future.

Comorbidities

Whether people living with HIV/AIDS (PLWHIV) should start primary preventive therapy for cardiovascular disease (CVD) at a different threshold than HIV-1 negative individuals remains

unclear because the risk scores used to predict myocardial infarction (MI) lack sensitivity and specificity in people with HIV infection. Researchers in Australia and Switzerland planned a study to see whether 96 weeks of rosuvastatin (ROSU) slowed carotid intima media thickness (cIMT)-determined atherosclerotic progression in people with moderate CV risk who do not meet the standard criteria for initiating statin therapy. Janine Trevillyan (University of California, Los Angeles, USA) presented results of this double-blind, placebo-controlled trial. Eighty-four individuals with well-controlled HIV-1 (<200 copies/mL, stable ART for >3 months) who were at moderate CVD risk (10 year Framingham risk score of 10–15%) with no clear indication for statin therapy, were recruited from a single centre in Australia and four centres in Switzerland [20]. All participants had cIMT assessment and fasting bloods at baseline, week 48 and 96. Seventy-six participants completed week 48 and 73 week 96 follow-up. Framingham risk score averaged 11% in both groups. Total cholesterol and LDL cholesterol both fell significantly with ROSU compared to placebo by week 24, with participants maintaining this difference through weeks 48 and 96 (P<0.001 for all). There was no difference in baseline cIMT between groups (P=0.115). Despite significantly decreases in low-density lipoprotein (LDL) cholesterol with ROSU (mean change −1.06 *vs* −0.06mmol/L, P<0.0001), there was no difference in IMT or cIMT progression from baseline to week 48 or 96 in those on ROSU (P=0.319). At week 96 there was no difference in cIMT between treatment arms (P=0.097). ROSU for 96 weeks decreased total and LDL cholesterol in PLWHIV at moderate CVD risk, but did not slow atherosclerotic progression as estimated by cIMT. Because the statin did increase the risk of side-effects, the conclusion was that 'the benefits of statin therapy in PLWHIV at low-moderate risk may not justify potential harms.' The currently running REPRIEVE trial will probably help in terms of the recommendations for primary preventive therapy in PLWHIV (REPRIEVE. Randomized trial to prevent vascular events in HIV: www.reprievetrial.org/).

Hugo Perazzo (Fundação Oswaldo Cruz, Brazil) delivered the results of the PROSPEC-HIV study (ClinicalTrial.gov. Prospective evaluation of HIV patients using non-invasive methods for estimation of liver fibrosis and steatosis [PROSPEC-HIV]) evaluating the accuracy of serological biomarkers to detect non-alcoholic fatty liver disease (NAFLD) and/or advanced liver fibrosis in HIV-1 mono-infected patients [21]. From June 2015 to January 2018, PLWHIV were prospectively enrolled and assessed clinically with laboratory testing and liver stiffness measurement (LSM)/controlled attenuation parameter (CAP) using transient elastography (fibroscan). Serological biomarkers for steatosis (Steato-ELSA, fatty liver index [FLI], hepatic steatosis index [HSI], NAFLD liver fat score [NAFLD-LFS]) and fibrosis (FIB-4, APRI and NAFLD fibrosis score [NFS]) were calculated. Among 674 people enrolled in the study, 437 met the entry the criteria for this analysis, among whom 167 (38%) had NAFLD and 46 (10.5%) advanced fibrosis. Median age of participants was 44 years with 57% women, 52% black or mixed parentage, and 42% current or former smokers. Among all participants, 96% took ART, 82% had a viral load <40 HIV-1 copies/mL with a median CD4 T cell count at 620 cells/mm^3. The FLI, NAFLD-LFS, HSI and Steato-ELSA were all significantly higher in participants with than without NAFLD (CAP ≥248) (P<0.001 for all). Area under the receiver operating characteristic curve (AUROC) for detecting NAFLD was high for all 4 biomarkers: 0.854 for Steato-ELSA, 0.840 for FLI, 0.805 for HSI, and 0.793 for NAFLD-LFS. Steato-ELSA ≥0.386 had reasonably balanced sensitivity and specificity for detecting NAFLD (81% and 74%), as did FLI ≥60 (75% and 76%). AUROC used for detecting advanced fibrosis (METAVIR F3/F4) was also high for each of the three biomarkers assessed: 0.7950 for NAFLD-Fibrosis Score, 0.736 for FIB-4, and 0.700 for APRI. Specificity and negative predictive values were high for FIB-4 at ≥3.25 (99% and 90%), APRI at ≥1.5 (99% and 90%), and NAFLD-fibrosis score at ≥0.676 (98% and 90%). Researchers concluded that serologic biomarkers (especially FLI and Steato-ELSA) had good accuracy in detecting NAFLD, while all three markers assessed had high specificity and negative predictive value for advanced fibrosis.

Researchers from Vancouver studied the effect of smoking and HIV-1 viremia on somatic mitochondrial DNA (mtDNA) point mutations and biological aging. Hélène Côté (University of British Columbia, Vancouver, Canada) presented results of this cross-sectional study on 92 HIV-1 positive and 72 HIV-1 negative girls and women aged 1 to 62 years, enrolled in the CARMA cohort, absence of HBV or HCV coinfection, and either current or never smokers [22]. Current theories on ageing describe both *de novo* mutations (low-level or somatic mtDNA substitutions) and clonal expansion of pre-existing mutations (higher-level or heteroplasmic mtDNA substitutions) as potential mechanisms for the accumulation of mtDNA mutations. Being older (P=0.003) and having a peak HIV-1 viremia ≥100,000 copies/mL (*vs* HIV-1 negative) (P=0.045) were independently associated with higher somatic mtDNA mutation frequency. The MtDNA heteroplasmic level among all participants (n=164), was associated with older age (P=0.008) and being a current smoker (P<0.001) but not with living with HIV-1 infection. An interaction was observed between age and smoking. Thus, exposure to high HIV-1 viremia may contribute to increased mtDNA mutations and accelerated ageing in some people living with HIV-1. In contrast, smoking seemed to promote clonal expansion of mutations rather than increase of *de novo* mutations. This too may be consistent with the knowledge that smoking promotes age-related diseases. Serological biomarkers accurately predicted steatosis, their use in patients with fibrosis demonstrating high specificity.

M Gabriella Cabanilla (University of new Mexico Hospitals) retrospectively assessed the risk of polypharmacy and inappropriate prescribing in PLWHIV who were at least aged 65 years when seen at their hospital from January 2015 to August 2018 [23]. Polypharmacy was defined as taking ≥5 medications and inappropriate prescribing using the 2012 Beers, 2011 STOPP, and START criteria. To identify potential HIV-1 drug–drug interactions, they used the University of Liverpool HIV drug interactions site (University of Liverpool, HIV drug interactions: www.hiv-druginteractions.org/checker). Of the 112 study participants, 99 (88%) were men, 97 (87%), were white and 66 (59%) were men who have sex with men (MSM). Average age was 68 years and duration of HIV-1 infection 20.3 years. Ninety-eight individuals (87.5%) were suppressed at <20 HIV-1 copies/mL. Participants were prescribed an average of 12.3 medications, including 9.0 non-HIV-1 related ones. Most of them (73%) took only one or two ARV pills and 86% an OD ARV. Amongst all participants, 98% and 84% met the criteria for polypharmacy when considering all or only non-HIV-1 medications. Two thirds of participants (65%) had ≥1 adverse events (AEs). Polypharmacy correlated with greater risk of inappropriate prescribing as judged by serious drug–drug interactions (r=0.54, P<0.01), Beers (r=0.30, P<0.01) and STOPP criteria (r=0.36, P<0.01). Inappropriate prescribing correlated with AEs by Beers (r=0.31, P<0.01), STOPP (r=0.29, P<0.01) and START criteria (r=0.29, P<0.01), and serious drug–drug interactions (r=0.26, P<0.01). Over half of the study participants had >1 prescribing errors by START (79%), drug–drug interaction (63%), or STOPP criteria (54%). The authors concluded that the study 'highlights the pervasiveness of polypharmacy in the aging HIV population, which was driven by non-HIV co-medications.'

HIV-1 prevention

Prevention of HIV-1 acquisition at the Conference included some outstanding sessions which were dominated by universal test and treat, HIV testing delivery, but especially ART for prevention (U=U campaign or Undetectable=Untransmittable) and pre-exposure prophylaxis (PrEP) for HIV-1 negative individuals.

Jean-Michel Molina (St-Louis Hospital and University, Paris, France) discussed the clinical management of PrEP users who test positive for HIV-1 [24]. There are multiple causes for testing HIV-1 positive in these individuals despite PrEP high efficacy, including prophylaxis discontinuation and low adherence [25], HIV-1 infection before PrEP initiation (generally due to false-negative results of HIV screening tests) [26,27], breakthrough infection with a resistant virus [28], breakthrough infection with a susceptible virus despite high PrEP adherence [29] and false-positive HIV-1 tests. The impact of the M184V mutation documented in all resistant clinical cases [30] does not seem to influence the effectiveness of tenofovir/emtricitabine (TDF/FTC) PrEP in the macaque models [31], potentially because although it confers high levels resistance to FTC, it also provides hypersensitivity to TDF. On the contrary, virus containing the K65R mutation may overcome the PrEP effectiveness in macaque models [32]. More experience is needed in order to manage ambiguous HIV-1 test results during PrEP and repeat testing should be considered to resolve false-positive results. It is critical to rule out PHI before initiating PrEP, as well as repeat testing at 1 month and every 3 months after PrEP initiation.

Daniel Kuritzkes (Harvard University Centre for AIDS Research, USA) discussed the concerns about HIV-1 resistance in the setting of PrEP as the drugs are similar to those used for treatment and selection of drug resistance after PrEP failure could compromise ART efficacy and increase the overall prevalence of pre-existing drug resistance [33]. Even if common drugs approved for PrEP require only a single mutation to confer high-level resistance, a low genetic barrier may be mitigated by the fitness cost of resistance mutations and high tissue concentrations. In a recent systematic review by Gibas *et al.* with 699 participants with HIV-1 seroconversion identified in 13 PrEP trials, drug resistance mutations were detected in 23% of participants with PHI at the time of enrolment and in only 3% of participants with incident infection during the follow-up period, suggesting that the greatest risk of developing resistance is the use of PrEP in undiagnosed acute HIV-1 infection [34]. Resistance to FTC is more likely to emerge than to TFV. Prevalence of the K65R mutation in the general population is quite rare in the US, Western Europe and Australia, but much higher at the time of treatment failure in resource-limited settings [35]. While long-acting formulations offer potential advantages for PrEP, their long half-life and extended tail [36] carry unknown risk of resistance if exposure to HIV-1 occurs during the tail period [37].

Jean-Michel Molina also described an interim report on the incidence of HIV-1 infection with daily or on-demand PrEP with TDF/FTC in the Paris area on behalf of the Prevenir ANRS Study Group [38]. This is an ongoing prospective cohort study enrolling individuals at high risk for the acquisition of HIV-1 infection on PrEP. From 3 May 2017 to 2 May 2019, 3057 individuals were enrolled across 26 sites in the Paris region. Median age was 36 years (IQR: 29–44) with 98.7% MSM. At enrolment, PrEP was used daily in 50.8% and on demand in 49.2% of participants. Median number of partners in the last 3 months was 12 (IQR: 6–25) in the daily group and 10 (IQR: 5–15) in the on-demand one (P<0.001). Median number of condomless sex events in the prior 4 weeks was 2 (IQR: 0–6) and 2 (IQR: 0–4), respectively, (P<0.001). Current follow-up was 1072.9 and 1132.7 person-years (PY) in the daily and on-demand groups, respectively. The HIV-1 incidence was 0 (95% CI 0 to 0.3) and 0.2 (95% CI 0 to 0.6) per 100 PY in the daily and on-demand groups, respectively (P=0.132). The HCV incidence was 0.8 and 1 per 100 PY, respectively, with a 38% per year (P<0.001) increased incidence of bacterial sexually transmitted infections (STIs). No breakthrough of HIV-1 infection was reported so far in participants choosing either daily or on-demand PrEP, supporting continuing use of both dosing regimens in this population.

Christophe Spinner (University Hospital Rechts der Isar, Germany) reported a supplementary analysis of the DISCOVER study for PrEP where F/TAF was found to be statistically non-inferior to F/TDF [39]. However, there were numerically 53% fewer HIV-1 infections in the F/TAF arm. Further analysis was performed on the sexual behaviour for HIV-1 risk of acquisition, STI incidence, adherence, and pharmacokinetic (PK) data to evaluate any differences between the two combinations which could explain this imbalance in this trial participants (n=5,387). There was no difference in HIV-1 risk behaviour, prevalence or STI incidence, self-reported adherence, pill count or adherence by TFV-DP levels in dried blood spots (DBS) at the HIV-1 diagnostic visit (n=536). The levels at week 4 of TFV-DP peripheral blood mononuclear cells (PBMCs) (n=324; randomised subset) were 6.3-fold higher with F/TAF *vs* F/TDF. There were 98% of F/TAF *vs* 68% of F/TDF participants who had TFV-DP above the protective threshold EC90 (P<0.001). Median duration of protection after the last dose at steady state was 60% longer for F/TAF as compared to F/TDF. A low DBS TFV-DP level (intake of less than two PrEP doses/week) was independently associated with an increased risk of HIV-1 acquisition with F/TAF (odds ratio [OR] 29.4) and for F/TDF (13.2), (P<0.001 for both) with similar results from sensitivity analyses, thereby excluding suspected baseline infections. The relationship between low PBMC TFV-DP concentrations and increased risk of HIV-1 acquisition was established from iPrEx data [40]. There was no difference in HIV-1 risk, adherence or STIs between arms, but significant differences in TFV-DP levels.

Therefore, TAF has advantageous PK parameters for HIV-1 prevention compared to TDF, including a more rapid onset of action and more prolonged sustained duration of TFV-DP levels above the protective threshold in PBMCs, which may explain the lower number of HIV-1 infections in the F/TAF *vs* F/TDF in the DISCOVER study.

Li Tao (Gilead Sciences, Foster City, USA) presented a pooled analysis of the effect of adherence on the renal safety (renal AEs and laboratory abnormalities) of FTC/TDF (Truvada) for PrEP in a large, globally diverse pool of seven PrEP international projects [41]. Among the 2823 participants receiving FTC/TDF PrEP, 99% were MSM, with 50% in the US, 47% in South America, 2% in Asia, and 1% in Africa. Median age at PrEP initiation was 29 years, (IQR: 24–38) and PrEP exposure duration 8.4 months (IQR: 2.9–11.0). A total of 157 (5.6%) participants reported renal AEs) within 1 year of PrEP initiation with an incidence rate/100 person-years for renal AEs (IR 0.63, 95% CI [0.27 to 1.48], 1.67 [0.80 to 3.51], 3.71 [2.13 to 6.47] and 4.77 [2.59 to 8.79], respectively, for participants taking <2, 2–3, 46 or ≥7 tablets/week. Of 2157 participants with >1 creatinine test during follow-up, 72 (3.3%) had at least one >1.3 mg/dL, 81% of whom were taking ≥4 [IR (95% CI), 1.21 (0.51 to 2.88)], 13% 2–3 [1.08 (0.42 to 2.79)], and 7% <2 PrEP tablets/week [0.30 (0.09 to 0.95)]. The percentage of creatinine change from baseline increased with level of adherence. Incidence of renal AEs and creatinine over 1.3 mg/dL increased with older age. Individuals who were 25 years and older and took ≥4 tablets/week were

more likely to have elevated creatinine, compared with younger or non-adherent individuals. These results underscore the importance of assessing and monitoring renal function for individuals using FTC/TDF for PrEP.

The main HPTN071 (PopART) trial result was reported at CROI 2019 in Boston and recently published [42] showing as in other HIV combination prevention trials such as the SEARCH [43] and Ya Tsie studies [44] that delivery of a community-wide HIV intervention has the capacity to reduce incidence. This was a randomised trial across 21 high HIV-1 burden urban communities in Zambia and South Africa reaching a total study population of 1 million individuals. In a special session at the Conference, data were presented on the mathematical modelled outcomes, using an individual-based model, on HIV-1 incidence by 2030. Models investigated HIV-1 incidence reduction between communities that continued to receive a PopART-like intervention, which included community-wide annual HIV testing, linkage to care for all those testing HIV-positive with immediate ART offered and referral to HIV prevention approaches for those testing HIV-negative, compared with the current standard of care in the same communities in Zambia and South Africa. William Probert (University of Oxford, UK) demonstrated that there would be an increased impact if a PopART-like intervention was to be supported out to 2030 and showed with high validity that up to 50% reduction in HIV-1 incidence could be achieved. Katharina Hauck (Imperial College London, UK) showed that continuing the same PopART-like community-based intervention would be highly cost effective in both countries up to 2030, although not cost-saving.

Janssen presented the results of two Phase 1/2a of an investigational preventive vaccine using their Ad26 mosaic vaccine, the APPROACH and ASCENT studies. Data from APPROACH, presented by Dr Tomaka, described a 2-year follow-up of healthy HIV-1 negative volunteers who received 4 dose of Ad26Mos.HIV and *gp140env* vaccine. No safety issues were reported and no HIV infections have been identified in any of the 65 participants up to week 144. Thirty-two participants received the high-dose *gp140* and 33 the low dose, and in both groups, there was 100% humoral response to autologous clade C *env* protein. Cellular response was also maintained out to week 144 against clade C *env* as measured by ELISpot. It was highlighted that participants who responded well to the first vaccine dose, as determined by antibody levels or ELISpot assay, had a higher level of response at all subsequent time points. When the response in human volunteers was compared to that in non-human primates (NHP) in challenge studies, it was shown that up to week 144, healthy volunteers maintained antibody levels higher than those in the NHP protected against subsequent SHIV challenge.

In the APPROACH study presented by Dr Stieh *et al*. a variant of the vaccine components used in the ASCENT study was tested. This contained either a monovalent clade C *gp140* or a bivalent clade C-Mosaic1 *gp140* with the aim of widening the breadth of response without compromising the clade C response. Data presented showed that the use of the bivalent Mosaic *gp140* increased the breadth and magnitude of the humoral response against a range of *gp140* and V1V2 antigens. The antibody-dependent cellular phagocytic response was comparable as was the ELISpot one against a series of *env* proteins. $CD4^+$ and $CD8^+$ T cell responses against *env* peptides were also greater in those given the bivalent vaccine. In terms of safety, there were no related serious adverse events (SAEs) or HIV infections up to the time of data collection at week 52, 4 weeks after the last vaccine immunisation. Adding the Mosaic *gp140* had no negative impact on the response to the clade C component of the vaccine and led to improved clade B and Mosaic specific responses. The Ad26Mos.HIV and bivalent *gp140* regimen has been chosen for the MOSAICO Phase 3 efficacy study planned to start recruiting from September 2019.

In an attempt to enhance the *gp120* antibody response following DNA/MVA vaccination, addition of *gp120* protein boosts using MVA/HIV62B was explored [45]. Boosts were given with or without alum-adjuvanted protein boosts. Either approach was shown to enhance antibody response to both *gp120* and V3. Boosting was shown to enhance *env* but not *gag* responses. Vaccinations were unable to prevent infection following challenge, but impacted on post-challenge viremia levels with the best control being seen in animals vaccinated with a regimen of a DNA prime, two boosts of MVA + B.635211 + rhFLSC, which correlated with levels of binding Ab to *gp120*.

A novel approach to vaccination, using twelve 20-amino acid peptides derived from protease cleavage sites was presented by Dr Luo *et al*. In a macaque model of infection, the group used a modified recombinant vesicular stomatitis virus (rVSV) to deliver peptides following with intramuscular or intranasal vaccination. Six months after the last booster, the vaccine regimen being five vaccinations over 72 weeks, animals were challenged intra-vaginally. In the group of eight, it took 11 challenges to infect 50% of the vaccinated animals compared to two challenges to infect 50% of the placebo-vaccinated animals, which the presenters found equated to over 80% risk reduction/challenge.

It is widely believed that for a vaccine to be effective, it needs to generate neutralising Abs. The presentation from Dr Arthos revisited what is probably the most successful vaccine study to date, the RV144 Thai study. The study looked at the role of non-neutralising Abs that mapped to the V2 region of the HIV *env* protein and protection following vaccination. They demonstrated a high degree of cross-reactivity between HIV and SIV Abs, something that is uncommon. They also showed that the V2 region is present in more than one conformation, and that it was the non-neutralising Abs against the helix/loop conformation that was linked with protection in the RV144 vaccine study. This raises the possibility that broadly cross-reactive non-neutralising Abs may be playing a key protective role in vaccine-induced immunity.

Dr Kopycinski presented data from the therapeutic vaccine arm of the RIVER trial that was aimed to assess an eradication strategy using ART, vaccination and latency-reversal. The study failed to demonstrate an impact of the added intervention on the size of the HIV-1 reservoir compared to the use of ART alone. What the study did find was that the CD4 T cell response dropped ~2.2-fold between enrolment and randomisation following ART, whereas the CD8 T cell response did not significantly do so during the same time period. Both CD4 and CD8 T cell responses were significantly enhanced following vaccination, with a median of 17- and 4.2-fold increase, respectively. No single marker was able to differentiate between virus- and vaccine-induced CD8 T cell responses. However, using machine learning, it was possible to identify distinct profiles and differences between the two arms. The ART-only arm showed evidence of dysfunction, whereas the ART and added intervention allowed boosting of HIVconsv-specific CD8 T cells, potentially leading to the induction of functional HIV-1 specific CD8 T cell responses.

Conclusions

This meeting provided for lots of excitement among attendees owing to the amount of new data in the various research and treatment fields which are important to PLWHIV, researchers and healthcare workers.

Conflicts of interest

Malcolm Macartney is a full-time employee of Janssen and a shareholder in Johnson and Johnson. Sabine Kinloch has received advisory board honoraria from ViiV and Janssen. Tristan Barber has received conference support, advisory board honoraria and speakers fees from Gilead, Roche, Janssen, MSD and ViiV. He has received grant support from Gilead and ViiV. Laura Waters has received Speaker/advisory fees from Gilead, ViiV, Janssen, MSD, Cipla and Mylan. All other authors declare no conflicts of interest.

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