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Highlights from the 9th IAS Conference on HIV Science, 23–26 July 2017, Paris, France

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Introduction

The 9th International AIDS Society Conference on HIV Science (IAS 2017) took place at the Palais des Congrès, in Paris, France, from 23 to 26 July 2017, chaired by Linda-Gail Bekker and Jean-François Delfraissy. It was organised by the International AIDS Society (IAS) in partnership with ANRS (the French national agency for research on AIDS and viral hepatitis), bringing together more than 6000 leading scientists, researchers and HIV professionals from around the world. The Conference featured more than 1800 abstracts selected for oral and poster presentations out of over 4300 submissions, in addition to plenary sessions and satellite symposia.

Prevention was high on the agenda of this year's Conference. Data relevant to children, adolescents and adults with HIV on recent advances in the understanding of viral–host interactions, targeting of the HIV reservoir, new oral and long-acting antiretroviral drugs, strategies for simplification of treatment regimens, immune-based therapies, pre-exposure prophylaxis (PrEP) to HIV, prevention of mother-to-child transmission, prophylactic and therapeutic vaccines, as well as comorbidities including hepatitis, were presented with an emphasis on translating science into practice and policies.

HIV prevention

In a satellite symposium around systemic pre-exposure prophylaxis (PrEP) organised by the HPTN/FHI 360, Myron Cohen (University of North Carolina School of Medicine, USA) gave an overview of the field. He discussed the combination of four preventative methods, namely behavioural to avoid exposure, precoital/coital and postcoital to decrease the effect of potential transmission, and treatment as prevention (TasP) in order to reduce infectivity of people living with HIV (PLWH). The challenge of sustained adherence to a daily PrEP regimen such as oral Truvada and the need to develop new agents such as long-acting (LA) injectable formulations, broadly neutralising antibodies (bNAbs) and antiretroviral (ARV) implants were also considererd.

The case for HIV prevention using monoclonal antibodies (mAbs) was presented by Nyradzo Mgodi (University of Zimbabwe)(MOSA0203). The AMP (antibody-mediated prevention) study is a Phase 2b trial that is under way and includes two harmonised proof-of-concept trials. It will evaluate the efficacy of the VRC01 bNAb that targets the CD4 binding site of the HIV-1 envelope protein among high-risk populations in 47 sites and 11 countries. VRC01 neutralises 90% of 190 strains tested. It is the first mAb to enter into advanced human clinical testing for prevention. Questions remain over whether it can provide protection from infection with adequate levels of mAb and if antibody-dependent cell-mediated cytotoxicity (ADCC) is needed for efficacy. The combination of VRC01 with a next-generation neutralising antibody, VRC07-523 LS, is likely to improve the potency and breadth of protection in humans.

Thomas Hope (Northwestern University, USA) presented the next generation drug and delivery modalities for PrEP (MOSA0204), namely sustained LA protection against HIV (SLAP-HIV). SLAP-HIV includes injectable formulations as well as biodegradable and removable implants. It remains to be shown whether these have an efficacy comparable to oral and systemic PrEP versus topical PrEP such as microbicides, and whether prevention of HIV acquisition also occurs at the cellular level. In a small study conducted in nine pigtail macaques that were vaginally challenged with SIVmac239, immunostaining and fluorescent microscopy revealed that smaller foci of infected cells were observed in animals treated with oral PrEP compared to topical PrEP, such as with an intravaginal ring. Indeed, in terms of herd immunity, systemic PrEP can prevent systemic infection even if the drug coverage is suboptimal.

Connie Celum (University of Washington, Seattle, USA) analysed how to optimise oral PrEP delivery (MOSA0205). PrEP is a safe and effective preventative option; however, stigma, and lack of knowledge and access, are key barriers to its use. Young African women are particularly at risk of HIV infection, representing over one-third of new HIV infections. Several studies are under way to try to understand PrEP uptake and adherence issues in these women in order to develop effective messaging, easier delivery options and interventions, and to maximise adherence, by using interventions such as peer support and open discussions. She concluded by suggesting a personalised PrEP approach to provide positive and engaging messaging, as well as simple delivery procedures.

During one of the plenary sessions Sheena McCormack (MRC, London, UK) (TUAC0101) presented in her talk 'Adding D to the ABC: Putting the Drugs in the ABC of Prevention' updated results of the PROUD study long-term follow-up through to November 2016. These data showed that the benefit of such intervention was sustained with high PrEP persistence [1]. In this study men who have sex with men (MSM) (n=544) attending sexual health clinics in the UK were randomised to receive daily tenofovir/emtricitabine (TDF/FTC), either immediately (IMM), or after a 12-month deferral period (DEF). PROUD was initiated after clinical trials that first established that TDF/FTC PrEP was efficacious for HIV prevention, but questions remained about what its effectiveness might be in real-world settings. The main efficacy outcomes were based on the DEF phase, when IMM, but not the DEF participants, had access to PrEP. It was shown in this trial that PrEP reduced HIV incidence by 86% among those assigned to IMM use. In the DEF group, 206 of 269 eventually started PrEP and about two-thirds were still taking PrEP at the end of the

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follow-up, which was, for some, 3 years after starting in the trial. Since November 2016 all participants have been offered PrEP and the trial has entered into the post-DEF phase. Investigators have compared HIV incidence rates and selective sexually transmitted infections (STIs) during the DEF and post-DEF phases. There was no difference in terms of HIV incidence between groups in the post-DEF phase (P=0.18), but a decreased incidence was noted in the DEF participants once they had had access to PrEP (P<0.0001). The rate of HIV acquisition in the IMM group remained similar during the two trial phases (P=0.66). Three years after PrEP initiation, reduction in HIV incidence was sustained, thereby confirming high adherence and durable effectiveness of PrEP in this population. The most likely reason for new HIV infections was the lack of PrEP intake at the time of exposure. The incidence of rectal STI infections was high in both groups and trial phases.

The MWRI-01 trial, headed by Ian McGowan (University of Pittsburgh, USA) (TUAC0103) aimed to evaluate the safety and acceptability of long-acting (LA) rilpivirine (RPV) given as an intramuscular (IM) injection, with exploratory analyses of HIV infection in cervical, vaginal and rectal explants after exposure to the compound [2,3]. Three 1200-mg IM doses of LA RPV were shown to be safe and acceptable. Mild-to-moderate injection site pain was the most common adverse event reported. In the rectal explant, inhibition of both subtype B and C virus persisted up to 4 months after the last injection and for 2 months in the cervical explant after the first injection.

Katherine Bunge (University of Pittsburgh, USA) presented the results of a Phase 2a trial in US adolescents of a 25-mg dapivirine (DAP) vaginal ring or placebo inserted every 4 weeks for 24 weeks (MTN-023/IPM-030) [4]. There had been no protection in the two previous double-blind placebo-controlled trials in 18–21-year-old participants because of poor adherence [5,6]. In this new trial, it was shown to be safe and acceptable in this population (15–17-year-olds) from six US cities in a 96-person (randomisation 3:1) placebo-controlled trial, and a high level of adherence was found when testing for plasma DAP levels and residual drug levels in used rings.

Sharon Hillier (University of Pittsburgh, USA), presented data evaluating whether vaginal microbiota associated with bacterial vaginosis impacted on dapivirine concentrations in the genital tract tissues and plasma following vaginal application [7]. There was no association found between increasing vaginal concentrations of *Gardnerella vaginalis* as detected by qPCR and dapivirine (DAP) concentrations in cervical tissue or plasma (P=0.93 and 0.99, respectively), this is in contrast to tenofovir, suggesting that DAP levels following vaginal application are not impacted by the microbiota associated with bacterial vaginosis.

Raphael Landovitz (Center for Clinical AIDS Research and Education, USA) presented results from the HPTN 077 study regarding safety, tolerability and pharmacokinetics of injectable long-acting cabotegravir (CAB LA) in low-risk HIV-uninfected women and men [8]. This study is a multi-site, double-blind, randomised (3:1), placebo-controlled trial including two ongoing cohorts (2×400-mg IM injections every 12 weeks or 1×600-mg IM injection every 8 weeks) in a total of 199 participants, aged 18–65 years, at eight sites in Brazil, South Africa, Malawi and the USA. The CAB LA was well-tolerated at doses of 800 mg (2×2 mL) and 600 mg (1×3 mL) in HIV-uninfected and low-risk males and females. Injection site reactions (ISR) were frequent but generally mild with only one (0.75%) participant discontinuing injections. The 600-mg IM every 8 weeks dosing schedule, after a 4-week loading dose, consistently met pre-specified pharmacokinetic (PK) targets in both sexes and is being evaluated in Phase 3 efficacy studies in at-risk individuals.

The session on the 'Next Wave of Prevention Options' (SUSA15) offered an update on the future pipeline of products. Alex Rinehart (ViiV Healthcare, USA) gave an update on prevention with the injectable CAB LA (SUSA1502). Preclinical and clinical data support its use for HIV treatment and prevention (HPTN 083 and HPTN 084 Phase 3 trials, in MSM/TGW and women, respectively, using CAB LA at 600 mg). Challenges remain, such as the date of the trial end, which is dependent on the background incidence and seroconversion rates, how to manage the 'PK tail', and the potential for resistance development.

Kenneth Mayer (Fenway Institute, USA) evaluated the community perceptions on HIV prevention options (SUSA1504). Among 4638 MSM, who responded to an online survey, a large majority (78%) had heard of PrEP, but only 15% had ever used it. Interest in other PrEP modalities was high, with a preference for antibody infusion and injectable ARVs rather than the topical rectal approach.

Antiretroviral therapy

New drugs and formulations were described in several trials as well as new ways to use current drugs, including treatment simplification and novel dosing.

The large focus on a new agent was for the single-tablet regimen (STR) of the new integrase inhibitor, bictegravir (BIC) 50 mg combined with tenofovir alafenamide (TAF) 25 mg and emtricitabine (FTC) 200 mg, with data presented from two trials (GS-1489/1490). The first, presented by Joel Gallant (Southwest CARE Centre, USA), a Phase 3, placebo-controlled study, compared BIC/FTC/TAF to Triumeq (dolutegravir/abacavir/lamivudine – DTG/ABC/3TC) and showed non-inferiority of the investigational combination drug [9].This study took place in North America and Europe and randomised (1:1) 629 subjects, with a median age of around 31 years. The subjects were 90% male and 36% were of black ethnicity. Entry requirements to the study included an eGFR above 50 mL/min, to be HLA-B*5701 negative and not to have any resistance mutations. Around 16–17% in both study arms had a viral load (VL) above 100,000 HIV-1 copies/mL at baseline. Overall both arms performed well, with a 92.4% suppression rate (<50 HIV-1 copies/mL) at 48 weeks in the BIC/FTC/TAF arm compared to 93.0% in the DTG/ABC/3TC arm, confirming BIC STR non-inferiority. Nausea was more frequently reported in the DTG-based arm (22.9% *vs* 10.2%; P<0.001) but both drugs were otherwise well tolerated. In the small (five subjects) number of virological failures (VF) above 200 HIV-1 copies/mL, there were no identified resistance mutations to any component drug. No discontinuations due to adverse events (AEs) occurred in the BIC arm. Four occurred in the DTG arm and were considered to be related to the study drug (nausea, thrombocytopenia, chronic pancreatitis/steatorrhoea, depression). The lipid, bone and renal parameters were comparable in both groups.

The second Phase 3 study (GS-1490) was presented by Paul Sax (Brigham and Women's Hospital, USA) in a Late Breaker session and compared BIC/TAF/FTC to DTG/TAF/FTC [10]. It was placebo-controlled with a 1:1 randomisation and 625 randomised participants. In the DTG arm 93% of participants met the primary endpoint of a VL<50 HIV-1 copies/mL at 48 weeks compared to 89% in the BIC arm. The non-inferiority criteria were met with no resistance observed in the failures in either arm. Eleven participants discontinued BIC compared to three receiving DTG. No difference in side effects, including nausea, was noted.

Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI), which can be used in the context of a background of

NNRTI mutations, including K103N. It has previously been shown to be non-inferior to ritonavir-boosted darunavir (DRV/r) in the Phase 3 DRIVE-Forward study [11]. Data from the DRIVE-AHEAD study were presented at the Conference [12], a placebo-controlled Phase 3 study comparing the STR of DOR/tenofovir disoproxil fumarate (TDF)/3TC with Atripla (efavirenz [EFV]/TDF/3TC). The primary end point was the proportion of people with HIV-1 RNA below 50 HIV-1 copies/mL at 48 weeks. There were approximately 730 participants randomised in a 1:1 allocation, with 85% male participants and a median age of 31 years. The mean baseline CD4 cell count was approximately 420 cells/mm^3, about 22% had a VL >100,000 HIV-1 copies/mL and 14% had a history of AIDS. Eighty-six percent of participants continued DOR at 48 weeks, compared to 83% in the EFV arm. Non-inferiority criteria were met with 84% of the DOR arm having <50 HIV-1 copies/mL at week 48, compared to 81% in the EFV arm. Resistance to NNRTIs emerged in 1.6% participants on DOR, and 3.3% on EFV. Half as many people in the DOR arm experienced drug-related AEs (31% *vs* 63%) but serious AEs were rare in both arms (<1%). The most common AEs in the DOR arm were headache (13%) and diarrhoea (11%). Skin rash was less common with DOR (5% *vs* 12%). However, DOR caused significantly fewer CNS side effects. Discontinuation rates in the EFV arm were higher, with dizziness, rash and abnormal dreams occurring more frequently. Lipid changes were more favourable on DOR/3TC/TDF, with better fasting low-density lipoprotein (LDL) and non-high-density lipoprotein (non-HDL) levels.

New antiretroviral routes

While modern oral ARV agents are generally well tolerated, adherence to a daily pill regimen remains challenging for some individuals, creating a need for alternatives. The 96-week results of the LATTE-2 study [13,14] were presented. In this study, following an oral induction phase, subjects either received IM injections of CAB and RPV, 4 or 8 weeks apart, or continued on oral triple therapy (ABC/3TC/CAB). Around 90% of participants maintained an undetectable VL (<50 HIV-1 copies/mL) over 2 years. Injection site reactions were common, but usually mild to moderate and transient, with subjects reporting overall high satisfaction. It is worth noting, however, that two participants (2%) in the 8-week group, eight (7%) in the 4-week group, and one (2%) in the oral group discontinued treatment because of AEs.

New ways to use antiretrovirals

ANDES is a study evaluating a generic fixed-dose combination of boosted darunavir (FD-DRV/r) plus 3TC versus FD-DRV/r plus TDF/3TC in ARV-naive subjects in Argentina. The primary study outcome was the proportion of participants in each study arm with a VL <50 HIV-1 copies/mL at week 48. Participants had a median age of 30 years, 91% were male, median baseline VL was 32,000 HIV-1 copies/mL and CD4 T cell count was 383 cells/mm^3. About 25% in each group had a VL at baseline >100,000 HIV-1 copies/mL. The data presented were of the 24-week analysis [15]. Seventy-five participants were randomised to the dual arm and 70 to the triple therapy, with 90% of them being male. Four people in the dual-therapy group stopped treatment and one dropped out of the triple-therapy arm. The primary end point at 24 weeks was met in 97% in the triple-therapy arm versus 95% in the dual-therapy arm (difference –2.5%, 95% CI –7.0–2.9). Non-inferiority was achieved and side effects were fewer in the dual-agent arm (22.9% *vs* 13.3%). Gastrointestinal and neurological complaints were seen more often in the triple therapy arm. Rash was present in 8% and 7.1% in the dual- and triple-therapy arms, respectively. The study will continue through 48 weeks.

In the MOBIDIP trial, dual therapy with boosted protease inhibitors (bPI) plus 3TC showed superiority to bPI monotherapy in maintaining virologically controlled patients on second-line ART at 48 weeks leading to the discontinuation of the monotherapy arm [16]. Data presented in Paris included the continuation of the dual therapy arm up to week 96 [17]. The trial was conducted in three countries in sub-Saharan Africa with 70% of the 132 patients in the dual arm being female. The bPI was darunavir in one-third of participants or lopinavir in two-thirds. Importantly, among those with first-line VF, 97% had an M184V mutation. At 96 weeks, in an intention-to-treat (ITT) analysis, 8.3% of participants failed in the dual arm (eight virological failures, one death, two lost to follow-up). In three patients, in which TDF had been reintroduced, a VL <200 HIV-1 copies/mL was achieved in a median of 13 weeks. The authors concluded that after viral suppression with bPI plus NRTIs in second-line therapy, maintenance with bPI plus lamivudine was associated with a high rate of long-term success, despite the presence of an M184V mutation. None of those whose treatment had failed developed any new mutations and there was no presumed impact on subsequent treatment options.

Dual therapy: integrase inhibitor plus nucleoside reverse transcriptase inhibitors

The ACTG A5353 pilot study evaluated dual therapy in ART-naive individuals as a single-arm study, with all participants receiving DTG/3TC [18]. At 24 weeks 108/120 (90%) participants had a viral load <50 HIV-1 copies/mL. All three virological failures were due to poor adherence and low drug levels. The study aimed to look at this combination in people with high VL and included participants with baseline VL up to 500,000 HIV-1 copies/mL. A previous study with the same treatment combination, PADDLE, had excluded those with a VL >100,000 HIV-1 copies/mL [19]. In the present study, 37 (31%) participants had a VL >100,000 HIV-1 copies/mL. Resistance testing detected an integrase mutation (R263RK) and a reverse transcriptase (RT) mutation (M184V) in one participant with VF. No participant stopped study drugs because of AEs.

While these data are reassuring, the two large randomised trials of DTG/3TC versus DTG/TDF/FTC (GEMINI-1 and GEMINI-2) are still ongoing and should provide further information regarding this type of combination as a first-line treatment.

Dual therapy: integrase inhibitor with nucleoside sparing

Safety data were presented from the SWORD studies showing that switching from TDF/FTC-based triple therapy (combined antiretrovirals; CAR) to the combination of DTG/RPV resulted in a significant improvement in bone markers [20]. A sub-study of the international, multicentre SWORD 1 and 2 studies looked at bone mineral density (BMD) using DEXA scanning with the primary end point being the percentage change in total hip BMD. At week 48 the DTG/RPV patients had an increase in hip bone density from baseline (1.34%), which differed from CAR patients (P=0.01), serological bone markers also showing improvement.

New frontiers: integrase inhibitors and resistance

An interim week-24 analysis of DAWNING, an international, multicentre, non-inferiority study, was presented during the Late Breaker session [21]. Its aim was to compare DTG/2 NRTIs to ritonavir-boosted lopinavir (LPV/r) during second-line therapy in

participants who had previously failed NNRTI-based first-line ART. The study was mainly conducted in resource-limited settings. It was an open-label, randomised trial in which the LPV/r arm had been stopped early. There were 624 participants randomised, of whom over 30% were female. At week 24 of the study the DTG arm had been found to be superior to the LPV/r arm ($P<0.001$). This effect was maintained at week 36 and week 48 with full results awaited. Drug-related AEs were lower in the DTG arm (2% discontinued DTG compared to 5% LPV/r). Central nervous system (CNS) events were similar in both arms.

Low failure rate with switch to integrase inhibitor STR despite archived mutations

A very low failure rate was found in this French retrospective study in which subjects who were virologically suppressed for a prolonged period of time switched for toxicity or simplification reasons to an elvitegravir or dolutegravir-based STR [22]. Participants, who had previously had a well-controlled VL (≤50 copies/mL at baseline) were switched to elvitegravir/cobicistat/tenofovir/emtricitabine or to dolutegravir/abacavir/lamivudine from two nucleos(t)ides plus an NNRTI (35%), a PI (36%), or an integrase inhibitor (17%), or from a different regimen (12%). Fifty-one (68%) of the 75 individuals enrolled had a previous genotype with 22 (32%) displaying one or more reverse transcriptase (RT) mutations. The M184V mutation (88%) was by far the most frequently detected. Median follow-up was 13 months. One (2%) participant in the genotyped group and none in the non-genotyped group had VF. These data indicate that an integrase inhibitor-based STR can generally maintain virological suppression in people with long ART experience, including in those with a record of archived RT or integrase mutation.

New formulations

The Phase 3 EMERALD study data were presented regarding a co-formulated, single daily tablet, consisting of darunavir, cobicistat, emtricitabine and tenofovir alafenamide (10mg) (D/C/F/TAF) [23]. Suppressed subjects were randomised to either receive D/C/F/TAF or remain on TDF/FTC plus a ritonavir-boosted PI. In total, 1141 patients were randomly allocated with 763 in the D/C/F/TAF arm versus 378 in the control arm. The non-inferiority criteria were met with comparable AEs in both arms. Some improvement in renal markers was noted, consistent with the TAF component, in the D/C/F/TAF arm.

New dosing: efavirenz 400mg

In a Late Breaker poster discussion Marta Boffito (Chelsea and Westminster Hospital, London, UK) presented data on low-dose EFV at 400 mg (EFV400) during pregnancy and postpartum [24]. ARV dose reduction may translate into greater benefits for more individuals. ENCORE-1 had shown no difference between EFV dosed at 600 mg and at 400 mg. The WHO clinical guidelines now recommend it as an alternative first-line agent with a disclaimer because of the absence of data on its use during the third trimester of pregnancy (TT). This study investigated its PK, efficacy and CYP2B6 pharmacogenetics in women living with HIV (WLWH) during the TT and postpartum (PP) in an open-label, multicentre study performed in the UK and Uganda. Twenty-two females of African origin with an undetectable VL were enrolled and switched from a stable regimen of TDF/FTC/EFV 600 mg to TDF/FTC/EFV 400 mg. Weekly therapeutic drug monitoring was performed 10–14 hours post-dosing and a bi-weekly VL was measured. Undetectable VL was maintained throughout the study with only two viral blips observed and later confirmed as <50 HIV-1 copies/mL when repeated. No WLWH were excluded from the study because of low EFV TDM levels. No children born were infected with HIV. Drug levels, Cmax, AUC and C_{24h} were lower in the third trimester than in non-pregnant women, but within the therapeutic range for EFV dosed at 600 mg. The drug was well tolerated with no grade 3 or 4 AEs. The conclusion was that EFV 400 mg may be safely considered in pregnant women.

Primary HIV infection and early ART treatment

The session included presentations on clinical, immunological and virological aspects of acute/primary HIV infection (PHI). Christine Rouzioux (Necker Hospital, Paris, France) (TUBS0102) emphasised the association between early/immediate treatment of HIV-1 and reduced reservoirs in blood, gut, lymphoid cells and semen. The timing of ART initiation has been shown to have an important impact on several aspects of the infection. Subjects treated during PHI display major differences in their HIV reservoir compared to those who have initiated treatment during the chronic phase (CHI), with a lower HIV DNA level. The T cell subset distribution of HIV-1 DNA also differs between PHI and CHI, the long-lived HIV reservoir in CHI patients being composed of central memory T cells (T_{CM}) [25] while PHI patients have a short-lived reservoir of transitional CD4 T cells (T_{TM}) [26]. Additionally, PHI patients show an improved level of CD4 T cell immune restoration [27]. The majority of early treatment studies have included participants at Fiebig stage 4 or 5, but, as shown, even days matter at this stage of the infection. Early ART limits the HIV reservoir seeding by restricting the VL burden before it reaches its peak, thereby preserving potent effector CD8 T cells. In terms of immune responses, we have to distinguish between the various Fiebig stages as the degree of immune impairment depends on the delay in treatment initiation after infection.

Lydie Trautman (Walter Reed Army Institute of Research, US Army, USA) (TUBS0103) presented data on B cell and T follicular helper cells (Tfh) immune dysfunction, which is better detected at Fiebig stage 3 than at stage 1–2. Very early ART results in the preservation of the B cell resting memory compartment, thereby preventing the impairment of circulating Tfh-dependent humoral responses and maintaining the HIV-specific CD8 T compartment with an enhanced memory potential.

However, it is now obvious that early treatment is still not enough to preserve a fully functional immune system and additional interventions are considered at this very early stage of the infection, such as therapeutic vaccines, neutralising antibodies, latency-reversing agents, or a combination of such interventions, in the hope of achieving a more rapid VL reduction, thereby potentially enabling a later VL control without daily medication as discussed by Jintanat Ananworanich (Military HIV Research Program, US Military, USA) (TUBS0106). John Frater (Oxford University, UK) (TUBS0104) emphasised the need to start treating patients as soon as possible during PHI in order to potentially improve long-term clinical disease outcome.

HIV eradication

The HIV reservoir remains a lasting hurdle in the search for HIV eradication and cure. New assays are being explored to achieve enhanced characterisation and quantification. Christine Fennessey *et al*. have generated a viral model to help the understanding of the mechanisms of persistence [28] in which rhesus macaques were infected withal a SIVmac239 virus tagged with a barcode (SIVmac239M). Using next-generation sequencing, viral clonotypes were identified in the original virus stock and plasma before and after ART. Only five distinct barcode variants were detected in the post-ART during peak VL out of a total of 250–2900 distinct viral clones present during the pre-ART period. In some cases, a few

rebound clones could not be detected in the pre-ART analysis. Since all clones virologically had a similar replicative capacity, these rebounding clones were representative of the reactivation kinetics. The SIVmac239M virus therefore allows assessment of the efficacy of reservoir-targeting interventions, based on the number and dynamics of rebounding variants, even if time to measurable VL remains unaffected.

Elisabeth Anderson (National Cancer Institute, Frederick, USA) described a method to investigate how the proviral landscape changes under ART [29]. HIV DNA was quantified by targeting an internal HIV DNA sequence, such as *gag*, considered representative of the full length proviral sequences and *LTR* of all sequences, including those proviral sequences containing deletions and/or defective on the ddPCR platform. In patients with years on ART, an increase of the *LTR:gag* ratio is observed. This can be explained by the clearance of *gag*-expressing viruses and/or the clonal expansion of defective viruses, and indicates an accumulation of viruses with deletions under ART.

In contrast, Eunok Lee (Westmead Institute for Medical Research, Westmead, Australia) detected no accumulation of defective HIV DNA sequences during ART by single genome/proviral sequencing [30]. The group identified effector memory cells as the main contributor to the increase in similar HIV DNA sequences caused by proliferation in peripheral blood during therapy.

When considering the group of HIV controllers, data were presented showing its heterogeneity as shown by HIV DNA levels in those with a detectable VL (bHIC) increasing over time in contrast to those with an undetectable VL (uHIC) with decreasing levels over time. The former also have lower levels of CD8 T cell activation [31]. These data may be influential in terms of ART prescribing in this population.

The assessment of HIV integration site location and frequency in latently infected CD4 T cells can help the understanding of viral persistence. Jori Symons described a modified method for integration site analysis that allows high-throughput workflow [32]. It was noticeable that viral integration occurred preferentially into genes known to be upregulated in TCR-activated CD4 T cells.

Genevieve Martin (University of Oxford, UK) discussed the expression of CD32+, a newly described marker of the viral reservoir, on CD4 T cells [33]. She confirmed the finding by Monsef Benkirane's (Institute of Human Genetics: CNRS, France) group in the symposium session 'Advances in HIV Transmission and Regulation of Replication' (MOSY0204) of a substantial HIV DNA enrichment in CD32 cells in patients 1 year after starting ART at PHI This phenomenon is not only observed in PBMCs but also in tonsillar tissue. The Benkirane group had previously suggested that proviral integration upregulated CD32; however, there was no difference found in its expression between HIV-infected individuals and healthy controls (1.5% of CD4 T cells). Further characterisation of these cells has shown that CD32 is co-expressed with other HIV reservoir markers such as PD1, HLA-DR, Tim-3, Tigit and CD2, and particularly on T cells with a differentiated memory phenotype (T_{EM} and T_{EMRA}).

Comorbidities and immune activation

Maud Lemoine (Imperial College London, UK) presented the METAFIB study results at the HIV and Liver Oral Abstract Session [34]. In 468 HIV-monoinfected individuals, obesity and insulin resistance were independent factors associated with significant liver fibrosis (≥F2). Serum leptin and sCD163 levels were associated with the degree of liver fibrosis.

Hugo Perazzo Pedroso Barbosa (Fundação Oswaldo Cruz, Brazil) presented the PROSPEC-HIV study evaluating the risk factors associated with liver fibrosis (LF) and steatosis using transient elastography in HIV-monoinfected patients on ART [35]. In an age- and gender-adjusted multivariate analysis, factors associated (OR, 95%CI) with LF were: age >45 years (2.91, 1.19–7.15; P=0.020), CD4 T cell count <200 cells (5.00, 1.38–18.21; P=0.014) and type 2 diabetes (3.04, 0.97–9.55; P=0.056). Male gender (5.69, 2.68–12.04; P<0.001), dyslipidaemia (2.86, 1.46–5.60; P=0.002), type 2 diabetes (6.00, 2.08–17.28; P=0.001), central obesity (10.24, 4.11–25.50; P<0.001) and metabolic syndrome were independently associated with liver steatosis by CAP. Longer ART treatment duration, especially with zidovudine as a backbone, was associated with steatosis, independently of metabolic factors.

The poster discussion session (MOPDB01) on 'Comorbidities in an Ageing Era' opened with the results from the German HIV Heart Study, an ongoing prospective multicentre trial that is being conducted to analyse the incidence, prevalence and clinical course of cardiovascular (CV) disorders in HIV-positive outpatients. It was presented by Stefan Esser (University Hospital Essen, Germany) [36]. The HIV-positive male subjects had an increased incidence of CV events compared to the negative controls, despite a similar Framingham risk score (FRS) at baseline, but a different smoking status (P<0.0001), in contrast to HIV-positive females with a higher FRS than controls but comparable rates of CV events. The HIV-positive males had a higher mortality rate, risk of death or of experiencing a CV event at a younger age than the general population. The authors observed adjusted hazard ratios (aHR) of 3.5 (95% CI 2.2–5.5) for CV events for male subjects in the HIV HEART (HIVH) study in comparison to the Heinz Nixdorf Recall (HNR) study that includes a sample from the general population, for stroke of 1.8 (96% CI 0.8–3.9) for males and 2.2 (95% CI 0.1–42.9) for females. Overall survival in male and female participants in the HIVH versus HNR had an hazard ratio of 3.9 (95% CI 2.5–6.1) and 1.7 (95%CI 0.2–12.3), respectively.

In a workshop on 'Residual Disease and Immune Activation/ Inflammation on ART' (MOWS03), Caroline Sabin (University College London, UK) (MOWS0302) discussed the basic rules of epidemiology in a time of abundance of studies on premature ageing and earlier age for comorbidities in PLWH. She described how the selection of a control group can affect our interpretation of the impact of HIV on comorbidities and/or biomarkers. PLWH have different characteristics compared to the general population, which may drive apparent ageing rather than HIV itself. For instance, cytomegalovirus (CMV) serostatus can be a major confounding factor, driving immune activation and CD4/CD8 T cell senescence, rather than HIV itself. In this context, age advancement (biological age-derived using a set of 10 biomarkers – chronological age) can be a variable refining the comparison between PLWH and controls, decreasing misinterpretation of studies and simplifying search for mechanisms.

Peter Hunt (University of California, San Francisco, USA) described viral cofactors associated with immune ageing such as CMV and HCV (MOWS0304). Cytomegalovirus elicits a massive immune response even in asymptomatic HIV-negative individuals and may plausibly contribute to CV and thromboembolic disease, HIV reservoir persistence and microbial translocation. Furthermore, HCV appears to increase the risk of type 2 diabetes, kidney disease and osteoporotic fractures, with an unclear impact on coronary artery disease surrogate markers and extrahepatic events after HCV treatment with direct-acting antivirals (DAAs).

Roger Le Grand (Service Immunologie des Infections Virales et des Maladies Auto-immunes [IMVA], France) provided a comprehensive review of the impact of inflammation in disease progression in non-human primate models (MOWS0305).

Linda Wittkop (Bordeaux Population Health, France) presented some heterogeneous results regarding the association between inflammation markers and non-AIDS events (MOWS0306). She described the complexity of the underlying mechanisms of inflammation for each of the non-AIDS events, and the evolution of markers on successful ART, which are not yet fully determined from existing cohorts.

Olivier Lambotte, (Paris-Sud University Hospital, France) presented interventions to reduce immune activation according to its different causes (MOWS0307). Interventions on viral persistence, microbial translocation, CD4 T cell depletion, interferon type I pathway, metabolism, co-infections and lifestyle should be put into practice and strategies should be combined in order to act on immune activation. However, reduction of immune activation is inseparable from that of HIV reservoirs and is a major objective in 'HIV cure' strategies aiming at improving the care of HIV-positive individuals.

The bridging session, 'Microbiome' (TUBS02), assembled presentations of outstanding importance. Jacques Ravel (University of Maryland School of Medicine, USA) described the vaginal microbiota (TUBS0203). It can be quantitatively and qualitatively different among ethnic groups, during infections (*Lactobacillus* spp normally dominant), and over women's lifespans or during menses. The intravaginal bacterial community state types may contribute to variations in the diffusional barrier properties of the cervico-vaginal mucus and influence the risk for the acquisition of HIV and other STIs.

Jason Brenchley, (Laboratory of Parasitic Diseases, NIAID, NIH, USA) discussed the microbiome in animal models (TUBS0204). He showed studies providing evidence that the gastrointestinal (GI) tract-resident microbes contribute to the exacerbation of inflammation and SIV/HIV progression. It is currently unknown to what extent dysbiosis may be responsible for susceptibility to HIV infection or whether it is caused by HIV infection itself. The microbiome dysbiosis does not influence untreated disease progression.

Nichole Klatt (University of Washington, USA) presented evidence from her latest study (CAPRISA-004) (TUBS0205). She showed that the vaginal microbiota impact microbicide/PrEP efficacy and HIV acquisition. Indeed, tenofovir is rapidly depleted by vaginosis-associated bacteria because it is metabolised to adenine by *Gardnerella vaginalis* more rapidly than target cells can take it up for protection.

The Track B Oral Abstract Session described a series of different comorbidities. Jessica Castilho (Vanderbilt University Medical Center, USA) discussed the trends of non-communicable disease (NCD) multimorbidity among adults initiating ARVs in the Coorte Brasil, presenting two or more cumulative NCDs [37]. The NCD incidence is increasing in this population and female sex is independently associated with increased risk. Hyperlipidaemia, diabetes and osteoporosis account for the majority of NCDs.

Matthew Freiberg (Vanderbilt University Medical Center, USA) discussed whether HIV-infected people have an increased risk of peripheral artery disease (PAD) compared to uninfected people [38]. When analysing data on 92,287 VACS participants without prevalent CV disease, he concluded that HIV infection is associated with an increased risk of incident PAD even after adjustment for traditional CV disease risk factors. Among HIV-infected veterans, those with higher HIV VL and lower CD4 cell counts have the highest PAD risk. It has an impact on mortality, which was greatest among those with immunodeficiency or unsuppressed virus.

Dominique Costagliola (Sorbonne Universités, Paris, France) presented an analysis from FHDH ANRS CO4 regarding the risk of fractures in HIV-positive individuals, and the impact of exposure to different ARVs [39]. It was a case–control study with individuals enrolled while naive to ARV and no evidence of excess risk of fracture was found following exposure to tenofovir or PIs. Cumulative exposure to efavirenz was associated with a lower risk of fractures.

Maartje Dijkstra (Public Health Service of Amsterdam, the Netherlands) discussed erectile dysfunction among older HIV-positive MSM [40]. HIV-1 status was independently associated with decreased erectile function in those aged ≥45 years. This higher prevalence of decreased sexual satisfaction and desire may be explained by a high prevalence of depression, frailty and age-related comorbidities.

Nithya Srinivas (University of North Carolina at Chapel Hill, USA) studied the ARV concentration in the brain tissue and cerebrospinal fluid (CSF) of uninfected and SHIV-infected rhesus macaques, in relation to the concentration of drug transporters in brain tissue [41]. Even if there was no difference in ARV concentrations between different parts of the brain, tissue concentrations were shown to be significantly higher than CSF for efavirenz, emtricitabine and tenofovir. Drug concentrations in the CSF were predictive of brain tissue concentrations only for EFV. Brain tissue concentrations of EFV were four-fold higher in uninfected animals compared to HIV-infected animals. The Breast Cancer Resistance Protein (BCRP) protein (drug transporter) concentrations were two-fold lower in uninfected animals than in infected ones. There was a trend noted between increasing concentrations of BCRP protein and lower efavirenz concentration in brain tissue.

Vaccines

Anthony Fauci (National Institutes of Health, USA) discussed the relevance of an HIV vaccine for ending the HIV pandemic (SUSA2202). Theoretically, HIV can be stopped without an HIV vaccine; available drugs have improved over the last 30 years. There are currently over 30 FDA-approved antiretroviral agents. Life expectancy has dramatically improved since 1980 and additionally, there is a strong focus on HIV prevention, namely treatment to prevent infection of HIV-negative partners in discordant couples and the availability of PrEP. There are no more excuses; we have all the tools necessary to end the HIV pandemic. However, new infections globally have only decreased by 2.3% annually and there is a persistent important treatment gap. The '90-90-90' targets for 2020 are met in only a few countries, and globally only 44% of HIV-infected people have viral suppression. Reaching the 2020 target is especially difficult when patients are living in rural areas and dispersed. Furthermore, in the US over 1.2 million people are at risk of HIV, but only 10% of them have access to PrEP. When considering vaccine development there are two approaches that can be considered. First, in a classical approach a vaccine candidate is tested to identify if it evokes an immune response, which can be protective (e.g. modified RV144 prime-boosted in the HVTN702 trial). A second approach is to assume a correlate of immunity and design a vaccine to induce this correlate. In this strategy, bNAbs have been the focus. For an HIV vaccine to have a strong impact a 50–60% efficacy rate in combination with prevention and treatment would suffice to end the epidemic.

During the symposium session, 'Translational Vaccinology' (MOSY04), Hanneke Schuitemaker (Janssen Vaccines and Prevention, the Netherlands) presented data from the APPROACH early clinical study aimed at developing a prophylactic vaccine. An immunogen should offer protection against all HIV-1 clades through a heterologous prime-boost regimen (double prime at month 0 and 3 and double boost at month 6 and 12)(MOSY0403). APPROACH is a multicentre, randomised, parallel-group, placebo-controlled, double-blind clinical trial in healthy HIV-uninfected

adults. Safety and immunological results of the APPROACH and TRAVERSE studies will inform the decision to proceed to a Phase 2b proof-of-concept study. In parallel preclinical studies the Ad26/Ad26+gp140 HIV vaccine regimen provided significant protection (94% per-exposure risk reduction) against intrarectal SHIV challenges in NHP. All vaccine regimens were 100% immunogenic after the third immunisation in terms of the humoral (total IgG against gp140 *ENV* Clade C by ELISA), ADCP (functionality of antibodies via antibody-dependent cellular phagocytosis) and cellular (ENV PTE peptide pool by ELISPOT) responses and also displayed a very favourable safety profile. There was a clear contribution of the gp140 boost and dose in all types of responses. The number of responders was maintained after the fourth vaccination. The ADCP, magnitude of response and *Env* boost criteria are considered supportive for the lead regimen (Ad26/Ad26+gp140 high dose) and results of the TRAVERSE study are close (end of 2017) in order to proceed with the proof-of-concept study that will consist of a multicentre, randomised, parallel group, placebo-controlled, double-blind clinical trial targeting sexually active HIV-1-uninfected women (born female, age 18–35 years) in five African countries.

Hepatitis C virus (HCV)

Chronic HCV disease is associated with substantial morbidity and mortality worldwide. It disproportionately affects PLWH, complicating the management of HIV and impacts on the ART response. The use of DAAs is associated with >95% sustained virological response (SVR) rate. DAAs have also demonstrated reasonable safety profiles. The availability of effective HCV treatment, with high cure rates for all genotypes, offers unprecedented opportunities. However, barriers to achieve a cure include high treatment costs, health services delivery issues, insufficient HCV screening programmes and limited HCV prevalence data.

French investigators Salmon *et al.* presented results regarding VF with DAA combinations in HIV/HCV-co-infected patients from the ANRS CO13 HEPAVIH cohort [42]. The rate of VF in this cohort was low and involved 32 of 619 HCV/HIV-co-infected individuals (5.2%, 95% CI 3.6–7.2). The majority were relapsers (78%) followed by non-responders (9%) and one breakthrough. People with VF had a lower median CD4 cell count (505 *vs* 614 cells/mm^3, *P*=0.008) and with a larger proportion with an undetectable HIV VL (75% *vs* 87%, *P*=0.0606) and a lower platelet count (141 *vs* 172; *P*=0.0669). Presence of cirrhosis or type of DAA regimen did not affect the probability of VF. Using a marginal structural model and after adjustment for ribavirin use, age, sex, cirrhosis, HCV genotype, and CD4 cell count, investigators identified two independent predictors: pretreatment with a non-DAA regimen almost tripled the chance of failure (odds ratio [OR] 2.8, 95% CI 1.2–6.2, *P*=0.004), and DAA treatment for 24 weeks versus 12 weeks lowered the chance of failure by 80% (OR 0.2, 95% CI 0.1–0.6, *P*=0.01). Age, gender, HCV genotype, HIV load, and CD4 cell count did not predict VF in this analysis. Some VF could also be due to suboptimal adherence as suggested by: (1) suboptimal DAA concentrations in 4/10 people with VF; and (2) a higher rate of detectable HIV RNA among people with VF in a separate logistic regression analysis (OR 2.1, 95% CI 0.9–5.1, *P*=0.11). The emergence of resistance-associated mutations (RAS) was frequent and varied according to the DAA class: 2/2 in the NS3 failure group and 6/12 in the NS5A failure group.

In the same cohort, investigators assessed the prevalence of overweight/obesity after SVR [43]. Cohort participants who completed at least one self-administered questionnaire during the 2005–2014 follow-up period were eligible for this analysis. Mixed logistic regression models were used to pinpoint predictors of overweight/obesity. Of the 1046 people analysed, 18.3% were overweight or obese at the start of follow-up. Ex-smokers and non-smokers presented a higher prevalence (29.4% and 29.5%, respectively) of overweight/obesity than current smokers (14.5%; *P*=0.0001). One-third of participants (35.2%) reported hazardous alcohol consumption, and half (49.7%) used cannabis. Cannabis users had a lower overweight/obesity prevalence than non-users (9.7% *vs* 23.8%, *P*<0.0001). After 5 years of follow-up, 27% were overweight or obese. In the multivariate analysis, HCV clearance did not significantly affect odds of overweight/obesity but a longer time after clearance boosted odds of overweight/obesity by about 75% (adjusted odds ratio [aOR] 1.74, 95% CI: 1.003–3.03, *P*=0.049). Other variables that independently lowered odds of HCV clearance were female gender (aOR 0.43, 95% CI 0.25–0.71, *P*=0.001), each year of ART at the first visit (aOR 0.91, 95% CI 0.87–0.96, *P*=0.0003), and cannabis use (aOR 0.22, 95% CI 0.08–0.61, *P*=0.005).

Nadine Kronfli (University Health Centre, Montreal, Canada) presented results from the Canadian HIV-HCV Co-infection Cohort (CCC) that looked into cause-specific mortality in co-infected people and changes in cause-specific mortality before and after increased use of HCV therapy in this group [44]. Investigators analysed 1477 people with an available date of birth and follow-up in the study period (median 4.1 years). Most participants (84%) were on ART, 64% had an undetectable HIV load, and 81% had no HCV therapy experience at baseline. During follow-up, 203 people (14%) died (death rate of 30.5 per 1000 person-years). People who died had a median age at death of 47 years, were more likely to report active IDU and current smoking, had a lower median CD4 cell count, were less likely to have an undetectable HIV load, had longer HCV infection, were more likely to be HCV treatment-naive at baseline, had worse fibrosis, and were more likely to have a prior end-stage liver disease (ESLD) diagnosis. ESLD accounted for 20% of deaths. Risk of death from ESLD fell over time in this analysis (HR 0.65) but not significantly (95% CI 0.28–1.5). Overall, death due to ESLD decreased only in people 50–80 years. ESLD deaths were about five-fold more likely with an AST to platelet ratio index (APRI) above 1.5 and with HCV RNA positivity, and about three-fold more likely with a CD4 cell count below 350 cells/mm^3. The all-cause death risk was higher in people positive for HCV RNA at the last visit. Death due to ESLD was common and did not decrease over time in people with poorly controlled HIV and HCV, especially with detectable HCV RNA. Thus, researchers suggested that the mortality benefit of DAA therapy will be concentrated among those with advanced fibrosis and efforts to expand treatment should prioritise this group.

Karine Lacombe (Université Pierre et Marie Curie, France, Paris) described the results from the Phase 3 Expedition-2 international study using co-formulated glecaprevir/pibrentasvir once daily in HIV-HCV-co-infected patients using an 8- or 12-week treatment duration in non-cirrhotic and cirrhotic patients, respectively [45]. The treatment was well tolerated and highly efficacious with a cure rate of 98% in a predominantly genotype 1 (including 1a) population. Glecaprevir is an HCV protease inhibitor and pibrentasvir an NS5A inhibitor. Both are pangenotypic. Most patients were on an integrase inhibitor-based ART. This combination could be the first 8-week pangenotypic treatment option for HCV-HIV co-infected patients without cirrhosis.

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