Highlights from HIV Glasgow, 28–31 October 2018, Glasgow, UK

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HIV Glasgow 2018 was launched in the context of the Global HIV Vaccine Enterprise Strategic Plan. This programme, hosted by the International AIDS Society, was unveiled at the opening of HIV Research for Prevention (HIVR4P 2018) in Madrid, Spain. It involves a 5-year strategy (2018–2023) aimed at accelerating the development of an effective vaccine to prevent HIV-1 infection.

On Monday 29 October the Conference opened with an address on the ‘Ongoing challenges while living well with HIV’. Fiona Burns (Centre for Sexual Health and HIV Research, University College London, UK) described engagement in care as a complex issue, driven by wider determinants of health, with substantial variations observed across European regions and among key populations [1]. Social and structural factors that may influence engagement in care are: access to healthcare; socioeconomic parameters, such as poverty and insurance; stigma and discrimination; social capital; as well as self-efficacy of health services. The groups most at risk of disengagement are invariably those most marginalised and with the least advocacy. These include people who struggle with HIV-related stigma, with insecure residency and/or employment, and those living with mental health, alcohol and drug dependency. Fiona Burns concluded that sustainable engagement will require a person-centred approach with personalised care, based on a responsive and flexible attitude on the part of services and clinicians.

Julian Falutz (Department of Medicine, McGill University, Montreal, Canada) analysed challenges with HIV and ageing [2]. Currently, the emergent demographics of the HIV-1 population in industrialised and developing countries allows the projection that, by the year 2030, 75% of people living with HIV will be over the age of 50 and 40% over the age of 60. This projection will significantly impact healthcare delivery. In addition to the earlier occurrence of common age-related conditions and increased multimorbidity, several common geriatric syndromes may impact this population, such as sarcopenia, impaired mobility, falls, sensory complaints (neuropathy, visual and auditory deficits), cognitive decline and frailty. This latter condition, a state of increased vulnerability to biological and environmental stressors, with reduced ability to maintain homeostasis, may be a useful surrogate to operationalise heterogeneous change in biological and chronological age in older people, even if its biological basis remains poorly understood. Overall, Julian Falutz pointed out that successful ageing for those living with HIV is possible only if we assess and manage comorbidities and other risk factors proactively by means of an interdisciplinary type of management, in order to achieve not only an increased, but also improved life span.

The 48-week results of the NEAT 022 study were presented by Esteban Martinez (Infectious Disease, Hospital Clinic, University of Barcelona, Spain) [3]. Within a pre-planned sub-study, researchers aimed to assess whether switching from a ritonavir-boosted protease inhibitor (PI/r) to dolutegravir (DTG) in those with sustained plasma virological suppression induced significant changes in several cardiovascular (CV) biomarkers. In 313 participants, switching was associated with significant decreases in sCD14 (-11%, P<0.001) and adiponectin (-11%, P<0.001), and a trend to decreased hsCRP (-13%, P=0.069) and oxidised LDL (-13%, P=0.084). Some correlations were found between adiponectin, sCD14, oxidised LDL and some plasma lipids. Patients switched to DTG had significantly higher increases in CD4 T cell counts (median change was +32 cells/mm³ in the DTG arm and -6 cells/mm³ in the PI/r arm, P=0.049). Percentage change in sCD14 was inversely correlated with that of CD4 T cell count (coefficient -0.113, P=0.049). Median body mass index (BMI) (kg/m²) change was +0.3 in the DTG arm and +0.2 in the PI/r arm (P=0.121). Percentage change in adiponectin was inversely correlated with that in BMI (coefficient -0.227, P<0.001), which highlights the importance of further assessing the potential impact of DTG therapy on the mechanisms involved in body weight, even though the overall CV impact of the switching strategy was positive.

Ferdinand Wit (Stichting HIV Monitoring, Academic Medical Center, Amsterdam, the Netherlands) investigated whether multimorbidity predicts mortality in people living with HIV on ART, and whether the relationship between multimorbidity and mortality differs by gender [4]. The data came from the ATHENA observational cohort, which is the national HIV cohort in the Netherlands and includes all adults living with HIV who were in active follow-up between 2000 and 2017 while on combination ART. The multimorbidity score was defined as the total number of comorbidities (cardiovascular disease, stroke, non-AIDS-defining malignancies, chronic kidney disease, diabetes mellitus, hypertension and obesity) present at any given time during follow-up. At ART initiation, the mean number of non-AIDS comorbidities in males and females was similar. At the last available follow-up in 2017, among those of higher ages, there were few differences in comorbidities between men and women; however, at younger ages women had more comorbidities, which was largely driven by a higher prevalence of obesity. Among a total of 2325 deaths occurring during 185,000 PYFU, the crude mortality rate increased with the number of comorbidities, from 5.9 per 1000 PYFU in those with zero comorbidities up to 21, 35.2, 81 and 173 deaths per 1000 PYFU in those with one, two, three and four or more comorbidities, respectively. The interaction of female gender on the association between multimorbidity and mortality shows that at zero comorbidity, women have significantly lower mortality compared to men (RR=0.55), but with each additional comorbidity the mortality risk for women increases at a greater rate than for men, so that with three or four comorbidities, the mortality risk for women is significantly higher than for men with the same number of comorbidities (RR=0.94, 1, 169 and 2.21 for one, two, three and four or more comorbidities, respectively). Excess risk in women with more extensive multicomorbidities was more pronounced in those with prior exposure to mono- and dual-nucleoside analogues.

Eva Wolf (MUC Research, Munich, Germany) presented results of a cohort analysis on the economic burden of comorbidities.
among people living with HIV in Germany [5]. It was a retrospective study, using the German InGef Health Insurance Claims Database, in order to estimate the total health-related costs of acute and chronic non-HIV-related comorbidities among those living with HIV. A multivariable generalised linear regression model (GLM) was used to estimate the contribution of comorbidities to total healthcare costs, excluding ART. Mean values for annual total healthcare costs including ART were €22,817, excluding ART €7,609, inpatient costs €1,467, outpatient costs €1,589, medication costs excluding ART €4,196, and ART costs €14,232. This model revealed the high economic impact of specific comorbidities, with estimated incremental annual costs ranging from €2581 to €16,023. These results demonstrate the importance of comorbidity management in those living with HIV in order to decrease the medical and economic burden.

During the Lock Lecture, Jean-Michel Molina (Department of Infectious Diseases and University of Paris VII, St Louis Hospital, Paris, France) gave an overview on sexually transmitted infections (STIs) among men who have sex with men (MSM) in the era of pre-exposure prophylaxis (PrEP) and the new challenges in terms of their prevention, diagnosis and treatment [6]. Over the last 25 years, we have all witnessed the great success of ART for the treatment and prevention of HIV, turning this disease into a chronic and manageable, mostly asymptomatic infection. This success has led to a reduction in the perception of risk of HIV/AIDS/death, leading to a change in sexual behaviour called risk compensation, with a reduced use of condoms, and this has coincided with an emergence of STIs in those with, or at risk for, HIV acquisition. Strategies to contain the STI epidemic include a number of behavioural interventions (promotion of condom use, reducing number of casual partners, being faithful), use of vaccines against viral STIs and antibiotic prophylaxis, ‘test and treat’ for STIs, partner notification and appropriate treatment. In terms of antibiotic prophylaxis, a randomised open-label trial enrolled in the ANRS iPERGAY open-label extension study assessed on-demand post-exposure prophylaxis (PEP) with doxycycline 200 mg, 24 hours after sex, in 116 HIV-1 negative, high-risk MSM compared to 116 controls [6]. While doxycycline PEP reduced the overall incidence of STIs during a median follow-up of 8.7 months (69.7/100 PY in no PEP arm, 37.7 in PEP arm, HR=0.53, 95% CI: 0.33–0.85, p=0.008), there was no effect of PEP on the incidence of gonorrhoea (probably because of the high rate of resistance to tetracycline) but a strong reduction (70–73%) in the chlamydia and syphilis incidence. Therefore, antibiotic prophylaxis for STIs is not routinely recommended because additional studies have to be conducted in order to assess the benefit/risk ratio. The present treatment for gonorrhoea consists of a combination of ceftriaxone and azithromycin, in order to prevent the occurrence of resistance to ceftriaxone, even if precision treatment (resistance-guided sequential treatment) is shown to be a very interesting option.

Catia Marzolini (Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland) opened the session on ‘Drug interactions, antiretroviral toxicity and switching’ [7]. Large surveys suggest that up to a quarter of patients living with HIV may be at risk of a clinically significant drug–drug interactions (DDI), even with the latest ART regimens, because of the high potential of ARVs for DDIs; their life-long use and the growing prevalence of non-HIV polypharmacy in the context of an ageing population. DDIs can lead to drug toxicity or treatment failure of the antiretroviral drugs and/or the co-administered drugs. She reviewed clinical management, including the mechanistic aspects of a number of DDIs (statins, antidepressants, PrEP and Chemsex, antihypertensives, metformin, rifampicin, corticosteroids, anticoaguants, antiplatelet agents, PPIs and antacids), which are frequently present. Searchable online DDI databases represent a valuable tool to recognise and manage unwanted DDIs in clinical practice. Educational programmes should be encouraged in order to improve awareness on this issue.

Victoria Pilkington (Faculty of Medicine, Imperial College London, UK) presented a meta-analysis of the risk of grade 3/4 or clinical adverse events (AEs) in 13 randomised trials of PrEP, using either tenofovir (TDF)/FTC or TDF, versus placebo or no treatment: VOICES, PROUD, iPERGAY, FEM-PrEP, TDF–2, iPREX, IAVI Kenya, IAVI Uganda, PrEPare, PARTNERS, US Safety Study, Bangkok TDF Study, W African TDF Study [8]. These trials included 15,678 participants, among whom 1305/7504 (17.4%) were on PrEP versus 1259/7502 (16.8%) controls (difference 0%, 95% CI: -1% to +2%, P=0.53) for grade 3/4 AEs. In terms of serious adverse events (SAEs), there was no significant difference between the two groups (9.4% versus 10.1%, respectively, difference 0%, 95% CI: -1% to 1%, P=0.80). Similarly, adverse renal and bone outcomes did not occur significantly more often in participants taking PrEP versus control regimens. When the analysis looked at creatinine elevations of all grades, a 2% increase in events occurred on PrEP, with a borderline significant increased (P=0.04) risk on PrEP (97% elevations were grade 1 and 2) being noted. It is worth mentioning that when comparing short- versus long-term follow-up studies (less or more than 1 year of average follow-up time), there was a significant decrease in risk of SAEs occurring on PrEP in longer-term follow-up studies, which is unexpected and counterintuitive, highlighting that the risk occurring on PrEP is associated with the baseline risk. In this meta-analysis, the safety profile of TDF/FTC would support more widespread PrEP use in populations at risk of HIV infection.

Zara Liew (Faculty of Medicine, Imperial College London, UK) described the results of a meta-analysis of several randomised trials with a two-drug combination of a PI/r, in combination with lamivudine (3TC) or TDF, in treatment-naïve or treatment-experienced and virologically suppressed patients [9]. Seven studies (three treatment naïve studies: ANDES, GARDEL and Kalead, and four treatment-experienced studies: ATLAS, DUAL, OLE and SALT) were identified in order to evaluate safety and efficacy of PI/r dual therapies which together enrolled 1635 patients. The pooled risk difference for viral suppression at week 48 of dual therapy compared to triple therapy was +2% (95% CI: -2% to +6%, P=0.04), which met the FDA criteria for non-inferiority. Results were consistent in treatment-naïve and switch studies (P=0.94). Virological failure and treatment-emergent resistance mutations were not different between the two arms (P=0.98 and P=0.89, respectively). Treatment discontinuation rate for AEs was not significantly different between the dual- and triple-therapy arms (2.4% vs 3.6%, respectively, P=0.10). In conclusion, efficacy and safety were similar in both arms according to a meta-analysis including seven randomised trials. Generic combinations of darunavir/ritonavir and lamivudine (DRV/r + 3TC) could be cost-saving compared to the branded triple combinations of TDF/FTC or tenofovir alafenamide (TAF)/FTC.

Babafemi Taiwo (Division of Infectious Diseases, Northwestern University, Chicago, IL, USA) discussed the results of residual viraemia measurements in patients included in the randomised controlled Antiretroviral Strategy to Promote Improvement and Reduce Exposure (ASPIRE) 48-week study [10]. Virologically suppressed patients on a standard three-drug ART regimen maintained viral suppression after switching to dolutegravir and lamivudine (DTG + 3TC) [11]. Using an integrase single-copy assay (sICA, limit of detection of 0.5 HIV-1 RNA copies/mL), plasma samples of 73 participants (36 DTG + 3TC and 37 cART) were
assessed at study entry, weeks 24 and 48. There was no difference in the level of residual viraemia at baseline, for example 4.9 copies/mL under (DTG + 3TC) versus 5.3 copies/mL in cART (difference -0.5 copies/mL, 95% CI: -3.8 to 2.8, P=0.78). No significant differences were observed between the two arms, adjusted for baseline values, at either week 24 (1.3 copies/mL, 95% CI: -2.1 to 4.7, P=0.45) or 48 (0.5 copies/mL, 95% CI: -2.9 to 3.9, P=0.77) in residual viraemia, even in the stratified analysis by ART duration and baseline CD4 T cell count. Overall, in this randomised trial, there was no evidence for increased viral replication after the switch to DTG + 3TC.

Hans-Jürgen Stellbrink (ICH Study Centre, Hamburg, Germany) opened the session on ‘Approaches to treatment and cure’. He reported week-96 secondary endpoint results from an ongoing, double-blind, Phase III study comparing bictegravir (B) with DTG, each given with FTC/TAF in treatment-naive, HIV-1-positive adults [12]. Both treatment regimens demonstrated high efficacy, with no development of viral resistance, and were well tolerated through week 48. At week 96, 84.1% on B/FTC/TAF and 86.5% on DTG + FTC/TAF had a plasma HIV-1 RNA level below 50 copies/mL (difference -2.3%, 95% CI: -7.9% to 3.2%, P=0.41), which met the criteria for non-inferiority. Numbers of participants with HIV-1 RNA ≥50 copies/mL at week 96 were zero for B/FTC/TAF and five (1.5%) for DTG + FTC/TAF. Through week 96, no participant developed treatment-emergent resistance to the study drugs. Occurrence of AEs led to study drug discontinuation in six (1.9%) B/FTC/TAF versus five (1.6%) DTG + FTC/TAF participants. There were no discontinuations due to renal AEs. Lipid changes were not significantly different between groups.

Chloe Orkin (Barts Health NHS Trust and Queen Mary University of London, UK) presented the week-96 analysis of efficacy, safety and resistance results from the AMBER study, which is a Phase III, active-controlled, double-blind, non-inferiority trial in which ART-naive HIV-1-infected adults were randomised to darunavir (D)/cobicistat (C)/FTC/TAF or D/C/FTC/TDF over at least 48 weeks [13]. In total, 725 patients were randomly allocated and treated, with 626 person-years (PY) exposure in the D/C/ FTC/TAF arm, 512 PY exposure to D/C/FTC/TDF and 109 PY to D/C/FTC/TAF in the control arm. High virological response rates (85% in the D/C/FTC/TAF arm, 84% in the control arm) and low failure rates (6% in the D/C/FTC/TAF arm and 4% in the control arm) were observed in both arms at week 96. No darunavir, primary PI or TDF resistance-associated mutations were seen post-baseline visits. Few SAEs and AE-related discontinuations were reported, and no deaths occurred. Bone, renal and lipid safety were consistent with known TAF and cobicistat profiles.

Babafemi Taiwo (Division of Infectious Diseases, Northwestern University, Chicago, IL, USA) described the dynamics of viral decay in DTG + 3TC versus DTG-based triple therapies [14]. A sub-study of the PADDLE trial showed comparable viral decay between these two drug regimens in two study comparators (SPRING-1 and SINGLE study), despite a small sample size (n=16 in the PADDLE study) and the exclusion of participants with baseline viral load (VL) >100,000 copies/mL or a CD4 T cell count <200 cells/mm³ at entry [15]. In a sub-study of the ACTG A5353 study (Phase II, single arm, open-label pilot study), the authors compared differences in plasma VL change at each time point between two-drug in A5353 and three-drug therapy in SPRING-1 and SINGLE. The VL change from baseline with two-drug was non-inferior to that of the DTG-based three-drug regimen (P<0.001). In the viral decay model, a two-drug regimen was associated with a faster initial decay rate compared to the three-drug regimen that was partially offset when baseline VL was greater than 100,000 copies/mL. Overall, decay rates were comparable, even in individuals with higher pre-treatment VL up to 500,000 copies/mL.

Flaminia Olearo (Infectious Diseases, University Hospital of Geneva, Geneva, Switzerland) presented results of an observational longitudinal prospective study including five different European HIV cohorts (ARCA and ICONA from Italy, ANRS C03 Aquitaine from France, ATHENA from the Netherlands and SHCS from Switzerland) aimed at defining the impact of the archived resistance mutation M184V/I on the virological failure (VF) rate in successfully treated patients switching to an abacavir (ABC)/3TC/DG regimen [16]. In total, 1626 patients were included in the analysis (median follow-up of 289 days, IQR 154–441). The ratio presence/absence of M184V/I mutations was 1:1.1. Individuals with an M184V/I mutation (n=137) were older, had a more prolonged follow-up, a longer duration of HIV-1 infection and ART, more prolonged virological suppression before switch, more frequent prior AIDS diagnoses and previous documented VF. Very few VF were observed (n=21, 1.29%) and were not significantly different between the two groups (3% VF with M184V/I vs 1.1% without M184V/I, P=0.78). The VF rate was 15.1 per 1000 person-years (95% CI: 9.9–23.2) and was higher in those harbouring an archived M184V/I mutation, although not significant (29.80 [11.17–79.39] vs 13.56 [8.43–21.83], P=0.093). There were no differences in treatment discontinuations for reasons other than VF between patients with and without documented M184V/I (10.22% vs 15.58%, respectively, P=0.12). Overall, no significant difference was found in terms of efficacy in patients switched to ABC/3TC/DG, regardless of the presence of the M184V/I mutation, which was not an explanatory factor for the composite outcome of VF and/or blips. However, data over a longer period are needed to confirm this observation.

Sarah Fidler (Department of GUM and HIV Medicine, Imperial College and Imperial College NHS Trust, London, UK) presented an overview on therapeutic approaches aimed at an HIV cure [17]. Even if ART has dramatically improved survival for people living with HIV, a cure or remission remains highly desirable because of constraints such as a life-long treatment and unsustainable global ART access. Only one individual has presently been cured of HIV-1 for 9 years, namely Timothy Brown or the Berlin patient, by means of an exceptionally challenging treatment. The currently accepted definition of a cure is that of a functional cure or remission, implying a significant period of maintained viral suppression off ART (post-treatment viral control), with a zero risk of onward viral transmission and individual health. The key barrier to cure remains the viral persistence within a pool of latently infected cells, the so-called HIV-1 reservoir. Different therapeutic approaches include inhibition of residual replication via enhanced ART or decrease of the reservoir to a low threshold, immune modulation (therapeutic vaccines and broadly neutralising antibodies) or the ‘shock and kill’ strategies and gene therapy. Despite earlier ART in order to obtain a lower reservoir size, the use of therapeutic vaccines to strengthen immunity and latency-reversal agents to activate latent virus, ART interruption in the majority of individuals leads to rapid viral rebound. Post-treatment viral control is, for the time-being, a rare occurrence. The ‘kick and kill’ approach combines the use of latency-reversal agents and immune boosting of HIV-1-specific responses to destroy latently activated cells. RIVER is the first randomised controlled trial testing the efficacy of this approach (ART versus ART + vorinostat + prime-boost HIV-1 vaccines) performed in the UK in individuals with recent or acute HIV-1 infection. Results showed no significant difference in total HIV-1 DNA or viral outgrowth assay between the two study arms but induction of HIV-1-specific immune responses.
Overall, multiple approaches towards HIV remission look encouraging, but a combination strategy will probably be necessary to achieve a cure.

Fiona Lampe (Department of Infection and Population Health, University College London, UK) discussed the prevalence of mental health disorders among people living with HIV [19]. These cover a wide range of conditions and diagnoses, with one of the most common being depression. She documented the high prevalence of depression and anxiety among those living with HIV in Europe in recent periods, across countries, and across methods of assessment. People living with HIV are substantially more likely to be experiencing mental health problems compared to HIV-negative people (PPPP study in the UK, AgeHIV study in the Netherlands, ASTRA and AURA studies in the UK), and the difference is greatest for those diagnosed with HIV-1 for a longer period of time. She finally described the evidence that mental health is poorer among those living with HIV than those living with other long-term physical health conditions (cohort study ’50/2010’ in Germany, ATHENA cohort in Netherlands) [20].

Margaret Hellard (Burnet Institute, Melbourne, Australia; and Viral Hepatitis Services, Department of Infectious Diseases, Alfred Hospital Melbourne, Australia) opened the session on co-infections, discussing the public health perspective of eliminating hepatitis C (HCV) by 2030 [21]. Hepatitis C is a major global health problem with more than 71 million people (1.1% of the global population) chronically infected, causing a significant number of deaths (estimated at 500,000 in 2015). The global burden of HCV/HIV co-infection is approximately 2.2 million people and the HCV risk in HIV-1-infected individuals varies between at-risk populations, predominantly occurring in MSM. Despite the large numbers of people infected with HCV, scientific advances that combine highly effective evidence-based prevention and HCV testing/treatment using direct acting antiviral therapy (DAA) means that HCV elimination is achievable. The World Health Organization (WHO) has set targets for its elimination as a public health threat by 2030. However, evidence suggests that currently only 12 countries are on track so far to achieve this goal. Treatment price and availability are not the only barriers, which is why it is important to integrate the HCV response into universal health coverage within the sustainable development goals, global and country investments with a multipronged approach, in the same way as the HIV cascade of care.

Andrew Hill (Department of Translational Medicine, University of Liverpool, UK) discussed the costs of generic production of HCV DAAs [22]. Worldwide in 2016, there were 1.6 million people cured of HCV using these drugs, but also 1.5 million new infections. To achieve the WHO elimination targets by 2030, we need to diagnose and treat at least 5 million people worldwide every year. Using data on exports of raw materials between 2015 and 2018, his research team assessed currently feasible DAA generic prices by looking at the active pharmaceutical ingredient (API), and compared them to current national prices. The cost of exported sofosbuvir (SOF) API has fallen from $10,100/kg in January 2015 to $970/kg in January 2018. Costs of API are currently $750/kg for daclatasvir (DCV), $2250 for ledipasvir (LDV) and $9,046 for velpatasvir (VEL). The predicted minimum production price of SOF/DCV is now $48 per 12-week treatment course. Prices of generic SOF/DCV for public tender in India are close to predicted minimum costs of production. By contrast, in high-income countries, costs per 12-week course are approximately $8000–$20,000, including discounts. Overall, the costs of generic production of these DAAs are rapidly decreasing and at these low prices, elimination of HCV worldwide could be feasible.

Andrea Calcagno (Infectious Diseases, Department of Medical Sciences, University of Torino, Italy) presented, on behalf of the ICONA Foundation Study Group, the results of the long-term follow-up of HIV-hepatitis B (HBV) co-infected patients according to the use of anti-HBV active drugs [23], in terms of advanced liver disease events (ALD), HBV DNA suppression and ALT trajectories. The authors included 624 HIV-1-positive patients with two positive HBsAg results (6 months apart) without end-stage liver disease (ESLD). Anti-HBV strategies were classified as TDF/lamivudine or emtricitabine (XTC), TDF monotherapy, XTC monotherapy, entecavir (ENT) or no anti-HBV treatment. Over 2203 PYFU, they observed 106 ALD events in treated patients, more frequent in those receiving XTC (4.39/100 PYFU), non-anti-HBV antiretrovirals (7.86/100 PYFU) and less common in those on TDF/XTC (2.12/100 PYFU) or TDF (0/100 PYFU). In the unadjusted model, patients on TDF/XTC had a lower risk of ALD compared to those on XTC (RR 0.483 [0.278 to 0.838]); in the fully adjusted model, the RR was 0.746 for TDF/XTC [0.389–1.430, NS]. HBV DNA suppression and ALT trajectories were similar among treatment groups. Despite the low number of ALD and small sample size in subgroups, anti-HBV monotherapy with 3TC or FTC was associated with a higher risk of severe hepatic outcomes in HIV/HBV-positive patients. Additional studies are warranted to verify this observation in randomised comparisons.

Wednesday’s poster discussion session opened with Richard Hauberich (Medical Affairs, Gilead Sciences, Foster City, CA, USA) who retrospectively assessed pre-existing M184V/I resistance substitutions and their impact on virological outcomes after switching to bictegravir/emtricitabine/tenofovir alafenamide (B/FTC/TAF) from a PI regimen [24]. In this study 380–1878, historical genotypes were available at screening for 49% (141/290) of participants and showed no evidence of pre-existing M184V/I. Baseline proviral HIV-1 DNA genotypes were obtained for 89% (259/290) and detected archived M184V/I in 16% (42/259) of participants. Among those with an M184V/I, 95% (40/42) were suppressed at their last study visit at the time of the week-48 snapshot analysis: 37 had an HIV-1 RNA <50 copies/mL at week 48 and three were missing at week 48, but had plasma HIV-1 RNA <50 copies/mL at their last study visit. Only two of 42 participants with a M184V/I experienced a blip. No B/F/TAF-treated participant developed new study drug resistance. Overall, pre-existing M184V/I did not affect HIV-1 RNA suppression or the occurrence of viral blips in B/F/TAF-treated patients.

Marc Underwood (Clinical Virology, Gilead Healthcare, Research Triangle Park, NC, USA) evaluated viral replication below <50 copies/mL between a two- and three-drug regimen in the SWORD-1 and SWORD-2 studies [25], assessing the number of participants having a viral load between 40 and 50 copies/mL and TD/TND for VL <40 c/mL (TD: target detected or HIV-1 RNA present; TND: target not detected or HIV-1 RNA not present) over 48 weeks for DTG + rilpivirine (RPV) two-drug regimen versus current antiretroviral regimen (CAR; PI- NNRTI- or INSTI-based three-drug CAR). Participants with baseline TD had more frequent TD occurrences post-baseline compared to participants who were baseline TND. Similar proportions of participants with TND were observed at each visit through week 48 for both arms.

David Margolis (Clinical Development, Viiv Healthcare, Research Triangle Park, NC, USA) shared the week-160 results of the LATTE-2 study regarding the safety, efficacy and durability of long-acting cabotegravir (CAB) and RPV [26]. At week 96, response rates were comparable between treatment arms: injections every 8 weeks (QBW), every 4 weeks (Q4W) and daily oral CAB 30 mg + ABC/3TC (PO). Intramuscular injections of CAB long-acting (LA) + RPV LA, dosed Q4W or Q8W, successfully
maintained HIV-1 viral load <50 copies/mL through 3 years. No participants met the protocol-defined VF criteria after week 48 across all arms. There was a good injection tolerability over time. The dose selection (Q4W or Q8W dosing) is under evaluation in ongoing Phase III studies.

Chloe Orkin (Barts Health NHS Trust and Queen Mary University of London, UK) presented subgroup analyses through week 48 of the GEMINI studies [27]. In these, DTG + 3TC have demonstrated a non-inferior efficacy to DTG + TDF/FTC in treatment-naive adults using as primary endpoint the proportion of participants with plasma HIV-1 RNA <50 copies/mL. Across both studies, six participants on DTG + 3TC and four on DTG + TDF/FTC met protocol-defined virological-withdrawal criteria through Week 48; none had treatment-emergent integrase-stand-transfer-inhibitor or NRTI resistance mutations. Both regimens were well tolerated. Subgroup analyses of efficacy and AEs performed based on the baseline disease status and demographic characteristics were consistent with the overall study results.

In the Late breakers/hot topics session Jakob Grobler (Infectious Disease Biology, Merck Sharp and Dohme, Kenilworth, NJ, USA) presented an evaluation of the MK-8591 antiviral activity against a broad panel of clinical isolates harbouring mutations that confer resistance to approved NRTIs, as well as 11 different wild-type HIV-1 subtypes [28]. MK-8591 is a novel and potent nucleoside reverse transcriptase translocation inhibitor (NRTTI), currently in Phase II clinical development, with a unique mechanism of action. Against wild-type HIV-1 in human PBMCs, MK-8591 (IC50=0.2 nM) was over 10-fold more potent than TAF, AZT and 3TC (IC50s of 3 nM, 10 nM and 144 nM, respectively). Against the common NRTI resistance mutations such as M184I and M184V, it exhibited an IC50 of 0.8 nM (3.9 fold change [fC] versus the wild-type strain) and 1.1 nM (5.0 fC), respectively. MK-8591 is more potent against common NRTI resistant HIV-1 isolates than any approved NRTI is against wild-type HIV-1.

Peter Ackerman (Clinical Development, Viiv Healthcare, Branford, CT USA) presented, on behalf of the BRIGHTE study team, the week-48 data from the ongoing BRIGHTE trial [29,30]. Fostemsavir (FTR) is an investigational first-in-class attachment inhibitor produg that is metabolised to its active moiety tamsavir, throughout the GI tract. It has been specifically developed for heavily treatment-experienced (HTE) patients living with multidrug resistant (MDr) HIV-1 that compared efficacy outcomes [33], and was then prolonged by an EAP for an additional 24 weeks. At week 25, median VL reduction was 1.8 log10 with 43% (17/40) of patients achieving full suppression (<50 copies/mL) in the ITT-MEF analysis. In the composite analysis, median VL decrease was 2.5 log10 with 55% (17/31) of patients reaching <50 copies/mL. At week 48, in the ITT-MEF analysis, median VL reduction was 2.8 log10 with 59% (16/27) of patients reaching <50 copies/mL. In the 24-week completers, a median VL decrease of 2.9 log10 was found with 16 patients (67%) reaching <50 copies/mL. All those who reached a VL <50 copies/mL remained on treatment, with no virological failure or breakthrough by week 48.

Scott Letendre (Antiviral Center, University of California, San Diego, CA, USA) evaluated cabotegravir (CAB) and rilpivirine (RPV) concentrations in CSF and plasma, CSF to plasma concentration ratios, and the impact of a dual CAB/RPV LA treatment regimen on CSF and plasma HIV-1 RNA at steady state in a subset of HIV-1-infected patients in the Phase IIb LATTE-2 study [34]. In 18 participants receiving CAB LA + RPV LA every 4–8 weeks achieved effective virological control in CSF and plasma. CAB and RPV total CSF concentrations were 0.30%–0.34% and 1.07%–1.32% of their paired total plasma concentrations. CAB and RPV total CSF concentrations were higher than their respective in vitro IC50 for wild-type HIV-1 viruses (CAB 0.000089–0.0003 µg/mL, RPV 0.066–0.081 ng/mL). All patients had HIV-1 RNA <50 copies/mL in plasma. There were no SAEs or AEs leading to discontinuation. Overall, a dual CAB LA + RPV LA administered every 4–8 weeks achieved effective virological control in CSF comparable to that observed in plasma.

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