Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Virus Eradication 7 (2021) 100049

Contents lists available at ScienceDirect

Journal of Virus Eradication

journal homepage: www.sciencedirect.com/journal/journal-of-virus-eradication

Highlights from the *virtual* conference on retroviruses and opportunistic infections (CROI) 2021: SARS-CoV-2 pathogenesis, new data about antiretroviral treatments, HIV-associated comorbidities, pediatrics and pregnancy

The CROI 2021 was virtually held in Chicago with the same scientific excitement and exchanges. Much data was presented about SARS-CoV-2, the hero of the current pandemic, helped by the fact that HIV researchers have had to put most of their work on hold over the past year. Despite its virtual format CROI 2021 succeeded to stimulate intense discussions and communicate the hot topics of the day to continue to move the HIV science forward.

SARS-CoV-2 versus the host: Virology, immunology and pathogenesis

Caterina Prelli Bozzo (Ulm University Medical Center, Germany) opened this session, explaining how the interferon-induced transmembrane (IFITM) protein family which is known as viral restriction factors (for viruses such as influenza, HIV, Zika and coronaviruses pseudotypes), may promote SARS-CoV-2 entry into cells.[1] Indeed, even if IFITMs blocked SARS-CoV-2 infection in transduced HEK293T cells in a dose-dependent manner, endogeneous expression of IFITMs in Calu-3 (lung cell line) and SAECells (primary small airway epithelial cells) promoted genuine SARS-CoV-2 infection entry. Moreover, IFITMs interact directly with the SARS-CoV-2 spike and antibodies directed against the intramembrane region of the IFITMs or IFITM-derived peptides could inhibit SARS-CoV-2 replication. Thus IFITMs are potential novel targets for SARS-CoV-2 inhibition.

Leila B. Giron (The Wistar Institute, Philadelphia, PA, USA) explored the possibility of a vicious cycle between lung, gut, and inflammation (Gut-Lung Axis), contributing to COVID-19 severity.[2] Researchers compared 60 SARS-CoV-2 positive versus 20 age-matched SARS-CoV-2 negative subjects, concluding that COVID-19 severity was associated with tight junctions' permeability (higher levels of zonulin). Zonulin is both a marker and driver of gut permeability, as the only non-physiological regulator of intestinal tight junctions. In this cohort COVID-19 severity was also associated with lipopolysaccharide-binding protein (LBP) and beta-glucan plasma levels as markers of microbial and fungal translocation, as well as soluble sCD14 and myeloperoxidase levels as markers of monocyte/neutrophil inflammation. Markers of intestinal barrier integrity strongly correlated with many markers of inflammation and immune activation, including IL-6, CRP and D-dimer. Moreover, severe COVID-19 disease was associated with a plasma metabolomic profile reflecting a disrupted gut function, as dysregulated metabolic pathways were all related to amino-acid metabolism. More specifically, citrulline (marker of intestinal function and absorption) showed reduced plasma levels, while markers of microbial dysbiosis (succinic acid and kynurenine/tryptophane ratio) increased in the plasma of the moderate and severe groups. All these markers were also associated with systemic inflammation (positive correlation with succinic acid and kynurenine/tryptophane ratio, negative correlation with citrulline). Severe COVID-19 disease was also associated with disrupted plasma lipidome and glycome in a manner consistent with gut dysfunction, even if a causal relationship is not yet established.

Minami Tokuyama (Icahn School of Medicine at Mount Sinai, New York, NY, USA) looked for evidence of *in vivo* SARS-CoV-2 intestinal infection in 29 participants undergoing clinically indicated endoscopic procedures with a concurrent or past diagnosis of COVID-19.[3] The average age of the participants was 51.5 years (±19.9) and 19 (65%) were male. The average number of days from the last positive nasopharyngeal swab was 51 (±44.8) days and from symptom onset to procedure 56.6 (±54.72) days. Seven (24.1%) out of 29 patients were PCR positive within 3 days of the procedure. Most patients had had mild disease during their acute COVID-19 illness (18 patients or 62.1%), 6 (20.7%) severe disease and 8 (27.6%) COVID-19 associated gastro-intestinal (GI) symptoms. SARS-CoV-2 antigen and presumptive viral particles were identified by immunofluorescence in the small intestinal biopsies from c 12/25 COVID-19 patients. At the time of biopsy, large number of cells with detectable antigen appeared to be goblet cells (MUC2+), however, the type of infected cells may be stagedependent. Despite the detection of viral products, inflammation was mild or undetectable in most cases. Detection of viral products did not correlate with gastro-intestinal symptoms in the acute setting in this cohort. Finally, viral antigen could be detected in intestinal tissue up to 7 months after symptom resolution.

Shelli F. Farhadian (Yale School of Medicine, New Haven, Connecticut, USA) described divergent and self-reactive immune responses in the central nervous system (CNS) of COVID-19 patients.[4] Neurological symptoms are present in about a third of in-patients with acute COVID-19. Other respiratory viruses such as respiratory syncytial virus and influenza can cause neurological sequelae through various pathways, including direct neuro-invasion and/or para-infectious processes, including exuberant immune responses within the CNS. Autopsy studies of patients who had died from COVID-19 disease suggest that viral neural invasion occurs in some patients but does not fully explain the degree of neuropathology seen in some cases. Researchers have evaluated in this study whether neural immune processes may contribute to the neurological sequelae during COVID-19 using paired blood and CSF samples from COVID-19 patients and healthy uninfected controls, in order to compare immune profiles in blood and CSF. In 6 acute COVID-19 patients with neurological symptoms (seizures, encephalopathy or intractable headache) they demonstrated divergent T cell responses in CSF and plasma, namely upregulated CSF Th1, Th2 and effector CD8 T cells during COVID-19, with activated IL-1 and IL-12

https://doi.org/10.1016/j.jve.2021.100049

Available online 5 July 2021

pathways only in the CSF. Moreover, B cells were also increased in the CSF and presented different SARS-CoV-2 antibody profile as compared to the blood (e.g., anti-receptor binding domain (RBD) antibodies were rare in CSF but uniformly present in plasma). Finally, when cloning individual monoclonal antibodies (mAbs) from clonally expanded B cell receptor sequences from CSF and blood, they found that unique CSF-derived mAbs target the spike protein, while all others mAbs had anti-neural immune reactivity. In summary, intrathecal antibodies were reactive to SARS-CoV-2 antigen, self-antigen or both and CNS symptoms during COVID-19 were likely multifactorial and may be due in part to CNS-specific immune responses.

New antiretroviral drugs

When considering that COVID-19 was an understandably dominant theme at the CROI 2021, there was still a lot of data on novel antiretrovirals (ARVs), from both existing and new classes. Long-acting (LA) formulations are a major focus for drug development and the news, just before the Conference, that Merck & Co (MSD) will be joining forces with Gilead Sciences[5] to develop their LA drug pipelines is welcomed.

The PK modelling data for the MSD investigational non-nucleoside inhibitor of the retrotranscriptase (NNRTI), MK-8507, supports once weekly dosing.[6] This opens the option for a weekly two-drug regimen (2DR) with their NRTTI (nucleoside reverse transcriptase translocation inhibitor) islatravir that has already shown promise as a daily 2DR with the NNRTI doravirine in a phase 2 trial.[7] We also saw new data on the resistance profile of MK-8507 which is essentially similar to doravirine.[8] Common NNRTI mutations, including the K103 N, confer less than a 5-fold reduction in susceptibility to MK-8507 which is predicted not to be clinically important. However, in the absence of clinical data in NNRTI-experienced patients, it is not possible to say with confidence what the clinical cut-off for susceptibility will be, so we should keep a degree of caution before more data is available. The outcome of combining these drugs will depend on the degree of the genetic barrier of islatravir and MK-8507 or doravirine.

Lenacapavir, the capsid inhibitor from Gilead Sciences, has already produced lots of excitement due to its pharmacokinetic data supporting a 6-monthly dosing by subcutaneous injection, a route and dosing frequency which seems preferable to the first LA generation with a 1–2 monthly intramuscular injection. At the conference results of the CAPELLA study were presented, a two-cohort study in highly treatment-experienced individuals who did not have history of virological failures (defined as viral load $\geq$ 400 HIV-1 copies/mL and resistance to $>$ 2 agents from 3 of the 4 major antiretroviral (ARV) classes and having $<$2 fully active agents). Eligible individuals entered a randomised cohort (2:1 daily oral lenacapavir versus placebo added in for 14 days, followed by lenacapavir plus an optimised background regimen [OBR] for all) if there was no significant change in their viral load (VL) between screening and a pre-randomisation visit (n = 36). The 36 participants who experienced a VL decline between those two time-points (implying a primarily adherence issue) went straight onto lenacapavir plus OBR. A November 2020 press release had already confirmed that lenacapavir had met the primary endpoint in terms of the proportion of participants achieving at least a 0.5 log reduction in VL by day 15 versus placebo in the randomised cohort. The CROI 2021 presentation confirmed this with 88% of participants on lenacapavir and 17% on placebo achieving or exceeding this VL decline at the end of the monotherapy period. We also saw the proportion of participants achieving viral suppression ($<$50 HIV-1 copies/mL) out to week 24. At this time-point the data seems difficult to interpret. At week 24, 73% of participants (randomised and non-randomised cohorts combined) had an undetectable VL but only 26 of the 72 participants had reached this time-point. It is worthwhile mentioning that in a study of this size these results could change markedly by the time everyone has reached 24 weeks of follow-up. In addition, there was no data on baseline resistance, OBR components and, crucially, predicted OBR activity. Beyond this impressive drop in VL at day 15 of monotherapy it is hard to draw firm conclusions about the efficacy of this agent in this type of patients. There were high levels of prior exposure to the four main drug classes, but no information on baseline resistance mutations, beside the fact that OBR could include investigational drugs (such as fostemsavir) and most licensed drugs (atazanavir being a notable exception). Did lenacapavir offer additional efficacy in individuals starting another novel agent, over and above twice daily dolutegravir and darunavir? Lenacapavir does not seem to have a high resistance barrier with 2 of the 72 participants developing high level capsid inhibitor resistance – whether these patients had been exposed to a period of monotherapy was not shown. This new compound offers a novel class for people with limited treatment choices, and the potential for a bi-annual, self-administered option for both treatment and prevention. However, we need more data and larger studies for this compound. Shortly after CROI 2021, Gilead Sciences announced in a joint statement with MSD that lenacapavir would be developed in combination with islatravir.[5]

When considering the maturation inhibitors which had rather disappointing initial results, the first investigational drug in this class, bevirimat, was abandoned when it transpired that baseline gag polymorphisms, particularly common in protease inhibitor (PI) experienced individuals, conferred clinically important resistance in a significant proportion of patients.[9] GlaxoSmithKline (GSK) is at the forefront of ongoing research in this class of drugs and, having ceased development of their boosted agent[10], the latest compound to emerge from this class pipeline is GSK3640254 (abbreviated herein to GSK-254). The presented study investigated GSK-254 monotherapy in treatment-naïve individuals with 14 days of monotherapy in 14 individuals,6 in each active arm (10mg or 200mg) and 2 in the placebo arm.[11] There was no VL change nor resistance on day 11 of the 10 mg arm but, despite a close to 2 log reduction in VL at day 11 in the 200mg group, 4 of the 6 participants developed the A364V mutation which confers high-level resistance to the compound. The analysis of this data prompted a shortening of the duration of monotherapy to 7 days for the part 2 of this study. Day 8 VL reduction was in the range of 1–1.5 log in the active treatment arms (40mg, 80mg and 140mg) with the greatest VL reduction at the highest dose, with no resistance development. Reassuringly, although there is marked loss of susceptibility with the A364V mutation, it is unaffected by gag mutations that impacted the activity of earlier agents in this class.[12] According to the phase IIa presentation, the next step for this drug in development is a study investigating its potential as a third agent with a 2 NRTI backbone, a somewhat old-fashioned approach for a new drug. However, a published phase 1 study investigating the pharmacokinetics of GSK254 and dolutegravir has concluded that “these agents could be used in combination for the treatment of HIV infection, in particular as part of a fixed-dose, 2-drug regimen” so presumably this is another direction of travel for GSK-254.[13]

Finally, the oldest of the ‘new’ drugs, are the injectable cabotegravir (CAB) and rilpivirine (RPV). These intramuscular (IM) ARVs were licensed in Europe in December 2020 and by the FDA in January 2021, though Canada was well ahead of the curve, approving them in March 2020! The roll-out has been rather limited to date but will likely accelerate over the course of this year. Many of the potential challenges in terms of real-life adherence, managing late/missed doses and real-life discontinuation rates are yet to be experienced by most of clinicians. The data supporting the efficacy, safety, and tolerability of IM CAB/RPV is provided by the ATLAS[14] and FLAIR studies,[15] along with impressive patient-reported outcomes indicating a strong preference for injectable over oral ARVs. Of note, the approval in Canada and the USA for IM CAB/RPV involves monthly dosing, whereas the European Medicines Agency has approved both monthly and 2-monthly dosing, based on the published 48-week results of the ATLAS-2M study.[16] At CROI 2021 the 96-week results for this study were reported which recruited 1045 people on suppressive antiretroviral therapy (ART).[17] Some participants had rolled over from the ATLAS study and were already on monthly IM ART, others were on oral therapy. These were randomised to IM

CAB/RPV every 1 or 2 months (those not already on injectables received an oral lead-in) and the 96-week snapshot analysis showed 91% of participants on 2-monthly and 90.2% on monthly dosing maintaining viral suppression. Of note, the proportion with snapshot detectable viraemia was higher on the 2-monthly schedule, 2.1% versus 1.1%, as were confirmed virological failures (CVFs) at 1.7% versus 0.4%, most CVFs failing with dual-class resistance. The number of CVFs was small. We must consider that this was in the context of 100% adherence as therapy was directly observed. Although several factors have been associated with a higher risk of CVF,[18] including the presence of ≥2 of proviral RPV resistance mutations, HIV-1 subtype A6/A1, and/or BMI ≥30 kg/m2, it is hard to reliably predict who is more likely to fail IM CAB/RPV. We will need to counsel patients about a small risk of virological failure with resistance, even in the context of optimal adherence. It is also important to note that modelling data presented at CROI showed that monthly dosing of CAB/RPV was likely to be more 'forgiving' and adherence to the 2-monthly dosing particularly important.[19,20] In the HPTN 083 study comparing oral tenofovir-disoproxil/emtricitabine and IM CAB for pre-exposure prophylaxis, there were four cases of incident HIV despite good CAB plasma concentrations.[21] Does this suggest a lack of potency in at least some individuals? Whilst the first generation of LA ARVs is undoubtedly a huge leap forward and welcomed by many people currently taking daily oral ART, some caution is advised. For some individuals with more than one negative predictor for CVF, particularly those who may struggle to commit to regular, on-time injections, delaying a switch to LA ART might be a sensible strategy.

HIV-Associated comorbidities

Tara McGinty (University College Dublin, Dublin, Ireland) introduced the session on complications of HIV, presenting a clinical trial on behalf of the APART study group on how a short-course of alendronic acid (AL) could prevent ART-associated bone loss.[22] Knowing that ART initiation has consistently been associated with a 2–6% loss of bone mineral density (BMD) in the first 48 weeks after treatment initiation, the study's primary aim was to determine if a short-course of generic oral AL could prevent bone loss associated with ART initiation in ART-naïve people. This study was a multicenter, prospective, randomized, double-blind, placebo-controlled phase IV trial comparing generic oral AL versus placebo for a total of 14 weeks. Fifty participants were well matched with no significant differences in demographics. Most participants were initiated on an integrase inhibitor (INSTI)- based regimen as their third agent. It is worth noting that there were more current or former smokers in the placebo group. There was no difference regarding BMD between the groups at baseline. When examining the primary endpoint of the percentage change in BMD at total hip at week 50 between groups, the investigators found that the active arm had a 0.5% gain in total hip BMD compared to a 2.7% loss in the placebo arm, resulting in a significant difference of 3.1% between groups. At the lumbar spine level participants receiving AL had a significantly higher BMD at week 14 and 26 (2.4% and 3.1%, respectively) but this gain did not persist till week 50. Although the AL arm had a smaller decline in lumbar spine BMD compared to the placebo group, the difference in BMD of 2.3% between the two groups was not statistically significant. AL was overall well tolerated during the study. Despite limitations regarding the small sample size, limited female representation and lack of alternative non INSTIs third agents, generic AL seemed to be an easily accessible option particularly in resource-limited settings.

Michael J. Silverberg (Kaiser Permanente Northern California, USA) presented data on the prevention of cardiovascular disease (CVD) in persons with and without HIV.[23] Researchers first measured the management below treatment targets of hypertension, dyslipidemia and diabetes mellitus. The Disease Management Index (DMI) is a measure of how effectively a condition is managed, considering both time and level of control. Participants in this cohort study included Kaiser Permanente (KP) members with HIV (PWH) (N = 8285) and age-, sex-, race/ethnicity-matched members without HIV (PWoH), (N = 170,517), excluding individuals with prevalent CVD. Regarding risk factor management, similar dyslipidemia, hypertension and diabetes control were observed in persons with and without HIV, while there was evidence for slightly worse triglycerides and better HbA1c control for PWH. Regarding CVD risk, PWH had a 26% higher CVD risk when there was no history of dyslipidemia, hypertension and diabetes. There was no difference in CVD risk by HIV status among those with adequate dyslipidemia and diabetes control. Finally, CVD risk was 35% higher when PWH had adequate hypertension control and 91% higher with inadequate hypertension control (specifically systolic blood pressure).

Priscilla Hsue (University of California San Francisco, USA) used large-scale proteomics to identify novel protein biomarkers associated with total mortality events in PWH, compared to HIV-related factors, inflammatory and coagulation markers and components of the Veterans Aging Cohort study (VACS) Index.[24] The authors performed a longitudinal, prospective, observational study of 1525 PWH and 853 uninfected veterans within the 2005–2019 time-period. Novel unique proteins were identified that were negatively or positively associated with PWH mortality. A risk score based on 10 proteins provided moderately good discriminatory accuracy, despite heterogeneous causes of death in this population. Proteins remained predictive of mortality despite the addition of HIV-associated characteristics, traditionally measured inflammatory/coagulation markers and VACS Index components.

Padraig McGettrick (University College Dublin, Ireland) presented the results of the HIV UPBEAT CAD sub-study on the inflammatory profile associated with subclinical coronary artery disease (CAD).[25] One hundred and one participants were enrolled, of whom 51 were PWH. The two groups were well-matched except for statin use and HDL cholesterol. Following unsupervised hierarchical clustering analysis, 3 biomarker-derived distinct inflammatory clusters were identified: cluster I was characterized by overall lower Tcell senescence, activation and systemic inflammation markers, cluster II by high Tcell senescence, activation and inflammation markers and low Th1 driven biomarkers, and cluster III by increased systemic inflammatory and microbial translocation markers. Cluster demographics were overall similar except for HIV status, because PWH were significantly over-represented in cluster II and under-represented in cluster I. Associations of inflammatory clusters with radiological end-points showed that, overall, 36% of participants had evidence of subclinical CAD on coronary computed tomography angiography (CCTA) imaging. In the unadjusted analysis, cluster II and III displayed a stronger association with partially calcified plaque and mixed plaque and a weaker association with any coronary plaque and calcified plaque. Cluster III was the only cluster associated with both calcium artery calcium (CAC) Agatston and calcium volume scores. Adjustment by HIV status did not significantly alter the associations seen between clusters and CAD, suggesting that it is inflammation rather than the HIV status that drives these associations.

Bastian Neesgaard (CHIP, Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark) and the RESPOND study group assessed if exposure to INSTIs was associated with an increased incidence of CVD.[26] The RESPOND participants were INSTI-naïve, followed from baseline (1st of January 2012) to the earliest CVD event, last follow-up or 1st of October 2018. Exposure to INSTIs was calculated following the D:A:D methodology and models adjusted for CVD risk factors, HIV characteristics and ARVs previously associated with CVD. Logistic regression examined odds of starting an INSTI (raltegravir [RAL], elvitegravir [EVG/c] and dolutegravir [DTG]) by D:A:D 5-year risk score. More than 21,000 individuals were included in this analysis of whom 46% (9782) were exposed to an INSTI during follow-up. Overall, most participants were white, of male gender and Western European origin, with MSM being the most frequent risk for HIV transmission. During a median of 6.3 years of follow-up (IQR 3.5–6.7), corresponding to 106,870 person-years of follow-up (PYFU), 517 CVD events occurred, giving an overall incidence rate of 4.9/1000 PYFU (CI

95%, 4.5–5.3). Myocardial infarction (MI) was the most frequent occurring event (210 MIs, 162 strokes and 145 invasive cardiovascular procedure). Looking at the population stratified by those who did not experience an event versus those who did, the latter were older with a larger proportion of CVD risk factors at baseline and a higher 5-year estimated D:A:D CVD risk score (46% versus 12%, $p < 0.001$). When examining the risk of starting an INSTI by baseline 5-year estimated D:A:D CVD risk and compared to those with low risk, the odds of starting an INSTI were higher for the higher risk score categories (moderate risk (1-<5%): 1.11 [1.00–1.21], high risk (5 - <10%): 1.19 [1.05–1.35], very high risk (>10%): 1.05 [0.89–1.25]). Figure A shows the results of the crude unadjusted incidence rates of CVD stratified by INSTI exposure, demonstrating the increase in the IR of those who were never exposed to those having a 0–6-month exposure, while thereafter IR declined to the levels of those who were never exposed. In Figure B are shown the IR Ratios after adjustment for confounding factors, confirming the 2.5 times greater incidence of CVD within the first 6 months of INSTI exposure when compared to the non-exposed group, regardless of underline CVD risk and HIV characteristics. Due to limited statistical power, there was no focus on individual INSTI drugs and ART-naïve individuals. To conclude, in the large RESPOND collaboration the use of INSTI was associated with an increased incidence of CVD in the first 6 months of exposure after accounting for known risk factors, including the ART backbone across a wide range of sensitivity analyses. While we cannot fully exclude possible channeling bias or residual confounding, these findings call for further investigations.

Kazuo Suzuki (St Vincent's Hospital, Sydney, Australia) presented data from his group about pathogenesis of HIV-associated neurocognitive disorders (HAND) despite prolonged suppressive ART.[27] Researchers investigated if HAND was related to active HIV-1 transcription

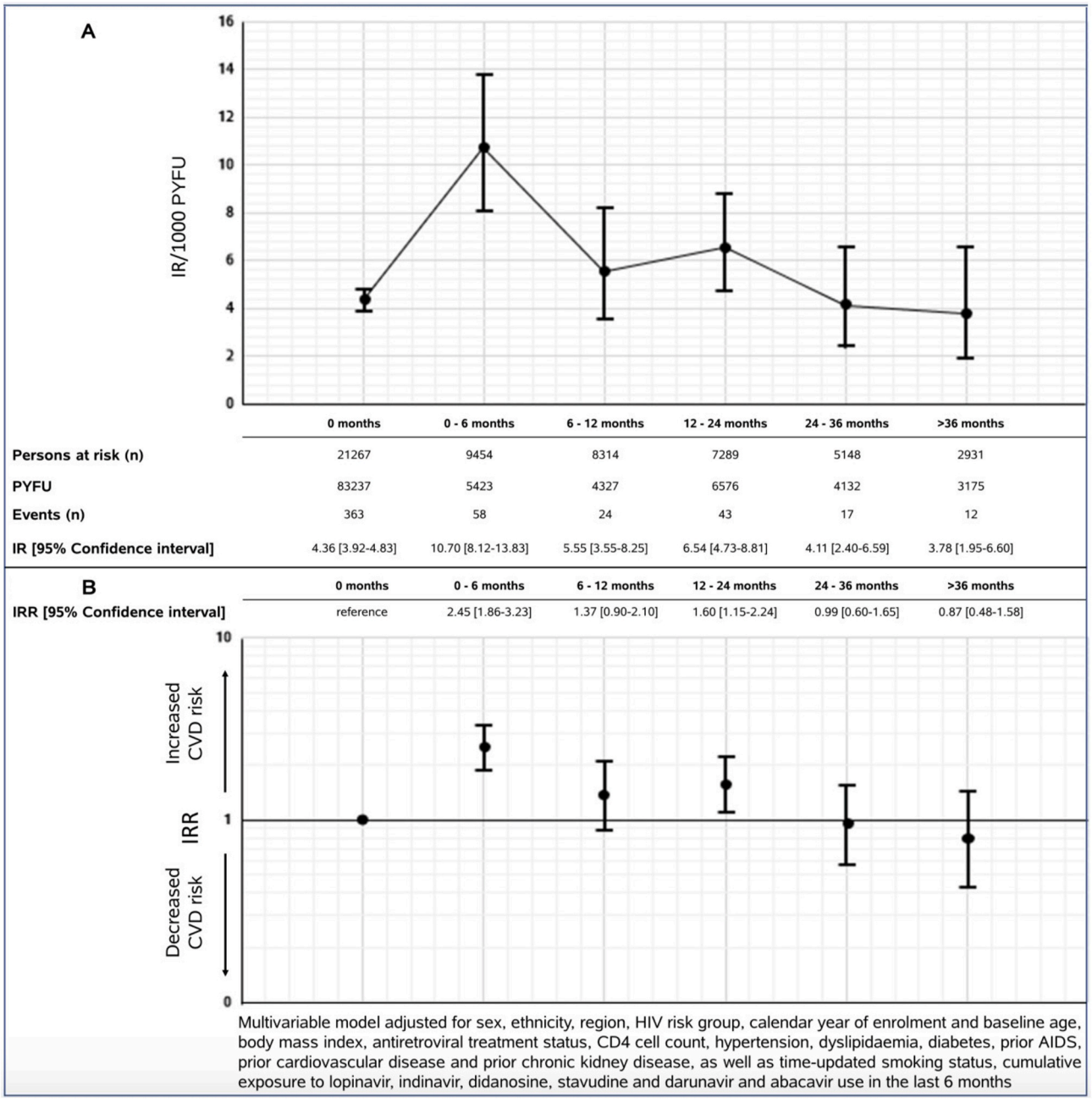

Figure 1. A. The RESPOND study. Crude unadjusted incidence rates of cardio-vascular disease stratified by INSTI exposure.
B: The RESPOND study. Cardio-vascular risk: IR Ratios after adjustment for confounding factors.

from the CNS reservoir without production of whole virions in 20 paired CSF and blood samples from virally- suppressed patients in plasma (<50 HIV-1 copies/mL) and CSF (<80 HIV-1 copies/mL) enrolled into a prospective study of HIV-1 CNS latency biomarkers. Patients had a median age of 62 years, were all male and had a median nadir CD4 T cell count of 202 cells/mm^3, and a median CD4 T cell count at the time of analysis of 656 cells/mm^3. Using the double-R assay (targeting the R region of the long-terminal repeat section), they detected cell-associated HIV transcription activity despite ART. This assay was 27 times more sensitive than a real-time assay that detects cell-free virus in plasma and CSF.

The HIV-1 RNA transcripts and HIV-1 DNA levels in CSF cells were significantly higher than in polymorphonuclear cells (PBMCs), even after normalization of HIV-1 copy number by number of infected cells, suggesting that the CSF is an HIV reservoir with high transcriptional activity despite ART. The CSF HIV-infected cells were mainly CD4 and CD8 T cells that were 20 times higher than monocytes. HIV-1 transcripts were quantified in CSF cells of 18/20 patients (90%), while HIV-1 DNA was quantified in cells from 16/20 patients (80%). Interestingly, HIV-1 transcript expression in CSF cells was highly correlated with levels in PBMCs. Most of the CSF infected cells were memory CD4 T cells expressing CXCR3, CD49d (integrin alpha 4) but lack integrin beta 7. This type of cells was highly enriched in CSF compared to PBMCs. Most of these memory cells were activated CCR5+ and likely to be the source of HIV-1 RNA transcripts, while monocytes seemed to be less important. Although there was insufficient data for correlation analysis of HIV-1 RNA transcript levels in CSF CD4 T cells and neuropsychological tests, there seemed to be an inverse correlation between HIV-1 transcripts and neuronal integrity, as reflected by brain metabolites (FWM-N-acetyl aspartate (NAA)- and PCC-NAA) in the MRI/S analyses.

Patrick Luckett (Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA) presented data about the effect of HIV and aging on resting-state networks.[28] The aims of this study were to i) utilize machine learning-based feature selection to identify resting networks as the strongest predictors of HIV status and cognitive impairment and ii) to use deep learning to analyze voxelwise maps of the networks identified by feature selection and therefore assess topological differences. Researchers used resting-state functional MRIs that allowed studying neuronal brain activity by measuring the blood-oxygen-level-dependence (BOLD) signal over time. The BOLD signal reflects brain activity via oxygen usage and can be used to identify unique brain networks as well as to evaluate the brain functional organization (hierarchy, topological boundaries, communicating signals). A total of 1806 participants were included in this study, of which 297 were HIV positive and virogically suppressed (viral load < 200 HIV-1 copies/mL) and matched for age, sex and education with control participants. Cognitive impairment was assessed in the learning, memory, executive, motor and language domains. A total of 15 resting-state networks were evaluated in HIV positive participants with or without cognitive impairment and in controls. Salience network was a strong predictor for all three groups in all age groups. Parietal memory network was a strong predictor of HIV status but not cognitive impairment status. The frontal parietal network was a strong predictor when comparing controls to PWH cognitive-impaired and PWH with normal cognition to cognitive impaired PWH, but not controls to PWH with normal cognition, suggesting that cognitive impairment was associated with both cortical and subcortical regions.

Existing antiretroviral drugs, new data

CROI 2021 offered many opportunities to look at new data on ARVs and treatment strategies. Here we will be looking first at two-drug (2DR) regimens, then first-line and finally second-line therapy as well as advanced HIV infection.

Dolutegravir and lamivudine

The previously much reported dolutegravir two-drug (2DR) studies, GEMINI and TANGO, reported new data. The GEMINI 1&2 studies are treatment-naïve studies where participants were randomised to receive dolutegravir (DTG) with either lamivudine (3TC) alone, or with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC). Having presented week 144 non-inferiority outcome data at the 2020 Glasgow HIV conference, the presentation of the week 144 secondary endpoint subgroup analysis, demonstrated that the 2DR arm (DTG/3TC) was non-inferior at week 144 regardless of age, gender, race and baseline CD4/VL.[29] The subgroup efficacy results at week 144 were generally consistent with the overall study results and further demonstrated that DTG and 3TC is an effective initial treatment for patients across a spectrum of disease characteristics and patient populations.

TANGO is a stable switch study where participants were randomised to remain on either tenofovir alafenamide (TAF)- based triple therapy (3DR) at baseline, or to switch to 2DR (DTG/3TC). Week 96 non-inferiority results were presented at the Glasgow 2020 conference. At this meeting the secondary end-point snapshot virologic success subgroup analyses by baseline regimen third agent class, disease and demographic characteristics were presented. The 2DR arm was demonstrated to be at least non-inferior at week 96 by age, gender, race, third agent at baseline and baseline CD4 T cell subgroups.[30] Efficacy by subgroup was consistent with the overall week 96 study results, demonstrating that switching from TAF-based regimens to DTG/3TC is effective at maintaining virological suppression, regardless of baseline regimen, patient or disease characteristics.

This is reassuring data and clearly supports the inclusion of DTG/3TC in treatment guidelines for both initiation and switch in appropriate patients. It is important to bear in mind that TANGO represents a switch from TAF-containing regimens, approximately 67% were receiving Genvoya (TAF/FTC/EVG/c) and a further 7% a booster protease inhibitor. This means two important things – first we must consider the metabolic data as representing, in approximately three quarters of participants, a switch away from a booster. Second, other stable switch data to this regimen is awaited.

What about the M184V mutation?

The impact of previous selection of the M184V mutation[31] on the virological response to DTG and 3TC in real life is still unclear. Santoro and colleagues presented a European retrospective study that aimed to assess the efficacy of this combination in a large set of virologically suppressed patients with or without a known M184V mutation Individuals with plasma HIV-1-RNA <50 copies/mL who switched to DTG/3TC and with at least 1 previous HIV-1 RNA measurement or HIV-DNA genotype before the switch were included. A survival analysis was used to evaluate the role of past M184V mutation on experiencing virological failure (VF: HIV-1 RNA >50 copies/mL in 2 consecutive determinations or >200 copies/mL in a single determination) or a blip (a single HIV-1 RNA in the range of 51–199 copies/mL preceded and followed by a <50 copies/mL measurements) after DTG/3TC switch. Resistance pattern at VF was also evaluated. Five hundred and thirty-three individuals followed in several clinical centres in France, Italy and Spain were analysed: 79.2% were male, with a median (IQR) age of 51 (43–58) years; median (IQR) time of virological suppression was 5.4 (2.7–9.5) years; median (IQR) number of previous VFs was 0 (0–1); median time under DTG/3TC was 22 (17–39) months. Past M184V was present in 37 (6.9%) individuals. Median (IQR) time of last detection of M184V before the switch was 11 (5–15) years. By stratifying for the presence/absence of M184V, no significant difference in the probability of VF was found (5.4% vs 2.6% at 1 year and 9.2% vs 4.4% at 2 years; $p = 0.345$). However, a significant higher probability of VF was found in individuals with M184V detected <5 years before the switch compared to those in whom M184V was detected >5 years and those

without M184V, at both 1 year (20% versus 0% versus 2.6%) and 2 years (20% vs 5% versus 4.4%; p = 0.007) after switch. This finding was confirmed by multivariable Cox regression analysis. Genotyping was available for 4/22 individuals with VF; no resistance to INSTIs or NRTIs was found. The authors concluded that in this real-life study, the probability of VF in patients switching to DTG/3TC was very low after 2 years of treatment. Furthermore, past M184V mutation influenced VF only in the context of a more 'recent' (<5 years) mutation detection. However, many would consider this as a scenario in which there does not appear to be a benefits that would outweigh the VF risk, particularly for an individual with other antiretroviral options available. Fortunately, no new resistance was demonstrated, but this strategy now does not seem one to have an ethical justification for further exploration.

Advanced HIV infection

Information on the impact of DTG-based ART in very advanced patients is limited in terms of clinical, immune reconstitution and virological outcomes, bacterial translocation, inflammation and immune activation. The authors of the Advanz-4 study wanted to consider also the impact on bacterial translocation given that boosted protease inhibitors (bPI) and INSTIs have different gut metabolic patterns. Advanz-4 trial is a multicentre randomized clinical trial with 104 antiretroviral-naïve patients with <100 CD4 T cells/mm^3 randomly assigned 1:1 to DTG (n = 52) or darunavir-ritonavir (DRV/r) (n = 52) plus abacavir and lamivudine at standard doses.[32] The primary endpoint was the median increase in CD4 T cell count at week 48. The secondary end-points were the proportion of patients with plasma HIV-1 RNA viral load (VL) < 50 copies/mm3, bacterial translocation, inflammation, immune activation, adverse events, IRIS, HIV disease progression and death. An intent-to-treat analysis was performed (3 patients in the DRV/r arm were excluded, none had started the study medication). The median (IQR) increase in the CD4 T cell count after 48 weeks was 172 (118; 255) and 157 (66; 277) cells/mm^3 in the DTG and DRV/r arms, respectively (p = 0.430). Plasma HIV-1 RNA suppression (<50 copies/ml) was significatively faster in the DTG arm at 4 and 12 weeks. At 48 weeks, the rate of suppressed patients was similar (77% vs. 63%, p = 0.191). IRIS and new AIDS defining events were low and similar in both arms. Only one patient died in the DRV/r arm. Treatment discontinuation was higher in the DRV/r arm (24.5% vs. 8%, p = 0.029). There were four virological failures (1 in DTG and 3 in DRV/r arm). Inflammation (TNF-alpha, IL-6, hsCRP), immune activation ($CD8^+CD38^+$ T cells, $CD8^+CD38$ + DR+) and apoptotic (annexin-V) markers were similar at baseline and declined significantly and similarly in both arms (p > 0.05 for all comparisons). A greater reduction in the shCD14 marker in patients treated with DTG was found (-802 [-1302; -398] vs. -396 [-924, 0.00] ng/mL; p = 0.011). The DTG-based ART regimen was as effective as te DRV/r-based one and had fewer discontinuations in very advanced ART-naive HIV-1-infected patients with superior reduction in bacterial translocation.

The Advanz-4 study is important as the undertaking of research in these advanced settings can be difficult. It has provided reassuring data in terms of DTG efficacy as well as of a decline in markers of inflammation and immune activation.

Second line therapy in Africa – the NADIA study

The NADIA Study was arguably one of the most important ones presented at this meeting.[33] It was set out to examine the performance of the World Health Organisation (WHO) Public Health approach to second-line therapy which recommends standardised sequential regimens with simplified monitoring (sparse viral load testing, safety monitoring, but no resistance testing). WHO recommends DTG with two NRTIs for second-line treatment of HIV infection after failure on an NNRTI-based regimen. There is limited evidence for efficacy of this DTG regimen when prescribed NRTIs lack predicted activity due to drug resistance or for the recommendation to switch from tenofovir to zidovudine in second line regimen.

NADIA therefore asked the following questions:

- Does DTG do as well as DRV/r in this scenario?
- Does DTG do well with fewer active NRTI?
- Is continued TDF/3TC non-inferior to switching to ZDV/3TC?

In a two-by-two factorial, open-label, non-inferiority trial, the NADIA Study randomized patients failing an NNRTI/tenofovir/lamivudine first-line regimen with confirmed VL > 1000 HIV-1 copies/ml to receive DTG orDRV/r and tenofovir or zidovudine with lamivudine. Treatment was monitored by VL at 24 and 48 weeks, following WHO guidelines. Baseline NRTI resistance testing was batched, and results blinded. The primary outcome was the percentage of patients with at week-48 a VL < 400 HIV-1 copies/ml using the FDA snapshot algorithm (non-inferiority margin 12%). NADIA enrolled 464 patients at 7 sub-Saharan African sites (61% female, 51% CD4 <200 cells/mm^3, 28% VL > 100,000 HIV-1 copies/mL). At baseline, 58.5% of participants had intermediate-high level resistance to tenofovir and 92% had resistance to lamivudine. Week 48 VL was <400 HIV-1 copies/ml in 90.2% in the DTG arm and 91.7% in the DRV/r one (difference -1.5%; 95% CI, -6.7 to 3.7%; p = 0.576; indicating non-inferiority of DTG, without superiority). In the subgroup with no predicted-active NRTIs in the prescribed regimen, VL was <400 HIV-1 copies/ml in 92.4% in the DTG group and 93.7% in the DRV/r one. To date, 4 participants have intermediate-high level DTG/r resistance; 0 have darunavir resistance. In the other randomized comparison, VL was <400 IV-1 copies/ml in 92.3% in the tenofovir group and 89.6% in the zidovudine one (difference 2.7%; 95% CI, -2.6 to 7.9%; indicating non-inferiority of tenofovir). Grade 3/4 adverse events were uncommon and similar in frequency between groups. The authors concluded that DTG with two NRTIs gives highly effective viral suppression up to 48 weeks, even in a patient population where many have extensive NRTI resistance and no predicted activity in the prescribed NRTIs. This finding is important for patients switching from NNRTI to DTG with NRTIs after known treatment failure; and for programmes switching stable patients systematically from NNRTI to DTG-based regimens without VL and resistance testing. Tenofovir can be maintained in second-line therapy without switching to zidovudine, with advantages for patients and programmes. These findings provide vital evidence needed following the DAWNING study in terms of the use of DTG with compromised NRTIs.[34] They are important for people switching from NNRTI to DTG second-line, after known treatment failure, as well as programmes switching stable people routinely from NNRTI to DTG-based regimens in settings without pre-switch VL and resistance testing. NADIA is continuing to 96 weeks which will mean further monitoring for major resistance among participants with vVF in the DTG group. Longer follow-up is key in monitoring late VF.

Impact of baseline resistance on second generation integrase inhibitors

Two Gilead Sciences-sponsored phase 3, randomized, double-blind, active-controlled studies of initial HIV-1 treatment demonstrated that bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) was non-inferior to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC, Study 1489) or to DTG + F/TAF (Study 1490) through 144 weeks.[35] In both studies, there was no emergent resistance to study drugs. At this meeting the effect of baseline transmitted drug resistance (TDR) on treatment response over 3 years was presented. Population sequencing of HIV-1 protease and reverse transcriptase (RT) was performed at screening; resistance to study nucleos(t)ide reverse transcriptase inhibitors (NRTIs) was excluded. Retrospective baseline next generation sequencing of protease, RT, and integrase (IN) was analysed at a ≥15% cut-off. Resistance analyses were performed on participants with confirmed viral rebound of HIV-1 RNA >200 copies/mL through week 144 or last visit when not resuppressed to <50 HIV-1 copies/mL while on study

drug. TDR was present in 19.5% (248/1274) of enrolled participants and consisted of INSTI resistance (-R) in 1.3% (17/1270 with data), NRTI-R in 2.7% (35/1274), NNRTI-R in 14.1% (179/1274), and PI-R in 3.5% (44/1274). Treatment outcomes by last observation carried forward at week 144 of participants with or without TDR were comparable (98% of those with primary TDR had an HIV-1 RNA <50 copies/mL versus. 97% of those without TDR), indicating that pre-existing TDR did not affect treatment outcomes. One participant had pre-existing Q148H + G140S in IN and K70R and K103 N in RT at baseline. This participant was randomized to B/F/TAF, had HIV-1 RNA <50 copies/mL at week 4, and maintained HIV-1 RNA <50 copies/mL through week 144. In total, 21 participants qualified for post-baseline resistance testing (1.3% [8/634] B/F/TAF; 1.9% [6/315] DTG/ABC/3TC; 2.2% [7/325] DTG + F/TAF); among those, 2/8 B/F/TAF, 6/6 DTG/ABC/3TC, and 4/7 DTG + F/TAF participants had multiple confirmed virologic rebounds during the studies. No participant had emergent resistance to study drugs. Initial HIV-1 treatment with B/F/TAF, DTG/ABC/3TC, or DTG + F/TAF achieved high, durable rates of virologic suppression. The presence of TDR did not affect treatment outcomes, with no treatment-emergent resistance through 144 weeks. This data is reassuring as it demonstrated that the second-generation INSTI offers a good genetic barrier and allows for robust regimens in those with some underlying ARV resistance.

Paediatrics

ODYSSEY is an international multi-centre randomised non-inferiority trial evaluating DTG with 2NRTIs versus standard-of-care (SOC) in children starting first- or second-line ART.[36] The primary outcome is a Kaplan-Meier estimated proportion of treatment failure defined as confirmed VL ≥ 400 copies/mL after week 36, lack of virological response by 24 weeks with ART switch, death or new/recurrent WHO4/severe WHO3 event by 96 weeks. The non-inferiority margin was 10% (12% for first-/second-line subgroups). Seven hundred and seven children ≥14kg were randomised (Uganda 47%, Zimbabwe 21%, South Africa 20%, Thailand 9%, Europe 4%) with 350 to DTG and 357 to SOC. Median age (range) was 12.2 years (2.9–18), weight 31kg (14–85) and 51% were male. Three hundred and eleven children started a first line (92% efavirenz among SOC); 396 a second line (72% lopinavir/ritonavir, 25% atazanavir/ritonavir among SOC) regimen. Median follow-up was 142 weeks with 687 (97%) reaching the primary endpoint or seen on/after 96 weeks. Forty-eight (14%) participants on DTG versus 75 (22%) on SOC had treatment failure by 96 weeks; difference (95% CI) –7.7% (-13.2, -2.3); p = 0.006. Forty versus 67 were virological failures and 8 versus 8 were WHO3/4 events/death. Treatment effects were similar in first- and second line, with no evidence of heterogeneity (p = 0.20; fig). Thirteen (4%) of the children randomised to DTG changed regimen during follow-up versus 32 (9%) to SOC (excluding NRTI changes and changes for growth, simplification, guideline change, stock-out) (p = 0.004), Two versus 21 changes were for treatment failure in the DTG and SOC arms, respectively. At 48 and 96 weeks, proportion with cross-sectional VL < 50 copies/mL and changes in CD4 T cell counts from baseline were similar between arms. There were 65 serious adverse events (35 children) in the DTG versus 46 (42) in SOC (p = 0.45), including 2 versus 3 deaths. One hundred and nineteen (73 children) grade 3 adverse events occurred in the DTG versus 135 (88) in the SOC one (p = 0.23). At week 96, the mean change in total cholesterol from baseline was -5 mg/dL (95% CI -8, -2) in the DTG versus 10 mg/dL (7,13) in the SOC arms (difference (DTG-SOC) -15 (-19, -11); p < 0.001). Weight, height and BMI increased marginally more in the DTG than the SOC arms (differences (SE) between arms 1kg (0.4), 0.7cm (0.3), 0.3kg/m2 (0.1), respectively at 96 weeks). The conclusion of the presentation was that DTG-based ART was superior to a SOC-based one regarding treatment failure by 96 weeks in children/adolescents starting first- or second line. There were no safety concerns about DTG use. These results were felt to support the WHO guidelines which recommend DTG-based regimens as preferred ART for children ≥14kg starting a first- or second-line ART, allowing harmonisation with adult treatment programmes.

Pregnancy

Delayed ART initiation in pregnancy is associated with failure to achieve viral suppression and increased risk of mother-to-child transmission (MTCT). The DolPHIN-2 study randomized pregnant women initiating treatment in the third trimester to either a DTG or efavirenz (EFV)-based regimen in South Africa and Uganda.[37] Between January and August 2018, 268 mothers (safety cohort) were randomized to receive EFV (133) or DTG (135), of whom 250 (EFV-125, DTG-125, intention-to-treat cohort) were evaluable for efficacy. In addition to measurement in pregnancy, VL was also measured at 6, 12, 24, 48 and 72 weeks postpartum (PP). The primary endpoints were a VL < 50 HIV-1 copies/mL for efficacy; and the occurrence of maternal and/or infant drug-related serious adverse events (SAE) for safety. The study team presented the final data with the follow-up of mothers and infants up to 72 weeks PP. As previously reported, DTG was associated with a superior response (VL < 50 HIV-1 copies/mL) during the first 26 weeks of therapy. At 72 weeks 116/125 mothers receiving DTG achieved a VL < 50 HIV-1 copies/mL with a median time of 4.14 (IQR 4.00, 5.14) weeks. In contrast, among 114/125 mothers randomized to the EFV arm, suppression was achieved at a median time of 12.14 (IQR 10.71, 13.29) weeks (adjusted HR 1.93 (95% CI 1.47, 2.53)). By 72 weeks PP, 21.3% of mothers and 56.2% of infants experienced an SAE, however in mothers only 3% were related to the study drug, with no infant drug-related events. DTG was well tolerated with a lower frequency of maternal drug-related AE (DTG 2.2% versus EFV 3.8%). Overall, the mean change in maternal weight from delivery to 72 w PP was -1.2kg, with nonsignificant differences observed by arm in weight retention (DTG -0.7kg versus EFV -1.6kg). No differences in maternal glycosuria or infant hyperglycaemia were observed by arm. Overall, there were 4 infant HIV infections diagnosed, 3 at delivery in the DTG arm and one detected at 72 weeks PP in the EFV arm despite optimal maternal suppression (VL < 50 HIV-1 copies/mL from delivery and serial negative tests in the child). Maternal DTG-based ART was found to be safe and well tolerated. Women randomized to DTG had more rapid viral suppression after ART initiation and maintained virological suppression through the breastfeeding period. The infant HIV infection in the EFV arm highlights the potential for transmission during breastfeeding despite evidence of virological suppression in the mother.

The IMPAACT 2010 study - efficacy

This IMPAACT 2010 study team had previously reported on the safety and virological efficacy of DTG and emtricitabine (FTC)/tenofovir alafenamide fumarate (TAF) versus DTG + FTC/tenofovir disoproxil fumarate (TDF) versus efavirenz (EFV)/FTC/TDF through delivery. Results from enrolment through week 50 PP were presented at this conference. Pregnant women with HIV-1 in 9 countries were randomized 1:1:1 to start open-label DTG + FTC/TAF, DTG + FTC/TDF, or EFV/FTC/TDF at 14–28 weeks gestational age (GA).[38] The safety outcomes included the pairwise regimen comparisons of grade ≥3 maternal and infant AEs, infant mortality and infant HIV infection. Efficacy analyses included comparison of maternal HIV-1 RNA <200 copies/mL at week 50 PP between the combined DTG and EFV arms. Six hundred and forty-three women were randomised: DTG + FTC/TAF (n = 217), DTG + FTC/TDF (n = 215), and EFV/FTC/TDF (n = 211). Baseline medians values were for GA 21.9 weeks, HIV-1 RNA 903 copies/mL, CD4 T cell count 466 cells/uL. Six hundred and seven (94.4%) women and 566 (91.7%) of 617 liveborn infants completed the study. Four hundred and seventy-nine (77.6%) infants were breastfed (median of 49.9 weeks). There were no apparent differences through week 50 PP between arms in the estimated probability of maternal grade ≥3 AEs or infant grade ≥3 AEs. The average change in women's weight from entry through PP was -0.027 kg/week in the DTG + FTC/TAF, -0.050 kg/week in the DTG +

FTC/TDF, and -0.084 kg/week in the EFV/FTC/TDF arms. The estimated probability of infant death was higher in the EFV (6.9%) compared to the DTG + FTC/TAF (1.0%, p < 0.001) and DTG + FTC/TDF (2.0%, p = 0.008) arms. Either stillbirths (previously reported) or infant deaths (combined) occurred as follows: 10 in the DTG + FTC/TAF, 15 in the DTG + FTC/TDF, and 18 in the EFV/FTC/TDF arms. Four infants were diagnosed with HIV with 2 in the DTG + FTC/TAF, 1 in the DTG + FTC/TDF, and 1 in the EFV arms. At 50 weeks PP, proportions of women with HIV-1 RNA <200copies/mL were similar in the combined DTG arms (96.3%) and EFV arm (96.4%). Regimen discontinuation or switches were more frequent in the EFV arm due to virologic failure/drug resistance, and in the DTG arms due to PP fertility choices. At week 50 PP, maternal and infant grade ≥3 AEs from enrolment through week 50 PP were similar across arms; infant mortality was higher (though stillbirths somewhat less frequent) in the EFV/FTC/TDF arm. Maternal HIV-1 RNA suppression was similarly high in the combined DTG and EFV arms, although more women stopped EFV due to virologic failure.

IMPAACT 2010-wt gain

Insufficient and excess weight gain (WG) during pregnancy have been associated with adverse pregnancy outcomes.[39] The IMPAACT 2010 team evaluated the association between antepartum WG and adverse pregnancy outcomes in the secondary analyses of the study data. By-arm differences in average antepartum weekly WG were estimated using generalized estimating equations. Low WG was defined as <0.18 kg/week and high WG as >0.59 kg/week. Time to event analyses were used to estimate the risk of the composite adverse pregnancy outcome of stillbirth (≥20 weeks GA), preterm delivery (<37 weeks GA) and small for gestational age (SGA) (SGA: <10th percentile), as well as each of these individual outcomes and neonatal death, using Cox-proportional hazards regression models with WG as a time-varying covariate. Six hundred and forty-three participants were randomized: 217 in the DTG + FTC/TAF, 215 in the DTG + FTC/TDF, and 211 in the EFV/FTC/TDF arms. Baseline medians were GA 21.9 weeks, HIV-1 RNA 903 copies/mL, CD4 T cell count 466 cells/uL. The rate of adverse pregnancy outcome was lowest with DTG + FTC/TAF. Weekly average WG was highest with DTG + FTC/TAF (0.378kg) compared to DTG + FTC/TDF (0.319kg, p = 0.011) and EFV/FTC/TDF (0.291kg, p < 0.001). Low WG was least common with DTG + FTC/TAF (15.0%) compared with DTG + FTC/TDF (23.6%) or EFV/FTC/TDF (30.0%), with the opposite pattern for high WG: DTG + FTC/TAF (12.7%) vs. DTG + FTC/TDF (9.9%) vs. EFV/FTC/TDF (6.3%). Overall, low WG was associated with higher risk of any adverse pregnancy outcome (HR 1.4, 95%CI 1.02,1.96) and of SGA (HR 1.5, 95% CI 0.99,2.22). For women in the DTG + FTC/TAF arm, low WG was also associated with higher risk of stillbirth (HR 6.2, 95%CI 1.16,32.81) and preterm delivery (HR 3.7, 95%CI 1.14,11.92) compared with normal WG. There were no associations between high WG and adverse pregnancy outcomes or low or high WG and neonatal death. Low (but not high) WG was associated with adverse pregnancy outcomes. Women starting DTG + FTC/TAF in pregnancy gained more weight antepartum than women starting DTG + FTC/TDF or EFV/FTC/TDF, while women starting EFV/FTC/TDF had the lowest WG.

This latest conference has provided as usual very useful data and updates on many aspects of HIV infection with the addition this year of many studies on COVID-19. We all look forward to CROI 2022.

References

1 Bozzo Caterina Prelli, Nchioua Rayhane, Volcic Meta, et al. *IFITM Proteins Promote SARS-CoV-2 Infection in Human Lung Cells. Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 112.

2 Giron Leila B, Dweep Harsh, Yin Xiangfan, et al. Severe COVID-19 is fueled by disrupted gut barrier integrity. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 114.

3 Tokuyama Minami, Ladinsky Mark S, Jha Divya, et al. *SARS-CoV-2 Persists in Intestinal Enterocytes up to 7 Months after Symptom Resolution. Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 115.

4 Song Eric, Bartley Christopher M, Ryan Chow, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 165.

5 Joint press release. *Gilead and Merck announce agreement to jointly develop and commercialize long-acting, investigational treatment combinations of lenacapavir and islatravir in HIV*; 15 March 2021. Accessed at https://i-base.info/htb/40280 10th April 2021.

6 Kandala Bhargava, Fancourt Craig, Krishna Ananthula Hari, et al., Model-informed dose selection for islatravir/MK-8507 oral once-weekly phase 2b study, Conference on Retroviruses and Opportunistic Infections, Chicago, 6–10 March 2021 Poster 376.

7 Molina JM, Yazdanpanah Y, Afani Saud A, et al. *Islatravir in Combination with Doravirine Maintains HIV-1 Viral Suppression through 96 Weeks*. HIV Glasgow; 2020. Oral Abstract 415.

8 Diamond T, Lai M-T, Feng M, et al. *Resistance Profile of MK-8507, a Novel NNRTI Suitable for Weekly Oral HIV Treatment. Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 129.

9 Van Baelen K, Salzwedel K, Rondelez E, al at. Susceptibility of human immunodeficiency virus type 1 to the maturation inhibitor bevirimat is modulated by baseline polymorphisms in Gag spacer peptide 1. *Antimicrob Agents Chemother*. 2009;53(5):2185–2188.

10 de Jesus E, Harward S, Jewell RC, et al. A phase IIa study evaluating safety, pharmacokinetics, and antiviral activity of GSK2838232, a novel, second-generation maturation inhibitor, in participants with human immunodeficiency virus type 1 infection. *Clin Infect Dis*. 2020;71(5):1255–1262.

11 Spinner C, Felizarta FB, Rizzardini G, et al. *Phase IIa Proof-Of-Concept Trial of Next-Generation Maturation Inhibitor GSK3640254. Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 126.

12 Jeffrey JL, Cockett M, Protack T, et al. GSK3640254 is a novel maturation inhibitor with an optimized virology profile. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Poster 421.

13 Dumitrescu TP, Joshi SR, Xu J, et al. Phase I evaluation of pharmacokinetics and tolerability of the HIV-1 maturation inhibitor GSK3640254 and dolutegravir in healthy adults. *Br J Clin Pharmacol*. 2021. https://doi.org/10.1111/bcp.14759.

14 Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet HIV*. 2021;8(4):e185–e196.

15 Swindells S, Lutz T, Van Zyl L, et al. Cabotegravir + rilpivirine long-acting as HIV-1 maintenance therapy: ATLAS week 96 results. In: *Presented at HIV Drug Therapy Glasgow*. October 5-8, 2020. Glasgow, UK. Poster P006.

16 Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2021;396(10267):1994–2005.

17 Jaeger H, Overton EG, Richmond G, et al. Week 96 efficacy and safety of cabotegravir + rilpivirine every 2 months: ATLAS-2M. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Abstract 401.

18 Cutrell AG, Schapiro JM, Perno CF, et al. Predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis across three phase 3 studies. *AIDS*. 2021. https://doi.org/10.1097/QAD.0000000000002883.

19 Han K, Baker M, Spreen WR, et al. Cabotegravir PPK simulation to inform Q2M strategies following dosing interruptions. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Abstract 373.

20 Rossenu S, Neyens M, Van Solingen-Ristea R, et al. POPPK modelling of Q2M IM RPV LA for managing dosing interruptions in HIV-1 patients. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Abstract 403.

21 Marzinke M, Grinztejn B, Fogel J, et al. Laboratory analysis of HIV infections in HPTN 083: injectable CAB for PrEP. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Abstract 183.

22 McGinty Tara, Alvarez-Barco Elena, Tinago Willard, et al. Short-course alendronate for the prevention of ART-associated bone loss. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 96.

23 Silverberg Michael J, Levine-Hall Tory, Anderson Alexandra, et al. Prevention of cardiovascular disease in persons with and without HIV. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 97.

24 Hsue Priscilla, Ganz Peter, Segal Mark, et al. Identification of unique proteins predictive of mortality and mechanisms in HIV. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 99.

25 McGettrick Padraig, Tinago Willard, Garcia-Leon Alejandro, et al. Biological profiles predict coronary artery disease in PWH and risk-matched controls. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 100.

26 Bastian Neesgaard. Association between integrase inhibitors (InSTIs) and cardiovascular disease (CVD). Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Abstract 488.

27 Suzuki Kazuo, Zaunders John, Levert Angelique, et al. Neuron damage and reservoir are secondary to HIV transcripts despite suppressive ART. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 162.

28 Luckett Patrick H, Hannon Kayla, Lee John J, et al. Effects of HIV and aging on functional connectivity and anatomy. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 164.

29 Orkin Chloe, Porteiro Norma, Berhe Mezgebe, et al. Durable efficacy of DTG+3TC in Gemini-1&2: year 3 subgroup analyses. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Science Spotlight abstract 414.

30 Benson Paul, Kinder Clifford A, Pérez-Elías María Jesús, et al. Switching to DTG/3TC FDC is non inferior to TBR for 96 weeks: TANGO subgroup analyses. Chicago. In:

Conference on Retroviruses and Opportunistic Infections. 6–10 March 2021. Science Spotlight abstract 417.
31 Santoro Maria M, Armenia Daniele, Teyssou Elisa, et al. Impact of M184V on the virological efficacy of switch to 3TC/DTG in real life. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Science Spotlight abstract 429.
32 Miro Jose M, Torres Ferran, Manzardo Christian, et al. Dolutegravir vs darunavir/r-based ART in very advanced patients: 48-week results. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Science Spotlight abstract 412.
33 Paton Nicholas, Joseph Musaazi, Kityo Cissy M, et al. Nucleosides and darunavir/dolutegravir in Africa (NADIA) trial: 48wks primary outcome. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Science Spotlight abstract 94.
34 Aboud M, Kaplan R, Lombaard J, et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. *IAS*. 2017, 23–26 July 2017. Paris. Oral abstract TUAB0105LB.
35 Acosta Rima K, Chen Grace Q, Chang Silvia, et al. HIV with transmitted drug resistance is durably suppressed by B/F/TAF at week 144. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Science Spotlight abstract 430.
36 Turkova A. Dolutegravir-based ART is superior to NNRTI/PI-based ART in children and adolescents. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 174.
37 Malaba Thokozile R, Nakatudde Irene, Kintu Kenneth, et al. DolPHIN2 final results dolutegravir vs efavirenz in late pregnancy to 72W postpartum. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 175.
38 Chinula Lameck, Brummel Sean, Ziemba Lauren, et al. Safety/efficacy of DTG vs EFV, TDF vs TAF in pregnancy/postpartum: IMPAACT 2010 trial. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 177.
39 Hoffman Risa M, Ziemba Lauren, Brummel Sean, et al. Antepartum weight gain and adverse pregnancy outcomes in impact 2010. Chicago. In: *Conference on Retroviruses and Opportunistic Infections*. 6–10 March 2021. Oral abstract 176.

Christina K. Psomas*
European Hospital Marseille, France

Laura J. Waters
Mortimer Market Center, Central and North West London NHS Foundation Trust, UK

Tristan Barber
Ian Charleson Day Centre, Royal Free London NHS Foundation Trust, London, UK
Institute for Global Health, University College London, UK

* Corresponding author.
E-mail address: c.psomas@hopital-europeen.fr (C.K. Psomas).