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# Highlights of the 31st Conference on Retroviruses and Opportunistic Infections (CROI), March 3–6, 2024 Denver, Colorado, USA

This year's meeting was exciting and presented newly-developed antiretrovirals as well as long-acting drugs for both HIV-1 prevention and treatment but also for other infectious diseases such as hepatitis C and tuberculosis.

## 1. Clinical trials of novel antiretroviral therapies and novel strategies

In the Monday session of Clinical Trials of Novel Antiretroviral Therapies (ART) presentations included mainly early phase trials of new compounds, including broadly neutralizing antibodies. Russ P. Carstens (Merck & Co, Inc USA) presented data on a novel oral long-acting HIV-1 nucleoside reverse transcriptase translocation inhibitor (nRTTI), MK-8527 in people living with HIV (PLWH).[1] A total of 37 treatment--naïve individuals were enrolled in two phase 1, single-dose, monotherapy studies to evaluate its antiretroviral activity, PK profile, safety and tolerability. Following single oral doses of 0.5–10 mg, the mean decrease in HIV-1 RNA at Day 7 post-dose was $\geq$1.0 $\log_{10}$ copies/mL (target reduction in viral load). MK-8527 at all dose levels was well tolerated. Safety and pharmacokinetics of single and multiple doses were also presented in adults without HIV in two different trials[2] as well as in rats and rhesus monkeys.[3]

Carl J. Fichtenbaum (University of Cincinnati, USA) et al. showed results of an open-label, multi-cohort Phase 1b study in viremic participants with HIV[4] using GS-1720, an orally bioavailable integrase strand transfer inhibitor (INSTI). Results of the Phase 1a study were presented, with GS-1720 median half-life of 9.4 days and a potential for once-weekly dosing. The Phase 1b study included 4 cohorts of a total of 28 ART-naïve or INSTI-naïve PLWH, each-one testing a different dosing, namely 30, 150, 450 and 900 mg administered on Day 1 and 2, followed up for 10 days, and compared to historical placebo. All doses led to a decline of viral load that was dose dependent and within the target therapeutic range in all participants on the 450 mg and 900 mg doses. Resistance testing data was not available for all the cohorts. GS-1720 was well-tolerated with a favorable safety profile.

Nicholas Paton, Yong Loo Lin School of Medicine, Singapore et al, presented the week 48 results of a randomized trial of long-acting (LA) cabotegravir and rilpivirine administered every 8 weeks in Africa (CARES).[5] The main interest of the study resided in the different populations (58% African women, 99.6% black race), HIV-1 subtypes (56.5% subtype A1, no subtype A6), high levels of non-nucleoside inhibitors of the retrotranscriptase (NNRTI) exposure (74% overall) and pre-treatment resistance (13.5% for rilpivirine and 16% for cabotegravir overall), and type of care with infrequent viral loads and safety monitoring. Interestingly, there was laboratory monitoring every 24 weeks according to the WHO guidelines, and proviral HIV-1 DNA was retrospectively sequenced for archived resistance in stored PBMCs at baseline. Adherence and timing of injections were satisfactory with 96% of scheduled injections within the protocol-mandated 7-day window period. With 97% of virological success in both arms, the authors concluded that LA therapy every 8 weeks was not inferior to standard oral therapy in maintaining virological suppression at week 48. There were two cases of virological failure with no delayed injections, one of which was confirmed (the second case had died with a baseline low level of rilpivirine resistance) and displayed high rilpivirine and intermediate cabotegravir resistance without any NNRTI or INSTI mutations at baseline. Long-acting therapy had a good safety profile, was well tolerated with only mild injection site reactions and with increased treatment satisfaction score over 48 weeks in those who had switched to LA versus oral therapy.

## 2. Prevention and sexually transmitted infections

The final data of the ANRS 174 DOXYVAC trial was presented by JM Molina[6] (St Louis Hospital, Paris, France) but results were slightly different from the interim analysis. With a total of 115 chlamydia or syphilis infections, the reduction in the incidence of these infections was strong, around roughly 83% after a median follow-up of 14 months, which is consistent with the interim analysis. However, when considering gonococcal infections (n = 238) which were more frequent, results were less spectacular than in the interim analysis and authors reported around 33% of reduction of infections compared to placebo (vs 50% reported in the interim analysis). Interestingly, the clinical relevance of the 4CMenB vaccine seemed limited, as there was no significant difference observed between the two arms (vaccine versus no vaccine). In the doxyPEP arm a 3-fold increase in high-level gonococcal resistance was observed, which may also explain, at least partially, why doxycycline efficacy was waning over time. Finally, in the era of intermittent use of doxycycline for PEP, syphilis serological titers could be difficult to interpret, and the impact on gut microbiota remains as yet undetermined.

## 3. Cardio-metabolic health in PLWH

The REPRIEVE trial presented at the IAS Conference last summer demonstrated that pitavastatin administered in the population of PLWH with low to moderate cardio-vascular risk dramatically reduced major adverse cardiac event (MACE) incidence. However, LDL changes and biomarkers were not significantly associated with changes in non-calcified plaques. Using a proteomics approach Márton Kolossváry et al. assessed the statin effects on plasma proteomic markers, in order to understand biological pathways mediating the statin effect on non-

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calcified coronary artery plaque volume (NCPvol).[7] Among the 558 individuals (age: 51 years, 18% female) included in the assessment of protein changes, 286 received placebo and 272 pitavastatin. After correcting for false discovery rates, pitavastatin use was significantly associated with increased expression of 3 proteins (PCOLCE, NRP-1, MIC-A/B) and decreased expression of 4 proteins (TFPI, TRAIL, ANGPTL3, MBL2), among which the largest treatment effect was observed on PCOLCE, which is a rate-limiting enzyme of collagen formation, with an overall relative increase of expression of 24% compared to placebo. In the multivariate regression analysis, only PCOLCE was statistically associated with changes in non-calcified plaque, namely each doubling in PCOLCE expression was associated with a 31%. decrease in non-calcified plaque. Beyond the plaque regression, increased PCOLCE expression was associated with plaque stabilisation, namely with fibro-fatty and fibrous plaque volume.

KM Erlandson (University of Colorado, USA) presented the REPRIEVE trial's PREPARE substudy which evaluated physical function in PLWH randomized to pitavastatin compared to placebo.[8] Many previous studies in the general population have suggested that statins may attenuate physical function declines, but these studies are observational, subjective or limited to one year of follow-up.[9–13] Authors hypothesized that physical function would decline over time, but PLWH randomized to pitavastatin would have slower declines compared to placebo. Physical function (10x chair rise, 4-m gait, balance, grip strength, mSPPB) was evaluated annually for up to 5 years. The primary treatment effect was estimated as the difference in the annual rate of change in the pitavastatin compared to placebo group. Of 602 PWH, 52% were randomized to pitavastatin and 48% to placebo. Median age was 51 years; 18% were natal female, 2% transgender 2 40% Black, and 18% Hispanic; median BMI was 27.2 (Q1, Q3 24.3, 30.1) kg/m$^2$. Forty-five percent of participants were enrolled at REPRIEVE study entry and 55% within 24 months after REPRIEVE treatment initiation. Median PREPARE follow-up was 4.7 (4.3, 5.0) years with 81% completing the follow-up. Physical function was similar between the two treatment groups at PREPARE entry. There was no evidence of decline in chair rise rate in either treatment group, and no significant difference in the pitavastatin group compared to placebo (difference −0.10 [95% CI: 0.30, 0.10] rises/min/year; p = 0.31). Small declines were observed in other physical function tests in both treatment groups, with no apparent differences between groups. There was a low prevalence of myalgiasreported both in PREPARE and in the overall REPRIEVE population. These findings do not support the use of statins to maintain physical function in this population, but do expand on the overall REPRIEVE trial findings to support the long-term safety of statin therapy on muscle and physical function when used in primary prevention among PLWH.

Jordan E. Lake (UTHHealth, Houston, USA) presented data on the SLIM-LIVER study (ACTG A5371), which is a phase IIb, single-arm, pilot study of the effects of semaglutide on magnetic resonance imaging-proton density fat fraction (MRI-PDFF)-quantified intrahepatic triglyceride (IHTG) content in PLWH and metabolic-associated steatotic liver disease (MASLD).[14] Participants (n = 49) had a median age of 52 years, BMI of 35 kg/m$^2$, 39% were of Hispanic ethnicity and 33% Black/-African American ; forty-three percent were cis or trans women and 82% were on INSTI-based ART. Semaglutide was well-tolerated. Mean baseline (standard deviation) IHTG was 12.7% (6.1%). Mean (95% CI) absolute and relative declines in IHTG were −4.2% (−5.4, −3.1) and −31.3% (−39.0, −23.6), respectively (both p < 0.001); 29% of participants had complete resolution of MASLD (absolute IHTG <5%) within a 24 week-period and 58% had a ≥30% relative reduction in IHTG. Trends toward greater improvements in IHTG were seen in women, Hispanics, non-Hispanic whites and with increasing age, but the study was not powered to detect differences between subgroups. Significant improvements in weight, waist circumference, fasting glucose and triglyceride concentrations were also observed throughout the 24 weeks. Improvements in IHTG correlated with weight loss on semaglutide (r = 0.54, p < 0.0001). Semaglutide non-responder rate was similar to that of the general population, at around 28%, but among those participants who lost weight on semaglutide, the reduction in the hepatic fat was even greater. The semaglutide effect on weight loss and hepatic fat decrease was associated with improvements in circulating lipids and glucose homeostasis. Low-dose (1 mg weekly) semaglutide is a safe and effective pharmacologic therapy for MASLD in PLWH and shows evidence of broader cardiometabolic benefits. Further analyses will assess specific immunological and inflammatory pathway changes with semaglutide therapy in PLWH, including those that may be unique to this population.

Grace L. Ditzenberger (university of Colorado, USA) presented data from a secondary analysis of the SLIM-LIVER study about semaglutide effects on muscle parameters.[15] The study enrolled PLWH who met the criteria for a MASLD diagnosis (defined by at least 5% liver fat content) who were administered semaglutide, in order to study the impact on physical function during rapid weight loss induced by medications like semaglutide. In this substudy the psoas muscle volume was evaluated overtime. Overall, its volume declined by approximatively 9% from baseline, but its muscle fat content did not significantly change. PLWH over 60 years had the greatest decline in muscle volume. Chair rise time and gait speed levels were preserved despite loss of muscle volume. These changes in function were not correlated with those in overall weight or BMI.

## 4. Cure and functional remission

During the last afternoon of the Meeting took place the Interactive Symposium-08/innovations in interventions: Towards and HIV Cure.

How can NNRTI)-induced early protease activity activate inflammasome and eliminate HIV-infected cells? Liang Shan from Washington University in St Louis, USA, presented from mechanisms to therapeutics: Eliminating HIV-infected cells by the CARD8 inflammasome. The CARD8 inflammasome is activated immediately after HIV entry by the viral protease encapsulated in incoming virions. Sensing of HIV protease activity by CARD8 leads to rapid pyroptosis of quiescent cells without productive infection, while T cell activation abolishes CARD8 function and increases permissiveness to infection. CARD8 activation leads to cell death in T cells and macrophages and is maintained across major HIV-1 subtypes. CARD8 NNRTI-mediated activation can be abrogated by a DPP9 inhibitor.[16,17]

The second talk on this theme was by Tracy Diamond from Merck & Co, USA who described targeted activator of cell kill (TACK) molecules which can kill HIV-infected cells through inflammasome activation. These bind the reverse transcriptase-p66 domain of monomeric *gag-pol*, accelerating dimerization and producing cell death through premature intracellular viral protease activation. This has been observed with NNRTIs but requires doses higher than the approved ones. The effect goes through caspase-1 induced pyroptosis.[18]

In terms of paediatric control of viral replication after early ART, Deborah Persaud (John Hopkins University, Baltimore, USA) presented results of the IMPAACT P1115 study which was a proof-of-concept trial studying ART-free remission in neonates with in utero HIV-1 acquisition.[19] In the neonate population of 30 clinical research sites over 11 countries (Brazil, Haiti and Africa), 6 out of 54 children were enrolled between 2015 and 2017, received very early ART to limit the establishment of HIV-1 reservoirs, and underwent analytical treatment interruption (ATI) in order to assess ART-free remission. An ATI is needed as there is no known biomarker predictive of ART-free remission. Authors tried to reproduce the "Mississippi Baby" example initiating ART within 48 hours of birth and administrated the study regimen (nevirapine + 2NRTIs with lopinavir/ritonavir added at ≥42 weeks of age) for up to 294 weeks between 2015 and 2017. Eligibility criteria for ATI included sustained virologic suppression with no plasma HIV-1 RNA detected from 48 weeks onwards and no HIV-1 DNA detected in ≥850, 000 PBMCs (droplet digital PCR), normal CD4 T cell count, and negative HIV-1 serostatus by 4th generation ELISA. Children meeting all these

criteria interrupted ART with frequent clinical, virological, and immunological monitoring. Remission was defined as no confirmed plasma HIV-1 RNA above the limit of detection of the assay for ≥48 weeks off ART. Six children underwent ATI at median age of 5.5 years. Three of 6 achieved study-defined remission, one through 80 weeks of ATI, when viral rebound (299,538 cp/mL) occurred. The other three who achieved remission remain on ATI (>48, >52 and > 64 weeks). This study provides proof-of-concept that very early ART in neonates with in utero HIV-1 significantly curtailed viral reservoirs and enabled ART-free remission. The proposed eligibility criteria and biomarker profiling was not fully predictive of ART-free remission, as evidenced by the viral rebound in two of six children who underwent ATI. The authors stressed the limit of the study in terms of the longer duration of ART due to the COVID-19 pandemic and the potential for a shorter course of ART.

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