CROI 2024 BHIVA Working Group Summary

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Key words:

Word count: 3844

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Introduction

The Conference on Retroviruses and Opportunistic Infections (CROI) is usually the most significant HIV conference of the year in terms of basic and clinical scientific output. CROI 2024 in Denver USA, felt very much back to 'business as usual' following COVID-19 disruptions that had impacted preceding years, but also felt more global and outward facing.

The British HIV Association (BHIVA) supports a working group to attend CROI annually and deliver feedback back in the UK. This article summarises the highlights from that meeting.

Prevention

HIV and sexually transmitted infection (STI) prevention was a major theme. Two studies, one Australian, one US, investigating HIV pre exposure prophylaxis (PrEP) persistence highlighted at least doubling of HIV incidence in people with less PrEP coverage (only ever receiving one prescription or experiencing 'gaps' in PrEP)[1,2]. The Australian study also concluded people of younger age and on concurrent hepatitis C treatment may benefit from tailored PrEP support. Several studies described interventions to increase HIV PrEP uptake in key groups including: women though hair salons in South Africa (combining PreP with contraception access) [3], incarcerated people in Zambia[4] , post abortion clinics in Kenya[5], and through increased choice of prevention modalities[6]. Mobile clinics in Miami and Healthcare workers using motorcycles in Tanzania both increased PrEP use[7,8].

Long-acting injectable cabotegravir (CAB LA) was approved as HIV PrEP by the FDA in 2021, but US roll out has been slow[9,10,11]. Where offered, uptake has been robust; in (e.g. the Opera Cohort people using CAB LA included 13% women and 32% black participants, with a 7% discontinuation rate[12] .

Finally, the first case of HIV seroconversion with cabotegravir emergent resistance in routine care was described[13].

For STI prevention, final DOXYVAC results showed continued significant reductions in chlamydia and syphilis (83%) but a smaller, 33% reduction in gonorrhoea at week 48 on doxycycline post exposure prophylaxis (doxyPEP, 200mg taken within 72 hours of condomless sex (CLS)). The proportion of gonococcal isolates with high level tetracycline resistance (TCN-R) was significantly higher in the DoxyPEP arm compared to no PEP; no TCN-R chlamydia was detected.

The DOXYPEP open label extension showed sustained STI reduction in the DoxyPEP arm and a reduction from 31% to 17% per quarter in the standard of care arm who started doxyPEP, despite increased rates of CLS[14]. Gut microbiome at month 6 showed no significant changes on doxyPEP although expression of TCN-R genes increased[15].

Disappointingly, 4CMENB vaccination had no significant effect on gonorrhoea incidence, including symptomatic or culture positive infections; despite this the authors concludes a small benefit could not be ruled out[16].

Finally, good news for people with HIV who have not responded to conventional hepatitis B vaccines; 2 or 3 doses of the HepB-CpG vaccine yielded superior seroprotective responses versus 3 doses of HepB-alum 17 vaccine[17].

Broadly neutralising antibodies

Broadly neutralising antibodies (bNAbs) have been a significant feature at recent meetings; five key studies explored their antiviral efficacy:

- BANNER: single dose N6LS monotherapy in people not on ART[18]; participants remained off ART for 84 days unless they met pre-defined lack of viral response criteria. Subcutaneous (SC) yielded lower bNAb exposure than intravenous (IV) administration and antiviral activity correlated with baseline susceptibility which was assessed retrospectively– (attributed to a desire to be as inclusive as possible, an unusual explanation for giving a novel agent to people with non-susceptible virus?).

- A5357: 71 virally suppressed people (25% were excluded at screening based on susceptibility testing) switched to LA-CAB plus VRC07-523S[19]. . Virological failure occurred in 5 (7%) people: 2 resuppressed without intervention but 1 person developed a new R263K INSTI mutation.
- A5377: SC and IV SAR441236, a trispecific bNAb, showed modest antiviral efficacy; transient drug-induced antibodies had no effect on pharmacokinetics[20].
- Lenacapavir (LEN) + teropavimab (TAB) + zinlirvimab (ZAB): SC LEN with IV TAB+ZAB previously demonstrated maintained viral suppression in 18/20 people susceptible to both bNABs[21]. This analysis included 11 people with baseline susceptibility to one bNAb only; two in the lower dose ZAB group experienced low level viral rebound , with no emergent resistance[22] .
- PGDM1400 + PGT121 + VRC07-523: three bNAbs administered IV to 12 virally suppressed people at baseline (when ART was stopped) and monthly for 6 months; only 4 maintained viral suppression out to week 44 with one case of emergent resistance[23].

What does this tell us? Baseline susceptibility is important and bNAbs do not necessarily achieve or maintain viral suppression in the same way as antiretrovirals., maybe unsurprising considering they are immune modulators, not antivirals. Whilst the quest for long-acting agents to accompany the limited current repertoire of long-acting antiretrovirals is understandable, it may not be the wisest use of bNAbs.

Injectable ART

The Cabotegravir and Rilpivirine Long-Acting in Africa (CARES) study[24],the first to investigate LA CAB+RPV in Africa, used a public health approach to viral load monitoring (every 24 weeks). CARES randomised 512 virally suppressed adults in Kenya, Uganda, and South Africa to switch to 8-weekly LA CAB+RPV or continue oral treatment (tenofovir-disoproxil, lamivudine and either dolutegravir, efavirenz or nevirapine). At week 48 97% maintained virologic suppression, demonstrating non-inferiority of LA-ART. Treatment satisfaction was improved in those receiving LA-ART. Although participants had no history of treatment failure, retrospective analysis of baseline proviral DNA, showed that 10% and 8% had intermediate/high-level resistance to rilpivirine or cabotegravir, respectively. These findings did not seem to impact virologic outcomes and further information is awaited.

The phase III LATITUDE trial (ACTG A5359)[25] evaluated LA CAB+RPV in 434 people with adherence challenges at more than 30 US sites. Participants had poor virological response (persistent viral load above 200 despite oral ART for at least six months) or had been lost to clinical follow-up with ART non-adherence. Most (65%) were men, median age was 40 years, early two thirds were black, 27% white and 17% Latino. People with active drug or alcohol use or unstable housing were included;14% had a history of injection drug use. About 14% had a viral load above 100,000 and median CD4 count was 270. Participants received intensive support and financial incentives to achieve viral suppression on daily oral ART before being randomised to continue oral ART or switch to monthly injectables. A total of 294 people were randomised and by baseline when randomised treatment was commenced, 17% in the injectables arm and 7% on oral ART had a viral load above 200 .

Study recruitment was stopped early after a planned interim review demonstrated superiority of injectables over oral therapy arm based on the secondary endpoints of virologic and treatment-related failure.

Only 7% on injectables experienced virological failure compared with 25% who stayed on daily pills; two in each group had emergent resistance. Treatment-related failure rates, which included both virological failure and discontinuation due to adverse events, were 10% in the LA-ART arm and 26% in the oral therapy arm. As demonstrated previously, LA CAB+RPV was safe and generally well tolerated. Follow-up continues, although people on oral ART have been offered switch to injectables – whether longer term follow-up would have seen different results, particularly in terms of loss of future options, will be difficult to assess.

The Ward 86 cohort in San Francisco presented the use of LA CAB+RPV in 59 people with adherence challenges and viraemia[26]. At 48 weeks, 81% met the primary endpoint of still being on LA CAB+RPV (defined as no discontinuations or injections given more than 14 days late) with viral suppression. At least one injection was given more than 7 or 14 days late in 17 and 7 people, respectively. Five people stopped the injections and resumed oral ART. Overall, 93% maintained viral suppression on LA CAB+RPV or another regimen.

Other LA-CAB+RPV studies included reassuring data in adolescents[27], early data exploring dosing cabotegravir every 4 months[28], and the possibility of the (self-administered) thigh route for bridging on injectable CAB[29].

Oral Antiretroviral Therapy (ART)

There was a lot of, mostly very early, data on novel oral drugs, many with potential for weekly dosing. ARTISTRY-1 randomised 128 people virally suppressed on complex ART with no prior lenacapavir (LEN) exposure and no bictegravir (BIC) resistance to switch to bictegravir 75mg (BIC) + lenacapavir 25mg (LEN-25) once daily (OD), switch to BIC + LEN 50mg (LEN-50) OD or continue ART on a 2:2:1 basis[30]. Complex ART was defined as a combination containing a boosted protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) with at least one from a class other than a nucleoside reverse transcriptase inhibitor (NRTI) or taking two or more pills/doses a day (a rather unusual definition of 'complex'), or a regimen containing parenteral ART other than CAB/RPV.

Participants (median age 60 years) had been living with HIV for a median of 27 years and taking a median of 3 pills; 81% were on a complex ART due to resistance (mutations not reported) and almost 2/3 were on boosted darunavir + dolutegravir ± TAF/FTC or an NNRTI. Viral suppression rates at week 24 were 100% on continued ART and 96% in both BIC+LEN arms with no confirmed virological failure. Drug-related adverse events (AEs) were more frequent in the switch arms, expected in a suppressed switch study, with one AE-driven discontinuation in each BIC+LEN arm (nausea and vomiting, respectively).

If results are maintained out to week 48 BIC + LEN shows promise as a simple option for people with resistance to other classes. Notably this two pill regimen would itself meet the definition of complex ART used in this trial, although from week 48 participants can switch to a fixed dose combination of BIC/LEN-50. Also of note is that the 75mg BIC dose used here is bioequivalent to the 50mg dose when co-formulated with TAF/FTC (Biktarvy).

Another novel two-drug regimen presented was weekly islatravir (ISL) 2mg plus LEN 300mg. People virally suppressed on BIC/TAF/FTC were randomised 1:1 to switch to ISL+LEN or continue BIC/TAF/FTC[31]. Viral suppression was maintained in 94% in each arm at week 24 with more drug-related AEs in the switch arm. Importantly, considering the previous pause in ISL development secondary to its impact on CD4 and total lymphocyte counts, there was no decline in either in the switch arm. The duration and sample size of this trial are inadequate for firm conclusions, but this could be a very attractive future option.

More options with the potential for non-daily dosing included:

- MK-8527: nucleoside reverse transcriptase translocation inhibitor (like ISL) with potential for weekly, monthly, and possibly longer interval dosing, for which phase 1 data demonstrated up to a 1.8log reduction in viral load[32]. .
- GS-1720: INSTI with potential for weekly dosing that yielded -1.7 to -2.4 log viral load decline in 28 people; no INSTI resistance had been detected so far (full analysis is pending)[33].
- GS-5894: NNRTI with pharmacokinetics supportive of weekly dosing and in vitro activity against isolates with high level resistance to other NNRTIs[34].

Finally, there was data on a novel PI which could address one of the main limitations for this class, major drug-drug interactions, by not requiring a booster. Once daily GS-9770 has predicted activity against darunavir & atazanavir resistant variants [35]. Considering the global rise in INSTI resistance, not surprising considering the volume of use, access to non-INSTI options will be all the more critical.

Weight

Whilst some believe that excess weight gain on drugs like TAF and second generation INSTI is entirely down to return to health and the comparative weight suppression associated with efavirenz and tenofovir-DF, data from CASCADE challenges this. A longitudinal analysis of 5698 people starting ART within 12 months of seroconversion showed weight gain was fastest on TAF, BIC and elvitegravir and, since participants has been living with HIV for only a short period prior to ART initiation, this was likely to reflect a direct drug effect[36].

Whilst we have seen data showing no impact of blinded DTG intensification on weight change, we lack similar data for TAF. INSTINCT randomised people virally suppressed on DTG/3TC to continue or switch to BIC/TAF/FTC so is effectively a TAF intensification trial[37]. Data at CROI demonstrated no impact on inflammatory markers (not surprising considering no well-designed trial has) and weight will be reported in the future, but the open-label nature will limit our ability to draw meaningful conclusions.

There has been a tsunami of GLP-1 agonist prescribing for obesity and whilst there is no reason for people with HIV to respond any differently to this drug class, it was reassuring to see data supporting semaglutide efficacy in this population:

- Semaglutide yielded close to 6% 1-year weight loss in a cohort of 111 people[38]
- Semaglutide yielded significant 24-week improvements in liver fat, weight, waist circumference, fasting glucose and triglycerides in 49 people with MRI-confirmed metabolic-associated steatotic liver disease (MASLD)[39]. The same study demonstrated loss of psoas muscle volume but maintained physical function in 48 people, concluding that interventions to prevent the loss of muscle mass that may accompany weight loss are important[40].
- A placebo-controlled randomised trial in 108 people with HIV-associated lipodystrophy, which previously demonstrated reduced total body/central fat & visceral adipose tissue (VAT) on semaglutide, showed significant decreases in hsCRP & sCD163 independent of changes in VAT[41].

Comorbidities

Cardiovascular Disease

Comorbidity research at CROI was dominated by further analyses of REPRIEVE, the primary results of which were published last year[42]. REPRIEVE demonstrated a 35% reduction in the incidence of a new major adverse cardiovascular events (MACE) among people with a low-to-moderate cardiovascular disease (CVD) risk randomised to pitavastatin compared to placebo. A major question about the findings is what drives the large effect seen? Based on data from general population trials, and the degree of LDL-reduction achieved, a far greater than anticipated benefit was observed. . This raises the question of whether there are other mechanisms through which statins reduce CVD risk. One rationale for the trial was the hypothesis that statins would reduce residual inflammation, and thus impact clinical outcomes . In the published mechanistic sub-study[43], pitavastatin not only reduced non-calcified plaque volume, but also the inflammatory biomarkers oxidised LDL and lipoprotein-associated phospholipase A2 (Lp-PLA2). At the conference further data showed that changes in these biomarkers, as well as high-sensitivity C-Reactive protein (CRP) and LDL, were not associated with changes in non-calcified plaque volume, suggesting that there may be other explanations [44]. The investigators used a targeted proteomic approach to identify biological pathways that mediated the statin effect on non-calcified plaque volume. PCOLCE (a protein that accelerates procollagen maturation and triggers the assembly of collagen molecules into fibrils), was independently associated with reduced non-calcified plaque volume, with each doubling in PCOLCE being associated with a 25% reduction in plaque. Overall, almost all of the effect of pitavastatin on non-calcified plaque could be explained by the drug's effects on PCOLCE[45].

REPRIEVE also demonstrated, unsurprisingly, that older age, a family history of CVD, black or African American origin, smoking, hypertension, and lower HDL were associated with a higher risk of MACE as was a detectable viral load. The lack of association between MACE and female sex (generally protective younger ages), body mass index (BMI), glucose or renal function, was surprising, and possibly a result of the strong collinearity between many factors in their dataset[46]. In a separate presentation[47], the authors noted that the Pooled Cohort Equation from the

American College of Cardiology/American Heart Association (ACC/AHA) was a poor predictor of MACE in some groups, under- and over-predicting risk in those from high-income and low-income countries, respectively. Among individuals from high-income countries, the score also under-predicted risk in women and in those of black African origin. Of note, the Pooled Cohort Equation has been widely reported to over-estimate the risk of CVD in other studies, so may not be applicable to non-US settings.

Other findings relating to CVD and diabetes

Data from combined D:A:D and RESPOND collaborations demonstrated a drop in true CVD incidence in people with HIV after accounting for cohort ageing over time[48]. Other than an increase in hypertension prevalence over time, which partially counterbalanced the drop in CVD, the decline did not appear to be mediated by changes in any particular risk factor, thus may simply reflect changes seen in the wider population.

Data from the Johns Hopkins cohortl[49] identified people without diabetes who had used either a NNRTI or a PI for at least 180 days and then emulated a trial of switching to an INSTI with new onset diabetes as their outcome. Overall the rate of incident diabetes was slightly higher in those switching to INSTI, particularly in the first two years post-switch.

Cognitive Function

The CONNECT study in South Africa[50] included 178 people virally suppressed on EFV who switched to DTG with follow-up a year later and compared them to a demographically similar group of people without HIV. Whilst at baseline there were quite large differences in the global T-score and the Global Deficit Score between the groups, a year after switching off EFV, there were none . Importantly, less than 10% of people with HIV had cognitive impairment based on the global deficit score, much lower than is often reported.

Data from ACTG A5322 was used to identify 8 different cognitive phenotypes among people with HIV[51]with phenotype 1 reflecting optimal cognitive performance, and phenotypes 6, 7 and 8 the poorest. Polypharmacy (use of 5 or more drugs), and hyper-polypharmacy (10 or more drugs), were more common in those with the poorest cognitive phenotypes. Although limited by its cross-sectional design, restricting conclusions regarding the direction or causality of the association, this was new evidence linking comorbidities and their treatment with cognitive function.

Two final studies on cognitive function came from a cohort at Washington University. In the first, sociodemographic factors, in particular education and premorbid IQ, rather than clinical or neurological features were the strongest predictors of cognitive profiles[52]. In the second, greater recent exposure to air pollutants was associated with worse cognition and changes to plasma markers of inflammation and neurodegeneration in those with HIV[53]. Despite potential for unmeasured confounding the findings are topical given current interest in the contribution of pollution to health outcomes.

Mental Health

Two studies from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) were of note. In the first[54], among those with diabetes, over half had diagnosed depression and higher depressive symptom burden was associated with poor diabetes control. The direction of this association differed by ethnicity, emphasising the importance of interventions tailored to specific populations. In the second study[55], a depressive symptom score at any time point was associated with a higher stroke risk, with this effect being stronger in younger people. Although the authors had controlled for many confounders, they didn't control for substance use over time so were not able to conclude causality.

A collaboration between the IeDEA Southern Africa cohort and NA-ACCORD[56], quantified life years lost due to mental illness in South Africa and North America. Overall, people with HIV and mental health diagnoses die from 1 to 17 years earlier than people with HIV without mental health diagnoses. Finally, a presentation from the CHANGE HIV study in Canada[57] reported concerningly low expectations regarding ageing among 320 people with HIV (median age 69 years) including believing that their energy levels will decline each year, that loneliness is unavoidable, and that forgetfulness in inevitable. Women, in particular, had lower expectations, as did those with depression and greater social isolation. As these expectations may drive behaviours, this is an area where there is an important need for interventions.

Pregnancy

The PHACS network[58] presented a descriptive analysis of participants who had received at least 7 days of bictegravir during pregnancy. There were no early safety signals for adverse birth outcomes, noting that 99/144 infants were exposed to bictegravir in the first trimester. Five babies had congenital anomalies, similar to background rates. SMARTT[59], a prospective study within the PHACS network, presented first trimester-exposure data on other "newer" antiretrovirals including rilpivirine (291 infants), darunavir (268), raltegravir (152), elvitegravir (193) and dolutegravir (186) and similarly found no obvious safety signals.

The DELIVER study [60] presented data on 200 women using dapivirine (monthly vaginal ring) PreP from 12 weeks' gestation and showed no difference in pregnancy or birth outcomes compared to background rates. No infectious complications were observed, nor any seroconversions.

An excellent themed discussion on hypertension and pregnancy[61] presented Zambian data demonstrating lower rates of preeclampsia in 1597 pregnant women with compared to 2579 without HIV (ARR 0.53; 95%CI 0.41-0.69). This reduced risk persisted when stratified by preconception ART exposure, detectable viral load and CD4 count.

Given increased use globally of dolutegravir-based ART, several studies examined the impact of dolutegravir on gestational hypertension. ORCHID [62] found no significant difference in incident hypertension in 797 pregnant women on TDF/FTC/DOL compared to 1097 HIV-negative pregnant women. In DOLPHIN2[63] (TDF/FTC/DOL versus TDF/FTC/EFV) there was no significant difference in postpartum hypertension. VESTED[64], which randomised pregnant women = to TDF/FTC/DOL, TAF/FTC/DOL or TDF/FTC/EFV, demonstrated very low rates of incident hypertension (BP>140/90) in all arms. When considering women with "elevated blood pressure" (BP>130/80), there was a non-significant trend towards higher rates in women taking TAF/FTC/DOL compared with TDF/FTC/EFV (HR 1.26[0.98,1.64} P=0.075). Hazard ratios between groups were, however, similar once adjusted for weight.

A large surveillance study from Botswana[65] demonstrated 20% less hypertension in women taking efavirenz compared with those on dolutegravir, and a 20% increased risk in HIV-negative women compared to those on dolutegravir. Differences in proportions of women with high weights in these groups (HIV negative>dolutegravir>efavirenz arms) may have driven these findings, leading the panel to conclude that maintaining a healthy weight in pregnancy remained key, regardless of ART used.

The ODYSSEY study [66] presented 192 week randomised data, demonstrating superiority of dolutegravir-based ART over SOC for first and second line treatment in 792 children aged 3 months-18 years. Whilst superiority was seen up to 240 weeks, 42% of SOC participants had switched to dolutegravir as part of clinic protocol (with no prior failure), hence data was presented at the earlier timepoint of 192 weeks (where this was 13%).

An excellent symposium on “Living into young adulthood with perinatally acquired HIV” highlighted ongoing challenges facing these young people, especially with regards mental[67] and cardiometabolic health[68]. Last but not least, The N’galy Mann Lecture[69], delivered by Dorothy Mbori-Ngacha, started CROI-2024 off with an inspiring look at how far we have come, and how far we have yet to go, to end perinatally acquired HIV.

Summary

Compared to previous years, there was greater variety of interesting research that can be applied to clinical practice at CROI 2024. The impact of statins on CVD in people with HIV is clear, but whilst standard CVD risk factors predict risk in some people with HIV, they do not perform well in all populations. Importantly, there was a greater appreciation of the role of socio-economic and non-HIV factors in the development of comorbidities and cognitive health, hence the importance of interventions to support both physical and mental health as people with HIV age.

Whilst novel drug developments are exciting, global equity must be prioritised to ensure no one is left behind. The role bNAbs will play in the future of HIV prevention, treatment and, thus far, the elusive goal of HIV cure remains unclear.

Acknowledgments

- BHIVA, for attendance support
- The following for references:
    - Aidsmap
    - HIV iBase
    - NATAP

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