Invited Review

CROI 2023: Metabolic and Other Complications of HIV Infection

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Abstract. *Comorbid conditions have major impacts on the health, quality of life, and survival of people with HIV, particularly as they age. The 2023 Conference on Retroviruses and Opportunistic Infections (CROI) featured excellent science related to specific comorbidities, such as cardiovascular disease (CVD), cancer, and obesity. Studies investigating factors that may contribute to CVD, such as mental health disorders, antiretroviral therapies, and activation of hormonal pathways, were featured prominently. Other studies sought to understand the epidemiology of non–AIDS-defining cancers in people with HIV. As at previous CROI conferences, weight gain attributable to antiretroviral therapies was a major theme, and several abstracts focused on the important question of whether weight decreases after discontinuation of antiretroviral therapy (ART) regimens associated with weight gain. This review focuses on abstracts presented at CROI 2023 in these areas, highlighting those with the most clinical impact.*

Keywords: CROI 2023, HIV, metabolic complications, comorbidities, antiretroviral therapy

Cardiovascular Disease in HIV

Anxiety and Depression and Myocardial Infarction

In addition to traditional cardiovascular disease (CVD) risk factors (smoking, hypertension, diabetes mellitus, and dyslipidemia), common mental health disorders may also contribute to CVD risk in people with HIV. In an analysis of more than 33,000 people participating in 7 clinical cohorts of NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) in the US, Hyle and colleagues investigated the associations of depression and anxiety with myocardial infarction (MI) (Abstract 145). This study examined 2 MI outcomes: type 1 MI, which is related to rupture of an atherosclerotic plaque and myocardial damage to areas distal to the arterial occlusion; and type 2 MI, which occurs when oxygen demand outstrips oxygen supply and is observed with secondary conditions such as substance use disorder, arrhythmias, and heart failure.

Among people with HIV, almost half (49.4%) had a history of depression or anxiety. During the follow-up period between 1998 and 2017, a total of 869 MIs were observed, of which 495 (57%) were type 1 and 374 (43%) were type 2. For type 1 MIs, the presence of depression was associated with a 23% increased risk of MI (adjusted hazard ratio [aHR], 1.26; 95% CI, 1.02-1.49), whereas anxiety was not associated with increased risk (aHR, 0.92; 95% CI, 0.74-1.16). Other factors associated with type 1 MIs were male sex, older age, tobacco smoking, hypertension, dyslipidemia, diabetes, renal disease, and protease inhibitor use. For type 2 MIs, anxiety increased the risk by 42% (aHR, 1.42; 95% CI, 1.10-1.83), with a similar trend for depression (aHR, 1.20; 95% CI, 0.96-1.51). In addition to traditional CV risk factors, type 2 MI was also associated with cocaine use and detectable levels of HIV RNA.

These data suggest independent effects of these mental health conditions on CVD risk and lead to the question of whether appropriate linkage to care and treatment of these conditions will improve CVD risk in the future. Another important consideration based on these data is whether persons with either anxiety, depression, or both may potentially benefit from more aggressive CVD risk reduction.

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Blocking the Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin-aldosterone system (RAAS) has been described in people with HIV and may play an important role in the pathogenesis of CVD (see Srinivasa for review).[1] As a final step in this pathway, aldosterone binds to the mineralocorticoid receptor in the kidney, which regulates sodium balance and blood volume; also, excessive RAAS activation in the heart leads to vascular dysfunction as well as myocardial injury and fibrosis. Mineralocorticoid receptor activation in macrophages and lymphocytes increases the elaboration of proinflammatory cytokines. Attenuation of RAAS activation through mineralocorticoid receptor antagonism may be an important strategy to decrease the CVD burden in people with HIV.

Activation of the renin-angiotensin-aldosterone system (RAAS) has been described in people with HIV and may play an important role in the pathogenesis of CVD

Srinivasa and colleagues investigated the effect of RAAS antagonism on cardiovascular function in people with HIV, using eplerenone, a US Food and Drug Administration (FDA)-approved mineralocorticoid receptor antagonist (Abstract 144). In a 12-month, placebo-controlled, randomized clinical trial of 40 antiretroviral therapy (ART)-treated people with HIV with central adiposity but without established CVD, more participants in the eplerenone group exhibited improved coronary flow reserve (CFR), as measured using coronary positron emission tomography, than those in the placebo arm. Moreover, among participants with impaired baseline CFR, those receiving eplerenone showed improvement in CFR compared with participants in the placebo group ($P = .04$). Eplerenone treatment was also associated with improvements in left ventricular end-diastolic volume ($P = .03$) and stress myocardial blood flow ($P = .03$). In addition to its cardiovascular effects, eplerenone treatment was associated with higher CD4+ T-cell count ($P = .02$) and a trend toward lower levels of high-sensitivity interleukin-6 (IL-6) ($P = .07$).

In summary, in this small, randomized trial, eplerenone treatment led to favorable changes in measurements of subclinical cardiovascular function as well as improved CD4+ T-cell count. Larger studies are needed to better understand the potential clinical benefit of eplerenone in people with HIV.

Are Integrase rand Transfer Inhibitors Associated With Heart Disease Events?

In the RESPOND (International Cohort Consortium of Infectious Disease) study, a large, multicenter cohort of people with HIV in Europe and Australia, exposure to integrase strand transfer inhibitors (InSTIs) was associated with an increased risk of CVD events over the first 2 years.[2] Surial and colleagues examined this important question in the Swiss HIV Cohort study; they investigated individuals with HIV who were treatment-naive before starting either InSTI or non–InSTI-containing ART (Abstract 149). The endpoint was the first cardiovascular event, defined as MI, stroke, or arterial intervention. Baseline characteristic differences between the InSTI and other ART groups were as follows: the InSTI group had fewer women and people of African origin as well as higher median CD4+ cell count nadir among participants. In adjusted analyses, the risk differences for CVD between the 2 groups were not statistically significant at 1 year (−0.02%; 95% CI, −0.32 to 0.21%), 2 years (−0.17%; 95% CI, −0.65 to 0.10%), or 5 years (−0.38%; 95% CI, −1.29 to 0.52).

In contrast to findings from the RESPOND study, this investigation did not confirm an association between InSTI exposure and CVD events. Additional data are needed to better understand whether InSTI exposure truly increases CVD risk.

Cancer Epidemiology in HIV

Cancer is a leading cause of death among people with HIV. Numerous important questions remain regarding cancer risk in people with HIV and the extent to which incidence differs from that in people without HIV, particularly for non–AIDS-defining cancers (NADCs), namely, breast, colon, head and neck, kidney, laryngeal, liver, lung, oropharyngeal, pancreatic, prostate, and anal cancers, as well as leukemia and Hodgkin's lymphoma.

Rudolf and colleagues examined incident cancers in Medicaid beneficiaries enrolled in 14 US states from 2001 to 2015; enrollees included more than 43 million people without HIV and 181,000 people with HIV (Abstract 155). For men and women, various NADCs, including leukemia and lung, head and neck, liver,

oropharyngeal, laryngeal, and anal cancers, were more common in people with HIV than in the general population. For colon cancer, the incidence was higher at younger ages in people with HIV but higher at older ages in people without HIV. For breast cancer, risk for early disease was similar for women whether with or without HIV, but after age 42, women with HIV had a lower risk than women without HIV. For prostate cancer, before age 50, men with HIV had a higher risk than men without HIV; however, after that age, the risk was higher among men without HIV.

The mechanisms underlying these risk differences by HIV serostatus as well as the interactions between age and HIV serostatus, as observed with some cancers, deserve further inquiry. Understanding how the differences in cancer incidence by HIV serostatus might impact screening practices is also important.

Are Cancer Outcomes Any Different in HIV?

Rava and colleagues compared mortality from NADCs in participants in the Spanish AIDS Research Network (CoRIS) cohort versus mortality in the general Spanish population between 2004 and 2020 (Abstract 871). Of the cancers examined, lung and liver cancers had the highest incidence in CoRIS participants. When NADCs were grouped together, mortality rates were higher in people with HIV than in the general population at younger ages (<60 years old), with the greatest difference by HIV serostatus observed in persons less than 40 years old. Factors associated with NADC mortality were viral hepatitis infection, smoking, and lower CD4+ count. It is unclear which cancers accounted for the differences in mortality by HIV serostatus and what factors may account for this difference (eg, stage at cancer diagnosis, type of or adherence to cancer treatments, and social determinants of health).

Does Obesity Contribute to Inflammation in HIV?

Overweight and obese states are steadily increasing in people with HIV, in parallel with increases in diseases associated with elevated weight. Because obesity is considered a proinflammatory state and chronic inflammation is thought to contribute to comorbidities in people with HIV, the relationship between inflammation and elevated body mass index (BMI) is of particular interest. Gelpi and colleagues studied the association between BMI and inflammation in people with HIV and in individuals without HIV in the Copenhagen Comorbidity in HIV Infection study (Abstract 253).

In an adjusted analysis, those with HIV with either normal or below-normal weight had greater levels of interleukin (IL)-6 (adjusted odds ratio [aOR], 5.82; 95% CI, 1.69–20.05) and interferon (IFN)-γ (aOR, 3.41; 95% CI, 1.01–11.46) than individuals without HIV. In contrast, greater levels of IL-6 and IFN-γ were not observed in people with HIV who were overweight or obese than in people without HIV with similar BMIs. Among participants with normal or below-normal weight, associations were observed in individuals with HIV between greater IL-6 levels and waist-to-hip ratio, age, and smoking, but not in participants without HIV.

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This study suggests that people with HIV who have normal or below-normal BMI may have unique factors that predispose them to greater inflammation, such as the distribution of adipose tissue. It also suggests that inflammation in people with HIV who are obese is not accentuated compared with persons without HIV who are obese.

Antiretroviral Therapy–Related Weight Gain: Is It Reversible?

InSTIs and tenofovir alafenamide (TAF) each have been associated with weight gain in people with HIV. An important clinical question is whether discontinuation of these drugs will lead to decreased weight and improved metabolic health. In SOLAR, a 12-month, phase IIIb noninferiority efficacy study, Tan and colleagues studied the effect of continuing on a treatment regimen that includes bictegravir (BIC) and TAF (BIC/emtricitabine [FTC]/TAF) versus switching from BIC/FTC/TAF to cabotegravir (CAB) and rilpivirine (RPV) (given as a long-acting

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[LA] injection every 2 months) (Abstract 146). In the CAB + RPV LA arm, 38% of participants had overweight state and 21% had obesity, and in the BIC/FTC/TAF arm, 34% of participants had overweight state and 23% had obesity. As such, more than 50% of participants in each arm had overweight state or obesity.

In ART initiation and switch studies, tenofovir alafenamide is associated with more weight gain than tenofovir disoproxil

The change in weight from baseline to the end of the study was similar in the 2 arms. The median (interquartile range [IQR]) weight change from baseline to the end of the study in the CAB + RPV LA arm was −0.40 kg (−2.95, 2.10) and in the BIC/FTC/TAF arm was 0.05 kg (−2.30, 1.95). Similarly, changes from baseline in waist circumference, waist-to-hip ratio, and the proportion of individuals with insulin resistance (as measured by a homeostatic model assessment for insulin resistance [HOMA-IR] ≥2) were similar between the 2 arms. This study indicates that switching patients to CAB + RPV LA from BIC/FTC/TAF (ie, removing BIC and TAF) is unlikely to lead to decreased weight and improved metabolic health.

Does Switching From TAF to TDF Decrease Weight?

In ART initiation and switch studies, TAF is associated with more weight gain than tenofovir disoproxil (TDF). These switch studies have examined the effect of switching from TDF to TAF, rather than switching from TAF to TDF. This is an important clinical issue for people who have gained weight while receiving TAF and may be considering switching to TDF to better manage their weight.

Bosch and colleagues investigated whether weight gain after initial ART containing TAF could subsequently be reversed (Abstract 671). Participants in the ADVANCE (Dolutegravir Plus Two Different Prodrugs of Tenofovir to Treat HIV) trial in South Africa were randomly assigned to 1 of 3 arms: TAF/FTC/dolutegravir (DTG), TDF/FTC/DTG, or TDF/FTC/EFV for 192 weeks, after which participants were given TDF/lamivudine (3TC)/DTG in an open-label arm as part of the CHARACTERISE (a Cross-sectional, Observational Study to Characterise the Transition to Dolutegravir-Based Regimens in South Africa in Terms of the Emergence of Obesity, Viral Re-suppression, and Integration Into Routine Programme Care) trial, as this combination is the standard of care in South Africa. Those who received TAF/FTC/DTG in ADVANCE and subsequently switched to TDF/3TC/DTG in CHARACTERISE had weight loss of 1.2 kg (P = .01) and decreased values for hemoglobin A1c (−0.10 mmol/L; P = .008), fasting glucose (−0.20 mmol/L; P = .001), and low-density lipoprotein cholesterol (−0.32 mmol/L; P = .001) levels. The effects appeared to be driven by women who lost approximately 4 kg over the 48 weeks after the switch, which equaled approximately 40% of the weight gained during the 192 weeks of ADVANCE. It is unclear whether the weight loss would have continued with further follow-up. Among men, no similar weight effect of switching from TAF/FTC/DTG to TDF/3TC/DTG was observed. This study demonstrated that switching to TDF from TAF may decrease weight among women. However, this benefit would need to be weighed against the bone and renal toxicities of TDF.

Verburgh and colleagues used the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort to also address this question of whether weight gain with InSTIs or TAF, or both, is reversible with switching off these medications (Abstract 673). In this study, they focused on participants who had 7% or higher weight gain after switching to TAF and/or InSTI, an extent considered clinically significant. Weight and BMI of participants who discontinued TAF, InSTI, or both were compared with those of participants who continued TAF, InSTI, or both, using at least 1 weight measurement taken 3 or more months after discontinuation.

Overall, the researchers found that the change in weight at 24 months was −1.48 kg (95% CI, −4.24 to 1.27) after discontinuation of TAF (n = 21), −2.73 kg (95% CI, -6.22 to 0.66) after discontinuation of InSTI (n = 37), and −7.95 kg (95% CI, −15.57 to −0.33) after discontinuation of both InSTI and TAF (n = 11). In participants who continued TAF, InSTI, or both, weight change at 24 months after the first weight measurement to indicate a weight gain of 7% or more following the switch was −0.77 kg (95% CI, −1.32 to −0.21).

Based on this small study, it appears that weight gain after discontinuation of TAF, InSTI, or both was partly reversible and that weight was stable after the initial 7% or higher weight gain in participants switching to TAF, InSTI, or both. The ART medications to which these participants switched was not reported.

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Financial relationships with ineligible companies within the past 24 months: Dr Sarkar reported no relevant financial affiliations with ineligible companies. (Updated June 27, 2023) Dr Brown reported serving as a consultant for Janssen, Merck & Co, Inc, Gilead Sciences, and ViiV Healthcare. (Updated June 27, 2023)

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All relevant financial relationships with ineligible companies have been mitigated.

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