Article Type: Invited Review

CROI 2022: Metabolic and Other Complications of HIV Infection or COVID-19

Sudipa Sarkar, MD; Todd T. Brown, MD, PhD
Johns Hopkins University, Baltimore, Maryland

Running Head: CROI 2022: Metabolic Complications

Abstract: *Comorbid conditions have a major impact on the health, quality of life, and survival of people with HIV, particularly as this population ages. The 2022 Conference on Retroviruses and Opportunistic Infections (CROI) featured excellent science related to specific comorbidities, such as cardiovascular disease, type 2 diabetes, cancer, and frailty. The role of systemic inflammation in the pathogenesis of cardiovascular disease was an important theme, with strong evidence regarding the impact of microbial translocation. Other studies examined functional impairment, frailty, and potential important contributors, such as concomitant medications and sleep disturbances. The ANCHOR (Anal Cancer/High-grade Squamous Intraepithelial Lesions Outcomes Research) study provided crucial evidence that treatment of high-risk anal lesions reduces the incidence of anal cancer, which has important implications in the prevention of this devastating comorbidity. In addition, numerous presentations demonstrated the importance of comorbid conditions in COVID-19 outcomes in people with HIV and described persistent symptoms after acute SARS-CoV-2 infection has resolved. This review focuses on the abstracts presented at CROI 2022 in these areas, highlighting those with the most clinical impact.*

Author Correspondence: Write to Todd T. Brown, MD, PhD, Professor of Medicine and Epidemiology, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University, 1830 East Monument Street, Suite 333, Baltimore, MD, 21287, or email tbrown27@jhmi.edu.

Cardiovascular Disease

Cardiovascular disease is one of the most common causes of morbidity and mortality among people with HIV, and emerging science in this area was featured prominently at the 2022 Conference on Retroviruses and Opportunistic Infections (CROI). Silverberg and colleagues compared the incidence of myocardial infarction (MI) by HIV serostatus over 2 distinct time periods in 2 large health systems: Massachusetts General Hospital (Partners) and Kaiser Permanente Northern California (KPNC) (Abstract 39). The study included people with HIV who were propensity matched at a ratio of 1 to 4 to people without HIV in the Partners cohort, and matched at a ratio of 1 to 3 to people without HIV in the KPNC cohort. In people without HIV, 1.1% of the group had an MI in the first time period (2005-2009), but the incidence was lower at 0.9% in the second time period (2010-2017). In contrast, this decrease in incidence over time was not observed in people with HIV. Although MI incidence was similar in 2005 to 2009 (1.1%), MI incidence among people with HIV in the second time period was higher than that observed in people without HIV (1.2% vs 0.9%, respectively). After adjustment for demographic factors and Framingham risk score components, the overall risk of MI was 60% higher in people with HIV than people without HIV in the second time period (hazard ratio [HR], 1.6; 95% confidence interval [CI], 1.1-2.4). This report underscores that in more recent years people with HIV are more likely to experience MI than people without HIV. The reasons why MI incidence in people with HIV is not decreasing over time, as seen in their counterparts without HIV, require further exploration. Effects of contemporary antiretroviral therapy (ART) and the impact of prolonged systemic inflammation could be among the contributing factors.

Systemic inflammation and arterial wall inflammation are thought to be a major driver of cardiovascular disease in people with HIV. Toribio and colleagues used a novel imaging technique to compare macrophage-specific arterial inflammation in people with HIV and people without HIV (Abstract 38). This imaging technique used a

macrophage-specific tracer, 99mTc-tilmanocept, and single-photon emission computed tomography (SPECT)/computed tomography (CT) imaging. In this study of 30 participants (20 people with HIV on ART and 10 people without HIV) without clinical atherosclerotic cardiovascular disease, the investigators found that people with HIV had greater tracer uptake than people without HIV (P=.03) and that a significant interaction (P=.0001) existed between HIV serostatus and noncalcified plaque volume in their associations with tracer uptake. This study is one of the first to link macrophage-specific arterial inflammation, systemic monocyte activation, and noncalcified plaque. The findings provide evidence that the pathophysiology of cardiovascular disease may differ by HIV status and raise the possibility that novel imaging could be used in the future to more fully characterize cardiovascular disease risk in this patient population, which is disproportionately affected by cardiovascular disease.

Bacterial Translocation and Cardiovascular Disease

The sources of systemic inflammation in people with HIV are likely multifactorial. One crucial hypothesized source of systemic inflammation is microbial translocation across the gut. Depletion of CD4+, CD8+, and Th17 cell counts in the gut early in HIV infection is not restored with systemic immune recovery. In this setting, bacterial products may move across from the gut lumen and lead to a systemic immune response and vascular inflammation. Currently, there are no treatments available that target this mechanism.

Diggins and colleagues hypothesized that teduglutide, a glucagon-like peptide (GLP)-2 agonist that is used for treatment of short gut syndrome and improves the integrity of the intestinal barrier, would decrease immune activation and thus also decrease arterial inflammation (Abstract 134). In this proof-of-concept study, 28 participants were randomly assigned to either teduglutide or placebo for 6 months. The participants underwent fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT to measure arterial inflammation

at baseline and at 6 months. In addition, peripheral blood mononuclear cells and plasma metabolites were measured. Treatment with teduglutide was associated with significant decreases in arterial inflammation (as measured by target-to-background ratio in the most diseased segments of the carotid arteries), activated monocytes (19.24% ± 5.31% vs -3.31% ± 4.96%, *P*<.05), and CD8+ T cells (-0.33% ± 0.39% vs 0.67% ± 0.33%, *P*<.05). Moreover, teduglutide treatment was associated with an increase, although not statistically significant, in kynurenic acid, which has anti-inflammatory properties. The results of this proof of concept appear promising, and larger studies on teduglutide in people with HIV may determine how GLP-2 agonist treatment affects immune activation and whether it impacts other sites of vascular inflammation.

In the setting of microbial translocation, the specific composition of the gut microbiome and the metabolites these bacteria produce may be important in the inflammatory response and subsequent risk of cardiovascular disease. Wang and colleagues conducted a cross-sectional study among women with or behaviorally vulnerable to HIV in the WIHS (Women's Interagency HIV Study) cohort to examine the relationships among carotid artery plaque, metabolomic and lipidomic profiles, and gut microbiome diversity and taxonomy (Abstract 37). *Proteus* and *Fusobacterium* in the gut microbiome had a significant, direct association with carotid artery plaque (*P*=.040 and *P*<.001, respectively), and 2 butyrate-producing bacterial genera were associated with a lower likelihood of having carotid artery plaque. The investigators also studied the associations among the lipidome, metabolome, and incident carotid artery plaque in 737 participants in the WIHS and MACS (Multicenter AIDS Cohort Study) , which includes men with or without HIV. Metabolites were organized into modules based on network analyses. The investigators demonstrated a direct association between *Fusobacterium* and a module that included lysophosphatidylcholines and lysophosphatidylethanolamines, and that an increase of 1 standard deviation in the score of this module was associated with increased incident carotid artery plaque (relative risk [RR], 1.34; 95% CI, [1.09-1.64]). This study highlighted the

links between the gut microbiome and subclinical atherosclerotic vascular disease, and the associations of the lipidome and metabolome with each.

Inflammation, Diabetes, and Fat Fibrosis

The issue of persistent inflammation and its relationship with metabolic comorbidities in people with HIV were a common theme at CROI 2022. Alba and colleagues focused on inflammation, type 2 diabetes, and adipose tissue fibrosis in people with HIV (Abstract 36). In one part of this study, plasma markers of inflammation were measured in 843 participants from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems who were on ART with viral suppression, and these inflammatory markers were studied in relation to incident diabetes. Greater levels of inflammatory markers, including interleukin (IL)-6 ($P<.01$) and soluble tumor necrosis factor receptor 2 (sTNFR2) ($P<.001$), were associated with incident diabetes. Separately, serum inflammatory markers, insulin resistance, and subcutaneous adipose tissue hydroxyproline, a marker of fibrosis, were measured in participants with and without HIV from the SCOPE (Observational Study of the Consequences of the Protease Inhibitor Era) cohort. Although a strong correlation between insulin resistance and subcutaneous adipose tissue hydroxyproline was not observed in people with HIV, among participants with a body mass index of less than 30 kg/m^2,people with HIV had greater levels of subcutaneous adipose tissue hydroxyprolinethan people without HIV ($P=.03$), indicating greater adipose tissue fibrosis in people with HIV than in people without HIV. Given the unique and incompletely understood risk factors that people with HIV have for developing diabetes and dysfunctional adipose tissue, this study provides insight into possible mechanisms that may contribute to diabetes and adipose tissue dysfunction in this patient population.

Predicting Weight Gain With Integrase Inhibitors

Guaraldi and colleagues used a machine-learning algorithm to predict a weight gain of 5% or more in people with HIV 9 months after switching to an integrase strand transfer inhibitor (InSTI)-based regimen, with or without tenofovir alafenamide (TAF) (Abstract 597). Weight gain associated with each of these ART approaches is an issue of high clinical relevance, and the mechanisms are incompletely understood. Data from 2817 patients from a single clinic and who were ART experienced were used. Highly ranked variables in the model included weight obtained at the time of prediction, and variables such as current CD4+ cell count and waist circumference were more highly ranked in the model than the type of ART switch. Machine learning models such as the one presented by Guaraldi and colleagues underscore the importance of developing predictive models to more accurately identify those people with HIV at risk of weight gain and the associated metabolic consequences.

Functional Impairment Around the Globe in People With HIV

Multiple studies have shown that people with HIV have decreased physical function compared to demographically matched peers. However, most of these studies have examined populations in resource-rich settings. Erlandson and colleagues used baseline data from the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) study (ie, before patients were randomly assigned to pitavastatin or placebo) to determine the prevalence of physical function impairment, the variation across global geographic regions, and its association with cardiovascular risk (Abstract 34). Participants (n=7736) from 5 World Health Organization (WHO)-defined super regions (high income [US, Canada, Spain], Latin America/Caribbean [Puerto Rico, Brazil, Peru, Haiti], South Asia [India], Southeast/East Asia [Thailand], and sub-Saharan Africa [Botswana, South Africa, Zimbabwe, Uganda]) were assessed using the Duke Activity Status Instrument (DASI). This self-administered instrument records the degree of impairment experienced

during a range of daily activities. Overall, 28% of the sample had some functional impairment, whereas 8% had moderate impairment, with the highest prevalence in South Asia (approximately 75%) and the lowest prevalence in Southeast and East Asia (10%). Some of the variation in this measure was hypothesized to be related to cultural differences in the activities probed. In addition, impairment in physical function with DASI was associated with higher cardiovascular risk score and higher waist circumference, providing a link between these important comorbid conditions.

Anticholinergic Medications, Falls, Frailty

Frailty may drive impairments in physical function in people with HIV, and its etiology, as it is in the general population, is multifactorial. As in the general geriatric population, concomitant medications with anticholinergic properties may increase the risk of falls and frailty. Investigators from the POPPY (Pharmacokinetic and Clinical Observations in People Over Fifty) study, a cohort from the United Kingdom and Ireland of older individuals with and without HIV, examined the prevalence of anticholinergic medication (ACM) use and its association with recurrent falls and frailty (Abstract 35). Among 699 people with HIV and a median age of 57 years, 18% were taking 1 ACM and 9% were taking 2 ACMs or more. The most commonly used ACMs were codeine, citalopram, loperamide, amitriptyline, and diazepam. Overall, 9% reported recurrent falls and 32% were frail based on the Fried frailty phenotype. After adjustment for demographic and lifestyle factors, those taking ACMs tended to be more likely to have recurrent falls (odds ratio [OR], 1.9 [0.9-4.0]; *P*=.08) and frailty (OR, 1.7 [0.9-3.0]; *P*=.08). However, when examining whether number of ACMs was associated with these outcomes, those who reported taking 2 or more ACMs had 3.6-fold increased odds of recurrent falls compared with those not taking ACMs (OR, 3.6; 95% CI, 1.4-9.4; *P*=.009). Similar results were seen with the frailty outcomes, but the effect was not statistically significant in fully adjusted models (OR, 2.1; 95% CI,

0.9-5.0; *P*=.09). Although causality cannot be established with this cross-sectional study, these findings support further studies to understand whether discontinuing these medications can lead to improvements in these important aging-related outcomes.

ANCHOR Study: Treatment of High-Risk Anal Lesions Decreases Incidence of Anal Cancer

Anal cancer is common among people with HIV and leads to significant morbidity and mortality. Unlike cervical cancer, another HIV-related malignancy, screening for anal cancer and treatment of high-risk lesions (eg, high-grade intraepithelial lesions [HSILs]) are not routinely recommended. This is due in part to the lack of evidence that identification and treatment of HSILs can reduce the risk of anal cancer. The ANCHOR (Anal Cancer/High-grade Squamous Intraepithelial Lesions Outcomes Research) study screened more than 10,000 people with HIV with high-resolution anoscopy, of whom 52% had biopsy-proven HSILs (Abstract 106). Of these, 2227 were randomly assigned to treatment and 2219 received active monitoring. Treatment consisted of topical or ablative therapy with retreatment, if needed, at 8 weeks and monitoring (and repeat treatment, if indicated) every 6 months. Active monitoring included clinical visits every 6 months and periodic biopsies if indicated. The study was planned to have 5 years of follow-up but was stopped after a median follow-up of 25.8 months and 32 anal cancers were diagnosed. An interim analysis of the 30 cases included revealed a 57% RR reduction in those receiving treatment of HSIL compared with those being actively monitored (9 participants in the treatment arm vs 21 in the active monitoring arm). These findings are essential to developing an evidence-based treatment strategy to prevent anal cancer.

Long COVID: Understanding the Syndrome

Many excellent studies regarding COVID-19 were presented at CROI 2022, including those on long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC). One of the challenges in understanding PASC is the lack of a standardized definition and whether the conditions observed after COVID-19 are specific to those with COVID-19 or would have occurred without SARS-CoV-2 infection. In a large study from Kaiser Permanente Mid-Atlantic States, Horberg and colleagues examined diagnoses in more than 70,000 people with a positive SARS-CoV-2 test between January 1, 2021, and December 31, 2021, and compared these diagnoses with approximately 70,000 people who tested negative for SARS-CoV-2 during the same period (Abstract 98). The study focused on 2 types of diagnoses: acute and persistent diagnoses, which were defined as occurring between 0 to 30 days after SARS-CoV-2 testing and persisting for 30 to 120 days, and incident/late diagnoses, which were new diagnoses that appeared between 30 and 120 days after testing. The investigators examined 15 different "conditions of focus" that were higher in incidence in those with a positive SARS-CoV-2 test. Overall, 4.1% of those with a positive test had an acute and persistent condition of focus compared with 2.5% of those with a negative test (RR, 1.6; 95% CI, 1.5-1.7), with the conditions most different between the groups being cardiac dysrhythmia, diabetes, electrolyte disorders, malaise, nonspecific chest pain, and lower respiratory disease. For the incident or late diagnosis group, those with a positive test were 12% more likely to have a condition of focus (RR, 1.12; 95% CI, 1.08-1.16), with the largest differences between the groups being for anosmia, cardiac dysrhythmia, diabetes, genitourinary symptoms, malaise, and nonspecific chest pain. These findings demonstrate that there are multiple conditions, both persistent and incident, that are more common in those with a positive SARS-CoV-2 test, and these could form the basis of a case definition for PASC.

Abstracts cited in the text appear in the CROI 2022 Abstracts eBook, available online at www.CROIconference.org.

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence this continuing medical education (CME) activity with regard to exposition or conclusion. The Accreditation Council for Continuing Medical Education (ACCME) defines ineligible companies (formerly described as commercial companies) as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients. All financial relationships with ineligible companies for the authors and planners/reviewers are listed below. To view the financial relationships of the *Topics in Antiviral Medicine* Editorial Board, please see the front material of this volume.

Financial affiliations in the past 24 months: Dr Sarkar has no relevant financial affiliations to disclose. (Updated May 15, 2022) Dr Brown has served as a consultant for Janssen, Merck & Co, Inc, Theratechnologies, and ViiV Healthcare. (Updated May 14, 2022)

Planner/reviewer 1 has been a consultant to Antiva Biosciences, Gilead Sciences, Inc., and Merck and Co, Inc. (Updated April 20, 2022)

Planner/reviewer 2 has no relevant financial relationships with ineligible companies to disclose. (Updated April 29, 2022)

Reviewer 3 has no relevant financial relationships with ineligible companies to disclose. (Updated April 26, 2022)

All relevant financial relationships with ineligible companies have been mitigated.

Top Antivir Med. 2022;30(3).