Invited Review

CROI 2021: Metabolic and Other Complications of HIV Infection or COVID-19

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Comorbid conditions have a major impact on the health, quality of life, and survival in people with HIV, particularly as they age. The 2021 Conference on Retroviruses and Opportunistic Infections featured excellent science related to specific comorbidities as well as multimorbidity. A number of presentations related to comorbidities in women with HIV reflected a new wave of research aimed at understanding how the epidemiology and pathogenesis of comorbidities may differ by sex. Weight gain related to antiretroviral therapy was also a major theme of the comorbidity abstracts presented at the meeting. Several 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, a nascent topic that will expand over time. This review focuses on research presented at the conference in these areas, highlighting those with the most clinical impact.

Keywords: HIV, CROI 2021, comorbidity, COVID-19, weight, cardiovascular disease

Multimorbidity

Comorbid conditions are common in people with HIV. When these comorbid conditions cooccur, it is termed multimorbidity, which is a major threat to lifespan and healthspan in people with HIV. Paudel (Abstract 525) used administrative claims data from Optum Research Database in the United States to determine whether the prevalence of specific comorbidities and multimorbidity in a single calendar year (2018) differed in 20,256 people with HIV and 40,512 people without HIV, matched by age, sex, race, region, and insurance type. The mean age was 52 years, 80% were male, 46% were white, and 59% lived in the US South. Multimorbidity, defined as the presence of 3 or more comorbidities based on International Classification of Diseases (ICD)-9/10 diagnosis codes from medical claims, was more common in people with HIV than in people without HIV (37.2% vs 31.7%, respectively; $P<.01$). Along with this higher prevalence of multimorbidity, polypharmacy (≥5 non-antiretroviral therapy [ART] medications) was more prevalent among people with HIV than among people without HIV (76% vs 61%, respectively; $P<.001$). Given the type of data used, some key variables, such as body mass index (BMI), were not accounted for in the analysis. Nevertheless, these findings provide strong evidence regarding the magnitude of multimorbidity and polypharmacy in people with HIV, a crucial indicator how people with HIV may age.

As the population living with HIV ages over the next 10 years, the prevalence of multimorbidity will increase. Investigators from the PEARL (Pilot Randomized Clinical Trial of Early Coronary Angiography Versus No Early Coronary Angiography for Post-Cardiac Arrest Patients Without ECG ST Segment Elevation) study used Centers for Disease Control and Prevention (CDC) surveillance data and longitudinal data from the NA-ACCORD (North American AIDS Cohort Collaboration On Research and Design) to estimate the number of people in the United States who will be receiving ART from a period from 2017 to 2030 and the prevalence of several key comorbidities, including diabetes mellitus, hyperlipidemia, hypertension, myocardial infarction, chronic kidney disease, end stage liver disease, depression, and anxiety (Abstract 102). The models also took into account projected changes in BMI, smoking, and chronic hepatitis C and examined specific risk groups.

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Overall, the median age of ART users in the United States is expected to increase from 50 years in 2020 to 53 years in 2030 with more than 25% being 65 years old and older. The prevalence of multimorbidity (defined as 2 or more of the conditions) is expected to increase in the population between 60 and 70 years and those older than 70 years. Among those older than 70 years, the prevalence of multimorbidity is expected to be 69% in 2030, up from 58% in 2020. In other age groups, the prevalence of multimorbidity increased from 2009 to 2020, but is expected to remain relatively stable until 2030. The comorbidities that are expected to rise the most in prevalence between 2020 and 2030 are anxiety (increase of 11.3%), chronic kidney

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disease (9.4%), and diabetes mellitus (8.6%). The greatest increases in multimorbidity prevalence were in men who have sex with men, particularly among African American and Latinx populations. These data have important implications for the health care needs of aging people with HIV over the next 10 years.

Sex Differences in Comorbidities

An emerging theme in HIV comorbidities at CROI 2021 was the potential difference in the prevalence and underlying pathogenesis of comorbid conditions by sex. Collins and colleagues used data from the MACS/WIHS (Multicenter AIDS Cohort Study/Women's Interagency HIV Study) Combined Cohort Study (MWCCS) to determine whether the increase in comorbidities with aging that is observed in people with HIV differs in women than in men (Abstract 526). Using data from 2009 to 2019 and summarizing data at the most recent available visit, investigators determined whether the burden of comorbidities (a count of 10 different common comorbidities) differed by sex, and whether older age and HIV serostatus modified these relationships. Overall, the mean number of comorbidities was higher in women than in men (3.4 vs 3.2, respectively; $P = .015$). Notably, the comorbidity burden increased markedly by age group in men and in women and was higher in those with HIV. These differences persisted after adjustment for race, BMI, smoking, drinking, crack/cocaine use, and socioeconomic status. The major finding of this analysis is that the 3-way interaction term between age, HIV status, and sex was statistically significant, meaning that the HIV-related differences in the increasing comorbidity burden with age was greater in women than in men. These data raise the question of whether or not screening and treatment practices for comorbid conditions in people with HIV should occur at an earlier age in women than men.

Increased systemic inflammation may drive the pathogenesis of multimorbidity in people with HIV and sex-based differences in inflammation and immune activation may be an important underlying mechanism to explain the increased comorbidity burden in women with HIV compared with men with HIV. Schnittman and colleagues (Abstract 98) conducted a case cohort study within CNICS (Centers for AIDS Research Network of Integrated Clinical Systems) examining 11 different inflammatory biomarkers measured 1 year after ART-mediated viral suppression in persons who were subsequently diagnosed with an incident type 1 or 2 myocardial infarction, ischemic stroke, or venous thromboembolism and at the same time point in a randomly selected group that did not develop the one of the outcomes. After adjustment for age, nadir CD4+ cell count, smoking, injection drug use, atherosclerotic cardiovascular disease (ASCVD) risk score, and hepatitis C history, women had higher concentrations of multiple biomarkers than men, including C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), soluble cluster of differentiation 14 (sCD14), soluble urokinase-type plasminogen activator receptor (suPAR), intercellular adhesion molecule (ICAM)-1, and cytomegalovirus immunoglobulin (CMV IgG) ($P < .03$ for all). In general, many of the biomarkers were associated with the outcomes. However, there were some inflammatory markers that were associated with cardiovascular disease (CVD) events more strongly among women than in men with HIV (ie, kynurenine to tryptophan [KT] ratio and sCD14). In contrast, the biomarkers sCD14 and soluble tumor necrosis factor receptor 2 (sTNFR2) were associated more strongly with venous thromboembolism in men than women. These data suggest increased immune activation in women with HIV compared with men. In addition, sex can modify the relationship between increased systemic inflammation and clinical events.

Cardiovascular Disease

CVD is a major cause of mortality in people with HIV. Silverberg and colleagues assessed traditional CVD risk factors in a cohort of patients, including people with HIV (n=8,285 [5% of the cohort]) and people without HIV (n=170,517 [95% of the cohort]), within a single integrated health care system (Abstract 97). Patients with a history of CVD were excluded from the study. The authors calculated a disease management index (DMI) to reflect how well traditional CVD risk factors, including hypertension, dyslipidemia, and diabetes, were managed. A DMI of 100% indicated optimal management of a condition over a period of time. They found that the prevalence values of these risk factors did not differ significantly by HIV serostatus and that the DMI for these risk factors were similar between people with HIV and peo ple without HIV, except for lower hemoglobin A1c values (DMI 73% and 65%, respectively) and worse triglyceride levels (DMI 78% and 86%, respectively) in people with HIV. The risk of incident CVD was higher overall in people with HIV (adjusted hazard ratio [aHR], 1.18; 95% confidence interval [CI], 1.07-1.30) than in people without HIV and higher in people with HIV with well-managed hypertension than in those without HIV with well-managed hypertension, although the risk was not significantly higher in people with HIV with well-managed dyslipidemia or people with HIV with well-managed diabetes than in people without HIV. That the DMIs for CVD risk factors were similar between people with and without HIV in this specific integrated health care system but the risk of incident CVD was nonetheless increased in people with HIV with well-managed hypertension points to the need for more studies on optimizing CVD risk management in people with HIV.

More studies are needed to determine goals of CVD risk management focused on people with HIV

McGettrick and colleagues studied immune cells and inflammatory biomarkers to better characterize how inflammation is related to coronary

artery disease (CAD) in people with HIV (Abstract 100). Using principal components analysis in a study of people with HIV (n = 51) and people without HIV (n = 50) without prevalent CAD and propensity score matched for CVD risk factors, the investigators observed 3 clusters of 28 proteins and 10 T-cell biomarkers. Clusters 2 (characterized by greater T-cell senescence) and 3 (characterized by greater inflammation) had significantly greater proportions of people with HIV and had the strongest associations with subclinical CAD, which were not significantly attenuated after adjusting for HIV serostatus. This study highlighted the potential major roles that these pathways play in the pathogenesis of CVD, suggesting future targets to reduce the risk of CVD in people with HIV.

Weight Gain and Antiretroviral Therapy

In the context of the risk of developing cardiometabolic complications in people with HIV, Palella and colleagues studied the differential effects

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of ART-related weight changes, specifically in participants in the HOPS (HIV Outpatient Study) who switched to an integrase strand transfer inhibitor (InSTI)-based regimen with or without tenofovir alafenamide (TAF) (n = 441) versus to a non-InSTI-based regimen with or without TAF (n = 295) from 2017 to 2018 (Abstract 504). Although InSTIs accounted for the initial 8 months of weight gain after ART switch, TAF contributed to subsequent weight gain. Moreover, no significant difference between InSTIs with regard to contribution to weight gain was observed.

On a similar note, Patel and colleagues studied the effects of the long-acting InSTI cabotegravir (CAB) plus the nonnucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (RPV), which is administered intramuscularly every 4 or 8 weeks, compared with the effect of oral daily protease inhibitor (PI)-, NNRTI-, or InSTI-based ART, on weight gain using data from the ATLAS, FLAIR, and ATLAS-2M studies (Abstract 505). Over the 48-week follow-up period after the switch, weight in people with HIV in all 3 treatment groups (CAB + RPV every 4 weeks, CAB + RPV every 8 weeks, and oral ART) increased, with median (range) weight changes as follows: 1.2 kg (95% CI, -27.5-40.9) in the every 4-week CAB/RPV group, 1.25 kg/m^2 (95% CI, -16.0-22.2) in the every 8-week CAB/RPV group, and 1.0 kg/m^2 (95% CI, -28.0-39.0) in the oral ART group. The proportions of people with HIV in the 3 treatment groups whose weight increased by 10% or more were also similar among the groups.

Overweight and obese states are increasing in low- and middle-income countries. Bourgi and colleagues addressed this concern in individuals with HIV in their study on the InSTI dolutegravir (DTG) and its effect on weight gain, compared with the effect of NNRTI-based ART, in ART-naive people with HIV in the AMPATH (Academic Model Providing Access to Healthcare) cohort in Kenya (Abstract 509). Of the 17,053 study participants, 3% were in the DTG-based treatment arm, and 97% were in the NNRTI-based ART arm. At baseline, 25% of participants were overweight or obese, 62% were female, and 64% had a CD4+ count of 200 or more cells/mL. At 18 months, females in the DTG arm had a projected weight gain of 6.1 kg, compared with 2.8 kg in females in the NNRTI-based ART arm, 4.1 kg in males in the DTG arm, and 3.6 kg in males in the NNRTI-based ART arm ($P < .001$). A greater than 10% increase in BMI was associated with the following variables: DTG treatment, female sex, older age, and lower baseline CD4+ cell count. These findings, especially as they pertain to females, should be considered in the context of the benefits of DTG use in this patient population.

Osteoporosis and Frailty

Bone mineral density (BMD) decreases with the initiation of ART and does not return back to baseline during follow-up. Short-term bisphosphonate treatment may be an important strategy to attenuate this bone loss. McGinty presented the results of a randomized controlled trial in which ART-naive people with HIV initiating ART with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)-containing regimen were randomly assigned to calcium/vitamin D3 supplementation with either oral alendronate 70 mg weekly or placebo for 2 weeks prior to ART initiation and for a total of 14 weeks (Abstract 96). Fifty people with a median age of

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35 years were entered, 86% of whom were male. The primary endpoint was at 50 weeks after ART initiation, at which time total hip BMD decreased by 2.7% in the placebo arm, and remained stable in the alendronate group (median change, 0.50%) ($P = .02$). This difference was seen also at the week-14 timepoint (ie, the end of alendronate course). Early differences were seen in the lumbar spine, however, between the arms at week 14 and week 26 (placebo -2.5% vs alendronate +0.05%; $P = .03$), but at week 50, the alendronate group had decreases in BMD, such that the week 50 differences between the arms were no longer statistically significant (placebo -3.7% vs alendronate -1.4%; $P = .10$). These data suggest that a short course of alendronate may be a useful strategy to attenuate BMD loss with ART initiation. Given the lack of differences between the arms at 50

weeks in the lumbar spine, it is possible that a longer course of alendronate would be needed to preserve lumbar spine BMD with ART initiation. It is also unclear the extent to which these findings are generalizable to women or to older persons with osteoporosis, 2 populations that may have the most clinical benefit.

Frailty has been defined as aging-associated decline and dysfunction across numerous physiologic systems leading to increased vulnerability to acute stressors and has been associated with various adverse outcomes. It has been operationalized using the 5 different phenotype criteria: low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss. Individuals with 3 or more of these criteria are considered frail. Although several studies have shown that the prevalence of frailty is higher than expected in people with HIV, the populations studied have been relatively young, generally 50 to 70 years old. The SEPTAVIH (Frailty in People Living with HIV Aged 70 Years or More: Screening Feasibility, Prevalence, Risk Factors and Impact on Pejorative Events) study enrolled ART-treated people with HIV 70 years and older in France and examined the prevalence and correlates of frailty (Abstract 537). Of the 510 participants, 13.5% were frail, 63.2% were prefrail (1 or 2 frailty criteria met), and 23.4% were robust. The factors associated with frailty were older age, increased comorbidity, and lower socioeconomic status, whereas HIV-related factors showed no association with frailty. Although there was no reference group without HIV, the prevalence of frailty was not markedly high for a population this age. Further follow up of this cohort will be essential to understand how the prevalence of frailty changes over time in this older people with HIV population.

Comorbidities in Special Populations

Turkova and colleagues studied treatment failure of DTG and 2 nucleoside reverse transcriptase inhibitors (nRTIs) versus standard of care ART (ritonavir-boosted PI, NNRTI, or non-DTG InSTI ART) as first- or second-line ART in the ODYSSEY (PENTA 20) randomized trial of 707 children with HIV younger than 18 years (Abstract 174). Among the participants, 88% were African, and 49% were female. The DTG arm was found to be superior with regard to treatment failure, and no significant difference in adverse effects was observed between the 2 groups. At 96 weeks, a greater increase in weight (difference [standard error {SE}], 1 kg [.4]) and BMI (difference [SE], 0.3 kg/m^2 [1]) was noted in the DTG-based treatment than in the standard of care arm. These changes occurred early and plateaued over the course of the study. In addition, lower total cholesterol was noted in the DTG arm at 96 weeks (-15 mg/dL; 95% CI, -19 to -11). Given the effect of DTG on weight gain that has been observed in specific groups of adult people with HIV, this study addresses the important point of the effect of DTG on weight in children. How the use of DTG may affect long-term weight in children is a subject for future study.

In addition to the effect of DTG on weight in children, another study presented at the conference investigated the effect of DTG on weight in pregnant women and the association of antepartum weight change with negative pregnancy outcomes, including stillbirth, preterm delivery before 37 weeks gestational age, small for gestational age (SGA) (<10% percentile), and neonatal death. Hoffman and colleagues studied 643 ART-naive pregnant women with HIV randomly assigned to 1 of 3 treatment arms: DTG plus FTC/TAF, DTG plus FTC/TDF, or efavirenz (EFV)/FTC/TDF (Abstract 176). The greatest weight gain (average, 0.378 kg/week) and the lowest number of adverse outcomes was observed in participants in the DTG plus FTC/TAF group. Women in the EFV/FTC/TDF group had the least weight gain (average, 0.291 kg/week). Low weight gain, as defined by less than 0.18 kg/week, was associated with a greater risk of the composite negative pregnancy outcome result of stillbirth, preterm delivery, and SGA. This study shed a needed light on the effect of DTG on weight in the special population of pregnant women and found that although DTG was associated with greater weight gain, greater weight gain was not associated with worse outcomes during pregnancy.

Biomarkers and Comorbidities

Large-scale proteomic studies have the potential to identify proteins that are associated with mortality risk in people with HIV. Using the VACS-BC (Veterans Aging Cohort Study Biomarker Cohort), a longitudinal study of veterans with and without HIV, of whom more than 90% were men and more than two-thirds were African American, Hsue and colleagues investigated the associations of proteins, which were measured using aptamer-based technology, with mortality risk from 2005 to 2019 (Abstract 99). An aptamer-based platform can measure about 5000 proteins with high sensitivity and specificity, using a relatively small sample amount. In this study, some of the proteins that were found to predict mortality in people with HIV, including EGF containing fibulin-like extracellular matrix protein 1 and vitamin K-dependent protein C, are involved in processes such as cell adhesion and coagulation. Adding the biomarkers interleukin (IL)-6, D-dimer, and sCD14 to a model of protein-based predictors did not affect the ability of the proteins to predict mortality in people with HIV. Given that CVD risk calculators for the general population underestimate CVD risk in people with HIV, the use of proteins in risk prediction models for people with HIV has the potential to have an impact on clinical decision-making in the future.

Similarly, McCrary and colleagues used proteomics to determine whether specific proteins were associated with cardiac dysfunction in children and young adults in Kenya who were perinatally infected with HIV. Cardiac dysfunction was defined by the myocardial performance index measured using echocardiogram (Abstract 612). The investigators found that in a study population of 176 participants, of whom 50% had cardiac dysfunction, those with cardiac dysfunction were older, had a greater body surface area (P < .001

for both), and had greater HIV RNA levels (P=.017). Proteins were measured using a proximity extension-antibody assay. Using the different models, the investigators found 4 proteins associated with an abnormal myocardial performance index. These proteins included suppression of tumorigenicity (ST2) and S100A12 (EN-RAGE), both of which are associated with negative cardiac effects. Similar to the findings in the study by Hsue and colleagues, the study by McCrary and colleagues highlights the role of proteomics in identifying patients with HIV at greater risk of morbidity.

Comorbidities and COVID-19

Comorbid conditions are important risk factors for worse COVID-19 outcomes. Sun and colleagues used data from the US National COVID Cohort Collaborative (N3C) to determine whether HIV or solid organ transplant (SOT) were associated with COVID-19 hospitalization and, among people with HIV, which of the comorbid conditions examined (determined by diagnostic codes in the 2 years prior to COVID-19 diagnosis) were associated with an increased risk of hospitalization (Abstract 103). Of 509,092 patients with COVID-19, 2932 were people with HIV, 4633 had a history of SOT, and 111 were people with HIV who had an SOT. Overall, 32% of the population with COVID-19 were hospitalized. Compared with those without HIV or SOT, the odds of hospitalization was 30% higher among people with HIV, 69% higher among those with SOT, and 65% higher among people with HIV with SOT, after adjustment for age, sex, race/ethnicity, site, liver disease, diabetes mellitus, cancer, renal disease, and comorbidity burden. These findings suggest that people with conditions associated with immune suppression like HIV and SOT have a higher risk of more severe COVID-19 outcomes, independent of other comorbidities. Whether comorbidities and HIV or SOT, when seen together, have an additive or multiplicative risk is unclear. Among those with HIV, individuals who were hospitalized with COVID-19 were more likely to have a history of myocardial infarction, congestive heart failure, peripheral vascular disease, pulmonary disease, or renal disease. Interestingly, diabetes mellitus and liver disease were not risk factors for hospitalization.

Frailty may also be a major risk factor for more severe COVID-19 disease among people with HIV. Lee and colleagues conducted a matched cohort analysis in which people with HIV who were hospitalized (n=68) were matched with HIV-negative persons hospitalized with COVID-19 (n=181) by hospital site, test date, age, sex, and socioeconomic status (Abstract 142). The primary outcome measure was clinical improvement over 28 days. People with HIV were less likely to have clinical improvement over 28 days (hazard ratio [HR], 0.57; 95% CI, 0.39-0.85; P=.005 compared with HIV-negative patients), but this effect was attenuated after adjustment for ethnicity, clinical frailty score, BMI, baseline hypoxia, duration of symptoms, hypertension, diabetes, malignancy, cardiac, lung, and renal disease. These findings suggest that concomitant comorbidity is a major driver of poorer outcomes in people with HIV hospitalized with COVID. Among the comorbid conditions examined, clinical frailty score (a even-point score) 1 was inversely associated with the primary outcome measure (HR, 0.79 per 1-point increase; 95% CI, 0.39-0.85), suggesting that frailty at baseline is a major determinant of COVID-19 hospitalization course.

Data were presented suggesting that frailty at baseline is a major determinant of COVID-19 hospitalization course.

Long-Term Complications of COVID-19

It has been more than a year since the first case of COVID-19 was diagnosed in the United States, and long-term complications of COVID-19 affecting numerous organ systems in survivors have become apparent. Shoucri and colleagues conducted a retrospective review using chart abstraction of long-term symptoms of COVID-19 at 3 months (n=488) and 6 months (n=364) in 1190 patients with COVID-19 who were hospitalized in New York City (Abstract 554). At 6 months, the following proportions of patients had evidence of symptoms: 28% with cardiopulmonary symptoms, 26.4% with generalized symptoms, 24.2% with neuropsychiatric symptoms, and 20.6% with gastrointestinal symptoms. Shoucri and colleagues' study demonstrates that a significant number of patients hospitalized with COVID-19 experienced at least 1 symptom months after initial hospitalization.

Along the same line, Darley and colleagues studied persistence of symptoms after COVID-19 infection in the ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer) study (Abstract 551). Eighty-five patients with mild to moderate COVID-19 infection who received community-based care and 11 patients who were hospitalized with COVID-19 were included. Hospitalized patients were significantly older, with a mean age of 59 years (+/–9.6), compared with 43 years (+/–14) in patients with moderate COVID-19 and 47 years (+/–16) in patients with mild COVID-19, and predominantly male (90.9% in hospitalized patients and 62.2% in those with mild COVID-19 and 47.9% in those with moderate COVID-19). In addition, hospitalized patients were more likely to have diabetes, at 36.4%, than those with mild or moderate COVID-19 (<10% for both groups). At 3 to 4 months of follow up, 18% of patients reported fatigue, and 16% reported shortness of breath; at 8 months of follow-up, 30% of patients reported fatigue, and 17% reported shortness of breath. However, at 8 months of follow up, a majority of patients (80%) said that they had resumed their usual activities of living. This study illustrates that although a sizeable minority of patients experienced adverse symptoms after initial infection with COVID-19, the majority

reported returning to their baseline level of function by 8 months.

All cited abstracts appear in the CROI 2021 Abstract eBook, available online at www.CROIconference.org

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