Title
CROI 2018: Complications of HIV Infection and Antiretroviral Therapy.

Journal
Topics in antiviral medicine, 26(1)

ISSN
2161-5861

Authors
Currier, Judith S
Havlir, Diane V

Publication Date
2018-05-01

Peer reviewed

Invited Review

CROI 2018: Complications of HIV Infection and Antiretroviral Therapy

Judith S. Currier, MD; Diane V. Havlir, MD

This year marked the 25th Conference on Retroviruses and Opportunistic Infections (CROI), and although there is much progress to celebrate in terms of treatment of HIV infection and expanding ART globally, many challenges remain. Tuberculosis is still the leading cause of death among people with HIV infection globally. This year, the results of investments in research to improve the prevention and treatment of tuberculosis were a highlight of the meeting. Noninfectious causes remain an important source of morbidity. Progress in identifying risk factors for non-AIDS complications and improvements in screening and monitoring for such conditions continue to be reported, but to date, despite the efforts of many investigators around the globe, interventions to effectively reduce HIV-related inflammation beyond effective and safer antiretroviral therapy (ART) remain elusive. This section will review highlights of the meeting on tuberculosis and cryptococcal infection as well as complications of long-term ART.

Keywords: HIV, CROI 2018, complications, tuberculosis, cryptococcosis, cardiovascular, antiretroviral therapy, biomarkers, renal, bone, fat

Tuberculosis

Prevention and Scale-up

The results of a phase III, randomized study in which 1 month of treatment with rifapentine plus isoniazid was noninferior to the standard 9 months of isoniazid for tuberculosis (TB) prevention were a highlight of the 2018 Conference on Retroviruses and Opportunistic Infections (CROI) (Abstract 37LB). Based on a body of evidence suggesting a more potent and sterilizing short-course regimen of isoniazid plus rifapentine would be as effective as the current standard of 6 to 9 months of isoniazid for TB prevention, investigators in the AIDS Clinical Trials Group (ACTG) 5279 study recruited 3000 HIV-infected individuals older than 13 years from 10 countries on 4 continents (Asia, Africa, and North and South America) from 2012 to 2014. Participants in this open-label study were randomly assigned to 1 month of daily rifapentine 450 to 600 mg plus isoniazid 300 mg or to 9 months of daily isoniazid 300 mg. Efavirenz-based or nevirapine-based but not protease inhibitor (PI)-based or integrase strand transfer inhibitor (InSTI)-based ART regimens were allowed. Study participants had a baseline median CDsz+ cell count of 470/µL (interquartile range, 346-635/mL), 54% were women, and 50% were receiving ART at baseline. The primary endpoint (TB infection or death) occurred in 34 participants in the 1-month arm and 35 participants in the 9-month arm. Corresponding incidence rates showed that the 1-month regimen was noninferior to the 9-month regimen. The 1-month regimen was better tolerated than the 9-month regimen, as measured by targeted safety events. Elevated transaminases were much more common with the 9-month isoniazid regimen. Rates of treatment completion were higher in the 1-month than in the 9-month arm. In summary, a 1-month regimen of isoniazid plus rifapentine is as effective, better tolerated, and more likely to be completed than a standard 9-month regimen of isoniazid for TB prevention. These data support the 1-month regimen of isoniazid plus rifapentine as a new global option for TB prevention. With the ongoing global transition to dolutegravir for initial ART, widespread implementation of the 1–month regimen of isoniazid plus rifapentine for TB prevention will depend on drug interaction studies to demonstrate that this course can be safely coadministered with dolutegravir-containing ART.

One month of treatment with isoniazid plus rifapentine was as effective as and better tolerated than the standard 9-month isoniazid regimen for TB prevention

Pregnant women have an increased risk of TB infection, and TB can be transmitted and harmful to an infant during pregnancy. However, TB prevention with isoniazid is most often initiated postpartum, potentially missing the opportunity to prevent TB in the vulnerable antepartum period. Gupta and colleagues in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network randomly assigned 956 HIV-infected pregnant women from sites in Africa, Asia, and Haiti to receive isoniazid for TB prevention either at 28 weeks antepartum or 12 weeks postpartum in a double-blind study (Abstract 142LB). The primary study endpoint was maternal adverse events. The

Dr Currier is Professor of Medicine and Chief of the Division of Infectious Diseases and Associate Director of the Clinical AIDS Research and Education (CARE) Center at University of California Los Angeles. Dr Havlir is Professor of Medicine at University of California San Francisco and Chief of the HIV, Infectious Diseases, and Global Medicine Division at Zuckerberg San Francisco General Hospital. Send correspondence to Judith S. Currier, MD, UCLA Care Center, 11075 Santa Monica Blvd, Suite 100, Los Angeles, CA 90025. Received on March 20, 2018; accepted on April 6, 2018.

median CD4+ cell count was 493/μL, and all the women were receiving ART. The primary endpoint occurred in 74 women in the antepartum arm and 73 women in the postpartum arm. Rates of TB infection were low: 3 cases each in the 2 study arms. An unexpected finding from this study was that isoniazid received antepartum was associated with higher rates of adverse pregnancy outcomes (fetal demise, low birth rate infant, preterm labor, and infant congenital anomaly) than isoniazid received postpartum (23% and 17%, respectively; $P = .0009$). Thus, isoniazid for TB prevention was comparably safe for women when given during or after pregnancy. However, fetal and infant outcomes were worse when isoniazid was initiated during pregnancy. Guidelines should be updated to recommend administration of isoniazid postpartum rather than antepartum.

Isoniazid preventive therapy is associated with fewer adverse pregnancy outcomes when given postpartum versus antepartum

Despite overwhelming evidence that isoniazid preventive therapy (IPT) reduces TB burden, countries globally have been slow to scale up prevention services. Karanja and colleagues reported impressive scale up of IPT among HIV-infected persons in care in Kenya—a 50-fold increase from 9981 persons in 2014 to 494,436 persons in 2016 (Abstract 1113). Clinics reported a 90% completion rate among persons prescribed IPT. This success of implementation was attributed to the leadership of the central Ministry of Health, integration of IPT into routine HIV care, and President's Emergency Plan For AIDS Relief (PEPFAR) targets and accountability. If reported IPT completion reflects high adherence and if scale-up continues, declining rates of TB infection among the HIV-infected population in Kenya are expected.

Uptake of TB chemoprevention among children younger than 5 years —a group at high risk for tuberculosis infection—is also poor globally. World Health Organization guidelines changed in 2006 from requiring TB skin testing (TST) to identify IPT candidates to symptom screening only, to reduce the barriers to IPT caused by TST logistics. Saladar-Austin and colleagues conducted a clustered, randomized study in 16 clinics, comparing TST to symptom screening only for identification of IPT candidates in nurse-led decentralized HIV clinics in South Africa (Abstract 32). Of index cases of TB infection, 1097 child contacts (550 in the symptom screening arm and 547 in the TST arm) were identified. Overall, there was no difference in IPT initiation between the 2 groups (51.4% in the symptom screening arm vs 54.6% in the TST arm). Rates of IPT completion in childhood contacts were low, at 9% overall in the study. These data emphasize that past and current approaches to TB prevention measures for children at high risk are inadequate and that new approaches are urgently needed.

TB Diagnostic and Case-Finding Strategies

Failure to rapidly diagnose TB among persons with advanced HIV disease, who often have disseminated disease without detectable TB on sputum microscopy, contributes to high mortality rates. Gupta-Wright and colleagues tested the hypothesis that rapid urine TB screening tests (urine lipoarabinomannan [LAM] or Xpert MTB/RIF, which identifies Mycobacterium tuberculosis (MTB) and rifampin (RIF) resistance) added to sputum Xpert MTB/RIF testing, the standard of care (SOC), would reduce mortality by allowing for more rapid identification and treatment of TB infection (Abstract 38LB). The STAMP (Rapid Urine-Based Screening for Tuberculosis to Reduce AIDS-Related Mortality in Hospitalized Patients in Africa) study randomly assigned 2600 HIV-infected, hospitalized persons (72% on ART) in South Africa and Malawi to SOC TB screening or SOC screening plus rapid urine TB screening. Clinicians were informed if any test results were positive for TB, but they were blinded to the randomized arm. Overall mortality rate was 20% at 56 days, and mortality risk difference did not differ between study arms (21.1% vs 18.3%, respectively). However, in 3 prespecified subgroups (persons with a CD4+ cell count <100/μL, hemoglobin level <8 mg/dL, or clinical suspicion of TB infection at baseline), risk differences in mortality were 5.7% to 9.0% lower among those who had urine screening plus SOC screening than those who had SOC screening only. Rate of TB diagnosis was statistically significantly higher in those who had urine screening plus SOC screening than those who had SOC screening only (21.9% vs 14.9%, respectively). In a related study, incorporating rapid urine TB screening tests was cost-effective and was associated with increased life expectancy (Abstract 1117LB). These results call for scale-up and implementation of rapid urine and Xpert MTB/RIF screening tests in hospitalized individuals at high risk for TB infection.

Adding rapid urine diagnostic tests for TB screening to standard sputum evaluations reduced mortality among high-risk hospitalized individuals in South Africa and Malawi

High mortality rates are observed among individuals presenting with CD4+ cell counts below 100/μL, even with more sensitive TB diagnostics. If high mortality rates are attributable to missed TB cases, empiric TB treatment could reduce mortality rates. The STATIS (Systematic Empirical vs Test-Guided Anti-TB Treatment Impact in Severely Immunosuppressed HIV-Infected Adults Initiating ART With CD4 Cell Counts <100/mm^3) study randomly assigned 1047 HIV-infected persons in Cote d'Ivoire, Uganda, Cambodia, and Vietnam to extensive TB screening (Xpert MTB/RIF sputum, urine LAM, and chest x-ray) or to empiric TB treatment (Abstract 29LB). All participants not infected with TB received immediate ART. At 24 weeks, there was no difference between the 2 study

arms in mortality rate, presence of invasive bacterial disease, or the combined endpoint. More TB cases were diagnosed in the arm that underwent extensive TB screening (17.7%) than in the arm that received empiric TB treatment (2.6%). This study confirms and extends the findings of a prior study[2] that failed to demonstrate mortality-related benefits of empiric TB versus IPT among individuals with low CD4+ cell counts.

Another approach to reducing TB-related mortality is to find and treat contacts of persons with TB infection. In Botswana, during the rollout of sputum Xpert MTB/RIF testing to replace sputum microscopy, an enhanced TB case–finding strategy was implemented that included contact tracing and intensified tracking for TB-infected individuals with missed visits in half of the 22 participating clinics (Abstract 31). Among 14,963 individuals, the 12-month mortality rate was lower with enhanced TB case finding with or without Xpert MTB/RIF testing than with preintervention. This study highlights that efforts to reduce rates of TB mortality should include intensified TB case finding and treatment.

TB Treatment and Adherence

Rifamycins are a cornerstone of TB treatment. Recent data suggest that higher doses of rifamycins may decrease time to culture conversion during TB treatment. Velasquez and colleagues conducted a randomized phase II study among 180 smear-positive, drug-susceptible, TB-infected persons to evaluate treatment efficacy (microbiologic response) and drug-related toxic effects of rifampin 10 mg/kg, 15 mg/kg, or 20 mg/kg during an 8-week TB treatment induction phase (Abstract 39LB). Faster declines in microbiologic measures were observed with higher doses of rifampin. Grade 2 adverse events were common and were similar across study arms (38.3%-51.7%). Of note, serious rifampin-associated adverse events were rare: a total of 4 study participants among the 3 arms. These data justify future study of higher doses of rifampin to potentially shorten and improve TB treatment.

Estimates of adherence guide the duration of TB therapy. Dosing of TB treatment is currently measured through directly observed therapy (DOT) that is resource intensive, of unknown accuracy, and variably implemented outside of a clinical trial setting. Browne and colleagues randomly assigned 61 TB-infected persons in the continuation phase of TB treatment to DOT or wirelessly observed therapy (WOT), in which isoniazid and rifampin is coformulated with an edible digital sensor accompanied by an external wearable patch and paired mobile device that can track medication ingestion remotely (Abstract 782). A statistically significantly greater percentage of prescribed doses were confirmed with WOT than DOT. More research is need to determine the effect of WOT on clinical outcomes in TB treatment programs.

Rifamycin and Antiretroviral Drug Interaction Studies

Metabolic pathways of rifamycins interact with InSTIs, nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), tenofovir alafenamide (TAF), and PIs, requiring drug interaction, genomic, and confirmatory clinical studies to ensure the safety and efficacy of coadministration of HIV and TB treatments. Levels of InSTIs are lowered when coadministered with rifampin. In a 24-week interim evaluation, investigators from the INSPIRING study compared clinical and safety outcomes in TB-infected individuals receiving efavirenz 600 mg daily plus 2 nucleoside analogue RTIs (nRTIs) or dolutegravir 50 mg twice daily plus 2 nRTIs (Abstract 33). Rates of virologic suppression among participants were similar between the 2 study arms, and plasma dolutegravir levels with twice-daily dosing during TB treatment were similar to dolutegravir 50 mg daily without rifampin.

In persons treated for TB infection, double-dose dolutegravir–based ART maintained therapeutic dolutegravir concentrations and had similar levels of viral load suppression compared with efavirenz-based therapy

To determine if twice-daily dosing of the InSTI bictegravir might overcome reduced levels observed when this drug is coadministered once daily with rifampin, investigators conducted a pharmacokinetic study comparing coformulated (/) bictegravir/emtricitabine/TAF twice daily plus rifampin with bictegravir/emtricitabine/TAF once daily in uninfected volunteers (Abstract 34). Bictegravir levels were reduced by 80% when coadministered with rifampin, with levels in some participants falling below minimal targeted concentrations for efficacy. More studies are needed to define optimal dosing for this combination.

Similarly, serum TAF levels are reduced when coadministered with rifampin. The interaction between TAF and rifampin was measured by examining intracellular levels—a key determinant of drug efficacy—of the active TAF metabolite in 17 uninfected volunteers (Abstract 28LB). In the presence of rifampin, intracellular levels of active TAF metabolites were decreased by approximately 40% but were still 82% higher than those achieved with standard dosing of tenofovir disoproxil fumarate (TDF). These results are encouraging and call for continued study and monitoring of clinical outcomes of this combination.

In a study evaluating interactions between efavirenz and rifapentine, Podany and colleagues evaluated the effects of rifapentine on efavirenz levels (Abstract 455). Among 23 individuals receiving daily rifapentine in the ACTG 5279 trial of short-course TB prevention, efavirenz levels remained in therapeutic range.

If countries plan to widely implement efavirenz 400 mg for ART, including among TB-infected persons, it is important to demonstrate that levels of efavirenz remain in therapeutic range when coadministered with rifampin. In a small study of 22 persons not infected with TB who were receiving rifampin and efavirenz 400 mg/TDF/emtricitabine, efavirenz levels

were lowered but remained in therapeutic range (Abstract 457). Larger studies are needed, including among TB-infected persons, if this combination is to be utilized.

Examining the possibility that higher doses of rifampin might become a part of TB regimens, Atwine and colleagues evaluated efavirenz levels with increased rifampin dosing (Abstract 456). Rates of viral suppression were high among TB-infected persons receiving double doses of rifampin with efavirenz 600 mg or 800 mg daily compared with persons receiving efavirenz 600 mg without rifampin (Abstract 456).

Lopinavir/ritonavir and rifabutin remains an important combination for TB treatment. In a randomized trial of the pharmacokinetics and efficacy of rifabutin among 21 individuals in Thailand, rifabutin 150 mg daily and rifabutin 300 mg thrice weekly were safe and effective among those receiving lopinavir 400 mg/ritonavir 100 mg twice daily (Abstract 781).

Cryptococcal Disease

Screening and Treatment for Cryptococcal Antigenemia

Nalintya and colleagues implemented and evaluated a cryptococcal screening and treatment program in 11 clinics in Kampala, Uganda, that tested reflexively for cryptococcal antigen (CrAg) from all samples with CD4+ cell counts below 100/μL (Abstract 785). Preemptive fluconazole treatment and ART were offered for asymptomatic CrAg-positive individuals. Amphotericin B was used for treatment of symptomatic cryptococcal disease. The prevalence of CrAg was 6.5% among 1446 persons. Seven persons died prior to clinical evaluation. Among the 53 persons with asymptomatic cryptococcal disease, the mortality rate was 13% at 6 months. Among the 26 persons with documented cryptococcal meningitis, the mortality rate was 44%. Even with optimized CrAg screening and treatment programs, mortality due to cryptococcosis or other AIDS-related illness remains high among persons in care with CD4+ cell counts below 100/μL and cryptococcal antigenemia.

To provide insight into the excess mortality rates observed among persons taking fluconazole for asymptomatic cryptococcal disease, even when treated with fluconazole and ART, Wake and colleagues performed minimally invasive autopsies on 4 persons with asymptomatic cryptococcal disease and 2 persons with advanced HIV disease and no detectable serum CrAg in a cohort study in South Africa (Abstract 788). At autopsy, all 4 persons with detectable CrAg at cohort entry had evidence of central nervous system (CNS) disease, and the 2 persons with advanced HIV disease did not. Current approaches to treatment of asymptomatic cryptococcal disease likely underestimate the burden and extent of disease, contributing to poor outcomes even among persons treated with fluconazole.

In the REALITY (Reduction of Early Mortality in HIV-Infected African Adults and Children Starting ART) study, which included an enhanced cryptococcal disease prevention regimen that included empiric fluconazole and did not require a positive result for serum CrAg, investigators evaluated baseline CrAg status from stored plasma specimens (Abstract 784). Rates of cryptococcal disease at 24 weeks among those who were CrAg positive at baseline were 20.3% (no fluconazole arm) and 7.8% (fluconazole arm). Rates among those who were CrAg negative were 0.4% (no fluconazole arm) and 0.1% (fluconazole arm). Thus, there was a reduction in new cases of cryptococcal meningitis among persons prescribed fluconazole, regardless of whether CrAg was detected at baseline. The investigators suggest that fluconazole be given to all persons with low CD4+ cell counts—not just those with detectable CrAg—in settings with a high burden of cryptococcal disease, as part of a comprehensive prevention package.

Treatment for Cryptococcal Meningitis

Sertraline, shown to have in vitro and in vivo activity against *Cryptococcus*, was evaluated as adjuvant therapy to amphotericin B–containing treatment for cryptococccal meningitis in a double-blind randomized study of 550 individuals (Abstract 36). The study was prematurely discontinued for futility after enrollment of 460 participants because mortality rates were similar between the 2 arms. Even in this optimized clinical trial setting, overall mortality rates were 52% in the sertraline group and 46% in the placebo group.

Of historical interest, high-dose oral fluconazole 1200 to 2000 mg daily was evaluated in a dose escalation study as induction treatment for cryptococcal meningitis (Abstract 35). Persons who received fluconazole 1600 or 2000 mg had better microbiologic outcomes than those who received fluconazole 1200 mg. Overall mortality rates were more than 30% among persons receiving all doses of fluconazole and 24% among those receiving amphotericin B, supporting current guidelines for low- and middle-income countries (LMIC) that no longer recommend fluconazole alone as induction therapy for cryptococcal disease.

Non-AIDS Complications

Sabin reviewed evidence demonstrating that life expectancy among persons with HIV disease is on the rise (Abstract 102). In some studies, the life expectancy of people with treated HIV infection is near that of the general population, especially among those who initiate ART early, when CD4+ cell counts are high, and among those who do not inject drugs. She pointed out the importance of measuring "health span" and not just life years, to capture the quality of life and the impact of comorbid conditions, an important concept for future studies in this area.

Biomarkers to Predict Non-AIDS Events

The field of HIV medicine continues to examine biomarkers that will identify which individuals with treated HIV infection are at greatest risk for non-AIDS events. Baker and colleagues

from the START (Strategic Timing of Antiretroviral Treatment) trial examined the proportion of ART effect (clinical benefit in reducing events) explained by individual and combinations of the biomarkers interleukin (IL)-6, D-dimer, and CD4+ and CD8+ cell counts at baseline and at month 8 after starting ART (Abstract 74). The CD4+:CD8+ ratio explained most of the treatment effect (20%), IL-6 and D-dimer were additive, and all 3 explained 29% of the treatment effect. These results again demonstrate the potential value of the CD4+:CD8+ ratio as a marker of disease progression and highlight that there is no single biomarker that explains a major portion of the treatment effect.

The drivers and sequelae of CD8+ cell expansion in treated HIV disease remain an active area of investigation. Freeman and colleagues used flow cytometry to compare the populations of CD8+ cells in HIV-infected individuals on ART with those in HIV-negative controls after stimulation with different cytokines (Abstract 222). In the HIV-infected group, IL-15 but not IL-2 induced the generation, proliferation, and survival of a population of senescent CD8+ cells (CX3C chemokine receptor 1 [CX3CR1] + CD57+), the presence of which may be important for the development of cardiovascular complications. These findings were further expanded in work by the same group using aortic endothelial tissue samples from a simian-human immunodeficiency virus (SHIV) nonhuman primate model of atherosclerosis atherosclerosis (Abstract 241). The investigators observed elevated expression of CX3C motif chemokine ligand 1 (CX3CL1) and IL-15 in the vascular endothelium of SHIV/simian immunodeficiency virus (SIV)-infected rhesus macaques and that endothelial cells from these tissues could produce CX3CL1 and IL-15 in vitro, resulting in enhanced CD8+ cell migration to the endothelium.

A higher incidence and greater progression of high-risk (low-attenuation, noncalcified) plaque was demonstrated in HIV-seropositive men than in controls

Whether interventions currently being tested to reduce the risk of cardiovascular disease (CVD) (eg, statins or other immune modulators) reduce IL-15 levels and influence populations of activated, senescent CD8+ cell populations remains to be determined.

In a novel analysis, Kusejko and colleagues examined associations between viral HIV-1 polymerase sequences and the occurrence of comorbidities among participants in the Swiss Cohort Study and found evidence of phylogenetic clustering among participants who experienced some HIV-related complications (Kaposi sarcoma, HIV-related thrombocytopenia, and HIV-related encephalopathy), suggesting a potential role for viral genetic factors in mediating these outcomes (Abstract 169). Of note, non-AIDS complications such as CVD appeared more related to demographic and clinical confounders than viral factors.

Cardiovascular Disease

Cardiovascular complications remain an important cause of potentially preventable morbidity and mortality in individuals with treated HIV infection. Identifying the pathogenesis of CVD and the contributions of traditional and HIV-specific risk factors remains a high-priority area of research. Post and colleagues in the Multicenter AIDS Cohort Study (MACS) reported the results of a longitudinal study using computed tomography (CT) angiography among middle-aged men (mean age, 54 years) with HIV infection compared with controls (Abstract 77). With a median interval of follow-up between CT scans of 4.5 years, investigators measured the presence, quality, and progression of coronary artery plaque in a group of men in their mid-fifties. There was a higher incidence and greater progression of high-risk (low-attenuation, noncalcified) plaque in the HIV-infected men than in controls. Of note, viremia was an important risk factor for plaque progression, underscoring the importance of optimizing ART as an intervention to reduce the risk of atherosclerosis in HIV disease.

Carotid artery intima-media thickness (cIMT) measured by ultrasound has been used as a surrogate measure of atherosclerosis in HIV studies because it is low cost, reproducible, and widely available. When cIMT is used, data are collected on the thickness of arterial segments, the presence of carotid plaque, and measures of arterial stiffness (referred to as Young's modulus of elasticity). Investigators from the Women's Interagency HIV Study (WIHS) and the MACS pooled data on cIMT in a large sample of HIV-seropositive and -seronegative men and women, to examine whether these measures predicted mortality in this group, and found that the presence of plaque and the measure of elasticity, but not common cIMT, were associated with mortality in HIV-seropositive and -seronegative persons (Abstract 78). These findings highlight the importance of studies that evaluate the impact of interventions on these measures.

Most studies of CVD in the context of HIV disease have focused on coronary artery disease (CAD) and to a lesser extent heart failure and arterial stiffness. This year, a group from Denmark reported on the prevalence of peripheral artery disease in a cohort of people older than 40 years who had HIV infection compared with a larger cohort from the general population (Abstract 76). Peripheral artery disease (PAD) was assessed by Doppler test, ankle brachial index was calculated, and symptoms of claudication were collected by self-report. The study found a higher prevalence of PAD in the HIV-infected group (12%) than in the control group, even after adjustment for the higher rate of smoking in the HIV-infected group as well as other factors. The investigators found no evidence that HIV disease severity or duration of ART were associated with the prevalence of PAD. Further studies are needed to determine whether rates of progression and response to treatment of PAD differ in those with HIV infection.

Antiretroviral Therapy and Cardiovascular Disease

CROI 2018 featured studies examining the associations between individual antiretroviral drugs and CVD, 10 years

after the first reports of a link between abacavir and CVD risk. Of reported associations between antiretroviral drugs and CVD, the reversible association between abacavir exposure and myocardial infarction (MI) risk remains of greatest interest. The search for a mechanism between abacavir exposure and MI risk has led several groups to examine the role of platelet function. Measures of platelet reactivity are difficult to perform due to the need for immediate testing of fresh blood samples. Mallon and colleagues utilized the design of a randomized switch study to embed evaluations of platelet and endothelial function in participants who were randomly assigned to switch or continue the abacavir component of their ART regimen (Abstract 677LB).

In the first report, 61 virally suppressed, HIV-infected individuals taking abacavir/lamivudine randomly assigned to switch to TAF/emtricitabine or remain on abacavir/lamivudine had measurements of platelet aggregation at baseline, week 4, and week 12 in response to concentrations of 5 agents known to stimulate platelet reactivity: collagen, thrombin receptor-activating peptide (TRAP), adenosine diphosphate (ADP), epinephrine, and arachidonic acid. Participants who switched from abacavir/lamivudine to TAF/emtricitabine experienced an improvement in platelet reactivity in response to the agonists TRAP and ADP at week 4, and collagen through week 12. A rise in the surface expression of glycoprotein VI (GPVI) was also reported.

The second report from this group focused on the measurement of soluble (s)GPVI in 545 participants from the same switch study. Measurements of sGPVI in platelet-poor plasma taken at weeks 0, 4, 12, 24, and 48 were obtained using electrochemiluminescence. Participants who switched from an abacavir-containing regimen to a TAF/emtricitabine-containing regimen experienced statistically significantly greater increases in sGPVI to week 48, with a 14.7% increase (95% CI; 4.1, 26.3) between groups. The greater increases in sGPVI after a switch from abacavir/lamivudine to TAF/emtricitabine were interpreted as evidence of an improvement in a reversible defect in platelet function.

The clinical studies by Mallon and colleagues align with the findings of Taylor and colleagues who performed in vitro experiments with abacavir, TDF, and TAF in the absence of HIV infection in which they noted that abacavir substantially enhanced expression of platelet activation markers, whereas TAF and TDF had no effect (Abstract 673). Work presented by a Spanish group (Abstract 674) using a mouse model of arterial thrombosis suggested that leukocytes were necessary to observe the thrombotic properties associated with abacavir exposure in their model. Taken together, these studies suggest a mechanism by which abacavir could potentiate the risk of MI. Confirmatory studies of changes in platelet measures among people initiating therapy with abacavir would be valuable to determine risk factors for these changes.

Kovari and investigators from the Swiss Cohort Study examined associations between ART exposure and coronary plaque using coronary artery calcium scoring and CT angiography among 428 participants, predominantly men (Abstract 670). Cumulative atazanavir exposure was associated with calcified plaque, whereas abacavir exposure was associated with noncalcified plaque after adjustment for CAD risk factors. Previous studies have suggested a reduced risk of MI associated with atazanavir exposure, and the possible role of residual confounding in this type of analysis should be acknowledged.

Interventions to Reduce Inflammation in HIV

Low-dose methotrexate has been used to treat chronic inflammation in rheumatoid arthritis, and epidemiologic data suggest a reduction in CVD events when the drug is used in this context. A large clinical endpoint study of weekly low-dose methotrexate is ongoing in the general population and excludes people with HIV disease. Hsue and colleagues performed a randomized trial to evaluate the safety and activity of low-dose methotrexate in individuals with treated HIV infection and risk factors for CAD (Abstract 79). The study enrolled 176 participants, mostly men, with a median age of 54 years and well-suppressed HIV infection.

Measures of inflammation, T-cell activation, and flow-mediated dilation of the brachial artery were assessed and read centrally. During 24 weeks of randomized treatment, safety events (eg, mostly CD4+ cell count decline and infections) were more common among those receiving low-dose methotrexate (12.8% vs 5.6%), but the difference between study arms did not exceed a 15% prespecified margin. No differences in soluble markers of inflammation or flow-mediated dilation were noted by treatment group; however, there was a statistically significant decrease in CD8+ cell activation in the group receiving low-dose methotrexate. In a substudy by Tawakol and colleagues, fluorodeoxyglucose (FDG)– positron emission tomography (PET) scans were performed on a subset of the participants, and there was evidence of reduced arterial inflammation among those receiving low-dose methotrexate (Abstract 684LB). Given the high rate of safety events among those receiving low-dose methotrexate, further studies of this intervention will need to await the findings of the larger ongoing study in the general population.

In addition to the focus on activated CD8+ cells and non-AIDS events, there continues to be intense interest in the role of activated monocytes in the pathogenesis of non-AIDS complications. Mallard and colleagues performed novel studies using ART plus methylglyoxal-bis-guanylhydrazone (MGBG; a polyamine biosynthesis inhibitor that targets myeloid cells) compared with ART alone or no treatment in a SIV-infected macaques model that included measures of CNS infection and atherosclerosis via cIMT (Abstract 421). The animals treated with the combination of MGBG and ART were less likely to have CNS SIV infection and had less cIMT thickening compared with ART alone or no ART. Whether it will be feasible and safe to block myeloid cell activation in humans remains to be demonstrated, but these studies pave the way for future interventions targeting this pathway.

Dietary interventions to reduce dyslipidemia in the context of HIV disease have reported mixed results. Stradling and colleagues conducted a pilot randomized trial that enrolled adults with stable HIV infection and elevated low-density

lipoprotein (LDL) cholesterol and compared a diet low in saturated fat with a Mediterranean diet that included plant stanols, soy, oats, nuts, and fish (Abstract 703). The study population included 60 adults, 50% of whom were women. After 6 months, those who ate a Mediterranean diet experienced a greater decline in LDL cholesterol and improvement in blood pressure than those who ate a low-fat diet. As is often seen in dietary intervention studies, adherence to the diet varied widely. No differences were noted in body composition, arterial stiffness, or gut function. These results confirm the potential benefits of a Mediterranean diet if people can adhere to it.

Although it is unknown whether guidelines for statin use should differ for people with HIV infection, most experts agree that the guidelines for the general population are reasonable to follow. Adherence to statin guidelines developed for the general population among people with HIV infection remains an area of great interest in various health care settings. Data from the US Military HIV Natural History Study were used to examine adherence to statin guidelines within a health system in which access to care is less constrained (Abstract 705). Using the 2013 American College of Cardiology/American Heart Association guideline[1] the investigators examined the proportion of eligible participants who received statin therapy between 2015 and 2016. Only 55% of eligible participants with HIV infection received a statin, and 58% of those had diabetes. Persons who were older, white, or taking a PI were more likely to receive statins. These results highlight the fact that even within a single payer system, disparities in care persist, as well as the work needed to improve primary health care for people with HIV infection.

Just more than half of statin-eligible patients received statin therapy in a single payer health care system

Renal Disease

Renal disease is a well-described complication of HIV infection and ART, most notably with tenofovir disoproxil fumerate (TDF). Whether the occurrence of kidney disease portends a higher risk for future clinical events is less well understood. Using data from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, Ryom and colleagues examined the rates of serious clinical events among participants who experienced confirmed chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 or a 25% decrease in eGFR in those with a starting eGFR of less than 60 mL/min/1.73 m^2 (Abstract 75). The investigators reported higher rates of death and serious clinical events among people who had CKD compared to those who did not have CKD. These findings, although unsurprising, highlight the need for closer monitoring of individuals once an episode of CKD occurs, and underscore the need for close attention to modifiable risk factors (eg, smoking) for future serious events, as well as the importance of controlling HIV infection.

Renal transplantation is not accessible for some individuals with HIV infection. In a large French study that matched HIV-seropositive persons receiving renal replacement therapy to HIV-seronegative controls (Abstract 728). Two years after initiating renal replacement therapy, 46% of the HIV-infected group had been placed on a waiting list for transplant compared with 64% of controls. Although improvements over time in rates of renal transplantation were observed in the HIV-infected group, access to transplantation for this group remains delayed.

Fat

There is continued interest in the interplay between fat, inflammation, and metabolic health. In addition to the quantity of fat, the quality of fat tissue likely plays an important role. Two studies examined fat quality, using CT scans, and its relationship to metabolic health outcomes (Abstracts 736, 737). On CT scans, small adipocytes appear denser than larger, less healthy adipocytes. Using data from the ACTG 5224s trial, investigators reported gains of visceral and subcutaneous adipose tissue over 96 weeks of ART and a correlation between fat density and measures of inflammation (Abstract 737). Decreases in density of visceral adipose tissue correlated with increases in IL-6 and soluble tumor necrosis factor–α receptor type II, suggesting that the quality of the fat gained was metabolically unhealthy. Using data from completed trials of the growth hormone–releasing factor tesamorelin, Lake and colleagues observed an improvement in fat density (increased density) among those receiving tesamorelin compared with placebo (Abstract 736).

The HIV UPBEAT (Understanding the Pathology of Bone Disease in HIV-Infected Patients) study is a longitudinal assessment of body composition in a group of participants with treated HIV infection compared with an HIV-uninfected control group (Abstract 733). This study addresses the important issue of whether changes in fat and lean body mass observed in those with HIV infection are caused by HIV infection, ART, or the aging process. Each demographically matched group of participants observed increases in arm fat and lean mass over time. These findings provide reassurance that the changes in body composition observed after initiation of ART may not persist over longer-term follow-up, compared with age-matched controls.

Changes in body composition observed after initiation of ART may not persist over longer term follow-up

Bone

Bone loss after the initiation of ART has been well described. What is less clear is whether this persists over longer follow up.

In the results from the bone substudy of the START trial, Carr and colleagues reported the rate of bone loss over 5 years in persons who initiated ART immediately compared with those who deferred until their CD4+ cell count dropped below 350/µL (Abstract 722). Bone mineral density (BMD), measured by dual-energy x-ray absorptiometry (DEXA), dropped more in the group that received immediate ART, over the first year of the study, even after controlling for TDF use. After the first year, rates appeared similar in the 2 groups, suggesting that the rate of bone loss slows after the first year of ART. Such early changes in BMD during ART may have more important consequences for pregnant women initiating therapy, as reported by Nabwire and colleagues (Abstract 721). Interventions to mitigate bone loss include discontinuing TDF, or the use of bisphosphonates (eg, zoledronic acid) to reduce bone resorption. In a follow-up report to a clinical trial that demonstrated that the use of zoledronic acid was more effective than discontinuing TDF, measures of bone turnover showed that bisphosphonate use was associated with a greater reduction in bone turnover than TDF discontinuation (Abstract 723). Pooled data from completed switch studies in which participants changed from a TDF- to a TAF-containing regimen examined changes in BMD and bisphosphonate use over time. The results suggest that both interventions improved BMD but highlight that individuals who both switched to a TAF-containing regimen and added a bisphosphonate had greater improvement in BMD in the spine but not the hip (Abstract 724). The optimal strategy for improving bone density after TDF use is yet to be defined.

Exercise and Functional Status

A randomized controlled trial of an exercise intervention among HIV-infected, sedentary adults aged 50 to 75 years who were virally suppressed found that those randomly assigned to high-intensity exercise showed greater gains in strength than did HIV-seronegative controls. These findings underscore the potential benefits of exercise as a scalable intervention to reduce long-term comorbidities in HIV infection.

All cited abstracts appear in the CROI 2018 Abstracts eBook, available online at www.CROIconference.org

Financial affiliations in the past 12 months: Dr Currier has received research grants awarded to her institution from Theratechnologies. Dr Havlir has no relevant financial affiliations to disclose.

Additional References Cited in Text

1. American College of Cardiology and American Heart Association. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. http://www.onlinejacc.org/content/accj/63/25_Part_B/2889.full.pdf?_ga=2.142815221.1185323657.1522185592-464558588.1522185592. Accessed on March 27, 2018.
2. Hosseinipour MC, Bisson GP, Miyahara S, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet*. 2016;387(10024):1198-1209.

Top Antivir Med. 2018;26(1):22-29.