Review

CROI 2015: Complications of HIV Infection and Antiretroviral Therapy

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

Noncommunicable diseases, such as cardiovascular disease, hypertension, renal and bone disease, and malignancies are an ongoing concern during the course of treated HIV disease. Research in this area continues to focus on the epidemiology and risk factors associated with these conditions, identifying the contributions of HIV-related immunopathology to specific and collective end-organ diseases, and evaluating interventions to prevent or reduce the morbidity associated with these conditions. Infectious complications of HIV, such as tuberculosis and cryptococcal disease, also continue to cause substantial morbidity and mortality; diagnosis, prevention, and treatment of these is an area of focus. The 2015 Conference on Retroviruses and Opportunistic Infections provided new insights into all of these areas.

Burden of Disease

At the 2015 Conference on Retroviruses and Opportunistic Infections (CROI), held from February 23 to 26, trends in age-adjusted rates of hypertension, diabetes, and chronic kidney disease were examined by Wong and colleagues from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) (Abstract 1053). Rates of all 3 conditions increased with each decade after age 40 years, with the highest rates among blacks of all ages and among older adults. These findings underscore the importance of primary care services for all adults with HIV infection.

Chronic noncommunicable diseases are not limited to people residing in high-income settings. In addition, the excess risk of these conditions that is attributable to HIV disease has not been well studied in low- and middle-income settings. In the massive, multidisease screening campaign SEARCH (Sustainable East Africa Research of Community Health) underway in Uganda, blood pressure measurements were obtained for 65,274 adults from 20 rural communities. The overall prevalence of hypertension was 15.6% after age standardization. Expected associations between age, male sex, higher body mass index (BMI), and alcohol use and higher risk of hypertension were observed. Notably, the adjusted relative odds ratio of hypertension was 1.2 times higher for HIV-seronegative than -seropositive individuals. Among the group with HIV infection, the rate of hypertension was 10.2%; viral suppression did not predict hypertension, and slightly more than half achieved control of blood pressure with treatment. These results suggest that HIV may not contribute to an excess risk for hypertension.

As highlighted above, traditional risk factors contribute most to the risk for hypertension, and the role of specific antiretroviral drugs as contributors to hypertension remains controversial. D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study investigators examined data on more than 30,000 people to address this question, and they confirmed that established risk factors rather than antiretroviral drugs predict hypertension risk (Abstract 739). Regardless of whether HIV infection augments hypertension risk, optimal strategies for treatment of hypertension for those with HIV infection will still be needed. Among 10-year survivors taking antiretroviral therapy who were followed up in Haiti, 25% had 1 or more noncommunicable diseases (58% hypertension, 3% diabetes, and 39% chronic lung disease) (Abstract 156).

Inflammatory Biomarkers and End-Organ Disease and Mortality

Elevations in interleukin (IL) 6, soluble CD14 (sCD14), and d-dimer levels are prevalent during treated HIV disease and have been shown to be strong predictors of mortality. An analysis done by Veterans Affairs investigators examined mortality in a group of HIV-infected individuals compared with -uninfected controls, to attempt to delineate the contributions of these biomarkers and their independence from HIV RNA level in predicting mortality. After adjusting for age, race, and other comorbidities, HIV RNA levels and these biomarkers (IL-6, sCD14, and d-dimer) remained independent predictors of mortality. These results support the hypothesis that inflammation contributes to mortality in HIV infection (Abstract 1049). The relative strength of the association between

Dr Havlir is Professor of Medicine at University of California San Francisco (UCSF) and Chief of the HIV/AIDS Division at San Francisco General Hospital. Dr Currier is Professor of Medicine, Chief of the Division of Infectious Diseases, and Co-Director of the Clinical AIDS Research and Education (CARE) Center at University of California Los Angeles. Send correspondence to Diane V. Havlir, MD, San Francisco General Hospital, 995 Potrero Avenue, UCSF Box 0872, San Francisco, CA 94110. Received on March 16, 2015; accepted on March 17, 2015. .

IL-6, high-sensitivity C-reactive protein (hsCRP), and d-dimer and clinical events was further investigated in a study combining data from the control arms (those who received only antiretroviral therapy) of the SMART (Strategies for Management of Antiretroviral Therapy) and ESPRIT (Evaluate Recombinant Interleukin-2 in HIV-Positive Patients Taking Antiretroviral Therapy) trials (Abstract 761). Independently, IL-6 level was a stronger predictor of mortality than other measures, especially for non-AIDS mortality, whereas d-dimer level was a stronger predictor of progression to AIDS. Whether interventions directed at reducing IL-6 level will alter the course of HIV disease remains to be shown.

sCD14 is a measure of monocyte activation that has been associated with all-cause mortality and progression of atherosclerosis in treated HIV infection.[1,2] Previous studies have suggested that daily acyclovir use reduced the risk of progression of HIV infection; however, the mechanism is unclear. Using stored samples from earlier studies of acyclovir in HIV-infected women, researchers identified that acyclovir use was associated with faster declines in sCD14, suggesting that a reduction in monocyte activation may be the mechanism of action of the acyclovir effect previously observed (Abstract 321). sCD163, a scavenger receptor expressed by monocytes and macrophages that is shed when these cells are activated, has been linked to vascular disease risk in HIV-infected and -uninfected patients.[3] Cytomegalovirus (CMV) coinfection is a candidate mediator of the excess inflammation observed during treated HIV infection. Investigators from the ICONA (Italian Cohort of Antiretroviral Naive Patients) study examined the relationship between CMV coinfection and measures of inflammation, noting that those with CMV coinfection had higher levels of sCD163, whereas although sCD14 levels were higher in the coinfected group, the difference did not reach statistical significance (Abstract 303). They also noted a strong correlation between the level of sCD163

and anti-CMV immunoglobulin G (IgG) levels. A correlation between anti-CMV IgG and higher levels of sCD14 was also noted, in another report comparing patients with CMV-associated end-organ disease with controls. (Abstract 302) These findings add to growing literature suggesting that persistent CMV infection may be an important driver of inflammation in treated HIV disease.

MACS (Multicenter AIDS Cohort Study) investigators used an exploratory factor analysis to examine the relationship between a panel of biomarkers of inflammation, in an attempt to sort out the underlying inflammatory pathways that contribute to decline in renal function among treated and virologically suppressed individuals. sCD14 emerged among the group of measures (including soluble tumor necrosis factor receptor 2 [sTNF-R2], sIL-2 receptor, soluble glycoprotein [sgp]130, and sCD27) that were associated with a decline in kidney function, whereas IL-6, IL-8, and TNF-α were not associated with this outcome (Abstract 797).

Whether antiretroviral therapy regimens differ in their impact on biomarkers of inflammation during initial treatment remains an open question. Hileman and colleagues reported that the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir led to a greater decrease in sCD14 and lipoprotein-associated phospholipase A2 [Lp-PLA2] levels over a period of 48 weeks than did efavirenz, emtricitabine, and tenofovir; no differences were noted in the impact of these regimens on IL-6, sTNF-R1, or sCD163 levels (Abstract 738). The clinical significance of the magnitude of the decline in sCD14 level (approximately 10%) in the group that received elvitegravir is unknown but warrants longer-term follow-up.

Cardiovascular Disease

Pathogenesis of Cardiovascular Disease in HIV

Two elegant studies examined the pathogenesis of cardiovascular disease

(CVD) in HIV infection using animal models and human tissue samples. Panigrahi and colleagues used the simian immunodeficiency virus (SIV) rhesus macaque model to examine the role of endothelial factors in atherosclerosis. In this study, investigators compared paraffin-embedded slides from the aortas of SIV-infected and -uninfected animals with staining for the endothelial factor Krüppel-like factor 2 (KLF2), a transcriptional master regulator that promotes an antithrombotic endothelial environment and endothelial nitric oxide synthase (eNOS) (Abstract 298LB). They observed focal endothelial proliferation and infiltration of monocytes, T lymphocytes, and platelets in 3 of the 4 SIV-infected animals, but in none of the controls. They also found reduced levels of eNOS and KLF2 in the SIV-infected group. Further, in experiments using cultured primary endothelial cells, the investigators noted that simvastatin could protect against the down regulation of KLF2, further supporting a potential beneficial role for statins in preventing CVD in the setting of HIV infection.

Walker and colleagues, using human tissue samples of the aorta and left ventricle in 10 HIV-seronegative and 10 -seropositive individuals with CD4+ counts less than 200 cells/µL, reported an increased number of macrophages in aortic tissue in the HIV-seropositive group compared with controls, and a strong correlation between increased numbers of CD163+, CD68+, MAC387+, and CD206+ macrophages and the percentage of collagen (fibrosis) in ventricular tissue in the HIV–seropositive group (Abstract 753). They also deployed the novel radioisotope tilmanocept in a probe that binds to CD206+ and CD163+ macrophages to demonstrate the presence of these macrophages in tissue sections. This probe is currently used as a diagnostic imaging agent in vivo in patients with head and neck cancers. These results suggest that tilmanocept could potentially have a role in the assessment of macrophage-related vascular inflammation in individuals with HIV infection.

Another intriguing area of investigation is the links between microbial translocation, the gut microbiome, and CVD risk in HIV infection. Srinivasa and colleagues examined the relationship between microbial-derived, choline-related metabolites (trimethylamine [TMA] and trimethylamine N-oxide [TMAO]) and coronary plaque using stored samples from an earlier study of computed tomography angiography (Abstract 138). They found that TMA, a microbial-derived precursor of TMAO, was associated with the number of total and calcified plaque segments, and with calcium plaque volume in HIV-infected participants.

These associations were only noted in the HIV-infected group and not in the control group, prompting speculation about the role of altered gut flora in the setting of HIV infection. Sinha and colleagues from University of California San Francisco also investigated the link between TMAO and atherosclerosis in patients with HIV infection (compared with HIV-uninfected controls) and coronary artery disease using carotid intima-media thickness (CIMT) as the measure of atherosclerosis (Abstract 755). In this study, TMAO levels were similar in the younger HIV-infected group and the older group of HIV-uninfected patients with known coronary artery disease, and appeared to be associated with antiretroviral therapy in the HIV-infected group. An association between higher TMAO levels and CIMT that weakened after adjustment was noted. Further study of this area is expected in the coming years.

Statins

Several studies examined the impact of statins on surrogate measures of atherosclerosis. Lo and colleagues reported data from a small randomized controlled trial in which atorvastatin reduced noncalcified coronary plaque volume and other features of high-risk plaque when compared with placebo (Abstract 136). McComsey and colleagues reported 96-week follow-up data from SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy Bone with Rosuvastatin in HIV), a

study that compared rosuvastatin with placebo among patients with HIV infection and low-density lipoprotein (LDL) cholesterol levels below 130 mg/dL and baseline elevation in T-cell activation (Abstract 137). CIMT progressed measurably over 96 weeks in the placebo group but not in the group that received rosuvastatin. No statistically significant differences in coronary calcium were noted.

Another important finding from the SATURN-HIV study was that higher levels of self-reported activity (eg, exercise) were associated with lower levels of inflammatory biomarkers at baseline and with improved measures of vascular health during study follow-up (CIMT, carotid distensibility, and flow-mediated dilation) (Abstract 745).

There is growing evidence of the potential benefits of statins in HIV treatment.

Statins may have benefits beyond reducing the risk of CVD in the setting of HIV disease. Nakanjako reported the results of a small randomized study comparing atorvastatin with placebo in patients taking antiretroviral therapy in Uganda in whom CD4+ cell count had not increased. During 12 weeks of follow-up a reduction in CD4+ and CD8+ T-cell activation was noted in the group that received atorvastatin (Abstract 322) (see also Nakanjako et al, 2015[4]).

A common question in clinical practice is whether patients who develop hypercholesterolemia while taking a ritonavir-boosted protease inhibitor (PI/r) should switch their antiretroviral regimen or add a statin drug. The answer depends in part on the PI/r involved and the specific lipid abnormality. Lee and colleagues enrolled virologically suppressed patients taking a PI/r with a total cholesterol of at least 5.5 mg/dL and an elevated Framingham risk score (FRS) to randomly add rosuvastatin 10 mg per day or switch the PI/r to another drug (raltegravir or rilpivirine). After 12 weeks of follow-up, those randomized to receive rosuvastatin had statistically significantly

greater declines in levels of total cholesterol and LDL cholesterol (-29.0% vs -1.0%, respectively), and ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, whereas triglyceride levels improved more in those who switched PI/r (-34.0% vs -9.8%, respectively) (Abstract 733). These results confirm that for improvement of LDL cholesterol level, the addition of a statin is likely to be more beneficial than a switch in antiretroviral regimen.

Predicting CVD Risk

Accurate estimation of CVD risk can help to prioritize patients for interventions aimed at reducing disease. Previous studies have documented the underestimation of CVD risk using FRS, leading to the development of an HIV-specific risk prediction rule by the D:A:D study group. Several groups reported studies examining the performance of the new pooled-risk equation included in the 2013 American College of Cardiology (ACC)/ American Heart Association (AHA) Guideline on the Assessment of Cardiovascular Risk.[5]

These studies were showcased during a themed discussion session chaired by Friis-Møller from the D:A:D study group (Session TD-P; Abstracts 747, 750, and 751). Using established cohorts of different sizes with different lengths of follow-up, results across these studies were remarkably consistent and demonstrated that although the new pooled-risk equation identifies more HIV-infected patients as having high risk than does FRS, it still under-

Currently available risk prediction scores likely underestimate CVD risk in the context of HIV infection.

predicts the rate of events. When Systematic Coronary Risk Evaluation (SCORE) and D:A:D pooled-risk equations were examined, the accuracy of estimation did not further improve, suggesting that further refinement of CVD risk prediction in the setting of HIV disease is warranted.

In the same session, investigators from NA-ACCORD reported on the incidence of and risk factors for primary (atherosclerotic) disease or secondary myocardial infarction (MI; supply-demand mismatch) in a cohort of 25,000 participants with more than 100,000 person-years of follow-up and central ascertainment, adjudication, and classification of MI by type. The incidence rates for primary and secondary MI were similar, whereas the risk factors for each type varied.

Sepsis and cocaine use were seen in 50% of secondary MIs, whereas HIV RNA level above 400 copies/mL, time-updated CD4+ cell count, and history of an AIDS-defining illness were risk factors for primary MIs. These findings highlight the importance of managing HIV disease–specific risk factors in order to reduce rates of primary MI, and of the importance of cocaine use in MI risk.

Abacavir and MI Risk

The anticipated results from the NA-ACCORD cohort analysis examining the relationship between abacavir exposure and MI risk were presented at CROI 2015. With more than 16,733 adults in follow-up and 301 incident MIs, it was once again found that those who initiated treatment with abacavir had a higher prevalence of traditional and nontraditional HIV-related risk factors (eg, detectable HIV RNA, history of injection drug use) for MI. After adjusting for traditional risk factors (similar to D:A:D analyses), an association between abacavir and MI risk persisted (adjusted hazard ratio [aHR], 1.71; 95% confidence interval [CI], 1.11, 2.64). However, when the HIV-specific, nontraditional risk factors that were present prior to abacavir use were included in the model, the association was no longer statistically significant (aHR 1.34; 95% CI, 0.96, 1.88). Although this may not be the final word on the association between abacavir and MI, it does add credence to the notion that for people with established risk factors for CVD, alternatives to abacavir should be considered (Abstract 748).

Dyslipidemia

Proprotein convertase subtilisin/ kexin 9 (PCSK9), an enzyme involved in lipid metabolism, is a new target for lowering LDL cholesterol levels using monoclonal antibodies that target this pathway (see also Robinson et al, 2015[6]). Little was known about PCSK9 levels in HIV-infected patients prior to the study reported by Kohli and colleagues from University of California San Francisco at CROI 2015. PCSK9 levels were 10% higher in the HIV-infected group than in the control group, after adjusting for demographics, statin use, and CVD risk factors. (Abstract 731). Whether this new class of lipid-lowering agents will have a role in the setting of HIV disease remains to be seen.

Antiretroviral therapy–induced dyslipidemia has been well described around the globe, but there have been fewer data from low- and middle-income settings, especially among children. Innes and colleagues reported on the prevalence of dyslipidemia and insulin resistance among a cohort of 100 perinatally HIV-infected children from South Africa who were receiving antiretroviral therapy. (Abstract 929). Although the prevalence of individual abnormalities (insulin resistance, total cholesterol, LDL cholesterol, and HDL cholesterol) occurred in less than 15% of the population, 40% of the children overall had at least 1 lipid abnormality or insulin resistance, suggesting that monitoring for early onset vascular disease may be warranted if treatment with current antiretroviral drugs (lopinavir/r and efavirenz) continues long term.

Other somewhat reassuring studies of children highlighted the use of pulse wave velocity as an easy, noninvasive way to measure CVD risk that correlates with CIMT (Abstract 925). In addition, among a group of HIV-infected, school-age children taking antiretroviral therapy in South Africa, pulse wave velocity did not appear altered compared with that of HIV-uninfected controls (Abstract 926).

Fat

The impact of initial and second-line antiretroviral therapy on body fat and inflammation are best evaluated using data from randomized trials. Erlandson and colleagues reported on the relationship between BMI, weight gain, and measures of inflammation in a random sample of adults (50% women) participating in the AIDS Clinical Trials Group (ACTG) A5175 study of antiretroviral therapy in diverse settings (Abstract 778). Changes in biomarkers of inflammation varied depending on baseline BMI. Among those who were underweight, initiation of antiretroviral therapy was associated with decreased hsCRP and stable or declining sCD14, whereas among those who were normal weight or overweight at baseline, increases in these markers were noted. These findings underscore the possible contributions of preexisting obesity to biomarker elevations during antiretroviral therapy.

The SECOND-LINE study evaluated a nucleoside analogue reverse transcriptase inhibitor (nRTI)-containing (lopinavir/r plus 2 nRTIs) and an nRTI-sparing (lopinavir/r plus raltegravir) regimen for patients whose initial antiretroviral regimen with an NNRTI plus an nRTI had failed (note: in this study, 48% of participants had prior thymidine nRTI exposure in their initial regimen, including stavudine). The study demonstrated the noninferiority of the nRTI-sparing combination, with respect to virologic suppression, with greater preservation of bone mass in the nRTI-sparing arm (Abstract 779). In a subanalysis of this trial using dual-energy x-ray absorptiometry (DEXA) scanning, the investigators hypothesized that the nRTI-sparing arm would be associated with greater gains in limb fat over 96 weeks of follow-up; however, after adjusting for covariates associated with limb fat loss, no difference was observed. These findings indicate that limb fat loss does not appear to be a progressive issue when thymidine nRTI exposure is minimized.

Metabolic changes were also examined in the 2LADY (Agence Nationale

de Recherches sur le Sida et les Hépatites Virales [ANRS] 12169) trial, which compared 3 regimens: lopinavir/r, tenofovir, and emtricitabine; abacavir, didanosine, and lopinavir/r; and tenofovir, emtricitabine, and darunavir/r (Abstract 782). Notably, 71% of study participants were women and 32% of study participants were overweight or obese at baseline. Over 48 weeks of follow-up, weight gain was greater in the group receiving the darunavir/r-containing regimen (>25% of participants had BMIs that increased from normal range to overweight range), whereas more abnormalities were noted among those who received abacavir and didanosine in the regimen, confirming the lack of enthusiasm for this regimen as a current treatment option.

A misconception persists that PIs are more likely to lead to central fat gain than other classes of drugs, despite data indicating the contrary from randomized trials and cohort studies.[7] The integrase strand transfer inhibitor raltegravir has negligible metabolic effects; however, its impact on visceral fat gain was not previously evaluated in well-powered studies.

McComsey presented the results of the ACTG 5260s study, which randomized HIV-infected, treatment-naive individuals to receive tenofovir and emtricitabine combined with one of atazanavir/r, darunavir/r, or raltegravir (Abstract 140). After 96 weeks of follow-up, the median percentage increases in limb fat, subcutaneous adipose tissue, visceral adipose tissue, trunk fat, and lean mass were observed in all groups (all participants gained fat in each of these areas) and did not differ between arms. Notably, the mean percentage increase in visceral adipose tissue was 31%, 33%, and 29% for those randomized to receive atazanavir/r, raltegravir, and darunavir/r, respectively.

These findings suggest that central fat gain after initiation of antiretroviral therapy is independent of the regimen selected. Further work is needed to determine whether these gains in fat have adverse health consequences or if they represent a "return to health"

among patients being treated for chronic HIV infection.

Bone

There continues to be considerable interest in the study of bone disease in the setting of HIV infection, with studies presented at CROI 2015 focused on risk factors for bone loss, strategies to identify patients at risk for this complication, and interventions aimed at reducing bone loss. Confirming previous observations, it was again found that measures of inflammation, immune activation (including monocytes expressing tissue factor), and replicative senescent T cells were predictive of bone loss (Abstract 772). In addition, a previous report[8] suggesting that rosuvastatin protected against bone loss at 48 weeks was updated this year, and indicated that this association was no longer present at 96 weeks (Abstract 771).

The Fracture Risk Assessment Tool (FRAX) calculator may underestimate fracture risk in HIV-infected patients.

Antiretroviral therapy use and HIV infection contribute to bone loss and fracture risk. The web-based Fracture Risk Assessment Tool (FRAX) has been used to help stratify patients for interventions to reduce bone loss, yet the performance of this tool among those with treated HIV infection is unclear. Yin and colleagues used data from the Veterans Aging Cohort Study to test the performance of the modified FRAX (without available bone mineral density [BMD]) in 26,000 HIV-seropositive and -seronegative men aged 50 years to 70 years with available data and follow-up information (Abstract 141). FRAX underestimated fracture rates more frequently in the HIV-seropositive than in the -seronegative group.

When secondary osteoporosis was included as a risk factor, the performance of the FRAX calculator improved for the HIV-seropositive group. When thresholds for pharmacologic intervention were evaluated, FRAX had a poor predictive value of for identifying

men who might benefit from therapy. These results suggest that modification of the existing risk calculator may improve the performance of this tool for men; however, further work is needed to determine the most appropriate threshold for intervention.

Tenofovir disoproxil fumarate (tenofovir) use is associated with bone loss of approximately 1% to 2% in the first few years of exposure. The newer investigational drug tenofovir alafenamide fumarate (TAF) has 90% lower plasma levels than tenofovir, with the prospect of lower bone effects. Sax presented the late-breaking bone outcome results of 2 combined phase III randomized trials comparing elvitegravir, cobicistat, emtricitabine, and tenofovir with elvitegravir, cobicistat, emtricitabine, and TAF over 48 weeks (Abstract 143LB). The reductions in bone density at the hip (-3.26% vs -0.66%, respectively; $P < .001$) and the spine (-2.86% vs -1.3%, respectively; $P < .001$) were significantly lower in the group receiving TAF than in the group receiving tenofovir, and increases in markers of bone turnover were less in the former group. These results confirm data from smaller earlier studies suggesting that TAF will have a more favorable bone safety profile than tenofovir.

Another approach to preventing bone loss during antiretroviral therapy is the use of tenofovir-sparing regimens. Taiwo and colleagues presented the results of a 48-week randomized trial comparing darunavir/r and emtricitabine combined with maraviroc 150 mg or tenofovir 300 mg. The regimens were comparable in terms of virologic outcomes, whereas declines in BMD were greater in tenofovir recipients (total hip BMD -1.51 in the group receiving maraviroc vs -2.40 in the group receiving tenofovir; $P < .001$; and lumbar spine BMD -0.88 in the group receiving maraviroc vs -2.35 in the group receiving tenofovir; $P < .001$) (Abstract 769LB).

Replacing tenofovir with abacavir has previously been shown to improve bone loss. Negredo and colleagues reported measures of bone turnover in the follow-up to an ongoing switch

study in which tenofovir was replaced with abacavir (Abstract 767). During treatment with abacavir, levels of C-terminal telopeptide of collagen type 1, osteocalcin, and procollagen type 1 N-terminal propeptide fell, whereas they remained unchanged during treatment with tenofovir. In addition, levels of sclerostin rose in the group receiving abacavir. Sclerostin, a protein produced by osteocytes that inhibits bone formation, is the target of a novel class of drugs for the treatment of osteoporosis.

Renal Disease

There is continued interest in the long-term renal effects of antiretroviral therapy. Although initial declines in renal function have been observed with some drugs, it has been less clear whether this continues to progress over time as a cumulative effect. Investigators from the D:A:D study group reported the incidence of chronic kidney disease—defined as a decline in estimated glomerular filtration rate (eGFR) from greater than 90 mL/min/1.73 m^2 to less than 60 mL/min/1.73 m^2—among 23,560 participants with normal renal function at baseline followed up for a median of 6.3 years (Abstract 142). Chronic kidney disease developed in 0.9% of the participants, and rates were increased for those exposed to tenofovir, lopinavir/r, and atazanavir/r but not for those exposed to abacavir or other boosted PIs. Notably, the decline in renal function occurred immediately after starting antiretroviral therapy and persisted with increasing durations of exposure. After discontinuing treatment, renal function improved only for those taking tenofovir.

In another presentation from the D:A:D study group, the link between renal impairment and risk for CVD was confirmed. Among HIV-infected individuals with a baseline eGFR of greater than 90 mL/min/1.73 m^2, the risk of incident CVD was 1.7%, compared with a 23.4% risk among those with an eGFR of up to 30 mL/min/1.73 m^2 (Abstract 742).

Pulmonary Disease

Studies examining the pulmonary complications of HIV disease at CROI 2015 included studies from African settings and studies of children. Risk factors for airway obstruction in Kenyans with HIV infection included vertically acquired HIV infection and, not surprisingly, cigarette smoking. No association was noted between CD4+ cell count, antiretroviral therapy use, or biofuel burning (Abstract 800). In the PHACS/AMP (Pediatric HIV/AIDS Cohort Study/Adolescent Master Protocol) study, pulmonary function of perinatally HIV-infected youth was compared with that of HIV-exposed, -uninfected youth in various US cities (Abstract 801). The rate of pulmonary function abnormalities was similar between the groups. However, the HIV-infected group had a lower rate of reversibility of airway function after use of bronchodilators, suggesting that respiratory symptoms in perinatally HIV-infected youth might be misclassified as asthma. Finally, Morris and colleagues examined the relationship between lung function and cognitive impairment in a subgroup of men who had measures of each and observed that lower diffusion capacity was associated with a worse cognitive summary score, independent of HIV infection (Abstract 490).

Malignancies

Observational studies continue to shed light on the epidemiology of malignancies in the era of antiretroviral therapy and aging HIV-infected patients. Yanik conducted a case-cohort study of 5% of US Medicare enrollees and all cancer cases among persons aged 65 years or older (Abstract 725). Over 1- or 5-year periods, 2.5% and 10%, respectively, of persons aged 65 years or older were diagnosed with cancer. HIV-infected persons had a higher risk for Kaposi sarcoma and Hodgkin lymphoma than HIV-uninfected persons. In this study, HIV infetction was associated with lower risk for prostate cancer. Althoff and colleagues evaluated the population-attributable

fraction for smoking and HIV-related risk factors for non–AIDS-defining cancers (NADCs) among adults in a North American cohort (Abstract 726). Among 39,554 adults, investigators identified 592 incident cancers; most frequent were lung cancer (17%), anal cancer (16%), prostate cancer (10%), Hodgkin lymphoma (9%), liver cancer (7%), and breast cancer (7%). Smoking was the most powerful risk factor for NADCs. HIV immunosuppression was also a detectable risk factor for NADCs. NADC risk was 34% higher for individuals with CD4+ counts below versus above 200 cells/µL (aHR, 1.34; 95% CI, 1.11-1.62). Hepatitis B virus infection was associated with a 64% increased risk for NADCs. The investigators estimated that smoking cessation programs starting in adolescence could prevent as many as 46% of NADCs in HIV-infected adults. Effective antiretroviral therapy could prevent 6% of NADCs. At the other end of the age spectrum, Bohlius and colleagues evaluated AIDS-related and non–AIDS-related cancers among HIV-infected children aged 16 years or younger in several South African cohorts (Abstract 724). Kaposi sarcoma and non-Hodgkin lymphoma were the most frequent cancers, and there were few NADCs. As expected, the overall risk for cancer was lower among children treated with antiretroviral therapy.

Tuberculosis and Cryptococcal Disease

Tuberculosis

Diagnosis. In 2010, the World Health Organization (WHO) recommended a rapid combined tuberculosis (TB) and resistance to rifampicin assay (Xpert MTB/RIF) as the first-line diagnostic test for individuals suspected of having HIV-associated TB or multidrug-resistant TB. South Africa, which has the highest burden of HIV/TB coinfection in the world, rapidly adopted this recommendation. One challenge that arose from adoption of this new assay was related to assay performance. The sensitivity of the assay—although greater than that of an acid-fast bacilli

(AFB) smear—remained less than that of a TB culture, and this appeared to be a limiting factor in terms of its impact on clinical decision making. The lack of data on assay performance in a settings with lower TB prevalence have also limited widespread use of the assay in places such as the United States. Two presentations at CROI 2015 provide support for wider use of this remarkable technology.

The standard Xpert MTB/RIF assay has the potential to rule out TB that requires isolation, in addition to providing faster confirmation of TB diagnosis. In other words, hospitalized patients with suspected TB that are initially placed in isolation rooms could be moved to standard rooms based on the results of this rapid test. Current Centers for Disease Control and Prevention guidelines call for serial negative AFB smear results before patients with suspected TB can be removed from isolation.[9] Luetkemeyer and colleagues compared the sensitivity and specificity of 2 Xpert MTB/RIF tests with 2 AFB smears among 633 patients with suspected TB (Abstract 824). Thirty-eight percent of these patients were HIV infected. The gold standard was a TB culture. As expected, the 2 Xpert MTB/RIF assays were more sensitive than the 2 AFB smears in detecting TB (85.2% vs 69.3% sensitivity, respectively). Two Xpert MTB/RIF tests detected all AFB smear–positive TB-infected patients, thus identifying all patients requiring isolation based on sputum AFB smear. Based on these and other data, the US Food and Drug Administration approved the Xpert MTB/RIF assay in 2015 as a tool for decision mak-

The Xpert MTB/RIF assay can be used for decision making with regard to respiratory isolation of TB-infected patients.

ing regarding respiratory isolation for patients with suspected TB.[10]

At one of the most exciting presentations at CROI 2015, Alland and colleagues presented data on a new and improved Xpert MTB/RIF assay "with sensitivity equal to culture"

Early evaluations of the optimized Xpert MTB/RIF assay show sensitivity similar to that of a TB culture.

(Abstract 91). The Xpert MTB/RIF assay optimization included 3 key elements: 1) an increase in the size of the DNA reaction chamber, 2) new probes for detection of TB (IS6110 and IS1081) and rifampin resistance, and 3) optimized cartridge fluidics and polymerase chain reaction (PCR) cycling. These changes improved the limit of detection from 130 colony-forming units (CFU)/mL to below 50 CFU/mL. The optimized assay detected 100% of smear-positive TB samples and 94% of smear-negative samples. Current sensitivity of the Xpert MTB/RIF assay is approximately 60% for smearnegative TB cases. There were also few rifampin-resistant false-positive results with the optimized assay. According to Alland, the new assay uses the same size (but different) cartridge, the time to assay results is the same, and the cost per sample is anticipated to be the same as that of the current assay in use. Field studies are underway, and results are eagerly awaited.

Transmission. Multidrug-resistant and extensively drug-resistant (XDR) TB pose threats to the progress being made in reducing TB burden and mortality. Shah and colleagues performed a cross-sectional study of 404 XDR TB isolates collected from KwaZulu-Natal, South Africa, from 2011 to 2014 in order to estimate the proportion of transmitted versus acquired drug resistance (Abstract 92). They performed IS6110-based restriction fragment length polymorphism genotyping and targeted sequencing of 9 resistance-conferring genes; for genotypic clusters with more than 20 participants, whole genome sequencing was performed. Cases were classified as ac-quired or transmitted based on a case definition and a genotypic analysis. Seventy-seven percent of participants were coinfected with HIV. Using the clinical case definition, 79% of cases were transmitted XDR TB and 21% were acquired XDR TB.

With genotypic analysis, 87% of cases had an isolate that belonged to 1 of 16 clusters; only 13% had isolates that were unique. Forty-seven percent of cases were part of 1 large cluster, confirmed by whole genome sequencing. Other clusters ranged in size from 2 to 16 cases. These results suggest that the majority of diagnosed cases of XDR TB is attributable to transmission. Ongoing analysis of epidemiologic and geospatial data should provide information on transmission hot spots and lead to more effective approaches for interrupting person-to-person transmission of this difficult-to-treat disease.

Prior epidemiologic and modeling studies suggested that TB transmission is primarily driven by HIV-uninfected persons, in part because of the higher frequency of smear-negative TB among HIV-infected persons. New data from Malawi, using 1687 cultures (representing 72% of all culture-confirmed pulmonary TB cases), suggest that HIV-infected patients may be contributing to TB transmission more than originally thought (Abstract 816LB). Investigators examined patterns of TB transmission using genotypic methods and case histories. Glynn and colleagues estimated that 30.8% of HIV/TB-coinfected patients and 28.6% of HIV-uninfected TB-infected patients were the source of transmission for at least 1 additional case. This report underscores the point that dramatically reducing TB transmission will require prompt diagnosis and treatment of TB infection in both HIV-infected and -uninfected patients.

TB prevention. Danel and colleagues presented much awaited results from the Temprano study (Abstract 115LB), a randomized study (2x2 factorial design) comparing early antiretroviral therapy with antiretroviral therapy initiation according to WHO guidelines and isoniazid preventive therapy (IPT) with no IPT. Study participants were 2056 adults living in Ivory Coast who did not meet criteria for antiretroviral therapy initiation according to current WHO guidelines and had CD4+ counts less than 800 cells/μL. In terms of the outcome of the IPT randomization, IPT produced a 33% reduction in TB

cases. IPT was well tolerated and there was no evidence that IPT resulted in an increased number of TB cases with isoniazid resistance. This is the second randomized study showing that IPT adds an additional protective effect when used with antiretroviral therapy. As in the previous study from South Africa, this effect was seen in a population not selected for higher risk of TB, with confirmed latent TB. Now the challenge is implementing the evidence-based recommendations.

Six months of IPT is not the only effective TB prevention strategy. Short-course (3-month) preventive therapy with weekly isoniazid and rifapentine by directly observed therapy (DOT) is safe and effective for treating latent TB infection. However, DOT with this regimen may not be affordable in many settings. Belknap and colleagues conducted a randomized study to evaluate completion rates of this regimen using DOT, self-administered therapy (SAT), or self-administered therapy with weekly text reminders (eSAT) (Abstract 827LB). They prespecified a 15% noninferiority margin based on cost-effectiveness modeling in the United States.

The primary outcome was completion of more than 11 doses within 16 weeks. Of the 998 patients enrolled, 1% were HIV infected. Overall, treatment completion rates were 87.2% with DOT, 74.0% with SAT, and 76.4% with eSAT. Treatment completion rates in US participants were 85.4%, 77.9%, and 76.7%, respectively. SAT and eSAT were not found to be noninferior to DOT. However, SAT was found to be noninferior to DOT in a secondary analysis restricted to patients in the United States only. This study indicates that implementation of TB prevention therapy with 3 months of weekly isoniazid and rifapentine may require DOT in settings outside the United States.

Korenromp and colleagues provided more evidence that antiretroviral therapy reduces TB risk on a population level in an analysis using data from 41 countries (Abstract 832). Their analysis suggests that a 1% increase in antiretroviral therapy scale-up is associated with a 0.9% faster decline in TB

deaths. Another interesting epidemiologic study from Durban, South Africa, addressed whether TB recurrence rates are reduced with antiretroviral therapy scale-up (Abstract 830). The case-defined TB recurrence was any case that occurred after treatment completion or any case in which there was history of a prior cured TB infection. Investigators compared time to first occurrence among those whose first visit occurred before (2000-2005) and after (2006-2012) the introduction of potent antiretroviral therapy. They found that TB recurrence risk decreased after antiretroviral therapy was scaled up in Durban and that the timing of these cases suggested that most were attributable to reinfection rather than recurrence. These studies support combined treatment with antiretroviral therapy and IPT as a maximal TB prevention strategy.

TB treatment and care. Boeree and Hoelscher presented the results of the open-label PanACEA MAMS-TB (Pan African Consortium for the Evaluation of Anti-tuberculosis Agents Multi-Arm-Multi-Stage-TB) study of new TB agents and high-dose rifampin (Abstract 95LB). This study aimed to identify regimen components that show promise for shortening of TB therapy. Investigators evaluated the investigational TB drug SQ109, moxifloxacin, and high-dose rifampin given with or as part of a backbone of isoniazid, pyrazinamide, and rifampin standard dosing. There were 4 intervention arms and 1 control arm in this study, which had a primary endpoint of time to culture conversion in liquid medium at 12 weeks. There was a planned interim analysis to discontinue study arms that showed a lack of benefit. The arm containing SQ109 and the arm containing SQ109 plus moxifloxacin were stopped prematurely during interim analysis owing to lack of efficacy. At the 12-week endpoint, the arms containing rifampin 20 mg/kg plus moxifloxacin or rifampin 35 mg/kg alone had faster times to culture conversion (55 days and 48 days, respectively, vs 62 days in the 4-drug control arm of isoniazid, rifampin, ethambutol, and pyrazinamide). Serious

adverse event rates occurred in 6% of participants in the 2 intervention arms and in 5% of participants in the control arm. Hepatic adverse events were higher in the arm receiving the highest dose of rifampin than in the other 2 arms. These data suggest that higher levels of rifampin can achieve faster time to culture conversion in drug-sensitive TB infection, although hepatic toxicity rates were higher in the arm receiving the highest dose of rifampin. Clinical trials are ongoing to evaluate higher-dose rifampin as part of combination TB therapy.

High-dose rifampin shows promise for studies of shortened TB regimens.

Linkage to and retention in care remain an ongoing challenge for patients with HIV infection and for those coinfected with HIV and TB. Bassett and colleagues tested the hypothesis that the addition of a patient navigator to the care plan of patients newly diagnosed with HIV would improve outcomes (Abstract 93). They addressed this question among 4093 HIV-infected patients randomly assigned to receive a patient navigator or the standard of care. Navigators provided psychosocial support and text message and phone reminders. All patients were screened for TB at the time of diagnosis of HIV infection.

The primary composite endpoint of the study was antiretroviral therapy–eligible patients receiving at least 3 months of therapy and completion of TB therapy for those patients diagnosed with TB. Only 21% of patients in both arms reached the primary composite endpoint of the study. Further, 13% of the patients died during the 9 months of follow-up, with no difference between the arms. This report is an urgent call to action on the need to strengthen linkage to care, antiretroviral therapy initiation, retention in care, and coordinated TB services. The high mortality rates in this study are alarming.

Once patients are effectively linked to care, ensuring adherence to TB treatment remains an Achilles' heel of

effective TB control. In one of the most innovative TB presentations at CROI 2015, Browne and colleagues studied a new drug delivery system that permits real-time measurement of drug levels with an ingestible sensor and monitoring patch attached to a patient's torso (Abstract 828LB). Information from this device is transmitted to a paired mobile device that is uploaded to a secure network server, allowing health workers to confirm ingestions remotely (wireless observed technology [WOT]). Investigators integrated combination isoniazid and rifampin in an ingestible sensor with gel caps and then participants were randomly assigned to receive either standard pills or the gel caps with the sensor (WOT). Drug levels were bioequivalent between the 2 methods of delivery. Investigators also compared WOT with DOT in 280 simultaneous DOT ingestions. The WOT was well tolerated, with only 1 rash associated with the device. WOT detected more dosing than reported DOT. More data on the potential uses of this new technology to measure and monitor TB therapy are still to come.

Cryptococcal Meningitis

Sertraline is a selective serotonin reuptake inhibitor that shows activity against Cryptococcus neoformans in vitro and in murine models. To evaluate efficacy in humans, Rhein and colleagues conducted a phase IIb randomized study in Uganda, where frequency, morbidity, and mortality of cryptococcal meningitis remain high (Abstract 838). One hundred forty-four patients with cryptococcal meningitis were assigned to receive cryptococcal treatment (amphotericin B plus fluconazole) with sertraline at a daily dose ranging from 100 mg to 400 mg. The primary study endpoint was early fungicidal activity, defined as rate of cryptococcal clearance measured by serial cerebrospinal fluid cryptococcal cultures. Investigators found that in patients receiving sertraline, the organism was cleared 28% faster than in historical controls. Investigators also characterized the pharmacokinetics of sertraline: it reached steady state

levels by 7 days, levels were in the predicted range of activity, and sertraline appeared synergistic with fluconazole in vitro. The clinical significance of these findings is undergoing evaluation in a larger randomized study.

Sertraline shows activity in vivo against cryptococcal meningitis.

Mortality rates for cryptococcal meningitis are high in sub-Saharan Africa, but few studies have compared mortality between patients developing cryptococcal meningitis before with after starting antiretroviral therapy. Rhein and colleagues measured 2-week mortality among 185 patients with cryptococcosis enrolled in a prospective cohort from August 2013 to August 2014 in Kampala, Uganda (Abstract 836). Forty percent were taking antiretroviral therapy at the time of the diagnosis of cryptococcal meningitis, and these patients had higher CD4+ cell counts and lower cryptococcal burden in cerebrospinal fluid than those not receiving antiretroviral therapy (4.0 $\log_{10}$ CFU/mL vs 4.8 $\log_{10}$ CFU/mL, respectively).

The 2-week mortality was significantly higher in those taking antiretroviral therapy for less than 14 days (54%) than in those taking antiretroviral therapy for 15 days to 4 months (16%; $P = .05$), for more than 4 months (12%; $P = .01$), or for those who were antiretroviral therapy naive (24%). This study shows that even patients who develop cryptococcal meningitis while taking antiretroviral therapy have a high mortality rate, and that mortality is extraordinarily high among those who present clinically soon after the initiation of treatment. These observations support screening for cryptococcal antigen before initiating antiretroviral therapy in patients who present for care with low CD4+ cell counts in places such as Uganda.

As mentioned above, mortality rates for cryptococcal meningitis are uniformly high in resource-limited settings. Ingle and colleagues sought to compile data from a 10-year period

in North America and Europe from Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), NA-ACCORD, and Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohorts, to assess mortality rates and analyze outcomes according to time between the initiation of antiretroviral therapy and the diagnosis of cryptococcal meningitis (Abstract 837). Among the 235 patients with available data, only 18% died within 6 months. The mortality rate was 11% within 6 months for 150 patients initiating antiretroviral therapy and did not differ between those who started therapy before or after diagnosis of cryptococcal meningitis (within 2 weeks). This study used dated observations but, nevertheless, shows that mortality rates for cryptococcal meningitis in developed-world settings are much lower than those reported from resource-limited settings.

All cited abstracts appear in the CROI 2015 Program and Abstracts eBook, available online at www. CROIconference.org.

Additional References

1. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis*. 2011;203(6):780-790.
2. Kelesidis T, Kendall MA, Yang OO, Hodis HN, Currier JS. Biomarkers of microbial translocation and macrophage activation: association with progression of subclinical atherosclerosis in HIV-1 infection. *J Infect Dis*. 2012;206(10):1558-1567.
3. Burdo TH, Lo J, Abbara S, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. *J Infect Dis*. 2011; 204(8):1227-1236.
4. Nakanjako D, Ssinabulya I, Nabatanzi R, et al. Atorvastatin reduces T-cell activation and exhaustion among HIV-infected cART-treated suboptimal immune responders in Uganda: a randomised crossover placebo-controlled trial. *Trop Med Int Health*. 2015;20(3):380-390.
5. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the

assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;129(25 Suppl 2):S49-S73.

6. Robinson JG, Farnier M, Krempf M, et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. *N Engl J Med.* 2015;[Epub ahead of print].

7. de Waal R, Cohen K, Maartens G. Systematic review of antiretroviral-associated lipodystrophy: lipoatrophy, but not central fat gain, is an antiretroviral adverse drug reaction. *PLoS One.* 2013;8(5):e63623.

8. McComsey GA, Jiang Y, Erlandson KM, Debanne SM. Rosuvastatin improves hip bone mineral density but worsens insulin resistance [CROI Abstract 134]. In Special Issue: Abstracts From the 2014 Conference on Retroviruses and Opportunistic Infections. *Top Antivir Med.* 2014; 22(e-1):67.

9. Centers for Disease Control and Prevention (CDC). Availability of an assay for detecting Mycobacterium tuberculosis, including rifampin-resistant strains, and considerations for its use - United States, 2013. *MMWR Morb Mortal Wkly Rep.* 2013;62(41):821-827.

10. US Food and Drug Administration. FDA News release: new data shows test can help physicians remove patients with suspected TB from isolation earlier. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm434226.htm. Accessed on April 2, 2015.

---

www.HCVguidelines.org

- Developed by a panel of experts in the field.

- Provides practitioners with regularly updated, evidence-based, consensus recommendations for screening, treating, and managing patients with HCV.

- Assists practitioners in treating the estimated 3 to 4 million Americans infected with HCV by highlighting the latest information in improved diagnostics and new drug options as they meet FDA approval.

- Offers guidance to practitioners about how to best use the next generation of direct-acting antivirals and other treatment options in the care of their patients.

Recommendations for Testing, Managing, and Treating Hepatitis C

Recommendations for Testing, Managing, and Treating Hepatitis C is a website sponsored by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA) to provide the most current guidance for the treatment of hepatitis C virus (HCV).

Recently, several sections of the Guidance were extensively revised based on newly available therapies approved by the US Food and Drug Administration. Visit www.hcvguidelines.org to review the updates to sections on Initial Treatment of HCV Infection; Retreatment of Persons in Whom Prior Therapy Has Failed; Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy; and Unique Populations (Patients With HIV/HCV Coinfection, Patients With Decompensated Cirrhosis, Patients Who Develop Recurrent HCV Infection Post–Liver Transplantation, and Patients With Renal Impairement).

Available sections:

- HCV Testing and Linkage To Care
- When and in Whom to Initiate HCV Therapy
- Initial Treatment of HCV Infection
- Retreatment of Persons in Whom Prior Therapy Has Failed
- Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy
- Unique Patient Populations
  - Patients With HIV/HCV Coinfection
  - Patients With Decompensated Cirrhosis
  - Patients Who Develop Recurrent HCV Infection Post–Liver Transplantation
  - Patients With Renal Impairment
- Management of Acute HCV Infection