

## Review

# CROI 2017: Complications and Comorbidities of HIV Disease and Its Treatment

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*Complications of HIV disease remained a major focus at the 2017 Conference on Retroviruses and Opportunistic Infections (CROI), and included studies focused on non-communicable chronic diseases (eg, cardiovascular disease, obesity, bone disease, and malignancies) and opportunistic infections (Mycobacterium tuberculosis and cryptococcosis). Progress in identifying predictors of specific complications as well as interventions for the prevention and treatment of these comorbidities are summarized below.*

**Keywords:** CROI, 2017, cardiovascular, tuberculosis, anti-retroviral, therapy, biomarkers, risk

## Inflammation and Cardiovascular Disease Risk

Previous studies have demonstrated that patients with HIV infection may have evidence of arterial inflammation using novel imaging techniques such as (fludeoxyglucose positron emission tomography [FDG-PET]). Zanni and colleagues took this one step further in a pilot study that used a molecular imaging strategy that included a radio-labeled tracer binding to CD206+ macrophages (<sup>99m</sup>Tc-tilmanocept) in vivo. They examined the uptake of <sup>99m</sup>Tc-tilmanocept using single-photon emission computed tomography (SPECT/CT) in 6 HIV-seropositive and 3 HIV-seronegative participants, and related the findings to measures of noncalcified plaque on CT angiography. Increased levels of aortic uptake of the macrophage-labeled tracer were seen in the HIV-infected patients. Correlations between uptake and noncalcified plaque volume and measures of systemic inflammation provided further support that macrophage infiltration underlies excess cardiovascular disease (CVD) risk in HIV-infected subjects (Abstract 635LB).

Hsue and colleagues reported results of a pilot study evaluating the impact of a single dose of canakinumab, the monoclonal antibody targeting interleukin 1 $\beta$  (IL-1 $\beta$ ), given to HIV-seropositive patients with increased CVD risk. FDG-PET scans obtained 8 weeks after treatment demonstrated a statistically significant reduction in aortic arterial wall inflammation and a reduction in IL-6 and high-sensitivity C-reactive protein (hs-CRP) without evidence of a change in T-cell activation. A larger follow-up study is planned to further evaluate the safety and efficacy of repeated dosing of this novel antiinflammatory agent (Abstract 126).

## Biomarkers, Mortality, and Non-AIDS Events

Several studies at the Conference on Retroviruses and Opportunistic Infections (CROI) examined relationships between the biomarkers IL-6, d-dimer, and hs-CRP, and antiretroviral therapy and outcomes this year. In addition, studies evaluating novel biomarkers of inflammation and their associations with clinical outcomes were reported. A few highlights of measures that were reported this year are included in the table.

Does better adherence further reduce inflammation once HIV-RNA levels becomes suppressed? Castillo-Manilla and colleagues used a medication event monitoring system device to study a cohort of individuals in Uganda who started on antiretroviral therapy, in parallel with measures of inflammation. After an initial response to antiretroviral therapy with HIV RNA levels under 400 copies/mL, higher levels of adherence were associated with further reductions in IL-6, D-dimer,

**Table.** Selected Studies of Biomarkers of Morbidity and Mortality at the 2017 Conference on Retroviruses and Opportunistic Infections

Biomarker Studied	Endpoint(s)	Results/Comments	Abstract No.
Soluble urokinase plasminogen activator receptor (suPAR)	All-cause mortality and non-AIDS events	Higher suPAR associated with all-cause mortality but not non-AIDS events	235
Serum soluble suppression of tumorigenicity 2 (sST2), a decoy receptor for IL-33	Mortality	Increased risk of death for every 2% increase in sST2 level	630
F2-isoprostanes (measure of oxidative stress)	Non-AIDS events and mortality	F2-isoprostanes were independent predictors of events after control for hs-CRP, IL-6, and D-dimer levels	647

Abbreviations: IL, interleukin; hs-CRP, high-sensitivity C-reactive protein.

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sCD14, and reductions in T-cell activation, suggesting that optimized adherence could potentially contribute to better long-term outcomes (Abstract 675).

### Antiretroviral Therapy and Risk of Cardiovascular Disease

Several groups reported data on the associations between specific antiretroviral drugs and risk of CVD. The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) group reported data on the relationship between newer protease inhibitors and CVD events in 35,711 patients over a median of 7 years of follow-up (Abstract LB 128). The D:A:D database includes more than 1000 events (stroke, myocardial infarction [MI], coronary bypass surgery, endarterectomy, and angioplasty), which is considerably more than other smaller studies. They found that exposure to ritonavir-boosted darunavir was associated with a 59% increase in the risk of CVD compared with not being on darunavir and this did not change after adjusting for lipid levels. In contrast, there was no statistically significant increase in risk of CVD associated with atazanavir use. Overall, 3.2% of participants had a CVD event and the crude incidence of MI after 6 years of exposure was 13.67 for darunavir and 6.68 for atazanavir. Adjusting for factors thought to be on the causal pathway between exposure and outcome, such as CD4 nadir, HIV RNA, and lipid levels, did not explain the excess risk observed with darunavir. The authors acknowledged the limitations of these observational data and called for further study of the potential mechanism underlying this observation.

Previous studies have identified a potential protective effect of atazanavir in reducing the risk of atherosclerosis progression; this is possibly linked to the antioxidant properties of unconjugated bilirubin, which rises in most individuals receiving the drug.<sup>1</sup> Marconi and colleagues examined the relationship between bilirubin levels and MI risk in 96,373 participants followed up in the Veteran Aging Cohort Study and found that higher bilirubin levels were inversely correlated with MI and heart failure risk in all patients and only heart failure risk and marginally MI risk among the HIV-seropositive group (Abstract 127). Notably, the majority of patients with bilirubin elevations in this study were not receiving atazanavir.

Several groups continue to investigate a mechanism to explain the possible association between abacavir use and MI risk. Andujar and colleagues expanded their previous reports on abacavir induction of leukocyte endothelial interactions to study thrombus formation in a mouse model using an endothelium damaging agent to provoke thrombosis in the presence of other agents. They observed a dose-dependent effect of abacavir on thrombus formation, whereas tenofovir had no effect. Using a knockout mouse model, they reported that the abacavir effect was blocked in the absence of ATP-P2X7 (a purinergic system). These results suggest a potential pathway, through interference of ATP-P2X7 by which abacavir could alter thrombus formation. Further studies are needed to confirm these observations (Abstract 609).

### Hepatitis C Virus and Cardiovascular Disease Risk

The extrahepatic and metabolic effects of hepatitis C virus (HCV) coinfection continue to be an area of active investigation. Many studies highlighted that patients with HCV infection may be at increased MI risk compared with patients without HCV infection (Abstract 574) and other medical comorbidities (Abstract 528). Treatment with sofosbuvir/ledipasvir and other HCV direct-acting antiviral drugs are associated with increases in low-density lipoprotein even prior to virologic response given that lipids rise before liver disease improves (Abstracts 573, 575, 589) and endothelial function is impaired in patients with untreated HCV infection.

### Cardiovascular Disease Risk Reduction and Screening Strategies

The impact of different strategies to reduce MI risk was explored in a Dutch modeling study led by van Zoest and colleagues (Abstract 129). Using data from individual patients followed up in the ATHENA (AIDS Therapy Evaluation in the

*Elimination of smoking, hypertension, and hypercholesterolemia were each associated with a 40% reduction in MI risk.*

Netherlands) observational HIV cohort, they constructed a model to estimate CVD events and to examine 4 different prevention intervention approaches that might impact CVD risk: using antiretroviral therapy in patients with no known increased CVD risk; smoking cessation; treatment of hypertension and dyslipidemia; and earlier antiretroviral therapy. Their model estimates the rate of CVD events will increase by 50% by 2030 and demonstrated that although each of these interventions would reduce CVD events, the treatment of hypertension and dyslipidemia would have the greatest impact.

In a related study, Althoff and NA-ACCORD (North American AIDS Cohort Collaboration) colleagues used data with validated type 1 MI events (those due to plaque rupture) to estimate the population attributable risk for factors linked to an increased risk of MI (Abstract 619). This method uses the strength of the association with a factor and the prevalence of that factor in the population and allows the ability to examine the impact of eliminating each factor. In this cohort, elimination of smoking, hypertension, and hypercholesterolemia were each associated with a 40% reduction in MI risk. The results of these 2 studies highlight the importance of traditional risk factor management in reducing MI rates in our aging HIV population.

Screening and treatment for noncommunicable diseases (NCD) is a growing concern in low-resource settings for HIV-seropositive and -seronegative people and efforts are underway to identify the optimal means for integration. Presentations detailing the prevalence of hypertension in Senegal (Abstract 642), the prevalence of abnormal pulse wave velocity

in HIV patients in Malawi that improved on antiretroviral therapy (Abstract 641), and novel programs for screening and treatment of CVD risk factors in Uganda, South Africa, and Swaziland (Abstracts 638, 639, 637) were presented in a themed discussion session this year. Investigators from the SEARCH (Sustainable East Africa Research in Community Health) study proposed a new composite HIV, hypertension, and diabetes metric for HIV care programs that encompasses the multidisease chronic care model. Their study, which screened 40,000 adults enrolled through multidisease community health fairs, reported on composite endpoint measures for the 193 who had HIV infection and an NCD. Sixty-nine percent achieved control of HIV and NCD after 2 years, lagging behind the 90% control of HIV achieved by the program (Abstract 638). This new composite metric should be used to monitor progress toward HIV-NCD integration globally.

### Statins

Statins have beneficial effects in primary CVD prevention and are recommended for use in those who meet current guidelines. Investigators from the NA-ACCORD evaluated trends in statin prescriptions from 2003 to 2012 using the Framingham Risk Score and the thresholds for use recom-

*The percentage of patients eligible but not receiving statins fell from 70% in 2003 to 58% in 2012, reflecting underuse of this important intervention for CVD risk reduction.*

mended during that time period. The percentage of patients eligible but not receiving statins fell modestly from 70% in 2003 to 58% in 2012, potentially reflecting underuse of this important intervention for CVD risk reduction (Abstract 619).

Patient beliefs about the value of medications taken to treat comorbid conditions need to be considered in efforts to reduce CVD risk. Kamal and colleagues reported results of a survey performed in the Swiss HIV Cohort study that asked patients about their beliefs and adherence to their medications, separating HIV treatments from medications taken for other conditions. Patients reported higher levels of adherence to antiretrovirals than to medications taken for comorbidities, suggesting that further work is needed to improve adherence to all medications (Abstract 671).

Statins have pleiotropic effects on inflammation and lipid metabolism but are also active against HIV infection in vitro. Dreschler and colleagues examined associations between statin use and rates of virologic rebound among US veterans. Continuous statin use was associated with a reduction in rates of virologic rebound after virologic suppression (Abstract 468). In another study, low levels of vitamin D (25[OH]D) blunted the beneficial effects of rosuvastatin on several measures in the SATURN-HIV (Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin in HIV) trial (Abstract 617).

### Exercise

Connick and colleagues reported results of a study that examined the impact of exercise training on endothelial release of tissue-type plasminogen activator (tPA), an important mediator of fibrinolysis. The capacity of the endothelium to release

*HIV-seropositive patients were less likely to undergo procedures such as cardiac catheterization, percutaneous coronary intervention, or coronary bypass grafting than HIV-seronegative patients, after controlling for demographic factors.*

tPA improved after a home-based exercise intervention (5 days a week of walking for 50 minutes/day), presumably through a reduction in oxidative stress. These findings underscore the potential impact of habitual exercise on endothelial function in HIV disease (Abstract 616).

The management of coronary artery disease once diagnosed is an emerging topic of interest to the field. Clement and colleagues examined the rate of CVD procedures in a database of more than a million hospitalizations for acute coronary syndromes in the United States. The 3783 HIV-seropositive patients identified in this sample were less likely to undergo procedures such as cardiac catheterization, percutaneous coronary intervention, or coronary bypass grafting than HIV-seronegative patients after controlling for certain demographic factors. These disparities in care warrant further investigation.

### Lipids: HDL Cholesterol Efflux Capacity

Several groups reported on the relationship between high-density lipoprotein (HDL) efflux cholesterol capacity or other measures of HDL function, monocyte function, and CVD (Abstracts 611-615). Angelovich and colleagues showed that dysfunctional HDL from HIV-infected patients promoted monocyte-derived foam cell formation in an in vitro model. O'Halloran and colleagues reported that initial antiretroviral therapy improves the antioxidant HDL function observed in untreated HIV, whereas impaired mononuclear cell cholesterol efflux remained increased. In another study, lower CD4+ cell counts and higher HIV RNA levels correlated with impaired cholesterol efflux, which further supported the link between impaired HDL function and immune status. Mannem showed that HDL cholesterol efflux is inversely associated with classical monocyte numbers. This raises the theory that interventions directed at restoring HDL function may have the potential to modulate monocyte function, and possibly CVD.

### Fat

The rising prevalence of obesity in HIV-infected patients was a widely covered topic (Abstracts 694, 695, 698, 699). Bhagwat and colleagues reported on predictors of severe weight

and body mass index gain with initial antiretroviral therapy using data from the completed ACTG 5257 (comparing raltegravir with atazanavir/ritonavir or darunavir/ritonavir, each combined with tenofovir/emtricitabine). The study focused on weight gain of more than 10% body weight; the mean increase in this group was 14.9 kg. Risk factors for severe weight

***A behavioral weight-loss program reported 4.4 kg weight loss in the intervention group compared with no change among controls.***

gain included lower baseline CD4+ cell count, higher HIV RNA level, use of raltegravir, and black race (Abstract 695). A study from Thailand on weight gain after antiretroviral therapy is started reported that rates of obesity increased from 13% at the start of antiretroviral therapy to 21% over an average of 11 years. Those with obesity, not surprisingly, had higher rates of other metabolic abnormalities and evidence of hepatic fibrosis (Abstract 698). A behavioral weight-loss program delivered via the Internet reported 4.4 kg weight loss in the intervention group compared with no change among controls. These findings suggest that interventions to reduce weight can be successful, at least over the short-term (Abstract 694).

### **Bone Density**

Reduced bone density appears to occur among many patients after initiation of antiretroviral therapy and progresses over time. The ability to predict fracture risk would help target interventions to improve bone density in this population. The fracture risk assessment tool (FRAX) algorithm predicts a 10-year risk of a major osteoporotic fracture in the general population, and it has been shown to underestimate risk in the HIV cohort data based upon clinical risk factors alone. Yang and colleagues from the WIHS (Women's Interagency HIV Study) cohort found that adding data from dual-energy x-ray absorptiometry (DXA) scans, including a measure of trabecular bone architecture, improved the accuracy of FRAX in HIV-seropositive women. These findings support the current recommendations for DXA screening in HIV-seropositive adults over the age of 50 years and incorporating DXA data in estimating fracture risk using FRAX (Abstract 132).

### **Malignancies**

Cancer is a growing cause of morbidity and mortality in the aging, treated population of people living with HIV infection. Several presentations highlighted the changing epidemiology of cancer and provided new data on cervical cancer.

Cervical cryotherapy is used in many low- and middle-income countries for screen-and-treat strategies to prevent cervical cancer. Greene and colleagues presented data on a randomized clinical trial that compared loop electrosurgical excisional procedure (LEEP) with cryotherapy to treat high grade cervical squamous intraepithelial lesions (HSIL) in HIV-infected women in Kenya (Abstract 22). The study

enrolled 400 women who had cervical HSIL on histology and cervical lesions that made them eligible for cryotherapy according to WHO criteria. After undergoing their treatment, the women were followed up every 6 months with cervical cytology. The women randomized to LEEP were less likely to have recurrent cytologic HSIL through 24 months after randomization (37% vs 26%,  $P = .018$ ) than those who underwent cryotherapy. These data suggest that LEEP may be preferable to cryotherapy for HIV-infected women who screen positive in see-and-treat programs.

Investigators from WIHS presented data on the natural history of cervical intraepithelial neoplasia-2 (CIN2) in HIV-infected women of reproductive age (Abstract 23). Cervical HSIL is the precursor lesion to cervical cancer and is composed of CIN2 and CIN3. CIN2 is more likely than CIN3 to regress and the risks from treating CIN2 may outweigh the potential risk to future pregnancies. The investigators analyzed 102 HIV-infected women diagnosed with CIN2 lesions: 41 HIV-infected women were treated for CIN2; 61 were untreated. The investigators found no statistically significant difference in the risk of progression to CIN3 in women who were treated than those who were untreated. The risk of progression was lower among women using antiretroviral therapy and those with higher CD4+ cell counts. These data suggest that it is reasonable to monitor CIN2 in HIV-infected women seeking pregnancy.

Several studies examined screening strategies for anal HSIL, the precursor lesion to invasive anal cancer. Investigators examined the role of high-risk human papillomavirus (HPV) testing in HIV-infected women (Abstract 591) and men (Abstract 592), and found that HPV testing in conjunction with cytology led to a more accurate diagnosis of anal HSIL

***HPV testing in conjunction with cytology led to a more accurate diagnosis of anal HSIL than cytology alone.***

than cytology alone. This risk of abnormal anal cytology was also related to a cumulative number of HPV types detected, which suggests that testing for the various HPV infections may have a role in anal cancer screening (Abstract 594). Serrano-Villar and colleagues reported on an enhanced cytology with p16/Ki67 dual stains. They found that this enhanced cytology did not perform as well as standard cytology and concluded that it should not be studied further (Abstract 595).

The START (Strategic Timing of Antiretroviral Treatment) study, a randomized clinical trial of early versus delayed initiation of antiretroviral therapy, found that early initiation of antiretroviral therapy led to a reduced risk of cancer.<sup>3</sup> An analysis from the Kaiser Permanente health care system found that early initiation of antiretroviral system led to a reduction in cancers similar to the START study findings (Abstract 598). Salters and colleagues reported on the cancer risk among HIV-infected women from British Columbia, Canada (Abstract 599). Cancer diagnosis was less common among women who started antiretroviral therapy at a CD4+

cell count greater than 350 cells/ $\mu$ L than among women who started antiretroviral therapy at a CD4+ cell count lower than 200 cells/ $\mu$ L.

Shepherd and colleagues reported on the association of tobacco cessation with cancer incidence in the D:A:D study (Abstract 131). Among patients who had quit tobacco, the rate of tobacco-related cancers other than lung cancer was elevated for up to 2 years in patients after they quit tobacco compared with rates in those who had never smoked. Rates of lung cancer remained elevated and did not decrease through 5 years of follow-up.

## Tuberculosis

### Prevention and Earlier Diagnosis

The TEMPRANO (Benefits and Risks of Early Antiretroviral Therapy in HIV-Infected Adults) study conducted in Cote d'Ivoire showed that early antiretroviral therapy and isoniazid preventive therapy (IPT) independently reduced tuberculosis (TB) risk.<sup>2</sup> Badje and colleagues analyzed mortality

*Isoniazid preventive therapy was associated with a 39% reduction in death in an Ivory Coast study.*

during an extended follow-up of trial participants in TEMPRANO, according to their IPT randomization (Abstract 78). Overall, there were 86 deaths among the 2056 participants followed up for 9494 patient-years of observation. There were 34 deaths in the IPT arm and 52 in the non-IPT arm; the hazard ratio (HR) was 0.61 (95% confidence interval [CI], 0.39-0.94) after adjusting for immediate versus deferred antiretroviral therapy. Thus, including IPT in the treatment of persons with a high CD4+ cell count prevents TB and is associated with a 39% mortality benefit.

If TB cannot be prevented, then early diagnosis is the key to reducing TB disease burden and spread. Xpert Ultra is the next generation of Xpert MTB/RIF, a rapid diagnostic for identifying *Mycobacterium tuberculosis* (MTB) and rifampin (RIF) resistance. The Xpert Ultra assay has built-in modifications to improve sensitivity for TB diagnosis. A prospective study compared Xpert and Xpert Ultra against a gold reference standard of 4 TB cultures. The study enrolled 1520 participants from 8 countries who had signs of pulmonary TB. Xpert Ultra was more sensitive than Xpert for TB detection for all cases (5% higher), HIV-associated TB cases (12% higher), and smear-negative TB cases (17% higher) (Abstract 76 LB). However, specificity decreased by 3.2% overall and decreased by 5.4% in persons with a prior history of TB. Whether the false-positive with Xpert Ultra represents detection of nonviable TB or the limitation of the gold standard culture cannot be ascertained from this study. The investigators report that the Xpert Ultra uses the same machine and cartridges at the same cost as the Xpert. The next step will be to determine an implementation of the Xpert Ultra that preserves the sensitivity advantage and optimizes specificity.

### Treatment

Defining optimal use of current TB drugs and testing new treatments to shorten and improve regimens is a priority of TB treatment research. Prior clinical and animal studies suggest that isoniazid used throughout a 6-month standard TB therapy contributes to bactericidal activity only during the first few days of treatment. Diacon and colleagues found that among 63 persons with pulmonary TB (94% HIV uninfected) randomly assigned to 1 of 4 different treatment arms (isoniazid, rifampin, pyrazinamide, ethambutol [HRZE] for 14 days; HRZE without isoniazid for days 3 to 14; HRZE replacing isoniazid with moxifloxacin for days 3 to 14; or rifampin, pyrazinamide, and ethambutol for 14 days), early bactericidal activity at 14 days did not differ among the 4 arms (Abstract 79). Failure to identify differences among the study arms may be attributed to overall lower bacterial counts in this study than in prior studies. These results do not support replacement of short-term use of isoniazid for its continuous use in current regimens.

Patients with extensively drug-resistant (XDR) TB and multidrug resistant (MDR) TB are the most difficult to treat and have the highest mortality. Conradie and colleagues presented early findings from the Nix-TB single-arm study treating patients who are culture-positive for XDR or MDR TB patients with bedaquiline (200 mg daily) plus pretomanid (200 mg daily) plus linezolid (1200 mg daily) for 6 months (Abstract 80LB). Among the 61 patients (49% HIV-infected; 79% XDR TB; 21% MDR TB), 4 participants died within the first 8 weeks of therapy from TB complications. All surviving pa-

*An experimental 6-month regimen for XDR/MDR treatment with bedaquiline, pretomanid, and linezolid has shown early favorable outcomes compared with historical data.*

tients had negative cultures by 8 weeks. Because of the high dose of linezolid used, 71% of patients had treatment interruptions for peripheral neuropathy and myelosuppression. Seven cases of grade 3 or 4 hepatic transaminase elevation all resolved with treatment modifications. No surviving patient had to permanently withdraw from the study because of serious adverse events. One microbiologic relapse has been reported to date. Favorable outcomes in historic XDR TB studies occur in only 40% of participants, mortality is more than 20%, and treatments require 6 or more drugs for years. Thus, these small and early results with a 6-month, 3-drug regimen, even with associated toxicities, are encouraging for treating this population and warrant further study.

Dawson and colleagues presented early results of an 8-week phase IIb study for MDR or drug-sensitive TB treated with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide, or standard HRZE (Abstract 724LB). The primary study outcome was bactericidal activity measured by rate of change in time in days to sputum culture positivity. There were 180 participants with drug-sensitive TB and 60 patients

with MDR TB enrolled; 22% were HIV-infected. Among the MDR TB patients, the change in time to sputum positivity was 5.3 days for the bedaquiline, pretomanid arm; 5.2 for the bedaquiline, pretomanid, and pyrazinamide arm; and 4.9 for the bedaquiline, pretomanid, moxifloxacin, and pyrazinamide arm, compared with 4.0 days for the HRZE arm. Elevated hepatic transaminases (3-fold elevation) were 10% to 15% in the 3 experimental treatment arms and 5% in the standard HRZE arm. The role of these investigational regimens will depend on larger efficacy and safety evaluations.

A new option for prevention of TB is a short-course, weekly, 3-month combination of rifapentine and isoniazid. This combination can be given safely with efavirenz, but there are no data on safety and interactions with dolutegravir. Brooks and colleagues reported the results of an open-label, fixed-sequence study of dolutegravir 50 mg daily alone, followed by the addition of weekly doses of isoniazid and rifapentine in noninfected volunteers (Abstract 409A). The study was prematurely stopped because 2 of the 3 patients who completed 3 doses of weekly isoniazid and rifapentine developed several adverse events, which included flu-like syndrome and elevation of hepatic transaminase levels that started 8 to 10 hours after the third dose of isoniazid and rifapentine. One patient was hospitalized for hypotension. Dolutegravir levels decreased 15% to 46%, rifapentine and metabolite levels were in the expected range, and isoniazid levels were on the high end. The clinical findings were most consistent with rifapentine reaction, but the mechanism is unknown and requires further study.

## Epidemiology

In Kwazulu Natal, South Africa, an area with a high prevalence of XDR TB, more than two-thirds of cases are attributable to transmission rather than incomplete treatment (Abstract 77). Nelson and colleagues used whole-genome sequencing and spatial analysis to determine if there were unrecognized connections between 671 genetically linked case-pairs and their proximity to health facilities. Only 17% case-pairs lived or were diagnosed at a health facility within 20 km of each other. The investigators speculated that ongoing migration contributes heavily to spread and transmission of XDR TB in this region.

Recurrent TB is common in South Africa accounting for as many as one-third of cases. Hermans and colleagues examined the attributable risk fraction of HIV infection among TB recurrence cases from 2003 to 2015 (Abstract 727). Among 245,495 persons with TB, 16% had 2 or more TB cases. Higher rates of TB recurrence were observed with each subsequent TB episode until episode 5, after which HIV serostatus did not matter. The proportion of retreatment of disease attributable to HIV infection increased from 42% in the second episode to 46% in the sixth episode. Although HIV infection is a risk for recurrence, fewer than half of the total recurrent cases occur in persons with HIV infection. These data would suggest that reinfection or treatment failure with progression to disease after previous TB treatment is a major

issue in all persons with TB. Bendavid and colleagues examined TB risk using the TB self-report (HIV serostatus unknown) from the South Africa General Household survey (Abstract 725). They observed that race was independently predictive of socioeconomic status for TB risk. For example, adult TB prevalence among black individuals in the highest socioeconomic households was 4 times that of white individuals in the lowest socioeconomic households. Understanding biologic and behavioral contributions to these observations may help inform TB intervention. Finally, in a population-based study of TB infection among 2093 children and 953 young adults given a purified protein derivative (PPD) skin test in rural Uganda, Marquez and colleagues reported that 23% of young adults 14 to 24 years of age already had evidence of TB infection (Abstract 726). However, only 5% had a known household contact. Undiagnosed household contacts or community- and school-based contacts rapidly establish a lifetime reservoir of TB infection in rural Uganda.

## Tuberculosis Immune Reconstitution Inflammatory Syndrome and Its Association With InSTI Use

Starting versus delaying antiretroviral therapy in the setting of TB is associated with reduced mortality, but also with increased risk for immune reconstitution inflammatory syndrome (IRIS), particularly in those with TB and low CD4+ cell

*A 4-week course of prednisone reduces frequency and severity of IRIS in TB patients with a CD4+ cell count under 100/μL in a randomized controlled study.*

count. Meintjes conducted a randomized, double-blind, placebo-controlled trial to determine if a brief course of steroids could safely mitigate the IRIS risk in patients starting TB and antiretroviral therapy with CD4+ cell count under 100 cells/μL. (Abstract 81 LB). The study enrolled 240 subjects with a median CD4+ cell count of 49 cells/μL. Participants in the intervention arm received prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks. TB-IRIS was diagnosed in 46.7% in the placebo arm and 32.5% in the prednisone arm ( $P = .02$ , RR, 0.70; 95% CI, 0.51-0.96). Twenty-seven patients were hospitalized in the placebo arm and 17 patients were hospitalized in the intervention arm. Grade 3 adverse events (45.4% and 29.4%, respectively) but not grade 4 adverse events (8.4% and 7.6%, respectively) were more common in the placebo arm. Severe infections occurred in 18 participants in the placebo arm and 11 participants in the prednisone arm. There were fewer interruptions of antiretroviral therapy or TB treatment in the prednisone arm (8.3%) than in the placebo arm (15.8%). This study makes a compelling case to use a brief 4-week course of prednisone for persons with TB and a low CD4+ cell count to reduce TB-IRIS by approximately 30%.

The IRIS risk is associated with rapid HIV RNA level decline after antiretroviral therapy initiation in addition to a low

starting CD4+ cell count. Because integrase strand transfer inhibitor (InSTI)-containing regimens are associated with a more rapid decline in HIV RNA level compared with non-InSTI-containing regimens, 2 studies examined whether patients treated with InSTI-containing regimens versus non-InSTI-containing regimens had a higher risk of IRIS. In the Dutch ATHENA observational cohort (Abstract 731), 360 patients starting an initial antiretroviral regimen with a CD4+ cell count below 200/ $\mu$ L had been diagnosed with an opportunistic infection from 2009 to present. Most common opportunistic infections were *Pneumocystis jirovecii* pneumonia (PJP; n = 172), *Candida sp* infections (n = 143), mycobacterial infections (n = 51), and Kaposi sarcoma (n = 38). IRIS occurred in 38% of patients treated with InSTI-containing regimens and in 16% treated with non-InSTI-containing regimens. Overall IRIS risk was 2.6-fold higher (HR, 2.6; 95% CI, 1.3-5.1) among patients treated with an InSTI-containing regimen. In a second study conducted in a cohort of hospitalized patients from 15 centers in France (Abstract 732), investigators examined inpatients with CD4+ cell counts below 200/ $\mu$ L starting antiretroviral therapy between 2010 and 2015. The IRIS incidence was 2-fold higher (HR, 1.99; 95% CI, 1.1-3.5) among patients receiving InSTI-containing antiretroviral regimens than those not receiving an InSTI. InSTIs are well established as a component of initial antiretroviral regimens with many beneficial attributes. These data suggest that late-stage patients with opportunistic infections treated with InSTI-containing regimens versus those taking other antiretroviral drug combinations may be at increased risk for IRIS and merit careful monitoring.

### Fungal Treatment Studies

Jarvis conducted a phase II randomized study to determine if short-course induction therapy with high-dose liposomal (L) amphotericin (AMB; 5-10 mg/kg) could be a reasonable alternative to standard 3 mg/kg for 2 weeks L-AMB induction (Abstract 82). Eighty patients were randomly assigned to 1 of 4 treatment arms: single-dose L-AMB; 2-dose L-AMB; 3-dose L-AMB; or 2-week standard L-AMB induction. All participants also received high-dose fluconazole 1200 mg daily. Rates of fungal clearance at 14 days for the 3 short-course induction arms were all noninferior to the standard 2-week regimen. Authors report that single-dose induction will be evaluated in a larger phase III clinical endpoint study. Notably, the mortality in this study was 29%, indicating that prevention of this disease is a high priority in addition to optimizing outcomes.

The disseminated fungal disease *Talaromyces marneffeii* (formerly *Penicillium*) is a major cause of mortality among persons with AIDS in South and Southeast Asia. Amphotericin B induction, which is also used to treat cryptococcal disease, is recommended but often not available. Observational and in vitro studies suggest that itraconazole has good

**All-oral itraconazole treatment for talaromyces is associated with increased mortality than a regimen with AMB induction in a randomized study.**

activity against *T marneffeii*, but there has not been a direct comparison of itraconazole and AmB. Kinh and colleagues randomly assigned 440 HIV-infected adults with confirmed talaromyces in Vietnam to a 2-week AmB induction regimen or itraconazole induction regimen (Abstract 83). All patients received continued therapy with itraconazole. The primary study endpoint was mortality. At 24 weeks, mortality was nearly 2-fold higher in the itraconazole group (21.3%) than in the AmB group (11.3%) (HR, 1.88; 95% CI, 1.15-3.09;  $P = .012$ ). Consistent with these findings, clinical resolution and fungal clearance were faster, and relapse of infection was higher in the itraconazole-treated group than in the AmB-treated group. All-oral itraconazole treatment for talaromyces is associated with increased mortality than is AmB induction. In the short-term, improving access to AmB in these regions needs to be a priority. 

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