

# Complications of HIV Disease and Antiretroviral Therapy

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*There is growing interest in the pathogenesis, treatment, and prevention of long-term complications of HIV disease and its therapies. Specifically, studies focused on cardiovascular, renal, bone, and fat abnormalities were prominent at the 17th Conference on Retroviruses and Opportunistic Infections. Although enthusiasm about the effectiveness of current antiretroviral therapy remains strong, collectively, the ongoing work in the area of HIV disease and treatment complications appears to reflect concerns that these clinical problems will continue to remain important and possibly increase over time in the current therapeutic era. This year's conference also highlighted important data on prevention and optimal treatment of common coinfections that occur in HIV-infected individuals, including tuberculosis, influenza, and viral hepatitis.*

## Cardiovascular Disease

### Risk Factors for Cardiovascular Events

Several current studies are focused on quantifying the contribution of host- and disease-related factors that contribute to cardiovascular risk in HIV infection. Elevated triglyceride levels are common in HIV-infected patients, caused both by untreated HIV infection and by ritonavir exposure, yet the independent role of triglycerides has not been evaluated in large studies. Analyses presented from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study identified triglyceride levels as an independent risk factor for myocardial infarction (MI), with data from 33,308 patients and 580 MI events (Abstract 127). However, after adjustment for other known cardiovascular disease (CVD) risk factors and specifically high-density lipoprotein (HDL) and total cholesterol levels, the magnitude of the effect was reduced but remained statistically significant (relative risk [RR], 1.11; 95% confidence interval [CI], 1.01–1.23).

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Smoking remains a common and potentially modifiable risk factor for CVD. In another D:A:D study analysis, Petoumenos and colleagues demonstrated that the risk of CVD (with a composite endpoint including MI, invasive coronary artery procedure, carotid artery endarterectomy, stroke, or death from other coronary heart disease) was reduced in those who stopped smoking (Abstract 124). Compared with risk in current smokers, the incidence rate ratio of CVD statistically significantly decreased after 3 years since the cessation of smoking. Although these results are not surprising, they provide concrete evidence that HIV care practitioners can use when discussing the importance of smoking cessation in patients with HIV infection, and they highlight the need to identify effective strategies for smoking cessation for this population.

Visceral fat and lipoatrophy remain common problems for patients, especially those who have been receiving long-term HIV therapy. The contribution of visceral fat, as measured by single-slice computed tomography (CT) scan, to CVD events in HIV patients has not been well studied. Guaraldi and colleagues examined the relationship between CVD and visceral fat and contrasted this with measures of general adiposity (waist circumference and body mass index [BMI]) in a cohort of HIV-infected patients with prevalent coronary heart disease (Abstract 703). In this cross-sectional study, visceral adipose tissue (VAT) but not BMI or waist

circumference was associated with the prevalence of CVD in patients with fat accumulation or a mixed-phenotype lipodystrophy. Despite the limitations of this type of cross-sectional analysis, these results suggest that interventions to reduce the quantity of visceral fat hold promise for reducing rates of cardiovascular events.

There is great interest in the role of biomarkers in predicting cardiovascular (and other serious non-AIDS-related) events in patients with treated HIV infection. Investigators from the National Institutes of Health examined the relationship between serum biomarkers and CVD events in a case-control analysis that included 52 events among nearly 2000 patients enrolled in clinical trials since 1995 (Abstract 713). Cases in this study included incident CVD events (MI, silent MI, acute coronary syndrome, coronary revascularization, stroke, or peripheral artery bypass). Serum samples from 2 years and 3 months before the event were included in the analysis. After adjustment for traditional cardiac risk factors, D-dimer levels were higher in cases than in control subjects at both time points.

In contrast to previous studies,<sup>1</sup> no relationship between serum C-reactive protein (CRP) levels and incident CVD was observed. Several other factors were examined (vascular cell adhesion molecule 1 [VCAM-1], intercellular adhesion molecule 1 [ICAM-1], amyloid A, and tumor necrosis factor alpha [TNF- $\alpha$ ]) and not found to be associated with cases versus control subjects. Although these results are not strong enough evidence to promote routine monitoring of D-dimer levels in clinical practice, they do confirm earlier studies that demonstrated an association between D-dimer levels and all-cause mortality in patients with HIV<sup>2</sup> and highlight the potential role for disorders of coagulation to contribute to cardiovascular risk in HIV-infected patients.

Biomarker concentrations were correlated with Framingham risk scores (FRSs) in stored samples from a completed clinical trial (Abstract 702). Statistically significantly higher levels of the biomarkers high-sensitivity (hs)-CRP, interleukin-6 (IL-6), and lipoprotein-associated phospholipase A2 (Lp-PLA2) were seen in the subgroup with higher FRSs at baseline and during follow-up. Whether any of these biomarkers add to the predictive value of the FRS remains to be determined.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker for the diagnosis and prognosis of heart failure and a predictor of CVD in the general population. Investigators from the SMART (Strategies for Management of Antiretroviral Therapy) study performed a case-control study and found that higher baseline levels of NT-proBNP were predictive of CVD (Abstract 712). This relationship persisted after adjustment for baseline level of IL-6 but was no longer statistically significant when hs-CRP level was included.

Several groups presented data to try to elaborate a mechanism to explain the association between recent exposure to abacavir and the risk of MI observed in the D:A:D and SMART studies. Investigators from the STEAL (Switching to Tenofovir-Emtricitabine or Abacavir/Lamivudine) study compared changes in levels of biomarkers associated with CVD in patients randomly assigned to abacavir/lamivudine- or tenofovir/emtricitabine-based antiretroviral therapy (Abstract 718). The study examined markers of inflammation, coagulation and thrombosis, and endothelial function. Although higher levels of amyloid P were seen among abacavir recipients at week 24, there was no consistent pattern between any of the biomarkers and abacavir exposure.

In vitro studies using a human endothelial cell culture system suggested that abacavir exposure induces activation of the leukocyte integrin Mac-1, which then interacts with its ligand ICAM-1 (Abstract 716). This interaction between abacavir and leukocyte activation could potentially lead to leukocyte accumulation in the endo-

thelium. However, as noted above, no statistically significant changes in the levels of ICAM-1 were seen in abacavir-exposed patients in vivo.

Finally, and possibly most important, an in vitro study suggested that the active metabolite of abacavir, carbovir triphosphate, competitively inhibits activity of soluble guanylyl cyclase, a negative inhibitor of platelet reactivity (Abstract 717). Platelet hyperreactivity in the setting of abacavir exposure is a plausible mechanism to explain the associations observed in clinical studies and merits further evaluation through in vivo studies of platelet function in the presence of abacavir therapy.

Incomplete immune recovery during antiretroviral therapy has been associated with poor long-term outcomes in some cohort studies, yet the relationship with immune recovery and CVD is less clear. Investigators from the ATHENA (AIDS Therapy Evaluation in the Netherlands) cohort compared the rates of CVD and non-AIDS-related events in a group of patients whose CD4+ cell count failed to increase above 200/ $\mu$ L despite an undetectable viral load. Patients in this group had a statistically significantly higher rate of CVD events (4.9% within 5 years) than did patients in other groups whose CD4+ cell count had increased to levels above 200/ $\mu$ L (1.9%) (Abstract 714). The mechanism that underlies this relationship remains poorly defined (see Subclinical Coronary Disease and Vascular Changes).

### **Subclinical Coronary Disease and Vascular Changes**

A variety of noninvasive imaging modalities are currently used to investigate the pathogenesis of and identify risk factors for CVD in HIV-infected patients. The results may vary depending on which modality and specific measurements are used. Some of these modalities are limited to use in research settings, whereas others may have direct clinical applications.

Exercise stress testing is an accepted noninvasive means to screen patients thought to have an intermediate pretest probability for disease.

In patients with HIV infection, it remains unclear whether conventional measures to categorize asymptomatic patients into risk groups apply. Stress testing with nuclear perfusion imaging was performed in 80 asymptomatic HIV-infected patients with a mean FRS of 9% and in 50 control subjects (Abstract 711). Surprisingly, 20% of the HIV-infected patients had abnormal radionuclide (technetium-99) exercise stress test results, leading to interventions such as angioplasty (n = 8), stent placement (n = 8), or coronary artery bypass graft (n = 3). Larger studies are needed to compare the utility of different noninvasive screening tests for clinical use in HIV-infected patients and to determine whether the current Framingham risk scoring system performs adequately in this population.

### **Inflammation, Immune Activation, Senescence, and Carotid Intima-Media Thickness**

Several groups have utilized the noninvasive measurement of carotid intima-media thickness (IMT) as a surrogate marker for future cardiovascular events in HIV-infected patients. The studies vary in the segments of the carotid that are measured and the specific techniques, even when measuring the same segments. Although there are differences in these technical aspects, important findings have emerged from all of these studies.

At this year's conference, several groups focused on measures of inflammation and immune function and progression of carotid IMT in longitudinal studies. Hsue and colleagues confirmed their earlier findings of more rapid progression of carotid IMT in HIV-infected patients than in control subjects and again showed that hs-CRP level was associated with progression of IMT in HIV-infected patients (Abstract 125). In this study using a measurement protocol on 12 segments of the carotid artery, evidence for progression in the HIV-infected patients was strongest in the bifurcation region, and the association between hs-CRP level and progression was evident only at this location. A 3-year follow-up study

of 239 patients presented by Mangili and colleagues (Abstract 710) did not see an association with hs-CRP and IMT progression, although only common carotid segments were measured in this study. In the analysis, traditional risk factors were the strongest predictors of progression.

Kaplan and colleagues from the Women's Interagency HIV Study (WIHS) identified a relationship between T-cell activation as measured by CD38+HLA-DR+ markers on CD4+ and CD8+ T cells as well as a marker of T-cell senescence (CD57+CD28-) (Abstract 709). They found that markers of activation and senescence were associated with carotid artery distensibility and the presence of carotid lesions. Together these studies add further support for the hypothesis that ongoing inflammation, as well as traditional risk factors, may contribute to the risk of CVD in HIV-infected patients. An in vitro study of human coronary artery endothelial cells found evidence that exposure to ritonavir or lopinavir plus ritonavir was associated with increased expression of the senescence protein p16, decreased nitrous oxide production, and increased oxidative stress, suggesting a possible mechanism through which these drugs could contribute to the development of early CVD in vivo (Abstract 699).

### **HIV Disease, Antiretroviral Therapy Exposure, and Intima-Media Thickness**

Baker and colleagues in the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) research group measured common carotid IMT progression in a large 4-center study of 424 HIV-infected patients and found *lower* rates of IMT progression in patients who maintained a plasma HIV RNA level below 400 copies/mL throughout follow-up (Abstract 126). Additionally, they noted that among the HIV-infected patients, those who were receiving nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) therapy at baseline had lower rates of IMT progression. A combined analysis of 3 cross-sectional

studies of common carotid IMT identified male sex, older age, low-density lipoprotein (LDL) cholesterol level, smoking, and duration of ritonavir exposure as factors associated with carotid IMT (Abstract 705), confirming observations from earlier longitudinal studies. These data add to the growing literature to suggest that suppression of plasma HIV RNA level, and possibly specific antiretroviral therapy regimens, may help reduce the longer-term risk of CVD.

### **Kidney Disease**

Although uncontrolled HIV replication is detrimental to the kidneys, antiretroviral medications and host risk factors may also contribute to development of nephrotoxicity. Several cohort studies sought to elucidate the contribution of HIV treatment in general, as well as specific antiretroviral drugs, to the development or progression of renal impairment.

The Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort demonstrated an improvement in the rate of glomerular filtration rate (GFR) decline in patients with impaired renal function at baseline and in those receiving antiretroviral therapy without tenofovir or ritonavir (Abstract 735). This improved GFR slope was statistically significant only during the first year of antiretroviral therapy, after which GFR slope appeared stable. Individuals with normal kidney function at baseline showed an initial decline in GFR slope when measured by the Modification of Diet in Renal Disease (MDRD) equation but an increase in GFR slope when determined using the Cockcroft-Gault equation. Tenofovir with ritonavir was associated with a statistically significant initial decline in GFR slope by MDRD determination only during the first year of antiretroviral therapy and with stable GFR slope thereafter. However, tenofovir therapy alone was not associated with statistically significant changes by MDRD determination.

The Swiss HIV Cohort also reported tenofovir-containing antiretroviral therapy to be associated with a statistically

significant decline in estimated GFR (eGFR) by MDRD determination compared with non-tenofovir-containing antiretroviral therapy, with an average decline in eGFR of 2.40 mL/min/1.73 m<sup>2</sup> over a median of 2.5 years (Abstract 740). However, initiation of antiretroviral therapy was generally associated with an increase in eGFR of 0.68 mL/min/1.73 m<sup>2</sup> during the same time period. In a cohort of individuals coinfecting with HIV and hepatitis B virus (HBV), tenofovir treatment lasting up to 5 years was associated with decreased renal function, as evidenced by a small but statistically significant increase in mean serum creatinine level from 0.87 mg/dL to 0.93 mg/dL ( $P = .002$ ) (Abstract 631).

The EuroSIDA investigators found an independent, statistically significant association of new renal impairment with several individual antiretroviral drugs, including tenofovir (incidence rate ratio [IRR], 1.16), indinavir (IRR, 1.12), atazanavir (IRR, 1.21), and lopinavir (IRR, 1.08), regardless of the method used for calculating renal impairment (Abstract 107LB). Although indinavir has a recognized association with renal insufficiency,<sup>3,4</sup> the atazanavir and lopinavir associations have not been previously reported. Atazanavir-related nephrolithiasis was suggested as a possible explanation of the observed renal toxicity. Considering that this was an observational cohort, it is possible that individuals with a higher risk of vascular disease were preferentially treated with atazanavir because of its reduced impact on lipids, leading to a channeling bias. The long-term impact of newer drugs such as maraviroc, raltegravir, darunavir, and etravirine on renal function could not be examined in this cohort.

### **Bone Disease**

#### **Osteopenia and Loss of Bone Mineral Density**

More data on the rates of and risk factors for osteopenia and bone loss over time were reported this year (Abstracts 746–748). Several studies confirmed the association between loss of bone

mineral density (BMD) and use of tenofovir, both as initial antiretroviral therapy (Abstract 106LB) and in the switch setting (Abstract 723). The metabolic substudy of ACTG (AIDS Clinical Trials Group) 5202 demonstrated a higher percentage change in lumbar spine and hip BMD in patients who received tenofovir/emtricitabine than in those who received abacavir/lamivudine, and in patients who received efavirenz than in those who received atazanavir/ritonavir (Abstract 106LB). Two-year follow-up of a French cohort identified a high rate of pathologic bone loss over time and a high prevalence (76%) of vitamin D deficiency in the cohort (Abstract 747). A high prevalence of low BMD was described in a small group of patients with primary HIV infection and appeared to correlate with plasma HIV RNA level, at least for hip BMD (Abstract 745).

## Fractures

This year, 3 groups reported data on risk factors for and rates of fractures in HIV-infected patients and compared these with data in control groups from the general population. Investigators from the HIV Outpatient Study compared age-standardized fracture rates among HIV-infected persons over time with population-based data (Abstract 128). They reported the fracture rate to be 4.3 times higher in the HIV-infected group than in patients from the National Hospital Discharge Survey in the time periods examined since 2002. Hepatitis C virus (HCV) coinfection, lower CD4+ count nadir, diabetes, and substance use were each found to be independent predictors of fracture risk.

In the Veterans Aging Cohort Study, using a contemporary control group observed in the same setting, HIV infection was found to be an independent predictor of fracture only among older male veterans (Abstract 129). Finally, investigators from the WIHS examined fracture rates for HIV-seropositive women compared with control subjects after an average of 5 years of follow-up (Abstract 130). They identified that whites, menopausal women, and renal insufficiency, but not HIV

serostatus, were all predictors of fractures. Within the HIV-infected population, a history of AIDS, but not CD4+ cell count or antiretroviral therapy exposure, were associated with fractures. Collectively, these studies highlight the importance of monitoring fracture events in HIV-infected populations and identifying for targeted interventions those patients who may be at greatest risk.

## Bone Disease in Children Exposed to Tenofovir in Utero

Tenofovir is increasingly used as a component of first-line antiretroviral therapy; however, there have been concerns about the potential for bone toxicity in the developing fetus based on animal studies. Viganò and colleagues used quantitative ultrasound to measure bone density (specifically, measuring tibial speed of sound [SOS] with ultrasound) and markers of bone turnover in tenofovir-exposed and -unexposed children (Abstract 926). The absolute values for the tibial SOS measures were lower in the tenofovir-exposed children; however, the z scores were the same, and there was no difference in the levels of bone alkaline phosphatase or C-terminal telopeptide of type I collagen in this relatively small study.

## Vitamin D Deficiency

In addition to its well-known associations with bone disease, vitamin D deficiency is linked to a number of disease states important for people with HIV infection. These include cardiovascular disease, immunologic response to infection, malignancy, and obesity. Several studies at this year's conference addressed the issue of vitamin D deficiency in the setting of HIV infection from both resource-limited settings and in the context of current antiretroviral therapy.

Mehta and colleagues from Dar es Salaam and the Harvard School of Public Health have been studying the contributions of nutritional factors to HIV disease progression for many years. This year, they reported results

from their examination of the relationship between vitamin D deficiency and HIV disease progression using stored samples from a cohort of pregnant women who participated in a study in Tanzania of multivitamin supplementation that did not include vitamin D (Abstract 753). They found that HIV-infected women with low vitamin D levels (serum 25-hydroxyvitamin D < 32 ng/mL) had a 25% higher risk of their disease progressing to AIDS than did those with adequate levels. In addition, women who were deficient in vitamin D were at higher risk of weight loss and of having a range of clinical problems develop, including upper respiratory infections, thrush, and mucosal ulcers. Vitamin D deficiency was also observed commonly among both HIV-seropositive and -negative US women in the WIHS, and it was associated with bacterial vaginosis, a finding previously described in pregnant women (Abstract 754).

Campbell and Spector presented *in vitro* studies suggesting that the addition of the active form of vitamin D, 1,25-dihydroxycholecalciferol (1,25-[OH]<sub>2</sub>D<sub>3</sub>), to monocyte-derived macrophages could inhibit HIV replication (Abstract 231). They postulate that this occurs through the effects of vitamin D on autophagy proteins that appear to be required for productive HIV infection. Given the low cost and simplicity of vitamin D supplementation, these results suggest the need for randomized trials to examine the benefit of routine supplementation.

The prevalence of vitamin D insufficiency (defined as a serum level of 25-hydroxyvitamin D [25[OH]D] < 30 ng/mL) was estimated to be 72% in the SUN investigation (Abstract 750). As expected, blacks, Hispanics, and those with lower levels of UV light exposure were at higher risk. In addition, lack of exercise and efavirenz exposure were also associated with an increased risk of having insufficient levels. In the SUN cohort, use of ritonavir and a GFR below 90 mL/min/1.73 m<sup>2</sup> were protective against lower vitamin D levels.

Swiss HIV Cohort Study investigators measured vitamin D levels in patients before and after starting anti-

retroviral therapy and reported lower 25[OH]D levels for injection drug users and patients receiving NNRTIs, whereas tenofovir exposure was associated with higher levels (Abstract 752). These results confirm earlier published data linking efavirenz exposure to lower levels of vitamin D.<sup>5-7</sup> The clinical importance of these results is not yet known.

### Fat Accumulation and Lipoatrophy

Changes in body fat remain an important concern in the long-term management of HIV infection. Other than locally injectable fillers and modest effects from switching off stavudine or zidovudine, there are no proven interventions to reverse lipoatrophy. Previous studies suggested that supplemental uridine might improve mitochondrial function and reverse lipoatrophy associated with ongoing exposure to thymidine nucleoside analogue reverse transcriptase inhibitors (nRTIs).<sup>8-10</sup> A well-powered, randomized, placebo-controlled ACTG trial reported by McComsey and colleagues failed to demonstrate any improvement in lipoatrophy using a uridine supplement (Abstract 131). Although small improvements in lipoatrophy were noted in the uridine group at week 24, they did not persist over time. In addition, the supplement was not well tolerated; however, only 1 subject receiving treatment discontinued it because of protocol-defined toxicity.

Evaluations of body fat changes within randomized antiretroviral therapy trials continue to be an important means to determine the contributions of newer regimens to these problems. The superior lipid profile of raltegravir compared with efavirenz was demonstrated after 96 weeks of follow-up of patients randomly assigned to receive either of these drugs combined with tenofovir/emtricitabine (Abstract 720). Data from a small ( $n=55$  per group) dual-energy x-ray absorptiometry (DEXA) substudy in this same trial showed comparable increases in limb, trunk, and appendicular fat in both groups. Regimens that spare nRTIs continue to be investigated as a potential means to

prevent lipoatrophy from developing. Investigators from the MONOI-ANRS (French National Agency for Research on AIDS and Viral Hepatitis) 136 trial reported interim results of a DEXA substudy that compared rates of lipoatrophy among virologically suppressed patients who switched to darunavir/ritonavir monotherapy with rates among patients taking a triple-nRTI-containing regimen (Abstract 721). Results demonstrated that higher rates of lipoatrophy were observed in the nRTI-containing group (11%) than in the monotherapy group (1%).

### Tuberculosis and Influenza Coinfections

Coinfections with tuberculosis (TB) and the H1N1 strain of influenza A were highlighted at this year's conference, with a focus on optimizing prevention of these diseases with treatment for latent TB and with influenza vaccination. Promising data were reported on the effect of extended courses of preventative TB therapy on TB incidence and mortality in different geographic regions of the world. Initial reports on the impact of the H1N1 influenza epidemic on HIV-infected populations and the efficacy of H1N1 vaccination in HIV-infected patients were presented.

#### Tuberculosis Coinfection

Prevention of TB was the focus of 3 oral presentations. Samandari and colleagues presented the results of the joint Botswana–USA Centers for Disease Control and Prevention Project, the BOTUSA trial, which evaluated 1995 HIV-seropositive adults living in Botswana randomly assigned to a 3- or 36-month course of isoniazid preventive therapy (IPT) (Abstract 104LB). In the intent-to-treat analysis, they found a 43% reduction in TB cases in the 36-month group versus the 6-month group. The protective effect of isoniazid was lost promptly after discontinuation of the drug in the 6-month group. Similar to previous studies, individuals testing positive on tuberculin skin tests (TST) had the greatest reductions in TB rates. Among TST-positive persons,

the 36-month IPT group had a 92% reduction in TB rates compared with the 6-month group. Only a 14% reduction in the 36- versus 3-month IPT regimens was seen among TST-negative persons, which was not statistically significant. Among breakthrough TB cases in this trial, isoniazid resistance was detected in 17% of those in the 6-month group and 14% in the 36-month group.

The association of IPT with mortality was analyzed in a retrospective cohort study presented by Innes and colleagues (Abstract 102). The investigators evaluated survival outcomes in 3635 antiretroviral therapy-naïve individuals receiving health care in a mining workplace program in South Africa. They found that the mortality rate was lower in those who received IPT than in those who did not (3.5 vs 9.8 per 100 person-years), with a hazard ratio of 0.37 (95% CI, 0.25–0.54). These reductions were still observed if patients previously treated for TB were excluded from the analysis. Whether mortality was a direct consequence of isoniazid preventing TB or isoniazid served as a surrogate for patients more actively engaged in care and likely to receive a prompt diagnosis of AIDS complications could not be discerned from the analysis. However, this report was reassuring in that it showed favorable outcomes for a program with large numbers of HIV-seropositive persons receiving IPT in a setting with a high prevalence of TB.

Swaminathan and colleagues presented the results of a second randomized study of efficacy of 2 TB preventive strategies among 712 HIV-infected adults in India (Abstract 103). This study compared 6 months of treatment with ethambutol plus isoniazid to 36 months of treatment with isoniazid for the prevention of TB. Rates of TB were not statistically significantly different between the 2 groups, with 2.4 TB cases per 100 patient-years in the short-course, 2-drug group and 1.6 TB cases per 100 patient-years in the isoniazid 36-month group. Execution of this study spanned the introduction of antiretroviral therapy in India; thus, the study included patients with low CD4+ cell counts who were not yet

receiving antiretroviral therapy. Consistent with other studies, rates of TB were higher in patients with low CD4+ cell counts. Although the trend favored greater benefits among TST-positive persons, it did not reach statistical significance. Among the patients with TB and isolates available for drug-susceptibility testing, isoniazid resistance was present in 6 of 16, and multidrug resistance was present in 2 of 16.

How should these seemingly differing results among the studies on IPT be reconciled? These data are actually consistent with an accumulating body of evidence that demonstrates that IPT can be delivered safely in resource-limited settings in the HIV-infected population, that the greatest reductions in TB rates are detected among those who are TST-positive, and that in places like sub-Saharan Africa, where ongoing and repeated episodes of TB occur among HIV-infected patients, longer durations of preventive therapy result in greater overall reductions in TB rates. The jury remains out regarding the effect of IPT on mortality. The relative contribution of antiretroviral therapy and IPT to the reduction in TB rates is also an area of current study. These data support the justification of the new World Health Organization (WHO) recommendations for IPT, for which duration of IPT depends on the epidemiologic setting.

One randomized TB–antiretroviral therapy trial was presented in an oral session by Kayunga on behalf of Walusimbi and colleagues (Abstract 105). This study evaluated whether a 6-month course of antiretroviral therapy (abacavir, lamivudine, zidovudine) given concurrently with TB therapy would improve outcomes in HIV-infected adults with CD4+ T-cell counts of at least 350/μL. This trial included 232 Ugandan adults with a median CD4+ count of 584 cells/μL. Subjects were randomly assigned to immediate (6-month punctuated course) or deferred antiretroviral therapy. All patients with a CD4+ cell count of 250/μL or less received antiretroviral therapy.

There was no benefit to short-course antiretroviral therapy in this population. There was, however, a demonstra-

ble clinical benefit favoring immediate over deferred antiretroviral therapy at the 1-year follow-up point, supporting current WHO guidelines recommending antiretroviral therapy in all patients with TB regardless of CD4+ cell count. In addition, this study reported viral suppression rates of 86% at 6 months, no abacavir hypersensitivity reactions, and no immune reconstitution inflammatory syndrome among this group of patients, who may have limited options for antiretroviral therapy because of the toxicity profile of nevirapine and the teratogenicity of efavirenz.

The poster session on TB covered a wide range of topics, starting with TB screening. Danel and colleagues reported preliminary results from an IPT study enrolling HIV-seropositive persons with CD4+ cell counts in the range of 350/μL to 600/μL and no symptoms of TB, in whom isoniazid was to be initiated 1 month after enrollment (Abstract 774). The investigators found that 36 (7.7%) of the patients had symptoms of TB that prevented isoniazid initiation at 1 month; TB was confirmed in 14 of them. These data point to evolving strategies in which isoniazid is started 1 month to 3 months after antiretroviral therapy initiation to ensure that TB is not present at the start of IPT.

Studies from the United States and Africa support prior investigations indicating that TB rates increase the first 6 months after initiation of antiretroviral therapy but then decline over time to rates much lower than pre–antiretroviral therapy levels (Abstracts 777–779). Bliven and colleagues reported that 2-month TB sterilization rates do not differ between HIV-seropositive and HIV-seronegative populations and called for greater inclusion of HIV-seropositive patients in new TB drug treatment trials (Abstract 782). O'Donnell and colleagues reported outcomes for 60 patients (43 of whom were HIV-seropositive) with extensively drug resistant (XDR) TB in a referral hospital in South Africa (Abstract 787). Survival at 2 years was 50%. Of surviving patients, 11 were cured, 7 patients defaulted, and 12 experienced treatment failure. These data represent an improvement

upon the abysmal outcomes reported from the recent outbreak in KwaZulu Natal,<sup>11</sup> but at the same time they demonstrate the need for rapid diagnosis, new TB drugs, and improved health systems for these patients.

### **Influenza A (H1N1) Coinfection**

“Swine flu” swept through the world in 2009, and the HIV community braced itself accordingly. In a themed discussion, “Swine Flu Meets HIV,” data on clinical presentation and outcomes from the 2009 epidemic were presented, and immune responses to the new influenza A (H1N1) vaccine were described. A series from Spain found that clinical symptoms associated with confirmed H1N1 influenza were similar among 567 HIV-seronegative adults and 56 HIV-seropositive adults, with the exception of more gastrointestinal symptoms in the HIV-seropositive influenza patients (Abstract 802LB). Pneumonia and respiratory failure were actually less common in HIV-seropositive (9%) than in HIV-seronegative (25%) patients, although after adjusting for comorbidities, which were higher in the HIV-seronegative group, there was no difference between the groups in this outcome.

Complications of influenza in the HIV-infected population were more likely to occur in the sicker patients and in injection drug users. Notably, oseltamivir use was higher in the HIV-seropositive than in the HIV-seronegative populations. As this was an observational study, it was difficult to compare clinical presentations between HIV-seropositive and HIV-seronegative populations because HIV-infected patients in care may receive more aggressive screening, detection, and treatment of disease than the HIV-seronegative population would.

A second series from Mexico City examined outcomes in 22 HIV-seropositive patients with H1N1 influenza (Abstract 803LB). Twelve of the patients were hospitalized, 7 required intubation, and 5 died. There appeared to be a delayed detection of serious influenza among the HIV-infected population in this case series, which was attrib-

uted to the observation that several patients had concomitant opportunistic infections. Interestingly, in a small subset of patients, this group reported that viral shedding among patients treated with oseltamivir persisted for as long as 11 days. They reported no detection of resistance mutations. In a study by Campos-Loza and colleagues, only 6 cases of H1N1 influenza were identified by polymerase chain reaction in an HIV program caring for 967 patients (Abstract 801). One patient with concomitant *Pneumocystis jiroveci* and cytomegalovirus pneumonia died.

H1N1 influenza vaccine efficacy was examined by several groups. Bickel and colleagues reported vaccine response rates to the adjuvanted H1N1 influenza vaccine in 160 HIV-infected adults (Abstract 805LB). Vaccine response rates (seroconversion) were 69% in this population. Bickel reported in the discussion that in unpublished observations, patients who received 2 doses of the vaccine had higher seroconversion rates. In the ANRS study, 237 HIV-seropositive adults were randomly assigned to receive 2 doses of the adjuvanted or 2 doses of the nonadjuvanted H1N1 influenza vaccine (Abstract 804LB). After the first vaccine dose, the seroconversion vaccination response rates were 92% with the adjuvanted vaccine and 72.1% in the nonadjuvanted vaccine.

Tebas and colleagues evaluated response to the nonadjuvanted H1N1 influenza vaccine in 120 HIV-infected adults (Abstract 806LB). They reported a 53% seroconversion rate in patients with no preexisting antibody at week 3. Lower current and nadir CD4+ cell count was associated with poorer response. Nachman and colleagues reported the results of H1N1 influenza vaccination of 130 HIV-infected pregnant women (Abstract 808LB). The vaccine schedule was 2 vaccine doses separated by 21 to 28 days. There were no grade 3 adverse events, and immune studies are ongoing.

Much of the needed additional clinical research in this area is now stalled as the result of the fortunate waning of the H1N1 influenza epidemic. At least in the most recent round, H1N1

influenza did not appear dramatically worse in the HIV-infected population, and not surprisingly was more serious in the most immune-compromised patients. Vaccination was well tolerated, although response rates even with the adjuvanted vaccine were quite variable and generally lower than in the HIV-uninfected population. Data are needed to determine if 2 doses are better than 1, and to determine optimal vaccine preparations and dosing schedules in all populations, including pregnant women and children.

### Hepatitis Coinfections

This year's conference highlighted the morbidity and mortality benefits of curative HCV therapy as well as the increasingly recognized nonhepatic complications associated with HCV coinfection. Several host factors were demonstrated to be linked with improved response to therapy, such as the interleukin-28B (*IL28B*) C/C genotype and lack of insulin resistance. Presentations on HIV-HBV coinfections focused on the efficacy of tenofovir for control of viral replication and the potential consequences of ongoing HBV replication despite nRTI treatment.

### Hepatitis C Virus Coinfection

At the 2009 conference, the GESIDA (Grupo de Estudio de SIDA) investigators demonstrated that attaining a sustained virologic response (SVR) with HCV treatment was associated with reduced liver-related complications and mortality. This year, the GESIDA group reported that SVR with interferon plus ribavirin therapy was also associated with decreased AIDS progression as well as non-liver-related death (Abstract 167). In a regression analysis adjusted for fibrosis, nadir CD4+ cell count, and HIV disease stage, the adjusted hazard ratio of nonhepatic mortality and new AIDS-defining conditions was 3.78 (95% CI, 1.48 – 9.65) in patients without SVR versus those with SVR.

Similarly, data from the Veterans Aging Cohort Study Virtual Cohort highlighted the nonhepatic complica-

tions of HCV infection, demonstrating an increased risk of stroke in patients with HIV infection (HR, 2.13) and HCV mono-infection (HR, 1.44), as well as HIV-HCV coinfection (HR, 2.21), in comparison with uninfected control subjects (Abstract 668). The increasingly recognized proinflammatory effects of HCV replication may contribute to the observed HCV-associated vascular disease and AIDS progression. HCV infection was associated with elevated levels of the endothelial dysfunction markers soluble ICAM and soluble VCAM (Abstract 667), increased CD14+ monocyte activation (Abstract 672), and increased Fas-induced CD4+ apoptosis (Abstract 673).

Selecting the optimal timing for HCV therapy remains challenging, as timely treatment of HCV must be balanced with the knowledge that better HCV therapeutic options are in development. Sulkowski and colleagues reported that a baseline hepatic biopsy fibrosis score of 2 or greater (on a Metavir scale of 0–4) was independently associated with hepatocellular carcinoma, end-stage liver disease, and death over a median of 5.4 years in their HIV-HCV coinfecting cohort (Abstract 166). The incidence rate of these clinical outcomes jumped from a range of 20.9 to 26.8 per 1000 person-years for patients with fibrosis stages 0 to 1 to a nearly doubled incidence rate of 50.1 per 1000 person-years for patients with fibrosis stage 2. Incidence rates continued to rise to 59.2 and 71.4 per 1000 person-years with stages 3 and 4, respectively. These findings may caution against waiting for newer treatment options, particularly if a fibrosis stage of 2 or greater is demonstrated. Once disease has progressed to cirrhosis, the mortality rate was 5.8% per year, as shown in a Madrid cohort study of compensated HIV-infected patients with cirrhosis, who were evaluated by ultrasound elastography (Abstract 684). This rate is higher than that previously reported in HIV-uninfected cirrhotic patients.<sup>12,13</sup> Of note, only half of the deaths reported in this cohort were liver related.

Given the lower-than-desired response rates to interferon plus ribavi-

rin-based HCV treatment, selecting the best patients for HCV treatment and optimizing individual factors that may boost response are priorities. There was a proliferation of data on the *IL28B* gene as a predictor of spontaneous HCV clearance and favorable response to HCV treatment. The *IL28B* C/C genotype was associated with high rates (90%) of spontaneous HCV clearance (Abstract 163), as well as favorable response to interferon plus ribavirin therapy. The C/C genotype was associated with an SVR rate with interferon therapy of 75% compared with 38% in non-C/C genotypes (Abstract 165LB), and an adjusted odds ratio of SVR of 5.05 ( $P < .001$ ) (Abstract 656). An additional abstract reported an association of the *IL28B* C/C genotype with SVR; however, this association was no longer statistically significant after multivariate analysis (Abstract 164). Testing for *IL28B* polymorphisms may help optimize HCV outcomes by identifying those who are more likely to attain SVR with treatment and potentially permit modification of treatment regimens based on *IL28B* genetic profiles.

Insulin resistance has consistently emerged as a negative predictor of SVR. Presence of insulin resistance, defined as homeostasis model of assessment of insulin resistance (HOMA-IR) value greater than 2, was the only independent negative predictor of SVR (adjusted odds ratio, 0.17; 95% CI, 0.03–0.55) reported by Vachon and colleagues in their study of coinfecting patients undergoing retreatment for HCV with peginterferon alfa-2a and ribavirin (Abstract 655). Thirty-five percent of patients retreated for HCV achieved SVR if their HOMA-IR value was below 2, 14% with a HOMA-IR value from 2 to 4, and only 7% with a HOMA-IR value above 4. Pretreatment assessment of insulin resistance may be a powerful predictor of response, and measures to reduce insulin resistance such as weight loss or insulin sensitizers, before initiating HCV treatment, are under investigation.

Increased recognition of acute HCV infection presents an opportunity for improved treatment response and possibly an abbreviated course of therapy.

Encouragingly, Vogel and colleagues found that the infection spontaneously cleared without treatment in 40% of patients with acute HCV infection (Abstract 640). For those requiring treatment, Hare and colleagues presented a kinetically guided strategy for acute HCV infection therapy (Abstract 639). Thirteen subjects with acute HCV infection and with an undetectable HCV RNA level at 4 weeks received an abbreviated 12-week course of ribavirin along with 24 weeks of interferon. All 13 achieved an end-of-treatment response (undetectable HCV RNA level), and none rebounded during treatment, despite shortened ribavirin treatment.

### Hepatitis B Virus Coinfection

Tenofovir has become a mainstay of treatment for HBV infection in HIV coinfection. Several abstracts demonstrated that tenofovir appears quite effective in suppressing HBV DNA replication when taken for a sufficient length of time. After 5 years of tenofovir treatment, 88% of hepatitis B e antigen (HBeAg)-positive patients in a Dutch cohort had undetectable serum HBV DNA levels (Abstract 631), and 86.5% to 100% of patients in a Thai study had HBV DNA levels below detection after a median of up to 8.7 years of tenofovir treatment (Abstract 630). Tenofovir's efficacy was not affected by prior lamivudine or emtricitabine use in either study.

Individuals with persistent HBV viremia despite tenofovir therapy did not show evidence of tenofovir resistance in 2 studies (Abstracts 631, 636). Patients who do not achieve suppression of HBV replication with tenofovir treatment may respond to added entecavir; a pilot study found 4 of 5 patients had undetectable HBV DNA levels after 36 weeks of entecavir intensification (Abstract 636).

Persistent HBV viremia despite HBV treatment may have important public health implications by selecting for hepatitis B surface antigen (HBsAg) “vaccine escape” mutations, which have been shown to evade HBV vaccine-induced antibody protection in animal models. Lacombe and col-

leagues detected HBsAg mutations in up to 12% of individuals (2.1% per patient-year) with detectable HBV levels during nRTI treatment (Abstract 638). The rate of escape mutations doubled from 6% to 12% of patients over 3 years of the study, which the authors suggest may be attributed to rising use of tenofovir from 20% at baseline to 63% at the study conclusion. A cohort from Ghana exposed to lamivudine-containing HIV treatment without tenofovir demonstrated a 9% prevalence of HBsAg mutations associated with possible vaccine escape and 6% with novel HBsAg mutations, suggesting that lamivudine monotherapy also selects for potential vaccine escape mutants (Abstract 696).

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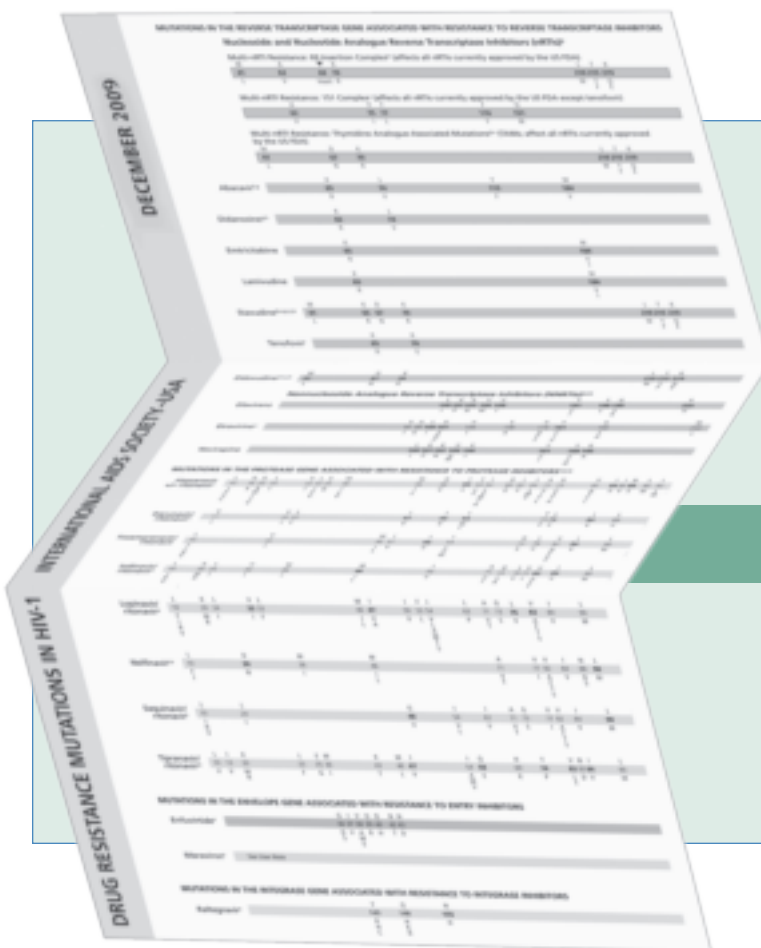
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