

# Complications of HIV Disease and Antiretroviral Therapy

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*Studies on new direct-acting antivirals (DAAs) for hepatitis C virus infection were a focus of the 2011 Conference on Retroviruses and Opportunistic Infections. Although the majority of the data were from HIV-uninfected patients, much-needed work has begun to characterize DAA and antiretroviral drug interactions and to evaluate performance of DAAs for HIV/HCV-coinfected patients. There was continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, lipodystrophy, renal disease, and alterations in bone metabolism. Malignancies, particularly non–AIDS-defining cancers, have emerged as a leading complication and cause of death in HIV infection that may not be fully mitigated by immune reconstitution with antiretroviral therapy. This year's conference also highlighted important data on the optimal timing of antiretroviral therapy in tuberculosis coinfection, as well as the treatment and prevention of common coinfections including cryptococcal meningitis and influenza.*

## Viral Hepatitis

### Hepatitis C Virus Protease Inhibitors: Boceprevir and Telaprevir

Some of the most exciting data presented at the 2011 Conference on Retroviruses and Opportunistic Infections came from the rapidly evolving field of new oral direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection, with the majority of data coming from HCV-monoinfected patients. Zeuzem gave an exceptional plenary presentation summarizing the current status of the HCV drug pipeline for both HIV-infected and -uninfected patients (Abstract 121). Data were presented on boceprevir and telaprevir, both of which are oral HCV NS3 protease inhibitors (PIs), the class of oral HCV drugs furthest along in development. Both NS3 PIs currently need to be given with pegylated interferon alfa and ribavirin to avoid the emergence

of drug resistance; however, development of entirely oral, interferon-sparing HCV treatment is actively being pursued.

Sulkowski and colleagues evaluated the use of boceprevir in HIV-uninfected HCV-genotype-1-infected, treatment-naïve patients in the SPRINT-2 (Serine Protease Inhibitor Therapy 2) study (Abstract 115). After an initial 4-week lead-in treatment period with pegylated interferon alfa plus ribavirin, patients were randomly assigned to 1 of 3 groups: a control group receiving 44 weeks of pegylated interferon/ribavirin; a group receiving boceprevir plus pegylated interferon/ribavirin for 44 weeks; and a group receiving boceprevir plus pegylated interferon/ribavirin in a response-guided strategy. In the response-guided group, participants with undetectable HCV RNA between week 4 and week 20 of 3-drug therapy discontinued treatment after a total of 24 weeks, whereas those with detectable HCV RNA between week 4 and week 20 of triple-drug therapy received an additional 24 weeks of pegylated interferon/ribavirin.

In the nonblack cohort, sustained virologic response (SVR) was attained in 40%, 67%, and 68% for the control group, the boceprevir response-

guided group, and the 44-week boceprevir group, respectively. As anticipated, cure rates in the black cohort were less than in the nonblack group, with SVR attained in 23%, 42%, and 53%, respectively.

Overall, patients receiving 44 weeks of boceprevir had SVR rates almost double those of the control group, and boceprevir response-guided therapy led to equivalent SVR rates in the nonblack participants. In those with a favorable response to the initial 4-week pegylated interferon/ribavirin treatment ( $\geq 1 \log_{10}$  drop in HCV RNA level), SVR was 2-fold higher than in those without initial favorable results. In patients not attaining SVR, those who responded to the lead-in treatment experienced reduced boceprevir resistance compared with those not responding to the lead-in treatment (4% vs 35%–47%, respectively). The most common adverse effects associated with boceprevir were anemia, which developed in 49% of boceprevir-treated participants, and dysgeusia.

Boceprevir treatment also led to robust SVR rates in HCV-treatment-experienced, HIV-uninfected patients. Boceprevir more than doubled SVR rates in patients with previous HCV treatment relapse (ie, undetectable HCV RNA at the end of therapy without subsequent attainment of SVR), with SVR rates of 29%, 69%, and 75%, respectively, after 48-week treatment with pegylated interferon/ribavirin, 44 weeks of boceprevir, or boceprevir response-guided therapy (32 weeks of boceprevir plus pegylated interferon/ribavirin, with an additional 12 weeks of pegylated interferon/ribavirin for those with detectable HCV RNA at 4 weeks of triple therapy) (Abstract 116). As observed in other HCV treatment series, patients previously nonresponsive to HCV treatment (ie, those showing a  $\geq 2 \log_{10}$  IU/mL decrease in HCV RNA by week 12 from baseline

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but with detectable HCV RNA on the remaining course of treatment) had lower rates of SVR than did patients with relapse, with SVR rates of 7%, 40%, and 52%, in the 3 groups, respectively. As in treatment-naïve patients, response to the initial 4-week lead-in therapy predicted SVR, with SVR rates of 33% to 34% (if  $< 1 \log_{10}$  IU/mL HCV RNA drop at week 4 from baseline) increasing to 73% to 79% (if  $\geq 1 \log_{10}$  IU/mL decrease) in the boceprevir groups, and from 0% increasing to 26%, respectively, in the control group.

In terms of anticipated drug interactions between boceprevir and antiretroviral drugs, boceprevir appears to be a strong inhibitor and modest substrate of cytochrome P450 3A4 (CYP3A4) (Abstract 118). Ritonavir coadministration had only a minimal effect on boceprevir steady state and reduced the boceprevir area under the curve (AUC) by 19%, whereas efavirenz coadministration reduced the boceprevir minimum plasma concentration ( $C_{min}$ ) by 44%, the clinical importance of which is unclear. Conversely, boceprevir modestly increased efavirenz AUC by 20% and maximum plasma concentration ( $C_{max}$ ) by 11%. Studies of boceprevir for HIV-infected, treatment-naïve and -experienced, HCV-coinfected patients are planned.

The first interim data on HCV PI use in HIV-coinfected, HCV-genotype-1-infected patients were presented by Sulkowski and colleagues (Abstract 146LB). The NS3 HCV PI telaprevir was administered for 12 weeks with pegylated interferon/ribavirin, followed by 36 weeks of pegylated interferon/ribavirin alone, and results were compared with those of a control group receiving 48 weeks of pegylated interferon/ribavirin. Unlike for boceprevir, studies of telaprevir have not used a 4-week lead-in treatment. Telaprevir treatment was associated with rapid virologic response (RVR, defined as undetectable HCV RNA after 4 weeks of triple-drug therapy) in 70% of participants, compared with 4.5% of control patients; it was also associated with complete early virologic response (cEVR, defined as undetectable HCV RNA at 12 weeks

of triple-drug therapy) in 68% versus 14%, respectively. These high early response rates with telaprevir treatment in hard-to-treat HIV/HCV-coinfected patients are very promising; SVR data from this trial are forthcoming. There was a trend toward lower cEVR rates with atazanavir-based antiretroviral therapy (57%) versus efavirenz-based antiretroviral therapy (75%) or no antiretroviral therapy (71%). However, the study was small ( $n = 60$ ) and had insufficient power to distinguish the effect of antiretroviral therapy on treatment response.

Van Heeswijk and colleagues examined the pharmacokinetic interactions of telaprevir and antiretroviral therapy (Abstract 119). Like boceprevir, telaprevir is also a substrate and inhibitor of CYP3A4. Despite increasing telaprevir dosing schedule to 1125 mg every 8 hours for coadministration with efavirenz, treatment with efavirenz plus telaprevir still leads to an 18% reduction in telaprevir AUC and a 25% reduction in telaprevir  $C_{min}$ .

Telaprevir had a heterogenous effect on HIV PI levels, raising atazanavir and lopinavir levels and decreasing darunavir and fosamprenavir levels. Telaprevir modestly decreased efavirenz levels and had minimal effect on tenofovir plasma levels. Until more data are available on appropriate dosing of coadministered telaprevir and antiretroviral therapy, caution is advisable with telaprevir use in antiretroviral-treated HIV/HCV-coinfected individuals, once telaprevir becomes available after US Food and Drug Administration (FDA) approval, which is anticipated to occur later in 2011.

### Acute Hepatitis C Virus Infection

As has been demonstrated in HCV mono-infection,<sup>1</sup> treatment of acute HCV infection (typically defined as the period up to 1 year since infection occurred) in HIV/HCV-coinfected patients leads to superior cure rates over those with chronic HCV infection. Boesecke and colleagues (Abstract 113) reported an overall 65% SVR rate in HIV-infected patients treated for acute HCV in-

fection with pegylated interferon alfa-based regimens, with higher SVR rates occurring in HCV genotypes 2 or 3 than in genotypes 1 or 4 (85% vs 61%, respectively;  $P = .003$ ). Heterogenous treatment regimens were used, but the median duration was 24 weeks, which is shorter than the 48 weeks typically recommended for treatment of chronic HCV infection in HIV coinfection. Ribavirin may not be needed for the full 24 weeks of pegylated interferon alfa administration for the treatment of acute HCV infection in those with a favorable early response in HCV RNA level. In a pilot study of a kinetically guided treatment strategy, in which ribavirin was discontinued after 12 weeks if HCV RNA was undetectable at week 8 and week 12, all patients who discontinued ribavirin attained an SVR after 24 weeks of pegylated interferon alfa, as did all patients who attained undetectable HCV RNA at week 4 (ie, RVR) (Abstract 959).

### Genetic Predictor of HCV Clearance: *IL28B*

Interleukin 28B (*IL28B*) single nucleotide polymorphisms (SNPs) have emerged as an important predictor of treatment response and spontaneous clearance of HCV in HCV mono- and HIV/HCV-coinfected patients. Favorable *IL28B* haplotypes predicted spontaneous clearance of HCV (Abstract 944) as well as response to pegylated interferon/ribavirin treatment for patients with HCV genotypes 1 and 4 (Abstracts 945 and 946) but interestingly not for those with genotype 3, for unclear reasons (Abstract 945). Consistent with data from HCV-monoinfected patients,<sup>2</sup> *IL28B* genetic polymorphisms do not appear to predict treatment response for patients with acute HCV infection (Abstract 943).

The favorable C/C *IL28B* genotype was associated with a higher baseline level of HCV RNA, which is somewhat counterintuitive, as a high HCV RNA level is associated with a worse response to therapy (Abstract 947). The authors postulate that this genotype may be associated with low endogenous levels of interferon alfa,

thus permitting high HCV RNA levels to develop, with enhanced sensitivity to exogenous interferon-based therapy and resultant higher SVR rates. Given the predictive value of *IL28B* status, this genetic marker is anticipated to become an important part of risk-versus-benefit analyses of optimal timing of HCV treatment.

### Complications of HIV/HCV Coinfection

Evidence for the nonhepatic complications of chronic HCV infection continues to accumulate. HIV and HCV infections are both known to independently reduce bone mineral density (BMD). A cohort study of Medicaid patients indicated that HIV/HCV-coinfected patients treated with antiretroviral therapy had a higher adjusted hazard ratio of both spine and hip fractures than did either HIV-monoinfected or HIV/HCV-uninfected patients. Coinfected patients also had a higher relative hazard of hip fracture than did HCV-monoinfected patients; the fracture risk was higher for HIV/HCV-coinfected women than for coinfecting men (Abstract 914).

Viral hepatitis may also be associated with increased intestinal permeability and an associated proinflammatory state, as indicated by findings from 3 studies: higher levels of gut-microbe-associated lipopolysaccharides (LPS) in HIV/HCV-coinfected patients than in HIV-monoinfected patients (Abstract 936); higher LPS and soluble CD14 (sCD14) levels in HIV/hepatitis B virus (HBV)-coinfected patients than in HIV-monoinfected patients (Abstract 937); and higher LPS, sCD14, and interleukin 6 (IL-6) levels in HCV- and HBV-monoinfected patients (Abstract 939) than in uninfected control subjects. Treatment of HIV and viral hepatitis infections was associated with reduction of these markers in some but not all of these studies.

In terms of predicting progression of liver fibrosis, low CD4+ cell count nadir and coinfection with HCV were independently associated with progression from no or moderate fibrosis (fibrosis stages F0–F2) to advanced fibrosis (stages F3–F4) over a 5-year time period (Abstract 921), support-

ing the need for early initiation of antiretroviral therapy for HIV/HCV-coinfected patients to avoid immunosuppression and progression of liver disease. Low-density lipoprotein (LDL) cholesterol level has also emerged as an important predictor of progression to hepatic fibrosis (Abstract 925). It is postulated that HCV uses the LDL cholesterol receptor to enter hepatocytes and disrupts the LDL cholesterol secretion pathway; low serum levels of LDL cholesterol may therefore reflect high levels of HCV intrahepatic activity.

Two studies were a sobering reminder for clinicians to counsel patients that they remain susceptible to HCV reinfection after HCV infection has cleared spontaneously or with treatment. In a cohort of 58 HIV/HCV-coinfected men who have sex with men (MSM) studied longitudinally, 21% were found to have a different strain of HCV virus from that at baseline, indicating interim reinfection (Abstract 912). Similarly, 6 of 26 HIV-infected MSM successfully treated for acute HCV infection were reinfected with a different strain during a median follow-up period of 1.1 years (Abstract 958).

### Hepatitis B Virus Infection

Although HCV coinfection with HIV infection is more common in the United States, coinfection with HBV remains an important contributor to morbidity and mortality. In the MACS (Multicenter AIDS Cohort Study) of HIV-infected and -uninfected MSM, liver-related death was statistically significantly higher for patients with chronic HBV infection than for those with HCV infection (incidence rate ratio [IRR], 2.04;  $P = .03$ ), including patients with HIV coinfection (IRR, 2.26), in whom the majority of liver-related deaths occurred (Abstract 968).

HIV/HBV-coinfected patients are frequently treated with tenofovir-based regimens for the drug's anti-HBV activity. In a model adjusted for several variables including race, CD4+ cell count, and plasma HIV RNA level, the presence of advanced liver fibrosis (fibrosis stages F3–F4) was associ-

ated with a 3.74 higher hazard ratio (95% confidence interval [CI], 1.57–8.9) of mild renal impairment (defined as glomerular filtration rate  $< 80$  mL/1.73 m<sup>2</sup> by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) in HIV/HBV-coinfected patients treated with tenofovir (Abstract 977). Monitoring of renal function may be of particular importance for HIV/HBV-coinfected, antiretroviral drug-treated patients with advanced fibrosis.

HBV/HIV-coinfected patients traditionally have a disappointing response to HBV vaccination.<sup>3</sup> Potsch and colleagues report a promising hepatitis B surface antibody (HBsAb) seroconversion rate of 83% with an accelerated schedule of a 40- $\mu$ g HBV vaccination administered at 0 months, 1 month, and 2 months, which increased to 91% with an additional dose administered at 6 months (Abstract 971). As in other series,<sup>4</sup> a CD4+ cell count greater than 350/ $\mu$ L was associated with a higher response rate to the additional dose at 6 months (85% for the 3-dose schedule and 93% for the additional dose).

### Cardiovascular Disease

There continues to be strong interest in the relationship between HIV infection and cardiovascular disease (CVD), with additional studies confirming independent contributions of HIV infection (Abstract 809) and immunodeficiency (Abstract 810) to myocardial infarction (MI) risk in large cohorts. New data on the pathogenesis, clinical outcomes, and risk factors for CVD were presented this year. The relationship between markers of inflammation and disordered coagulation remain an active area of investigation.

### Endothelial Function and Altered Coagulation

Measurement of the capacity of endothelium to release tissue type plasminogen activator (t-PA) is one index of endothelial function. Mestek and colleagues previously reported that treatment-naïve, HIV-infected patients have impaired release of t-PA as as-



sessed by the response to infusion of bradykinin and nitroprusside into the brachial artery.<sup>5</sup> At this year's meeting, the group examined t-PA release in treated HIV-infected patients and in age-matched and older HIV-uninfected adults and found that the HIV-infected group, regardless of treatment status, had impaired endothelial t-PA release (Abstract 802). Of note, the HIV-infected patients had a level of impairment comparable with that of uninfected adults 25 years to 30 years older, suggesting that vascular aging might be contributing to the higher rates of CVD observed in HIV-infected patients.

The SMART (Strategies for Management of Antiretroviral Therapy) study demonstrated a strong relationship between levels of D-dimer at baseline and all-cause mortality in patients who either discontinued or continued antiretroviral therapy.<sup>6</sup> The relationship between D-dimer and mortality was further explored using stored samples from the completed, randomized trials of interleukin 2 (IL-2), ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial), and SILCAAT (Study of Interleukin 2 in People with Low CD4+ T-Cell Counts on Active Anti-HIV Therapy) (Abstract 375). Overall, higher D-dimer levels were associated with mortality. Of note, those with the D-dimer levels in the highest quartile had an excess risk of death if they were assigned to receive IL-2; the mechanism explaining this association remains elusive.

Hsue and colleagues performed a comprehensive assessment of coagulation biomarkers, comparing 308 HIV-seropositive men with a small group (n = 38) of uninfected control men to determine which abnormalities were more prevalent in treated and untreated HIV-infected patients than in control subjects (Abstract 797). Untreated HIV infection was associated with a decrease in thrombin generation (which did not appear to be further altered by antiretroviral therapy) and an increase in a thrombin inhibitor, whereas no difference in D-dimer, tissue factor, or other coagulation markers were noted in this group of asymptomatic patients, suggesting

a more complex interaction of factors contributing to vascular events. On the other hand, higher levels of D-dimer, along with P-selectin and hyaluronic acid, independently predicted the risk of venous thromboembolic events in a case-control study of HIV-infected patients (Abstract 799).

Morse and colleagues from the National Institutes of Health compared biomarkers of coagulation and endothelial function in a group of HIV-infected patients with those of uninfected control subjects (Abstract 798). Higher levels of D-dimer correlated with levels of plasma HIV-1 RNA, markers of endothelial function, and tumor necrosis factor alpha (TNF- $\alpha$ ) in the HIV-infected group. Higher levels of the endothelial activation markers soluble intracellular adhesion molecule (sICAM), soluble vascular adhesion molecule (sVCAM), TNF- $\alpha$ , IL-6, and tissue factor, but not D-dimer, were noted in the HIV-infected group. These authors hypothesize that HIV infection may increase D-dimer levels through induction of endothelial activation, mediated by TNF- $\alpha$  released from monocyte and macrophage activation.

### Risk of Myocardial Infarction

Novel markers that might help identify increased CVD risk continue to be evaluated. Müllerian inhibiting substance (MIS), a marker of ovarian reserve, is an objective measure of menopause in women. LaCross and colleagues examined the association between levels of MIS and surrogate markers of atherosclerosis, carotid intima media thickness (IMT), and coronary artery calcium (CAC) in HIV-seropositive women (Abstract 804). Low levels of MIS, but not self-reported menopausal status, was strongly associated with the presence of CAC but not carotid IMT after control for age. The authors conclude that measurement of MIS might help identify HIV-seropositive women who are candidates for more aggressive risk factor management to prevent CVD.

The prognostic values of different lipid indices as predictors of MI risk were evaluated in a case-control study from the SMART study (Abstract 807).

Using age- and gender-matched cases (n = 100) and controls (n = 176), the ratio of apolipoprotein B to apolipoprotein A1 and the ratio of total cholesterol level to high-density lipoprotein (HDL) cholesterol level had similar predictive value and provided more information about MI risk than did individual lipoprotein measures in HIV-infected patients. Finally, measurement of soluble CD163, a marker of activated macrophages, was shown to be increased in men with well-controlled HIV disease and was associated with the presence of noncalcified coronary plaque, as measured by multidetector computed tomography (CT) angiography (Abstract 813).

The outcomes of acute coronary syndromes in HIV-seropositive patients were compared with those of HIV-seronegative control subjects using data from the Nationwide Inpatient Sample, a database of almost 300,000 patients at US hospitals (Abstract 801). Excluding patients over the age of 65 years, the authors reported that HIV-infected patients admitted to the hospital with acute coronary syndrome were younger and more likely to have a history of renal disease but less likely to have hypertension, hyperlipidemia, or diabetes than uninfected control patients. Importantly, HIV-seropositive patients had an increased risk of in-hospital death (3.3%) compared with HIV-seronegative patients (2.3%) and were more likely to incur acute renal failure during the hospitalization. These findings suggest that clinicians need to remain vigilant for signs and symptoms of coronary syndromes in younger patients with HIV infection who may not have traditional risk factors.

The relationship between recent abacavir exposure and MI risk remains controversial. An FDA meta-analysis of 26 randomized clinical trials with nearly 10,000 patients attempted to lay the issue to rest (Abstract 808). The analysis found no association between abacavir treatment and MI events, and the authors calculated that the sample size evaluated had sufficient power to exclude an MI-risk difference of 1%. The lack of independent adjudica-

tion of MI events and the comparison of abacavir to PI-based antiretroviral therapy in many of the trials still leaves some degree of lingering uncertainty. Studies evaluating in vitro and in vivo (animal model) effects of abacavir on leukocyte adhesion suggest a potential mechanism that could underlie this uncertain association (Abstract 815).

### **Bone Loss: Host Factors, Antiretroviral Drugs, or HIV Disease?**

Several studies this year helped untangle the contributions of host factors, HIV disease status, and antiretroviral drugs to the prevalent condition of bone loss observed in patients with treated HIV infection. Randomized clinical trials of tenofovir/emtricitabine or tenofovir alone used as preexposure prophylaxis (PrEP) in HIV-uninfected MSM provided the opportunity to evaluate the contribution of these drugs to bone loss in the absence of HIV infection.

Mulligan and colleagues reported the results of a bone substudy from the larger iPrEx (Preexposure Prophylaxis Initiative) trial (Abstract 94LB).<sup>7</sup> Dual-energy x-ray absorptiometry (DEXA) scans measuring BMD at the hip and spine were performed at 24-week intervals in 503 men randomly assigned to receive tenofovir/emtricitabine or placebo. The groups were well matched at baseline; notably, 36% had low BMD ( $z$  score  $< -1$ ) in the spine and 18% in the hip. BMD tended to increase in the placebo group (as would be expected in young men); however, the decrease in the tenofovir/emtricitabine group resulted in a modest ( $-0.7\%$  to  $-1.0\%$ ) but statistically significant difference between the groups by week 24.

In the smaller tenofovir PrEP safety study (Abstract 93), conducted in men with a median age of 40 years, there was a 1.1% decrease in mean BMD in the tenofovir versus pretreatment or placebo groups at the femoral neck and a 0.8% net decline at the total hip; both decreases reached statistical significance. Overall, 13% of the tenofovir recipients compared with 6% of the placebo group experienced

a 5% or more loss in BMD at the femoral neck in this study. Together, these studies demonstrate that low bone density appears to be common among young MSM at risk for HIV infection and that exposure to tenofovir, either alone or combined with emtricitabine, and in the absence of HIV infection, is associated with a small but statistically significant decline in BMD. The clinical importance of these changes is currently unknown and requires further study.

Peak bone mass is achieved in early adulthood, hence the effects of HIV infection and exposure to antiretroviral therapy among younger patients has become an active area of research, with several groups reporting new data this year (Abstracts 705–707, 823). Investigators in the Adolescent Trials Network examined associations between antiretroviral therapy exposure and HIV serostatus on BMD in a cross-sectional study of age-matched and race- or ethnicity-matched youth aged 14 years to 25 years (Abstract 705). Importantly, norms for the DEXA  $z$  scores included in this study were from a similarly aged population.

Total and regional fat measures were higher in the HIV-seronegative groups and lower in the antiretroviral therapy-naïve groups. Lean body mass and total and regional fat measures were lower in all HIV-seropositive groups and higher in the HIV-seropositive group that was antiretroviral therapy-naïve than in those receiving treatment. Mean BMD and  $z$  scores were consistently lower among HIV-seropositive participants receiving antiretroviral therapy, particularly in those receiving PIs, than in the HIV-seronegative group.

Of note, the low BMD in those receiving antiretroviral therapy was not explained solely by tenofovir use. Brazilian investigators identified low BMD in about a third of perinatally infected youth and a strong correlation between low BMD and lean body mass, highlighting the importance of interventions to improve nutrition to prevent bone loss in this age group (Abstract 706). An Israeli study of young women with HIV infection reinforced the importance of sun exposure, calcium intake, and

vitamin D status, in addition to skin color as contributors to BMD status (Abstract 823).

In one of the first randomized intervention studies for bone health among HIV-seropositive youth, perinatally HIV-infected children and adolescents aged 6 years to 16 years were randomly assigned to receive vitamin D (100,000 IU bimonthly) and calcium (1 g daily) ( $n = 30$ ) or placebo for both ( $n = 29$ ) for 2 years (Abstract 707). At follow-up, 25-hydroxy vitamin D concentrations were higher among the treated patients at 1 year and 2 years. However, although BMD improved in both groups, there was no additional improvement in the group receiving the supplemental vitamin D and calcium. The observation that three-fourths of the children in the intervention group had vitamin D levels below 30 ng/mL at least once during study follow-up suggested that challenges with adherence may have undermined the benefits of the supplements evaluated in this trial.

### **Is Bone Loss Mediated by Immune Reconstitution?**

Several studies have demonstrated that bone loss occurs within the first 6 months after the initiation of antiretroviral therapy but then stabilizes. To date, much of the work in this area has focused on the contributions of antiretroviral therapy to bone loss. Ofotokun and colleagues from Emory University examined the time course of changes in bone resorption among a small group of treatment-naïve HIV patients initiating antiretroviral therapy (tenofovir/emtricitabine/lopinavir/ritonavir) (Abstract 78). The researchers measured changes in the serum biomarker C-terminal telopeptide of type 1 collagen (CTX), an index of in vivo bone resorption, and in the receptor activator of nuclear factor kappa-B ligand (RANKL, an osteoclastogenic cytokine that can be secreted by T cells) at weeks 0, 2, 12, and 24.

During the early timepoints, they observed statistically significant increases in both of these markers, suggesting that early improvements in

immune cell function might mediate bone loss. The same group also examined the effects of T-cell reconstitution by the adoptive transfer of T-cells into T-cell null, T-cell receptor beta chain (TCR $\beta$ ) knockout mice and found that when the mice received the new T cells, a loss of bone density occurred that mirrored the effects observed in humans, with a rise in levels of CTx and RANKL.

Early changes in markers of bone resorption were also identified in the MEDICLAS (Metabolic Effect of Different Classes of Antiretrovirals) study, a randomized clinical trial that demonstrated a greater degree of bone loss with zidovudine/lamivudine/lopinavir/ritonavir than with nevirapine/lopinavir/ritonavir (Abstract 833). Bone biomarkers of resorption (tartrate-resistant acid phosphatase 5b [TRAP5b] and CTx) and biomarkers of bone formation (bone-specific alkaline phosphatase [BAP] and procollagen type 1 N-propeptide [PINP]) were measured on stored samples at baseline and at months 3, 12, and 24. Peak resorption appeared to occur by month 3; no data from earlier timepoints were available. Together these studies suggest a possible early-intervention window to prevent bone loss after the initiation of antiretroviral therapy. In addition, these findings suggest that a component of early bone loss may be mediated by immune reconstitution.

### Connections Between Bone Density and Fat Depots

Associations between regional body fat and bone density were explored in a cross-sectional study from the Women's Interagency HIV study (WIHS) (Abstract 835). Total fat and lean mass were independently associated with greater BMD in HIV-infected and -uninfected women. Of note, greater amounts of leg fat correlated with lower BMD, suggesting that regional fat depots may contribute to changes in BMD independently.

The impact on bone density of drugs used to manage lipodystrophy in HIV infection was evaluated in 2 studies. In a small, randomized clinical

trial, rosiglitazone did not reduce BMD compared with placebo (Abstract 832). The impact of tesamorelin, a growth hormone-releasing hormone agonist recently approved for the treatment of fat accumulation in HIV-infected patients, on markers of bone turnover (osteocalcin and N-terminal telopeptide [NTx]), was evaluated over 26 weeks in a randomized, placebo-controlled study among HIV patients with excess abdominal fat (Abstract 834). Treatment with tesamorelin 2 mg daily resulted in higher increases, relative to placebo, in markers of bone formation (osteocalcin) than in NTx, a marker of resorption. Whether these changes in bone turnover markers will translate into improvement in BMD remains to be seen.

### Fracture Risk and Antiretroviral Therapy

Cohort studies have suggested that HIV-infected adults are at higher risk of fracture than the general population.<sup>8</sup> Whether specific antiretroviral drugs contribute to this risk remains an active area of investigation. Yin and ACTG (AIDS Clinical Trials Group) colleagues examined the association between antiretroviral drug classes and risk of fracture in the ALLRT (ACTG Longitudinal Linked Randomized Trials) study, a long-term follow-up study of patients who have been enrolled in randomized trials of antiretroviral therapy (Abstract 830). In this analysis of 3372 mostly male (83%) HIV-seropositive participants with a median age of 39 years, the incidence of new fractures was 0.3 per 100 person-years (95% CI, 0.2–0.4). In univariate analysis, no single class of antiretroviral drug (PI, nucleoside analogue reverse transcriptase inhibitor [nRTI], or nonnucleoside analogue reverse transcriptase inhibitor [NNRTI]) or individual drug (tenofovir or efavirenz) examined was associated with fracture. In a multivariate analysis, factors associated with increased fracture risk were HCV coinfection and a diagnosis of osteoporosis at study entry, whereas Hispanic ethnicity was protective. These data suggest that over the long

term, antiretroviral therapy may not be an important contributor to fracture risk.

### Vitamin D

There continues to be great interest in the relationship between vitamin D deficiency and a variety of outcomes in HIV-infected populations. Investigators from the WIHS confirmed the high prevalence of low vitamin D levels in HIV-infected women and observed the absence of the expected variation with season (Abstract 822). Stored serum samples from the ECHO (Efficiency Comparison in Treatment-Naive HIV-Infected Subjects of TMC278 and Efavirenz) trial were used to compare changes in 25-hydroxy vitamin D (25(OH)D) serum levels and proportions of patients with 25(OH)D deficiency in patients receiving the investigational drug TMC278 (rilpivirine) versus efavirenz over 48 weeks (Abstract 79LB). The study demonstrated a decline in 25(OH)D with efavirenz (–6.2 ng/dL) and no change with TMC278 (–0.6 ng/dL). Patients with an insufficiency or deficiency in 25(OH)D at baseline had a statistically significantly lower risk of experiencing severe 25(OH)D deficiency with TMC278 (4%) than with efavirenz (20%).

Low levels of vitamin D and use of tenofovir both appear to be associated with elevations in parathormone (PTH) levels in HIV-infected patients (Abstract 825). The impact of vitamin D<sub>3</sub> replacement on levels of vitamin D and PTH was evaluated in an Adolescent Trials Network randomized, placebo-controlled trial of directly observed, monthly dosing of 50,000 IU vitamin D<sub>3</sub> or placebo for 12 weeks. Subjects were 18- to 24-year-olds stratified by use of tenofovir. At week 12, 52% in the vitamin D-replacement group had sufficient 25(OH)D serum levels, an increase from 17% at baseline, compared with 16% at baseline and at week 12 in the placebo group ( $P < .001$ ). A statistically significant decline in PTH levels (–6 pg/mL) was observed only in the tenofovir group receiving vitamin D<sub>3</sub>. These results suggest that vitamin D<sub>3</sub> replacement may



mitigate hyperparathyroidism in patients taking tenofovir; whether this translates into improvements in bone density must await the DEXA data from this trial.

Other studies evaluated the relationship between vitamin D and diabetes and surrogate markers for CVD. A retrospective Italian study suggested that vitamin D<sub>3</sub> supplementation was associated with a lower risk of incident diabetes (Abstract 827); however, data on vitamin D levels were not reported. No improvement in brachial artery flow-mediated dilation (FMD) was observed in a randomized controlled trial of vitamin D<sub>3</sub> supplementation (4000 IU daily for 12 weeks) (Abstract 829). Although the study was adequately powered to detect a 3% improvement in FMD, it was notable that during the relatively short period of follow-up, vitamin D<sub>3</sub> replacement led to only modest increases in vitamin D levels. Recent recommendations for screening and replacement of vitamin D may provide a starting place for patients with HIV infection until more definitive studies are available.<sup>9</sup>

## Lipodystrophy

### Fat in All the Wrong Places

There is little doubt that increased visceral fat is associated with poor long-term outcomes in HIV-uninfected adults,<sup>10</sup> but the contribution of visceral fat to mortality in HIV-infected persons has not been well studied. Investigators from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study (Abstract 76) examined the relationships between muscle mass, visceral fat, and survival in the HIV-infected cohort of this observational study. Participants in the highest tertile for visceral fat had a 2-fold higher mortality than those in the lowest tertile. Causes of death were not known, nor was it possible to compare the magnitude of the effect of visceral fat on mortality with that from an uninfected population. Despite these limitations, the findings serve as a reminder that excess visceral fat may have important long-term consequences in patients with HIV infection.

The relationships among visceral fat, coronary plaque, and coronary artery calcification were examined in HIV-infected and -uninfected men using data from the MACS (Abstract 806). Noninvasive coronary computed tomography angiography (CCTA) was used to measure total plaque area and coronary artery calcium (CAC). Abdominal (total, visceral, and subcutaneous) fat was measured by non-contrast CT scans; liver fat was also assessed. After adjustment for age, there were stronger associations observed between visceral abdominal tissue (VAT) and subclinical atherosclerotic plaque (defined as CCTA-diagnosed, combined calcified and noncalcified plaque) in HIV-uninfected men than in HIV-infected men. No associations were found between measures of CAC and specific fat depots in either group.

Epicardial adipose tissue (EAT) can be measured when coronary calcium is measured with noncontrast CT scans. EAT was associated with older age, greater amounts of VAT, male sex, waist girth, and liver fat in an Italian study (Abstract 805). Not surprisingly, increased amounts of EAT were associated with greater amounts of fat in other places (VAT and liver) and with CAC. The only clinical variable associated with greater amounts of EAT was CD4+ cell count increase from nadir, suggesting that immune reconstitution might play a role in the pathogenesis of the excess fat observed.

### Antiretroviral Therapy and Body Fat Changes: Coming and Going

Weight and body fat content are known to increase when antiretroviral therapy is initiated, especially among those with more advanced disease and pre-treatment weight loss. Newer regimens have been assumed to have minimal effects on body composition before now. A metabolic substudy of the ACTG study 5202<sup>11</sup> was a 4-arm trial of HIV-infected, treatment-naïve subjects randomly assigned equally to double-blinded abacavir/lamivudine versus tenofovir/emtricitabine with open-label efavirenz or ritonavir-boosted (/r) atazanavir. Endpoints in A5224s included

changes from baseline to week 96 in VAT and the ratio of VAT to total adipose tissue by CT scan (Abstract 77).

The study demonstrated that trunk fat and VAT increased 28% and 19%, respectively, for all subjects, with greater gains for those receiving atazanavir/r than for those receiving efavirenz, 36.5% versus 21.1%, respectively. Similar increases in trunk fat and VAT were observed between those receiving abacavir/lamivudine and those taking tenofovir/emtricitabine. The clinical importance of the greater amounts of VAT gained in the atazanavir/r arm are not immediately clear and may depend on the baseline starting point. These findings highlight the concept that different antiretroviral regimens may vary in their contributions to various metabolic and body fat changes.

The question of whether switching from a PI/r-based to a raltegravir-based antiretroviral regimen might reverse changes in abdominal and subcutaneous fat was evaluated in the 48-week SPIRAL (Switching from Protease Inhibitor to Raltegravir in HIV Stable Patients) study (Abstract 845).<sup>12</sup> In this study, patients (n = 73) who were virologically suppressed with any PI/r regimen were randomly assigned to either continue the same treatment or switch to a raltegravir-based regimen.

After 48 weeks, statistically significant increases in total abdominal fat area and visceral fat area as measured by CT were observed in the PI/r group, without changes in the subcutaneous fat area or in the ratio of subcutaneous fat to visceral fat. At the same time, no statistically significant changes were observed within the raltegravir group or between treatment groups. No significant changes were observed within or between groups in body fat distribution measured by DEXA (measures of limbs, trunk, total fat, and fat mass ratio). Although statistically significant increases occurred in total BMD and femoral BMD within the raltegravir group, these differences were not statistically significant when compared with the PI/r group. These findings, while not definitive, suggest that with a larger sample size or longer follow-up period, differences between the study

treatment groups might emerge. Results from comparative studies in treatment-naive patients examining these issues may provide more definitive results.

Earlier studies demonstrated that zidovudine and stavudine are both associated with loss of subcutaneous fat.<sup>13</sup> The degree to which this fat loss improves when zidovudine is switched to tenofovir has not been well studied but is important to determine as tenofovir becomes more widely available in resource-limited settings. A comprehensive, randomized study examined changes in limb fat, subcutaneous abdominal fat, and mitochondrial DNA (mtDNA) quantity and quality as well as adipocyte size and measures of gene expression in patients who continued with zidovudine or switched to tenofovir (Abstract 846). The tenofovir group experienced statistically significant increases in both subcutaneous adipose tissue and limb fat at week 48, with a statistically significant between-group difference in percentage of change in subcutaneous adipose tissue at week 48. In the molecular substudy, switch to tenofovir resulted in statistically significantly greater increases in mtDNA content and quality at weeks 24 and 48 and an increase in adipocyte size.

## Renal Disease

Chronic kidney disease (CKD) remains an important cause of morbidity in HIV patients. Investigators from the UK Consumer Health Information Consortium examined the effects of baseline renal function to long-term outcomes in more than 20,000 patients observed for a median of nearly 6 years (Abstract 836). Although the results are not surprising—lower baseline measures of renal function predicted which patients were at greater risk of progression of renal disease and risk of death—these findings underscore the importance of careful monitoring of renal function in patients who enter care with impairment.

Investigators from the SMART study evaluated the relationship between lipid levels and measures of renal function using stored samples from 396 patients. They found that unfavorable

lipid profiles (unfavorable total cholesterol: HDL cholesterol ratios and apolipoprotein B: apolipoprotein A1 ratios) were associated with higher cystatin C levels but not with estimated glomerular filtration rate (GFR) (Abstract 839). Another analysis from SMART observed that the rate of new or progressive CKD was higher among patients randomly assigned to discontinue antiretroviral therapy and that among those who continued antiretroviral therapy, progression of CKD was predicted by hepatitis coinfection and, as expected, by diabetes, hypertension, and older age (Abstract 837).

As the availability of tenofovir continues to expand in resource-limited settings, it is important to understand the patient characteristics that might preclude the safe use of fixed-dose regimens. In a randomized 3-arm trial, a small but statistically significant and nonprogressive decline in GFR was observed when tenofovir/emtricitabine was combined with atazanavir/r compared with efavirenz or abacavir/zidovudine (Abstract 841). Investigators from the University of North Carolina Project in Malawi reviewed data on patients (predominantly young women) who were screened for clinical trials that required a creatinine clearance of greater than 50 mL/min; the study aimed to identify factors associated with exclusion to inform strategies for antiretroviral treatment programs. Fortunately, among the 1224 patients eligible for antiretroviral therapy (those with CD4+ cell counts < 350/μL), 98% had creatinine clearance above the required 50 mL/min level (Abstract 838). Only lower BMI predicted reduced renal function. These results suggest that few patients would need to be excluded from a tenofovir-based initial regimen in this setting.

## Malignancy

AIDS-defining malignancy (ADM) and non-AIDS-defining malignancy (NADM) continue to grow as important causes of mortality. The Swiss HIV Cohort Study (SHCS) reported that NADM (19.1%) surpassed AIDS (16.4%) as the primary cause of death from 2005

through 2009 (Abstract 789). Together, NADM and ADM accounted for 25.8% of all deaths, in this largely antiretroviral therapy-treated cohort. HCV coinfection status substantially impacted the cause of death. Liver disease (excluding hepatocellular carcinoma) was the most frequent cause of death (27.2%) in HCV-coinfected individuals, whereas NADM (24.2%) was most common in HCV-uninfected persons.

The risk of death from NADM, as well as from liver disease and CVD, appears to increase with cumulative exposure to antiretroviral therapy in the EuroSIDA cohort, compared with those receiving antiretroviral therapy for less than 2 years (Abstract 790). These data suggest that HIV viral control alone may be insufficient to reverse the higher rates of malignancy associated with HIV infection. The US HIV Outpatient Study (HOPS) also reported an increase in rates of non-infection-related NADM but stable rates of infection-related NADM (Abstract 867). Encouragingly, however, HOPS data also indicated that survival in HIV-infected patients with any cancer diagnosis improved over time.

In a German cohort with limited immunosuppression and high uptake of antiretroviral therapy, mortality caused by lung cancer remained high, with a 2-year overall survival rate of 23.7% for HIV-infected patients with lung cancer (Abstract 868). Fifty of 51 (98%) of these patients were former or current heavy smokers, a reminder that smoking cessation is a key part of cancer prevention in the HIV-infected population, in whom smoking rates remain alarmingly high.<sup>14</sup>

Records from US children diagnosed with HIV infection between 1980 and 2008 indicate that the risks of Kaposi sarcoma and non-Hodgkin lymphoma remain elevated but have declined with widespread antiretroviral therapy use and that rates of NADM have remained stable, with a persistent, elevated risk of leiomyosarcoma in particular (Abstract 82LB). Persons diagnosed with HIV infection in childhood will need ongoing surveillance for cancer in adulthood, despite adequate immune reconstitution with antiretroviral therapy.



## Human Papillomavirus

Human papillomavirus (HPV) is an important driver of malignancy in HIV infection, and the risks of HPV acquisition and related complications do not appear to decline with antiretroviral treatment. Hoffmann and colleagues found the development of anal squamous cell carcinoma was not associated with level of immunodeficiency or HIV viremia and that disease-related mortality after a median of 2 years was 13% (Abstract 870). In a group of HIV-infected MSM, 24 months of antiretroviral therapy did not reduce rates of acquisition of HPV, with 23% and 12% acquiring new oncogenic HPV strains 16 and 18, respectively (Abstract 871). It was notable that HPV infection in this group was dynamic, with 29% and 57% clearing HPV strains 16 and 18, respectively.

In several HIV-infected cohorts of men and women from the United States and international settings, HPV strain 16 prevalence ranged from 30% to 50% and HPV strain 18 from 12% to 23% (Abstracts 762, 763, and 871), suggesting that HPV vaccination in HIV-infected individuals may have the potential to prevent acquisition of further oncogenic strains. However, a Thai study reported that 43% of high-grade anal intraepithelial neoplasia was associated with non-HPV 16 or 18 strains, highlighting the limitations of currently available HPV vaccines to prevent all oncogenic HPV infections (Abstract 872).

## Tuberculosis

The optimal timing of antiretroviral treatment during therapy for tuberculosis (TB) was addressed in 2 large, randomized clinical trials. The ACTG 5221 STRIDE (Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy) randomly assigned 806 HIV-seropositive persons with CD4+ cell counts less than 250/ $\mu$ L initiating treatment for TB to receive either immediate antiretroviral therapy (within 2 weeks of initiating TB therapy) or early antiretroviral therapy (within 8–12 weeks of initi-

ating TB therapy) (Abstract 38). This treatment strategy study included persons with either confirmed (46%) or probable (54%) TB and enrolled patients from 4 continents. At the end of 48 weeks, there was no difference between groups in the primary endpoint of death or AIDS-defining condition (12.9% in the immediate-treatment group vs 16.1% in the early-treatment group). However, in the prespecified analysis of those patients with a CD4+ cell count less than 50/ $\mu$ L, there was a 42% reduction in AIDS or death at 48 weeks, favoring the immediate-over the early-treatment arm (15.5% vs 26.6%, respectively;  $P = .02$ ). At 48 weeks, neither viral suppression rates (>70%) nor CD4+ cell count rise differed between the treatment groups. The frequency of TB immune reconstitution inflammatory syndrome (IRIS) was statistically significantly higher in the immediate- (11%) than in the early-treatment group (5%) ( $P = .009$ ).

In the SAPIT (Starting Antiretroviral Therapy at Three Points in Tuberculosis Therapy) study, 429 HIV-seropositive subjects in South Africa with CD4+ cell counts less than 500/ $\mu$ L and culture-positive TB were randomly assigned to initiate antiretroviral therapy either within 4 weeks of TB therapy initiation or within 4 weeks of completion of the intensive phase of TB therapy (Abstract 39LB). There was no difference between the 2 groups in the primary endpoint of AIDS or death. Similar to findings in the STRIDE study, in a prespecified analysis of those with CD4+ cell counts less than 50/ $\mu$ L, the rates for AIDS or death were lower in the immediate-treatment (8.5/100 person-years) than in the early-treatment (26.3/100 person-years) group (IRR, 0.32;  $P = .06$ ).

Rates of viral suppression and CD4+ cell count rise did not differ between groups, but rates for TB IRIS were higher in the immediate-treatment than in the early-treatment group (46.8/100 person-years vs 9.9/100 person-years, respectively, in those with CD4+ cell counts <50/ $\mu$ L; IRR, 4.71;  $P = .01$  and 15.8/100 person-years and 7.2/100 person-years in those with CD4+ cell counts  $\geq$ 50/ $\mu$ L; IRR, 2.2;  $P = .02$ ). Patients in the

immediate-treatment group also had more antiretroviral drug switches than did those in the early-treatment group.

In a symposium titled “Colliding Epidemics: Controlling HIV-Related TB,” Burman summarized the results and insights from the STRIDE, SAPIT, and CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals)<sup>15</sup> studies (Abstract 166). The important message from these studies is that combined antiretroviral therapy and TB therapy reduces mortality. For patients with CD4+ cell counts less than 50/ $\mu$ L, antiretroviral treatment needs to be initiated within 2 weeks of TB therapy initiation to reduce AIDS or mortality. For those with higher CD4+ cell counts, antiretroviral therapy can be initiated after the intensive phase of TB therapy (8 weeks) to avoid higher rates of TB IRIS that occur when antiretroviral treatment is initiated early.

Burman pointed out that TB meningitis may be the one exception to these recommendations because a prior randomized study in this population revealed no benefit, and possible detrimental effects, of initiating antiretroviral therapy immediately in this situation.<sup>16</sup> Challenges to implementing the new findings from the STRIDE, SAPIT, and CAMELIA investigations include ramping up HIV testing rates in TB patients, improving linkages between HIV and TB treatment programs, improving access to antiretroviral therapy for patients with HIV and TB, and equipping practitioners with information to manage TB IRIS.

In this year’s posters on TB in HIV-infected patients, a large observational study of 4908 HIV-seropositive patients with TB living in western Kenya reported improved survival among those starting early antiretroviral therapy, consistent with the results of the randomized clinical studies (Abstract 881). In a clinic-based study evaluating 1499 patients with HIV and TB from South Africa, it was similarly reassuring that there was no compromise in viral suppression rates or CD4+ cell count restitution among those initiating antiretroviral therapy earlier than later (Abstract 882).

New TB diagnostics is a very active and exciting field, although there was surprisingly little data presented at this meeting. Neither the interferon-gamma-release assay measuring free interferon gamma levels nor the urine lipoarabinomannan test showed good performance for the diagnosis of TB in HIV-seropositive patients (Abstracts 877 and 878).

However, in a very interesting abstract by Van Rie and colleagues, investigators from South Africa evaluated the performance of a new rapid polymerase chain reaction (PCR) assay (manufacturer: Cepheid, Sunnyvale, CA) as a diagnostic test for *Mycobacterium tuberculosis* and for resistance to rifamycin for the diagnosis of TB from lymph node aspirates (Abstract 879). They reported a sensitivity of 100% and a specificity of 93.8% compared with TB culture using a Mycobacteria growth indicator tube. Importantly, the PCR assay results were used to justify TB treatment initiation in 19 of 51 subjects.

Prior studies indicated that the performance of this rapid assay would be excellent using sputum specimens<sup>17,18</sup>; data from this pilot study now suggest that the assay may also be clinically useful for lymph node specimens. Additional studies are needed to evaluate other aspiration sites, including cerebral spinal fluid for the diagnosis of TB meningitis.

Another important topic and obstacle to implementing optimal treatment of TB in HIV-infected patients is the effective integration of HIV and TB services and care delivery. MacPherson and colleagues presented sobering results in an analysis from Zimbabwe of outcome of HIV-infected and HIV-uninfected patients suspected of TB who had negative results on acid-fast bacteria smears (Abstract 887). In a cohort of 1234 patients, mortality was 16.5% in the HIV-infected TB suspects, nearly 5-fold greater than for the HIV-uninfected TB suspects. Antiretroviral therapy was initiated in only 14.7% of eligible HIV-infected patients, in large part because of the fragmentation in care between HIV and TB treatment programs.

Combining HIV and TB care poses additional challenges, as highlighted by work presented by Bassett and colleagues (Abstract 886). Among 144 subjects identified with TB by sputum culture in an HIV care clinic in Durban, South Africa, only 42% had documented TB treatment completion at the end of 1 year. Twenty-five percent of the treatment-noncompleter subjects died, and 16% were lost to follow-up. The authors suggested that financial constraints and poor TB education represented barriers to accessing care in this population.

On a more optimistic note, Brown and colleagues examined the time to antiretroviral therapy initiation among patients with TB at a Khayelitsha, South Africa, clinic both before and after the clinic integrated HIV and TB care (Abstract 890). The median time to antiretroviral therapy initiation decreased from 110 days to 58 days for pre- and postintegration, respectively. Comparing outcomes with those of a clinic without treatment integration, the authors confirmed that “one-stop” care for HIV and TB was associated with a shorter time to antiretroviral treatment initiation, and that TB outcomes were not adversely affected.

### Cryptococcal Meningitis

Cryptococcal meningitis remains a major cause of morbidity and mortality, even in areas that have experienced rapid scale-up of antiretroviral therapy in resource-limited settings. Amphotericin-based regimens remain the gold standard in the developed world,<sup>19</sup> but even properly treated patients with severe disease still have suboptimal outcomes; amphotericin toxicity is substantial, and cost and delivery are challenging for many areas in Africa, where the burden of disease is high. For these reasons, investigators have designed a new generation of treatment studies for cryptococcal meningitis in attempts to improve efficacy and identify alternatives to the standard amphotericin regimens.

Several pilot studies were presented at the conference this year. Jarvis and colleagues randomly assigned 90 pa-

tients with cryptococcal meningitis to standard treatment of amphotericin B plus 5-fluorocytosine versus standard treatment plus either interferon-gamma 2-dose therapy (on days 1 and 3 of treatment) or 6-dose therapy (on days 1, 3, 5, 8, 10, and 12) (Abstract 40). The primary outcome of the study was the decline in quantitative cryptococcal cultures from the cerebrospinal fluid. Rates of fungal clearance were faster in each of the 2 interferon-gamma groups than in the standard treatment group. There was no increase in cryptococcal IRIS or toxicity in the interferon-gamma groups. Of note, mortality was 31% overall at 10 weeks and did not differ between the groups.

Muzoora and colleagues presented results of a single-arm pilot study evaluating a short-course amphotericin B-containing regimen in western Uganda (Abstract 894). Subjects were treated with amphotericin B (1 mg/kg/day) plus fluconazole for 5 days and then fluconazole for the remainder of the treatment regimen. Serial quantitative cryptococcal cultures showed a consistent decline that continued beyond the administration of amphotericin B. Patients tolerated the treatment well, and there were no interruptions for toxicity. Mortality was also high in this study—28% at 10 weeks.

In a third study, 80 patients with cryptococcal meningitis were randomly assigned to 1 of 4 groups: amphotericin B plus 5-fluorocytosine; amphotericin B plus fluconazole 800 mg daily; amphotericin B plus fluconazole 1200 mg daily; or amphotericin B plus voriconazole 300 mg twice daily (Abstract 893). There was no difference in fungicidal activity as measured by the decline in cerebrospinal fluid cryptococcal burden between the 4 treatment groups. Mortality was 39% at 10 weeks. Together, these studies demonstrate the possibility of deploying all oral, more effective, and more affordable regimens. However, much more work is needed in this area as evidenced by the extraordinarily high mortality rates (30%) observed among these patients in a carefully monitored, clinical trials setting.

## Influenza A (H1N1)

The focus on influenza A (H1N1) this year at the conference was not on clinical aspects of influenza A, as the number of cases has waned globally over the past 2 years. Rather, several new and follow-up studies examined the frequency, intensity, and durability of immunologic responses elicited by various H1N1 influenza A vaccination strategies.

Bickel and colleagues evaluated 135 HIV-seropositive patients after the first and second dose of adjuvanted H1N1 influenza A vaccine (Abstract 906). Seroconversion was 68% after the first dose and increased to 92% after the second dose; low CD4+ cell count was associated with lower rates of seroconversion. Cooper and colleagues examined the effects of a booster to an initial H1N1 adjuvant vaccine immunization in a randomized study of HIV-infected adults (Abstract 907). Seroconversion and seroprotection titers with the first vaccine were comparable to historical controls and were increased from the initial range of 73% to 76% to levels in the range of 83% to 94% in persons who received the booster, at days 21 and 42, respectively. Similar changes were not observed in the control group.

In a follow-up study from France that showed the benefit of adjuvant over nonadjuvant H1N1 influenza A vaccine, Durier and colleagues demonstrated that seroprotective titers persisted at 12 months in 60% of adjuvant-vaccine recipients and that predictors of a durable response included use of adjuvant versus nonadjuvant vaccine and the use of antiretroviral therapy (Abstract 909).

In an ongoing study comparing 2 single doses of adjuvanted H1N1 influenza vaccine in HIV-infected and HIV-uninfected adults, seroconversion and seroprotection H1N1 titers were higher among HIV-infected patients than among HIV-uninfected patients. Within the strata of HIV-infected patients with CD4+ cell counts less than 200/ $\mu$ L, seroconversion was higher with the double than with the single dose (Abstract 910).

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