

# Complications of HIV Disease and Antiretroviral Therapy

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*Studies on the efficacy of and drug interactions with the hepatitis C virus (HCV) direct-acting antivirals (DAAs) in HCV/HIV coinfection were a highlight of the 2012 Conference on Retroviruses and Opportunistic Infections. The addition of an HCV protease inhibitor (PI) to pegylated interferon alfa/ribavirin increased HCV cure rates by 30% to 35% in HCV genotype 1 treatment-naïve HIV-coinfected patients, an increase similar to that observed in HIV-uninfected HCV-infected patients. Drug interactions with antiretrovirals can be complex, and DAAs are recommended for use only with antiretroviral drugs for which pharmacokinetic data are available. Further drug interaction and clinical data are needed to ensure the safe coadministration of DAAs with antiretroviral therapy. The conference placed continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, lipodystrophy, renal disease, alterations in bone metabolism, and vitamin D deficiency, along with a growing focus on biomarkers to predict development of end-organ disease. HIV has increasingly been recognized as a disease of accelerated aging, manifested by increased progression of vascular disease, cellular markers of aging, and a heightened risk of certain non-AIDS-defining malignancies. This year's conference also highlighted data on diagnosis, prevention, and complications of tuberculosis coinfection as well as the treatment and prevention of coinfections that are common with HIV, including cryptococcal meningitis, influenza, and varicella zoster.*

## Viral Hepatitis

### DAAs in HIV/HCV Coinfection

The 2012 Conference on Retroviruses and Opportunistic Infections (CROI) provided long-awaited phase II sustained virologic response (SVR) data for the hepatitis C virus (HCV) direct-acting antivirals (DAAs) of the HCV protease inhibitor class, telaprevir and boceprevir, in HIV/HCV-coinfected individuals. In a phase II pilot study, 60 HIV/HCV-coinfected, HCV genotype 1 treatment-naïve patients were randomized 2:1 to receive 12 weeks of telaprevir or placebo, each with 48 weeks of peginterferon alfa-2a plus ribavirin (Abstract 46). Antiretroviral therapy (ART) was limited to efavirenz, ritonavir-boosted (/r) atazanavir, or no ART. Those on

efavirenz received telaprevir 1125 mg every 8 hours, rather than the standard 750 mg every 8 hours, due to the reduction in telaprevir levels caused by efavirenz coadministration. Overall, the SVR (HCV undetectable) rate at 12 weeks (SVR12) was 74% in the telaprevir group and 45% in the placebo group, for a difference of 29%. This is comparable to the increase in SVR rate demonstrated with telaprevir in HIV-uninfected, HCV genotype 1 treatment-naïve patients (75% SVR rate with telaprevir vs 44% with placebo).<sup>1</sup> Similarly, in a retrospective study comparing 25 HIV/HCV-coinfected patients with 34 HCV monoinfected patients all receiving therapy with telaprevir/peginterferon alfa/ribavirin, the on-treatment responses at week 4 (rapid virologic response [RVR]) and week

12 (early virologic response [EVR]) did not differ between HIV-infected and uninfected subjects. The SVR data are forthcoming (Abstract 754). It is notable that the placebo group in the phase II study attained an SVR12 rate of 45%, which is higher than typically reported in studies of peginterferon alfa/ribavirin treatment for HIV/HCV coinfection; this may in part reflect the limited fibrosis of the participants. The 24-week SVR (SVR24) data will be forthcoming, but SVR12 has an excellent predictive value for SVR24<sup>2</sup> and was accepted as an endpoint by the US Food and Drug Administration (FDA) in 2010. SVR12 rate in the atazanavir/r group was higher (80%) than in the efavirenz group (69%) and in the no-ART group (71%). The numbers in each group are too small to draw conclusions about differential efficacy of telaprevir in terms of concomitant ART. Telaprevir is associated with rash, which was more common in the group assigned to that drug (34%) than in the placebo group (23%). However, no cases of severe rash were reported. Pruritus, nausea, fever, and headache were more common in the telaprevir group, and, overall, more serious adverse events occurred with telaprevir (18%) than with placebo (9%). No virologic breakthrough of HIV occurred in any of the treatment groups. Of note, all study participants received 48 weeks of therapy. Data are not yet available on the feasibility of response-guided treatment to shorten treatment with telaprevir in HIV/HCV coinfection.

SVR12 data were also presented from a phase II trial of 100 HIV/HCV-coinfected, HCV genotype 1 treatment-naïve patients who were randomized 2:1 to receive boceprevir or placebo, each with 48 weeks of peginterferon

alfa-2b plus weight-based ribavirin (Abstract 47). Boceprevir 800 mg was administered 3 times a day for 44 weeks after a 4-week lead-in period with peginterferon alfa/ribavirin alone. Permissible ART included raltegravir, maraviroc, nucleos(t)ide analogue reverse transcriptase inhibitors (nRTIs) (with the exception of didanosine or zidovudine), and HIV protease inhibitors (PIs) boosted with ritonavir (PI/r), with the majority of participants on a PI/r. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) were not permitted. The SVR12 rate was 60.7% in the boceprevir group and 26.5% in the placebo group, for a difference of 34%, a difference similar to that observed with telaprevir in HIV/HCV coinfection, as well as with boceprevir in HCV mono-infection (66% SVR rate with boceprevir vs 38% with placebo).<sup>3</sup> Three participants in the boceprevir group have not yet reached the SVR12 time point. Adverse events leading to discontinuation were more frequent in the boceprevir group than in the placebo group (20% vs 9%, respectively), and adverse effects occurred more often with boceprevir than with placebo. These adverse effects included dysgeusia, fever, vomiting, anemia, and neutropenia. At week 48, virologic breakthrough of HIV occurred in 3 individuals in the boceprevir group and 4 in the control group. HCV resistance data are forthcoming from both phase II studies.

Drug-drug interactions with HCV PIs have been of particular interest since a 2012 FDA warning cautioned against coadministering boceprevir with HIV PIs, which substantially reduced HIV PI levels.<sup>4</sup> The supporting data from non-HIV-infected volunteers were more fully presented in Abstract 771LB. Coadministering boceprevir led to reductions in atazanavir/r, lopinavir/r, and darunavir/r areas under the concentration-time curve (AUC) by 35%, 34%, and 44%, respectively, and minimum concentration ( $C_{min}$ ) levels by 49%, 57%, and 59%, respectively. Conversely, boceprevir AUC and  $C_{min}$  were lowered by 45% and 57% in the presence of lopinavir/r, 32% and 35% by darunavir/r, and 5% and 18% by

atazanavir/r. Boceprevir does not appear to affect raltegravir AUC (Abstract 772LB). Pharmacokinetic data from non-HIV-infected volunteers for the investigational HCV PI TMC435, which is a substrate of CYP3A4, demonstrated that efavirenz greatly reduces TMC435 AUC by 71% and  $C_{min}$  by 91% and these drugs should therefore not be coadministered (Abstract 49). However, neither rilpivirine, tenofovir, nor raltegravir substantially affected TMC435 concentrations and were not in turn affected substantively by TMC435. They are therefore attractive ART options to pair with this HCV PI. Because TMC435 is a CYP3A4 substrate, data on coadministration with HIV PIs will be needed. Pharmacokinetic data for the investigational nonstructural protein 5A (NS5A) inhibitor daclatasvir were also presented (Abstract 618). Efavirenz decreased daclatasvir concentrations, and atazanavir/r increased daclatasvir levels. The recommended increase in daclatasvir dosage to 90 mg with efavirenz and decrease to 30 mg with atazanavir were each estimated to lead to therapeutic drug levels in an extrapolated dose model. Daclatasvir did not have a clinically relevant impact on tenofovir, efavirenz, or atazanavir concentrations.

Overall, these data serve as a reminder to proceed with caution when using HCV PIs and other DAA agents in HIV coinfection. HCV PIs may improve HCV cure rates by 30% to 35% but come with increased toxicity, and drug-drug interactions with ART may be complex and unpredictable. This was demonstrated by pharmacokinetic data on telaprevir, indicating that telaprevir increases atazanavir and lopinavir levels and decreases darunavir levels.<sup>5</sup> Although the rates of virologic breakthrough on HIV in the phase II study of boceprevir (Abstract 47) were similar to the rates in the largely HIV PI-treated boceprevir and placebo groups, prescribing HIV PIs or NNRTIs with boceprevir is not recommended until the clinical significance of the drug-drug interactions is better understood. Boceprevir is expected to have minimal drug interactions with raltegravir. However, clinical data for coad-

ministration are limited. Telaprevir can be coadministered with atazanavir/r, efavirenz (with appropriate adjustment of the telaprevir dose), and likely raltegravir, but coadministration with antiretroviral drug classes other than nRTIs is not yet recommended.

Additional DAA data from HCV-monoinfected patients were presented. The investigational nRTI GS7977 (formerly PSI 7977) generated excitement earlier this year with pilot data for the interferon alfa-free combination of GS7977/ribavirin for 12 weeks that resulted in a 100% SVR12 rate in 10 HCV genotype 2/3, treatment-naive, non-cirrhotic patients.<sup>6</sup> At this year's CROI, data were presented from a subsequent pilot study in which 10 HCV genotype 1 (90% genotype 1a), previous null responders received 12 weeks of GS7977/ribavirin (Abstract 54LB). The initial virologic response was robust, with all participants' HCV RNA undetectable by week 4, but 9 of the 10 participants relapsed by week 4 off treatment, demonstrating that in this harder-to-treat population, 12 weeks of this dual therapy was not sufficient. Findings on the efficacy of 12 weeks of GS7977/ribavirin in treatment-naive genotype 1 patients are expected to be presented this year; preliminary data from the 2012 EASL (European Association for the Study of the Liver) annual meeting demonstrated an 88% SVR4 (SVR after 4 weeks) rate in treatment-naive genotype 1 patients, the majority of whom (22/25) had genotype 1a.<sup>7</sup> The data illustrate that RVR, which is a positive predictor of attainment of SVR with interferon alfa-based regimens, does not appear to predict reliably SVR with interferon alfa-sparing treatments. The combination of GS7997 with ribavirin has not yet been evaluated in HIV-coinfected subjects.

### Acute HCV, HCV Reinfection, and Sexual Transmission

The European AIDS Treatment Network (NEAT) cohort presented observational data on outcomes associated with the treatment of acute HCV (Abstract 50). In a sobering reminder of the importance of screening for HCV

in at-risk populations of men who have sex with men (MSM), 95% of acute HCV infections were attributed to MSM sexual transmission, and only 25% of those were symptomatic. When diagnosed and treated during the first year of infection, 69.7% of the subjects were cured, far exceeding SVR rates typically seen with interferon alfa/ribavirin in chronic HIV/HCV coinfection. Of interest, the cure rates in patients with HCV genotype 2/3 improved from 60% to 94% ( $P = .007$ ) with the addition of ribavirin. There did not appear to be a significant difference in sustained virologic response rates between peginterferon alfa monotherapy and peginterferon alfa/ribavirin in patients with genotype 1 HCV (66.5% vs 70%, respectively;  $P = \text{ns}$ ). However, the administration of ribavirin was not randomly assigned, and the duration of therapy was variable, which may confound the interpretation of the apparent effect of ribavirin in genotype 2/3 HCV.

Once HCV has cleared spontaneously or with treatment, HCV reinfection can occur. A retrospective German cohort study reported that 45 HIV-infected MSM who had cleared a first episode of HCV, either spontaneously or with treatment, went on to develop second, third, and in one case fourth reinfections with HCV (Abstract 752). All reinfections were attributed to sexual acquisition. This report reinforces the need to counsel patients successfully treated for HCV about the risk of reinfection and patients with sexual risk factors about the possibility of HCV transmission through MSM sexual contact. The role of sexual transmission of HCV was highlighted in data from the SHCS (Swiss HIV Cohort Study), which showed that the epidemiology of HCV has shifted from a disease of injection drug users (incidence rate [IR] declined from 13.5/100 person-years of observation in 1998 to 1 incident case during 2008-2011) to a disease predominantly of MSM (IR of 0.2/100 person-years in 1998 increased to 7.4/100 person-years in 2011) (Abstract 743). Heterosexual transmission was rare, with an IR of 0.7/100 person-years.

### **Predicting Progression of Liver Disease and Cure with Peginterferon Alfa**

Understanding the risk of liver fibrosis progression is an important component of deciding on initiation of HCV treatment. In HIV/HCV-coinfected patients with limited fibrosis (transient elastography scores of  $\leq 9.5$  kPa, corresponding to Metavir fibrosis score of F0-F2), the Ariadne Index found the major determinants of progression to transient elastography scores greater than 9.5 kPa (approximate fibrosis score, F3-F4) included age (odds ratio [OR], 1.10 per year), extent of baseline fibrosis (OR, 1.98 per kPa), HCV genotypes 1/4 (OR, 5.02), and alanine aminotransferase (OR, 1.23 per 10 IU/L). The logistic regression model had a positive predictive value of 0.88 and a negative predictive value of 0.71 for progression to a fibrosis score of F3 or F4 over 5 years. Relying on elastography, which is not FDA approved, limits its usefulness in the United States for the Ariadne and Prometheus (see below) models.

Insulin resistance is also a risk factor for fibrosis progression, occurring in 56% of an HIV/HCV cohort and associated with an adjusted hazard ratio (aHR) of 5.79 (95% confidence interval [CI], 2.08-16.10) for progression to substantial fibrosis (defined as an aspartate aminotransferase to platelet ratio index [APRI] score  $> 1.5$ ) in those without frank diabetes (Abstract 782). Weight loss or therapies to improve insulin resistance prior to HCV treatment have been suggested. However, in a pilot study of HIV-coinfected patients with HCV genotype 1 and baseline insulin resistance while undergoing HCV retreatment, administering the insulin sensitizer pioglitazone for 24 weeks prior to as well as during peginterferon alfa/ribavirin treatment appears not to substantially improve week-24 HCV RNA virologic response compared with historical controls (15.8% vs 10%, respectively) and was associated with SVR in only 1 of 19 (5.3%) subjects (Abstract 783). Hepatic steatosis frequently occurs in HIV/HCV-coinfected patients. In a Spanish cohort, hepatic

steatosis occurred in 60% of HIV/HCV-coinfected patients who underwent 2 or more biopsies (Abstract 781). Fibrosis progression of stage 1 or higher was independently associated with persistence or progression of steatosis (adjusted OR, 2.4). Elevated fasting plasma glucose levels and the use of dideoxynucleoside RTIs (stavudine or didanosine) were also associated with a trend toward steatosis, although these are modifiable risk factors.

Considerable progress has been made in understanding the factors that predict a favorable response to peginterferon alfa-based HCV treatment. The Prometheus score, which incorporated IL28B genotype, liver stiffness by elastometry, HCV genotype, and baseline HCV RNA level, had a favorable area under the receiver operator curve (AUROC) of 0.87 (Abstract 761). Given that the prediction score was derived from an HIV/HCV-coinfected cohort, it is not surprising that the model performed less well in HCV monoinfection (AUROC, 0.77). A free, easy-to-use Internet application for this prediction tool is available at <http://www.fundacionies.com/prometheusindex.php?lang=ing>.<sup>8</sup> A large German cohort demonstrated that older age predicts a lower rate of SVR in HCV monoinfection and does so more markedly in HIV/HCV coinfection, in which the SVR for those aged 50 years to 60 years declined by more than half to 23.5%, compared with 50% in those aged 18 years to 30 years, with an adjusted OR for SVR at age 50 years to 60 years of 0.17 ( $P = .006$ ). Favorable IL28B genotype and low-density lipoprotein (LDL) receptor genotype have both been associated with SVR and, when evaluated together, may improve predictive value. The favorable LDL receptor allele C/C was correlated with a faster HCV RNA decline in patients on peginterferon alfa/ribavirin with an already favorable IL28B C/C allele (Abstract 765), suggesting a synergistic effect. A lack of the favorable IL28B C/C allele and of the LDL receptor C/C allele was associated with a 10-fold lower rate of RVR than was the presence of both favorable alleles in a small study (Abstract 765) and with an odds ratio of



0.13 for SVR ( $P < .001$ ) (Abstract 764). The importance of IL28B and LDL receptor genotype status with the newer DAA agents in HIV/HCV coinfection is not yet established.

### Impact of HCV on ART Hepatotoxicity and Efficacy

HCV coinfection has been associated with increased hepatotoxicity on ART. Although hepatotoxicity has declined somewhat with current ART in HCV-coinfected patients (37.5/100 person-years in 2004-2009 vs 24.6/100 person-years in 1997-1999), HCV-coinfected patients in the most recent time period still had up to a 12-times-higher relative risk of developing hepatotoxicity on ART than patients without HCV infection (Abstract 778). Similarly, in an analysis of several randomized AIDS Clinical Trials Group (ACTG) trials, the hazard ratio (HR) for developing earlier hepatotoxicity on ART was 1.53 for patients with HCV coinfection compared with those without HCV (Abstract 779). HCV-coinfected patients had statistically significantly earlier virologic failure of ART (72 weeks vs 182 weeks;  $P < .01$ ) than their HCV-infected counterparts, an aHR of virologic failure of 1.42, and a blunted CD4+ cell response to ART initiation.

### Low Rates of HCV Testing and Treatment in the HIV Population

Despite the importance of HCV as a growing driver of morbidity and mortality in the HIV population, HCV coinfection is underdiagnosed and undertreated. In a Florida cohort of more than 14,000 HIV-infected patients evaluated over 10 years, only 51% were ever tested for HCV. Of the 17.6% diagnosed with HCV infection, 44% were referred for hepatitis care, 12% were treated for HCV, and only 10% attained an SVR (Abstract 751). Improved diagnosis of HCV coinfection and access to HCV treatment will be crucial for HIV/HCV-coinfected patients to benefit from the HCV DAAs' tremendous promise of improved efficacy and shortened treatment.

### Hepatitis B Virus

Decline in quantitative hepatitis B surface antigen (HbsAg) levels has emerged as an important predictor of patient response to hepatitis B virus (HBV) treatment. In HIV-coinfected patients positive for hepatitis B e antigen (HbeAg) treated with up to 8 years of tenofovir, a decline in HbsAg of 2  $\log_{10}$  or more at month 6 was correlated with HbeAg loss by year 6. Patients with HbsAg less than 100 IU/mL at 6 months of treatment had a 71% probability of HbsAg loss, and none of the patients with HbsAg greater than 100 IU/mL attained HbsAg loss during a median follow-up of 56 months (Abstract 53). However, overall HbsAg loss was infrequent, occurring in 18% (8% HbeAg+ and 8% HbeAg-), indicating the long-term nature of HBV treatment in most HIV/HBV-coinfected patients. Suppression of HBV DNA alone with tenofovir can take years; only 56% had HBV DNA below the limit of detection after 1 year of tenofovir therapy (Abstract 796). Where available, tenofovir is the mainstay of HIV/HBV treatment, because lamivudine monotherapy for HIV is associated with high rates of HBV resistance in HIV/HBV coinfection.<sup>9</sup> A Malawi cohort of HIV/HBV-coinfected patients treated for HBV with only lamivudine as part of ART demonstrated that 85% of those with detectable HBV DNA at 48 weeks had HBV-resistance mutations, reinforcing the need for access to tenofovir-based regimens for managing HBV coinfection in resource-limited settings (Abstract 797).

### CVD and Ischemic Stroke

Identifying the mechanisms that underlie cardiovascular disease (CVD) risk in the setting of HIV infection continues to be an active area of investigation. Studies of treatment-naïve patients may provide some insights into the role of HIV infection. A cross-sectional study of relatively young (median age, 36 years) treatment-naïve patients found that traditional risk factors (ie, age, weight, small LDL) were independently associated with carotid

intima-media thickness (IMT), whereas HIV RNA, CD4+ T-cell counts, and markers of immune activation (CD38 expression on CD8+ and CD4+ T cells) were not (Abstract 801). A prospective study of carotid IMT progression in a group of untreated HIV patients matched to an HIV-uninfected group followed for 1 year demonstrated a higher rate of progression of carotid IMT in the HIV-uninfected group (Abstract 802). Independent predictors of a greater change in common carotid artery IMT in this study were higher body mass index and family history of CVD, whereas predictors of greater change in bulb IMT were higher soluble tumor necrosis factor receptor 1 (sTNF1) and higher diastolic blood pressure, and not other markers of inflammation. Together, these studies underscore the importance of traditional risk factors as a driving force for CVD in untreated HIV infection.

The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study, a prospective cohort, has yielded many important observations about risk factors for CVD in patients with HIV. Now with more than 223,242 person-years of follow-up, a larger number of events has been recorded, including 716 myocardial infarctions (MIs), 1056 coronary heart disease (CHD) events (MI or invasive procedure), 303 strokes, and 1374 CVD events, with overall rates of 3.21, 4.75, 1.35, and 6.21 events/1000 person-years, respectively (Abstract 822). Sabin and D:A:D colleagues examined the relationships between nadir CD4+ cell count and latest CD4+ cell and CVD events. The associations between immunodeficiency and the CVD events varied. The investigators found no evidence of a higher risk of MI or CHD (MI plus invasive procedures) in those with lower latest or nadir CD4+ cell counts. However, stroke and CVD (stroke plus CHD) rates were substantially higher in those with a latest CD4+ cell count less than 100/ $\mu$ L. Of note, prior cytomegalovirus disease was significantly associated with CVD risk but not with stroke and did not modify the relationship between latest CD4+ cell count and the risk of stroke or CVD. These findings underscore the

potential importance of preventing CD4+ cell count decline with earlier treatment of HIV infection as a means of reducing CVD.

Hypertension, an important risk factor for CVD, is receiving more attention in HIV-infected patients. Armah and colleagues from the VACS (Veterans Aging Cohort Study) Project Team, using data from the VACS database that includes more than 80,000 veterans free of CVD at baseline, examined whether the association between systolic blood pressure and risk for acute MI differed by HIV serostatus (Abstract 120). The risks of MI by JNC-7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) blood pressure categories were compared in the HIV-seropositive and -seronegative groups after controlling for other known CVD risk factors. The association between blood pressure category and the risk of acute MI was greater in the HIV-infected group at all levels, including the prehypertension group (systolic blood pressure 120 mmHg-139 mmHg on no medications). These findings have important implications for how we screen and manage CVD risk factors in patients with HIV.

The relationship between renal dysfunction and CVD risk received further attention this year at CROI. Investigators from the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) identified an association between declining kidney function and progression of carotid IMT (Abstract 804). The greatest impact of this association was found in those with the most impairment in renal function and among persons of older age or black race. An association between impaired renal function and CVD events was also noted in an Italian cohort with a small number of clinical events (Abstract 868).

Data from a large health care database that included an HIV-uninfected control group indicated an association between HIV infection and the risk for ischemic stroke (Abstract 820). The incidence rate of ischemic stroke in the HIV-seropositive cohort was 5.27/1000

person-years, compared with 3.75/1000 person-years in the HIV-seronegative cohort. After adjustment for several important confounders, the excess risk in the HIV group was attenuated but remained significant (HR, 1.21; 95% CI, 1.01-1.46;  $P = .043$ ). The excess risk associated with HIV was most notable in younger patients, a finding that was previously observed for CVD in a similar database analysis.<sup>10</sup> Within the HIV-infected cohort, higher viral load was associated with increased stroke risk, and the use of NNRTIs was associated with decreased stroke risk. The issue of sensitivity of ICD-9 (International Statistical Classification of Diseases and Related Health Problems, ninth edition) codes for the diagnosis of secondary MIs, was raised by a study from the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) (Abstract 821). Using data from an ongoing cohort that includes laboratory and electrocardiography (ECG) data from all inpatient and outpatient encounters, a group of reviewers adjudicated potential MI events and found that only 35% of the definite or probable MI events would have been captured by ICD-9 codes and that this was due to a high rate of secondary MIs (in the setting of sepsis or cocaine use). The results of this study underscore the importance of secondary MI events in the setting of patients with HIV infection and highlight the limitations of the reliance on ICD-9 codes for epidemiologic research.

Rates of sudden cardiac death (SCD) for patients with HIV infection have not been well studied. Tseng and colleagues examined such SCD rates by studying the records of 2860 patients who died between 2000 and 2009 (Abstract 824). SCD events were determined using standard criteria, and deaths in hospice or due to overdose, violence, suicide, cancer, or opportunistic infections were excluded. SCD accounted for 13% of all deaths and 86% of the cardiac deaths. Patients who died from SCD tended to have higher CD4+ cell counts and lower HIV RNA levels. The risk factors for SCD in patients with HIV warrant closer study.

## Endothelial Dysfunction

Asymmetric dimethylarginine (ADMA), a marker of NO<sub>2</sub>-mediated endothelial dysfunction that predicts the risk of CVD in the HIV-uninfected population, received a lot of attention at the conference (Abstracts 831-833, 841). In a cross-sectional study comparing HIV-seropositive patients to controls, ADMA levels were higher in the HIV-infected group. Lower CD4+ cell count and higher HIV RNA level were associated with higher ADMA level (Abstract 833). ADMA level was also associated with pulmonary hypertension in another study (Abstract 841). Previous studies have demonstrated that endothelial function, as measured by flow-mediated dilatation of the brachial artery, improves when ART is initiated. It was therefore reassuring to see improvements in ADMA in patients started on ART (Abstracts 831, 832). Baker and colleagues from the INSIGHT/SMART (International Network for Strategic Initiatives in Global HIV Trials/Strategies for Management of Antiretroviral Therapy) Study Groups reported a decline in ADMA among patients starting ART compared with those who deferred therapy (Abstract 831). The decline in ADMA was greater among those with higher baseline levels of high-sensitivity C-reactive protein (hsCRP) and D-dimer but did not differ according to HIV RNA level or CD4+ cell count. More long-term studies are needed to determine whether declines in ADMA on ART predict reduced risk for future CVD events.

Questions remain about the association between specific antiretroviral agents and changes in endothelial function and markers of inflammation. Wohl and colleagues reported the results of the NICE (Nucleoside Inflammation, Coagulation, and Endothelial Function) Study (Abstract 838), a cross-sectional study in which flow-mediated dilation (FMD) of the brachial artery and markers of inflammation were compared among patients who had originally been randomly assigned to receive ART including either abacavir or tenofovir. Individuals who had been receiving ART regimens containing

zidovudine served as the control group. Lower (more impaired) FMD was observed in the abacavir group (3.9%) and the tenofovir group (4.5%) than in the zidovudine group (6.1%). However, lower levels of hsCRP and D-dimer were observed in the abacavir and tenofovir groups. Prospective randomized studies will be required to lay this issue to rest.

### Novel Imaging Methods and CVD

New data from novel imaging modalities were employed to investigate the prevalence and mechanisms of CVD in HIV patients. Subramanian and colleagues used fludeoxyglucose positron emission tomography ( $^{18}\text{F}$ FDG-PET) to evaluate arterial-wall inflammation in HIV-infected patients in relation to traditional and non-traditional risk markers, including coronary calcium and a marker of macrophage activation, soluble hemoglobin scavenger receptor (sCD163) (Abstract 121). HIV-infected participants with low Framingham Risk Scores (FRS) were compared with a matched HIV-seronegative group. A third group with known atherosclerotic disease served as positive controls. Arterial inflammation was higher in the HIV-seropositive subjects than in the FRS-matched control subjects but was similar to that of the atherosclerotic controls. When the analysis was restricted to the group with zero coronary calcium detected by computed tomography (CT) scan, the intensity of arterial inflammation remained greater in the HIV-seropositive group. Arterial inflammation as measured by  $^{18}\text{F}$ FDG-PET was associated with the macrophage activation marker sCD163 but not with hsCRP. These findings suggest that macrophage activation may contribute to atherosclerosis in HIV; they also uncover a substantial amount of disease in patients deemed to be at low risk according to traditional measures. Cardiac magnetic resonance imaging and magnetic resonance spectroscopy were used to assess myocardial fibrosis, cardiac systolic and diastolic function, cardiac torsion, and intramyocardial lipids in a descriptive study of myocardial disease in an observational

study of 104 HIV-infected patients and 39 age-matched controls without a history of CVD (Abstract 810). In addition, transthoracic echocardiography was used to measure cardiac diastolic function. The prevalence of midwall and epicardial myocardial fibrosis of the left ventricle was significantly higher in the HIV-infected group. Myocardial lipid content was 43% higher in the treated HIV-infected patients than in the controls. The prevalence of systolic and diastolic dysfunction was higher in the HIV-infected group and most notable among the smaller group of ART-naïve participants. Longitudinal assessments of HIV-infected patients initiating therapy are needed to determine the time course and relationship between the development of myocardial fibrosis and steatosis and ART and to determine the clinical significance of these findings.

The MACS (Multicenter AIDS Cohort Study) group investigated the relationship between fat depots, markers of inflammation, and other factors associated with coronary plaque in a large cohort of HIV-seropositive and -seronegative men. Using CT angiography, the group was able to examine the prevalence of coronary plaque and to distinguish calcified plaque from the earlier-stage, noncalcified plaque. This distinction is important, as non-calcified plaque may be more prone to rupture. Plaque composition was graded in coronary segments to generate scores for total, noncalcified, mixed, and calcified plaque (Abstracts 807-809). The prevalence of coronary plaque did not differ between the HIV-seropositive and seronegative men, but non-calcified plaque was more common in those with HIV and appeared to be associated with nadir CD4+ cell counts. Higher plasma levels of interleukin 6 (IL-6) and tumor necrosis factor- $\alpha$  receptor 1 (TNF $\alpha$ -R1) were associated with measures of advanced HIV disease and increased subclinical coronary atherosclerotic plaque (Abstract 808). In both HIV-seropositive and -seronegative men, larger amounts of visceral fat were associated with higher plaque scores. However, the relationship between subcutaneous fat, liver

fat, and plaque varied by HIV serostatus. Lower amounts of subcutaneous fat correlated with greater amounts of mixed plaque only in the HIV-seropositive group. These findings support the idea that inflammation contributes to atherosclerosis in HIV-infected patients and might shed light on the importance of noncalcified plaque in patients with HIV infection.

### Interventions to Reduce Cardiovascular Risk

There are limited data from randomized controlled trials on outcomes of interventions aimed at reducing cardiovascular risk. Fitch and colleagues reported the results of a small, double-blind, placebo-controlled, 12-month study of 50 HIV-infected patients with metabolic syndrome that compared the effect of lifestyle modification (LSM; 60 minutes of exercise 3 times per week, with weekly nutrition counseling) with metformin (500 mg twice daily for 3 months, followed by 850 mg twice daily) on the progression of coronary artery calcification (CAC) as measured by CT scan (Abstract 119). After 48 weeks of follow-up, 72% of the participants remained in the study. Progression of CAC was statistically significantly reduced in the metformin-treated group compared with the LSM group. These results were driven by a high rate of CAC progression in the placebo groups (these groups also had a higher prevalence of CAC at baseline) compared with minimal change in the metformin group. The finding of a 56% change in CAC over 1 year in the placebo groups was noted as a striking rate of progression, much greater than what has been reported in the general population. The authors also noted that the sample size may have been too small to demonstrate an effect of LSM. This is the first study to show a potential benefit of metformin for reducing CAC progression in general and, in particular, in patients with HIV infection with metabolic syndrome. The findings warrant further research in a larger study and more investigation to determine whether metformin will reduce cardiovascular events.



Statin drugs have been demonstrated to reduce mortality in patients with prior cardiovascular disease, and there is great interest in other properties of the drugs in its class due to their potential to reduce inflammation. By examining the outcomes of patients who initiated statin therapy during long-term follow-up in ACTG studies, Overton and colleagues explored whether statins reduce the risk for serious non-AIDS events and all-cause mortality (Abstract 124). Statin use was not associated with a reduction in mortality in the group overall; however, among the subgroup over the age of 50 years, the risk of mortality was lower among the statin users. In exploratory analyses, statins appeared to have a protective effect in reducing malignancy events (see Malignancies, below). Although limited by the observational nature of this cohort, these pilot findings should help to guide future efforts to explore the potential benefits of statin drugs for patients with HIV.

Finally, a pilot study examined the impact of pravastatin and lisinopril in virologically suppressed patients with a modest level of CVD risk. The researchers found a statistically significant reduction in biomarkers of inflammation (hsCRP and TNF $\alpha$ -R1) in the lisinopril-treated patients but saw no improvement in lipids or inflammatory markers in the group receiving 20 mg of pravastatin (Abstract 825). Future studies of statin therapy, targeting patients at highest risk of long-term complications, appear to be warranted.

### **Biomarkers of Inflammation and Risk of End-Organ Disease**

There continues to be tremendous interest in identifying biomarkers that predict the risk of end-organ disease (eg, CVD and hepatic and renal events) in HIV-infected patients. Previous studies have found strong associations between markers of inflammation (hsCRP and IL-6), altered coagulation (D-dimers) and microbial translocation, and morbidity and mortality in treated and un-treated HIV infection. Investigators from VACS examined lev-

els of these biomarkers in HIV-infected veterans and a matched group of HIV-uninfected veterans with a similar burden of comorbid diseases and found that higher levels of the biomarkers IL-6 and D-dimer (> 75th percentile) were most notable in the HIV-seropositive veterans with an unsuppressed HIV viral load or a low CD4+ cell count. Higher levels of soluble CD14 (sCD14) were only seen in the HIV group with CD4+ counts lower than 200 cells/ $\mu$ L (Abstract 829).

### **Microbial Translocation and Clinical Outcomes**

It has been postulated that the loss of gut lymphoid tissue early in the course of HIV infection can lead to microbial translocation. However, the direct relationship between markers of microbial translocation and the progression of clinical disease and mortality remains incompletely understood. Hunt and colleagues examined the relationship between plasma markers of inflammation, monocyte activation, coagulation, indoleamine 2,3-dioxygenase (IDO)-induced tryptophan catabolism, and gut epithelial barrier dysfunction (intestinal fatty acid binding protein [I-FABP] and zonulin, a protein involved in tight junctions between gut cells), and mortality in a case-controlled study of treated virally suppressed patients with a history of AIDS (Abstract 278). Strong associations between markers of inflammation (OR for IL-6, 119), gut epithelial barrier dysfunction (independent associations for both I-FABP and zonulin after controlling for the other markers were noted), IDO-induced tryptophan catabolism and coagulation (OR for D-dimer, 29) were observed. Other studies investigating relationships between sCD14, a measure of monocyte activation, and clinical outcomes found associations between higher plasma levels of sCD14 and progression of atherosclerosis (as measured by carotid IMT) in adults (Abstract 122) but not in children (Abstract 976), as a predictor of the development of hypertension (Abstract 814), and as a marker for the risk for mother-to-child transmission (Abstract 1039). In addition, several studies

examined the associations between cerebrospinal fluid (CSF) levels of sCD14 and neurologic outcomes (see Spudich et al in this issue). These findings confirmed the important relationship between markers of gut permeability and outcomes in treated HIV infection and open the door for interventions aimed at reducing the impact of microbial translocation in treated HIV infection. Further support for such studies came from the results of Pandrea and colleagues, showing that administration of rifaximin and sulfasalazine during acute simian immunodeficiency virus (SIV) infection reduced markers of microbial translocation and coagulation and had an impact on SIV replication in pigtail macaques (Abstract 162). Results from ongoing studies of similar interventions in patients with HIV infection are eagerly awaited.

Interesting new insights into how different ART regimens might contribute to changes in biomarkers of microbial translocation emerged at the conference. Small studies using stored samples from randomized clinical trials examined changes in these biomarkers (Abstracts 277, 338, 836). Barqasho found that sCD14 declined during 72 weeks of ART with either lopinavir/r or efavirenz; however, a greater decline in anti-flagellin antibodies and I-FABP was noted among those who received lopinavir/r than in those who received efavirenz (Abstract 836). In the SPIRAL (Switching from Protease Inhibitor to Raltegravir in HIV Stable Patients) study, patients who were virologically suppressed on a lopinavir/r-based regimen were randomly assigned to switch to raltegravir or remain on lopinavir/r. A greater decline in sCD14 was observed in the raltegravir-treated group than in those remaining on lopinavir/r. A study of raltegravir intensification failed to document a greater decline in sCD14 (Abstract 338). Further work is needed to determine whether specific ART regimens have varied effects on gut healing.

### **Lipids**

Metabolomic profiling is a novel method for investigating associations between

specific circulating metabolites and clinical conditions. Cassol and colleagues reported one of the first in-depth studies of the metabolome in HIV-infected patients on suppressive ART with risk factors for hepatic dysfunction to investigate the relationship between hepatic dysfunction and metabolic abnormalities (Abstract 118). Studies were conducted in an initial and a validation cohort that included noninfected controls in both cohorts. More than 300 metabolites were detected by mass spectroscopy in each cohort, and a distinct signature of metabolite levels was observed in the HIV-infected patients in both cohorts. The majority of abnormal metabolites in the HIV group were lipids, followed by amino acids. Summarizing an enormous amount of data, the investigators concluded that the patterns of metabolites observed indicated decreased lipolysis associated with mitochondrial dysfunction and altered regulation of nuclear receptors controlling lipid metabolism and inflammation. In addition, there appeared to be an association between processes involved in hepatic steatosis, microbial translocation, and dyslipidemia in HIV patients.

Nuclear magnetic resonance (NMR) spectroscopy was used to further define lipid changes that occur in treatment-naïve patients randomly assigned to efavirenz or atazanavir/r. In both groups, ART promoted a restoration of high-density lipoprotein (HDL) and an increase in the large HDL subclass. However, 16% of the participants did not reach normal levels after 48 weeks of treatment. Patients on efavirenz had greater increases in HDL, but these were in the large HDL particles that are believed to be protective (Abstract 850).

### Lipoatrophy

Discontinuation of thymidine analogue nRTIs is the only proven beneficial strategy for recovery from lipoatrophy. An open-label, 96-week study of lopinavir/r twice daily plus abacavir and lamivudine versus lopinavir/r twice daily monotherapy was conducted in patients with moderate to

severe lipoatrophy while they received zidovudine/lamivudine/abacavir (Abstract 846). The primary endpoint was change in limb fat at 48 weeks; the secondary, at 96 weeks, was limb-fat change; HIV RNA level, lipid level, and adverse events were also measured. Switching either to lopinavir/r plus abacavir and lamivudine or to lopinavir/r monotherapy led to non-statistically significant limb-fat increases at 2 years that were lower than those previously reported. There were no differences in limb-fat gain between both strategies.

Calculating the fat mass ratio using dual-energy x-ray absorptiometry scanning (DEXA) data (percentage of trunk fat/percentage of limb fat) has been reported as a useful metric for assessing the prevalence of lipodystrophy.<sup>11</sup> Martinez and colleagues reported an improvement in limb fat as well as a normalizing of the fat mass ratio among patients who switched from a zidovudine-based regimen to tenofovir in the RECOMB (Peripheral Body Fat Distribution After Switching Zidovudine and Lamivudine to Truvada) study (Abstract 845).

The pathogenesis of dorsocervical fat depots in patients with HIV infection remains poorly defined, and it has been postulated that this fat may have some characteristics of brown fat. In an intensive study involving <sup>18</sup>F-DG-PET and fat biopsies to measure gene expression in patients with HIV lipodystrophy and in non-HIV-infected adults, Torriani and colleagues reported that the adipose tissue in the dorsocervical area did not appear to be classical brown fat (Abstract 849). However, the study did demonstrate an increase in deiodinase 2 expression, which may be related to increased energy expenditure.

Gerschenson and colleagues reported that lower baseline measures of mitochondrial function (mitochondrial oxidative phosphorylation protein levels) measured in peripheral blood mononuclear cells predicted greater amounts of fat loss in Thai patients starting ART. These results further support the notion that mitochondrial dysfunction underlies fat loss related to thymidine nRTIs (Abstract 848). Final-

ly, it is important to note that lipodystrophy remains an important clinical problem in areas in which stavudine continues to be used as first-line ART. Shiao and colleagues, using a standardized exam, reported that nearly 20% of children treated with ART prior to the age of 2 years had definite or probable lipodystrophy (Abstract 973). The long-term consequences of these early fat changes require further study as efforts to obtain alternative initial ART regimens continue.

### Vitamin D

Significant interest continues in the relationship between vitamin D deficiency and a variety of outcomes in HIV infection, specifically metabolic complications and HIV-disease progression. A previous study in adults demonstrated a relationship between specific vitamin D receptor mutations and rapid progression of HIV disease. Moodley and colleagues demonstrated this same finding among children, suggesting a possible role of vitamin D in HIV pathogenesis (Abstract 996). Vitamin D insufficiency (defined as < 32 ng/mL) before the start of ART was associated with HIV-disease progression and mortality among participants from resource-limited settings enrolled in the PEARLS (Prospective Evaluation of Antiretrovirals in Resource-Limited Settings) study confirming the results of earlier reports from cohort studies (Abstract 886). Low levels of vitamin D have been correlated with carotid IMT in adults, but these findings were not replicated in a small study of children (Abstract 977). In an observational study, replacing vitamin D reduced glucose and (unexpectedly) adiponectin levels but had no effect on insulin levels (Abstract 884). In a large group of patients in a French cohort ANRS COPANA (Agence Nationale de Recherches sur le SIDA Cohorte de Patients Non traités par Antirétroviraux à l'inclusion), low 25-hydroxyvitamin D (25[OH]D) levels were associated with lower CD4+ cell counts and higher levels of inflammation markers in black and white patients. However, the associations between low vitamin



D and body mass index, visceral adipose tissue, and leptin levels were only observed among white patients. In contrast to findings in HCV monoinfection, baseline 25(OH)D levels did not predict early virologic response in patients with HIV/HCV coinfection (Abstract 767).

The efficacy of different vitamin D replacement strategies has not been well studied in patients with HIV infection. Pacanowski and colleagues reported the results of a large prospective study (n = 483) in which cholecalciferol (D3) supplementation 100,000 IU/month was prescribed in escalating doses to patients according to the degree of vitamin D deficiency. Uvedose 100,000 IU/ampoule was prescribed for patients according to baseline 25(OH)D: for participants with baseline 25(OH)D levels of 10 ng/mL to 30 ng/mL, 100,000 IU/month for 4 months, and for those with 25(OH)D levels below 10 ng/mL, 100,000 IU every 2 weeks for 2 months and then 100,000 IU/month for 2 additional months. Not surprisingly, the follow-up levels of 25(OH)D correlated with the number of doses received. No cases of hyperkalemia were reported, but overall efficacy was difficult to ascertain.

## Bone Disease

Low bone mineral density (BMD) is common in patients with HIV infection, and screening guidelines recommend considering DEXA scans for those over the age of 50 years with 1 or more risk factors for osteopenia. Chu and colleagues from the Houston Veterans Administration Medical Center reviewed compliance with these screening recommendations in a large HIV practice (Abstract 876). Among the 476 men over the age of 50 years, 84% had 1 or more risk factors for osteopenia (> 95% if use of tenofovir was considered a risk factor), yet only 15% had undergone DEXA screening, and few who were found to have osteopenia when screened had complete work-ups.

The relationship between HIV infection, specific ART drugs, immune reconstitution, and bone loss continues

to be explored. Brown and ACTG colleagues found a low prevalence of low BMD among treatment-naïve patients enrolling in an ART clinical trial and no associations between parameters reflective of HIV-disease status or immune activation and low BMD (Abstract 875). On the other hand, Gazzola reported an association between the level of CD4+ and CD8+ T-cell activation and lower BMD in a small group of ART-treated patients (Abstract 879). Ofotokun and colleagues previously demonstrated a relationship between early bone loss after starting ART and immune reconstitution. They further explored the contributions of ART to bone loss by examining markers of bone resorption and formation in a cohort of patients with suppressed HIV-1 RNA who were switched from nRTI-based ART to lopinavir/r and raltegravir (Abstract 877). Over 48 weeks following the change in ART, markers of bone resorption (C-terminal telopeptide [CTX]) were stable. However, a statistically significant drop in osteocalcin, a marker of bone formation, was noted. The mechanism explaining this drop in bone formation requires further study to determine whether this might represent a late effect of ART or the sequelae of immune restoration. Finally, 2 studies examined the association between tenofovir exposure and bone loss in switch studies. Cotter and colleagues examined bone turnover markers and DEXA results in a randomized trial comparing continued therapy with ART containing zidovudine/lamivudine with a switch to ART containing tenofovir among patients who were virologically suppressed (Abstract 125LB). After 48 weeks of follow-up, BMD declined (-2% in lumbar BMD) in the tenofovir group, corresponding to increases in markers of bone turnover. Bloch and colleagues examined bone markers in a study of patients switching from tenofovir to raltegravir while continuing a PI/r (Abstract 878). The participants in this open-label study had been aviremic and on ART containing tenofovir for an average of 3 years. BMD increased after the change in regimen, and markers of bone turnover declined statisti-

cally significantly, suggesting that in this setting, tenofovir was probably contributing to bone loss prior to the change to raltegravir. Together, these switch studies provide further support for the likely contribution of tenofovir exposure to bone loss. However, the clinical significance of these changes remains unclear and warrants further follow-up.

## Renal Complications

Understanding and predicting the renal toxicity of ART agents, particularly tenofovir, was highlighted at this year's CROI. In patients with normal baseline estimated clearance (by Cockcroft-Gault) the D:A:D study reported a statistically significant association of estimated glomerular filtration rate (eGFR) decline to less than 70 with tenofovir, and eGFR decline to less than 70 as well as to chronic kidney disease (eGFR < 60) with atazanavir/r and lopinavir/r. However, overall rates of renal toxicity in this cohort of more than 22,000 subjects were low, with 2.1% developing eGFR below 70 mL/min/1.73m<sup>2</sup> and 0.6% developing eGFR below 60 over a median 4.5 years of follow-up (Abstract 865). Renal function appeared to normalize when these drugs were discontinued, suggesting reversibility. By contrast, in a Spanish cohort, although 60% of tenofovir-associated nephrotoxicity rapidly reversed after tenofovir was discontinued, 31% of patients had persistently abnormal kidney function after a median period of 22 months (Abstract 870). Suggesting a value for predicting tenofovir toxicity, higher tenofovir plasma levels were associated with renal toxicity in a Dutch cohort, but a clear threshold for tenofovir levels that identified the risk for renal toxicity with acceptable sensitivity and specificity could not be identified (Abstract 603). Elevated tenofovir trough levels were linked to accompanying ART; both boosted and unboosted PIs were associated with higher tenofovir troughs compared with NNRTIs and integrase inhibitors, suggesting that the association of PIs with renal dysfunction may in part be mediated by increased tenofovir levels.

## Aging and HIV

Many of the common problems observed in long-term treated HIV infection resemble those seen in normal aging. Factors that contribute to the phenotype of premature aging in HIV infection continue to be explored. One hypothesis is that mitochondrial dysfunction may contribute to loss of muscle volume and function. Payne and colleagues examined mitochondrial function by studying phosphorus magnetic resonance spectroscopy (<sup>31</sup>P-MRS) of the gastrocnemius/soleus muscle at rest and during recovery from brief exercise in a group of older HIV patients and age-matched controls (Abstract 856). The study also included data on muscle biopsies. The findings of higher levels of basal adenosine triphosphate (ATP) metabolite levels combined with preserved function during exercise in the HIV group were thought to be consistent with functional compensation for an acquired mitochondrial DNA defect. In addition, the authors concluded that the disordered muscle pH handling noted in the HIV group may contribute to fatigue. Another potential contributor to the aging phenotype in HIV is immune activation and immune senescence. Hearps compared the phenotypes of monocytes in young HIV-seropositive men with those in matched controls and in older patients and found that HIV infection was associated with changes in monocyte phenotype and function that resemble those observed in elderly uninfected individuals (Abstract 324). Specifically, elevated plasma levels of innate immune activation markers (sCD163, neopterin, and interferon gamma-induced protein 10 [IP-10]) correlated with the phenotypes observed in the HIV-infected patients. In addition, monocytes from HIV-seropositive patients have shorter telomeres than do healthy controls. These findings suggest that chronic HIV infection may be associated with the aging of monocytes, which in turn may contribute to the development of complications observed with long-term HIV infection.

## Malignancies

There has been increasing recognition of the elevated risk in the HIV-infected population of non-AIDS-defining malignancies (NADM), both infectious in etiology, such as anal and hepatocellular carcinoma, and noninfectious cancers, such as colon and lung cancer. In the D:A:D cohort, immunosuppression and low nadir CD4+ cell count emerged again as risk factors for NADM (Abstract 130). Lung cancer was associated with a nadir CD4+ cell count, Hodgkin's lymphoma with lower recent CD4+ cell count and HIV viremia, and anal cancer with lower recent CD4+ cell count and duration of immunosuppression. HIV-infected patients generally had a younger age at the time of diagnosis with NADM, with a trend toward more advanced stages of lung and anal cancers at the time of diagnoses, than HIV-uninfected counterparts in the Kaiser database (Abstract 903). HIV-infected patients with prostate cancer (84% vs 91%;  $P = .038$ ) and lung cancer (8% vs 22%;  $P < .001$ ), had reduced 5-year survival rates compared with HIV-uninfected subjects. The NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) found higher incidence of oral-cavity and pharynx cancer in HIV-infected patients compared with an HIV-uninfected cohort, and this risk increased with age over 50 years and baseline CD4+ count less than 350 cells/ $\mu$ L (Abstract 133).

Given accumulating data for the use of CT scan for lung cancer screening in HIV-infected patients<sup>12</sup> and elevated rates of lung cancer in HIV infection, it was encouraging to note that HIV-seropositive patients undergoing chest CTs in prospective evaluations of HIV-associated lung disease did not have higher rates of incidental pulmonary nodules than did HIV-uninfected patients (Abstract 907). Further data are needed to define the role of screening chest CTs for lung-cancer detection in HIV infection.

In an analysis of several ACTG randomized trials, statin use (prescribed as indicated by the practitioner) was associated with a statistically signifi-

cant decrease in malignancy of 55% compared with those not on a statin (Abstract 124). Prior studies<sup>13-15</sup> of HIV-uninfected populations have also suggested an association of statin use with a decrease in malignancies. This association to date has not been borne out in subsequent meta-analyses.<sup>16,17</sup> Whether statins are indeed driving the reduction in malignancy in HIV infection or the results are due to confounding given the observational nature of the study will require further study.

## Tuberculosis

### Prevention

Whether to provide at least 36 months (vs 6 months) of isoniazid (INH) preventive therapy (IPT) for HIV-infected persons living in high tuberculosis (TB)-incident regions is still debated, despite evidence from several randomized controlled trials. Samandari contributed to this debate by analyzing TB rates in an IPT trial in Botswana after all study participants were randomly assigned to 6 or 36 months of INH discontinued IPT (Abstract 147). During the evaluation of 1995 HIV-seropositive subjects within the 36-month study period, TB rates were 1.26% versus 0.72% ( $P = .047$ ) in the 6- versus 36-month IPT groups, respectively. After the study period, when no participants were taking IPT, rates of TB among tuberculin skin test-positive persons who had been randomly assigned to 36 months of IPT increased by 70%. These data suggest that HIV-infected persons living in high TB-incident areas are susceptible to repeat TB infection and benefit from prolonged IPT.

TB infection rates are extraordinarily elevated in certain settings, such as mines, due to poor ventilation and silicosis. In South African gold mines, up to 30% of workers are HIV infected, making this work environment a high priority for TB-prevention efforts. Churchyard presented the first glimpse into results from the eagerly awaited Thibela study in TB (Abstract 150aLB). Using a cluster randomized study design in South African gold mines,

investigators tested the hypothesis that providing IPT to all gold-mine workers, regardless of their HIV serostatus, would reduce the incidence of TB. There were 41,387 miners in the intervention cluster and 37,209 in the control cluster. HIV infection was reported in 12% of the study participants, though actual HIV testing of study participants was prohibited by organized labor. Within the intervention group, 67% of miners participated in the study, and 87% of these started IPT. Uptake of IPT as measured by medication pick-up varied in the range of 35% to 79%. In the analysis of the primary endpoint of TB incidence, there was no difference between the treatment groups: 3.04 TB cases/100 person-years in the intervention group versus 2.96/100 person-years in the control group (incidence rate ratio [IRR], 1.02; 95% CI, 0.77-1.31).

In part 2 of the Thibela trial results, investigators presented the individual-level benefit of IPT in the gold mines (Abstract 150bLB). For this analysis, the investigators included only patients in the intervention group who started IPT. During the first 9 months of observation when patients were receiving IPT, rates of TB were 63% lower in the intervention group, with 0.95 cases/100 person-years, than in the control group, with 2.53 cases/100 person years. After 9 months, rates in the 2 groups were similar in the range of 2.1/100 person-years to 2.6/100 person-years. Thus in the Thibela study, widespread IPT was not successful in reducing TB rates at the community level but showed evidence of individual-level benefit. The most obvious explanation for these findings is that the uptake of the intervention by individuals was insufficient to confer a benefit detectable at the community level. Failing to start IPT and nonadherence to IPT both contributed. In addition, the analysis of the individual-level benefit underscored the importance of lifelong IPT because the beneficial effect of IPT was lost after its discontinuation. The authors concluded that their study supports targeted (eg, for HIV-seropositive subjects) versus community-wide IPT. However, some would

argue that abandoning evaluation of a community-level approach could be premature because community uptake in this trial was limited.

Further insights into TB prevention efforts were gained in the ZAMSTAR (Zambia/South Africa TB and AIDS Reduction) trial conducted in Zambia and South Africa (Abstract 149bLB). This study evaluated both enhanced case finding at the community level and household TB case prevention and detection strategy using a community cluster randomized design that covered nearly a million persons. TB prevalence and transmission were both lower in the household-intervention populations than in the control, although the reported data showed confidence intervals that crossed 1. There was no difference between the enhanced case finding using community-based intervention and the control communities. The authors posited that the trend for reduction in TB prevalence and transmission to favor household intervention was promising. Upon questioning, Ayers stated that the cost of intervention was around US \$1 per person but added that detailed costing studies were under way.

### Diagnosis

Identifying active TB prior to the start of ART remains a challenge. Swindells reported 13% prevalence of TB among HIV-seropositive patients who were waiting to start ART and were screened for TB using clinical symptoms and culture at sites in sub-Saharan Africa (Abstract 927). As expected, clinical-symptom screens were sensitive for TB, although notably 5 of 52 patients with TB reported no cardinal symptoms. The positive predictive value of symptoms was only 24%. This study underscores the need for more sensitive and specific diagnostic algorithms. The Xpert® MTB/RIF molecular diagnostic technology holds promise for rapid detection of TB in HIV-infected patients and is more sensitive than routine acid-fast bacillus smear. However, there are still a substantial number of persons with TB who screen negative using this technology. In South Africa,

where the Xpert® technology is the first line for TB diagnosis, TB suspects who have a negative Xpert (X) had a follow-up culture (C) for screening. Because a second Xpert test can increase detection of TB, investigators performed a cost-assessment model of an algorithm comparing 2 sequential Xperts (X/X) with an Xpert followed by culture (X/C) (Abstract 923). In this model, the X/X was superior to X/C because the former detected cases faster, simplified logistics, and saved costs.

In another study examining potential benefits of the line-probe assay GenoType® MTBDRplus to identify multi-drug-resistant TB (MDR-TB) cases in South Africa, the detection of MDR-TB increased and the time to start MDR-TB treatment decreased after the introduction of MTBDRplus. However, median time to start MDR-TB treatment from the initial clinic visit was still unacceptably high, at 2 months (Abstract 925). Finally, Dorman reported that the point-of-care test Determine™ TB-LAM, which detects urinary mycobacterial lipoarabinomannan (LAM), reported a sensitivity of 44.8% and a specificity of 90.1% (Abstract 149aLB). The test had a higher sensitivity in patients with lower CD4+ cell count and could be an adjunctive test for clinicians. However, more work is needed to determine the relative contribution of this assay in view of limitations arising from its sensitivity and positive predictive value.

### ART and TB Treatment

Global guidelines now recommend that ART start in TB patients at 2 weeks after the initiation of TB treatment, based on randomized controlled trials. Does starting ART even earlier, at 1 week after initiation of TB treatment confer any further benefit? In a study of 474 patients with TB starting ART in Ethiopia, Degu reported that starting ART at 1 versus 2 weeks did not confer additional benefit or harm in terms of mortality (Abstract 144). Starting ART at 2 weeks after initiation of TB treatment means that programs will need to be prepared to diagnose and manage TB-associated immune



reconstitution inflammatory syndrome (TB-IRIS), a known complication of early ART. Luetkemeyer reported that in STRIDE (Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy), the overall incidence was 7.6%, and most cases were mild to moderate in severity (Abstract 145). Nevertheless, 31% of TB-IRIS cases were diagnosed while the patient was hospitalized; 34% required at least 1 invasive procedure, such as a fine needle aspirate; 54% required steroids for treatment; and the median duration of the TB-IRIS event was approximately 3 months. Compatibility of new ART agents and rifampin (which induces hepatic enzymes that lower levels of many ART drugs) is a key issue for optimal comanagement of these diseases. Dooley's drug-interaction study between the investigational ART dolutegravir and rifampin showed that doubling the dose of dolutegravir to 50 mg twice daily achieved dolutegravir levels similar to those in standard dosing in the absence of rifampin (Abstract 148).

### Cryptococcal Disease

Rolfes and colleagues evaluated a new lateral flow point-of-care assay (LFA) for cryptococcal disease in stored CSF and serum from Uganda with cryptococcal meningitis (Abstract 953). There was high sensitivity for the LFA and high concordance between the standard serum cryptococcal antigen (CrAg) assay and the LFA. Of note, titers of the LFA were 3-fold higher than CrAg; expanded evaluation of the LFA assay is under way. Asymptomatic cryptococemia, defined as detectable serum CrAg without symptoms, is known to occur among patients with AIDS who have low CD4+ cell counts. Kwan examined banked plasma from Thai women and found 11% prevalent CrAg in 84 women with less than 100 CD4+ cells/ $\mu$ L and none in women with greater than 125 CD4+ cells/ $\mu$ L (Abstract 954). These women were not evaluated for cryptococcal meningitis; approximately half received fluconazole prophylaxis. Not surprisingly, women with CrAg in plasma at baseline were at highest risk

to develop cryptococcal meningitis. Among the women who had positive CrAg, decreased titers were observed in 8 of 9 women after 48 weeks of antiretroviral therapy. Restoration of immunity provides protection against cryptococcal disease, but all patients with CrAg should have evaluation of CSF to determine whether treatment with amphotericin is indicated for meningitis.

### Malaria

HIV PIs are active against *Plasmodium falciparum* in vitro. Achan and colleagues tested the hypothesis that an ART regimen containing lopinavir/r versus an ART regimen based on an NNRTI would decrease malaria among HIV-infected Ugandan children living in a high malaria-endemic region (Abstract 26). The study enrolled 176 children and randomly assigned them to an NNRTI or a lopinavir/r combination ART regimen; malaria cases were treated with artemether-lumefantrine. Malaria incidence was 2.25 episodes/year versus 1.32 episodes/year in the NNRTI group versus the lopinavir/r group, respectively (IRR, 0.59; 95% CI, 0.36-0.97). The 41% reduction in risk for malaria conferred by the lopinavir/r group compared with the NNRTI group was primarily driven by a reduction in the rate of recurrent malaria, confirmed by genotypic analysis. The authors proposed that this effect was mediated by elevated levels of lumefantrine as a result of a pharmacokinetic interaction with ritonavir. No added toxicity was observed in the children with the elevated lumefantrine levels. Ritonavir thus may be valuable as a pharmacoenhancer for malaria drugs as well as for HIV agents. This trial is continuing to follow participants to evaluate the HIV outcomes.

### Vaccination for Influenza and Herpes Zoster

HIV infection is an established risk factor for herpes zoster reactivation and severe clinical disease. However, little is known about the safety and efficacy of the zoster vaccine in HIV-infected adults. In a US ACTG study,

HIV-infected adults with CD4+ counts greater than 200 cells/ $\mu$ L on suppressive ART were randomly assigned 3:1 to receive 2 zoster vaccinations or placebo (Abstract 96). Zoster vaccination appeared safe in HIV infection, meeting the protocol's safety definition. Injection-site reaction and rash were more common with the active zoster vaccine; however, there were no confirmed vaccine-related zoster cases, and 2 cases of clinical zoster occurred in each group. The vaccine appeared immunogenic, with an increase in geometric-mean zoster-antibody titer that was higher in vaccine recipients than in placebo at week 12 (6.4 vs 5.15;  $P = .017$ ). These data suggest that zoster vaccination may be a safe option for virologically suppressed patients with CD4+ counts greater than 200 cells/ $\mu$ L. Larger studies will be needed to evaluate the vaccine's ability to prevent zoster reactivation in HIV disease. The second administration of zoster vaccine did not appear to lead to increased antibody response and may not be required to generate a protective antibody.

The higher dose trivalent influenza vaccine (60  $\mu$ g/strain) resulted in a modest increase of 4% to 12% in geometric-mean influenza titers for the 3 vaccine strains at week 3 post vaccination, compared with standard influenza vaccination (15  $\mu$ g/strain) (Abstract 97). In this study, median current CD4+ count was 452 cells/ $\mu$ L (IQR 293-629), and a nadir CD4+ count was 180 cells/ $\mu$ L (IQR 53-318). It is unclear whether this increase would confer a clinical benefit, but high-dose influenza vaccination may be a consideration for HIV-infected patients considered to be at higher risk for complications from influenza or less likely to respond to standard-dose vaccination.

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