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CROI 2013: Complications of HIV Disease, Viral Hepatitis, and Antiretroviral Therapy

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Studies with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) monoinfection and HIV coinfection were highlighted at the 2013 Conference on Retroviruses and Opportunistic Infections (CROI). In HCV monoinfected patients, several interferon alfa–sparing, all-oral regimens demonstrated cure rates of greater than 90% with 12 weeks of treatment, including for hard-to-treat patients. Cure rates of 75% were attained in HIV/HCV coinfected patients with the addition of the investigational HCV protease inhibitor (PI) simeprevir to peginterferon alfa and ribavirin. Drug-drug interaction data to inform safe coadminstration of antiretroviral therapy with DAA-based HCV treatment were presented. There was continued emphasis on pathogenesis, management, and prevention of the long-term complications of HIV disease and its therapies, including cardiovascular disease, renal disease, alterations in bone metabolism, and vitamin D deficiency, along with a growing focus on biomarkers to predict development of end-organ disease. Understanding the elevated risk for non–AIDS-defining malignancies in the HIV-infected population and optimal management was a focal point of this year's data. Finally, the conference provided important information on tuberculosis coinfection and cryptococcal meningitis.

Keywords: *HIV, coinfections, comorbidities, hepatitis C virus, HCV, cardiovascular, tuberculosis, bone, vitamin D, malignancies, cryptococcosis*

Hepatitis C Virus

Hepatitis C virus (HCV) drug development continues at a breakneck pace, with remarkable data emerging on highly effective interferon alfa–containing and –sparing regimens. Much of the data presented were from phase II studies with small sample sizes; these results must be interpreted with caution. Nonetheless, this year's conference bolstered growing evidence that that 12-week, interferon alfa–free regimens that are highly effective in curing HCV should soon be a reality.

HCV Monoinfection Trials

Impressive HCV cure rates were attained with several investigational interferon alfa–free combinations of the ritonavir-boosted (/r) HCV protease inhibitor (PI) ABT-450 with ribavirin, a nonnucleoside polymerase inhibitor, or an NS5A inhibitor. In 10 of ll (91%) of treatment-naive individuals with HCV genotype 1, 12 weeks of treatment with the HCV PI ABT-450, the nonnucleoside polymerase inhibitor ABT-072, and ribavirin led to a sustained virologic response (SVR) at 24 weeks (HCV undetectable 24 weeks after discontinuation of treatment; SVR24). However, 2 relapses were reported, at weeks 8 and 36, respectively, after discontinuation of treatment. When ABT-072 was substituted with the nonnucleoside polymerase inhibitor ABT-333, SVR24 was attained in 18 of 19 (95%) of subjects who were given a higher dose of ABT-450, with no reports to date of late relapses, out to 48 weeks post treatment discontinuation. In those who previously did not respond to treatment (60% with partial nonresponse and 40% with null response), SVR24 was lower, at 47%, but still above what has historically been seen with peginterferon alfa and ribavirin retreatment in this population (Abstract 38). The late relapse at week 36 after treatment discontinuation (confirmed to be a relapse, not a reinfection) stresses the importance of long-term follow up of participants receiving novel interferon alfa–free regimens to ensure durability.

In updated data from the AVIATOR trial, a triple direct-acting antiviral (DAA) regimen of HCV PI ABT-450/r, the NS5A inhibitor ABT-267, the nonnucleoside polymerase inhibitor ABT-333, and ribavirin administered to treatment-naive patients for 8 weeks led to an SVR 12 weeks after discontinuation of treatment (SVR12) in 88% of patients. The same regimen administered for 12 weeks increased SVR12 to 99%. Notably, patients with prior null response responded equally well, with a 93% SVR12 after 12 weeks of triple DAA treatment. Higher relapse rates were associated with higher baseline HCV RNA and with HCV genotype 1a, but not with IL28b phenotype (Abstract 39).

In the latest results from the ELECTRON trial, the HCV polymerase inhibitor sofosbuvir was combined with the NS5a inhibitor ledipasvir (GS-5885) and ribavirin for 12 weeks of therapy. SVR rates 4 weeks after discontinuation of treatment (SVR4) were attained in 25 of 25 (100%) of treatment-naive patients with HCV genotype 1, and in 9 of 9 (100%) of patients with prior null response (Of note, SVR4 is an early marker of off-treatment response

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but has not been established to indicate HCV cure, as have SVR24 and, increasingly, SVR12.[1,2]) By contrast, in previously presented ELECTRON data, patients with prior null responses who were treated with sofosbuvir and ribavirin alone for 12 weeks experienced near universal relapse (90%) after treatment discontinuation.[3] Although these new results are early and from a small sample size, they suggest that the addition of an NS5A inhibitor to sofosbuvir may offer a highly effective 12-week interferon alfa–free regimen for even the hardest-to-treat patients with prior null response and HCV genotype 1.

DAA Regimens in Hard-to-Treat Populations

The COSMOS (Combination of Simeprevir and Sofosbuvir in HCV Genotype 1 Infected Patients) study evaluated treatment with sofosbuvir in combination with the pangenotypic PI simeprevir (TMC-435), with or without ribavirin, in patients with HCV genotype 1, prior null response, and limited fibrosis (Metavir score of F0-F2) (Abstract 155LB). In an interim analysis, rapid virologic response (RVR; HCV undetectable at 4 weeks on therapy) was 85% in those treated with 12 weeks of simeprevir, sofosbuvir, and ribavirin versus 57% in those treated with 12 weeks of simeprevir and sofosbuvir alone; however, 100% of patients in each of these arms had HCV undetectable by the end of treatment. Two relapses have occurred to date after treatment discontinuation, 1 in each arm of the study. The SVR rate 8 weeks after discontinuation of treatment (SVR8) was 96.3% (26 of 27) in the 12-week ribavirin-containing arm versus 92.9% (13 of 14) in the arm that did not contain ribavirin. There was no difference in response between those with HCV genotype 1a and 1b. Common adverse effects included headache, fatigue, and anemia (anemia limited to the ribavirin-containing arm). Grade 3 and 4 adverse events were uncommon, occurring in only 10% of patients. Although the sample size is small and these results are preliminary, this study demonstrates remarkable potential for 12-week, interferon alfa–sparing, oral therapy with an anticipated high cure rate, in one of the hardest-to-treat patient populations, those with HCV genotype 1 and prior nonresponse. Unlike many interferon-sparing regimens to date, ribavirin may not be needed to attain high cure rates with this HCV PI and NS5A combination; however, further data are needed.

The SPARE study evaluated the use of sofosbuvir and ribavirin in a Washington, DC, population in which factors made HCV-infected patients harder to treat (ie, non-CC IL28b genotype, high baseline HCV RNA level, high body mass index [BMI], black race, advanced liver fibrosis)(Abstract 157LB). Fifty treatment-naive patients with HCV genotype 1 received 24 weeks of sofosbuvir and were randomized to receive either weight-based ribavirin (1000 mg–1200 mg daily) or low-dose ribavirin (600 mg daily). Eighty-two percent of participants were black, 50% were obese (BMI > 30), 84% possessed the unfavorable non-CC IL28B genotype, and 6% had advanced fibrosis (histologic activity index [HAI] score of 3/4). SVR12 was 68% in patients who received weight-based ribavirin and was 48% in those who received low-dose ribavirin (by intention-to-treat analysis). All virologic failures were relapses after treatment discontinuation, and high baseline HCV RNA levels and male sex were associated with virologic failure. The 12-week interferon alfa–sparing regimen, with weight-based ribavirin, performed well in this traditionally hard-to-treat population. It would be interesting to investigate whether higher cure rates might be attained by extending the treatment period to longer than 12 weeks or by the addition of a third agent.

HCV Treatment in HIV Coinfection

Data in HIV/HCV coinfection were generally more preliminary than those presented in HCV monoinfection. However, important early data for several DAA-containing treatment strategies were presented at this year's conference.

In the TMC435-C212 phase III study, simeprevir (TMC-435), an HCV PI with pangenotypic activity, was given in conjunction with peginterferon alfa and 800 mg daily of ribavirin to HIV/HCV-coinfected patients with HCV genotype 1, who were treatment-naive or treatment-experienced (Abstract 154LB). All participants received 12 weeks of simeprevir, peginterferon alfa, and ribavirin followed by peginterferon alfa and ribavirin alone. Treatment-naive patients who did not have cirrhosis and those with prior relapse were eligible for response-guided therapy (24 weeks of total therapy if there is sufficient HCV response at weeks 4 and 12), and patients with cirrhosis and those with null or partial response received 48 weeks of treatment. Permitted antiretroviral therapy included raltegravir, rilpivirine, maraviroc, and nucleoside analogue reverse transcriptase inhibitors (nRTIs); HIV PIs and nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs) were not permitted due to concerns of drug-drug interactions with simprevir.[4,5] In an interim analysis of the data, the overall SVR12 rate was 77%, with 75% in treatment-naive patients and 80% in patients with prior nonresponse (no cirrhosis). Eighty-eight percent of participants eligible for response-guided therapy qualified to receive shortened therapy of 24 weeks total; the SVR12 rate with shortened therapy was 75%. Data from 48 weeks of treatment in patients with prior null response or cirrhosis were not yet available. Adverse events were largely attributed to peginterferon alfa, and increased bilirubin attributed to simeprevir was reported in 5% of patients.

In the STARTVerso 4 study, the HCV PI faldaprevir was given in conjunction with peginterferon alfa and weight-based ribavirin to HIV-infected patients with HCV genotype 1, with a response-guided strategy of 24 weeks to 48 weeks, depending on HCV RNA levels at weeks 4 and 12. Efavirenz, ritonavir-boosted HIV PI- (atazanavir/r and darunavir/r), maraviroc-, and raltegravir-based antiretroviral therapy regimens were permitted in the study. Among HCV treatment-naive patients,

60% had undetectable HCV RNA at week 4 and 82% had undetectable HCV RNA at week 12, using the more stringent below the limit of detection (BLD) cutoff for HCV RNA levels. Patients with prior relapse had similar responses, with 74% with HCV undetectable at week 4 and 91% with HCV undetectable at week 12. Seventy-seven percent of treatment-naive patients and 88% of those with prior relapse qualified for randomization to shortened, 24-week, response-guided therapy versus 48 weeks (Abstract 40LB). By comparison, in HIV-uninfected patients with HCV genotype 1, faldaprevir with peginterferon alfa and ribavirin led to similar week 4 and week 12 response rates and, ultimately, SVR24 in 72% to 84% of treatment-naive patients[6] and 29% to 42% of those with prior nonresponse to peginterferon alfa.[7]

When a combination of the HCV PI telaprevir, peginterferon alfa, and ribavirin was evaluated in 33 HIV/HCV-coinfected patients in an observational cohort, 61% attained SVR12 compared with 43% of 113 HIV-monoinfected patients (Abstract 679). This is consistent with phase II data demonstrating that HIV coinfection cure rates with telaprevir-containing regimens are similar to those seen in patients with HCV monoinfection.[8] Notably, the SVR12 rates for HCV-monoinfected patients are lower in this instance than what is reported in most clinical trials of telaprevir.

Data on DAA-based treatment in acute HCV infection are limited. In a cohort of 20 HIV-infected men who have sex with men (MSM) with acute genotype 1 HCV–infection, a shortened course of 12 weeks of telaprevir, peginterferon alfa, and ribavirin was initiated within 6 months of first alanine aminotransferase (ALT) elevation (Abstract 156LB). SVR4 was attained in 17 of 20 patients (85%) and SVR12 was attained in 14 of 17 (82%). Three failures occurred during therapy and there have been no relapses to date after treatment discontinuation. Notably, the majority of patients had the more favorable IL28B-CC (13 of 20) or -CT (4 of 20) genotypes. These SVR rates compare favorably to published SVR24 rates of 59% to 80% in HIV/HCV-coinfected patients who received 24 weeks of peginterferon alfa and ribavirin alone for treatment of acute HCV infection.[9-11] These results should be interpreted with caution because there are no control or comparison arms in this small cohort. However, these preliminary data suggest that 12 weeks of telaprevir, peginterferon alfa, and ribavirin may be an attractive shortened treatment option for acute HCV infection.

Retreatment of Patients With Prior Nonresponse

Patients with prior nonresponse to peg-interferon alfa and ribavirin are some of the hardest to successfully cure with retreatment for HCV infection. In the ANRS (Agence Nationale de Recherche sur le Sida et les Hépatites Virales) HC26 TelapreVIH study, HIV/HCV-coinfected patients with prior nonresponse to peginterferon alfa and ribavirin (patients with null response and cirrhosis were excluded from the study) were given telaprevir, peginterferon alfa, and ribavirin, with a response-guided strategy, for 32 weeks to 56 weeks; length of treatment was determined by HCV RNA level at week 4 of triple-drug therapy (Abstract 36). Patients received a 4-week lead-in treatment with peginterferon alfa and ribavirin alone, which is not standard practice with this triple-drug regimen. Efavirenz-, atazanavir/r–, and raltegravir-based antiretroviral therapy regimens were permitted. Of patients in the study, 88.4% qualified for shortened triple therapy at week 4 of triple therapy (week 8 of overall HCV treatment) if HCV RNA levels were below 15 IU/mL. Early virologic response (EVR, HCV RNA < 15 IU/mL at week 12) was also reached in 88.4% and did not substantially differ by baseline fibrosis (F1/F2, 88.1% vs F3/F4, 88.9%), type of prior treatment failure, or type of antiretroviral therapy used. Despite a considerable burden of treatment-associated toxicity, with grade 3 or 4 adverse events occurring in 28%, and 61% requiring epoetin alfa for anemia, this study demonstrated a robust early response in a traditionally hard-to-treat population. Data on SVR rates are forthcoming.

In a similar study design, the ANRS HC27 BocepreVIH study examined HIV/HCV-coinfected patients with prior nonresponse (again, those with prior null response and cirrhosis were excluded) with a response-guided regimen of boceprevir, peginterferon alfa, and ribavirin for 48 weeks to 72 weeks. The length of treatment was determined by HCV RNA levels at week 4 of triple therapy (week 8 of overall HCV treatment) (Abstract 37). Raltegravir and atazanavir/r were permitted. RVR occurred in 60% of patients at week 4 of triple therapy and EVR occurred in 63% at week 16 of triple therapy. In contrast with the ANRS HC26 TelapreVIH study, patients' previous responses to peginterferon alfa–based treatment were predictors of EVR; EVR was attained in 90% of those with prior relapse, 60% of those with breakthroughs, 61% of those with previous partial response, and 38% of those with prior null response. Of note, fibrosis score was not associated with EVR. There was a trend toward decreased efficacy with atazanavir-based antiretroviral therapy compared with raltegravir-based therapy (EVR, 56%, or 18 of 32, vs EVR, 70%, or 19 of 27, respectively). Grade 3 or 4 adverse events were common, occurring in 61% of patients. Final SVR rates will be important to clarify boceprevir-based regimens given with atazanavir- versus raltegravir-based antiretroviral therapy and to provide comparative data with telaprevir performance (Abstract 36). A Spanish observational cohort (in which 12%-18% were HIV coinfected) reported increased RVR rates with telaprevir plus peginterferon alfa and ribavirin compared with boceprevir-based treatment (84% vs 60%; $P < .001$) (Abstract 676). However, fibrosis was more advanced in those receiving boceprevir than in those receiving telaprevir (95% and 66%, respectively) and this was not a randomized study. SVR data were not presented.

Antiretroviral Drug Interactions With DAAs

Several studies provided important new information on drug-drug interactions between DAAs and antiretroviral drugs. Faldaprevir, an HCV PI that has shown promising responses when used in combination with interferon alfa and ribavirin, is metabolized by and moderately inhibits CYP3A4. Faldaprevir did not meaningfully impact tenofovir or darunavir/r levels. However, the area under the curve (AUC) of levels of faldaprevir was markedly increased (130%) with darunavir coadministration. To account for this drug interaction, faldaprevir has been given at a lower dose (120 mg daily) with darunavir and atazanavir in an ongoing phase III study (Abstract 40LB). In contrast, faldaprevir concentration was decreased by tenofovir (AUC decreased by 22%) and by efavirenz (AUC decreased by 35%), although it is unclear if these decreased concentrations are clinically significant (Abstract 35).

Boceprevir coadministration with the NNRTI rilpivirine increased rilpivirine exposures slightly but not to a clinically significant degree, and boceprevir exposure was unaffected by rilpivirine (Abstract 537). This adds another antiretroviral drug to those that can be used with boceprevir. The current boceprevir package insert permits raltegravir coadministration but advises against the use of other NNRTIs or HIV PIs.[12] Further evaluation of boceprevir with antiretroviral drugs, including ritonavir-boosted HIV PIs, is currently under way.

Epidemiology of HCV Infection in HIV

Sexual transmission of HCV between MSM has increasingly been seen in the HIV-infected population. Several abstracts highlighted the predominant role of MSM sexual transmission in current HCV epidemics in the United States and Europe (Abstracts 638, 704, 707, and 708). The frequency of HCV reinfection after successful treatment was high in a cohort of MSM, with 31% experiencing reinfection during a follow-up period of 5 years. The majority of patients in the cohort were reinfected with a different genotype of HCV, suggesting partial protective immunity against the initial HCV genotype (Abstract 708). Testing for HCV is recommended at the time of engagement in HIV care, given the high rate of HCV coinfection in HIV-infected individuals in the United States. However, guidance on repeat HCV testing is limited. Analysis from the SUN (Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy) study found that incident HCV infection was associated with elevated liver transaminases 50% of the time and with MSM exposure in 50% of cases, suggesting that repeat testing should not be limited to patients with transaminitis, and reiterating the role of MSM sexual exposure as an important route of HCV transmission (Abstract 704).

Complications of HCV: Fibrosis Progression and Extrahepatic Disease

HIV coinfection in those with HCV infection has generally been associated with faster progression of fibrosis. In a cross-sectional study from Thailand, 66.7% of HIV/HCV-coinfected patients had substantial fibrosis (liver stiffness > 7.5 kPa) compared with 41% of HCV monoinfected patients (Abstract 646). The NEAT (European AIDS Treatment Network) followed up patients with acute HCV, 93% of these infections attributable to MSM sexual contact, for a median of 130 weeks, and found that 14 of 122 (11.5%) developed advanced fibrosis (liver stiffness > 9.0 kPa) (Abstract 637). Progression to fibrosis was associated with persistent viremia and did not appear to be correlated with other risk factors (ie, alcohol use, drug use, diabetes, d-drug [didanosine, d4t] use, etc), although the small number of patients with advanced liver disease limits this evaluation. Using serum markers to detect fibrosis (FIB-4 index), or clinical evidence of cirrhosis, an Italian cohort reported a lower overall fibrosis rate, with 11% progression to cirrhosis from the time of HCV diagnosis, during a period of up to 9 years (Abstract 638). Notably, HCV acquisition decreased in all risk groups except MSM, in whom incidence remained unchanged. The presence of advanced fibrosis is an important risk factor for hepatic decompensation. In one study, 41% of those with stage F4 fibrosis (by liver biopsy) experienced decompensation during a 5-year period. Advanced fibrosis is also a risk factor for decompensation in those with precirrhosis (F3 by biopsy or liver stiffness from 9.5-14.6 kPa), highlighting the importance of prompt HCV therapy (Abstract 727).

The extrahepatic impact of HCV infection has increasingly been recognized. Patients with HIV/HCV coinfection demonstrated elevated pre-treatment nonhepatic markers of cardiovascular disease (CVD; eg, soluble intercellular adhesion molecule 1 [sICAM-1], lipoprotein-associated phospholipase [Lp-PLA2], soluble platelet [sP]-selectin, and interleukin [IL]-6), and curative HCV therapy was associated with a statistically significant decrease in sICAM-1, suggesting that successful HCV treatment may lower systemic inflammation and thus CVD risk (Abstract 715). However, despite a recognized increased risk for CVD with HCV[13] and HIV/HCV coinfection,[14] use of the Framingham Risk Score (FRS) did not identify HCV- and HIV-infected individuals as being at increased risk (Abstract 716), suggesting this risk score may underestimate cardiovascular risk in HCV and HIV infection. Compared with HIV-monoinfected individuals, HIV/HCV-coinfected patients had an increased risk of renal impairment, particularly in those with HCV viremia (Abstract 718). In a Veterans Affairs (VA) analysis, overall mortality was nearly twice as high in patients with HIV/HCV coinfection than in HIV-monoinfected patients (all-cause mortality, 74.1/1000 person-years vs 39.8/1000 person-years, respectively), and SVR was strongly associated with mortality reduction (hazard ratio [HR], 0.35).

HCV Assays

Stopping rules for and duration of therapy with DAAs rely on interpretation of HCV RNA levels during the early months of therapy. Evaluation of 5 commercially available HCV RNA assays indicated that there were substantial discrepancies between test performances in samples with low levels of HCV RNA (Abstract 661). Thus, the same assay should be used throughout HCV treatment to inform clinical decisions and to avoid interassay variability.

Hepatitis B Virus

A Dutch cohort evaluated the effect of the hepatitis B virus [HBV]–active antiretroviral drugs tenofovir, emtricitabine, and lamivudine in the prevention of new HBV infections. In 530 HBV-uninfected individuals who were followed up for a median of 7.8 years, 35 HBV infections occurred, the majority (32) in MSM. As anticipated, tenofovir use (in conjunction with lamivudine and emtricitabine in most cases) reduced the risk of HBV acquisition, with no new HBV cases occurring during tenofovir administration ($P < .001$). Use of emtricitabine and lamivudine without tenofovir also reduced the risk of HBV acquistion; however, 3 HBV infections still occurred during treatment.

Several studies evaluated the efficacy of lamivudine and emtricitabine, with or without tenofovir, in the suppression of HBV. There was a trend toward increased HBV suppression and hepatitis B e antigen (HBeAg) loss with the combination of tenofovir plus lamivudine or emtricitabine compared with lamivudine or emtricitabine alone, in a longitudinal AIDS Clinical Trials Group (ACTG) cohort (Abstract 665). Notably, HBV viral rebound was only reported in patients who received lamivudine or emtricitabine alone. Tenofovir-based therapy is generally very effective in HBV viral suppression, with 92% HBV DNA undetectable after 5 years of treatment (Abstract 666). However, despite effective HBV DNA suppression, HBeAg loss occurred in only 35% (25 of 85) of patients and hepatitis B e antibody (HBeAb) conversion in 10.5% (9 of 85). To investigate strategies to improve HBeAg loss and seroconversion, 2 French studies looked at the addition of peginterferon alfa to tenofovir-containing treatments. In the first study, a median of 7 months of peginterferon alfa was added to the regimens taken by HBeAg-positive patients (4 with detectable HBV DNA) on tenofovir-containing antiretroviral therapy. Peginterferon alfa was associated with more rapid HBeAg loss, but not with an overall increased HBeAg loss, than that which occurred for those on tenofovir-containing antiretroviral therapy alone (46.7% vs 45%, respectively; P = not significant) (Abstract 668). In a single-arm study, ANRS HB01 EMVI-PEG, 1 year of peginterferon alfa was added to the regimens of patients who had at least 6 months of tenofovir plus lamivudine and emtricitabine; the addition of peginterferon alfa was associated with 24% HBeAg loss during treatment but did not result in long-term HBeAg loss, HBeAb conversion, or hepatitis B surface antigen (HBsAg) loss and was associated with substantial peginterferon alfa–related adverse effects (Abstract 669). Thus, the addition of peginterferon alfa does not appear to improve immunologic control of HBV infection in HIV/HCV-coinfected individuals.

Hepatitis E Virus

Hepatitis E virus (HEV) infection is an increasingly recognized cause of acute hepatitis worldwide, particularly in patients who are pregnant or immunocompromised. Although HEV infection is typically enterically transmitted and self-limiting, similar to hepatitis A virus (HAV), a Spanish group reported 2 HIV-infected patients with chronic HEV viremia associated with transaminitis and increasing liver stiffness. The use of ribavirin appeared to temporarily control replication in both patients, but 1 developed subsequent HEV viremia. Chronic HEV may be a consideration in the evaluation of HIV seropositive patients with transaminitis that is not attributable to other etiologies (Abstract 664).

End-Organ Complications of HIV Infection

The constellation of chronic diseases such as cardiovascular, renal, bone, and liver diseases, as well as non–AIDS-defining malignancies, persist as major causes of morbidity and mortality in treated HIV infection. Research in this area is focused on the epidemiology and risk factors for these problems, identification of the contributions of HIV-related immunopathology to specific and collective end-organ diseases, and evaluation of interventions to prevent or reduce the morbidity associated with these conditions. This year's Conference on Retroviruses and Opportunistic Infections (CROI) provided new insights into all of these areas.

Biomarkers to Predict the Risk of End-Organ Disease and Mortality

IL-6, d-dimer. Previous work by investigators in the SMART (Strategies for Management of Antiretroviral Therapy), ESPIRT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial), and SILCAAT (Subcutaneous Recombinant, Human Interleukin-2 in HIV-Infected Patients with Low CD4+ Counts Under Active Antiretroviral Therapy) study groups identified a strong association between biomarkers of inflammation and coagulation and the risk for mortality during treated HIV infection. Now these groups have expanded the analyses to explore the relationship between the combined measurement of IL-6 and d-dimer and the risk for serious non-AIDS (SNA) events and all-cause mortality among treated patients. They modeled the data to evaluate the expected reduction in events associated with lowering levels of either or both of these biomarkers (Abstract 60). The rates of SNA morbidity or all-cause death (SNA/death) were 14% lower among patients with 25% reductions in IL-6, and 9% lower for a 25% reduction in d-dimer. These were not actual reductions in the levels of the markers but, rather, were event rates among those with lower baseline values. Although causality between

these markers and end points remains to be determined, these analyses highlight the potential utility of a combined marker score and help set the stage for planning interventional trials aimed at reducing levels of these specific measures of inflammation and coagulation.

Endothelial activation biomarkers. Endothelial cell activation markers may play an important role in the long-term complications of HIV disease. Vascular cell adhesion molecule 1 (VCAM-1) is an immunoglobulin-like adhesion molecule expressed on activated endothelial cells. Intracellular adhesion molecule 1 (ICAM-1) is present on endothelial cells and leukocytes. Graham and colleagues reported that levels of sICAM-1 and VCAM-1 rose soon after HIV infection (Abstract 264). They also reported that VCAM-1 measured at the time of the HIV viral load set point was independently associated with time to HIV progression or death (after control for HIV-1 RNA and ICAM-1 levels) in a prospective study of Kenyan women who seroconverted. Whether VCAM-1 remains an important predictor of outcome during treated HIV infection remains to be determined.

Myocardial Infarction, End-Stage Renal Disease, and Non-AIDS Cancer

There continues to be some debate as to whether people with HIV infection experience the onset of chronic noncommunicable diseases at an earlier age than the general population. A study by Shiels and colleagues[15] highlighted the importance of controlling for the age distribution of the general population when comparing rates of malignancies in the HIV population and the general population. Althoff and colleagues explored this issue further using the Veterans Affairs Health System database (Abstract 59). They examined rates of myocardial infarction (MI), cancer, and end-stage renal disease (ESRD) in veterans with HIV compared with an age-, sex-, race-, and ethnicity-matched group of HIV-uninfected veterans. The scope of this analysis is therefore limited to the age distribution of US veterans with HIV disease and may not completely reflect that of the US HIV-infected population. Nonetheless, Althoff and colleagues clearly demonstrated that within the large group examined, who had a median age of 55 years, the risk of each of these diseases is more common among those with HIV infection: an 87% increase in the risk of MI, a 37% increase in cancer, and a 55% increase in ESRD. However, they saw no difference in the age at which these conditions occurred (for most conditions, the median age of onset was close to 55 years). Notably, less than 10% of the matched population was under the age of 40 years and few were women. Therefore, the generalizability of these results to the younger HIV-infected population and to HIV-infected women is limited.

CVD

Several studies examined trends in causes of death, prevalence of chronic disease risk factors, and outcomes of cardiovascular events among patients receiving HIV care. In France, the proportion of deaths due to cardiovascular-related disease increased from 8% in 2000 to 10% in 2005, and increased again to 14% in 2010 (Abstract 1048). This trend likely reflects the aging of the HIV-infected population, but it was notable that the proportion of smokers also increased, from 58% to 75%, among those who died. A German cohort study compared cardiovascular risk profiles in men and women with HIV infection compared with a matched HIV-uninfected group. They found that FRSs were comparable between HIV-infected and -uninfected men, and the women with HIV disease had a higher predicted risk, due in part to higher rates of smoking and hypertension in the HIV-infected group (Abstract 774). Among a large cohort of patients in Uganda receiving antiretroviral therapy with a median age of 34 years, the prevalence of hypertension was 28% and stage 2 hypertension (systolic blood pressure [BP] ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg) was 14% overall (Abstract 776).

Not all the news was discouraging, however. Investigators from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study (Abstract 748) reported improvements in survival during the first month following MI in the period from 2009 to 2011 compared with the period from 1999 to 2002, when more than a quarter of patients died within the first month following an MI. The improved outcomes appeared to be attributable to enhanced patient management following an MI in more recent years. Collectively, these studies confirm the need for integration of primary prevention of CVD into HIV disease management across all settings.

Noncalcified plaque and monocyte activation markers. Noncalcified coronary plaque (NCP) represents an early stage of atherosclerosis and it can be detected by computed tomography (CT) angiography, by which plaque can be characterized as noncalcified, mixed, or calcified. Investigators from the MACS (Multicenter AIDS Cohort Study) and Grinspoon's group at Massachusetts General Hospital have described the prevalence of and examined factors associated with NCP in HIV disease. Post and colleagues working in the MACS reported that older age was associated with increased rates of NCP in those infected with HIV but not in HIV seronegative men (Abstract 62). Zanni and colleagues examined plaque morphology in a matched study of HIV seropositive and HIV seronegative men, all matched for cardiovascular risk factors (Abstract 63). Using standard definitions and blinded readings by cardiologists or radiologists, arterial segments with plaque were graded on the presence of factors associated with vulnerability, including positive remodeling, low attenuation, and spotty calcification. The major finding of this study was that among a well-treated HIV-infected group, with low FRS, they observed a higher prevalence of vulnerability factors in plaque (8% in the HIV-infected group vs 0% in the control group), suggesting a higher risk for future cardiac events.

Activated monocytes and soluble markers of monocyte activation. Baker and colleagues examined factors associated with the progression of coronary artery calcium among 436 HIV-infected adults with a median age of 42 years (Abstract 66 LB). Higher frequencies of activated monocytes were associated with higher rates of progression but not tissue factor expression, T cell activation, or senescence phenotype. Tenorio and colleagues reported the results of a case-control study evaluating the relationship between cellular and soluble markers of inflammation and the risk for SNA events (ie, MI, stroke, non–AIDS-defining malignancy, serious bacterial infections) and nonaccidental death in participants with suppressed HIV-1 RNA enrolled in ACTG treatment studies (Abstract 790). As has been reported from other studies, higher levels of IL-6, soluble tumor necrosis factor receptor (sTNFR), soluble CD14 (sCD14), and d-dimer are associated with the risk of SNA events. Notably, these associations existed pre–antiretroviral therapy and persisted despite antiretroviral therapy, whereas cellular markers of T cell activation did not appear to predict the risk of SNA events.

Walker and colleagues used the simian immunodeficiency virus (SIV)-infected, CD8 T lymphocyte–depleted rhesus macaque model (SIV+/CD8-) to examine the features of CVD and to test the effects of PA300, an antitumor drug that inhibits macrophage activation and trafficking, on the development of CVD (Abstract 64). A substantial increase in CD163+ macrophages (a measure of macrophage activation) was seen in SIV-infected macaques compared with SIV-uninfected macaques. After 28 days of daily doses of PA300, the number of CD163+ macrophages and the degree of cardiac damage, measured histologically, declined. These data add to the growing body of evidence supporting a role for innate immune response and specifically activated monocytes in the pathogenesis of HIV-related CVD and pave the way for interventional studies aimed at reducing macrophage activation.

Heart failure. The prognostic value of the suppression of the tumorigenicity 2 (ST2) gene, a member of the IL-1 receptor family, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), biomarkers of cardiac dysfunction that are predictive of heart failure and mortality in the general population, were assessed in a cohort of HIV-infected patients who underwent echocardiograms and clinical follow-up (Abstract 749). Both markers were found to be higher in the HIV-infected group than in the control group and each was associated with mortality, suggesting that these markers may have the same predictive value in HIV-infected individuals as they do in the general population.

Rates and characteristics of heart failure were examined in HIV-infected and -uninfected veterans in the VACS-VC (Veterans Aging Cohort Study–Virtual Cohort) (Abstract 750). Rates of heart failure (with preserved or reduced ejection fraction) and mortality due to heart failure were higher in the HIV-infected group. These findings highlight the importance of heart failure as a clinical consideration for patients with HIV disease.

Statins. Several studies explored different aspects of statin use in HIV-infected individuals. The prevalence of statin use among patients with HIV infection compared with controls was examined in the MACS. Only 10% of the HIV-infected group who had an indication for a statin were not receiving it, compared with 16% of the HIV-uninfected control group (Abstract 771). With regard to aspirin use in patients with HIV disease, just the opposite was seen. Among patients with 2 or more risk factors for coronary heart disease in a large Boston, Massachusetts, database, only 22% of the HIV-infected group were receiving aspirin compared with twice that in the HIV-uninfected control group (Abstract 65).

A large Danish study examined the outcomes of virologically suppressed patients who were prescribed a statin compared with those who did not take statins and found a nonstatistically significant reduction in deaths among those patients who had been prescribed a statin (Abstract 764). An even larger VA analysis (25,884 patients) suggested a trend toward mortality benefit and a reduction in malignancy rates with the use of high-potency statins (rosuvastatin or atorvastatin). These studies highlighted the issue of confounding by indication that limits these types of analyses.

Drug-drug interactions complicate the use of some statins in patients taking PIs; hence, there is interest in the use of newer drugs that may have fewer interactions. Sponseller and colleagues demonstrated that 4 mg of pitavastatin, a newer statin with a low potential for cytochrome P450 drug interactions, was superior to 40 mg of pravastatin in lowering low-density lipoprotein (LDL) cholesterol, in a 12-week randomized trial of HIV-infected patients. Declines in high-sensitivity C-reactive protein (hs CRP) were modest in this trial, though it was notable that oxidized LDL declined substantially in the pitavastatin group (Abstract 187LB).

The potential for statins to reduce immune activation and inflammation in the setting of treated HIV infection has been a topic of great interest. McComsey and colleagues presented preplanned, interim, 24-week results from a 96-week, double-blind, placebo-controlled trial of rosuvastatin in patients with well-controlled HIV infection. In the group treated with rosuvastatin, the results showed a reduction in monocyte activation markers (sCD14 and circulating $CD14^{dim}CD16^{+}TF^{+}$ monocytes) and in the vascular inflammation marker Lp-PLA2 (Abstract 186LB).

Statins may increase the risk of diabetes in the general population; 2 groups who addressed this potential risk in HIV-infected patients reached different conclusions. Italian researchers found that HIV-seropositive patients who used statins had a reduced risk of diabetes compared with those who did not use statins (Abstract 766), whereas US researchers found statin use to be associated with a higher rate of incident diabetes (Abstract 767). Differences in the distribution of risk

factors for diabetes in different populations may have contributed to these disparate findings.

Renal Disease

The increased prevalence of chronic kidney disease (CKD) among people with HIV disease was once again highlighted at this year's conference. The higher prevalence of CKD, as defined by an estimated glomerular filtration rate (eGFR) of greater than 60 mL/min/1.73 m^2, among people with HIV disease who are in care (estimated at 1 in 13 adults in the United States) (Abstract 809) and the higher rates of ESRD among HIV-infected veterans, as noted above (Abstract 59), are 2 examples of this increased prevalence.

Creatinine clearance. Debate continues about which formula should be used to estimate GFR in clinical practice and research settings. The Cockcroft Gault (CG) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were compared using a very large dataset from the EuroSIDA study. No gold standard for measuring renal function was included in this analysis; however, the equations were compared for their ability to diagnose moderate to advanced kidney disease and to predict the risk for CKD and mortality. Incidence of moderate CKD was higher when the CG was used, though CG and CKD-EPI performed similarly in predicting the risk of ESRD and all-cause mortality (Abstract 808).

Renal function. Observational studies have suggested that ritonavir-boosted PIs may increase tenofovir levels, increasing the risk of renal toxicity. Several studies, including 2 that focused on women, presented at this year's CROI added further evidence to support this notion. However, an analysis from the D:A:D study identified lower CD4+ cell counts and traditional renal risk factors as being most important for predicting ESRD (Abstract 810). Baxi and colleagues conducted an intensive pharmacokinetic study among 105 women enrolled in the WIHS (Women's Interagency HIV Study) who were receiving tenofovir. They identified ritonavir use, older age, lower BMI, and reduced renal function at the start of tenofovir use as risk factors for higher tenofovir plasma levels (Abstract 522). From the ACTG A5208 OCTANE (Optimal Combination Therapy After Nevirapine) study, Mwafongo and colleagues compared renal events and increases in grade 3 or 4 serum creatinine among 741 African women who were randomly assigned to receive tenofovir and emtricitabine combined with either lopinavir/r or with nevirapine (Abstract 152). Although rates of renal events and grade 3 or 4 creatinine increases were generally low (3% and 5%, respectively), the times to first renal event were shorter and overall event rates were higher among the women randomized to receive lopinavir/r than among those who received nevirapine. In a small study, tenofovir plasma levels did not vary between pre- and postmenopausal women (Abstract 900). However, in another study, tenofovir plasma levels were higher in lower-weight patients and were associated with drug-related renal and bone toxicity (Abstract 523). A detailed analysis of renal events using several different measures of GFR, in the ACTG A5224s trial, similarly found higher rates of decline in eGFR when tenofovir was combined with atazanavir/r as opposed to efavirenz (Abstract 811). These findings suggest that combining tenofovir with NNRTI-based regimens, especially among patients weighing less than 50 kg may be associated with lower rates of renal dysfunction. Weight-based dosing of tenofovir (a reasonable but somewhat impractical strategy) in Thai children appeared to be safe but did not fully mitigate changes in bone mineral density (BMD) (Abstract 972).

Tenofovir alafenamide fumarate (GS-7340), a prodrug of tenofovir, is currently in phase II studies. Unlike tenofovir, this prodrug does not appear to interact with the renal transporters organic anion transporter 1 (OAT1) or OAT3 in vitro and therefore is unlikely to accumulate in renal tubules and lead to toxicity (Abstract 540). The 24-week results of a study comparing GS-7340 with tenofovir combined with elvitegravir, cobicistat, and emtricitabine demonstrated comparable efficacy and statistically significant improvements in bone density and renal function in those receiving GS-7340 versus tenofovir (Abstract 99LB).

Impact on Bone Health

Examination of the risk factors for and pathogenesis of bone loss in HIV disease remains an important area of investigation. Several studies at this year's CROI confirmed and extended prior observations highlighting the importance of this complication.

A large cross-sectional Irish study confirmed that bone density is lower in men and women with HIV disease than in well-matched controls (Abstract 817). Despite similar levels of vitamin D in both groups, the HIV-infected group had higher levels of alkaline phosphatase, and despite adjustment for this, the independent effects of HIV persisted. A detailed study of a small group of adolescents with HIV disease (some infected at birth and others during adolescence) documented lower values of peak bone mass in those with HIV disease than in controls. High-resolution peripheral quantitative CT found markedly abnormal trabecular and cortical bone microarchitecture in both groups of HIV-infected adolescents, suggesting that they will have an increased life-long risk of fractures. Using quantitative morphometry assessments of lateral chest x-rays, an Italian group reported a higher rate of asymptomatic vertebral fractures in a group of HIV-infected patients than in control subjects (Abstract 822). In a pooled analysis of data from 3 ACTG trials, lower CD4+ counts, particularly those below 50 cells/μL, were an independent risk factor for bone loss after the initiation of antiretroviral therapy (Abstract 823).

In vitro studies using bone marrow–derived mesenchymal stem cells (MSC) suggested that exposure to the PI lopinavir/r, more so than atazanavir/r, reduced the proliferative activity of the cells and led to premature cell

senescence, as measured by the presence of farneslyated prelamin A (a marker of cell aging) (Abstract 799). This effect appeared to be blocked by statin treatment of the cell cultures. In addition, exposure of the MSC to the HIV proteins Tat (transactivator of transcription) and Nef (negative regulatory factor) also increased cell senescence. These findings suggest a mechanism for HIV-associated bone loss attributable to HIV proteins and lopinavir/r. The clinical significance of these findings, in particular the effects of statins, remains to be determined.

Switching antiretroviral therapy because of bone loss. It is reasonably clear that untreated HIV infection and antiretroviral therapy may contribute to bone loss; the clinical question remains of how best to manage osteoporosis when detected in HIV disease. Negredo and colleagues conducted the OsteoTDF study to investigate whether switching from tenofovir to abacavir would provide any benefit to patients with virologic suppression and documented osteopenia or osteoporosis, who were on a tenofovir-based regimen (Abstract 824). After 48 weeks of follow-up there was a statistically significant improvement in the abacavir-treated group in femur BMD (+1.98%), with more modest improvements in bone density at the trochanter. How this strategy compares with other interventions for osteoporosis is still to be determined but it is one option for clinicians to consider.

Vitamin D. Low levels of vitamin D are common among HIV-infected patients and several studies have identified a link between low levels of vitamin D and poor clinical outcomes. However, the causal relationship between vitamin D and HIV disease progression remains undefined. In vitro studies by Campbell and Spector suggest that TLR8 ligand activation of macrophages upregulates the expression of the human cathelicidin antimicrobial peptide (CAMP) gene through a vitamin D–dependent mechanism that is required for the autophagic inhibition of HIV (Abstract 285). These data may suggest that the maintenance of adequate vitamin D levels could help to modulate the effects of HIV infection. Results from a 12-week randomized trial comparing supplementation with a daily dose of 4000 IU or 7000 IU of vitamin D_3, conducted across a wide age range of HIV-infected patients in Botswana, demonstrated no detrimental effects overall and improvement in vitamin D status, with some suggestion of greater improvements in CD4+ cell counts among the group receiving the higher dose (Abstract 965).

Several studies have documented a decline in 25-hydroxyvitamin D (25[OH]D) in patients on antiretroviral therapy, in particular with exposure to efavirenz. The body composition substudy of SMART noted an improvement in BMD in the group that was randomized to receive intermittent antiretroviral therapy and updated these results to include information on vitamin D levels and BMD. Levels of 25(OH)D increased during periods when antiretroviral drugs were not being taken. These increases correlated with improvement in BMD, suggesting that some component of bone loss during antiretroviral therapy may be mediated through reductions in vitamin D levels. However, Adeyemi and colleagues measured the levels of 1-25-dihydroxyvitamin D ($1,25[OH]_2D$) among women with low levels of 25(OH)D who were taking efavirenz and found that the levels of $1,25(OH)_2D$ were within the normal range for 84% of these women. This suggests that levels of $1,25(OH)_2D$ remain tightly controlled even when levels of 25(OH)D are low (Abstract 807).

Malignancy

Non–AIDS-defining cancers (NADCs), particularly those caused by infectious etiologies (ie, hepatocellular carcinoma caused by a hepatitis virus, Epstein-Barr virus [EBV]-related Hodgkin lymphoma, and human papillomavirus [HPV]-related genital or head and neck malignancies), are more prevalent among the HIV-infected population and effective antiretroviral therapy does not appear to mitigate this risk. Using data from 8 US clinics, the CNICS (Centers for AIDS Research [CFAR] Network of Integrated Clinical Systems) analyzed cancer incidence following the initiation of antiretroviral therapy in more than 11,000 patients during a 16-year period (1996-2011).

Incident cancers were evenly divided between AIDS-defining cancers (ie, Kaposi sarcoma [KS] and non-Hodgkin lymphoma [NHL]) and NADCs. In the first 6 months after initiation of antiretroviral therapy, KS and lymphomas (Hodgkin lymphoma and NHL) were the most frequent incident cancers. As expected, the majority of cases of KS occurred in individuals with CD4+ cell counts below 200/μL and incidence of KS and lymphoma declined after 6 months of antiretroviral therapy. Low CD4+ cell counts were associated with KS, lymphomas, and virus-related NADCs (such as cervical and anal) but not with cancers unrelated to viral infections (such as lung and colon). Conversely, there was a trend toward increased incidence of NADCs in the years following antiretroviral therapy initiation (Abstract 141). A German multicenter cohort found that although 62% of cases of NHL occurred in patients who had not received antiretroviral therapy, 75% of cases of Hodgkin lymphoma occurred in patients who were taking effective antiretroviral therapy, suggesting that antiretroviral therapy did not provide protection from this EBV-related cancer (Abstract 745).

The VACS reported a 37% increase overall in the risk of NADCs among HIV-infected subjects compared with HIV-uninfected controls, but they also found that NADCs did not occur at younger ages in HIV-infected individuals compared with their HIV-uninfected counterparts (Abstract 59). Lung cancer remains a key cause of NADCs in the HIV-infected population. Observations from the US SEER (Surveillance, Epidemiology, and End Results) registry indicate that HIV seropositive patients with non–small cell lung cancer had a higher risk of lung cancer mortality than HIV seronegative patients (odds ratio [OR], 1.7; 95% confidence

interval [CI], 1.2-2.4) despite effective antiretroviral therapy and adjustment for known risk factors of poor prognosis and competing causes of death. These data suggest that HIV infection plays a role in lung cancer–related mortality (Abstract 740).

Unlike traditional AIDS-defining cancers, HPV-related dysplasia and malignancy incidence does not decline after initiation of antiretroviral therapy. This was demonstrated in various settings, including in the Swiss HIV Cohort Study (Abstract 730), in Botswana (Abstract 731), and in Senegal (Abstract 733). Despite effective antiretroviral therapy, high rates of genital HPV infection (50%-90%), particularly oncogenic strains, were reported in several studies (Abstracts 732, 733, 734, and 735), contributing to the development of HPV-related dysplasia and malignancy. PI use was associated with a higher rate of oncogenic HPV infection (Abstract 735) as well as the development of squamous cell carcinoma of the anus (Abstract 736). Given the observational nature of these 2 studies, this may reflect confounding but merits further exploration.

Random cervical biopsies may improve the detection of high-grade squamous intraepithelial lesions (HSILs),[16,17] although there is substantial debate about the advisability of routine random biopsies during colposcopy.[18] To investigate the yield of random biopsy in the evaluation of anal dysplasia, random biopsies of normal-appearing rectal mucosa were performed during high-resolution anoscopy of 372 men, 70% of whom were referred due to abnormal pap smears and 70% of whom were HIV seropositive. Of the 372, 132 (33.8%) patients were diagnosed with HSL, and of those 132, 13 patients had HSIL that was detected solely via random biopsy. HSIL was detected in 25% of biopsies of abnormal mucosa and 3.7% of random biopsies. Although it appears that random biopsies may slightly improve HSIL detection, the vast majority of HSILs were diagnosed with standard biopsies of abnormal mucosa. As has been the case with random biopsy in colposcopy, questions remain about the advisability of routine random biopsy in light of the additional cost, lower yield, and uncertain benefit this strategy would have on the prevention of HPV–related disease (Abstract 140).

Tuberculosis

The tuberculosis (TB) research presented at CROI continued to pick up steam this year, fueled by new drug developments, treatment strategies, and diagnostics. Presentations on TB science were concentrated on Wednesday, starting with a plenary session by Andreas Diacon from Capetown, South Africa. Diacon reviewed opportunities and challenges facing researchers as they approach using new drugs to develop shorter and more compact TB therapies (Abstract 123). Even with advances in antiretroviral therapy rollout, TB remains a major cause of mortality and requires better diagnostics, treatments, and care delivery systems. In a Kenyan study, autopsies of persons dying while on antiretroviral therapy revealed TB infection in 52% of cases (Abstract 831). In another study from South Africa, it was found that in a third of deaths occurring at home, there was microbiologic evidence of undiagnosed infectious TB (Abstract 837).

Simplifying and shortening TB treatment. The RIFAQUIN (High-Dose Rifapentine and a Quinolone in the Treatment of Pulmonary Tuberculosis) study examined 2 moxifloxacin-containing regimens for the treatment of drug-sensitive TB (Abstract 147LB). This was a randomized noninferiority trial of adults with smear-positive pulmonary TB. The control arm was given a standard 6-month TB treatment regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for a 2-month induction phase, followed by isoniazid and rifampin for a 4-month continuation phase. In 1 experimental arm evaluating treatment simplification, moxifloxacin replaced isoniazid during the 2-month induction phase. The continuation phase consisted of a 4-month, once-weekly regimen of rifapentine (1200 mg) and moxifloxacin. The second intervention arm evaluated treatment shortening in a 4-month TB treatment regimen. In this arm, moxifloxacin replaced isoniazid in the 2-month induction phase, and the 2-month continuation phase consisted of twice-weekly rifapentine (900 mg) and moxifloxacin. The primary end point of the study was a favorable outcome (survival, TB cure, and tolerance of TB medications) at 18 months. Of 827 subjects with smear-positive pulmonary TB enrolled, 730 were eligible for study and 28% were HIV-infected.

The 6-month experimental regimen, with a weekly continuation phase, was not inferior to the control arm. Favorable results were reported in 95% of subjects in the control arm compared with 96% of subjects in the experimental arm. In contrast, the 4-month experimental regimen was inferior to the control regimen, with only 83% of subjects achieving a favorable outcome. The use of quinolones in TB treatment remains controversial. The RIFAQUIN study indicates that replacing isoniazid with moxifloxacin does not achieve treatment shortening. For patients with quinolone-susceptible TB, isoniazid can be replaced with moxifloxacin, combined with weekly high-dose rifapentine, to simplify the continuation phase of TB treatment. Until further information about drug-drug interactions between antiretroviral drugs and rifapentine is available, HIV-infected patients are not candidates for this regimen because all HIV-infected patients with TB should be receiving antiretroviral therapy. In addition, prior studies of rifapentine in TB treatment of HIV-infected patients have revealed unacceptable rates of rifamycin resistance in instances of treatment breakthrough.

Optimal rifampin dose. Despite the desire to replace current TB regimens with new drugs to shorten treatment duration, current TB drugs may have some untapped potential. In a late-breaking presentation with the provocative title "What Is the 'Right' Dose of Rifampin?" Boeree and colleagues presented data suggesting that rifampin may be underdosed (Abstract 148LB). In a 14-day study, adults with smear-positive pulmonary TB received

1 of 5 possible doses of rifampin: 10 mg/kg, 20 mg/kg, 25 mg/kg, 30 mg/kg, or 35 mg/kg—for the first 7 days. At day 7, standard doses of isoniazid, pyrazinamide, and ethambutol were added. Both the fall in colony-forming units and the time to TB culture negativity increased with higher doses of rifampin, suggesting higher potency with higher rifampin doses. Dose-limited toxicity attributable to rifampin was not observed in this 68-patient study. Early studies of rifampin, conducted more than 40 years ago, did not establish the maximal tolerated dose (MTD). These new data are intriguing in their suggestion that greater microbiologic potency could potentially be achieved without added toxicity, leaving the door open to the prospect of higher rifampin doses contributing to shorter TB treatment regimens. More study is needed to define the MTD of rifampin, to more fully characterize safety at these higher doses, and to understand the effects, if any, on enzyme inductions that result in drug-drug interactions with many antiretroviral and commonly used drugs.

Optimal raltegravir dose. Antiretroviral therapy is necessary for all HIV-infected patients with TB, and the compatibility of newer antiretroviral drugs, such as the HIV integrase strand transfer inhibitors, with TB therapy is important to understand. Previous drug interaction studies have shown that raltegravir levels are reduced in the presence of rifampin. In a study by Grinsztejn and colleagues, 155 patients starting TB treatment were randomized to receive raltegravir- (either 800 mg twice daily or 400 mg twice daily) or efavirenz-based antiretroviral treatment regimens (Abstract 853). The primary end point of the study was virologic response at 48 weeks. Treatment success rates were 63% in the arm receiving raltegravir 800 mg, 76% in the arm receiving raltegravir 400 mg, and 67% in the arm receiving efavirenz. The researchers concluded that raltegravir-containing regimens are compatible with standard TB therapy and that no dose adjustment of raltegravir is required. For patients unable to take an efavirenz-based regimen, this study tells us that raltegravir is an excellent option.

Drug interactions between a new investigational TB drug, PA-824, and efavirenz. Characterizing interactions between new TB drugs and antiretroviral drugs is critical because HIV-infected patients who acquire TB will either already be receiving antiretroviral therapy or in need of starting it. PA-824, an investigational nitroimidazole under study for TB treatment, undergoes metabolism through the P450 3A enzyme (CYP3A). Efavirenz, a CYP3A inducer, is recommended as the antiretroviral drug of choice for TB-infected patients starting antiretroviral therapy. Dooley and colleagues reported the results of an open-label crossover study examining interactions between PA-824 and efavirenz (Abstract 188LB). The AUC and trough concentrations of PA-824 were reduced by 35% and 46%, respectively, among healthy, HIV-uninfected adults who were also receiving efavirenz. The AUC and trough concentrations of efavirenz were unaffected by PA-824. As PA-824 continues to be developed for TB treatment, the clinical significance of this interaction and potential dose adjustments will need to be considered.

Rifampin-resistant TB and urinary lipoarabinomannan assays. The rapid combined TB and resistance to rifampicin assay (Xpert) is a revolutionary advance in TB diagnostics, providing results within 2 hours and improving on the sensitivity of TB smear for pulmonary TB diagnosis. However, there remains a need for complimentary rapid tests, because the test falls short of detecting all culture-positive TB cases. The lateral-flow, point-of-care, urinary lipoarabinomannan (LAM) test is a tool that could potentially fill this gap. The LAM test can detect the presence of a 12.5 kDa component in the mycobacterial cell wall in 20 minutes, with an estimated cost of $3.50. Shah and colleagues reported the results of a cross-sectional study examining TB diagnosis using an array of tests among HIV-infected adults in Uganda (Abstract 146). As expected, the sensitivity of Xpert alone was greater than that of the urinary LAM (76% vs 49%, respectively). However, adding urinary LAM to Xpert increased sensitivity from 76% to 85%. As reported in previous studies, LAM performs best with persons whose CD4+ cell counts are in the lower ranges. For example, in this study, among patients with CD4+ cell counts lower than 50/μL, Xpert sensitivity was 74%, versus 65% with LAM. In patients whose CD4+ cell counts were above 200/μL, Xpert sensitivity was 71%, versus 19% in LAM. In complimentary studies evaluating LAM, Van Rie and colleagues reported an 82% sensitivity of urinary LAM for smear-negative, Xpert-negative, culture-positive TB among HIV-seropositive adults with CD4+ cell counts above 10/μL (Abstract 841). In an outpatient evaluation of LAM, where patients had high CD4+ cell counts, sensitivity was low and there was a high false-negative rate (Abstract 842).

These studies substantially contribute to a growing body of data suggesting that the lateral-flow, point-of-care, urinary LAM test is a valuable addition to TB diagnostic tools for patients with low CD4+ cell counts. Hospitalized patients with the lowest CD4+ cell counts would benefit the most from access to the urinary LAM test, which could rapidly identify those with advanced TB, a group with high mortality rates that requires faster diagnosis and treatment.

Cryptococcal Meningitis

Cryptococcal meningitis remains one of the most common and deadly opportunistic infections (OIs) in resource-limited settings. Practitioners do not agree on the optimal timing of the initiation of antiretroviral therapy, because data are conflicting and generalizability of prior studies is limited by small sample sizes, inconsistent practices for intracranial pressure management, and use of substandard cryptococcal treatment regimens.

Boulware and colleagues presented the results of a randomized study conducted in Uganda and South Africa that provides the best data to date on this topic (Abstract 144). Antiretroviral therapy–naive adults experiencing their first episode of cryptococcal meningitis were randomized to start antiretroviral therapy 1 week to 2 weeks, in the early arm, or 4 weeks, in the deferred arm, after diagnosis. Amphotericin B and fluconazole (800 mg daily) were given for a 2-week induction period, followed by fluconazole alone. Clinicians performed serial lumbar punctures to monitor and manage elevated intracranial pressure.

The Data and Safety Monitoring Board (DSMB) stopped the study because of excess mortality in the early treatment arm after only 177 of the 500 planned participants were enrolled (hazard ratio [HR], 1.7; 95% CI, 1.1-2.8). The median time to start of antiretroviral therapy was 8 days in the early arm and 35 days in the deferred arm. The 26-week survival rate was 70% in the deferred arm and 55% in the early arm. Most deaths occurred within the first month of treatment and cryptococcal disease was the most common cause of death. Using a standard case definition, there was no difference between arms in the rates of cryptococcal immune reconstitution syndrome. No autopsies were reported, thus it is difficult to assess whether immune restorative effects of early antiretroviral therapy may have contributed to this finding. Independent risk factors for mortality included altered mental status (Glasgow Coma Scale score < 15) and a white blood cell count in cerebrospinal fluid of less than 3/μL. This study provides convincing evidence that cryptococcal meningitis is an exception to the rule that starting antiretroviral therapy early during acute OIs reduces incidence of AIDS and death. For patients with cryptococcal meningitis, the start of antiretroviral therapy should be delayed for 4 weeks after diagnosis

Prevention With Cotrimoxazole

In the developed world, cotrimoxazole prophylaxis can be safely discontinued after antiretroviral therapy restores immune function but the optimal strategy for its use after a response to antiretroviral therapy in resource-limited settings has not yet been evaluated in a randomized study. To address this question, researchers randomized 758 children living in malaria endemic areas in Uganda or Zimbabwe, who had received at least 96 weeks of antiretroviral therapy and had no prior history of *Pneumocystis jiroveci* pneumonia, were randomly assigned to stop or continue cotrimoxazole prophylaxis (Abstract 86). Hospitalization rates for malaria and non-malaria illness were higher in those who stopped than in those who continued (HR, 1.57; 95% CI, 1.09-2.26). Pneumonia, sepsis, and meningitis contributed to greater hospitalization rates in those who stopped cotrimoxazole prophylaxis. This study supports prior observational data from malaria endemic regions. Cotrimoxazole prophylaxis should not be stopped even among children who are responding to antiretroviral therapy, because it still confers significant clinical benefit.

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A list of all cited abstracts appears on pages 90-95 and is available online at www.iasusa.com.

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Cases on the Web

NEW Neurologic Issues in Advanced HIV Infection

Scott L. Letendre, MD
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Level: Advanced

Neurocognitive problems are common in people with HIV, even those on successful antiretroviral therapy. In addition to HIV, several other common conditions can injure the brain, making diagnosis and management complex.

NEW Preventing Anal Cancer in HIV-Infected Men and Women

Timothy Wilkin, MD, MPH
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Anal cancer is an increasingly common cancer among HIV-infected adults. High-grade anal intraepithelial neoplasia, for which there are several treatment options, can be diagnosed using anal cytology and high-resolution anoscopy with biopsies.

These activities have been approved for *AMA PRA Category 1 Credit*™.

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Neurologic Issues in Advanced HIV Infection
Scott L. Letendre, MD
May 21, 2013

For upcoming webinars, please visit www.iasusa/webinars.

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COMING SOON

Look for these new *Cases on the Web* activities.

April: Transitioning HIV-Infected Youth Into More Mature Care Settings Case 2: Transition of Adults from Adolescent to Adult Care

Aracelis D. Fernandez, MD, and Stephen Stafford, BA

As young HIV-infected patients age, they will transition to medical and psychosocial services at adult care settings. This involves an adjustment to new practitioners and surroundings and to a health care approach that is reliant on a young person's capacity for self-care.

May: Pretreatment Counseling on Hepatitis C Virus (HCV) Protease Inhibitor-Based Therapy for HIV/HCV Coinfected Patients

Kara W. Chew, MD, MS, and Debika Bhattacharya, MD, MS, University of California Los Angeles

Two first-generation hepatitis C virus (HCV) protease inhibitors, boceprevir and telaprevir, each in conjunction with peginterferon alfa plus ribavirin, are in off-label clinical use for the treatment of HCV in HIV-coinfected persons. HIV practitioners need to understand potential adverse effects associated with these agents and counsel their patients before initiation of therapy.

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David B. Clifford, MD

The Use of Hepatitis C Virus (HCV) Protease Inhibitors in HIV/HCV-Coinfected Patients

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Management of Chronic Hepatitis C Virus Infection in Advanced Liver Disease

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