Complications of HIV Disease and Antiretroviral Therapy

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Continued progress in the diagnosis, management, and prevention of complications of HIV disease and antiretroviral therapy were reported at the 16th Conference on Retroviruses and Opportunistic Infections. This year’s conference brought new data on the optimal management of antiretroviral therapy in the presence of different opportunistic infections and included a number of important studies on pathogenesis and epidemiology of long-term complications. Major areas in which new information was presented are highlighted in this article.

Tuberculosis Coinfection

When to start antiretroviral therapy in patients with tuberculosis (TB) was addressed in the SAPIT (Starting Antiretroviral Therapy in Three Points in Tuberculosis Therapy) trial (Abstract 36a). In this 3-arm study, 645 South African adults with a CD4+ count lower than 500 cells/µL and a positive acid-fast bacillus (AFB) smear for TB underwent randomization to start antiretroviral therapy at TB treatment initiation or after the intensive phase of TB therapy but before TB treatment completion (the “integrated” groups), or after TB treatment completion (the “sequential” group). The antiretroviral regimen was daily didanosine, lamivudine, and efavirenz. The Data and Safety Monitoring Board (DSMB) halted the trial when the mortality of patients in the 2 integrated antiretroviral therapy and TB treatment groups was 56% lower than those in the sequential group.

These data support current World Health Organization (WHO) guidelines that patients with TB who meet criteria for antiretroviral therapy should not wait until completion of TB therapy to start antiretroviral therapy. Although mortality in patients with CD4+ counts between 200 cells/µL and 500 cells/µL was lower in patients in the integrated treatment groups, the study was not powered to determine the benefit of antiretroviral therapy in persons with a CD4+ count between 350 cells/µL and 500 cells/µL, for whom guidelines currently recommend completion of TB therapy before starting antiretroviral therapy. An important remaining question is the optimal timing of antiretroviral therapy during TB therapy, for which the ongoing 2 integrated treatment groups of the SAPIT trial, the CAMELIA (Cambodian Early Versus Late Introduction of Antiretrovirals) study and the AIDS Clinical Trials Group (ACTG) A5221 study, will inform the field.

Which antiretroviral therapy to start in patients with TB was addressed in Swaminathan and colleagues’ Chennai, India–based TB treatment study (Abstract 35). In this study, 127 HIV-seropositive adults with TB underwent randomization to 1 of 2 once-daily antiretroviral regimens after completing a 2-month TB treatment induction phase: nevirapine, didanosine, and lamivudine or efavirenz, didanosine, and lamivudine. The DSMB also recommended stopping this study early when virologic suppression rates were 28% higher in the efavirenz- than in the nevirapine-containing regimen. The once-daily dosing of nevirapine and its interaction with rifampin likely resulted in lower levels of nevirapine and worse virologic outcome. Thus, when using a once-daily antiretroviral regimen in patients with TB, an efavirenz-based regimen is preferred to a nevirapine-based one to optimize virologic outcome.

In general, HIV-seropositive patients with TB are prescribed the same TB regimens as are HIV-seronegative patients. However, some TB regimens using intermittent therapy during TB treatment may not be optimal for HIV-infected patients. Swaminathan and colleagues evaluated TB treatment outcomes in HIV-seropositive (n = 212) and HIV-seronegative (n = 250) persons with TB treated with the Indian national TB-treatment regimen, which includes intermittent therapy for the intensive and continuation phase of TB treatment (Abstract 783). Among TB treatment failures, only 0.4% of HIV-seropositive persons had acquired rifampin resistance, whereas 8.9% of HIV-seropositive persons had acquired rifampin resistance. Several subjects had preexisting isoniazid resistance leading to multidrug-resistant (MDR) TB failures. Rifampin resistance was associated with a lower CD4+ cell count. None of the HIV-seropositive patients had access to antiretroviral therapy at the time of this study, which may have amplified the differences between the study groups. However, in view of the crucial role of rifampin in TB treatment and the dire outcomes in HIV-infected patients with MDR TB, the conclusion of this study is that intermittent TB treatment should be avoided.

Meintjes and colleagues presented the results of a randomized, placebo-controlled trial of a 4-week course of prednisone in mild to moderate TB-associated immune reconstitution syndrome (IRIS) (Abstract 34). The prednisone dose was 1.5 mg/kg daily for 2 weeks, then 0.75 mg/kg daily for 2 weeks. The major findings in this study were (1) a reduction in hospitalizations and procedures in the prednisone recipients compared with the placebo recipients, and (2) greater improvement in symptoms in the prednisone than in the placebo recipients at 2 weeks. Corticosteroid side effects were more frequent in prednisone (9 events) than in placebo (3 events) recipients, but serious infections were uncommon and did not differ between the groups. Thus, physicians can utilize steroids...
in such patients, knowing that at least in the first 4 weeks, benefits appear to outweigh risks. Of note, and as the authors acknowledged, extended steroid courses may be required to avoid recurrence of symptoms, which could increase toxicity over the long-term.

The enormous burden of TB among patients starting antiretroviral therapy and the difficulty in diagnosing these cases without access to TB culture was highlighted in several studies conducted in South Africa. Of 236 patients presenting to care in Capetown screened with TB smear, culture, and the urine-based test for lipoarabinomannan (LAM), 26.3% had culture-positive TB (Abstract 780). Sputum TB smear sensitivity was only 13%, and 22% of all cases were asymptomatic. LAM testing had a sensitivity of 51% in those with fewer than 100 CD4+ cells/µL. Symptom screens had a sensitivity of 78% but a poor specificity of 35%. Sputum induction did not improve diagnostic yield of cultures.

In another study in Durban, South Africa, 824 patients with a median CD4+ count of 100 cells/µL (range, 48–154 cells/µL) were screened for TB (Abstract 779). Nineteen percent of patients had a positive result from TB culture. The TB smear had a sensitivity of 9%, and 22% reported no TB symptoms. In a cost analysis, screening with cultures doubled the number of cases identified compared with cases identified using current WHO guidelines, with only a modest increase of cost per case identified. TB was detected in 18.1% of participants who provided sputum samples.

Another study conducted in Zimbabwe, where TB culture is not routinely available, tracked the outcomes of 240 smear-negative, TB-suspect cases (Abstract 778). Of these, HIV prevalence was 78%, and TB was ultimately confirmed by culture in 85 cases. Not surprisingly, undiagnosed and untreated TB was associated with a high mortality rate. Martinson and colleagues reported on 729 patients suspected of having TB (91% HIV-seropositive) admitted to 1 of 3 public hospitals in South Africa (Abstract 789). Among HIV-seropositive, TB-culture-positive patients, mortality was 15.2% at 90 days, compared with 2.3% for HIV-seronegative patients. Few patients were receiving antiretroviral therapy despite low CD4+ counts. This study underscores the high mortality rates in hospitalized patients coinfected with HIV and TB as well as the potential for nosocomial TB transmission.

Early data are emerging on the use of polymerase chain reaction (PCR) testing to obtain a more rapid assessment of TB and to facilitate early identification of MDR TB and extensively drug-resistant (XDR) TB. Hassim and colleagues presented preliminary data evaluating the use of TB smear, culture, and PCR testing results for diagnosis of TB in a cohort of 489 patients suspected of having TB (Abstract 781). TB was detected in 18% of patients. AFB smear testing was 37% sensitive. PCR testing revealed the diagnosis weeks before culture results did and was 97% sensitive for smear-positive TB and 37% sensitive for smear-negative TB. MDR TB accounted for approximately 20% of the TB cases in the cohort, with prior TB treatment the greatest risk factor. PCR testing rapidly identified MDR TB in 7 of the cases in this ongoing study.

Reported survival among HIV-infected patients living in South Africa with XDR TB or MDR TB has been abysmally low. Two reports from South Africa provided updated information on this group of patients. In a retrospective review of 272 MDR (41%) and XDR (59%) TB cases diagnosed from 2005 to 2007 in Tugela Ferry, 82% of patients with XDR TB and 69% of those with MDR TB were dead at 1 year (Abstract 784). Early mortality at 30 days was 54% for XDR TB patients and 40% for MDR TB patients. For MDR TB patients but not XDR TB patients, there was a trend for improved survival over time. In 2005, 87% of patients with MDR TB died, compared with 45% of such patients in 2007.

Better survival rates were reported in a review of 60 patients with XDR TB referred to a public TB hospital in KwaZulu-Natal, South Africa (Abstract 785). Of these patients, 43 were HIV-infected and had a median CD4+ count of 200 cells/µL, and 49% were receiving antiretroviral therapy. Forty-two percent of patients in this cohort died. Twenty percent had documented conversion of sputum cultures. The primary reason for the better outcomes in the KwaZulu-Natal study likely stems from the fact that only patients who survived from the time of diagnosis of MDR or XDR TB to entry into the TB referral center were included in the analysis.

Identifying optimal prevention strategies for TB remains a high research priority. Martinson and colleagues presented the results of a 4-year, 1150-patient study of 4 TB-preventive regimens conducted in South Africa (Abstract 36bLB). HIV-infected adults who were positive for purified protein derivative (PPD) of tuberculin underwent randomization to receive rifapentine plus isoniazid for 12 weeks, rifampin plus isoniazid for 12 weeks, or isoniazid continuously for the study duration; the control group received isoniazid for 6 months. The main finding of this study was that neither the short-course, 2-drug regimen nor the continuous isoniazid treatment was superior to the control group. In addition, rifampin resistance was detected in some of the breakthrough TB isolates in the combination-therapy groups. Toxicity and adherence issues led to an approximately 50% drop-off in the continuous isoniazid group at 2 years. However, in an on-treatment analysis, continuous isoniazid treatment resulted in a 70% reduction in TB compared with the other regimens. Thus, in highly TB-endemic areas, continuous isoniazid treatment for those who can adhere to it and tolerate it is highly effective in reducing TB, compared with the currently recommended 6-month course of isoniazid. How these data will be applied in the public health setting is currently under debate.

Mitchell and colleagues presented the results of an isoniazid prophylaxis study conducted in 3-month-old HIV-seronegative, perinatally HIV-exposed South African children (Abstract 907). In this study, 804 HIV-uninfected children underwent randomization to isoniazid treatment or placebo for 96 weeks, with an additional 96-week planned follow-up. The primary end-
points were defined as acquisition of latent TB, pulmonary TB disease, and death. The DSMB stopped the study at 96 weeks, at which point no difference was apparent between the 2 groups. Investigators reported similar findings for children in the HIV-infected groups of this study in 2008.1 Thus, primary TB prophylaxis in infants does not appear to be an effective strategy for such patients, and new studies must address the most effective regimen and optimal time to prevent TB acquisition in TB-endemic areas.

A big challenge in the management of TB in resource-limited settings is determining the optimal antiretroviral therapy and TB regimen when HIV protease inhibitors (PIs) are required for efficacy. This situation is increasingly common in HIV-infected children for whom PIs are prescribed after previous use of nevirapine for prevention of mother-to-child transmission of HIV. The management is particularly complicated because of limited availability of pharmacokinetic information and drug preparations for the pediatric population. McIlleron and colleagues presented the results of a pharmacokinetic study comparing lopinavir exposure in 15 children treated for TB and HIV coinfection using double-dose lopinavir/ritonavir (lopinavir/ritonavir) and in 24 control patients monoinfected with HIV treated with standard-dose lopinavir (Abstract 98). This study was prematurely stopped by the DSMB because double-dose lopinavir/ritonavir could not overcome the effects of rifampin in this population and resulted in 60% of children with subtherapeutic levels of lopinavir.

Underdosing of lopinavir/ritonavir would be expected to lead to lower rates of viral suppression and to drug resistance, which is exactly what happened in 2 other studies conducted in South African children with TB. Reitz and colleagues compared virologic suppression rates in 254 children with and without TB (Abstract 910). As per country guidelines at the time, children were treated with lopinavir only (those younger than 6 months) or lopinavir/ritonavir (those older than 6 months). Virologic suppression rates were 94.8% in children never treated for TB compared with 74% in those treated for TB at antiretroviral therapy initiation and 51.6% in those treated for TB after suppression with antiretroviral therapy. In a complementary report of drug resistance mutations among pediatric patients for whom PI therapy failed, major PI mutations were more frequent in children receiving full-dose ritonavir in the presence of rifampin than in children receiving standard lopinavir/ritonavir regimens not concurrent with TB therapy (Abstract 888). These studies call for research optimizing antiretroviral therapy and TB therapy among infants and children, including studies exploring safety and efficacy of rifabutin-containing TB regimens.

Cryptococcal Disease

Cryptococcal disease is an important cause of morbidity and mortality in Africa, yet there are limited data on optimal prevention and management strategies. Parkes-Ratanshi and colleagues presented the results of a double-blind, randomized trial comparing fluconazole 200 mg thrice weekly with placebo (Abstract 32). The study enrolled 1519 HIV-infected adults residing in rural Uganda who had a CD4+ count lower than 200 cells/µL and a negative result for cryptococcal antigen. Of these patients, 1335 started antiretroviral therapy a median of 74 days after enrollment. Cryptococcal meningitis developed in 18 patients receiving placebo versus 1 patient receiving fluconazole. Of these, 12 cases occurred before antiretroviral therapy and 7 after. Candidal esophagitis was 86% lower in the fluconazole-treated recipients than in placebo recipients. Adverse events attributed to fluconazole were minimal. Thus, fluconazole was extremely effective in reducing the burden of both cryptococcal meningitis and candidal esophagitis. These results should stimulate discussion of the prophylactic use of fluconazole for high-risk persons starting antiretroviral therapy in Africa.

A second study of cryptococcal disease focused on determining the optimal point to start antiretroviral therapy in patients with acute cryptococcal meningitis. In this study, 54 antiretroviral therapy–naive, HIV-seropositive patients with cryptococcal meningitis living in Harare, Zimbabwe, underwent randomization to receive antiretroviral therapy at the initiation of cryptococcal meningitis treatment or 10 weeks later (Abstract 36cLB). The treatment regimen for cryptococcal meningitis was 800 mg of fluconazole daily. There was a 2-fold increased risk of death for patients treated immediately with antiretroviral therapy compared with those treated at 10 weeks. Overall mortality rates were extremely high, with 87% and 37% of patients in the immediate and delayed antiretroviral therapy groups dead at 2 years, respectively. Mortality rates were highest in the first 2 months of fluconazole treatment, suggesting a detrimental effect of early antiretroviral therapy.

These data stand in contrast to the results of a largely US-based trial presented at the 2008 conference by Zolopa and colleagues, which enrolled patients with a variety of opportunistic infections including cryptococcal meningitis and showed a benefit to early antiretroviral therapy.2 More aggressive management of elevated intracranial pressures, use of amphotericin, and less ill patients in the United States compared with those in Zimbabwe could explain some of these differences. However, these data underscore the need for caution in very early antiretroviral therapy initiation in patients with inflammatory central nervous system infections such as cryptococcal meningitis.

Trimethoprim-Sulfamethoxazole Prophylaxis Strategies in Africa

Stopping trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis treatment in patients who have restored immunity with antiretroviral therapy is safe and is the standard of care in most developed and middle-income countries. However, data are limited on the safety of TMP-SMX discontinuation in resource-limited settings, where malaria and bacterial diarrhea diseases are more common. Campbell and colleagues’ data suggest that TMP-SMX discontinuation in areas such as rural Uganda is not particularly safe (Abstract...
Hepatitis C Virus Coinfection

The first systematic evaluation of the influence of hepatitis C virus (HCV) RNA level and HCV genotype on liver-related death was presented by Rockstroh and colleagues (Abstract 101). The study included 1952 HIV and HCV-coinfected patients, of whom 21% had an HCV RNA level lower than 650 U/mL, 37% had an HCV RNA level between 650 U/mL and 500,000 U/mL, and 42% had a level higher than 500,000 U/mL. Among 1537 subjects with HCV genotype, 52%, 14%, 30%, and 3% had genotypes 1, 4, 3, and 2, respectively. In the multivariate analysis, persons with the highest HCV RNA levels had a 1.8-fold higher risk of liver-related death than did people with the lowest HCV RNA levels. Patients with genotypes 2 and 3 had lower risks of death than did those with genotype 1. HCV RNA level did not predict response to HIV therapy, but having genotype 4 was associated with a worse response to antiretroviral therapy, as measured by HIV RNA levels lower than 500 U/mL or a 50% gain in CD4+ count.

Predictors of death, hepatocellular carcinoma, or liver transplant among 248 patients coinfected with HIV and HCV with compensated cirrhosis in the GESIDA (Grupo de Estudio de SIDA, AIDS Study Group) Spanish cohort study were presented by Montes and colleagues (Abstract 106). Characteristics of this cohort included 27% with HCV genotype 2 or 3, 72% who had received antiretroviral therapy, and 63% with prior or current treatment for HCV. In the multivariate analysis, only liver disease classified as Child-Pugh class C and interrupted antiretroviral therapy were associated with decreased survival. Of interest, in this cohort, first hepatic decompensation was not delayed in patients who received treatment for HCV. HCV-specific T-cell responses augmented by antiretroviral therapy in coinfected patients may be an explanation, as demonstrated in a study presented by Rohrbach and colleagues (Abstract 105). Before starting antiretroviral therapy, 13% to 14% of patients had detectable HCV-specific T-cell responses as shown by ELISPOT assay. After antiretroviral therapy, up to 54% had detectable T-cell responses. Median plasma HCV RNA levels were inversely correlated with T-cell responses in the absence of specific therapy for HCV.

The efficacy of extended therapy with 72 weeks of treatment with peginterferon alfa and weight-based ribavirin in 169 patients who had achieved HCV early virologic response (EVR) in the ACTG SLAM-C (ACTG A5178) study was presented by Chung and colleagues (Abstract 103LB). Fifty-one percent of patients achieved SVR at week 24, 72 weeks after HCV treatment discontinuation. Virologic response at 12 weeks was predictive of this long-term outcome. Seventy-four percent of patients who had HCV RNA levels lower than 600 IU/mL at week 12 (complete EVR, cEVR) had sustained virologic response (SVR) versus 15% without cEVR. SVR was achieved by 60% in the on-treatment analysis of the 62 patients who completed the HCV treatment. This study reports some of the highest SVR levels seen among HCV- and HIV-coinfected patients with use of weight-based ribavirin; characteristics of patients most likely to achieve SVR included achieving cEVR and completion of HCV therapy.
Hepatitis B Virus Coinfection

Hepatitis B virus (HBV) suppression rates in patients receiving tenofovir-containing regimens were reported by Lacombe and colleagues (Abstract 100). The median follow-up period was 32 months. In this French cohort of 168 patients, median time to achieve an HBV DNA level lower than 2000 IU/mL was 9.1 months, and 89.3% of patients had undetectable HBV DNA levels at the end of the follow-up period. Among the patients experiencing virologic failure, only one-third had detectable tenofovir levels, suggesting poor adherence as the major factor in failure. The L217R polymorphism but no other Pol mutations were identified in those with virologic failure. Thus, in this cohort, high rates of HBV suppression were achieved among patients adherent to tenofovir-containing therapy, and tenofovir drug resistance was not identified in those whose virus was not suppressed.

Treatment of HBV infection in patients not yet willing or prepared to take HIV therapy relies on drugs with anti-HBV but not anti-HIV activity, to avoid the selection for HIV drug resistance. In a case report of a 45-year-old man with HIV infection treated with adefovir and telbivudine at doses thought not to have anti-HIV activity, plasma HIV RNA levels decreased from 14,462 copies/mL to lower than 50 copies/mL (Abstract 813a). When telbivudine was stopped temporarily, his HIV RNA level increased to 3903 copies/mL. When rechallenged with telbivudine, his HIV RNA level resuppressed. An in vitro study presented next to this poster came to the opposite conclusion (Abstract 813b). In this study, numerous HBV strains were tested using a standard culture and a phenotypic assay. Telbivudine showed no activity against HIV isolates, in contrast to other drugs such as entecavir and efavirenz (as a control). Although the in vitro data are reassuring, even a single patient in whom HIV activity is exhibited with telbivudine treatment raises concern that the in vitro assays may not entirely reflect the in vivo environment.

Coinfection with HBV and HIV is prevalent in many resource-limited settings, but HBV screening is rarely performed, and tenofovir is not part of initial antiretroviral therapy in most countries. Burnett and colleagues reported that in a South African cohort, 23% of HIV-infected patients tested positive for hepatitis B surface antigen (HBsAg) and for HBV, and an additional 23% tested positive for HBV but not HBsAg (Abstract 799). In another report from South Africa, persistent HBV DNA was detected in 15.5% of patients receiving an antiretroviral therapy regimen containing lamivudine but not tenofovir (Abstract 813c). Cost but not toxicity appears to be a major barrier in the treatment of patients with a tenofovir-containing regimen in resource-constrained settings.

Serious Non-AIDS-Related Events

The past several years have seen a sharper focus on the relationship between HIV infection and a range of serious non-AIDS-related clinical events such as cardiovascular, renal, and hepatic complications. At this year’s conference, several groups reported on the epidemiology and outcomes related to this collective group of serious non-AIDS-related events (Abstracts 706, 707, 708, 145).

Investigators from the Antiretroviral Therapy Cohort Collaboration (ATCC) examined causes of death in nearly 40,000 patients who initiated triple-drug therapy between 1996 and 2006 (Abstract 708). During the first year of antiretroviral therapy, AIDS events predominated as a cause of death (63% of all deaths); thereafter, they fell and were replaced by other types of events. Baseline levels of CD4+ were associated with AIDS events, non-AIDS malignancy, and renal failure. Of note, the rates of non-AIDS-infection, liver-related, non-AIDS-malignancy, violence-related, heart or vascular, and respiratory deaths were markedly elevated in patients infected via IDU. Strategies to reduce the rates of these non-AIDS-related events and to effectively manage IDU are needed to further reduce rates of mortality in patients receiving antiretroviral therapy.

Mocroft, Lundgren, and their EuroSIDA colleagues reported on the incidence and risk factors for serious non-AIDS-defining events in Europe (Abstract 707). The incidences of non-AIDS-defining events (malignancies, end-stage renal disease, liver failure [grade III/IV hepatic encephalopathy, death from liver-related disease], pancreatitis, cardiovascular disease [CVD; acute myocardial infarction or stroke]) and of AIDS-defining illnesses were evaluated. The incidence of non-AIDS-defining events was slightly higher than that of AIDS events (16.5 and 15.5 per 1000 patient-years, respectively). Malignancy, CVD, and liver failure were the most common events, and rates of all of these events were lower in patients with higher CD4+ counts, suggesting again that immunodeficiency contributes to the pathogenesis of non-AIDS-defining events. Collectively, these studies highlight the importance of non-AIDS-defining events as a focus in HIV research, including the need for standard reporting of clinical trials and cohort studies and as a target for future interventions.

The finding that smoking, hypertension, and diabetes were all risk factors for the development of non-AIDS-defining events is an important reminder about the role of management of these issues in HIV primary care. The crucial role of these modifiable risk factors, especially smoking and diabetes, was also highlighted by analyses from the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) cohort and the FRAM (Fat Redistribution and Metabolism) study examining causes of death (Abstracts 145, 706).

Smoking cessation has become an important topic in HIV management; however, data are limited on the efficacy of different interventions in HIV populations. Tashima and colleagues reported results of a large randomized trial to evaluate a smoking cessation intervention conducted in an HIV treatment setting (Abstract 148). Four hundred and forty-four patients underwent randomization to receive either a brief 2-session or more intensive 4-session motivational counseling intervention based on Public Health Service guidelines. Participants were provided
an 8-week supply of nicotine patches if they set a quit date. Unfortunately, overall quit rates in the intent-to-treat analysis were only 9%, with higher rates noted among Hispanic participants (19%). Use of the nicotine patch appeared to be an important factor for success in this study. Future intervention studies, possibly including medications that target nicotine receptors, are needed in HIV-infected individuals.

**Cardiovascular Disease**

As noted above, CVD remains an important contributor to overall mortality in the aging population of HIV-infected adults, much as it does in the general population. Rates of myocardial infarction (MI) in HIV-infected patients continue to be monitored in several cohort studies. Data from the California Kaiser Permanente cohort, a setting in which primary prevention and HIV care are integrated, demonstrated that rates of hospitalization for MI have declined since 2002 in the HIV-infected population (Abstract 710). In fact, the difference in relative rate of hospitalization for MI in HIV-infected versus HIV-uninfected participants than in an HIV-uninfected control group. These data suggest they might lower plasma concentrations of HDL cholesterol, as a consequence of chronic HIV infection, has been appreciated for decades. The mechanism mediating the HIV effect on HDL cholesterol metabolism has not been clear. Using the simian immunodeficiency virus macaques model of HIV (SIVmac239), Bukrinsky and colleagues evaluated the impact of the HIV accessory protein Nef on cholesterol efflux in vitro, an effect that was diminished when Nef was removed from the sera. Collectively, these studies suggest a potential role for Nef in the development of dyslipidemia in HIV infection.

The importance of HDL cholesterol particle size and risk of CVD events was further explored by investigators from the SMART (Strategies for Management of Antiretroviral Therapy) study (Abstract 149). Earlier reports from this group identified that in the setting of treatment interruption, declines in HDL cholesterol concentration were an important risk factor for serious cardiovascular events. Using nuclear magnetic resonance analysis, the investigators evaluated the relationship between lipoprotein particle size and risk of CVD. When comparing a subset of patients from the viral suppression and discontinuation subgroups of the study, the authors noted that the change in lipoprotein particle concentration was greatest for total HDL particles and for the small- and medium-size HDL particles. In addition, lower concentration values of total HDL particles and small HDL particles were associated with a statistically significant increased risk of CVD, whereas very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) particle concentrations were not associated with CVD risk. The relative contributions of HDL fractions to CVD risk during continuous treatment is an important topic for future study.

Lipid-lowering therapy is routinely recommended for HIV-infected patients based on guidelines developed for the general population, although limited information about the success of such interventions in HIV-infected patients is available from controlled studies. Statins are often the initial therapy, especially in patients with elevated levels of non-HDL cholesterol. Statins are thought to have immunomodulating properties, and in vitro studies suggest they might lower plasma HIV-1 RNA level.
Ganesan and colleagues performed a randomized, placebo-controlled study with a cross-over design to evaluate the role of high-dose atorvastatin (80 mg) versus placebo on immune activation and HIV-1 RNA level in chronically infected patients not receiving antiretroviral therapy (Abstract 577). Atorvastatin reduced the proportion of CD3+, CD4+, and CD8+ cells expressing the activation marker HLA-DR without changing absolute lymphocyte count or HIV-1 RNA level. As expected, LDL cholesterol levels fell statistically significantly during atorvastatin therapy. These findings suggest that the immune-modulating effects of statins occur without any change in HIV-1 RNA level. The longer-term sequelae of dampening-down immune activation in chronic HIV infection during statin therapy requires further investigation.

Ezetimibe, a drug that inhibits intestinal absorption of dietary and biliary cholesterol, is sometimes used as an adjunct to statin therapy. Chow and ACTG colleagues observed 44 statin-recipient patients with LDL cholesterol levels higher than 130 mg/dL who underwent randomization to ezetimibe (10 mg) or placebo for 12 weeks followed by a 4-week washout period, then 12 weeks with the alternative treatment (Abstract 712). Adverse events were very common (63%); however, no grade-4 events occurred. Statistically significant reductions in levels of LDL cholesterol, total cholesterol, non-HDL cholesterol, and apolipoprotein B occurred during ezetimibe treatment, leading the authors to conclude that addition of this drug to statin therapy is an option for HIV-infected patients whose LDL cholesterol levels are elevated while receiving statins.

Antiretroviral Therapy and Risk of Cardiovascular Disease

There is strong interest in determining how different drugs used in the treatment of chronic HIV infection might contribute to CVD risk. Data from cohort studies and randomized trials are now focused on the role of specific drugs (rather than broader drug classes) in CVD risk.

The D:A:D cohort was designed to examine the associations between various antiretroviral drugs and CVD risk. The D:A:D group has set a threshold of 30,000 patient-years of exposure needed before an individual drug can be analyzed. At the 2008 (15th) Conference on Retroviruses and Opportunityistic Infections, the unexpected finding of an association between abacavir and MI was reported; however, the cohort did not meet the exposure threshold for tenofovir that would allow comparison of these 2 drugs. This year, an updated analysis of individual nucleoside analogue reverse transcriptase inhibitors (nRTIs) and PIs was reported (Abstract 44LB). Of note, atazanavir is not included in this analysis because the level of exposure to atazanavir in the D:A:D cohort remains below the required threshold level to examine any association with MI risk.

The D:A:D cohort now includes 580 MIs during 178,835 person-years of follow-up. The new findings include the absence of any statistically significant association between recent or cumulative use of tenofovir and MI risk. As before, recent exposure to abacavir (RR, 1.68) or didanosine (RR, 1.41) remained associated with an increased risk of MI. Cumulative (but not recent) exposure to indinavir (with or without ritonavir) or lopinavir/r was also associated with an increased risk of MI. Cumulative use to PI was associated with an increased risk of MI for all study drugs (indinavir: OR, 1.11/year; 95% CI, 0.98–1.25; nelfinavir: OR, 1.13/year; 95% CI, 0.99–1.30) except saquinavir (OR, 0.96/year; 95% CI, 0.80–1.15), reaching statistical significance for lopinavir (OR, 1.38/year; 95% CI, 1.10–1.74) and amprenavir/fos-amprenavir (OR, 1.55/year; 95% CI, 1.20–1.99).

Consistent findings between these 2 studies are the association between abacavir and MI, albeit with a different timeframe, and the statistically significant association of lopinavir/r with MI risk. These signals warrant further investigation in studies designed to investigate the mechanisms that could mediate the association.

Benson and colleagues examined the relationship between abacavir and MI risk in prospectively followed patients whose treatment assignments were randomized in the ongoing ALLRT (ACTG Longitudinal Linked Randomized Trials) study (Abstract 721). The analysis included 3205 patients who underwent randomization to their first antiretroviral therapy regimen, and endpoints included 63 severe CVD events, including 27 MIs. No statistically significant associations were identified.
between either MI or severe CVD and recent abacavir use (RR, 1.02; 95% CI, 0.4–2.5; P = .96; and RR, 0.8; 95% CI, 0.5–1.6; P = .58, respectively). These findings are consistent with a previous report of randomized clinical trials in the past year.\(^3\)

Several groups of investigators reported results of studies evaluating potential mechanisms to explain the association between abacavir exposure and MI risk. These included studies of inflammatory markers, endothelial function, and platelet function.

McComsey and colleagues measured markers of inflammation and endothelial activation from the HEAT (Head-to-Head EpiCom and Truvada) study, a randomized comparison of abacavir/lamivudine or tenofovir/emtricitabine combined with lopinavir/ritonavir in treatment-naive patients (Abstract 732). Samples from more than 400 patients were assayed for endothelial marker vascular cell adhesion molecule-1 (VCAM-1), interleukin–6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) at baseline, week 48, and week 96. Levels of all markers fell with treatment; however, there was no statistically significant difference between the abacavir- and the tenofovir-treated patients.

Similarly, data from the ACTG 5095 study were used to examine changes in hs-CRP levels in patients who underwent randomization to a combination of zidovudine, lamivudine, and efavirenz with or without abacavir (Abstract 736). Again, no difference in changes in hs-CRP level were seen in those receiving or not receiving abacavir. (An interesting observation from this study was the finding that hs-CRP levels did not fall during treatment in either group of efavirenz-treated patients, an effect that appeared to be more exaggerated in women than in men.) Collectively, these studies, along with analyses from the WIHS (Women’s Intergency HIV Study) and the MACS (Multicenter AIDS Cohort Study), failed to confirm the relationship between abacavir exposure and markers of inflammation that had been suggested from earlier, nonrandomized data.\(^6\)

Alteration in platelet function is under investigation as another possible mechanism to explain HIV- and antiretroviral therapy–associated CVD risk (Abstract 151LB). Satchell and her colleagues from Dublin assessed platelet function in a cross-sectional study comparing 30 patients receiving abacavir-containing antiretroviral therapy with 28 patients receiving nonabacavir regimens. Platelet reactivity in response to different standard stimuli (collagen, epinephrine, and thrombin-receptor-activating peptide, TRAP) was higher in the abacavir-treated patients than in the nonabacavir recipients, an effect that remained statistically significant for all but the TRAP stimuli after adjustment for other covariates. These preliminary data, if confirmed by prospective, preferably randomized studies, suggest a potential mechanism for the abacavir-MI association. Future research to determine the time course and reversibility of these changes is awaited.

Finally, alteration in endothelial function is another potential mechanism for antiretroviral therapy–associated influence on CVD. Previous studies suggest that untreated HIV infection is associated with impaired flow-mediated dilation of the brachial artery and that this effect generally improves when treatment is initiated. Hsue and colleagues reported the results of a cross-sectional study measuring endothelial function in 61 patients with undetectable plasma HIV RNA levels, half of whom were receiving abacavir (Abstract 723). Flow-mediated vasodilation of the brachial artery was more impaired in abacavir-treated patients than in control patients, an effect that remained statistically significant after control for duration of antiretroviral therapy and CD4+ count. Although limited by the nonrandom assignment of abacavir, these findings suggest that further study of changes in endothelial function during treatment with abacavir are warranted.

How do we reconcile these seemingly conflicting clinical results and the mechanistic studies examining abacavir and CVD? This issue was reviewed in a comprehensive summary delivered by Reiss (Abstract 152), in which he contrasted the clinical studies demonstrating an abacavir signal (D:A:D, Abstract 44LB; French Hospital Case-Control Study, Abstract 45LB; and STEAL [Switching to Tenofovir-Emtricitabine or Abacavir-Lamivudine], Abstract 576) to those studies that did not see the association (ALLRT; Abstract 721).\(^5\) One difference between the studies is the fact that a greater proportion of patients in the cohort studies and STEAL trial were virologically suppressed when abacavir was added, whereas in the clinical trials all patients were treatment-naive when exposed to abacavir.

Reiss presented a preliminary supplementary analysis from the French Hospital Database that provided further support to his hypothesis that an undetectable viral load may be an important factor for the association. Alternatively, it is still possible that unmeasured confounders are operating in the observational studies, although it is hard to reconcile this idea with the fact that the abacavir signal is no longer apparent in patients who discontinue the drug. As more data are compiled to address this important question, clinicians are reminded of the importance of addressing proven modifiable risk factors for CVD in HIV-infected patients.

### Should Antiretroviral Therapy be Switched to Reduce Cardiovascular Disease Risk?

Clinicians are often faced with the dilemma of deciding whether to switch 1 or more of the antiretroviral drugs in a regimen as an option for reducing CVD risk. Prospective studies suggest more favorable lipid profiles with several newer drugs, but the short-and long-term consequences of these changes have not been well studied. Three switch studies addressing lipids and other measures of cardiovascular risk (all with catchy monickers) were presented this year.

**SABAR study.** Atazanavir is a well-tolerated PI that has been shown to have a favorable lipid profile in randomized clinical trials. Murphy and colleagues conducted a prospective randomized trial, the SABAR (Switch to Atazanavir...
and Brachial Artery Reactivity) study, of 50 virologically suppressed, hyperlipidemic, PI-treated patients who underwent randomization (1:1) to switch to ritonavir-boosted atazanavir or remain on their current PI (80% were receiving lopinavir/r) for 24 weeks (Abstract 722). Measures of lipids, markers of inflammation, and endothelial function were obtained at baseline and after 24 weeks of follow-up. Declines in total cholesterol and triglyceride levels were greater in those who switched to atazanavir; however, no changes in endothelial function or cardiovascular inflammatory markers were observed. These findings suggest that although safe and associated with improvement in lipid profiles, the switch to atazanavir did not improve endothelial function over the short-term.

**SWITCHMRK-1 and -2 trials.** In studies of treatment-naive patients, raltegravir has demonstrated no impact on lipids, and hence there is great interest in the role of this drug in the treatment of dyslipidemic patients well suppressed with other drugs. The SWITCHMRK-1 and -2 studies were parallel, multicenter, double-blind, randomized, active-controlled studies conducted in patients who had virologic suppression with a lopinavir/r-containing regimen (Abstract 70aLB). Participants underwent randomization (1:1) to substitute raltegravir or remain on lopinavir/r. After 12 weeks, raltegravir was superior to lopinavir/r with respect to improvement in levels of total cholesterol (−12% vs 1%, respectively), triglycerides (−43% vs 8%), and non-HDL cholesterol (−15% vs 3%). After 24 weeks, however, the proportion of patients who remained virologically suppressed (as indicated by plasma HIV RNA level < 50 copies/mL) did not meet the noninferiority bound (−12%) for the raltegravir group (88% vs 93%; treatment difference, −5.8%; 95% CI, −12.2–0.22). Patients with prior virologic failure were allowed to enroll in this study, and based on the preliminary findings among those who did not remain suppressed after the switch, preexisting drug resistance to components in the background regimen may have contributed to the higher-than-expected rate of failure after substitution of lopinavir/r with raltegravir, similar to observations in earlier switch studies with abacavir. Identifying those patients most likely to benefit from treatment switches with respect to dyslipidemia remains a high priority.

**Simplification with fixed-dose tenofovir-emtricitabine or abacavir-lamivudine study.** The fixed-dose nRTI combinations of tenofovir/emtricitabine and abacavir/lamivudine reduce pill burden and offer the possibility of improved lipid levels compared with thymidine-containing nRTI regimens. The STEAL study randomly assigned 360 virologically suppressed patients receiving either nRTI or PI-based antiretroviral therapy to substitute tenofovir/emtricitabine or abacavir/lamivudine for their current nRTI(s) (Abstract 576). Of note, approximately 20% of patients in each group were previously receiving the nRTI to which they were assigned as a single agent. Although virologic response rates did not differ by group, patients who underwent randomization to abacavir/lamivudine experienced a higher rate of the predefined secondary endpoint of lipid changes (new cholesterol level > 6.5 mmol/L, or increase in level > 2 mmol/L; new HDL level < 0.9 mmol/L or decrease in level > 0.5 mmol/L, or new lipid-lowering therapy). The rate of serious non–AIDS-defining events was also higher in the group receiving the abacavir/lamivudine, and the rate of cardiovascular events was also higher in the abacavir/lamivudine recipients than the tenofovir/emtricitabine recipients (7 vs 1, respectively). Bone mineral density fell in the hip and spine in the tenofovir/emtricitabine group, whereas it increased in the abacavir/lamivudine group. Although this study did not target patients with dyslipidemia, it does suggest a potential lipid and possible cardiovascular benefit associated with the change to tenofovir/emtricitabine.

Does tenofovir have a direct effect on lipids? This question was addressed in a pilot study in patients receiving stable antiretroviral therapy to which tenofovir was added during a double-blind, placebo-controlled, randomized, cross-over-design ACTG trial (Abstract 714). Dyslipidemic patients had tenofovir or placebo added for 2 12-week periods separated by a 4-week washout period. Despite the small size of the study (only 13 patients with complete data); levels of non-HDL cholesterol, total cholesterol, and LDL cholesterol all showed statistically significant improvement during tenofovir exposure compared with placebo. An unexpected finding in this study was the observed rebound in triglyceride levels during the tenofovir washout period. The mechanism by which tenofovir improves lipid levels requires further study.

**Renal Complications**

The impact of antiretroviral therapy, host factors, and direct or indirect effects of HIV replication on changes in renal function remain active areas of investigation, as evidenced by presentations at the conference.

The important association between HIV replication and loss of renal function was demonstrated in at least 3 studies. Choi and colleagues examined factors associated with continued loss of renal function among participants in the University of California San Francisco SCOPE (Study of the Consequences of the Protease Inhibitor Era) cohort and identified that in treated patients, transient increases in viral load (blips) were a risk factor for loss of renal function (Abstract 38). Similarly, in a randomized study evaluating intermittent use of antiretroviral therapy, the strategy of 7 days on followed by 7 days off antiretroviral therapy was associated with a greater rate of decline in glomerular filtration rate (GFR) than continuous antiretroviral therapy or the strategy of 5 days on followed by 2 days off therapy (Abstract 742). No statistically significant difference was found in the rate of GFR decline between the latter 2 groups. Finally, among a large group of Kenyans not yet meeting local criteria for antiretroviral treatment, renal function, as measured by estimated GFR, was an independent risk factor for HIV progression (Abstract 741).

The relationship between tenofovir exposure and renal function remains
an active area of investigation. Small but statistically significant changes in GFR have been observed with tenofovir in cohort studies and randomized trials. The HEAT study team reported vir in cohort studies and randomized GFR have been observed with tenofovir but statistically significant changes in an active area of investigation. Small studies are needed in patients treated with tenofovir/emtricitabine and abacavir/lamivudine combined with lopinavir/r (Abstract 744). Consistent with earlier studies showing an improvement in renal function after initiation of antiretroviral therapy, small increases in the estimated GFR and creatinine clearance were observed in both treatment groups, although the improvement was slightly greater in the abacavir/lamivudine group. Progression to an estimated GFR of less than 60 mL/min occurred more commonly in the tenofovir/emtricitabine recipients (n = 11) than in the abacavir/lamivudine group (n = 4). Proximal renal tubule dysfunction occurred rarely but only in tenofovir/emtricitabine-exposed patients (n = 5).

Risk factors for proximal renal tubular (PRT) dysfunction were examined in 2 cohort studies (Abstracts 743, 745). PRT dysfunction was identified in 18 of 92 consecutively studied patients who received tenofovir for longer than 6 months (Abstract 745). A higher mid-dose plasma level of tenofovir (> 160 ng/mL) was identified as an important predictor of PRT and had a sensitivity of 61% and specificity of 80%. A larger cross-sectional study from the Swiss HIV cohort (n = 1202) identified the highest prevalence of PRT in patients treated with tenofovir with (49%) or without (16%) concurrent PI therapy (Abstract 743). In a multivariate model adjusting for several factors associated with renal disease, both tenofovir and PI exposure remained statistically significant predictors. Currently, only limited data are available to examine the longer term outcomes of patients identified with subclinical tubular dysfunction; however, there is concern that increased excretion of phosphate could lead to bone loss over the longer term. Longitudinal studies addressing this issue are needed in patients treated with a range of therapies for HIV infection.

Is there a genetic predisposition for tenofovir-associated PRT dysfunction? Novoa and colleagues hypothesized that polymorphisms in genes encoding for drug transporters in the renal tubules could explain why some patients may be predisposed to this complication (Abstract 37). The study was limited to patients receiving tenofovir at a single center. In examining 12 single nucleotide polymorphisms in 5 genes, they identified an association between patients harboring the genotype GG in the ABCC2-24 gene and the development of renal tubulopathy. The authors noted that the mechanism through which this polymorphism may operate is unclear because tenofovir is apparently not a substrate for this particular transporter. Nonetheless, this emerging area of investigation could lead to testing to identify patients at highest risk of this complication.

Bone Disease

Contributions of HIV disease, immune activation and inflammation, antiretroviral therapy, and host factors to loss of bone density in HIV infection continue to be explored. Data from cross-sectional studies confirm high rates of osteopenia and osteoporosis in men (higher rates in men than in postmenopausal women, in fact), without an excess rate in hypogonadal men (Abstract 754) compared with eugonadal men, and a higher rate of low bone density in women with HIV and HCV coinfection (Abstract 820). In one of the few longitudinal studies, investigators from the Menopause Study (MS) noted a higher prevalence of low bone density in HIV-infected women than in HIV-uninfected women but no difference in the rate of bone loss in the 2 groups over 18 months of follow-up (Abstract 757). Opioid use and the presence of depressive symptoms were associated with bone loss in the women in this study.

Potential mechanisms of bone loss in HIV were explored in clinical and in vitro studies. Gazzola and colleagues reported an association between lower frequency of central memory CD8+ CD127+ cells and low bone density as measured by dual x-ray absorptiometry scan, suggesting that immune activation (a possible contributor to the loss of CD127+ cells) might be an important contributor to bone loss (Abstract 752). Levels of several cytokines involved in bone loss (tumor necrosis factor-alpha, IL-6, and receptor activator for nuclear factor κB ligand), although higher in postmenopausal HIV-infected women than in HIV-uninfected women, did not correlate with levels of bone mineral density (Abstract 758). Among HIV-infected women, markers of bone resorption (N-telopeptide and C-telopeptide) were higher in those receiving antiretroviral therapy, but the duration of antiretroviral therapy did not appear to be associated with lower bone mineral density. A small study of changes in markers of bone turnover in patients starting antiretroviral therapy with different regimens demonstrated increases in bone resorption and formation markers. Initiation of treatment with tenofovir or a PI was associated with greater increases in osteocalcin (a bone formation marker); these effects did not appear to be mediated through osteoprotegerin receptor agonist and the receptor activator for nuclear factor κB ligand (Abstract 760).

Collectively, the studies presented at this year’s conference extend our understanding of the prevalence, pathogenesis, risk factors, and in some cases treatment for the expanding array of complications of HIV disease and antiretroviral therapy. A consistent theme across many of these areas of research is the attempt to more accurately define and quantify the contributions of the virus, the host, and antiretroviral therapy to the development of these important clinical problems.

A list of all cited abstracts appears on pages 89-95.

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Additional References


