Complications of HIV Disease and Therapy

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Complications and consequences of untreated and treated HIV infection in domestic and international settings continue to be a major focus of HIV clinical research efforts. In this review major findings in these areas are highlighted, with a focus on studies that have application to clinical practice. As the field of clinical research in HIV continues to mature, we are repeatedly surprised by the findings from well-designed studies.

Opportunistic (and Non-opportunistic) Clinical Events

AIDS-defining conditions have been included as major endpoints of clinical trials evaluating the efficacy of antiretroviral therapies with the assumption that all AIDS-defining conditions carry a similar impact on outcome. Mocroft and colleagues analyzed data on antiretroviral-naive patients starting antiretroviral therapy from 15 HIV cohort studies in Europe and North America and compared mortality rates associated with different AIDS-defining conditions (Abstract 80). This large study examined nearly 2500 AIDS-defining endpoints among more than 30,000 patients with a median of 3.5 years on antiretroviral therapy. The greatest hazard of death was following a diagnosis of non-Hodgkin's lymphoma (NHL; hazard ratio [HR], 19.31), followed by progressive multifocal leukoencephalopathy (PML; HR, 9.56), cryptococcosis (HR, 9.00), toxoplasmosis (HR, 5.10), and *Mycobacterium avium* complex (MAC; HR, 5.07). Although this study did not determine whether the AIDS-defining condition was the cause of death, these results suggest that some consideration should be given to the impact of different clinical endpoints when comparing therapeutic interventions.

As rates of traditional opportunistic events continue to decline among populations with access to antiretroviral therapy, other sources of morbidity and mortality grow in importance. Investigators from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort examined the contribution of both AIDS-defining and non-AIDS-defining malignancies as causes of death for nearly 24,000 patients on treatment (Abstract 84). It is important to recognize that this report only considered malignancies as causes of death and may underestimate the contribution of malignancies to morbidity. The most common non-AIDS-defining malignancies were lung cancer, cancers of the gastrointestinal tract and anal canal, and hematologic malignancies. As expected, CD4+ counts less than 50 cells/μL were associated with higher incidence rates for AIDS-defining malignancies than non-AIDS-defining malignancies; however, overall the non-AIDS-defining malignancies were more common than AIDS-defining malignancies as causes of death in this treated population. These results stress the importance of cancer screening and prevention efforts in a population of aging patients successfully treated for HIV infection.

It has long been known that the risk of different opportunistic AIDS-defining conditions relates to the level of immunodeficiency as measured by CD4+ cell counts. However, there has recently been more focus on the spectrum of clinical events that occur in patients with varying levels of immunodeficiency. Investigators from the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) examined the relationship between current CD4+ counts and risk of opportunistic diseases and non-opportunistic diseases among patients enrolled in a clinical trial of antiretroviral therapy (Abstract 37). Fatal and non-fatal opportunistic diseases and non-opportunistic diseases were examined over a 5-year median follow up. Non-opportunistic disease events included: liver events (cirrhosis and grade 4 transaminase elevations), cardiovascular events, non-opportunistic cancers, and renal events (end-stage renal disease [ESRD] or renal insufficiency). After adjusting for age, sex, race, baseline CD4+ count, and viral load, the authors reported that the relationship between latest CD4+ count and risk of opportunistic disease was strongest (for every 100 CD4+ cell/μL increase the risk of opportunistic disease was reduced by 42%). However, the risk of non-opportunistic disease also appeared to fall by 17% per 100 CD4+ cell/μL increase, suggesting that immunodeficiency may contribute to the risk of these non-opportunistic events as well. These results add to the growing interest in consideration of earlier initiation of antiretroviral therapy with the hopes of reducing morbidity from both opportunistic and non-opportunistic diseases.

Opportunistic Infections In Resource-limited Settings

Although antiretroviral therapy is associated with dramatic reductions in morbidity and mortality in resource-limited settings, morbidity and mortality from opportunistic infections remains high early in the course of antiretroviral therapy. Moore examined determinants of mortality in 1120 subjects followed for a median of 2 years receiving antiretroviral therapy in the Tororo, Uganda cohort (Abstract 34). Median CD4+ count at entry was 127 cells/μL. Cumulative mortality was 3.3% at 3 months and 7.5% at 12 months. Tuberculosis (TB) accounted for 21% of the deaths, cryptococcosis for 11%, candidiasis for 11%, and *Pneumocystis jiroveci* pneumonia (PCP) for 9%. In 41% of deaths, no etiology could be identified. Low CD4+

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count, low body mass index, and hemoglobin at baseline were the strongest predictors of mortality. Authors suggested that interventions such as food supplments, treatment of anemia, and preventive antibiotic approaches should be evaluated to reduce early mortality. A retrospective review of 76,989 patients from 4 continents receiving antiretroviral therapy and co-trimoxazole through Médecins Sans Frontières reported high rates of opportunistic infections among the first 6 months of antiretroviral therapy (Abstract 839). Bacterial pneumonias, TB, and candidiasis were the most frequently reported opportunistic infections. Rates of Kaposi's sarcoma (KS) were highest in Africa, and rates of cryptococcal disease were highest in South America. Similar to other reports, rates of all opportunistic infections among patients receiving antiretroviral therapy in Africa, Asia, and Latin America decreased over time.

The benefits of co-trimoxazole prophylaxis among children and adults were highlighted in several presentations. The first study quantified the benefit of co-trimoxazole among adults receiving antiretroviral therapy. In this study conducted in Malawi, clinical outcomes among 1295 patients receiving antiretroviral therapy with or without co-trimoxazole were examined (Abstract 83). The striking finding of this study was that co-trimoxazole was associated with a 46% reduction in mortality among patients receiving antiretroviral therapy. There were also data about the added benefit of co-trimoxazole to prevent malaria in pediatric populations. Gasaseira and colleagues compared rates of malaria between HIV-seropositive children receiving co-trimoxazole plus insecticide-treated bednets with rates of malaria among HIV-seronegative children living in Uganda (Abstract 78). Co-trimoxazole plus bednets are associated with a 97% reduction in risk for malaria. Only 4% of fevers in the HIV-seropositive children compared with 33% of fevers in the HIV-seronegative children were due to malaria. Thus, combined co-trimoxazole and insecticide-treated bednets is highly effective for malaria prevention among HIV-infected children living in Uganda.

Tuberculosis And HIV Coinfection

Increased mortality among HIV-infected patients with TB coinfection, including those starting antiretroviral therapy in resource-limited settings, has been reported in several cohorts. What is the contribution of TB to the immediate cause of death in these patients? Martinson and colleagues attempted to address this question by taking on the difficult task of obtaining complete autopsies for 47 patients who died during hospitalization for HIV and TB coinfection in Soweto, South Africa (Abstract 82). Pulmonary TB was identified as the cause of death in 19 patients and bacterial pneumonia in 4. Among 28 patients, disseminated TB was considered a contributory cause of death. *Salmonella* species were identified among 11 patients. Other opportunistic infections such as PCP and cytomegalovirus (CMV) accounted for the remainder of the cases. All but 2 subjects had more than 1 major opportunistic infection. This report suggests that extensive mycobacterial disease, a high burden of bacterial infections, and opportunistic infection all contribute to mortality in seriously ill HIV and TB coinfected patients.

After noting that mortality rates were 2-fold higher among HIV-infected patients with TB who were starting antiretroviral therapy than those without TB in his Capetown, South Africa, program, Lawn evaluated predictors of outcome among 213 HIV-infected patients with TB and 675 without (Abstract 81). In a multivariate analysis, a CD4+ count below 100 cells/μL and World Health Organization (WHO) stage IV disease (adjusted HR, 2.9; 95% confidence interval [CI], 1.8-4.8) were the only independent predictors of death. Among patients with TB, 70% of the deaths occurred before antiretroviral therapy was initiated. The authors hypothesized that delays in accessing antiretroviral therapy among patients with TB contributed to the high mortality rates, and they recommended earlier initiation of antiretroviral therapy particularly in patients with advanced immune deficiency.

One of the concerns about early initiation of antiretroviral therapy among patients with TB is exaggerated inflammatory reactions, called paradoxical reactions or immune reconstitution disease. Lawn and colleagues reported the morbidity, mortality, and hospitalizations attributed to immune reconstitution disease in 160 TB patients starting antiretroviral therapy in the Captetown cohort (Abstract 863). Antiretroviral therapy was begun a median of 105 days after TB treatment. Twelve percent of patients had immune reconstitution disease. Starting antiretroviral therapy earlier after TB therapy was associated with a higher risk of immune reconstitution disease. Only 4% of patients required hospitalization, and there were only 2 deaths. Thus, in this nonrandomized study, early antiretroviral therapy initiation was associated with higher risk of immune reconstitution disease, but hospitalizations and mortality were rare. Randomized trials to address optimal timing of antiretroviral therapy initiation in this setting are ongoing.

There were several reports evaluating algorithms to diagnose TB in resource-limited settings. Conradie screened 650 HIV-infected adults with a 5-point symptom screen. Excluding patients with smear-positive TB, there were 38 patients in whom TB was suspected (Abstract 852). Among these, 2 of 3 were given presumptive TB treatment, and 14 were culture confirmed. One case of TB was diagnosed among the patients not started on TB therapy. Authors concluded that their clinical algorithm was 96% sensitive and 85% specific. A second report by Were and colleagues found that in a Ugandan cohort initiating antiretroviral therapy, a clinical index was highly sensitive but not very specific (66%) for TB (Abstract 848).

Isoniazid preventive therapy (INH) is recommended for HIV-infected persons in TB endemic settings. One of the main obstacles to intermittent preventive treatment (IPT) implementation is the exclusion of active TB. Samandari and colleagues reported the TB screening results from a large randomized study of INH preventive therapy in Botswana (Abstract 861). Among 4328 adults screened, 2608 of the asymptomatic patients had a chest radiograph. Twelve

percent of subjects had an abnormal chest radiograph, and 31 individuals had active TB. Thus, in a small but statistically significant proportion of asymptomatic individuals, chest radiographs can help identify persons with active TB during screening for preventive therapy. Phillips reported preliminary findings from a large IPT program in Kenya (Abstract 852). Among 561 patients with WHO stage I or II disease who started IPT, 86% completed or will still be receiving IPT. Twelve percent of patients were lost to follow up. Only 2 patients were diagnosed with TB during IPT. The study is ongoing.

Approaches and trends in the prevention of TB in low-incidence settings were addressed in several posters. One report evaluated whether persons who presented with TB in an HIV comprehensive care clinic in Nashville, Tennessee, had been previously evaluated for IPT (Abstract 849). Investigators found that the majority of the TB cases had not had tuberculin skin testing prior to TB diagnosis despite being in routine care. In view of sensitivity of current diagnostic tests, the authors' conclusion that 80% of cases were preventable could be considered an overstatement. However, the authors convincingly demonstrated that there are missed opportunities to prevent TB in low-incidence settings. Furrer and colleagues analyzed tuberculin skin testing, IPT, and antiretroviral therapy among patients in the Swiss cohort (Abstract 850). A positive tuberculin skin test without IPT was associated with the highest risk of TB, and similar to prior studies, antiretroviral therapy reduces the risk of TB.

Morento reported TB incidence rates from 4269 HIV-infected patients receiving HIV care from clinics in Spain (Abstract 847). The median follow up was 3.8 years. The strongest predictor of TB was injection drug use and CD4+ count below 200 cells/μL. Antiretroviral therapy was associated with a decreased risk of TB. Interestingly, TB rates decreased among nonantiretroviral therapy-treated patients over time. The authors speculated that decreased transmission rates accounted for this decline. Golug and colleagues reported the 8-year follow up from a longitudinal study of HIV-infected and -uninfected injection drug users residing in Baltimore. This cohort had been offered tuberculin skin testing and IPT from 1990 to 1998. Overall, TB rates declined in the cohort, but reductions were not observed in the HIV population. IPT reduced rates of TB in those who took it, but adherence to the 6-month regimen was poor.

Emerging data on performance of quantiferon assays for use of diagnosis of latent TB infection were presented in a poster discussion session. The Centers for Disease Control and Prevention (CDC) currently recommends interferon gamma release assays for screening of latent TB in the United States, although there are no large studies of the performance of these assays among HIV-infected persons. Luetkemeyer and colleagues compared the quantiferon gold in-tube assay (QTF) with standard tuberculin skin testing in a cross-sectional study of 196 HIV-infected patients living in San Francisco (Abstract 860). The overall concordance of the 2 assays was 89%. The majority of the patients (85%) had a negative test by both assays. However, there was a low concordance among those with positive test by either assay. Only 28% were positive on both assays. Fifty-six percent of tuberculin skin test positive results occurred in QFT-negative subjects. In addition, the QFT assay, which depends on a positive control, was "indeterminate" or uninterpretable in 16%. Luetkemeyer concluded that replacing tuberculin skin testing with QFT may miss a small but concerning proportion of HIV-infected patients and that QFT performance may be limited in advanced HIV disease by an elevated rate of indeterminate results.

In a study evaluating the same assay among 111 adults commencing antiretroviral therapy in Cambodia, indeterminate results were reported in 18% of the assays (Abstract 859). Repeat assays among patients with indeterminate results did not become interpretable after 3 to 6 months of antiretroviral therapy.

Perhaps one of the biggest pieces of news in the HIV and TB arena for resource-limited settings was the recognition that drug-resistant TB is being transmitted among the HIV-seropositive population. Last year, highly resistant TB strains now designated as extensively drug-resistant (XDR) TB were identified among HIV-infected patients in Kwa Zulu Natal. HIV-infected patients presenting with this strain of TB had a median survival of 24 days. These XDR strains are resistant to first-line TB agents, to an injectable agent such as streptomycin, and to quinolones. The extent of XDR and multiple drug-resistant TB in sub-Saharan Africa is under intense investigation, but data collected to date suggest that community and nosocomial transmission are occurring. Although there were no primary data presented at this meeting, Paul Nunn from the WHO summarized this information (Abstract 8).

HIV and Hepatitis B Virus Coinfection

Entecavir is a guanosine analogue recently approved by the US Food and Drug Administration (FDA) for the treatment of hepatitis B virus infection (HBV). In patients without an indication for antiretroviral therapy, it is considered a preferable option for HBV treatment because unlike lamivudine, tenofovir, and adefovir, it was previously reported to have no activity against HIV. After making the clinical observation that HIV RNA levels decreased in a patient taking entecavir only for HBV, McMahon and colleagues conducted a series of studies to evaluate entecavir for potential anti-HIV activity (Abstract 136LB). In vitro experiments using primary CD4+ lymphocytes showed a dose-response curve for entecavir against HIV. Clonal analysis of polymerase chain reaction (PCR)-amplified HIV RNA from plasma from a patient receiving entecavir monotherapy showed an increased proportion of clones with M184V over time. Entecavir's inhibitory activity against HIV with an M184V mutation in reverse transcriptase was reduced. Based on these data, the authors cautioned against the use of entecavir as monotherapy for HBV in HIV-infected

patients. On February 24, 2007, the FDA and the manufacturer announced a change to the label of entecavir to include the new information from these 3 cases. (see http://www.fda.gov/medwatch/safety/2007/safety07.htm#Baraclude)

HBV drug resistance mutations accumulate in patients receiving HBV active agents that fail to suppress viral replication. Sheldon performed genotypic analysis of HBV isolates from HIV-infected and -uninfected patients who were treated with numerous nucleoside and nucleotide agents (Abstract 135). They found that HBV genotype A was more common in HIV-infected persons in their cohort and more likely to select for mutations in HBV surface antigen than genotype D. HBV *env* mutations were also selected in both groups in the presence of HBV therapy, and may have implications for vaccine efficacy.

Adefovir and tenofovir antiviral potencies and viral dynamics were compared in a nonrandomized French cohort study of HIV- and HBV-coinfected patients (Abstract 945). Twenty-nine patients received adefovir and 56 patients received tenofovir. HBV RNA levels declined rapidly in both groups, but declines were more rapid in patients receiving tenofovir than in those receiving adefovir. In addition, hepatic transaminase declines were more frequent among the patients treated with tenofovir. These data are consistent with prior randomized studies demonstrating superiority of tenofovir over adefovir for HBV treatment. Lewin and colleagues also measured viral dynamics in Thai patients receiving lamivudine, tenofovir, or both as part of a combination antiretroviral therapy study (Abstract 949). They reported no differences in viral decay rates among the 3 treatment arms, and noted that estimates of viral clearance were very similar to HBV-monoinfected patients exposed to the same HBV regimens. Long-term viral HBV suppression rates in 44 patients receiving tenofovir and lamivudine were reported by de Vries-Sluijs (Abstract 939). After a median follow-up of 36 months, the HBV viral suppression rate was 86%. Loss of HBeAg was reported in 57% of patients.

In HBV-infected patients receiving antiretroviral therapy with HBV active drugs, transient elevations in hepatic transaminases occur frequently. Chauvel described rates of transaminase elevations (5 per 100 person-years of observation) or cholestasis (6.7 per 100 person-years of observation) among French patients followed up in a 3-year prospective cohort (Abstract 938). Independent risk factors included hepatitis delta virus, HBV genotype G, older age, alcohol use, and longer duration of HBV infection. Protease inhibitors (PIs) were associated with higher rates of cholestasis.

The prevalence of HBV among HIV-infected populations was reported for 2 African countries. In South Africa, 5.6% of patients were HBV surface antigen positive, and two-thirds of these patients had elevations in liver transaminases (Abstract 919). In contrast, hepatitis C virus (HCV) was present in only 1%. In Nigeria, 11% of patients in a cohort of 1968 HIV-infected persons were HBV-infected (Abstract 920). In this cohort, 6-month HIV RNA suppression rates were the same between patients with and without HBV infection. Hepatotoxicity occurred in 4.3% of the HBV-infected patients and 0.4% of the non-HBV-infected group.

HIV and Hepatitis C Virus Coinfection

HCV seroconversion has been reported among cohorts of HIV-infected men having sex with men (MSM), and has been attributed to high-risk sexual practices. Fisher evaluated HCV seroconversion among a cohort of MSM that included both HIV-infected and -uninfected participants (Abstract 130). HCV seroconversion rates ranged from 40 to 60 per 100 person-years of observation in both HIV-infected and -uninfected men. Seroconversion rates in both groups increased between 2001 and 2005. It was difficult to compare HIV-infected and -uninfected rates, because there was a third group of unknown HIV serostatus. The authors suggested that routine HCV screening should be considered for MSM presenting to sexually transmitted disease centers.

A small proportion of HIV-infected patients spontaneously clear HCV after acute infection. Schnuriger and colleagues conducted immunologic studies to identify predictors of spontaneous clearance among this group (Abstract 887). Consistent with previous reports, less than 5% of patients spontaneously cleared acute HCV. In patients without spontaneous clearance, HCV-specific T cell responses assessed by enzyme-linked immunospot (ELISPOT) were low. Patients with the best responses to HCV treatment developed the most robust T-cell responses over time. Interestingly, the authors found the T-cell responses, which evolved among patients with good responses to HCV, were of similar magnitude to those among patients who exhibited spontaneous clearance.

Another interesting report on patients with acute HCV examined liver biopsies within 5 months of seroconversion (Abstract 889). Three of the 4 patients had stage 2 fibrosis with no other identifiable infectious or toxic cause. More data are needed to corroborate this finding, and to determine if patients with this profile of liver pathology exhibit more rapid clinical progression of liver disease.

To explore mechanisms to explain why HCV progresses more quickly in HIV-infected versus uninfected patients, Yeu and colleagues examined lymphocyte subsets in liver biopsies among HCV patients with (n = 14) and without HIV (n = 6) coinfection (Abstract 133). They hypothesized that HIV-specific T cells producing tumor necrosis factor alfa (TNFα) promote hepatic inflammation through bystander activation. Coinfected patients had lower levels of lymphocytes, but the frequencies of HCV-specific cells were similar. The combined frequency of TNFα-producing HIV and HCV cells was higher in the coinfected than the monoinfected patients. Antiretroviral therapy was associated in a reduction of TNFα-producing lymphocytes. These intriguing findings support but do not conclusively prove the authors' hypothesis.

There was continued discussion at this year's conference on how to pre-

dict which patients are likely to respond to HCV treatment, and the use of prolonged HCV therapy in nonresponders, but no data on new treatments. There were 2 reports showing that early virologic responses (4 weeks) could predict HCV treatment success (Abstracts 891, 894). In the report by Mira, the failure of HCV RNA to decrease by 0.6 $\log_{10}$ copies/mL by week 4 was highly predictive (96%) of treatment failure (Abstract 891). Hernandez evaluated transcription-mediated amplification (TMA) to quantify HCV at the end of a treatment course (interferon alfa plus ribavirin) to determine if it could detect low-level viremia and predict relapse (Abstract 892). The threshold for detecting HCV was 5 IU/mL for the TMA assay compared with 50 IU/mL for the PCR assay. All patients in this study had undetectable HCV by the PCR assays at the end of treatment. Eighty percent of the patients with HCV detectable by TMA relapsed compared with 11% with negative TMA.

TMA of HCV may help predict patients likely to relapse after completing treatment, but data from Nunez and colleagues suggest that extended treatment in these patients is unlikely to be successful (Abstract 899). In a multicenter study of interferon alfa plus ribavirin conducted in Spain, patients with genotypes 1 or 4 were offered extended 18-month treatment regimens. Many patients dropped out during the study, but overall sustained virologic response did not differ between the 12- and 18-month arms. Response rates for genotypes 1 and 4 remained disappointingly low, in the 20% to 30% range.

Disappointing HCV treatment responses were also observed among HIV-infected patients who had received a liver transplant for HCV and required HCV post-transplant treatment (Abstract 890). These 33 patients had a mean CD4+ count of 288 cells/μL, and all but 1 patient had undetectable HIV RNA levels. The early (2-$\log_{10}$ copies/mL drop at 12 weeks) and sustained virologic responses were seen in 56% and 25% of persons, respectively. Thirty-seven percent of the patients stopped HCV treatment due to toxicity. Among the patients who did not respond to HCV treatment, 50% died due to HCV-related graft loss. This sobering study underscores the need for new HCV drugs.

Complications of Therapy

Body Fat Changes

Lipoatrophy continues to be a major concern as a complication of long-term HIV treatment. Thymidine nucleoside analogues have been shown to contribute to the development of lipoatrophy (stavudine and zidovudine) and substitution of these agents with non-thymidine nucleoside analogues (abacavir or tenofovir) appears to improve lipoatrophy. Two new studies presented at this year's conference confirm and extend the observations from earlier work in this area. In both studies lipoatrophy was defined as a 20% loss of limb fat as measured by dual-energy x-ray absorptiometry (DEXA) scan. Cameron presented the results of a study demonstrating that maintenance therapy with lopinavir/ritonavir monotherapy (after suppression with a 3-drug regimen including zidovudine for 24 weeks) was associated with a lower rate of lipoatrophy (5%) than maintenence on zidovudine/lamivudine/efavirenz (43%) for the same period of time, demonstrating the contribution of ongoing therapy with zidovudine to the development of lipoatrophy (Abstract 44LB). Investigators from the AIDS Clinical Trials Group (ACTG) randomized treatment-naive patients to receive lopinavir/ritonavir plus nucleoside analogue reverse transcriptase inhibitors (nRTIs), efavirenz plus nRTIs, or the nRTI-sparing combination of lopinavir/ritonavir/efavirenz (Abstract 38).

The assignment to specific nRTIs was not randomized within the trial, but it was well-balanced. As expected, the nRTI-sparing combination had lower rates (9%) of lipoatrophy at 96 weeks. In this group (lopinavir/ritonavir/efavirenz) limb fat increased by a median of 1 kg at week 96. Median change in limb fat also appeared to be greater than 0 in the other 2 groups; however, a surprising finding was that the proportion of patients with protocol-defined lipoatrophy was twice as high in the efavirenz group than in the lopinavir/nRTIs group. In both nRTI-treated study arms, rates of lipoatrophy were highest for those on stavudine (51% efavirenz, 33% lopinavir/ritonavir) and zidovudine (40% efavirenz, 16% lopinavir/ritonavir). However, even among the patients on tenofovir the rate of lipoatrophy was twice as high in the efavirenz treated group (12% efavirenz/tenofovir vs 6% lopinavir/ritonavir/tenofovir). No data on weight gain were reported; nonetheless, these results suggest that lopinavir/ritonavir was *less likely* than efavirenz to contribute to limb fat loss over 96 weeks. These surprising results remind us that we have more to learn about the optimal treatment of HIV infection, leaving clinicians and patients with the challenges of balancing virologic and metabolic outcomes over the long term.

Lipohypertrophy, specifically trunk fat gain, has also been documented in treatment-naive studies of a variety of regimens. Diet and exercise interventions remain the mainstay of treatment. Grinspoon reported the results of a phase III study comparing an injectable novel growth hormone-releasing factor analogue TH9507 with placebo in patients on stable antiretroviral therapy with evidence of abdominal fat accumulation (Abstract 45LB). After 26 weeks of treatment, visceral adipose tissue as measured by computed tomography (CT) decreased by 15% in the TH9507 arm compared with an increase of 5% in the placebo arm. No significant changes in limb fat were observed and notably lipids also improved in the TH9507 group. The treatment was well tolerated, with 2% of the TH9507-treated group developing hypersensitivity reactions. The magnitude of reduction in visceral adipose tissue seen with TH9507 is comparable with what was previously reported with human growth hormone. Whether the benefits of treatment will persist after the drug is stopped is currently being evaluated.

Diabetes

Diabetes, an important cause of morbidity and a known risk factor for car-

diovascular disease (CVD), continues to be a concern in the management of HIV infection. The Swiss cohort study reported the incidence of diabetes was 4.4 per 1000 person years of observation among participants and identified older age, male sex, non-white race or ethnicity, and obesity as risk factors for developing diabetes. Current treatment with PIs and nRTIs was also marginally associated with the risk of diabetes in this treated cohort. Of note, no association was seen between risk of diabetes and coinfection with HCV or HBV in this study. PIs appear to vary in their ability to induce changes in glucose metabolism in carefully conducted metabolic studies. Moyle reported that saquinavir/ritonavir (2000 mg/100 mg daily) was associated with a modest reduction in glucose disposal (–10%) compared with a 2% increase with atazanavir/ritonavir (300 mg /100 mg daily) in treatment-naive patients.

Cardiovascular Disease

Options to manage cardiovascular risk include smoking cessation, diet modification, the use of lipid-lowering therapy, and avoidance of antiretroviral regimens associated with the development of lipid abnormalities. Keogh reported on the dietary intake of a group of HIV-seropositive patients compared with an age-matched community sample and found that the HIV-seropositive group had a higher intake of total fat, saturated fat, and trans fat than controls, correlating with higher levels of total cholesterol, triglycerides, and lower high-density lipoprotein (HDL) in the HIV-seropositive group (Abstract 813). These results provide support for a greater role for dietary interventions among patients with HIV. Intermittent use of antiretroviral therapy, as studied in the SMART study, was shown to be associated with a marginally higher risk of CVD (Abstract 41). After further analysis of these data, it appeared that the group at greatest risk for a CVD event among those in the intermittent treatment group were the patients who were not on antiretroviral therapy at the start of the study, suggesting that untreated HIV infection may play some role in overall cardiovascular risk in HIV infection. However there was no association between CD4+ cell count or HIV RNA level and CVD events. Reductions in HDL cholesterol off antiretroviral therapy appeared to be an important contributor to CVD in this study.

Use of lipid-lowering therapy was examined in several cohorts. Among patients with a CVD endpoint in the DAD study, less than half had started lipid-lowering treatment 6 months after the first event (Abstract 816). Among patients with diabetes in this study, only 20% had started a lipid-lowering drug. Overall use of lipid-lowering therapy was comparable among dyslipidemia HIV-seropositive and -seronegative Kaiser enrollees (Abstract 814). However, the magnitude of triglyceride- and total cholesterol-lowering effects of treatment appeared blunted in the HIV-seropositive group. The authors speculate that drug interactions between antiretroviral therapy and statins limit the options for lipid lowering in the HIV-infected population. Ezetimibe, a drug that inhibits intestinal absorption of dietary and biliary cholesterol was shown to be well tolerated and to have a modest impact on low-density lipoprotein (LDL) cholesterol when used as monotherapy compared with a placebo in HIV-infected patients (Abstract 39). Rosuvastatin is a newer statin that is not metabolized by CYP 3A4, however, it has not been well studied in HIV-infected patients. Hoody and colleagues conducted a formal pharmacokinetic study of rosuvastatin and lopinavir/ritonavir in HIV-uninfected volunteers and reported an unexpected 2- and 4-fold increase in rosuvastatin area under the concentration curve and maximum concentration (C_{max}), respectively, with 1 case of a grade 4 creatine phosphokinase level (Abstract 564). These authors concluded that rosuvastatin should be used with caution in patients treated with lopinavir/ritonavir until more is known about this interaction.

Rates, risk factors, and clinical features of cardiovascular events and subclinical atherosclerosis continue to be examined by several groups (Abstracts 807, 808, 810, 811). Within the Kaiser population rates of hospitalization for myocardial infarction (MI) or coronary heart disease (CHD), although higher for HIV-seropositive patients than matched controls, appear to be stable over time. Women with HIV infection appeared to have an even greater risk than controls, something not previously reported from this database (Abstract 807). Angiographic features of acute coronary syndromes did not appear to differ between 100 HIV-seropositive and 84 HIV-seronegative patients undergoing cardiac catheterization, suggesting that the patterns of atherosclerosis in the HIV patient population are likely to be similar to that observed in the general population (Abstract 811). A cross-sectional study of carotid intima-media thickness (IMT) and coronary calcium scores (as measured by CT) among 657 HIV-infected patients identified traditional risk factors (age, hypertension, obesity), but not specific to antiretroviral therapy as predictors of increased carotid IMT. Notably the majority of HIV-infected patients (78%) had no measurable calcium by CT, suggesting that this non-invasive testing modality may have limited value in HIV-infected patients (Abstract 810).

Renal Disease

Renal disease is an important cause of morbidity among African Americans with HIV disease. ESRD among African Americans were reported to be 12-fold higher in those with HIV infection than in those without and do not appear to be declining with the availability of antiretroviral therapy (Abstract 839). Specific etiologies for ESRD in this study were not reported. It has previously been shown that treatment of HIV infection can improve renal function and this was demonstrated again among patients with low glomerular filtration rate (GFR) at the time of initiation of antiretroviral therapy in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort study.

The contributions of certain antiretroviral therapy regimens, and specifically those containing tenofovir, to the development of renal dysfunction re-

mains an active area of investigation. Owing to the higher rates of renal disease among African Americans, some clinicians are cautious about the use of tenofovir in this population. However, Gallant and colleagues presented results of a subanalysis of African American patients enrolled in treatment-naive studies comparing tenofovir-containing regimens with thymidine nRTIs (Abstract 505). Results from this pooled analysis demonstrated that race did not alter the beneficial effects of tenofovir compared with thymidine nRTI therapy. Virologic response rates were superior among tenofovir-treated patients and renal function remained stable and similar between treatment groups.

Cohort studies continue to produce somewhat conflicting results regarding risk factors for renal insufficiency and use of tenofovir. Treatment-experienced patients and patients with a history of AIDS appear to be at greater risk for declines in renal function than treatment-naive patients (Abstracts 832, 834). In addition ritonavir-boosted PIs appear to contribute to renal impairment in some studies (Abstracts 833, 835). Whether the use of ritonavir-boosted PIs is a marker for more advanced HIV disease could not be determined from the collective group of studies. Studies using more sensitive markers of renal function such as the measurement of cystatin C, which is not dependent on weight, may yield more consistent results in future studies (Abstract 830).

Bone Diseases

Higher rates of osteopenia among HIV patients continue to be reported from cohort studies (Abstract 836). The impact of specific antiretroviral drugs on osteopenia remains unclear. Modarrisi (Abstract 838) reported an in vitro study suggesting that low-dose ritonavir alters the expression of genes important for osteoclast differentiation and activity. The clinical significance of this finding is unknown. In the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN) study, risk factors for osteopenia in this group include older age, lower body mass index, lower baseline CD4+ cell count, and prolonged duration of HIV infection. Alendronate, a biphosphonate approved by the FDA for the treatment of osteoporosis along with vitamin D and calcium supplementation was compared with vitamin D and calcium alone in 82 HIV-infected patients with osteoporosis. Treatment with alendronate was well tolerated and associated with significant increases in bone mineral density in the lumbar spine, hip, and trochanter after 48 weeks of treatment.

Antiretroviral-associated Toxicities in Resource-limited Settings

Several presentations at this year's conference focused extended information on antiretroviral therapy toxicities associated with first-line regimens being used in resource-limited settings. Although expanding access to antiretroviral therapy is the highest programmatic priority in resource-limited settings, 2 studies underscored the drug-associated morbidity and mortality associated with widely used stavudine regimens and the need for resource-limited countries to have access to affordable, coformulated regimens with less-toxic drugs.

Predictors and outcomes in patients with severe lactic acidosis were evaluated in a case-controlled study reported by Osler and colleagues (Abstract 792). The group performed a retrospective chart review of all case patients presenting to a referral center for 6 antiretroviral therapy clinics in Capetown, South Africa. Patients referred to this center were being treated with stavudine, lamivudine and an NNRTI. The authors identified 73 cases of lactic acidosis. Fifteen percent of patients died acutely, and 2 patients died subsequently. A low serum bicarbonate was the only risk factor associated with mortality. In a nested, case-controlled study, female sex, low CD4+ count nadir, and baseline weight greater than 60 kg were independent risk factors for lactic acidosis. In 29 patients who survived, only 1 patient developed recurrent lactic acidosis during a median follow up of 10 months. At the poster discussion session, the authors also pointed out that among women, weight gain after starting antiretroviral therapy was predictive of a higher risk for lactic acidosis. One potential explanation for this finding is that the stavudine dosage was higher during this period based on current dosing algorithms (40 mg for those weighing more than 60 kg).

Lactic acidosis was also a major toxicity reported from a retrospective chart review of 305 patients receiving stavudine, lamivudine and efavirenz in a public-sector antiretroviral therapy program in Johannesburg, South Africa (Abstract 795). The most common adverse events in this cohort were peripheral neuropathy (32%), lipodystrophy (8.5%), gynecomastia (8.9%) and lactic acidosis (6.6%). In this cohort 19.7% of patients had a treatment-limiting side effect. Treatment changes were made after a median of 14 months of follow up.

Amoroso evaluated antiretroviral therapy switches for dose-limiting toxicity among patients receiving antiretroviral therapy in the US President's Emergency Plan for AIDS Relief (PEPFAR)-sponsored programs in Zambia, Kenya, and Uganda (Abstract 789). Stavudine was switched in 24% of patients. Zidovudine was switched in 12% of patients. In this cohort, where routine creatinine assessments were available, only 0.6% of 2938 patients switched from tenofovir for toxicity. Dose-limiting toxicity was recorded for 5% of patients receiving nevirapine and 2% of patients receiving efavirenz.

In resource-limited settings, zidovudine is substituted for stavudine in patients with dose-limiting toxicity. Switching to zidovudine in patients who start therapy with stavudine before they reach a dose-limiting toxicity owing to stavudine to avoid cumulative stavudine toxicity has also been raised as a potential therapeutic strategy. Investigators from the CDC reviewed zidovudine tolerance among 261 patients in the Tororo, Uganda, cohort who switched from stavudine to zidovudine for dose-limiting toxicity (Abstract 793). After switching to zidovudine, rates of anemia and leukopenia increased slightly. However, 95% of

patients successfully tolerated a switch from stavudine to zidovudine.

Peters and colleagues found that renal function actually improved among antiretroviral treatment-experienced patients with advanced HIV disease living in rural Uganda (Abstract 791). In 507 patients receiving antiretroviral therapy in the Tororo, Uganda, cohort creatinine clearance was measured over time using the Cockcroft-Gault equation. At baseline, 21% of patients had creatinine clearance of less than 50 mL/min/1.73 $m.^2$ After 24 months of antiretroviral therapy, renal function of the cohort improved, and only 6% had clearance of less than 50 mL/min/1.73 $m.^2$ Although low creatinine clearances may be due to numerous reasons in this population, these data support current thinking that antiretroviral therapy can improve kidney function in patients with HIV-associated renal disease.

There were 2 abstracts on lipid and metabolic changes associated with antiretroviral therapy in resource-limited settings. In the Tororo cohort, where patients received an NNRTI plus 2 nRTIs, fasting lipid measurements from baseline and 24 months after initiation of antiretroviral therapy were compared (Abstract 790). Total cholesterol (TC) increased by 24%, HDL by 62%, and LDL by 54%. Triglycerides decreased by 24%. TC was greater than 200 mg/dL for 11% of patients after 24 months compared with 3% at baseline. Studies with fasting lipid specimens linked to nutritional evaluations status will be needed to interpret these kinds of data sets in the future. A second study followed up 43 patients prospectively in Johannesburg (Abstract 796). Lipodystrophy was based on patient and physician assessment. This group reported that 39% of patients receiving stavudine/efavirenz/lamivudine developed lipodystrophy. Changes were first detected after 18 months of follow up. Lipodystrophy was associated with increases in waist-to-hip ratio and glucose and triglyceride levels. Elevations in TC, LDL, and HDL were reported in patients with and without lipodystrophy. Although this study was small and relied on subjective measures, the cumulative increase in lipodystophy was striking in this cohort.

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