

Complications of HIV Disease and Antiretroviral Therapy

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As antiretroviral treatment regimens become more potent and easier to administer, differences in the rates of adverse events and complications associated with treatment will increasingly drive decisions regarding the selection of therapy. This year's Conference on Retroviruses and Opportunistic Infections featured a wide range of research directed toward understanding the pathogenesis, treatment, and long-term consequences of complications associated with HIV infection and the use of antiretroviral therapy in both resource-limited settings and in the developed world. This review will summarize information on complications of antiretroviral therapy in resource-limited settings, hepatitis C virus, tuberculosis, and discussion of metabolic, cardiovascular, and renal complications.

Antiretroviral Drug Toxicity in the International Setting

Zidovudine, Stavudine, Nevirapine, and Abacavir

At this year's conference, several international groups provided analyses of drug toxicities being observed in the global rollout efforts. These programs are utilizing World Health Organization first-line regimens including nevirapine or efavirenz and zidovudine or stavudine plus lamivudine. Although many of these analyses were limited by ascertainment bias, all data suggested that these populations were susceptible to the same significant toxicities—such as peripheral neuropathy and lactic acidosis—that have been observed in studies in the developed world.

Boulle and colleagues presented follow-up on 1700 HIV treatment-naive adults in the Khayelitsha cohort from South Africa (Abstract 66). Initially patients in this cohort utilized zidovudine, lamivudine, and efavirenz, but then switched to a nevirapine- and stavudine-based regimen. By 2 years, similar proportions of patients had switched off of stavudine (8.5%), zidovu-

dine (8.7%), and nevirapine (8.9%). For patients on stavudine, lactic acidosis and peripheral neuropathy were the main reasons for switching. The risk for lactic acidosis was particularly high in obese women. The risk of peripheral neuropathy was greatest among patients older than 50 years with CD4+ cell counts below 50/ μ L. At 36 months, 59% of patients in this cohort were still receiving their original antiretroviral regimen. Investigators concluded that switches early on were concentrated around zidovudine, for which anemia was the treatment-limiting toxicity. With a stavudine regimen, reasons for dose-limiting toxicity were peripheral neuropathy and lactic acidosis.

Forna and colleagues presented results from the Tororo, Uganda, cohort in which 1073 persons started antiretroviral therapy (Abstract 142). This was the same cohort in which tuberculosis (TB) outcomes were described (see below). The initial regimen for almost all patients (96%) was nevirapine/stavudine/lamivudine. Drug-related toxicities developed in 417 (39%) patients. Peripheral neuropathies developed in 31% of patients; 8% were classified as "severe." Rash occurred in 6% of patients; 2% of patients had severe cases and 2% had a hypersensitivity reaction. Five percent of patients had acute hepatitis. The probability of remaining free of any toxicity at 6, 12, and 18 months was 76%, 59%, and 47%, respectively; the probability of

remaining free of severe toxicities was 92%, 86%, and 84%, respectively. Twenty-one percent of patients in the cohort had drug changes for toxicity: 181 patients switched from stavudine to zidovudine and 30 from nevirapine to efavirenz. There was no mention of lactic acidosis.

A cohort study from Nairobi, Kenya, included 284 patients with a median CD4+ cell count of 159/ μ L (Abstract 143). The most commonly used regimen was nevirapine/stavudine/lamivudine. Neuropathy was reported in 23%, rash in 20%, hepatotoxicity in 1.4%, and lipodystrophy in 0.4%. Toxicity-free survival was reported at 6, 12, and 18 months and was 45%, 27%, and 21%, respectively. The probability of staying on the original regimen was 98%, 97%, and 96%, respectively. Patients in this cohort continued treatment in the face of moderate and mild toxicity. The investigators concluded that tolerance of antiretroviral therapy was not a barrier to care in this resource-poor setting. However, in spite of this optimistic conclusion, cumulative toxicity from stavudine remains a major concern with the regimen, and better outcomes may be achievable with other regimens, resources permitting.

Lipoatrophy

Very little data have been presented on lipoatrophy in resource-limited settings. Two presentations addressed this topic. Wanchu and colleagues reported results from a study in India of 300 patients (Abstract 562). Two hundred thirty-five patients had a nevirapine-based regimen, and 65 had an efavirenz-based regimen. The median duration of follow-up was 8 months. During follow-up, 47 patients (15.5%) changed at least 1 drug. The most common reason to change drug was lipoatrophy; other reasons for

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changing included peripheral neuropathy, TB, and anemia. In this cohort, more than 15% of patients had to change drug for toxicity. The authors reported that an additional 12.6% would have liked to change for various reasons, such as peripheral neuropathy, but were limited by the availability of alternatives. The authors concluded that more options are needed for patients with drug toxicity, including lipoatrophy.

The second study was specifically designed to look at lipoatrophy in the Doctors without Borders program in Kigali, Rwanda (Abstract 560a). The study used a standardized case definition and questionnaire to evaluate 141 patients presenting to clinic who had been on antiretroviral therapy for at least 1 year. The study population was 78% female, with 112 subjects on stavudine and 15 on zidovudine. Body fat changes were reported in 38 subjects, all of whom were on stavudine. Lipoatrophy was confirmed in 33 cases with a prevalence of 23%. Risk factors for lipoatrophy were female sex and receipt of stavudine. Based on these results, tenofovir is preferred over stavudine. The authors suggested that the body habitus changes associated with stavudine are likely to affect adherence and increase stigmatization.

Tenofovir Experience

Some early data on tolerance to tenofovir in West Africa were reported by Landman and colleagues (Abstract 543). Forty treatment-naïve subjects received tenofovir/emtricitabine/efavirenz. Median plasma HIV RNA level at baseline was more than 5 log₁₀ copies/mL and the median CD4+ cell count was 122/μL. The viral suppression rate was 87.5% at 24 weeks. Two patients died, 2 developed TB, and 1 changed drug for pregnancy. One patient switched for dizziness, but otherwise no serious toxicities were reported. There was no report of renal toxicity. These results are encouraging, but tenofovir is not yet available in most resource-limited settings.

Abacavir Compared with Nevirapine: Toxicity

The first study providing systematic data on the safety of abacavir in an African population was presented by Munderi (Abstract 109LB). The 24-week results of the Nevirapine or Abacavir (NORA) study, a randomized substudy of the Development of Antiretroviral Therapy in Africa (DART) trial, were presented. There were 599 patients with a median CD4+ cell count of 99/μL. This was a double-blind comparison; all patients received zidovudine/lamivudine as the nucleoside analogue reverse transcriptase inhibitor (nRTI) backbone. Serious adverse events were reported in 20 patients, and 19 of 20 were consistent with hypersensitivity reactions. Fourteen patients on abacavir (4.7%) and 30 on nevirapine (10%) discontinued the drug. The clinical symptoms that resulted in the syndromes included fever, rash, and respiratory and constitutional symptoms. Hepatotoxicity rates were significantly higher in those who received nevirapine. Abacavir had a discontinuation rate of approximately 2% in this African population with advanced HIV disease. This rate was lower than the rate for nevirapine. Results of viral load testing are not yet available for this study.

Hepatitis C Virus Infection

The elegant descriptions of protease and polymerase inhibitors for hepatitis C virus (HCV), highlighted in the symposium by Kwong (Abstract 172) and Hazuda (173 Abstract), generated a great deal of excitement regarding HCV at the conference. Several HCV protease inhibitors (HCV PIs) are already in clinical development. With both HCV PIs and polymerase inhibitors, resistance emerges with selective pressure, and antiviral activity to polymerase inhibitors was heterogeneous. It is likely that combination therapies will be required for the best outcomes with these new drug classes.

Refining Current Strategies for Hepatitis C Virus Treatment

Attempts to refine current strategies with available drugs have met with limited success. Ruys and colleagues conducted a randomized study to evaluate if high-dose peginterferon alfa plus ribavirin would be more effective than the standard dose (Abstract 852). In this open-label study, patients were randomized with either (1) induction therapy (peginterferon alfa 3 μg/kg/week for the first 4 weeks, followed by 2 μg/kg/week for 4 weeks, and then followed by the standard 1.5 μg/kg/week for the remaining 40 weeks), or (2) with the standard-of-care (1.5 μg/kg/week dose throughout). Patients were stratified by genotype, CD4+ cell count, and plasma HCV RNA level. The primary endpoint was virologic response 24 weeks after the completion of therapy. There was no difference in response between the 2 arms. Neuropsychiatric events were more common in the patients receiving induction therapy.

Extension of therapy was likewise not an effective strategy. In the trial presented by the Hepatitis Resource Network Clinical Trials Group (Abstract 854), all patients were treated with standard dose peginterferon alfa and weight-based ribavirin. Patients with undetectable plasma HCV RNA at 24 weeks were randomized to a standard 48 weeks or 72 weeks of therapy. The study enrolled 177 patients, of whom 80% were infected with HCV genotype 1; 61 patients qualified for the randomization. The sustained virologic response rates were approximately 50% in both groups. More than half of the patients randomized to the extended therapy were unable to complete the therapy due to patient preference and toxicity.

More success was achieved in identifying predictors of treatment response. Dieterich and colleagues analyzed the APRICOT study looking at treatment success rates in subjects with a rapid virologic response defined as undetectable HCV RNA at week 4 (Abstract 856). In the APRICOT study,

22 of 289 patients (13%) had a rapid virologic response and 18 (82%) had a sustained virologic response. Peginterferon alfa plus ribavirin produced a sustained virologic response of 81% in genotype 1 regardless of baseline viral load. This was even higher than response rates in subjects with low viral loads. A small study looking at ribavirin levels as predictors of early virologic response found that higher ribavirin levels were associated with improved responses only for patients with genotypes 1 and 4 (Abstract 857).

Predictors of treatment response in acute HCV were also evaluated among a cohort of 21 patients who received treatment with interferon alfa (Abstract 83). Investigators looked at cytokine genotypes to interleukin-6 (IL-6), tumor necrosis factor alpha (TNF α), transforming growth factor-beta (TGF- β), interferon gamma (IFN- γ), and interleukin-10 (IL-10) as predictors of sustained virologic response to treatment. IL-6-high producers exhibited the best responses to treatment. Investigators speculated that IL-6-mediated activation of signal transducers and activators of transcription enhance activity of the anti-HCV effects of interferon alfa in hepatocytes.

When HCV therapy fails, or when patients present at an advanced stage of liver disease, liver transplantation may be the only option. Miró and colleagues reported on their 4-year experience (median follow-up time of 1 year) in Spain with liver transplantation in HIV-infected patients (Abstract 875). Of the 50 transplant patients, 49 had HCV. All patients were receiving highly active antiretroviral therapy (HAART), and 48 had undetectable plasma HIV RNA. Forty-eight percent of patients had an acute rejection episode. Ten patients died, and half of these deaths were attributed to HCV. HCV therapy was reinstated in 16 cases, but only 18% of patients achieved a sustained virologic response. The authors identified rejection episodes and HCV relapse as the major challenges of transplantation in this population.

Hepatitis C Virus: Updates on Sexual and Mother-to-Child Transmission

Accumulating evidence suggests that HCV is spreading within the men who have sex with men (MSM) community via a sexual route in some large urban cities. Coutinho and de Laar presented a molecular epidemiologic analysis of acute HCV among the MSM population in Amsterdam (Abstract 87). The study population included 1836 MSM participating in the Amsterdam cohort; acute cases of HCV were identified from hospital records. The main findings from this study were that in the period from 1985 to 2003, there was a dramatic increase in HCV among HIV-seropositive, but not -seronegative, men and that the cases of acute HCV clustered phylogenetically within a few specific subtypes (1a, 1b, 3a, and 4d). The authors speculated that HCV was introduced into the population during this period and that mucosal trauma during sexual events contributed to the high rates of transmission. A study from the United Kingdom also supported evidence of transmission of HCV within the MSM community (Abstract 86). The authors identified 111 HCV seroconverters from 2002 to 2005. Molecular analysis revealed multiple clusters of independent HCV lineages. Risk factors for new cases included multiple sexual partners and mucosal trauma. A poster of an analysis from the French PRIMO cohort was presented by Ghosn and colleagues (Abstract 843). In addition to finding increased incidence of HCV among MSM, these investigators reported cases of acute HCV among women for whom sexual exposure was the only identified risk factor. Although these and other studies support evidence of sexual transmission of HCV, the inability to completely exclude drug use as a risk factor has prevented complete consensus among experts in the field on the frequency of HCV sexual transmission.

The risk for mother-to-child transmission of HCV is increased in the setting of HIV. In Catalonia, Spain, where the HCV prevalence is over 60% among HIV-seropositive pregnant wo-

men, Fortuny and colleagues hypothesized that HAART or cesarean delivery would reduce HCV transmission (Abstract 841). Interestingly, cesarean delivery, but not antiretroviral therapy, was associated with reduced rates of HCV transmission. Children with HIV also had a higher rate of HCV acquisition.

High-Risk Populations and Barriers to Hepatitis C Virus Treatment

Injection drug users (IDUs) remain most at risk for HCV, and the high incidence rates among even the youngest IDUs were highlighted in a report from San Francisco. Page-Shafer and colleagues performed 2 different antibody tests (enzyme immunoassay [EIA] 2.0 and EIA 3.0) and measured plasma HCV RNA levels among a cohort of young IDUs (Abstract 844). Among the cohort of 321 youth, 93 new infections were identified, giving an estimated incidence rate of 26%. The median age of the infected persons was 22 years. More than a third of the new infections were detected before antibody conversion by measurement of plasma HCV RNA. The EIA 3.0 detected infection approximately 3 weeks earlier than the EIA 2.0. Thirty-nine percent of patients had elevations in liver function tests. Despite aggressive public health campaigns, new HCV infections among young IDUs occur at an alarming rate.

HCV treatment remains challenging, and out of the reach of many populations for various reasons. Two presentations underscored this point. Scott and colleagues looked at the outcomes in a cohort of 369 HIV and HCV coinfecting patients in an urban Seattle hospital (Abstract 882). Only 28% of the Seattle cohort was evaluated for HCV; 5% received treatment and 1.6% had a sustained virologic response. Mehta and colleagues reported the experience from a similar study of 845 HIV and HCV coinfecting patients in Baltimore (Abstract 884). Thirty-three percent of patients in this cohort were referred for evaluation. Approximately one third of patients completing an

evaluation initiated treatment, representing a small percentage of the HIV and HCV coinfecting population. Reasons cited for deferral of treatment in both studies included active substance abuse, psychiatric illness, and patient choice. Treatment for this population is likely to remain challenging even with simpler therapies.

Hepatitis B Virus: Combination Therapy and Entecavir Drug Resistance

As with HCV, treatment studies of hepatitis B virus (HBV) in HBV and HIV coinfecting patients have lagged behind studies of HBV in HBV-monoinfecting patients. Nevertheless there were 2 studies of interest presented at this year's conference. Nelson and colleagues presented the results of an open-label 59-patient randomized study of tenofovir versus lamivudine versus tenofovir/lamivudine (Abstract 831). Twenty-seven of the patients were lamivudine-naïve at entry. In lamivudine-experienced patients, the median reductions in plasma HBV RNA level at 24 weeks were 3.41, 0.82, and 3.93 log₁₀ copies/mL, respectively. Among lamivudine-naïve patients, reductions were 4.66, 3.31, and 5.03 log₁₀ copies/mL, respectively. Thus in lamivudine-naïve patients, combination therapy with tenofovir plus lamivudine was superior to either monotherapy. For lamivudine experienced patients, adding or switching to tenofovir was superior to lamivudine only.

Entecavir is a recently approved drug for HBV treatment that has no activity against HIV. Lamivudine resistance predisposes to the development of entecavir resistance. Colonna and colleagues presented the results of resistance testing done on 50 subjects with lamivudine resistance at baseline randomized to entecavir or placebo (Abstract 832). The plasma HBV DNA level dropped by 4.2 log₁₀ copies/mL at 48 weeks in patients treated with entecavir. There was no viral rebound, but entecavir resistance mutations were detectable in 2 patients. More sensitive assays performed on pre-

treatment isolates detected minority entecavir-resistant variants. Entecavir treatment was effective, but also enriched for minor drug-resistant variants. With the high HBV viral loads that exist in most patients undergoing treatment, prevention of drug resistance is likely to be an important goal of treatment.

Insulin Resistance and Diabetes

The relationship between HIV infection, antiretroviral drugs, and the development of insulin resistance and diabetes remains an active area of investigation. Three groups examined the rates of diabetes or impaired glucose tolerance in HIV-infected adults compared with population-based uninfected controls (Abstracts 759, 760, 761). Howard and colleagues prospectively evaluated oral glucose tolerance tests in a diverse sample of 198 HIV-seropositive and 125 at-risk adults at 2 points 18 months apart and found no difference in the incidence of impaired glucose tolerance (IGT) or diabetes by HIV status. Within the group of HIV-seropositive subjects, the use of protease inhibitor (PI)-based HAART did not appear to increase rates of abnormal glucose tolerance. The independent risk factors for developing abnormal glucose tolerance or diabetes included only older age and obesity. Diabetes prevalence among antiretroviral therapy-naïve HIV-infected subjects enrolled in Community Programs for Clinical Research on AIDS (CPCRA) studies was compared with population-based data from the National Health and Nutrition Examination Survey (NHANES) III. The prevalence of diabetes was **lower** in the HIV-infected group than in NHANES III and factors associated with the presence of diabetes included HCV coinfection, older age, and body mass index (BMI), emphasizing the importance of traditional risk factors for diabetes. Finally, the prevalence of diabetes was further assessed among 2000 HIV-seropositive subjects (mostly men) and a similar number of control men in the Veterans Aging Cohort Study (Abstract

761). The prevalence of diabetes was again lower in the HIV-infected group. Among the HIV-infected subjects, higher BMI and the use of a PI at any point were associated with an increased risk of diabetes, and a CD4+ cell count below 150/μL was associated with a lower risk. Collectively these results suggest that un-treated HIV infection may not increase the risk of diabetes; however, traditional risk factors, use of PI therapy, and possibly HCV coinfection may contribute to diabetes risk among patients with preserved CD4+ cell counts. These studies highlight the importance of control groups when assessing the contributions of HIV infection and antiretrovirals to metabolic complications.

Investigators from the Multicenter AIDS Cohort Study (MACS) previously reported a slightly higher prevalence of metabolic syndrome among men with HIV than controls (Abstract 747). At this year's conference they extended these observations to include an analysis of the association between specific antiretrovirals and metabolic syndrome. Each additional year of HAART contributed to an increased risk of metabolic syndrome, in part driven by the increased risk of elevated triglycerides with PI use and efavirenz. In contrast to the diabetes data noted above, lower CD4+ cell counts appeared to correlate with increased risk of this syndrome, suggesting that perhaps chronic uncontrolled HIV infection may contribute to the development of metabolic syndrome.

Insulin resistance was examined in several studies as a marker for other vascular outcomes. In the Hawaii Aging with HIV Cohort, insulin resistance, independent of diabetes, was a marker for cognitive impairment in older but not younger HIV-infected patients (Abstract 349). Insulin level was also identified as a predictor of higher rates of progression of carotid intima media thickness in adults (Abstract 145), thicker carotid intima media thickness in children (Abstract 691), and progression of coronary calcification (Abstract 739).

Dyslipidemia and Cardiovascular Disease

Over the past several years there has been a growing focus on minimizing cardiovascular risk by addressing dyslipidemia and other modifiable risk factors among patients with HIV infection and we are beginning to see evidence that these efforts may be yielding a benefit. Several large cohort studies demonstrated that rates of myocardial infarction (MI) and coronary heart disease among HIV-infected adults seem to be stabilizing or declining (Abstracts 735,737). This change has been attributed to changing patterns of antiretroviral use and increased attention to lipid-lowering and antihypertensive therapy (Abstract 740). However there is room for improvement as noted in the Swiss HIV Cohort Study in which only one third of patients with dyslipidemia or hypertension were receiving lipid lowering or antihypertensive therapy.

Options for managing dyslipidemia range from antiretroviral drug substitutions to the use of lipid lowering agents. Fish oil was shown to be effective in a small trial at last year's meeting and at this year's conference 2 additional randomized trials presented data on the use of fish oil for hypertriglyceridemia. Twelve weeks of treatment with salmon oil 3 gm/day reduced mean values for fasting triglycerides by 95 mg/dL (20%) compared with an increase of 26 mg/dL among placebo recipients in HAART-treated patients with elevated fasting triglycerides at baseline (Abstract 756). At the end of 24 weeks of treatment, the overall benefit of the salmon oil was more modest (59-mg/dL decrease) compared with baseline values. Fish oil was compared with fenofibrate in a randomized trial of 100 patients who had elevated triglycerides (but normal low-density lipoprotein) on HAART. After 8 weeks of therapy the median reduction in triglycerides was slightly greater in the fenofibrate group (58% versus 46%) and a higher proportion of patients achieved triglyceride levels below 200 mg/dL in the fenofibrate group (17%

versus 9%). Combination therapy with fish oil and fenofibrate was administered to those with triglyceride levels above 200 mg/dL at week 8 and further reductions were seen with the combination. At the end of 18 weeks, median triglycerides fell by 65%, and 22% of subjects achieved a triglyceride level below 200 mg/dL. These results show the added benefit of combining fish oil and fenofibrate for those patients who do not respond to single-agent therapy with either drug.

Several studies at this year's conference seemed to strengthen concerns about the relationship between dyslipidemia on antiretroviral therapy and cardiovascular risk in the setting of HIV infection while continuing to emphasize the importance of traditional risk factors in predicting cardiovascular events. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study had previously reported an association between longer exposure to combination antiretroviral therapy and risk of MI (Friis-Moller, *N Engl J Med*, 2003). At this year's conference, observations from the DAD investigators were extended to include an analysis of exposure to specific classes of drugs and MI risk. With 94,469 person-years of follow-up, the risk of MI appeared to be stabilizing and not increasing over time. For each additional year of PI exposure, the risk of MI increased by 16%. After adjustment for lipid levels, this risk was diminished, suggesting that the lipid levels could mediate the MI risk. Of note, the risk of MI was also slightly increased with longer duration of nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) exposure; however, this was not statistically significant after adjustment for nRTI use.

In a matched cohort of HIV-infected and -uninfected adults, 3-year rates of progression of carotid intima media thickness were not statistically greater in PI-treated patients than in non-PI-treated HIV-seropositive or -seronegative controls; however, among the HIV-infected patients there was a suggestion of a PI effect on greater rates of progression of carotid intima media thickness (Abstract 145). In another

study examining predictors of increased intima media thickness, cytomegalovirus-specific T-cell responses and higher levels of high-sensitivity C-reactive protein, but not levels of T-cell activation, correlated with cross-sectional values for intima media thickness (Abstract 741).

Lipoatrophy and Fat Accumulation

Management of lipoatrophy and fat accumulation continue to be challenging clinical issues. Although objective measures of body fat are crucial to intervention studies these measurements are not practical in many clinical settings. McComsey and colleagues reported that patient self-report and physician exam correlated well with objective measures of limb fat by dual-energy x-ray absorptiometry using data from a study of lipoatrophy (Abstract 751). News from this year's conference extends previous observations that a change from zidovudine or stavudine to either abacavir or to an nRTI-sparing regimen (Abstract 755) seems to be the best currently available option for managing lipoatrophy.

Pioglitazone, which is a thiazolidinedione and PPAR- γ agonist, was evaluated at a dose of 30 mg/day as a potential treatment for lipoatrophy in a randomized, placebo-controlled trial conducted in France (Abstract 151LB). The magnitude of the increase in limb fat (0.33 kg) was not noticeable by the subjects; however, it is within the range of increase noted by other interventions over a similar time period of follow-up. Of note, no increase in limb fat was observed among subjects who remained on stavudine, and the significant increase was driven by subjects who were not receiving stavudine during study follow-up time. "Normal values" for limb fat are approximately 6 kg and it is possible that further increases will accrue over longer follow-up in the absence of stavudine treatment.

Disappointing results were seen in studies evaluating treatments for fat accumulation. Metformin and rosiglitazone in combination or alone failed to

significantly reduce visceral fat in randomized controlled trials (Abstracts 147, 148) and a modest increase in limb fat was noted among the rosiglitazone-treated patients in one study (Abstract 147).

In obese HIV-uninfected men, testosterone replacement has been shown to reduce visceral fat. A randomized placebo-controlled trial was conducted to evaluate the use of supplemental testosterone (10 gm of topical gel applied daily) in men with low serum testosterone and increased waist circumference or an increased waist to hip ratio (above 0.95; Abstract 149). After 24 weeks of treatment a surprising finding of the study was a statistically significant decline in total body fat (and notably in extremity fat) in the testosterone-treated group with no change in visceral fat in the testosterone-treated group compared with placebo. Lean body mass did increase modestly in the testosterone-treated patients. The results of this study suggest that an unexpected outcome of testosterone replacement in this group of patients could be loss of limb fat. The magnitude of the decline (0.48 kg) is greater than the magnitude of increases seen in studies examining therapies for the treatment of lipodystrophy.

Pulmonary Hypertension

Pulmonary hypertension was a recognized complication of HIV infection prior to the HAART era and it appears that this problem has not diminished. Prospective studies by 2 groups confirmed that HIV-infected patients appear to be at increased risk for pulmonary arterial hypertension, and that the incidence (0.21%) does not appear to have decreased in recent years (Abstracts 743, 744). Treatment with the oral endothelin antagonist bosentan appears to be well tolerated in HIV-infected patients based on a report of more than 100 treated HIV-infected patients; no efficacy data were included (Abstract 745). Clinicians are reminded to consider pulmonary arterial hypertension in the differential diagnosis of dyspnea in the setting of HIV.

Genetic Predisposition to Metabolic Complications

The growing interest in the relationship between host genetics and HIV complications was evident at this year's conference. A poster discussion session moderated by Telenti and Mallal reviewed potential genetic markers for metabolic complications. The moderators emphasized the need to validate the findings of associations between genetic markers and adverse outcomes identified in one cohort to another; the importance of having a biologic mechanism to explain the association and follow-up of the association studies with in vivo work to explain the mechanism of the effect. Many of the studies presented at the conference could be categorized as first-time associations between the presence of a specific polymorphism and an adverse event.

For example, adverse metabolic changes were examined in AIDS Clinical Trials Group (ACTG) 384 study participants (Abstract 736). Subjects with similar baseline values for metabolic parameters were grouped based on metabolic results after 32 weeks of follow-up. Genetic markers were then compared between the high-risk group and a lower risk group based on values of BMI, total cholesterol, low-density lipoproteins, triglycerides, and the homeostasis model assessment of insulin resistance. A single nucleotide polymorphism (C-to-T) in the second intron of the resistance gene was associated with a significantly increased risk for developing a constellation of adverse metabolic changes on HAART ($P = .001$). Heterozygotes ($n = 65$; odds ratio [OR], 2.8; 95% confidence interval [CI], 1.4–5.7) and homozygotes ($n = 5$; OR, 19.4; 95% CI, 2–182) were at increased risk relative to wild type ($n = 117$) of being in this high-risk group. This polymorphism consistently increased the risk of adverse metabolic changes on HAART in all races. Confirmation of these findings in other cohorts is required.

In another study polymorphisms in genes involved in lipid metabolism were examined in a testing cohort and

positive findings were examined in a second smaller validation dataset. Potentially clinically significant differences in high-density lipoprotein and triglyceride levels were found when these genotypes were examined (Abstract 764). For example, ritonavir recipients with the most unfavorable **APOE/APOC3/APOA5/CETP/ABCA1** genotype had median triglyceride levels that were markedly higher than the triglyceride levels of those without ritonavir exposure and a favorable genotype. Likewise, patients receiving NNRTI-based treatment with a favorable **CETP/APOA5** genotype had higher high-density lipoprotein levels than those on no antiretroviral therapy with an unfavorable genotype. Although not yet ready for clinical use, these types of genetic profiling studies suggest that at some point in the future we might be able to minimize treatment-related dyslipidemia.

Bone Complications

A cross-sectional study of menstrual irregularities, HIV infection, and bone mineral density found that both menstrual irregularities and HIV infection were independent predictors of low bone mineral density; however, HAART use was associated with higher bone mineral density. These results suggest that the detrimental effect of HIV on bone mineral density may be mediated by menstrual irregularities (Abstract 734).

Renal Disease

The prevalence of renal disorders was assessed among a large cohort of children with HIV disease with 7 years of follow-up (Abstract 699). Renal diagnoses were noted among 6% of the children followed up, and 22% had persistently abnormal lab results. Of the children who died during follow-up, 28% had persistent abnormal lab results. The authors concluded that renal pathology in HIV-infected children is a common complication associated with HIV-related morbidity and mortality.

Several presentations examined risk

factors for renal disease among HIV-infected adults with a focus on the relationship between tenofovir exposure and renal insufficiency. Previously reported data from clinical trials demonstrated a low rate of renal insufficiency among patients treated with tenofovir, and several presentations at this year's conference attempted to extend the understanding of risk factors for renal insufficiency in cohort studies and postmarketing safety databases (Abstracts 778, 779, 780, 781). The 2 largest studies, one from the Centers for Disease Control and Prevention (CDC) and the other from the Gilead Early Access Program (EAP) and postmarketing surveillance, suggest that the rates of serious renal adverse events among patients receiving tenofovir remain low. The CDC analysis includes follow-up data from 9535 patients with 34,814 6-month person-observations (17,357 person-years) of follow-up. The percentage of persons with renal impairment as defined by categories of glomerular filtration rate were 40% with any impairment, 32% with mild impairment, 6.1% with moderate impairment, and 2.4% with severe impairment. Factors associated with renal impairment included lower CD4+ cell counts, lower hemoglobin, the presence of diabetes, and hypertension. The authors acknowledged that the relationship between the use of tenofovir and renal impairment in the analyses may have been confounded by the fact that patients with more advanced disease were using tenofovir during the first years the drug was available. In addition, data on co-administration of nephrotoxic drugs and information about appropriate dose reduction were not available. The Gilead analysis of the EAP program included 3700 person-years of follow-up and reported an incidence of 0.5% for serious renal adverse events. In addition, the postmarketing surveillance database included 455,392 person-years of follow-up with 43.3 serious renal adverse events per 100,000 person-years. Although the rates of serious renal events remain low, clinicians are reminded to estimate

and follow creatinine clearance during HIV treatment, to avoid co-administration of nephrotoxic agents with tenofovir, and to dose-reduce tenofovir among patients with creatinine clearance below 50 mL/minute to avoid this complication.

Opportunistic Infections

Opportunistic infections remain rare among patients responding to antiretroviral therapy. In a large cohort of treatment-naïve patients who received antiretroviral therapy in controlled clinical trials, the median CD4+ cell count at the time of an opportunistic infection was 55/ μ L. A lower CD4+ cell count, higher viral load, history of a prior opportunistic infection, and female sex were independent predictors of an opportunistic infection during 3 years of follow-up (Abstract 782). There continues to be interest in the use of oral valganciclovir to prevent cytomegalovirus infection among patients with CD4+ cell counts below 100/ μ L and uncontrolled HIV infection. Wohl and ACTG colleagues conducted a randomized controlled trial designed to evaluate the utility of pre-emptive oral valganciclovir therapy to prevent end-organ disease (Abstract 150). Patients with low CD4+ cell counts who were not responding to antiretrovirals were monitored for cytomegalovirus viremia and then randomized to valganciclovir or placebo and followed-up closely for end-organ disease. An unexpected outcome of the trial was a very low rate of cytomegalovirus end-organ disease in the viremic patients rendering the study underpowered to detect an impact of the intervention. The results of this study suggest that there is a lingering benefit of antiretroviral therapy even among patients who appear to be failing both virologically and immunologically using standard markers.

Tuberculosis

Tuberculosis Associated with High Rates of Mortality

TB in the setting of HIV was the central theme of an overview talk by Harries

from Malawi in the opening symposium of the meeting (Abstract 9) and the topic of many of the international abstracts at this year's conference. Several studies highlighted that TB is one of the most common causes of mortality in HIV-infected persons before and after antiretroviral therapy initiation in TB-endemic areas. The contribution of TB to mortality prior to antiretroviral therapy was highlighted in a study presented by Peters (Abstract 30). This report included a cohort of 1582 discordant HIV-infected couples living in Rwanda. This group developed a modified HIV disease staging classification, coined as the Kigali Combined Stage (KCS), which included BMI, erythrocyte sedimentation rate, and hematocrit. The 3-year mortality rates for KCS stages 1, 2, 3, and 4 were 12.7%, 11.4%, 24.7%, and 51.3%, respectively. TB and chronic gastroenteritis were primary causes of death accounting for 24% and 20%, respectively. Other AIDS-defining illness such as Kaposi's sarcoma, cryptococcal meningitis, and candidal esophagitis were causes of mortality in 6.3% of deaths combined.

Several programs reported the mortality and morbidity rates after initiation of antiretroviral therapy, and TB rose to the top of the list. All presenters acknowledged the difficulty in precise classification of causes of mortality. In a prospective cohort of 404 adults treated with a PI- or NNRTI-based tri-ple drug regimen in Senegal, with a follow-up of 46 months, mortality was 11.7%. Among the 76 cases where cause of death was ascertained, mycobacterial disease was the most common (Abstract 63). In the Antiretroviral Therapy in Lower Income Countries (ART-LINC) cohort study, which includes patients receiving antiretroviral therapy through care programs in Africa, Asia, and Brazil, there were 696 new HIV illness in 4655 patients over 12 months. TB was the most common cause of death with a rate of 5.8 per 11 person-years. The majority of these events occurred within the first 2 months of antiretroviral therapy initiation with rates of 13 per 100 person-years in the

first month. Predictors of TB were younger age, lower baseline CD4+ cell count, and a history of TB (Abstract 67).

Multidrug-Resistant Tuberculosis Outbreak in South Africa—Contributor to Mortality?

Drug-susceptibility testing for TB is not routinely performed in Africa. When an extraordinarily high rate of mortality was observed among patients with TB in a South African district who were receiving antiretroviral therapy, investigators asked the question as to whether TB was multidrug resistant (Abstract 795). Among 93 sputum cultures, 40 patients (43%) were infected with multidrug-resistant TB. Twenty-six of these patients had resistance to all first- and second-line TB therapies. The median survival for a patient was 25 days, echoing observations from the United States in the early 1990s when multidrug-resistant TB was nosocomially transmitted in urban hospitals. Preliminary molecular analysis from the South African study suggests that a single strain is associated with multidrug-resistant TB. It remains unclear whether this is an isolated event, or more widespread than previously appreciated.

Antiretroviral Therapy as Prevention for Tuberculosis

Lawn and colleagues presented findings that antiretroviral therapy is associated with an overall reduction in rates of TB, even taking into account that some of the early cases probably represent undiagnosed disease present prior to antiretroviral therapy initiation (Abstract 68). In a prospective, hospital-based cohort of 346 persons receiving antiretroviral therapy in Cape Town, South Africa, the incidence rate of TB for the first year was 3.5 cases per 100 person-years. This rate declined to 1.0 case per 100 person-years after 5 years of antiretroviral therapy. Risk of TB was 2-fold higher in patients with CD4+ cell counts below 100/ μ L and age under 33 years. In this study TB was not associated with plasma HIV RNA level, previous

history of TB, low socioeconomic status, or gender. Another interesting observation from this study was that the CD4+ cell response to antiretroviral therapy was lower in patients with TB than in those who did not have TB.

The prevalence, incidence, and outcomes of TB in a cohort of 1044 patient treated with antiretroviral therapy in Tororo, Uganda, were presented by Moore and colleagues (Abstract 794). At baseline, all subjects were screened for TB with a questionnaire, exam, chest x-ray, and sputum smear. TB cultures were not performed as part of screening. Among the cohort of 1044 antiretroviral therapy-eligible subjects screened to start antiretroviral therapy, 75 subjects (7.2%) were identified as having TB during this screening process. Risk factors for TB included low BMI and prior history of TB. An additional 52 subjects were diagnosed with TB during a median of 1.4 years of follow-up. Mortality rates of those diagnosed with TB at baseline or follow-up was 17.9 per 100 person-years and 3.8 in those without TB. Investigators estimated that TB was associated with 36% of the deaths in this cohort. They also observed that rates of TB declined over time. Rates were 7.27 per 100 person-years, 2.29 per 100 person-years, and 1.77 per 100 person-years at 1 to 6, 7 to 12, and 13 to 18 months after antiretroviral therapy initiation, respectively.

Diagnostics: Undiagnosed and Latent Tuberculosis

There were 2 abstracts looking at identification and treatment of tuberculin skin test reactors in Thailand. In a Thai Mother-to-Child Transmission (MCTC)-plus treatment cohort program with 621 participants, 456 of whom were women (Abstract 792), the tuberculin skin-test positive rate was 20%. Discordance between couples was 37%. After 2 years of follow-up, new tuberculin skintest reactions in the absence of TB were found in 13.8%: a 7-fold increase in skin test conversion after 2 years. A positive skin test in a partner was the highest predictor of

skin test conversion. It was not clear whether the increased risk of TB within households was due to risk of asymptomatic active disease transmission, or reflects similar exposure risk in the household members.

In a second Thai study of a TB screening program in a clinic among 1078 HIV-infected subjects (Abstract 799), 22% were currently receiving antiretroviral therapy. In a multivariate analysis, CD4+ cell count above 200/ μ L, male sex, and antiretroviral therapy use were associated with a positive tuberculin skin test. Of 250 persons with positive tuberculin skin tests, 92% received isoniazid. Active TB was diagnosed in 14 persons with a positive skin test. Ten of these were diagnosed during the initial process of TB evaluation following skin-test results. Three developed active TB during isoniazid prophylaxis, and 1 at a later time. The authors concluded that tuberculin skin testing combined with isoniazid prophylaxis was a useful strategy in this population.

In a complementary study from Cape Town, South Africa, Bekker and colleagues estimated age- and sex-specific TB trends among a community of 13,800 between 1996 and 2004. During this time, reported TB cases increased 2.4-fold. Highlighting the challenges of TB case finding, there were more individuals in the community with undiagnosed TB than individuals already in treatment. Undiagnosed cases were not limited to the HIV-infected population, and smear-negative cases among both groups represented a large pool of undiagnosed cases (Abstract 69).

Immune Reconstitution Inflammatory Syndrome in Subjects with Tuberculosis

Preliminary data were presented from a randomized trial of early (2 weeks) versus delayed (8 weeks) initiation of antiretroviral therapy in patients diagnosed with TB in Tanzania (Abstract 796). One of the main objectives of this study was to see if immune reconstitution inflammatory syndrome (IRIS) dif-

ferred between patients starting antiretroviral therapy early or late after TB treatment initiation. Data were reported on 70 patients with smear-positive pulmonary TB. Subjects in this study received lamivudine/zidovudine/abacavir (fixed-dose combination) for antiretroviral therapy. They were observed as inpatients for the first 8 weeks of the study. At entry, the median CD4+ cell count was 103/ μ L. Outcomes of this preliminary report included the death of 3 subjects not attributed to TB (disseminated Kaposi's sarcoma, pneumonia, cerebral malaria). There were 6 changes in antiretroviral therapy: 2 for anemia due to zidovudine and 4 with suspected abacavir hypersensitivity. The surprising finding of this study was that there were no cases of IRIS despite 516 patient-months of follow-up and inpatient observation. Other African investigators commented that these findings differed from their clinical experience where IRIS occurred in HIV-infected, and to a lesser degree, HIV-uninfected patients.

An interesting study from the Autran lab in Paris looking at reconstitution of immune responses in patients with TB treated with antiretroviral therapy was presented by Bourgarit and colleagues (Abstract 797). In a prospective study of 22 patients starting TB therapy and antiretroviral therapy, 9 experienced IRIS. Purified protein derivative (PPD)-specific Th1 IFN- γ cells increased sharply during IRIS; a similar increase was not observed to cytomegalovirus antigens. These PPD-specific cells represented up to 22% of all cells, and all expressed human leukocyte antigen (HLA) DR. Only 3 IRIS patients had ESAT-6 responses. Those without IRIS did not develop acute PPD-specific responses. It is interesting that immune restoration to mycobacterial antigens containing tuberculin but not ESAT-6 was associated with expansion of IFN- γ producing cells.

The Tuberculosis Clinic as Entry Point for HIV Testing

HIV testing is recommended for all persons diagnosed with TB. Srikanitah and colleagues provided data to extend these recommendations to all patients presenting to a TB clinic (Abstract 798). Among 395 subjects referred to a TB clinic, 82% consented to voluntary HIV counseling and testing. TB diagnosis was based on clinical symptoms and acid-fast bacillus (AFB) smears; cultures were not available. The HIV seroprevalence rate was high both among those with a TB diagnosis (43%) and those without (54%). The presentation also highlighted an opportunity for HIV prevention as the majority of clients reported ongoing sexual activity with at least 1 partner and condom usage was reported at less than 10%.

Tuberculosis Diagnosis

TB diagnosis is one of the Achilles heels of TB control and treatment programs. There are increasing reports of HIV-infected patients who have TB confirmed by culture but who are chest-x-ray negative, smear negative, and who may even be asymptomatic. More sensitive rapid diagnostic tests are available that increase diagnostic yield (Abstract 793). In this study of 73 subjects with proven TB, polymerase chain reaction direct amplification was performed in 20 patients who each had 3 negative AFB smears. Direct amplification diagnosed 75% of smear-negative cases. These types of tests are needed but are not yet feasible in resource-limited settings where perhaps they could have greatest benefit.

Drug Interactions

The controversy regarding safety of using nevirapine plus rifampin in patients treated for TB continued at this year's conference. Pharmaco-

kinetic studies from the United States and Europe showed dramatically reduced levels of nevirapine in the presence of rifampin. However, recent data from Thailand suggest that the combined use of nevirapine and rifampin is effective and safe in HIV-infected patients with TB. Many programs in Africa are utilizing this combination because of its access, cost, and practicality. In a study of healthy volunteers from India, single-dose pharmacokinetics of nevirapine was assessed by Pujari and colleagues (Abstract 574). Pharmacokinetic studies were repeated after these volunteers took rifampin for 7 days. The pharmacokinetics of nevirapine after addition of rifampin showed no significant change in C_{max} . However, C_{24} was reduced by 60%; area under the curve by 80%; and half-life by 66%. The authors concluded that this combination should not be used in HIV-infected patients with TB.

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A list of all cited abstracts appears on pages 63 to 70.

Additional Reference

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