Complications of HIV Disease and Therapy

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Managing and preventing complications of HIV disease remain high priorities for research worldwide. At the 15th Conference on Retroviruses and Opportunistic Infections, continued areas of focus were on understanding the pathogenesis of complications, identifying risk factors for these problems, and defining optimal management strategies for complications and infections. As in past years, there was an increase in studies focused on problems predominantly occurring in resource-limited settings.

Morbidity and Mortality in the Potent Antiretroviral Therapy Era

As highlighted by Phillips in the opening morning plenary session of this year's conference, the greatest source of morbidity in the potent antiretroviral therapy era is undiagnosed and undertreated HIV infection. He discussed the relationship between serious non-AIDS events (cardiovascular disease and renal and hepatic events) and HIV infection, demonstrating that these events are both more common in patients with lower CD4 + cell counts and reduced in frequency by the use of antiretroviral therapy (see also Abstract 963). He concluded by suggesting that all-cause morbidity might be further reduced if treatment were started at higher CD4 + cell counts. Additional data from his group demonstrated a higher rate of mortality for treatment-naive patients with CD4 + counts above 350 cells/μL than for the general population in the UK (Abstract 141). In this study, age-standardized mortality ratios for 47,474 antiretroviral therapy–naive patients with CD4 + counts greater than 350 cells/μL were compared with ratios of the general population. For each risk group examined, men who have sex with men (MSM), injection drug users, and heterosexuals, the risk of death was higher for the HIV patients than for the controls, and the excess mortality was greatest for injection drug users, possibly the result of non-HIV–related morbidity in this population. These data support the notion that earlier treatment of HIV infection should be explored with the hope of further improving the overall outcomes for people with HIV infection.

As treatment improves, it is clear that rates of failure and opportunistic infections remain low among those who are able to obtain and stay on therapy. This is not to say that toxicity and adverse events related to long-term HIV infection and its treatment are not important issues. In this article, we review some of the new data presented at this year's conference on managing complications of HIV disease and therapy.

Cardiovascular Disease

As patients with HIV age, there is ongoing concern about the long-term risk of cardiovascular disease in this population. Previously the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) collaboration, a prospective multicohort study, reported that each additional year of protease inhibitor (PI) treatment was associated with 16% excess risk of myocardial infarction (MI).[1] Preplanned analyses from this cohort were presented at this year's conference examining the association between the nucleoside analogue reverse transcriptase inhibitor (nRTI) component of therapy and MI risk (Abstract 957c).

At the outset, it is important to emphasize that the absolute risk of MI in this updated report from the DAD study is low, with 517 events among 33,400 patients (1.6%) during 5 years of follow-up. The investigators had hypothesized that the thymidine nRTIs zidovudine and stavudine would be associated with an increased risk of MI because of the known relationship between these drugs and modest changes in dyslipidemia. An unexpected finding emerged from these analyses: both didanosine (relative risk [RR], 1.49) and abacavir (RR, 1.9) appeared to be associated with the risk of MI. Interestingly, the risk was not evident in patients who previously took abacavir and stopped it more than 6 months beforehand.

Careful analyses of these data suggested that patients who received abacavir had a greater burden of traditional cardiovascular risk factors, but after control for these factors, the relationship between recent abacavir use and MI persisted. Also, within the abacavir group, the excess risk was greatest for patients with a higher underlying risk of cardiovascular disease, which is a reminder to clinicians to screen and manage all patients for modifiable cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes.

The results of this study will launch a closer look at the relationship between abacavir and didanosine exposure and MI in other large databases and clinical trials. In the interim, clinicians should interpret these unexpected findings cautiously while more data are compiled.

An active area of investigation is the relationship between chronic HIV infection, markers of inflammation, and cardiovascular risk. Sparked initially by data from the Strategies for Management of Antiretroviral Therapy (SMART) study that demonstrated a marginally increased risk of cardiovascular events among patients who interrupted therapy, interest is growing in the role of inflammation as a mediator of cardiovascular risk in HIV. Kuller and the SMART team reported a case-control study (Abstract 139) that examined the relationship among (1) the levels of the inflammatory markers interleukin-6, high-sensitivity C-reactive protein, and

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amyloids A and P; (2) the markers of thrombosis, d-dimer and prothrombin fragments 1 and 2, at the time of treatment interruption; and (3) cardiovascular events and overall mortality. They found a striking association between the levels of both interleukin-6 (odds ratio [OR], 12.6) and d-dimer (OR, 13.3) and all-cause mortality. They also found a statistically significant, but of lesser magnitude (OR, 2.0 for d-dimer) association between the markers of thrombosis and fatal and nonfatal cardiovascular events. These results suggest that among patients who stop antiretroviral therapy, increases in generalized immune activation may be associated with the excess morbidity observed

Other studies examined the relationship between biomarkers of inflammation and endothelial activation and measures of subclinical cardiovascular and metabolic disease. Ross and colleagues reported higher levels of endothelial activation markers in untreated HIV patients than in uninfected controls (Abstract 954). In a second study (Abstract 949), these same investigators examined the association between several biomarkers and carotid intima media thickness (IMT) in a cross-sectional study of HIV-infected and -uninfected patients. They reported higher levels of the inflammatory cytokines and endothelial activation markers in the HIV-infected patients than in the controls and a correlation between the inflammatory cytokines (but not endothelial activation markers) and carotid IMT.

Data from one of the few longitudinal studies presented demonstrated higher levels of several endothelial activation markers (soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, tissue-type plasminogen activator inhibitor, and high-sensitivity C-reactive protein) among untreated HIV patients with an improvement (reduction in activation markers) during potent antiretroviral therapy (Abstract 953). After 12 months of potent antiretroviral therapy, the difference in endothelial activation markers between the HIV-infected and -uninfected groups was no longer statistically significant.

A novel approach to examining the relationships among HIV infection, viral replication, HIV treatment, and atherosclerosis was reported by Hsue and colleagues in a cross-sectional study comparing carotid IMT in HIV-infected patients with that of uninfected controls (Abstract 951). The novel aspect of this study was the inclusion in the HIV groups of patients in whom HIV replication was controlled without treatment as well as patients on potent antiretroviral therapy. After adjustment for traditional risk factors, both HIV infection and duration of PI therapy were associated with carotid thickness. Notably, the untreated HIV patients with controlled viral replication also had greater carotid thickness than the uninfected controls did, suggesting that factors other than viral replication or immunodeficiency may contribute to carotid thickness.

An intriguing pilot study by Gupta and colleagues at Indiana University examined the impact of pentoxifylline on endothelial function in HIV-infected patients (Abstract 955). Previous studies have suggested that impaired flow-mediated dilation (FMD) of the brachial artery is common in HIV-infected patients.[2] Pentoxifylline is known to reduce tumor necrosis factor production in vivo and in vitro; however, it did not have a significant impact on HIV replication when it was evaluated as a potential HIV treatment.[3] In this single-arm study, a 400-mg, 3-times-daily dosage of pentoxifylline given to 9 HIV patients not on antiretroviral therapy was associated with an improvement in FMD of the brachial artery after 4 and 8 weeks, suggesting that systemic inflammation is likely to contribute to the abnormal FMD of the brachial artery seen among untreated patients. Controlled studies are needed to determine whether pentoxifylline has any role in reducing systemic inflammation during effective HIV therapy.

Dyslipidemia

Randomized trials of new or existing treatments in treatment-naive patients now routinely include the measurement of fasting lipid levels,

as this information is important for the long-term management of HIV infection. The CASTLE study (Abstract 37) compared ritonavir-boosted atazanavir with lopinavir/ritonavir, both in combination with tenofovir/emtricitabine, in treatment-naive patients; it demonstrated higher triglyceride, total cholesterol, and non-high-density-lipoprotein (HDL) cholesterol levels in the lopinavir/ritonavir-treated patients. In the MERIT study, in which zidovudine and lamivudine provided the nRTI backbone, efavirenz therapy was associated with high median increases in levels of total cholesterol (35 mg/dL vs 2 mg/dL), HDL cholesterol (13.5 mg/dL vs 6.9 mg/dL), triglyceride (20 mg/dL vs –9 mg/dL), and low-density-lipoprotein (LDL) cholesterol (20.7 mg/dL vs –9 mg/dL).

These results highlight the fact that first-line therapy with efavirenz, especially when combined with zidovudine plus lamivudine, is not lipid-neutral (Abstract 929). In the HEAT study, lipid changes in patients on abacavir plus lamivudine were comparable with those on tenofovir plus emtricitabine, both combined with once-daily lopinavir/ritonavir (Abstract 774).

Ritonavir is used in different doses to boost PIs and other drugs. Boffito and colleagues examined the relationship between low doses of ritonavir and values of triglycerides and HDL cholesterol (Abstract 930). Effects of ritonavir doses of 100 mg either once daily or twice daily were examined in uninfected volunteers over a 14-day period. Only the 100-mg, twice-daily dose of ritonavir was associated with an increase in triglyceride levels, and there appeared to be a relationship between ritonavir exposure and change in triglyceride level. In a small study (n = 40) comparing the lipid profiles of the new (tablet) and old (capsule) formulations of lopinavir/ritonavir, higher levels of triglycerides and lower levels of HDL were observed with the newer tablet formulation (Abstract 934). Higher lopinavir trough levels were seen during therapy with the tablet formulation; unfortunately, no information about ritonavir levels was available in this study.

Lipoatrophy and Lipohypertrophy

Factors associated with the development of a 20% loss of limb fat as measured by dual-energy x-ray absorptiometry (DEXA) scan were evaluated in the AIDS Clinical Trials Group (ACTG) 5142 study that compared 3 class-sparing regimens for initial treatment of HIV infection (Abstract 935). In this study, lipoatrophy was greater for efavirenz plus 2 nRTI arms (32%), more so with stavudine (43%) and zidovudine (27%) than with tenofovir and the lopinavir plus efavirenz arms (8%-10%). Independent of the antiretroviral therapy received, higher baseline CD4+ cell count and lower gain in body weight were associated with the development of lipoatrophy. Other factors associated with limb fat loss included male sex, absence of AIDS diagnosis at baseline, and smaller increases in total and LDL cholesterol levels. These results suggest that additional factors contribute to fat loss during treatment of HIV infection.

Currently, the most effective intervention for management of lipoatrophy is switching patients off zidovudine or stavudine to either an abacavir- or tenofovir-based regimen. Moyle reported his group's 48-week DEXA results from a randomized trial that enrolled 250 patients who were well suppressed on efavirenz and fixed-dose zidovudine/lamivudine and who underwent randomization to either remain on this treatment or change the nRTI component to tenofovir and emtricitabine (Abstract 938). Mean limb fat (as measured by DEXA) increased by 261 g in the tenofovir group compared with a 187-g decline in those remaining on zidovudine. Importantly, virologic control was maintained during follow-up, and no statistically significant differences were noted in a post hoc analysis of bone mineral density during the 48-week period.

Further support for the role of nRTIs in the pathogenesis of lipoatrophy and visceral fat accumulation comes from the MEDICLAS trial (Abstract 937). Antiretroviral-therapy-naive men underwent randomization to lopinavir/ritonavir combined either with zidovudine plus lamivudine or with nevirapine.

Both DEXA and abdominal computed tomography measures were included, and follow-up to 24 months was reported. Lipoatrophy and abdominal fat accumulation were more common when lopinavir/ritonavir was added to the nRTI combination of zidovudine plus lamivudine. However, higher levels of total and LDL cholesterol were observed in the nRTI-sparing regimen of lopinavir/ritonavir plus nevirapine, indicating that alternative nRTI-sparing regimens should probably be explored.

Currently, weight loss and exercise are the mainstays in managing central fat gain during HIV treatment. Mun and colleagues conducted a randomized trial comparing the insulin sensitizer rosiglitazone with a diet-and-exercise intervention including either placebo or rosiglitazone (Abstract 944). Eligible patients had an elevated body mass index (BMI) and fasting insulin level at or above 16 µIU/mL. Treatment with rosiglitazone was associated with weight gain, which was ameliorated in the group who received the diet-and-exercise intervention with rosiglitazone. It was not possible to measure an additional benefit provided by rosiglitazone over the diet-and-exercise intervention in this small study.

The growth-hormone-releasing factor analogue tesamorelin is under investigation as a treatment for HIV-associated central fat gain. Previous 26-week results reported a decrease in visceral adipose tissue with a 2-mg daily dose of tesamorelin, compared with placebo. At this year's conference, 52-week results were presented that compared the long-term outcomes for patients who underwent rerandomization at week 26 to either discontinue or remain on treatment through 52 weeks (Abstract 943). Within the group that remained on treatment, loss of visceral fat was maintained without a significant loss in limb fat or evidence of worsening glucose tolerance. Unfortunately, the improvement in visceral adipose tissue seen during the first 26 weeks of therapy was not maintained in subjects who were switched to placebo, suggesting that continued treatment will be needed to maintain the benefit of this drug.

Bone Density

Low bone density is common among HIV-infected men and women; however, the role of antiretroviral treatment as a cause of osteopenia and osteoporosis remains controversial. Investigators from the Women's Interagency HIV Study (WIHS) evaluated changes in bone mineral density (BMD) among 114 HIV-seropositive and 74 HIV-seronegative premenopausal women over a 2-year period (Abstract 965). At baseline, the HIV patients were older and had lower BMI and—not surprisingly—also had lower BMD, most notably in the PI-treated group. During the 2 years of follow-up, however, the rate of bone loss and occurrence of fractures did not differ between the treatment groups. These results suggest that antiretroviral therapy–treated HIV patients may have comparable rates of bone loss to age-matched controls.

Two studies examined the role of different antiretroviral treatment regimens and bone loss within randomized clinical trials and produced somewhat conflicting results. Brown reported the results of a randomized trial comparing initial treatment with either efavirenz plus zidovudine plus lamivudine or lopinavir combined with zidovudine plus lamivudine and later simplified to lopinavir monotherapy (Abstract 966). After 96 weeks of treatment, the rate of bone loss (−2.3%, −2.5%) was similar in both groups. These results suggest that the loss of BMD that occurs after initiation of antiretroviral therapy is independent of the treatment regimen. In addition, the baseline data from this study confirm earlier observations that nonblack patients and those with lower baseline CD4+ cell counts are more likely to have lower BMD.

In contrast, Duvivier and colleagues (Abstract 967) compared rates of bone loss among patients who underwent randomization to a nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-PI combination or to therapy with either a PI or NNRTI combined with nRTIs. Follow-up in this study was 48 weeks, at which point bone loss at the hip and lumbar spine was greater in both of the PI-containing arms than

in the NNRTI arm. Clearly, larger studies with longer follow-up periods are needed to sort out the contribution of specific antiretroviral therapy regimens to bone loss. One point that all studies appear to agree on is the high prevalence of osteopenia among antiretroviral-therapy-naive patients, suggesting a role for untreated HIV infection in the pathogenesis of bone loss (Abstracts 968, 969).

Renal Disease

A theme throughout this year's conference was the role of HIV infection and immunodeficiency in the pathogenesis of many important complications; renal disease is a prime example. Kirk and the EuroSIDA Study Group (Abstract 971) examined predictors of deterioration of renal function among 5526 patients observed prospectively with measurement of estimated glomerular filtration rate (GFR). Loss of renal function (25% decline) was observed in 2% to 3% of patients and appeared related to the level of immunodeficiency in addition to traditional risk factors (most notably hepatitis C virus [HCV] coinfection).

Data from the Multicenter AIDS Cohort Study (MACS) were used to examine predictors of GFR decline in HIV-infected men compared with uninfected controls (Abstract 973). In this study of 2163 men (1206 HIV-uninfected), GFR decline was not associated with HIV status or potent antiretroviral use but rather with black race, diabetes, hypertension, smoking, and HCV status. Proteinuria was identified as an important early marker of future decline in renal function.

Gupta examined the urine protein-to-creatinine ratio (P:Cr) in 2827 patients observed since 2002 in the ACTG Longitudinal Linked Randomized Trials (ALLRT) cohort and found a decline in P:Cr over time; notably, those with plasma HIV RNA levels below 400 copies/mL had reduced odds of clinically significant proteinuria (Abstract 974). Again, hypertension, diabetes, older age, and black race were important factors in predicting a decline in renal function over time.

Optimal methods for monitoring renal function in clinical practice are often debated, and the accuracy of different formulas for estimating creatinine clearance in HIV patients is unknown. Investigators from the PREPARE study compared a gold standard measure of GFR, that is, GFR measured by iodine[125]-iothalamate using a 24-hour urine collection, with other estimates of GFR using either the Cockcroft-Gault method, the modification of diet in renal disease formula, or a measurement of cystatin C (Abstract 977b). Among this small group of predominantly male patients with preserved renal function, the Cockcroft-Gault method compared most favorably with the measured creatinine clearance using the isotope method. The reasons for the poor performance of the cystatin C measure in this study are unknown; however, the authors postulate that HIV-related inflammation may play a role.

Toxicity in Resource-limited Settings

Toxicities associated with stavudine, the most commonly used nRTI in first-line antiretroviral therapy in resource-limited settings, were the focus of the majority of abstracts on this topic. From a cohort of 305 patients receiving stavudine-containing antiretroviral therapy regimens for 2 years, Wong and colleagues reported that stavudine-specific toxicities were frequent and cumulative (Abstract 990). Peripheral neuropathy incidence rates were 0.27 and 0.22 (expressed as events per person-year) in years 1 and 2, respectively. Lactic acidosis incidence rates were 0.04 in year 1 and 0.06 in year 2 of follow-up. Lipodystrophy presented more commonly in year 2 with an incidence rate of 0.21. Ninety percent of the 60 regimen changes in this cohort were because of toxicity, with lipodystrophy (37%), peripheral neuropathy (32%), and lactic acidosis (15%) accounting for the majority of the regimen switches. The concern for lactic acidosis among patients has led to the development of methods to measure lactate that are feasible in a resource-limited setting. Hand-held, point-of-care lactate analyzers compared favorably with traditional

laboratory evaluations of lactate, and authors concluded that these devices were useful for evaluating patients with symptoms consistent with symptomatic hyperlactemia (Abstracts 991,992).

Substituting zidovudine for stavudine to limit toxicity is standard practice in resource-limited settings, but few studies have evaluated outcomes of this approach. Mwima and colleagues reported outcomes of 860 adults in Uganda who developed peripheral neuropathy after starting antiretroviral therapy with a stavudine-based regimen (Abstract 988). Thirty-six percent of adults reported symptoms of neuropathy a median of 28 days after antiretroviral therapy initiation, and 143 patients with mild neuropathy remained on stavudine, with 54% reporting improvement, 40% remaining the same, and 6% worsening. One hundred fifty-three subjects with grade 3 or 4 neuropathy switched to zidovudine, of whom 75% had improvement in their neuropathy at follow-up. Improvement in neuropathy was most likely when the CD4+ count was above 200 cells/μL and the subject was not receiving isoniazid. Although these data demonstrate improvement in many individuals after discontinuation of stavudine, many individuals did not improve, and many progressed, underscoring the need for the use of alternatives to stavudine.

Risks for lipodystrophy and the metabolic syndrome in a cohort of 171 patients living in Abidjan, Cote d'Ivoire (West Africa), were reported by Eholie (Abstract 947). Lipodystrophy was defined by 1 or more signs of peripheral lipoatrophy and central lipohypertrophy. Metabolic syndrome was defined as the presence of abnormalities in at least 3 of the following laboratory measures: triglycerides, HDL, glucose, waist circumference, and blood pressure. The 2 most commonly used antiretroviral therapy regimens were efavirenz plus zidovudine plus lamivudine (57%) and nevirapine plus stavudine plus lamivudine (21%). The cumulative incidence of metabolic events after a mean follow-up period of 16 months was: blood pressure increase, 38%; waist hypertriglyceridemia, 16%; circumference increase, 14%; and hyperglycemia, 2%. Lipohy-

pertrophy was reported in 23% and lipoatrophy in 4%. Although the absence of standardized case definitions in the field make comparison between studies challenging, these data contribute to accumulating evidence that metabolic abnormalities are not uncommon among patients receiving standard first-line regimens in resource-limited settings.

Toxicities to stavudine continue to follow a predictable pattern in resource-limited settings, and the high cost of alternative drugs is the major reason for its continued used. One modeling study suggested that only modest reductions in tenofovir prices would be enough to make it cost-neutral to stavudine, when the costs of stavudine toxicity are considered (Abstract 989). Tenofovir is now included as first-line therapy in the World Health Organization guidelines, and all data continue to point to the importance of avoiding cumulative exposure to stavudine.

Aging

With the improved long-term prognosis of treated HIV patients comes an awareness of the intersection between normal aging and the management of HIV infection. A 2-hour symposium at this year's conference highlighted the special considerations about aging in the setting of HIV infection. With speakers focused on epidemiology (Ledergerber), immunology (Effros), pharmacology (Flexner), and clinical management (Powderly), an array of special issues were reviewed.

The session addressed the growing number of patients with established HIV infection who are aging, along with the importance of identifying new infections among the over-50-year-old population. Data suggesting that people older than 50 years are more adherent to therapy were counterbalanced by evidence of limited immune reserve and blunted CD4+ cell responses in older patients. Immune exhaustion in chronic HIV infection and normal aging were explored, with an emphasis on the role and measurement of CD8+ T-cell exhaustion as an important issue for the aging HIV-infected population. Special issues related to diseases of aging such as diabetes, hypertension, os-

teoporosis, and cardiovascular disease were highlighted, as was concern about polypharmacy and drug interactions. Finally, optimal systems of care for the management of an aging HIV-infected population were brought into question. Viewing of this session on the webcast is highly recommended for those with an interest in this important new area of investigation.[4]

Tuberculosis Coinfection

Drug-resistant Tuberculosis

The toll and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) were reviewed by Friedland in the tuberculosis symposium (Abstract 112). Friedland provided an update on the South African situation in Tugela Ferry, KwaZulu-Natal province, since the original report of the epidemic. Between January 2005 and September 2007, there have been an additional 471 cases of drug-resistant TB. The outcomes continue to look grim, with mortality rates in the 60% to 80% range. Strains of MDR-TB have not been limited to Tugela Ferry. In mid-2007, XDR-TB cases had been identified from 60 facilities in KwaZulu-Natal. Of the 5019 cases identified in the province, over half were outside Tugela Ferry. Only 25% of the total cases had records of care at the MDR referral hospital, the only location where second-line TB drugs are available. An additional 9 South African provinces had identified cases of XDR-TB. There are also reports of resistant strains in neighboring Mozambique and Botswana. Studies are ongoing to define the extent of this emerging epidemic in sub-Saharan Africa.

Reminiscent of the outbreaks of MDR-TB in the United States in the 1980s, new data presented by Andrews and colleagues documented that some patients acquire MDR- or XDR-TB in health care facilities, and that many of these infections represent TB reinfections among patients already being treated for drug-susceptible TB (Abstract 143). This group examined baseline and follow-up TB cultures from 17 individuals from Tugela Ferry who de-

veloped drug-resistant TB after initiating TB treatment. Results of spoligotyping of the culture pairs demonstrated that the patients were reinfected with a drug-resistant TB strain. All 17 patients were hospitalized at the same facility. Supporting the conclusion of nosocomial reinfection, unique TB strains for each patient were identified at the start of therapy, and common MDR- or XDR-TB strains were found to account for reinfection. Infection-control measures are nonexistent in most parts of Africa. These data call for rapid implementation of measures to reduce in-hospital transmission.

High prevalence of TB drug resistance is not limited to Africa. Eastern Europe has among the highest rates of drug-resistant TB in the world. In an epidemiologic survey from Ukraine, MDR-TB rates were 1.7-fold higher among HIV-infected than -uninfected patients (Abstract 144). The overall prevalence of MDR-TB was alarmingly high in isolates from these individuals living in Ukraine. Among HIV-seropositive individuals, 28% of TB cases in the civilian sector and 58% in the prison sector harbored MDR strains of TB.

Tuberculosis Outcomes

The bulk of early mortality observed after initiation of antiretroviral therapy in Africa has been attributed to TB. Westreich and colleagues evaluated outcomes of 6080 adults initiating antiretroviral therapy in Johannesburg, South Africa (Abstract 145), of whom 17.3% had TB at the time of antiretroviral therapy initiation. In the multivariate analysis, TB was not associated with increased mortality nor loss to follow-up. However, individuals with low BMI, a CD4+ count below 50 cells/µL, and TB had increased mortality rates.

In this same cohort, Faesen reported a study comparing suppression rates of plasma HIV RNA levels among patients with TB receiving antiretroviral therapy with those of similar patients but without TB (Abstract 1002). As in reports from other cohorts, there was no difference in reductions in plasma HIV RNA levels between the patients with or without TB.

Immune Reconstitution Inflammatory Syndrome

The immunologic basis of TB-associated immune reconstitution disease has yet to be elucidated. Meintjes and colleagues evaluated sequential interferon gamma (IFN-γ) enzyme-linked immunosorbent spot (ELISpot) data from 63 adults with TB who were initiating antiretroviral therapy, as well as a cross-sectional cohort of 42 persons with TB-associated immune reconstitution inflammatory syndrome (IRIS). In the longitudinal cohort, IRIS developed in 22% of persons. Although IFN-γ responses to a number of TB antigens increased after antiretroviral therapy, these changes did not predict development of TB-IRIS (Abstract 1006). Similarly, Tieu and colleagues examined T_H1 cytokine responses and IFN-γ responses among 51 Thai patients with TB who initiated antiretroviral therapy. In this cohort, 21.6% developed TB-IRIS, with 8 requiring corticosteroid treatment (Abstract 1008).

Similar to the South African study, Boulware and colleagues found no association between the immunologic markers tested and the development of TB-IRIS (Abstract 1007). Gazzola and colleagues presented an interesting poster on FoxP3 (T-regulatory)-expressing cells (Abstract 1003). These investigators examined lymph nodes for FoxP3 expression from patients with and without HIV and with and without TB. They found the lowest expression of FoxP3 markers to be among patients with TB and HIV. They suggested that fewer T-regulatory cells may result in the poorer control of inflammatory responses and increased inflammation observed with TB among HIV patients, particularly during IRIS events.

Numerous posters and a poster discussion session (Session 29) highlighted the absence of a uniform, validated case definition for TB-IRIS. In addition, one of the requirements for the diagnosis of immune reconstitution disease, or transient worsening of TB after initial clinical improvement, is the exclusion of other possible causes of clinical deterioration.

In this regard, one of the most important TB-HIV presentations at this year's conference was the report by Meintjes and colleagues (Abstract 1009), who prospectively evaluated 100 suspected TB-IRIS cases between February 2005 and July 2006. In 7 cases, an alternative opportunistic infection was the explanation for the clinical deterioration. In 12 cases, rifampin resistance, either alone or as a part of an MDR-TB infection, was present at baseline and was the reason for the clinical worsening. In 8 cases, the clinical deterioration was the manifestation of an inadequate treatment regimen in a patient with rifampin resistance. This report, along with the TB reinfection data cited above, indicate that suspected TB-IRIS may be the result of failure of a drug-resistant first-line regimen or reinfection with a second drug-resistant strain. Rapid diagnostic tests for drug resistance are urgently needed, both for clinical care and research studies in this population.

Pharmacokinetics

In resource-limited settings, efavirenz is recommended as the preferred NNRTI for patients requiring rifampin-based TB therapy because of the greater effect of hepatic enzyme induction by rifampin on nevirapine than on efavirenz. Matteelli evaluated 16 subjects from Burkina Faso, Italy, treated for TB, who started a nevirapine-based antiretroviral therapy regimen within 30 days of the start of TB therapy (Abstract 760). About 33% of the patients had subtherapeutic nevirapine trough levels in the presence of rifampin compared with about 12% when only nevirapine was present and rifampin had been discontinued. This sample size was too small to evaluate clinical outcomes, but the results add to the body of literature demonstrating the short-term effect of rifampin on nevirapine trough levels during rifampin administration.

Haas and colleagues evaluated the interaction between boosted atazanavir and rifampin (Abstract 766b). After 8 days of rifampin treatment, HIV-uninfected volunteers received twice-daily atazanavir 300 mg and ritonavir 100 mg. The study was halted after only 3 participants were entered. After starting the atazanavir/ritonavir treatment, all subjects experienced severe nausea and vomiting and significant elevation in hepatic transaminase levels. Authors postulated that a toxic metabolite of either ritonavir or rifampin caused these effects.

Hepatitis C Virus

Epidemiology

Sexually transmitted HCV has been reported among MSM. Jones and colleagues reported reinfection with HCV among MSM who had been successfully treated previously for HCV. They identified 16 patients with hepatitis C viremia after either sustained virologic response (SVR) posttreatment or spontaneous clearance (Abstract 61LB). Among 8 individuals for whom paired samples of the 2 episodes were available, results of phylogenetic analysis suggested that 6 of the 8 patients were reinfected with a new strain of HCV, and 2 had late relapses. All of the subjects had ongoing high-risk sexual activity. Although there is the possibility that the patients were initially infected with more than 1 strain, these data suggest that even patients for whom the HCV achieves SVR or spontaneous clearance are at risk for HCV reinfection.

In a second epidemiologic study of HCV in MSM, van de Laar and colleagues used results of phylogenetic analysis to characterize ongoing new HCV outbreaks (Abstract 1066). They evaluated 200 isolates from MSM with acute HCV infection from England, the Netherlands, Germany, and Australia. Results of phylogenetic analysis revealed 12 HCV clusters. Data were consistent with clusters within Europe but not between Europe and Australia. These data underscore the importance of including HCV evaluations among sexually active MSM and targeting prevention messages to this population.

Outcomes

Sustained virologic response is the goal of HCV therapy. Few studies have attempted to quantify outcomes in patients whose treatment did and did not achieve SVR. Berenguer and colleagues

examined outcomes from 711 HIV-infected patients from 11 clinical centers in Spain who received HCV treatment with interferon alfa (including pegylated forms) plus ribavirin (Abstract 60). The follow-up period was approximately 2 years, during which SVR was achieved in 31% of subjects. Mortality was 6.9% among non-SVR patients and 0.9% in the SVR group. Liver decompensation was 9.1% and 0.5% in the non-SVR and SVR groups, respectively. Liver transplants were performed in 2.2% and 0.5% of patients in the non-SVR and SVR groups, respectively. These data, which demonstrate 20-fold higher rates of liver decompensation and 9-fold increased rates of mortality among patients for whom treatment failed to achieve SVR compared with those for whom treatment did achieve SVR, underscore the value of achieving SVR and the urgent need for better HCV treatments.

Lars Peters and colleagues evaluated HIV treatment outcomes among patients with and without HCV in the EuroSIDA cohort (Abstract 1069). They specifically examined whether the presence of HCV infection influenced CD4+ cell count changes among HIV-infected patients who had 2 consecutive test results of plasma HIV RNA values below 50 copies/µL. In this analysis of 3892 patients, 21% were HCV-seropositive. After adjusting for potential factors associated with influencing CD4+ cell count recovery or viral load suppression, there was no difference in CD4+ cell count recovery among patients with and without HCV antibody.

Treatment

The value of maintenance therapy with peginterferon alfa in HCV patients whose infection failed to achieve an early virologic response (EVR) is not known. Some data suggested that continued interferon therapy for such patients could potentially provide improvement in histologic disease progression. To test that hypothesis, patients for whom treatment with peginterferon alfa and weight-based ribavirin had failed to achieve EVR (defined as a 2-$\log_{10}$ reduction in plasma

HCV RNA levels at 12 weeks) underwent randomization to either peginterferon alfa or no therapy (Abstract 59).

Sherman and colleagues used sequential liver biopsies to assess liver disease progression. The study was prematurely halted because of the slow rates of progression in the observation (control) arm that received no interferon. The expected rate of change of fibrosis in the control arm was 0.18 metavir units/year, and the observed rate was undetectable. Possible explanations for these results include the influence of high rates of SVR suppression during the initial treatment phase, a duration of follow-up that was not long enough, or that the differences were too modest to detect by this study. These data do not support maintenance interferon alfa therapy among patients for whom prior treatment with interferon alfa and weight-based ribavirin failed to lead to EVR.

Rapid virologic response (RVR), defined as HCV titers below 50 IU/mL at 4 weeks, has been utilized to predict HCV treatment responses in HCV-monoinfected patients. Rodriguez-Torres and colleagues examined RVR and EVR among 271 HIV-coinfected patients who underwent treatment for HCV (Abstract 1073). Rates of SVR were highest in those with RVR. When the researchers stratified results of those with EVR into "complete" EVR (defined as plasma HCV RNA levels below 50 IU/mL at week 12, not week 4) and "partial" EVR (defined as a 2-log reduction in HCV titer at week 12 and plasma HCV RNA titer above 50 IU/mL), they found higher SVR rates in the complete than in the partial EVR subjects. Matthews and colleagues examined RVR as a predictor of SVR among patients with acute HCV infection (Abstract 1070). They had 96 patients, 28 of whom were coinfected with HIV. An RVR occurred in 39% of HCV-HIV-coinfected subjects and in 49% of HCV-monoinfected subjects. Sustained virologic response was achieved in 100% of subjects with RVR and in 56% of subjects without RVR. There was no difference in the positive predictive value of EVR for SVR between the HIV-infected and -uninfected subjects.

Finally, 3 abstracts from Spain evaluated the potential effect of nRTIs on HCV infection outcomes. There are conflicting data on whether abacavir-containing regimens reduce HCV response rates.

Mira and colleagues compared HCV treatment outcomes among 256 patients receiving either antiretroviral therapy with an abacavir plus lamivudine regimen or a tenofovir plus lamivudine or emtricitabine regimen (Abstract 1074). In the intention-to-treat analysis, 29% and 45% of subjects achieved SVR with the abacavir and tenofovir regimens, respectively (P = .02). The differences between SVR rates for abacavir and tenofovir were most pronounced among patients with high plasma levels of HCV RNA genotypes 1 and 4 and among patients who received daily as opposed to weight-based regimens of ribavirin.

Gonzalez-Garcia and colleagues evaluated the association between SVR and the use of tenofovir versus nontenofovir drugs among patients undergoing HCV treatment (Abstract 1076). In a model controlling for variables that predict SVR, the use of a tenofovir regimen and not a nontenofovir regimen was associated with SVR. As reported previously, zidovudine use, which often coincides with ribavirin dose reduction, was associated with lower rates of SVR. In this analysis, abacavir was not associated with lower rates of SVR.

Moreno and her group examined nRTI backbone as a predictor of SVR. They found that plasma HCV genotype, HCV RNA level, and fibrosis scoring were associated with SVR (Abstract 1075), and the use of abacavir versus tenofovir versus triple-nRTI had no effect on SVR. These seemingly conflicting data do not provide a definitive answer to the question of when to avoid using certain nRTIs, including guanosine analogues such as abacavir.

Opportunistic Infections and Timing of Antiretroviral Therapy

In a plenary presentation, Phillips highlighted that even in the developed world, presentation of HIV-infected patients to care at the time of severe im-

mune compromise concomitant with an opportunistic infection or malignancy remains common (Abstract 8). The optimal time to initiate antiretroviral therapy in such individuals is not known. Although immediate administration of antiretroviral therapy should slow HIV progression, the absence of randomized data creates concerns about toxicity, drug interactions, and more severe immune reconstitution syndromes and has led many clinicians to defer therapy until after resolution of an acute infection.

In ACTG A5164, 282 adults with an acute infection underwent randomization to immediate (within 2 weeks of the acute event) or deferred (4 weeks after randomization) antiretroviral therapy (Abstract 142). Persons with TB were excluded. Events that occurred within 30 days of randomization were not included in the analysis. The study population included 63% of patients with *Pneumocystis jirovecii* pneumonia, 13% with cryptococcal meningitis, and 10% with non-*Pneumocystis* pneumonia. Median entry CD4+ count was 29 cells/µL and plasma HIV RNA level was 5 $\log_{10}$ copies/mL. Immediate and deferred antiretroviral therapy started at a median of 12 days and 45 days, respectively. There was no difference between the 2 arms in the primary endpoint, which was defined as an ordered categorical variable of (1) death or AIDS progression, (2) no progression and plasma HIV RNA level above 50 copies/mL, and (3) no progression and plasma HIV RNA level below 50 copies/mL. However, the time to progression to AIDS or death was significantly shorter in the immediate than in the deferred antiretroviral therapy arm (P = .035).

Immediate antiretroviral therapy was associated with more rapid time to CD4+ count above 50 cells/µL and virologic suppression but more therapy changes. Immediate antiretroviral therapy was not associated with a greater risk for IRIS, toxicity, worse adherence, or hospitalizations. For patients with the spectrum of infection and illness included in this study, these data strongly support the early institution of antiretroviral therapy to prevent further HIV disease progression.

Immune Reconstitution

The spectrum and frequency of IRIS among children living in Africa has not been well characterized. Smith and colleagues reported findings from a South African cohort of HIV-infected children less than 2 years of age who were starting antiretroviral therapy with a lopinavir/ritonavir-based regimen (Abstract 75). Twenty-five of 148 children were classified as having IRIS events, and median time to first IRIS event was 15 days. Multiple events occurred in 5 children. Twenty of 25 children had BCG-vaccine-injection-site inflammation or adenitis with abscess. There were an additional 7 children with TB and other pneumonias and dermatologic events. Younger age and lower CD4+ cell count were associated with more frequent incidences of IRIS. Rabie reported on IRIS events associated with BCG vaccine in the Children with HIV Early Antiretroviral (CHER) trial, in which children underwent randomization at 6 weeks to 12 weeks of life to either early or deferred antiretroviral therapy, based on CD4+ cell counts or clinical criteria (Abstract 600). All children received BCG vaccination. Incidence of BCG-vaccine adenitis did not differ between the early (6.9%) and the deferred (10.4%) arms. No BCG-vaccine adenitis was observed in an HIV-uninfected contemporary cohort of children, but rates of local BCG-vac- cine reactions were similar between the 2 groups. There was 1 death attributed to BCG vaccine in the deferred antiretroviral therapy arm. These data demonstrate that BCG-vaccine adenitis is associated with antiretroviral therapy initiation, but that early antiretroviral therapy did not appear to increase risk of BCG-vaccine adenitis.

Additional References

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