NEW INSIGHTS INTO HIV-RELATED COMPLICATIONS

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EPIDEMIOLOGY

A consistent theme at this year's conference was the continued decline in rates of opportunistic infections (OIs) and AIDS-related deaths in the developed world. In a plenary session, DeCock from the Centers for Disease Control and Prevention (CDC) reported a 44% decline in the rate of AIDS deaths and a 12% decline in new AIDS cases for the first half of 1997, compared with 1996 **(Abstract L2).** DeCock discussed strategies for improving prevention efforts and identified improved treatment of sexually transmitted disease (STD) treatment and educational efforts targeted at HIV-infected individuals as priorities.

Evidence for improved treatment outcome was reported by several groups of investigators. Chiasson and colleagues from the New York City Department of Health reported a 33% decline in AIDS deaths for the first half of 1997, compared with 1996. This rate of decline was even greater than that observed in 1996 **(Abstract 9B).** The number of deaths declined for both men and women, and the greatest change compared to the prior year was seen among black women. In this subgroup there was a 30% decline in deaths compared with a 16% decline in the previous year. A population-based, case control study of AIDS-related deaths in New York conducted by Reggy et al identified the use of protease inhibitors as an important factor in reducing the risk of death **(Abstract LB7).** Researchers from the CDC-funded Adult Spectrum of Disease Project examined predictors of survival among more than 8000 adults receiving HIV care at United States sites, and identified the use of combination antiretroviral therapy, and prophylaxis of *Pneumocystis carinii pneumonia* (PCP) and *Mycobacterium avium complex* (MAC), as contributing factors **(Abstract 10).**

SPECTRUM AND RISKS FOR OPPORTUNISTIC INFECTIONS

As rates of OIs have declined there has been interest in the spectrum and presentation of specific diseases. At this year's conference, data were presented by several groups on the magnitude of the decline in rates of OIs. The French Clinical Epidemiology Database represents one of the most comprehensive sources of data on the rates of OIs **(Abstract 182).** Costagliola and colleagues from this group reported the declines in specific OIs, comparing the first semesters of 1996 and 1997 among nearly 60,000 HIV-infected adults enrolled in a prospective cohort study. Declines were seen in all types of AIDS-related conditions, but the greatest declines were observed in diseases that occur in patients with the most advanced disease.

Cytomegalovirus (CMV) disease was reduced by 80%, MAC by 73%, cryptosporidiosis by 70%, and esophageal candidiasis by 69%. Interestingly, bacterial pneumonia (1.7 cases per 100-patient-years) emerged as the most common complication observed during the first half of 1997 followed by esophageal candidiasis (1.0 case per 100-patient-years). Canadian investigators reported on trends in AIDS diagnoses between 1994 and 1996 and observed a decline in new AIDS diagnoses, but no change in the relative frequency of different infections and no change in the CD4+ cell count at which OIs occurred **(Abstract 179).** Several groups of US investigators **(Abstracts 180,183,184)** reported similar findings with declines in the rates of all OIs and a consistent finding of dramatic declines in CMV and MAC infections. Huang and colleagues reviewed the records of patients who developed PCP in San Francisco and noted the decline in PCP rates and identified that new PCP cases were occurring in patients who were either not on prophylaxis or non-adherent to therapy **(Abstract 185).**

Defining the relationship between routine laboratory markers such as viral load or CD4+ cell counts and the risk for OIs remains an area of active investigation. Investigators from the Multicenter AIDS Cohort Study examined risk factors for CMV, MAC, and PCP during the pre-therapy era and found that plasma viral load, CD4+ cell count, and prior AIDS diagnoses were all important factors but contributed differently to the risk of each infection. Data from ACTG 320, a trial comparing combination nucleoside analogue reverse transcriptase inhibitor (nRTI) therapy with a triple combination of zidovudine/lamivudine/indinavir, identified PCP, CMV, and MAC as the most common OIs occurring after the initiation of protease inhibitor therapy **(Abstract 257).** In this study, the OIs that occurred in the three-drug arm tended to occur early. Higher pretreatment plasma HIV RNA values, and failure of CD4+ cell count to increase or of HIV RNA level to decrease identified patients at continued risk to developing an infection. In other words, the patients who developed OIs on the three-drug arm were those

who were not responding to therapy. Data from the Hopkins cohort presented by Moore also reported no OIs occurring in patients on therapy with CD4+ cell counts greater than 200 cells/μL, supporting the notion that therapy-induced CD4+ cell count increases provide protection against clinical progression **(Abstract 184).**

A new area of investigation highlighted at this year's conference was the metabolic complications of HIV disease and HIV therapy. Abnormal accumulations of fat, both in the neck and shoulder region ("buffalo hump") and in the abdomen were described in small numbers of patients receiving protease inhibitor therapy by seven different groups **(Abstracts 407-413).** A common theme in these reports was a finding of normal cortisol levels and a range of abnormal triglyceride responses. One group identified this syndrome in a few patients who were not on protease inhibitor therapy **(Abstract 409),** while the others all focused on the syndrome in patients receiving protease inhibitors. A novel hypothesis put forth by Carr and colleagues suggested that sequence homology between the 12 amino acids spanning the catalytic site of the HIV protease and low density lipoprotein receptor-like protein might explain the interaction between protease inhibitor therapy and lipodystrophy. Clearly, further work is needed to define the cause of these abnormal fat depositions. Further data on hyperglycemia during protease inhibitor therapy were also reported. Keruly et al reported an incidence rate of 0.35 cases of severe hyperglycemia per 100 person months of protease inhibitor, and 0.52 cases of any degree of hyperglycemia during protease inhibitor therapy from the Hopkins cohort **(Abstract 415).** Six additional cases of hyperglycemia associated with protease inhibitor therapy were reported, and highlighted the fact any protease inhibitor can produce this effect, but the frequency of this metabolic abnormality is relatively rare **(Abstract 416).**

Clinical Presentation and Outcome of Opportunistic Infections

A more complete picture of the outcome of established OIs after the initiation of potent combination therapy is emerging. In a prospective follow-up of patients with CMV retinitis from San Diego, Freeman and colleagues noted a delay in time to CMV reactivation in individuals receiving potent antiretroviral therapy who had discontinued CMV maintenance therapy **(Abstract 757).** Specifically, 7 of 8 patients who discontinued CMV therapy had no reactivation after a median of 156 days (range, 92-558 days) of follow-up. The one patient who relapsed with CMV retinitis had experienced an increase in HIV RNA level and a fall in CD4+ cell count suggesting that failure to control HIV replication ultimately led to a loss of protection against CMV. Another important observation made in these patients with CMV retinitis who had responded to antiretroviral therapy was the finding of retinal inflammation with vitritis and macular edema suggesting an enhanced local immune response. This inflammatory response subsided with corticosteroid therapy. From this same group, Torriani described CMV-specific proliferative responses in vitro among 4 of the 8 patients. The patients with the most robust responses tended to be the ones in whom HIV replication was best controlled **(Abstract 747).** Taken together these findings suggest that pathogen specific immunity can be restored with combination antiretroviral therapy, but that an inflammatory component may be protracted and require corticosteroid therapy.

Inflammatory manifestations of MAC were reported during early protease inhibitor therapy at last year's conference. This year there was a report of acute worsening of symptoms of MAC with unusual manifestation (cutaneous nodules, subcutaneous granulomas) in patients with established MAC who began protease inhibitor therapy **(Abstract 726).** These syndromes were characterized as "reversal reactions" similar to what has been described in leprosy and were attributed to improved immunity. These complications improved with antiinflammatory therapy. Further evidence of restored immunity was demonstrated by the preliminary results of a study of discontinuation of MAC therapy conducted by Aberg and colleagues **(Abstract 729).** Four patients with prior disseminated MAC who completed 12 months of MAC therapy and who had a CD4+ cell count of at least 100 cells/μL and HIV RNA level less than 10,000 copies/mL after potent antiretroviral therapy discontinued MAC therapy. At an average of 6 months of follow-up after MAC treatment was discontinued, none of these patients had a recurrence of MAC disease. Further follow-up and a larger study are planned to determine the immunologic correlates of protection against relapse in patients with a history of established MAC.

Effect of Opportunistic Infections on HIV Disease

Reports on the effects of OIs on HIV disease extended observations presented at last year's conference. A transient increase in plasma HIV RNA level had been previously observed in patients developing PCP or bacterial pneumonia. Morris and colleagues presented a study on the natural history of HIV RNA levels in patients undergoing treatment for pulmonary tuberculosis in Africa **(Abstract 259).** These patients did not receive antiretroviral therapy. Plasma HIV RNA levels were 5.6, 5.7,

5.4 and 5.4 log copies/mL at months 0, 1, 3, and 6 of tuberculosis treatment, respectively. Seventy-four percent of patients had no change in viral load, 11% experienced an increase, and 15% had a decrease in plasma viral load. Although there were data for only 19 of the 115 patients at the 6 month time point, more robust data from the earlier time points demonstrated that plasma HIV RNA levels did not uniformly decrease in patients undergoing tuberculosis treatment, despite clinical improvement. This report suggests that treatment and improvement of OIs is not invariably associated with prompt reductions in HIV RNA levels. Immune responses to infection may have variable effects on the cellular activation necessary to sustain productive HIV infection.

A similar study evaluating effects of herpes simplex virus (HSV) on HIV RNA levels was presented by Schacter **(Abstract 259).** The investigators instructed a cohort of HSV-infected patients in Seattle. Specimens from the mouth and genital areas were obtained daily, and were cultured for HSV. Culture results were correlated with plasma HIV RNA levels. A subset of these patients were empirically treated with acyclovir after an 8 week period of observation to determine if the prevention of HSV shedding or clinical disease influenced plasma HIV RNA levels. Although one half of the patients were reportedly on dual-nucleoside therapy, none of the study participants was receiving potent antiretroviral therapy. Nine percent of patients had clinical herpes infection and 3% had subclinical shedding. Plasma HIV RNA levels were higher during these episodes. In addition, the incidence of HSV reactivation during the observation period (15%) and plasma HIV RNA levels were significantly higher than during the acyclovir treatment period, during which no cases of clinical HSV developed. If in fact HSV symptomatic or asymptomatic infection enhances HIV replication which in turn accelerates HIV disease progression, these results offer a potential explanation to the long debated observation that acyclovir offers a survival advantage in the HIV infected population.

Prevention and Treatment of OIs

Much less intensive research efforts are currently being directed at treatment and prevention of OIs in part due to the declining frequency of these infections and in part due to availability of effective regimens for many common infections. Nevertheless, as illustrated by several presentations at the Conference, there is ample room to improve the effectiveness of prophylaxis with new and simplified strategies, as well as to increase the therapeutic options for serious OIs such as CMV.

Short-course prophylaxis for tuberculosis was evaluated in a randomized trial presented by Gordin and colleagues **(Abstract LB5).** In this 6-year trial conducted in North and South America, 1583 HIV-infected subjects with reactive tuberculin skin tests were randomized to either a one year course of daily isoniazid 300 mg or a two-month course of daily rifampin 600 mg and pyrazinamide 20 mg/kg. The median CD4+ count was 454 cells/μL and the mean follow-up time was 3 years. Rates of confirmed or probable tuberculosis were identical in the two arms. There was no difference in mortality between the arms. Completion of therapy was significantly higher in the 2-month (80%) versus the 6-month (68%) regimen. These results suggest that a 2-month, two-drug regimen is as effective as the currently recommended one-year isoniazid course. This simplified regimen may be more amenable to programmatic implementation; however, rifampin cannot be administered with HIV protease inhibitors and thus short-course prophylaxis may be limited in some situations.

A novel approach to CMV therapy using the antisense oligonucleotide fomivirsen was reported by Muccioli and colleagues **(Abstract LB6).** In this study, AIDS patients with previously untreated zone 2 or 3 retinitis were randomized to immediate therapy or to deferred treatment. The median time to CMV retinitis progression was 71 days in the immediate therapy group versus 14 days in the deferred treatment arm. In general, fomivirsen, which must be administered via intravitreal injection, was well tolerated. Transient increases in intraocular pressure and mild inflammation were noted but were not dose-limiting. The optimal role of fomivirsen in new cases of CMV and disease due to relapse will need to be defined through additional clinical study.

Treatment of CMV neurologic disease was the focus of a presentation by the NEUROCMV group from Paris led by Katlama. This study represented the first prospective cohort study of patients with central nervous system (CNS) CMV infection. Patients with encephalitis or myelitis received combination induction twice-daily ganciclovir and foscarnet for 3 to 6 weeks, followed by once-daily maintenance therapy. Seventy-four percent of patients had partial or complete clinical response to this regimen, and 26% had CMV disease progression that led to death. Drug toxicities were very frequent and required at least temporary discontinuation of one of the drugs in 68% of patients. Only about half of the patients were still alive after 3 months of therapy, and the outcome was improved with longer duration of combination therapy. Despite the grim survival data, dual-therapy still appeared more favorable than historical monotherapy data. Potent antiretroviral therapy was not available during the course of this

study and one might expect this intervention to have a potentially favorable outcome on the natural history of this CMV disease.

KAPOSI'S SARCOMA

Recent advances in our understanding of the epidemiology of Kaposi's sarcoma (KS) were summarized by Ganem in a plenary session. First-generation serologic assays measuring antibody to antigen expressed on KS-associated herpesvirus (KSHV) latently-infected cells suggested that the seroprevalence is 1% to 2% in HIV-uninfected blood donors. Second-generation assays measuring an antigen expressed during lytic infection estimate slightly higher (ie, 6%) seroprevalence in this population. With this later assay, seroprevalence for KSHV was found to be 60% in a male gay population and 97% in a Baltimore cohort of patients with KS **(Abstract 439).**

In retrospective studies evaluating KSHV antibody in longitudinal cohorts, it appears that infection with KSHV precedes clinical disease and that the presence of antibody is associated with an increased risk of disease. In a San Francisco cohort of 185 HIV-infected men with evidence of KSHV infection, the probability of developing KS was 50 percent at 10 years **(Abstract 430).** Studies demonstrating that the risk of acquisition of KSHV infection is associated with the development of other sexually transmitted diseases argues that KSHV infection is acquired via sexual exposure. Pediatric KSHV was evaluated in a Zambian study. A seroprevalence of 39% was reported among Zambian women and the seroprevalence of KSHV was 29% in offspring of those women with KS. All three children with KS had mothers with KSHV antibody **(Abstract 526).**

KSHV infection targets spindle cells and the infection remains latent in most cases. It is estimated that only 5% of infected cells are in a lytic state. The preponderance of data would suggest that infection with KSHV is a necessary but not sufficient event in the pathogenesis of KS. Bais reported that a KSHV G protein coupled receptor is a viral oncogene that can induce cell signaling pathways to enable angiogenesis and cell transformation **(Abstract 527).**

There was sparse new information on therapeutic approaches for KSHV. Carr described a local inflammatory reaction at the site of cutaneous KS lesions after the initiation of ritonavir therapy. He speculated this reaction was due to improved immunity to KSHV **(Abstract S28).** Others reported improved long-term outcomes of KS associated with reductions of plasma HIV RNA levels and immune improvement produced by potent antiretroviral therapy **(Abstracts 431, 434).** Looney used polymerase chain reaction (PCR) assays to quantitate KSHV in peripheral blood mononuclear cells and found that higher KSHV burden in patients with visceral versus cutaneous-only disease, as well as a decline in KSHV levels after administration of chemotherapy **(Abstract 525).**

HIV IN WOMEN

This year's conference featured several poster sessions that focused on issues related to HIV-infected women. A number of groups reported on efforts to isolate and identify HIV from genital secretions **(Abstracts 709-714).** While there is no consensus on the optimal method for collecting or analyzing genital tract specimens, it appears that virus can be readily detected using a variety of methods. Comparisons of HIV genotypes isolated from genital tract and blood revealed conflicting results. Data from Shaheen et al **(Abstract 710)** identified a similar genotype among isolates from the blood and genital tract while Subbarao **(Abstract 708)** found differences in the major species of HIV in vaginal secretions compared to blood in 2 of 4 women studied suggesting local HIV expression in the genital tract. Further work including larger numbers of subjects will be needed to resolve this issue. Other important observations included the finding of a direct correlation between plasma and genital tract viral load **(Abstract 712),** a reduction in genital tract viral load during antiretroviral therapy **(Abstract 713)** and the suggestion of a correlation between plasma viral load and rates of cervical dysplasia **(Abstracts 716, 258).**

NEUROLOGIC COMPLICATIONS

Despite advances in HIV therapy, peripheral neuropathy remains a common problem that can be difficult to treat. One approach to treatment has included acupuncture, which was evaluated in a randomized trial reported by the CPCRA. In a four-year study, 250 patients were randomized to receive acupuncture or control points, amitriptyline versus placebo, or both in a factorial design. After 16 weeks of treatment no differences were seen in relief of pain with either acupuncture or amitriptyline compared with the placebo groups. The results of this study add acupuncture and amitriptyline to the long list of ineffective therapies for peripheral neuropathy.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the brain caused by the JC polyomavirus. In a comprehensive review, Major discussed the pathogenesis of PML and reviewed data suggesting that PCR for JC DNA from cerebrospinal fluid (CSF) correlates with a tissue diagnosis of PML in the brain in 75% of cases. Rates of PML appear to be declining along with other OIs. However, in the French series of OIs, the rate of decline for PML was the lowest over-

all **(Abstract 182).** Again at this year's conference, reports indicated that potent combination antiretroviral therapy including a protease inhibitor could improve the outcome of PML in some patients **(Abstracts 463, 464, 465).** The need for better specific therapy for PML was highlighted by a report from Piliero et al, who described two patients who developed PML while receiving protease inhibitor therapy and did not respond to changes in their antiretroviral therapy **(Abstract 466).** One agent that has been considered for PML therapy is cidofovir and a report of PML treated with cidofovir was presented by Matheson et al **(Abstract 457).** In this series of seven cases of PML diagnosed by CSF PCR or brain biopsy (all patients were on protease inhibitor-containing therapy) the response was variable. Three patients improved, two stabilized, and two worsened. These initial results suggest that further evaluation of cidofovir for PML may be warranted. ■

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