International AIDS Society-USA

IMPROVING THE MANAGEMENT OF HIV DISEASE

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HIGHLIGHTS OF A SYMPOSIUM SERIES:
An Advanced Course in Antiretrovirals, Prophylaxis, and the Treatment of Opportunistic Diseases

Health Care Worker Occupational Exposure to HIV

Occupational exposure of health care workers (HCWs) to HIV was discussed at the Chicago meeting by Harold A. Kessler, MD, from Rush-Presbyterian St Luke's Medical Center in Chicago. As related by Dr Kessler, education regarding occupational exposure to HIV and training in universal precautions for preventing exposure constitute the only effective methods for reducing risk of occupation-related HIV infection in HCWs.

According to Dr Kessler, approximately 2 million of the 5 to 6 million individuals involved in health care services in this country can be considered to be at risk for percutaneous or mucous membrane exposure to patient blood or body fluids. Although current epidemiologic data indicate that HIV infection among HCWs is predominantly related to nonoccupational factors, occupational exposure carries a quantifiable risk of transmission and transmission does occur in this setting. According to Dr Kessler, the risk of HIV transmission for a defined, high-risk exposure appears to have remained stable over several years of tracking by the Centers for Disease Control and Prevention (CDC) at approximately three to four cases per 1000 exposures (0.3% to 0.4%). It is estimated that 800,000 sharps-related injuries occur in HCWs each year; if it is estimated that approximately 1% of hospital admissions are HIV-infected, then it can be hazarded that as many as 24 HCWs per year become infected through such exposures (800,000 × .01 × .003). As related by Dr Kessler, risk differs accord-

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Introduction

The International AIDS Society-USA (IAS-USA) is a nonprofit organization dedicated to promoting communication and education in the field of HIV disease management and related disciplines. IAS-USA shares the goals and objectives of IAS, a worldwide institution involved in the organization of the International Conferences on AIDS.

Six IAS-USA-sponsored regional symposia under the program title "Improving the Management of HIV Disease: An Advanced Course in Antiretrovirals, Prophylaxis, and the Treatment of Opportunistic Diseases" were conducted in early 1994, the second consecutive year of the symposium program. The symposia are designed to provide physicians with an advanced-level review of the characteristics, treatment, and management of HIV disease. Program faculty members are regarded as authorities on their respective topics. The content of this publication is drawn from presentations made at the first two symposia, held in Chicago and Los Angeles, covering the topics of pathogenesis and

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Immunopathogenesis of HIV Infection

Immunopathogenesis of HIV infection was discussed at the Chicago meeting by Robert T. Schooley, MD, from the University of Colorado School of Medicine and University of Colorado Health Sciences Center in Denver, and at the Los Angeles meeting by Daniel R. Kuritzkes, MD, from the University of Colorado Health Sciences Center.

As related by both speakers, there is accumulating evidence that HIV continues to replicate in sequestered sites after acute infection and that host immunologic mechanisms are active in containing infection during the period of disease course traditionally characterized as one of clinical latency. Current evidence suggests that HIV infection is initially established in mucosal dendritic cells and other susceptible cells (eg, CD4+ lymphocytes and monocytes) and spread to the central nervous system, spleen, lymph nodes, and other lymphoid tissue. During acute infection, there is a burst of viral replication, during which infectious virus or infected cells can be detected in peripheral blood (Figure 1). Viral titers then decrease dramatically with development of specific immunologic responses.

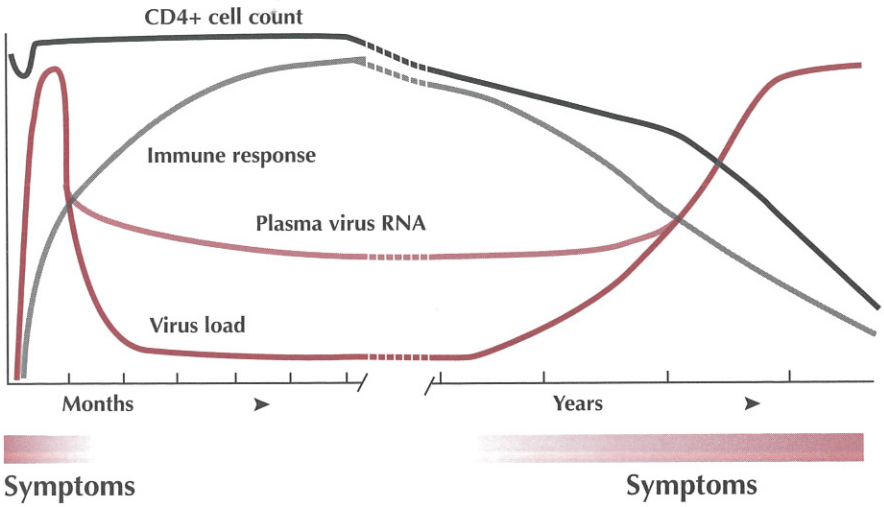

Figure 1. Hypothetical course of HIV infection in adults.

IAS-USA Improving the Management of HIV Disease

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Recent findings indicate that despite the apparent disappearance of infectious virus from the peripheral circulation, HIV replication continues in lymphoid tissue. This phenomenon has recently been demonstrated by a number of groups through histocytochemical studies of lymphoid tissue biopsies from patients at different stages of infection; further, the use of PCR and branched-DNA techniques has shown that high levels of HIV RNA in plasma persist after acute infection, indicating ongoing viral replication. After a variable period, there is a decline in overall immunity and HIV-specific immune responses, with virus again being detectable in the peripheral circulation; continued decline of immune function is associated with the onset of symptomatic illness.

As related by Dr Schooley, there are three primary immune mechanisms likely to play a role in containing infection. Neutralizing antibodies capable in vitro of rendering HIV less infectious recognize components of the viral envelope, with the

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Introduction *continued from page 1*

treatment of HIV disease, occupational risk of HIV exposure, maternal-fetal HIV transmission, and opportunistic disease prophylaxis. A second publication, based on the content of these and the subsequent symposia, will be largely devoted to treatment of opportunistic diseases and related management issues.

We are proud that the symposium program has again been designed and implemented without the influence of the three pharmaceutical companies providing the unrestricted educational grants: Bristol-Myers Squibb Company, Burroughs Wellcome Co., and Roche Laboratories. In joining to provide funding for this program, these companies show a commitment to supporting unbiased educational efforts at improving treatment of persons living with HIV disease; we hope that this trend becomes common practice within the pharmaceutical industry. It should also be noted that it is part of IAS-USA program protocol to request that all faculty members disclose affiliations, including grant/research support and financial involvement, with commercial organizations or companies that have interests related to the contents of the symposia program; this information is furnished in the program/abstract booklets distributed to symposium attendees and is available from the IAS-USA upon request.

Maternal-Fetal Transmission of HIV

A number of recent studies on mechanisms and prevention of in utero and intrapartum transmission of HIV infection were reviewed at the Los Angeles meeting by Yvonne Bryson, MD, from the Los Angeles Pediatric AIDS Consortium and the University of California at Los Angeles.

The rate of transmission of HIV from infected mothers to infants is estimated at 13% to 40%. Prospective study data suggest that 30% to 50% of infected infants acquire infection in utero, with there being evidence suggesting that most acquire it late in gestation; most of the remainder acquire infection intrapartum, with an added risk of transmission of 14% having been attributed to breastfeeding. A definition of in utero infection proposed by Dr Bryson and colleagues consists of positive viral quantitative co-culture within 48 hours of birth followed by subsequent positive co-cultures, with intrapartum infection being defined as negative co-culture within 48 hours of birth followed by positive co-cultures within 90 days. A study by Dr Bryson's group has shown that infants acquiring infection in utero have more rapid progression of disease, regardless of SI vs NSI HIV phenotypes, indicating that those with positive quantitative PCR or co-culture findings at birth should be targeted for early antiretroviral treatment and *Pneumocystis carinii* pneumonia (PCP) prophylaxis.

Transmitters vs nontransmitters in prospective study group

Dr Bryson and colleagues analyzed immunologic and virologic factors in a subgroup of infected mothers who were enrolled in a prospective study of vertical transmission of HIV; in the prospective study, transmission had occurred in 25 of 82 infants with known infection status (30.5%) and of 111 with any follow-up (22.5%). The subgroup in which risk factor analysis was performed consisted of 61 women, 58 of whom were asymptomatic, 19 of whom had received zidovudine during pregnancy and/or during labor and delivery, and six of whom were entered in the blinded ACTG protocol 076 (discussed below). The analysis showed significant differences between nontransmitters and transmitters with regard to measures of cell-associated HIV (ie, quantitative DNA PCR and quantitative co-culture), measures of cell-free HIV (ie, ICD p24 antigen and quantitative plasma culture), and CD4+ cell count. Further, it was found that the presence of autologous neutralizing antibody in the mother was associated with decreased risk of transmission. This finding was particularly significant among women transmitting infection in utero, only 11% who had measurable antibody titer (>10).

Citing studies by other groups, Dr Bryson related that the finding that a relatively homogenous viral population appears to be transmitted in maternal-fetal cases, as well as adult cases, may be due to the escape of the transmitted strain from neutralizing antibody. In one study indicating a correlation between autologous neutralizing antibody and reduced transmission, it was found that nontransmitters also had broader range of antibody against heterologous viral isolates; in Dr Bryson's analysis, sera from nearly all of the transmitting mothers assessed failed to neutralize the first isolate from the infected infant. Additional analysis showed that neutralizing antibody titers correlated significantly with maternal CD4+ cell counts and quantitative DNA PCR and co-culture findings. As related by Dr Bryson, the overall findings support the attempt at therapeutic intervention aimed at reducing maternal viral load or enhancing maternal autologous neutralizing antibody levels.

Absence of transmission by zidovudine recipients

A striking finding of the analysis was that no transmission of HIV occurred in the 19 infants of women receiving zidovudine, compared with 11 (32%) of 35 infants of women not receiving the drug. Zidovudine recipients had received dosages of 500 to 1000 mg/d during pregnancy and/or during labor and delivery on the basis of having CD4+ cell counts <500/μL or inclusion in a phase I study (ACTG 082; n = 6): 12 received oral zidovudine antepartum for a mean of 16.5 weeks and an intrapartum infusion; four received oral drug antepartum only for a mean of 17.8 weeks; three received only an intrapartum infusion. Three were enrolled in ACTG 076 and were not included in this analysis. As noted by Dr Bryson, the women receiving zidovudine had lower CD4+ cell counts than did the remainder of the patients, with the mean count being equivalent to that in the group of transmitters (402 vs 420/μL) and markedly lower than that in the other nontransmitters (803/μL).

Significant preventive effect of zidovudine in ACTG 076

As related by Dr Bryson, these findings have been followed by reporting of an interim efficacy analysis of the double-blind, placebo-controlled ACTG 076. In this multicenter trial, HIV-infected women at 14 to 34 weeks of gestation with no prior zidovudine treatment and CD4+ cell counts >200/μL were randomized to receive oral zidovudine 500 mg/d and a zidovudine infusion during labor and delivery or placebo, with their newborns receiving oral zidovudine for 6 weeks or placebo. At the time of interim analysis, with data current as of late December 1993, 477 of an anticipated approximately 800 women had been enrolled, with the group having a median age of 25 years, median CD4+ cell count of 550/μL and treatment having begun at a median gestational age of 26 weeks. A total of 364 infants had known infection status at the time of analysis; infection was observed in 13 (8.3%) of 180 in the zidovudine group and in 40 (25.5%) of 184 in the placebo group, a highly significant difference ($P = 0.00006$). No significant toxicity was observed in mothers or infants, with the zidovudine infants having a slight decrease in hemoglobin count that corrected spontaneously. As related by Dr Bryson, further evaluation of the data will include analysis of the characteristics of the zidovudine mother-infant pairs for whom transmission occurred, including viral load and viral phenotype, compliance with and duration of treatment, mode of delivery, and presence or absence of drug resistance, as well as examination of such issues as the contribution of postnatal zidovudine treatment to the findings. ■

Initiation of Antiretroviral Therapy

Initiation of antiretroviral therapy was discussed at the Los Angeles meeting by Paul A. Volberding, MD, from the University of California at San Francisco and San Francisco General Hospital, and at the Chicago meeting by John P. Phair, MD, from Northwestern University Medical School and Northwestern Memorial Hospital in Chicago.

As stated by both Dr Volberding and Dr Phair, existing data do not provide a single compelling answer to the question of when antiretroviral therapy is optimally begun. As noted by both speakers, the increasing evidence that HIV continues to replicate at high rates during the period of clinical latency supports the use of effective treatments very early in disease course; as noted by Dr Volberding, the improving understanding of HIV disease pathogenesis also indicates a need for reassessing the notion of 'early' disease, insofar as what has been considered early treatment in clinical trials – eg, therapy initiated at a CD4+ cell count of 500/μL – is actually occurring at a relatively late stage of infection. Despite the theoretical motivation for early intervention, the results of clinical trials have raised concerns regarding such a strategy using currently available treatment options. One major debate over the timing of initiation of existing treatments has been fueled by the reporting of apparently contradictory findings in asymptomatic patients in ACTG 019 and the Concorde study, which were reviewed by both Dr Volberding and Dr Phair.

Long term study of ACTG 019 patients

The initial ACTG 019 analysis, reported in 1990, showed that zidovudine was associated with a significant effect in delaying clinical progression of disease over approximately 13 months in asymptomatic patients with CD4+ cell counts <500/μL, with the optimal dosage being 500 mg/d; overall mortality was too low to hazard conclusions regarding any potential treatment effect. Subsequently, data available from an extended analysis of ACTG 019 patients, expected to be published in the fall of 1994, have indicated a durable benefit of early initiation of treatment. In this study extension, approximately 1000 patients who either initially received zidovudine 500 mg/d or switched to this regimen from the original placebo group or the zidovudine 1500 mg/d group were followed for an average of more than 2.5 years. It was found that patients initially receiving zidovudine had a significant delay in progression to AIDS or death compared with patients beginning treatment after approximately 13 months of no treatment on the placebo arm. No significant effect on mortality alone was observed. Although the effect on progression was observed for all initial zidovudine recipients combined, subgroup analysis showed that statistically significant benefit was confined to patients initially receiving the 500 mg/d dosage. Similarly, subgroup analysis showed that significant benefit of zidovudine treatment occurred only for the comparison of zidovudine patients and initial placebo patients beginning treatment with CD4+ cell counts >300/μL and that the benefit was confined to those zidovudine patients initially receiving 500 mg/d. Dr Volberding noted that results of the ACTG 019 substudy in 1600 asymptomatic patients with CD4+ cell counts >500/μL are likely to be available later this year.

Concorde

In the Concorde trial, results of which have been published since the time of the meetings, approximately 1800 asymptomatic patients with any CD4+ cell count received immediate zidovudine 1000 mg/d or the same treatment deferred until development of AIDS-related complex (ARC) or AIDS. Available data from an intent-to-treat analysis indicate that there has been no difference between immediate and delayed treatment groups with regard to progression to ARC or AIDS or mortality during approximately 3 years of follow-up, although average CD4+ cell count in the immediate treatment group remained approximately 30/μL higher than that in the delayed-treatment group.

A primary concern with the Concorde findings has been the change in the protocol made on the basis of the initial ACTG 019 findings whereby, approximately halfway through patient accrual, patients in the deferred treatment group were permitted to begin treatment at a CD4+ cell count of <500/μL. According to Dr Volberding, approximately one third of deferred treatment patients actually began treatment when they were asymptomatic, with these patients nevertheless not being considered to have begun therapy early in intent-to-treat analysis. According to Dr Phair, deferred group patients were receiving treatment for approximately 15% of the study duration and approximately 20% of the immediate-treatment group dropped out of the study, potentially confounding intent-to-treat analysis. Further, opportunistic infection prophylaxis, permitted in an amendment to the study, may have been more frequent in the deferred-treatment patients (given the lower CD4+ cell counts in the group), potentially confounding survival analysis. A retrospective analysis of a Concorde study patient group comparable to the patient population in ACTG 019 has shown benefits of early treatment comparable to those observed in ACTG 019 over a similar period.

Among the questions posed by Dr Volberding regarding the Concorde findings was whether analysis on other than an intent-to-treat basis would reveal benefit of early treatment. He also suggested that the data raise the questions of whether treatment was continued for too long – in the face of evidence that nucleoside analogues provide a time-limited benefit – and whether optimal treatment might involve using available agents in sequence or combination after an optimal period of monotherapy.

- ***ACTG 019 extension: benefit of zidovudine for ≥2.5 years in >300 CD4+ cells/μL subgroup***
- ***Concorde shows no benefit of early treatment after three years: methodologic problems confound interpretation?***
- ***Initiation of treatment: driven by virology, changes in lab markers, CD4+ threshold, symptoms?***
- ***Treatment strategies should reflect variability of patient course and treatment response***

Current options

With regard to the range of currently available treatment options, Dr Volberding identified zidovudine as the most active drug in initial monotherapy based on comparative studies with didanosine and zalcitabine in previously untreated patients; he pointed out, however, that as-yet unpublished data from ACTG 116A indicate that although zidovudine was superior to didanosine in delaying mortality in zidovudine-naive patients, the contrary was true in patients with 8 to 16 weeks of prior zidovudine.

The relative benefits of beginning treatment with combination therapy currently are being evaluated in ACTG 175, results of which will not be available for some

time; Dr Volberding suggested that some rationale for this approach may be provided by findings in ACTG 155, in which patients with baseline CD4+ cell counts of 150 to 300/μL, the highest stratum in the study, were found to have delayed disease progression with the combination of zidovudine and zalcitabine compared with either alone, although overall results showed no benefit of combination treatment.

With regard to when to begin antiretroviral therapy, Dr Volberding enumerated four options based on available evidence: (1) at any stage of HIV disease – eg, based on pathogenesis data and some data from European-Australian Collaborative Group protocol 020 (see below); (2) when laboratory studies indicate rapid deterioration regardless of CD4+ cell count – eg, based on declining cell count, increased HIV p24 antigen, or HIV titer; (3) at an arbitrary CD4+ cell count regardless of clinical state – eg, 500/μL, as supported by ACTG 019, or 200/μL, as supported by the Veterans Affairs Cooperative Study Group protocol 298; or (4) when clinical condition deteriorates regardless of laboratory values – eg, based on the current Concorde study data. He suggested that the decision should be one jointly made by the patient and physician on the basis of discussion of evidence supporting a given approach and with the acknowledgement that the courses of disease and responses to treatment in individual patients are likely to be highly variable.

Table 1. National Institute of Allergy and Infectious Diseases Consensus Conference HIV Therapy Guidelines

Patients Naive to Antiretroviral Therapy

CD4+ cell count >500/μL
- Continued observation (see text for potential exceptions)

CD4+ cell count 200-500/μL, asymptomatic
- Continued observation, OR
- Zidovudine monotherapy: 600 mg/d in three divided doses

CD4+ cell count 200-500/μL, symptomatic
- Zidovudine monotherapy

CD4+ cell count <200/μL, symptomatic or asymptomatic
- Zidovudine monotherapy

Patients Tolerating Initial Antiretroviral Therapy

CD4+ cell count >300/μL
- Continued zidovudine monotherapy

CD4+ cell count <300/μL
- Didanosine monotherapy, OR
- Continued zidovudine monotherapy

Patients Intolerant of Zidovudine

CD4+ cell count >500/μL, asymptomatic
- Discontinue antiretroviral therapy
- Continued observation

CD4+ cell count 50-500/μL
- Alternative monotherapy; the majority of the panel would select didanosine

Patients Experiencing Progression on Zidovudine

CD4+ cell count 50-500/μL
- Alternative monotherapy, OR
- Combination therapy

Patients With CD4+ Cell Count <50/μL

Intolerant of zidovudine
- Didanosine monotherapy, OR
- Zalcitabine monotherapy, OR
- Discontinue antiretroviral therapy

Experiencing progression on zidovudine
- Didanosine monotherapy, OR
- Zalcitabine monotherapy

Adapted from Sande et al, JAMA 1993;270:2583

As stated by Dr Volberding, the decision to initiate treatment early could be made with more confidence if rational strategies for long-term treatment were available and if there were promise of availability of additional effective agents; he cited the ability of quantitative PCR and branched-DNA methods to measure ongoing viral replication, and outlined a potential strategy for optimizing response to treatment based on use of such techniques. In this strategy, therapy could be started at a predetermined CD4+ cell count or HIV load and load monitored regularly, with treatment being altered after a specified time by adding a drug (or drugs) or switching drugs if no decline in viral load is observed; therapy would be continued so long as viral load remained suppressed, with alteration occurring when the viral concentration increased by a specified amount. With regard to newer potentially useful agents, he identified stavudine (d4T), 3TC, nevirapine, delavirdine, and several candidate protease inhibitors as agents about which more should be known within the year.

NIAID Guidelines

In addressing the issue of optimal use of currently available options on the basis of currently available data, Dr Phair presented the recently published recommendations of a National Institute of Allergy and Infectious Diseases State of the Art panel, of which he was a member; the recommendations are shown in Table 1.

The recommendation of zidovudine 600 mg/d in three divided doses as first-time treatment was supported by results of comparative trials with didanosine (ACTG 116A) and zalcitabine (ACTG 114); the recommendation of tid dosing was supported by clinical experience indicating enhanced compliance without obvious changes in efficacy or safety. Although the panel recommended monitoring in asymptomatic patients with CD4+ cell counts above 400/μL, it also indicated that exceptions might include individuals with laboratory changes suggesting disease progression. As pointed out by Dr Phair, the European-Australian Collaborative Group study results indicate a benefit in delaying CD4+ cell count decline and progression to clinical symptoms, but no effect on mortality, in patients with CD4+ cell counts above 400/μL; he noted that findings in the ACTG 019 substudy in patients with cell counts greater than 500/μL would be likely to provide further guidance with regard to earlier initiation of treatment.

Debate over whether treatment should be instituted in asymptomatic patients with lower cell counts (200 to 500/μL) included balancing concern over whether such treatment uses up a time-limited benefit of currently available agents and the belief that earlier treatment can serve to prolong the period of asymptomatic disease. With regard to the recommendation that zidovudine be continued or a switch to didanosine instituted at CD4+ cell counts less than 300/μL, data supporting the switch are primarily those from ACTG 116B/117. In this trial, didanosine 500 mg/d was found to have a significant effect in delaying AIDS-defining events and death compared with continued zidovudine in advanced-disease patients with a median of 13.5 months of prior zidovudine; Dr Phair stated that it remains unclear at what point zidovudine efficacy may begin to wane in comparison with didanosine. Although the majority of panelists indicated that didanosine would be preferable for alternative therapy in patients not tolerating zidovudine on the basis of greater experience with the agent, some suggested that zalcitabine might be preferable on the basis of relative ease of administration. Combination therapy was cited as an option in patients experiencing progression on zidovudine; Dr Phair stated that a better idea of the role of combination therapy awaits the results of ongoing trials and that some available data indicate that tolerance of combination treatment in patients with cell counts <100/μL is relatively poor.

Variability of disease course and treatment response

Dr Phair emphasized that proposed treatment strategies are complicated by the variability in course of disease and response to treatment. Observational study data presented by Dr Phair showed a wide

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Continuing Benefit from Antiretroviral Therapy

Strategies for continuing benefit from antiretroviral therapy were discussed at the Chicago meeting by Thomas C. Merigan, Jr, MD, from the Stanford University School of Medicine, Stanford, California.

According to Dr Merigan, such factors as genotypic resistance to antiretroviral agents, presence of SI vs NSI variants, and viral burden must be taken into account in accurately determining patient response to treatment and guiding ongoing therapy. His presentation focused on recent investigations of development of antiretroviral resistance and the relationship of genotypic resistance to disease progression.

Genotypic resistance in monotherapy

Using a double-nested PCR technique to detect the HIV RT codon 215 mutation conferring zidovudine resistance in patients from ACTG 019 and ACTG 016 who were treated at their institution, Dr Merigan and colleagues initially found that patients with virus exhibiting this mutation had experienced a 50% decline in CD4+ cell count over the course of 3 years, whereas counts had remained stable in those with wild type virus, and that appearance of the mutation preceded decline in CD4+ cell count by several months. It was also determined that the appearance of mutant strains in serum preceded PCR quantitated increase in viral burden, with viral load in patients with wildtype virus in PBMCs and mutant virus in serum being comparable to that in patients with wildtype virus in both PBMCs and serum and a marked increase in viral load being observed when mutant virus was present in both PBMCs and serum.

A subsequent investigation assessing the impact of presence of the codon 215 mutation and SI strains in zidovudine-treated patients showed that each was a significant independent predictor of both CD4+ cell count decline and increase in viral burden (Table 2). For the next three years, patients with neither viral characteristic exhibited a slight increase in CD4+ cell count and those with both characteristics had the greatest viral load and the greatest decline in CD4+ cell count. Dr Merigan stated that whereas resistance genotype can now be readily assessed via PCR, determination of SI vs NSI phenotype via culture still requires several weeks; he suggested that investigation of the viral envelope changes associated with the SI property might ultimately lead to a more rapid molecular biologic identification technique.

Dr Merigan also presented data from 70 patients showing that the didanosine resistance mutation at codon 74 was present in mixed form in 10% of patients within 8 weeks after switching from zidovudine to didanosine treatment, with the proportion of patients exhibiting either a mixed population or all mutant virus increasing to nearly 60% by 24 weeks. More than 85% of these patients had a codon 215 mutation at the time of the switch to didanosine; during didanosine therapy, virus in 28% of those with this mutation reverted to wild-type codon 215 within 24 weeks. Analysis of CD4+ cell count trajectory during 24 weeks of didanosine treatment showed that appearance of the codon 74 mutation was associated with a precipitous decline; analysis of viral burden by quantitation of serum HIV RNA showed that patients developing the mutation had a 2.69-fold increase compared with a 1.66-fold increase in those without the mutation.

Genotypic resistance in combination therapy

Patterns of genotypic resistance are more complicated in the setting of combination therapy. In ACTG 143, asymptomatic patients with CD4+ cell counts of 200 to 500/μL, half of whom had received <12 months prior zidovudine therapy and half of whom had received no prior antiretroviral therapy, received either didanosine alone or a didanosine-zidovudine combination. Resistance traits in didanosine monotherapy recipients were limited to the RT codon 74 mutation. In some patients, combination therapy was associated with the development of the same zidovudine resistance mutations associated with zidovudine monotherapy – ie, at codons 215, 70, 41, 67, and 219, with the codon 74 mutation being seen in only a small proportion during the first year of treatment. However, six combination therapy patients followed for up to 2 years developed mutations at codons 151, 62, 75, 77, and 116; isolates with these mutations were resistant to both didanosine and zidovudine despite the absence of the codon 74 and 215 mutations and exhibited decreased susceptibility to zalcitabine and stavudine (d4T), agents not previously encountered by the patients.

According to Dr Merigan, it appears that these multidrug resistance mutations result from the selective pressure on the virus to avoid development of concomitant codon 74 and codon 215 mutations, which has been associated with reversion to susceptibility to zidovudine; Dr Merigan noted that a compensatory reduction in zidovudine resistance for virus with the codon 215 mutation has also been observed with concomitant mutations conferring resistance to NNRTIs or to the nucleoside analogue 3TC. Measurement of viral burden (plasma HIV RNA) over 2 years in the combination-therapy patients showed that it generally was maintained after an initial drop in patients with drug-susceptible and culture-negative strains, whereas increases were generally observed in patients with zidovudine-resistant, multidrug-resistant, or SI strains. According to Dr Merigan, the time of increase in patients with the multidrug resistant strains has correlated with the appearance of the codon 151 mutation in mixed form, with full-blown failure of drug treatment occurring once the mutant form has become the predominant species. Dr Merigan also presented data from these patients indicating that although an increase in viral load measured as HIV RNA in plasma corresponded with decline in CD4+ cell count, it did not necessarily occur prior to cell count decline.

Monitoring genotypic resistance and SI vs NSI phenotype in clinical trials

In summarizing these data, Dr Merigan stressed that the behavior of virus in response to treatment must be known to guide further treatment, citing develop-

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Table 2. CD4+ Cell Count Change and Viral Burden According to Proviral DNA Codon 215 Genotype and SI vs NSI Phenotype in Patients Receiving Zidovudine

	Wildtype 215 NSI	*Wildtype 215 SI*	*Mutant 215 NSI*	*Mutant 215 SI*
No. of patients	10	6	10	6
CD4+ cell count change (cells/μL)	+28	–66	–160	–252
% CD4+ cell count change	+10%	–16%	–41%	–54%
HIV copies/10^6 CD4+ cells	467	1380	2510	21,480
HIV RNA copies/mL plasma	43,650	60,230	100,460	210,000

Opportunistic Infection Prophylaxis

Robert L. Murphy, MD, from Northwestern University Medical School in Chicago, reviewed recent information regarding prophylaxis of PCP, toxoplasmosis, and fungal, cytomegalovirus (CMV), and Mycobacterium avium-complex (MAC) infections.

Dr Murphy stressed that a number of major issues remain to be confronted in the area of prophylaxis, including whether prevention is associated with survival advantage compared with treatment of acute infection, whether prevented disease is being replaced by infections of other types with no overall survival advantage, and the effect of prophylaxis-induced resistance on delivery of effective therapy for acute infection.

PCP and toxoplasmosis

As related by Dr Murphy, MACS data show that the prevalence of PCP as presenting AIDS diagnosis has declined to the 15% to 20% range since the introduction of prophylaxis; at the same time, there have been increases in the prevalence of MAC infection, wasting syndrome, CMV disease, and esophageal candidiasis. Dr Murphy noted that these data leave unresolved whether the decline in PCP prevalence has been accompanied by prolonged survival. According to these data, approximately 25% of patients ultimately develop PCP despite prophylaxis.

Trimethoprim-sulfamethoxazole (TMP-SMX) remains the agent of choice, although optimal dosage remains a matter of debate, followed by dapsone or aerosolized pentamidine. It is now generally believed that TMP-SMX prophylaxis for PCP also provides protection from toxoplasmosis. The recent published data reviewed by Dr Murphy support superiority of TMP-SMX over other treatment options for PCP prophylaxis and superiority of TMP-SMX and dapsone-pyrimethamine over aerosolized pentamidine in prevention of toxoplasmosis; however, demonstration of survival benefits remains elusive. In a Dutch study, 215 patients received TMP-SMX at either 80/400 mg daily or 160/800 mg daily or 300 mg aerosolized pentamidine monthly as primary prophylaxis. After mean follow-up of 264 days, PCP had developed in none of the TMP-SMX patients and in 11% of pentamidine patients ($P = 0.002$). Although baseline toxoplasmosis serology was not performed, it was observed that three pentamidine patients and no TMP-SMX patients died of toxoplasmosis. In a Spanish study, 166 patients without history of PCP or toxoplasmosis were given double-strength TMP-SMX bid three times weekly or dapsone 100 mg/week plus pyrimethamine 25 mg/week, dosages characterized as unorthodox by Dr Murphy. During mean follow-up of 380 days, PCP developed in 3.7% of TMP-SMX recipients and 15.2% of dapsone-pyrimethamine recipients ($P = 0.01$). No differences in survival or incidence of toxoplasmosis were observed. TMP-SMX was less well tolerated than dapsone-pyrimethamine. In a French study, 349 patients, 75% of whom were *Toxoplasma* seropositive, received dapsone 50 mg/d or aerosolized pentamidine. PCP rates in the two groups were comparable; however, the relative risk for toxoplasmosis in the pentamidine group was 2.37. In ACTG 021, 310 patients received either TMP-SMX (1 double strength tablet qd) or aerosolized pentamidine as secondary PCP prophylaxis. PCP recurred in 11.4% of TMP-SMX recipients and 27.6% of pentamidine recipients over the course of 18 months, with the CD4+ cell count-adjusted relative risk of PCP in the pentamidine group being 3.25 ($P < 0.001$). No difference in survival rates were observed. Toxicity requiring a switch of therapy occurred in 27% of TMP-SMX and 4% of pentamidine patients. A trend to decreased toxoplasmosis rates was observed in patients who continued to receive TMP-SMX.

Dr Murphy also presented the as-yet unpublished results of ACTG 081, in which 842 patients with CD4+ cell counts <200/μL received one TMP-SMX double-strength tablet bid, dapsone 100 mg/d, or aerosolized pentamidine for primary PCP prophylaxis. As noted by Dr Murphy, the TMP-SMX and dapsone dosages were higher than those commonly used in current practice. Dr Murphy also suggested that the crossover scheme, in which patients exhibiting intolerance were crossed between the TMP-SMX and dapsone arms and thence to the pentamidine arm or randomized from the pentamidine arm to another study arm, may have produced a negative bias for pentamidine and otherwise made some of the findings difficult to interpret. Analysis of outcome by original treatment showed no major differences among the TMP-SMX, dapsone, and pentamidine groups with regard to PCP rates (9.8%, 8.6%, and 14.0%, respectively, at 24 months, and 17.6%, 16.5%, and 20.7%, respectively, at 36 months), all-cause mortality rates (19.7%, 23.2%, and 23.2%, respectively at 24 months, and 42.7%, 48.2%, and 48.2%, respectively, at 36 months), or toxoplasmosis rates, although analysis among patients beginning with CD4+ cell counts <100/μL showed a significant PCP-preventive effect for the systemic treatments ($P = 0.03$). Switching of treatment occurred significantly less frequently among patients beginning treatment with pentamidine ($P < 0.0001$), with crossover due to intolerance occurring in 50.7%, 41.3%, and 12.0% of TMP-SMX, dapsone, and pentamidine recipients, respectively. Dr Murphy emphasized that only 7% of the failures overall were actually receiving TMP-SMX at the time of development of PCP. Fever, rash, and granulocytopenia were more common among patients receiving the systemic treatments; however, despite the frequency of intolerance of TMP-SMX, use of aerosolized pentamidine was not associated with advantages in terms of disability, utilization of health care services, or health-related quality of life. According to Dr Murphy, one of the conclusions to be drawn from the study is that higher doses of TMP-SMX and dapsone are not well tolerated; he also maintained that such dosages may not be necessary.

- ***Recent PCP prophylaxis studies tend to support superiority of TMP-SMX: parenteral pentamidine successful in patients not tolerating other treatments***
- ***Fluconazole associated with significant prevention of fungal infection, including invasive disease and cryptococcosis, but no mortality benefit in ACTG 981***
- ***Uveitis associated with rifabutin MAC prophylaxis***

With regard to other treatment options, Dr Murphy related that a retrospective review of the use of parenteral, primarily intramuscular, pentamidine in 96 patients intolerant of TMP-SMX, dapsone, and aerosolized pentamidine showed that only three cases of PCP occurred during 350 months of primary prophylaxis in 47 patients and 426 months of secondary prophylaxis in 49 patients; eight significant but non-life-threatening adverse reactions (sterile abscesses, glucose intolerance, hypotension, and hypoglycemia) were reported. According to Dr Murphy, findings showing lack of tolerance of clindamycin in clindamycin-pyrimethamine regimens indicate unsuitability of the regimen for prophylaxis. Azithromycin also is not

considered a likely candidate for use. Atovaquone, which recently has been approved for treatment of mild to moderate PCP, is to be compared with dapsone in a large-scale prophylaxis study in TMP-SMX-intolerant patients; Dr Murphy cautioned that since atovaquone is poorly absorbed in its current formulation, requiring administration along with a high-fat snack, prophylactic use is difficult and probably requires full treatment doses.

Fungal infection

Cryptococcosis develops in 5% to 10% of AIDS patients not receiving prophylaxis and generally occurs at CD4+ cell counts <100/µL. In ACTG 981, involving 428 of the patients enrolled in ACTG 081 PCP study, patients were randomized to fluconazole 200 mg/d or clotrimazole troches 10 mg five times daily for prevention of fungal infection. Fluconazole was associated with significant reductions in the incidence of invasive fungal disease (9 vs 23 patients) and cryptococcosis (2 vs 15 patients); the 24-month risk of invasive disease was 2.8% in the fluconazole group and 9.1% in the clotrimazole group, and the CD4+ cell count-adjusted relative risk for invasive disease in the latter group was 3.25. Fluconazole was also associated with significant reductions in the incidence of esophageal candidiasis (3 vs 20 patients) and superficial fungal infection (10 vs 36 patients). No differences in mortality were observed, however. Dr Murphy maintained that such findings leave it unclear whether fluconazole prophylaxis should be utilized, given the absence of survival benefit, the low lethality of properly managed first-episode cryptococcosis, and the potential for development of resistance to an otherwise highly useful agent; he stated, however, that if prophylaxis is contemplated, fluconazole appears to be the azole of choice, since it does not have the absorption problems associated with ketoconazole or itraconazole, and suggested that fluconazole prophylaxis would be optimally begun at CD4+ cell counts below 100/µL and at a dosage lower than that investigated the study (eg, on the order of 100 mg/d).

CMV infection

Recent data indicate that approximately 40% of patients with CD4+ cell counts below 50/µL develop CMV retinitis within a 27-month period. Currently, no agents suitable for prophylactic use are available. Trials of an oral form of ganciclovir are under way, and study of oral forms of foscarnet has been initiated in the United Kingdom. One European-Australian study evaluating high-dose acyclovir (3200 to 4000 mg/d) found no protective effect against CMV disease, but documented an increase in survival in acyclovir-treated patients; according to Dr Murphy, recent MACS data may provide some support of an acyclovir-associated survival benefit.

MAC infection

MAC infection has been observed to occur in more than half of patients within 24 to 30 months following diagnosis of AIDS. On the basis of two studies involving approximately 1000 patients showing that rifabutin provided significant protection from development of MAC bacteremia, it was recommended in June 1993 that prophylaxis at a dosage of 300 mg/d be considered for patients with CD4+ cell counts below 100/µL. Azithromycin and clarithromycin have activity against MAC and a large-scale trial comparing rifabutin plus clarithromycin and clarithromycin in MAC prophylaxis currently is under way. In noting that many practitioners are already using clarithromycin for prophylaxis, Dr Murphy suggested a more prudent current course might be to reserve the agent for treatment.

As noted by Dr Murphy, daily doses of rifabutin should not exceed 300 mg given recent reports of uveitis in higher-dose trials. Although uveitis was not observed at dosages of at or below 600 mg/d in initial studies, 23 cases have been reported in a Canadian treatment study in which patients are receiving rifabutin 600 mg/d, clarithromycin 1000 mg bid, and ethambutol 15 mg/kg/d; uveitis also has been observed in 11 of 1215 patients enrolled in an ongoing US ACTG/Community Programs for Clinical Research on AIDS trial. The uveitis has been reported to resolve with drug withdrawal or dose reduction. It is believed that there may be a bidirectional drug interaction between clarithromycin and rifabutin that increases blood levels of both agents. Further, it is known that fluconazole may increase rifabutin levels by as much as 80%, warranting caution in the concomitant use of these agents. ■

Future Directions for Anti-HIV Therapy

Future directions for anti-HIV therapy were discussed at the Chicago meeting by Douglas D. Richman, MD, from the University of California San Diego and the San Diego Veterans Affairs Medical Center, and at the Los Angeles meeting by Steven A. Miles, MD, from the University of California Los Angeles.

According to Dr Richman, the conclusion beckoning from the current status of antiretroviral therapy is that combination therapy will be required to improve effectiveness of treatment and that agents in addition to the nucleoside analogues are needed. Dr Richman identified the NNRTIs and protease inhibitors as classes of newer agents that show promise of utility.

NNRTIs: nevirapine

As stated by Dr Richman, data on the several NNRTIs under development indicate that the compounds have potent anti-HIV activity but rapidly select for drug resistance. Data from a group of patients receiving nevirapine at Dr Richman's institution show that resistance appears rapidly in virtually all patients, regardless of whether the drug is administered alone or in combination with zidovudine, and is evident as early as 1 week after the start of treatment. Several specific RT mutations associated with resistance have been identified, with those observed under monotherapy generally differing in distribution from those observed under combination therapy with zidovudine. Typical responses to low-dose nevirapine monotherapy have consisted of an impressive increase in CD4+ cell count within a week of treatment but a return to baseline levels within 1 month due to acquisition of drug resistance. However, the use of higher doses in an attempt to achieve plasma levels sufficient to exceed viral resistance – an attempt encouraged by the absence of dose-limiting toxicity at lower doses – has shown that many patients have markedly prolonged response to high-dose monotherapy. The median CD4+ cell count in patients with higher baseline CD4+ cell counts receiving a dosage of 400 mg/d increased about 75 cells/µL for 9 to 12 months. A similar maintenance of decreases in p24 antigen levels and PCR quantitated HIV RNA levels has been observed in patients.

Dr Richman emphasized that such a response is not seen in all patients receiving a higher dosage and that factors predictive of such response remain undetermined. Nevertheless, he stated that these findings and data from another group utilizing monotherapy and combination therapy in newborns indicate that the agent may have a role in some patients. The rationale for use despite the observation of resistance is that

- *Nevirapine: rapid development of resistance, maintained response in some patients at 400 mg/d despite resistance*
- *Protease inhibitors: activity, resistance, design-based and other potential strategies*
- *Early experience with Ro31-8959*

a drug selecting for virus with reduced susceptibility may be clinically effective if it has a therapeutic index and pharmacokinetic properties sufficient to allow achievement of plasma concentrations exceeding the viral susceptibility and if there are constraints on the mutability of the virus. Dr Richman suggested that there is at least some evidence that the mutability of HIV is limited. He also stated that any potential exploitation of apparent limitations of mutability in the context of combination therapy remains the object of further study. This principle should also apply to the utility of protease inhibitors in the face of the inevitable development of some level of resistance.

Protease inhibitors

As explained by Dr Miles, protease inhibitors act by blocking the activity of the HIV aspartyl protease, which is responsible for cleaving precursor gag and gag/pol polyproteins into the functional proteins p17, p24, p9, protease, RT, and integrase; there is also evidence that protease inhibitors may inhibit the viral preintegration complex from gaining entry to the host cell nucleus. A potential advantage of protease inhibitors over nucleoside analogue RTIs, for example, is that they appear to be active in chronically infected host cells, as well as acutely infected and activated cells.

Among the types of protease inhibitors that have thus far been developed are C_2-symmetric inhibitors and transition state mimetic inhibitors, analogues of the protease substrate that substitutes nonhydrolyzable elements for the amide bonds normally cleaved by the enzyme. Such inhibitors bind to the active site of the enzyme, preventing production of active proteins and resulting in immature, noninfectious virus. As related by Dr Miles, characteristics of the C_2 symmetric inhibitor, A80987, as an example of this class of agent, include activity against both HIV-1 and HIV-2 at nanomolar to micromolar concentrations, absence of cellular toxicity, and activity against both zidovudine-susceptible and zidovudine-resistant strains. Sterilization of HIV in culture has also been observed with sufficient concentrations, although the mechanism of this phenomenon remains unclear. Another class of inhibitor is represented by the nonpeptidyl inhibitor DM323; this cyclic urea compound prevents polyprotein cleavage by excluding the water molecule used by the protease to actually perform cleavage. Characteristics of the compound include very low molecular weight, as well as the spectrum of activity and absence of cellular toxicity observed with A80987.

Clinical experience has thus far been greatest with the oral transition-state analogue Ro31-8959. In two small early-phase trials in patients with advanced (CD4+ cell count 50 to 250/μL) or early untreated (≤500/μL) HIV disease, maintenance of CD4+ cell counts over baseline levels and positive slopes of CD4+ counts were observed with a 600 mg tid dose, the highest dosage tested, over a 16-week treatment period (other dosages were 25, 75, and 200 mg tid). In patients with advanced disease, the 600 mg dosage was associated with a median maximum CD4+ cell count increase from baseline of 56/μL at week 2 and a median increase of 17/μL at week 16. In patients with early disease, the 600 mg dosage was associated with a median maximum increase of 104/μL over baseline at week 6 and a median increase of 36/μL at week 16. Of adverse effects observed, only abnormal LFTs were considered possibly related to Ro31-8959 treatment; no dose-related adverse effects were observed. In an additional study, untreated patients with advanced disease (CD4+ cell count ≤300/μL) received zidovudine 200 mg tid alone or combined with Ro31-8959 75 mg, 200 mg, or 600 mg tid or Ro31-8959 600 mg tid alone for 16 weeks. All groups exhibited maintenance of median CD4+ cell counts over baseline for 16 weeks, with Ro31-8959 alone appearing to be more active than zidovudine alone and the greatest responses being observed in the combination groups receiving the highest Ro31-8959 dosages. Median increases from baseline CD4+ cell counts associated with the regimens at 16 weeks were 24/μL for zidovudine alone, 32/μL for Ro31-8959 alone, and 24/μL, 73/μL, and 56/μL for the combination regimens including 75 mg, 200 mg, and 600 mg Ro31-8959 doses, respectively; respective median maximum increases from baseline were 66/μL, 113/μL, 91/μL, 121/μL, and 147/μL. Response of at least a 50/μL or 50% increase in cell count maintained for at least 4 weeks was observed in eight of 12 patients in the highest-dose combination group, five of 12 in the middle-dose combination group, three of eight in the lowest-dose combination group, four of 12 in the zidovudine monotherapy group, and five of 13 in the Ro31-8959 monotherapy group.

Some data are also available for the compound L735,524, which is active against multiple HIV strains at nanomolar concentrations and possesses the potential advantage of having greater absorption than Ro31-8959. According to Dr Miles, the latter agent has bioavailability of approximately 5% to 6%, whereas that of L735,524 is approximately 17%. Findings in a small group of p24 antigen-positive patients have included suppression of p24 antigen to undetectable levels at week 6, decrease in viral RNA by PCR and bDNA measurements with return to baseline values at approximately 12 weeks, and a dramatic increase in p24 antibody levels. Large scale trials of the agent have been put on hold, with the development of resistance being suspected. Some small scale trials involving higher doses and combination treatment are ongoing.

Dr Miles stated that resistance is likely to be a generic problem with the protease inhibitors. The HIV protease point mutations that have thus far been associated with resistance include: codon 8, 32, 46, and 82 mutations in vitro conferring 4- to 100-fold reduction in sensitivity to A80987; codon 48 and 90 mutations in vivo conferring ≥60-fold reduction in sensitivity to Ro31-8959; and codon 82 mutation in vitro conferring 4- to 5-fold resistance to DM323. According to Dr Miles, although no in vitro resistance to L735,524 was found during initial development, cross resistance with the agent has since been demonstrated by several groups. However, Dr Miles maintained that one of the advantages posed by the protease inhibitor approach is the ability to design or redesign specific agents based on needed properties. In this regard, he indicated that once mutations associated with in vivo resistance are identified, it may be possible to develop or exploit inhibitors without cross resistance for use in combination. Further, it may be possible to produce directed mutations, with use of agents that force known mutations to occur being followed by use of agents specifically designed to be active only when such mutations are present. Other areas of protease inhibitor research identified by Dr Miles include: potential use of the agents as natural vaccines (exploiting a new antibody response observed with protease inhibitor adminis-

continued on page 15

Exposure *continued from page 1*

ing to type of exposure, with hollow core needle exposure carrying greater risk than solid core needle exposure and much greater risk than mucous membrane or skin exposure. He noted that he is unaware of any documented cases of solid core needle transmission; several cases of transmission via mucous membrane or skin exposure have been documented.

With regard to documented cases of transmission, CDC statistics as of September 1993 indicate a total of 39 cases of confirmed seroconversion following occupational exposure, including 15 lab technicians, 13 nurses, 5 physicians, 1 pathologist, and no surgeons. Of these cases, 35 were associated with percutaneous exposure and 36 with exposure to blood. In most cases, inoculation was due to unexpected movement by patient or coworker. Needle recapping injury, a common form of high-risk exposure prior to institution of educational efforts at limiting this type of accident, has been cited in only six of the cases. In addition, 81 cases in which HCWs were found to be HIV seropositive on first postexposure testing have been reported and are considered highly suspicious for occupational transmission given the absence of other identifiable risk factors.

Study of exposure: inoculation without infection?

Recent findings by Dr Kessler and colleagues, including investigators at the National Cancer Institute, suggest that the low overall risk of HIV transmission following high-risk exposure may not be due to absence of actual inoculation of the virus. In this study, peripheral blood mononuclear cells (PBMCs) of eight HCWs having needlestick exposure to HIV and nine HCWs having similar needlesticks involving patients not infected with HIV were regularly evaluated for specific T-helper lymphocyte response to five immunogenic synthetic HIV-1 gp160 peptides (T_1, T_2, Th4.1, P18-IIIB, and P18-MN). T-helper cellular response was measured as interleukin-2 (IL-2) production; positive response was defined as at least a 4-fold increase in IL-2 production from antigen-stimulated PBMCs for at least two of the peptides. During up to 64 weeks of follow-up, positive response, suggesting prior priming of T-helper cells with an antigen at least related to the HIV proteins, was observed in six of eight HCWs with HIV exposure and in one of nine controls ($P < 0.008$); overall, there were six responses to each of the five antigens in the former group and one response to three of the five in the latter group. All of the HIV-exposed HCWs remain free of HIV infection according to HIV antibody, p24 antigen, polymerase chain reaction (PCR), and viral culture findings. Kinetics of the cellular response indicate a lag time of 8 to 12 weeks, followed by a peaking of immunologic reactivity and waning of reactivity back to baseline levels, suggesting that no permanent immunologic memory is induced. It is unknown whether the observed T cell responses are associated with a protective effect.

Comprehensive management plan

Dr Kessler outlined a comprehensive program for management of HIV exposure comprising the major components of preexposure education, immediate postexposure care, postexposure counseling, and long-term postexposure care; elements of the program are shown in Table 3. With regard to preexposure education, Dr Kessler stressed the importance of effective teaching and utilization of universal precautions as the primary mechanisms for reducing risk of transmission; he predicted that some type of high-risk procedure training would eventually be mandatory.

In summarizing the role of antiviral prophylaxis in postexposure care, he stated that there have been 13 documented failures of zidovudine prophylaxis, which is widely used in this setting, including five cases of massive exposure; in a subsequent question and answer period, it was noted that in one European case, intravenous zidovudine started within 1 hour of exposure failed to prevent infection. In the absence of an extremely large-scale controlled trial, there currently is no way of obtaining definitive evidence of efficacy; animal models of zidovudine prophylaxis have yielded inconclusive results. At least two cases of transmission of zidovudine-resistant HIV are known; as noted by Dr Kessler, since there may be a greater likelihood of encountering zidovudine-resistant HIV in the hospital setting, with patients being likely to have advanced disease and to have undergone prolonged therapy, zidovudine may not be an optimal prophylaxis choice. According to Dr Kessler, no systematic data on the prophylactic use of didanosine, zalcitabine, interferon, or drug combinations are available. ■

Table 3. Program for Management of Occupational Exposure to HIV

Preexposure education
- Preemployment education
- Institution area-specific education
- Postemployment education (annual retraining mandated by Occupational Safety and Health Administration)
- Universal precautions instruction
- High-risk procedure training
- High-risk procedure certification

Immediate postexposure care
- Reporting of exposure
- Risk assessment
  - Type of exposure
    - Needlestick: hollow vs solid
    - Sharp injury
    - Mucous membrane exposure
    - Abnormal skin exposure
  - Type of fluid or tissue
- Reeducation for risk
- Baseline serologies: HIV, hepatitis B, hepatitis C, syphilis
- Antiretroviral prophylaxis?
  - *Current status* –
    - Zidovudine
    - – Animal models inconclusive
    - – 13 postexposure failures in humans
    - – In CDC series, adverse reactions occurred in 75% of 265 HCWs receiving regimens ranging from 1000-2000 mg/d for 2 weeks to 1000-1200 mg/d for 6 weeks; 31% completed prescribed course
    - – Zidovudine-resistant HIV transmission reported
    - Alternatives
    - – No data available on didanosine, zalcitabine, interferon, or combinations

Postexposure counseling
- Assurance of confidentiality
- Safer-sex counseling
- Other preventive measures: proper management of body fluids, hygiene, etc
- Psychosocial support services

Long-term postexposure care
- Clinical monitoring
  - Serial HIV serology for 6-12 months
  - Monitoring of antiretroviral prophylaxis
- Ongoing psychosocial support
- Treatment of infection

Immunopathogenesis

continued from page 2

principal neutralizing domain being the V3 loop of the third hypervariable region of the envelope; other epitopes recognized include the CD4 binding domain. A second mechanism is the activity of antibodies mediating antibody-dependent cellular cytotoxicity, in which cells expressing viral envelope components are marked for lysis by killer cells. The third mechanism, one thought to be of particular importance in anti-HIV response, is activity of cytotoxic T (CD8+) lymphocytes (CTLs), which recognize and destroy autologous cells presenting viral antigen in the context of major histocompatibility complex molecules. The significant HIV-specific activity of CTLs has been demonstrated in a number of in vitro studies over the past several years, and serial evaluation of CTL activity in patient blood indicates that HIV-specific activity declines as disease progression occurs and as measurable viral load increases.

Dr Schooley stated that although a number of groups have demonstrated that HIV-specific CTL activity is marked during primary infection, it is unlikely that CTL activity alone is effective in containing primary infection, with it being more likely that there is a coordinated humoral and cellular response; neutralizing antibodies have been found to be present in primary infection, as well. CTLs are found in the peripheral circulation, with less being known about whether they are also present in fixed lymphoid tissue. As related by Dr Schooley, although the exact components

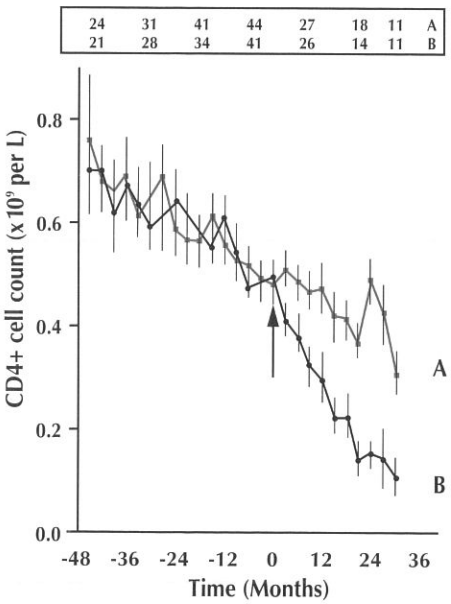

Figure 2. Mean CD4+ cell count related to HIV-1 phenotype conversion. A = no development of SI variants (ie, NSI strains). B = conversion to SI phenotype. Adapted from Koot et al, Ann Intern Med 1993;118:681.

and relative contributions of the immune response remain to be defined, the potency of the response is suggested by the 3 to 4 log decline in peripheral blood viral titer that is typically observed after acute infection and the maintenance of this degree of suppression for prolonged periods.

An important implication of the ongoing replication of HIV in lymphoid tissue is that genotypic diversity of the viral population may begin to develop at an early stage. As related by Dr Schooley, retroviruses have a high mutation rate, appearing to have a replicative error rate 10^9 times greater than that of mammalian cells. He speculated that the increasing diversity of viral genotypes might overmatch the capacities of the HIV-specific immune responses. Important consequences of the ability of the virus to achieve great genotypic diversity are drug resistance and the appearance of a highly cytopathic syncytium-inducing (SI) HIV phenotype.

SI variants

Early infection is characterized by predominantly non-syncytium-inducing (NSI) virus; these strains grow relatively slowly and are found in CD4+ lymphocytes but may preferentially grow in monocytes. In later infection, syncytium-inducing (SI) strains, which are more highly cytopathic and lymphotropic, can be isolated in many patients; the SI property appears to be correlated with specific alterations in the viral envelope. Accumulating data indicate that conversion to the SI phenotype is associated with a more rapid decline in CD4+ cell count and disease progression (Figure 2).

According to Dr Kuritzkes, transmission of SI variants appears to be less likely than transmission of NSI virus, with these variants developing later in infection course and possibly accounting for a minority of the viral population at any given time in those patients in whom they are present. However, a number of cases of transmission of SI phenotype have been documented, with more severe symptomatic primary infection and more rapid clinical progression being observed. Dr Kuritzkes indicated that ongoing studies by several groups include investigation of the potential role of SI virus in those patients exhibiting rapid progression of disease during the initial years of infection. He maintained that it will be important for antiretroviral treatment trials to evaluate for the presence of SI strains in enrolled patients to ensure that findings in comparison groups are not confounded by disproportionate inclusion of patients exhibiting the phenotype.

Resistance

In discussing antiretroviral resistance, Dr Kuritzkes emphasized findings indicating that resistance mutations for different reverse transcriptase inhibitors (RTIs) interact in a relatively unpredictable and complex manner and suggested that the detection of phenotypic or genotypic resistance does not yet have clear-cut ramifications for clinical management. In discussing interaction of resistance traits, he presented data showing that: switching to didanosine treatment in the case of high-level zidovudine resistance can result in eventual resistance to didanosine and reversion to zidovudine susceptibility; development of resistance to the non-nucleoside RTI (NNRTI) delavirdine is associated with increased susceptibility to the NNRTI nevirapine; and mutations conferring resistance to zidovudine are associated with reversion to susceptibility to the experimental nucleoside RTI 3TC. Dr Kuritzkes emphasized that it remains unclear whether and how such modulation can be utilized in the clinical setting.

After noting that zidovudine resistance develops slowly and progressively, with time to detection of resistance after start of treatment being markedly prolonged in patients with early disease compared with those with late disease, Dr Kuritzkes also maintained that assessment of the impact of zidovudine resistance on disease progression currently is confounded by such factors as declining CD4+ cell count, increasing viral load, and emergence of SI variants, each of which may be as important in determining disease progression as the presence of resistance. In this regard, he presented data from patients from AIDS Clinical Trials Group (ACTG) protocol 116B/117, in which patients with advanced disease who were receiving zidovudine either continued on zidovudine or were switched to didanosine. An analysis reported by D'Aquila *et al* at the IX International Conference on AIDS in Berlin showed that high-level zidovudine resistance at baseline was a significant risk for disease progression and for death. The increased risks of progression and death conferred by high-level zidovudine resistance remained significant even after adjustment for other risk factors, including baseline CD4+ cell count, presence of SI virus, and diagnosis of AIDS at baseline. Notably, the increased risk of progression and death was independent of the effect of didanosine treatment – ie, patients receiving didanosine showed benefit regardless of whether they harbored zidovudine-re-

sistant virus.

Dr Kuritzkes stated that despite the advent of PCR techniques for detection of specific mutations identified with resistance, which are much less time-consuming and cumbersome than phenotypic assays, findings such as those in the ACTG 116B/117 patients suggest that it is premature to utilize such techniques for managing at least nucleoside analogue antiretroviral treatment on the basis of detection of resistance.

Viral quantitation techniques

As explained by Dr Kuritzkes, there are significant drawbacks to several techniques traditionally used to assess patient prognosis and response to treatment – eg, p24 antigen assay and quantitative viral culture. Newer techniques of potentially greater value, particularly in light of the improved understanding of disease pathogenesis, include the immune-complex-dissociated (ICD) p24 antigen assay and PCR and branched-DNA techniques for quantitating viral RNA in plasma. The ICD p24 assay measures antigen bound with antibody that may escape detection by the standard p24 assay; thus far, it has proven to be useful in diagnosing HIV infection in very young infants, in whom positive HIV antibody testing is equivocal due to presence of maternal antibodies.

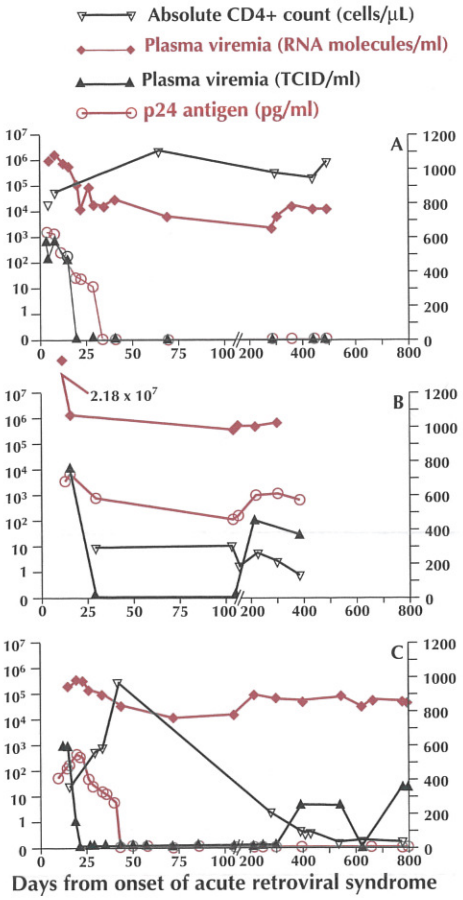

Figure 3. Relationship of CD4+ cell count, plasma HIV RNA, p24 antigen, and plasma culture after acute infection. Adapted from Piatak et al, Science 1993;259:1749.

The PCR and branch-DNA techniques differ in that the former involves increasing the number of RNA copies present to detectable levels, whereas the latter involves amplification of the RNA signal from a single molecule; the techniques have been found to yield comparable results in identical plasma specimens. According to Dr Kuritzkes, although these techniques still require rigorous clinical validation and currently may be too expensive or complex for widespread use, they are being rapidly adopted in the clinical trial setting. Investigation thus far has shown that plasma RNA quantitation with these methods inversely correlates with CD4+ cell count. Further, it has been demonstrated that the amount of RNA remains strikingly elevated in acute infection after disappearance of culturable virus or p24 antigen from the peripheral blood (Figure 3). Dr Kuritzkes suggested that continued detection of viral RNA in this setting is correlated with ongoing replication in lymphoid tissues. Whether the circulating RNA is from infectious virus or incomplete portions of the virus is unknown and is currently being investigated. He stated that such techniques may thus provide a means of assessing both extent of viral replication at early stages of infection and effect of treatments in suppressing replication. He maintained that the goal of treatment is to suppress and maintain suppression of replication with the hope of preventing progression or lengthening the duration of clinical latency and suggested that the ability to accomplish this might improve in the next several years with the advent of newer antiretroviral agents.

Rationale for immunologic treatment strategies

As related by Dr Schooley, immune-based therapeutic strategies are motivated by evidence that host immune response is a relatively powerful antiretroviral mechanism and the likelihood that the status of such response is a very important determinant in progression of disease. He noted that given the ability of immune mechanisms to contain infection for a prolonged period, augmentation of the response might present the possibility of significantly affecting HIV replication over the long term.

Among immune-based strategies currently under investigation is nonspecific immunomodulation with cytokines, involving either upregulation of those with antiviral or immunomodulatory effects or downregulation of those associated with deleterious effects in infection pathogenesis. With regard to the former approach, the ability of recombinant IL-2 and polyethyleneglycosalated IL-2 (PEG-IL-2) to expand CD4+ cell populations in vivo is currently being assessed. IL-12 has been found to augment CTL and natural killer cell proliferation and activity in vitro and to have a synergistic effect with IL-2 in CD8+ and CD4+ (TH1) cell proliferation; it is currently being evaluated in a single-dose tolerance trial. With regard to the latter approach, thalidomide and pentoxifylline have been shown to downregulate production of tumor necrosis factor, which upregulates HIV replication in vitro; however, initial study of pentoxifylline has indicated an inability to reduce tumor necrosis factor production to physiologic levels and no apparent effect on viral replication. An additional approach is based on exploiting a distinction between T cells that produce cytokines associated with cellular immunity (TH1 cells) and those producing cytokines associated with humoral immunity (TH2). It is believed that TH1 and TH2 populations are maintained in balance via counterregulatory mechanisms in most clinical situations. However, in the case of early HIV infection, there is a predominance of TH1-like responses (eg, HIV-specific CTL activity), with these responses diminishing over time and later disease being characterized by a predominance of TH2-like responses and excessive humoral activation; it has been found that some of the cytokines involved in TH2 responses stimulate HIV replication. According to Dr Schooley, a potential mechanism for maintaining predominance of TH1 cells may be to administer relatively physiologic doses of TH2 cytokines to invoke the counterregulatory mechanisms, although this is controversial.

Additional approaches to augmenting immune response include bolstering HIV-specific responses with passive immunotherapy employing monoclonal antibodies or sensitized effector cells that have undergone ex vivo expansion. According to Dr Schooley, a number of monoclonal antibodies with good HIV neutralizing activity have been developed and attempts at improving techniques for expanding CD8+ cell and HIV-specific CTL populations ex vivo are ongoing. He maintained that it is of importance that the clinical investigations of these modalities be conducted not only as therapeutic trials per se, but as tests of the relevant hypotheses regarding disease pathogenesis and host response. ■

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Future Directions *continued from page 9*

tration by augmenting immune response with IL-4 to further increase antibody response or IL-2 to augment CTL activity); potential immunologic priming of the host with gene therapy to recognize protease mutations (with subsequent treatment with the mutation-inducing agent resulting in enhanced immunologic clearance of virus); focus on development of small-molecule agents (eg, DM323) that would be easier and cheaper to design and produce; and investigation of combination therapy – eg, with protease inhibitors and NNRTIs. Dr Miles noted that protease inhibitors currently are under development at more than 15 pharmaceutical companies.

Other promising agents

Other promising agents under development include nonimmunosuppressive cyclosporin analogues. As related by Dr Richman, recent studies have shown that the gag proteins of the HIV ribonucleic protein complex bind to host cell components and are active in transporting the complex to the host cell nucleus, with a similar phenomenon likely occurring in transport of virion components from the nucleus and cytoplasm to the budding membrane. The finding that cyclosporin can inhibit these processes has led to identification and development of nonimmunosuppressive analogues – eg, SDZ 811 – as potential antiretroviral agents. SDZ 811 has been found to bind to cyclophilin in the host cell and inhibit the HIV gag-cyclophilin interaction, inhibiting transport of reverse transcripts to the nucleus at micromolar concentrations. Further, it inhibits the infectivity of virions at later steps of replication at 10- to 100-fold lower concentrations. Marked inhibitory effects have been observed in vitro in CD4+ lymphocytes and in monocytes at achievable drug concentrations.

Another class of compounds that have been shown to have potent activity in vitro is the bicyclams. These agents prevent uncoating of the virus after cell entry; the exact mechanism of action of the agents remains unclear, although it is known that they do not bind to the virion. Dr Richman anticipated that some of the bicyclams may enter development within the year. Other types of agents that have engendered interest but that are not likely to enter advanced phase clinical trials in the near future include the antisense oligonucleotides, ribozymes, and integrase inhibitors. ■

Initiation *continued from page 5*

variety of patient courses and associated prognoses after the start of zidovudine treatment; stratification of best and worst responses based on a baseline CD4+ cell count of 300/μL and CD4+ cell count increase or decrease of at least 50/μL, serum neopterin level changes, and increase or decrease in physical symptoms over 1 year of treatment indicated a 17-fold difference between best-case and worst-case response in risk for mortality within the following year. CD4+ cell count data from patients who had experienced rapid cell count declines for 5 to 6 years of follow-up prior to the start of zidovudine treatment similarly indicate heterogeneity of cell count response in association with time to clinical progression to AIDS: some exhibited continued steep cell count decline and rapid progression to AIDS, some exhibited reduced rate of cell count decline and progressed to AIDS after 2 years, and some exhibited relative maintainence of cell counts and did not progress to AIDS during the observation period. Dr Phair emphasized the variability of course of disease by presenting a histogram of 6-month changes in CD4+ cell count among individuals in a MACS cohort followed by his group for 8 years. Although most patients have decreases in cell count, with the majority experiencing 6-month decreases of 30 to 40/μL, some 15% have exhibited increased cell counts over the course of infection (Figure 4); similar observations have been made in San Francisco cohorts and in an Australian transfusion cohort. According to Dr Phair, although there is some evidence that such patients exhibit reduced viral load, how they differ from other patients in their response to infection remains unexplained. ■

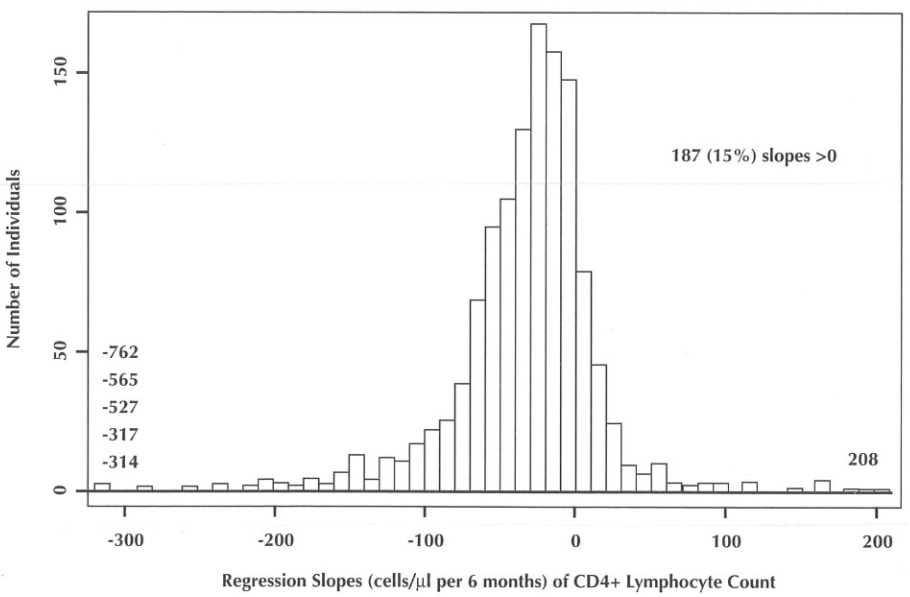

Figure 4. CD4+ cell count changes over 6-month intervals in patients with HIV infection followed for up to 8 years. Figure from Kirby et al (submitted for publication).

Upcoming Events from Yokohama*

The UCLA AIDS Institute is sponsoring a clinical research symposium, Treatment of HIV Disease: Advances and Future Challenges. In Yokohama, August 12. The symposium will be broadcast live by satellite to 10 US sites (Aug. 11). Registration required for admission to the symposium or satellite sites. Contact: Call 800-535-1307 for site information, registration or copies of proceeedings. Educational grant support: Roche Laboratories.

Live interactive videoconferences from Yokohama presenting community and medical updates will be broadcast to US sites on Aug. 9 and 11. Contact: World Health Communications at 800-433-4584 (or 800 521-1177 in New York State) for site information and registration. Educational support: Burroughs Wellcome Co.

*These programs are not affiliated with IAS-USA

Continuing Benefit *continued from page 6*

ment of specific resistance and the presence of SI strains as the two major pathways by which failure of treatment currently occurs. He maintained that resistance markers and viral load quantitation will become increasingly important in performance of drug trials. In this regard, he described the recently initiated ACTG 244, in which patients with CD4+ cell counts of 300 to 600/μL who have received zidovudine for less than 2 years and in whom viral DNA and RNA is free of the codon 215 mutation will be followed for development of the mutation. At the time that mutation is observed, patients will be randomized to receive didanosine plus zidovudine, didanosine plus zidovudine plus the NNRTI nevirapine, or continued zidovudine. CD4+ cell count, viremia, HIV proviral load, SI vs NSI phenotype, and codon 215 mutation status will be followed to determine if immunologic and virologic deterioration can be blocked by early detection of the mutation and early alteration of therapy. He stated that virologic information also is to be used in a phase I/II study of the protease inhibitor Ro31-8959 to be conducted at his institution. Assessment in this trial will include identification of the HIV protease codon 48 and 90 mutations associated with protease inhibitor resistance, identification of phenotypic resistance, and PCR quantitation of plasma HIV RNA. According to Dr Merigan, after the initial 24 weeks of study, patients will be followed and have protease inhibitor administration resumed if there is an increase in PCR quantitated viral burden. ■

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