International AIDS Society-USA

IMPROVING THE MANAGEMENT OF HIV DISEASE

VOLUME 2, NUMBER 2 AUGUST, 1994

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

Pathogenesis of HIV Infection

The pathogenesis of HIV infection was discussed at the New York meeting by David D. Ho, MD, from the Aaron Diamond AIDS Research Center and New York University School of Medicine, New York. Dr Ho's presentation focused on research on the immune response to acute HIV infection, the role of viral load and syncytium-inducing (SI) HIV phenotype in disease progression, and viral and immune studies in long-term nonprogressors.

Immune response in symptomatic acute infection

As related by Dr Ho, a number of studies in patients with symptomatic acute HIV infection employing culture, polymerase chain reaction (PCR)-based, or branched-DNA techniques have shown that such infection is characterized by a massive burst of viremia that is rapidly cleared in apparent association with the onset of host immune response, with the clearance being followed by seroconversion. Although virus remains detectable in plasma and peripheral blood mononuclear cells (PBMCs) on a number of quantitative techniques, the decline in viral load in the circulation is precipitous. Investigations by Dr Ho and colleagues to determine characteristics of response resulting in the dramatic decline in viral load in the peripheral blood have included evaluating patients for antibody response and cytotoxic T (CD8+) lymphocyte (CTL) activity. With regard to the former, Dr Ho presented data from a patient showing that whereas antibody capable of cross-neutralizing divergent standard strains of HIV did not appear in the patient's blood over the course of 1 year of follow-up, functional antibodies response to the patient's own isolates appeared at 3 months after infection, lagging behind the initial decline in viremia (Figure 1). In contrast, evaluation of specific CTL response directed at cells expressing HIV envelope or core proteins or polymerase products in

continued on page 3

CONTENTS

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 as well as an update on the ongoing clinical research in the field. Program faculty members are regarded as authorities on their respective topics. The contents of this publication are primarily drawn from presentations made at four symposia, held through April of 1994; the summarized presentations were on the topics of pathogenesis of HIV disease, treatment of HIV disease, antiretroviral drug resistance, HIV disease in women, tuberculosis, treatment of fungal infections, developments in treatment of cytomegalovirus disease, and diarrheal illness.

We are proud that the symposium program has again been designed and implemented without the influence of the three pharmaceutical companies providing unrestricted educational grants: Bristol-Myers Squibb, 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 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 on request from IAS-USA.

IAS-USA Improving the Management of HIV Disease

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Pathogenesis *continued from front page*

this patient and in the small number of additional patients who have been examined has shown that CTL precursors are present in the blood as early as presentation with acute illness, with CTL activity peaking during the first month of infection.

Dr Ho emphasized that the recent findings of persistent lower-level viremia in the circulation and of ongoing viral replication in lymphoid tissue during the asymptomatic period of disease following primary infection underscores the need to consider HIV infection as a persistently active viral infection, providing rationale for early treatment intervention given drugs of suitable effectiveness. He noted that there is also a good theoretical rationale for drug trials during acute infection to determine whether such early treatment could dampen the magnitude of initial viremia, potentially having a beneficial impact on subsequent course of disease. Given the high replication and replicative error rates of HIV, this initial burst could produce many HIV variants in blood cells and in the lymphoid compartment; the quantity of variants could have a significant impact on the subsequent course of infection, with greater diversity likely being associated with greater probability of proportions of the viral population evading the effects of the host immune response or antiretroviral agents.

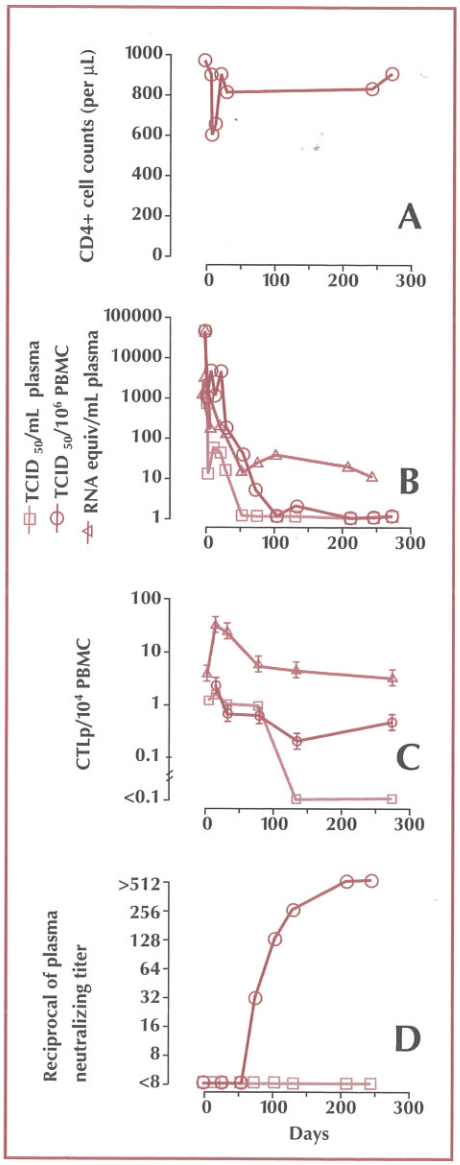

Figure 1. Viral load and immune response in patient during and after symptomatic acute infection. A, CD4+ cell count. B, HIV-1 in blood by plasma culture (□), PBMC culture (○), and branched-DNA (Δ) results. C, CTL precursor response to gag (○), pol (Δ), and env (□) viral epitopes. D, Serum neutralizing antibody response. HIV strain P1 is a patient isolate (○); strains IIIB and JR-FL are laboratory strains (□). TCID-50 = 50% tissue culture infectious dose; Day zero = the day the patient presented with symptoms. Adapted from Koup et al. J Virol. 1994;68:4650-4655.

Characteristics of viral load and syncytium-inducing (SI) phenotype in disease progression

As related by Dr Ho, recent findings indicate that rapid progression of HIV disease is associated with increased viral load in blood and tissue and, in approximately 50% of patients, switch in viral phenotype from non-syncytium inducing (NSI) to SI. Noting that the characterization of SI vs NSI is based on the behavior of virus in MT2 tumor cell line assays, Dr Ho described findings in studies performed by his group in an attempt to characterize the in vivo biologic properties of the SI phenotype. Investigation of samples from patients in whom the phenotypic switch was observed to occur has indicated that there is a gradual transition in ability of the virus to replicate with increasing efficiency in vitro in both CD4+ lymphocytes and monocyte-macrophages. This shifting in replicative efficiency correlates with the conversion to SI phenotype. After showing data from individual patients who, in the context of increasing viral load, exhibited dramatic CD4+ cell count declines in association with phenotypic conversion to SI type, Dr Ho related findings in a SCID-Hu mouse model indicating that SI-type virus exhibits an increased pathogenic effect. In these studies, SCID-Hu mice were engrafted with human fetal thymic tissue to permit HIV infection. The tissue was subsequently infected with a preconversion NSI isolate and a later SI isolate from one patient and an isolate from a long-term nonprogressor with HIV infection. Infection with the SI strain was associated with dramatic reduction of CD4+ cells, marked abnormality of CD4:CD8 ratio, and dramatic increase in p24 antigen level compared with effects in tissue infected with the other strains. Dr Ho noted that a series of more basic studies has validated the SCID-Hu model, which could prove to be of great utility in other pathogenesis studies.

Studies in long-term nonprogressors

Dr Ho related findings in studies that he and colleagues have been performed in a group of long-term nonprogressors in an attempt to characterize mechanisms that may contribute to the apparent enhanced control of infection in these individuals. The initial criteria used to define long-term nonprogression were HIV infection for at least 12 years, with seroconversion documented by history or stored serum samples, absence of symptoms, and normal and stable CD4+ cell counts. Eight subjects studied consisted of seven males, two with IV drug use and five with homosexual intercourse as route of transmission, and one female with heterosexual intercourse as route of transmission; ages ranged from 37 to 46 years and durations of infection ranged up to 15 years. According to Dr Ho, no distinctive HLA class I or II patterns have been identified in these individuals. No infectious virus has been detected in quantitative plasma culture in any of the subjects. Branched-DNA quantitation of plasma viral RNA has shown that six have levels below assay detection limit (1<10,000 copies/mL) and two exhibit levels lower than those observed in subjects with progressive infection. One subject readily yielded virus in culture of PBMCs, exhibiting a load of approximately 50 TCID/10^6 cells. Another yielded culturable virus after multiple attempts, and a third was culture-positive only after CD8+ CTLs were depleted from culture; virus was never recovered from samples from the five remaining subjects. Virus from one patient subsequently exhibited markedly reduced growth in comparison with isolates from individuals with progressive infection, and isolates from the other two grew so poorly that attempts to propagate the strains for further characterization proved futile. According to Dr Ho, these findings suggest that virus in nonprogressors differs from that in patients with progressive infection in some respect.

As related by Dr Ho, possible explanations for enhanced control of infection in these individuals in addition to weakened or defective virus include resistant CD4+ cells and stronger cellular or humoral immune response. In studies of antibody response, it has been found that these individuals exhibit a markedly better neutralizing antibody response than do individuals

with progressive infection; as noted by Dr Ho, the absence of waning of the humoral response indicates continued priming by viral proteins and, thus, persistence of some level of viral replication. Additional studies have suggested that there is a very potent cellular immune response and that no inherent resistance of CD4+ cells to infection is present. In studies in which virus was added in vitro to activated mononuclear cells isolated from the subjects and from normal donors, it was found that virus growth over 2 weeks, measured by antigen production, reached very high levels in normal donor cells, whereas nonprogressor subject cells exhibited a smaller initial peak antigen response followed by decline. Contrary to the notion that this might indicate inherent resistance of nonprogressor CD4+ cells to infection, it was found that depletion of CD8+ cells from nonprogressor samples resulted in marked growth of virus in the CD4+ cells (Figure 2). Sequential readdition of each subject's own CD8+ cells to the CD8+ cell-depleted cultures resulted in dramatic return of suppressive effect. As related by Dr Ho, identical effects have been observed in samples from each of six subjects studied thus far; the magnitude of the suppressive effect has been observed to be greater than that observed in samples from individuals with progressive disease.

Other researchers have found that infection of rhesus monkeys with simian immunodeficiency virus (SIV) in which the *nef* gene has been deleted results in controlled infection, with administration of SIV in this form being found to serve as a vaccine protecting the animals from subsequent challenge with wild type SIV. Given these findings, Dr Ho and colleagues performed PCR analysis of HIV *nef* sequences in isolates from nonprogressor subjects. No gross defects have thus far been observed and no clustering of the identified sequences has been identified in analysis including sequences from virus isolated from patients with AIDS. Dr Ho suggested that although the precise role of *nef* as a virulence factor remains to be determined, it would not be surprising if infected individuals with *nef*-defective virus were eventually identified and found to exhibit enhanced control of infection. He maintained that it is likely that defects of another portion of the viral genome are operative in the nonprogressor subjects that have thus far been analyzed.

In summarizing results so far obtained in these ongoing studies, Dr Ho stated that the findings indicate that there is a remarkably low level of HIV in the blood of nonprogressors, with work being done by others suggesting that nonprogressors also exhibit low levels of replication in lymphoid tissue. With regard to the potential mechanisms of enhanced control, the findings suggest that CD4+ lymphocytes in the nonprogressors are not atypically resistant to infection, that these individuals mount particularly strong cellular and humoral immune responses to infection, and that there appears to be some attenuation of viral replicative ability in infecting strains, although the precise viral defects remain to be defined. ■

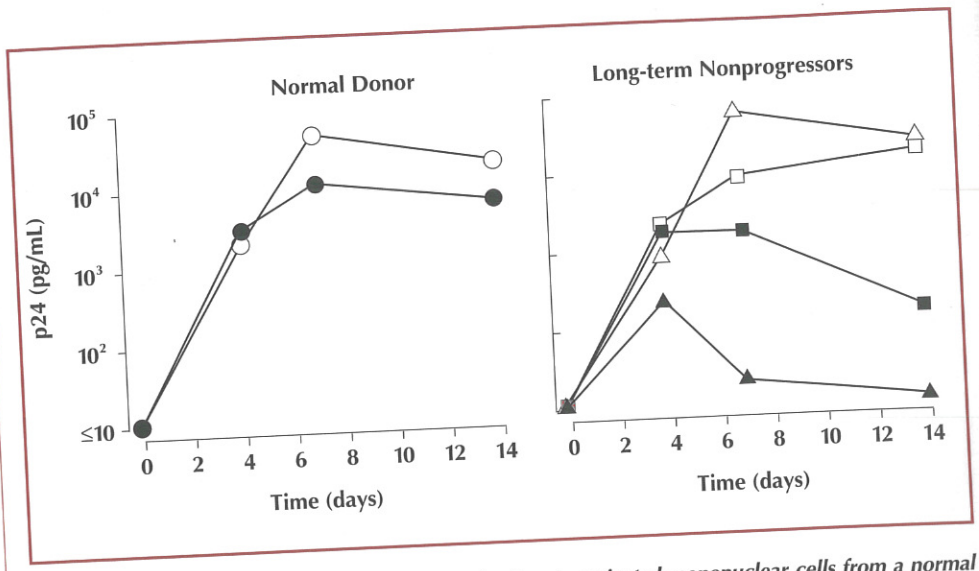

Figure 2. Viral growth, measured as antigen production, in activated mononuclear cells from a normal donor (left) and from two long-term nonprogressors (right). Closed symbols = growth in culture; open symbols = growth after CD8+ cell depletion.

Continuing Antiretroviral Therapy

Strategies for continuing antiretroviral therapy were discussed at the Los Angeles meeting by Michael S. Saag, MD, from the University of Alabama at Birmingham.

Dr Saag began his presentation by contending that from a virologic viewpoint, including the evidence that HIV continues to replicate during the period of clinical latency and that viral burden remains high throughout the earlier course of infection in untreated patients, very early institution of treatment makes eminent sense. The problem with this strategy, he maintained, is that currently available agents offer a time-limited benefit, citing a maximal 3- to 4-year period during which monotherapy with nucleoside analogue reverse transcriptase inhibitors (RTIs) can be expected to reduce replication; the issue is thus posed of when best to utilize the time-limited benefit. He suggested that if one does not believe that additional or better agents or treatment options will be available within the coming few years, it makes sense to delay institution of treatment until more advanced stages of disease develops (eg CD4+ cell count <300/μL). However, if one shares his own anticipation of the development of new agents and treatment approaches, one would be encouraged to start treatment early with the hope that some of these options will be available in the near future.

Viral quantitative techniques and viral replicative characteristics

In discussing the potential importance of viral markers in treatment, Dr Saag presented data on quantitative competitive PCR measurement of plasma HIV RNA levels in three previously untreated patients before, during, and after a 6-week period of zidovudine administration. Viral RNA levels decreased markedly with the start of zidovudine, remained suppressed during zidovudine administration, and exhibited a steep increase during the 1-week interruption of treatment (Table 1). In one patient with a baseline level of 173,600 HIV RNA copies/mL, a maximum decrease to 9200 HIV RNA copies/mL at week 6 of zidovudine administration was followed by an increase to 136,300 HIV RNA copies/mL in the week during which no zidovudine was given. Immune complex-dissociated (ICD) p24 antigen was undetectable in two patients before, during, and after drug administration and standard p24 antigen assay

was negative in each of the patients at all time points; each of the patients was plasma-culture negative prior to administration, with one becoming culture positive during interruption.

Dr Saag stated that accumulating findings such as these indicate that PCR and branched-DNA techniques for assessing plasma viral RNA provide a sensitive indicator of viral replication and virologic response to treatment. He also suggested that the strength of the viral prime directive, to survive and replicate, is indicated by the rapid resurgence of viral replication immediately upon withdrawal of the suppressive effects of zidovudine. He noted that although agents such as zidovudine are not all that could be desired in terms of magnitude of anti-HIV effect, producing a 1- to 2-log decrease in viral levels, or of duration anti-HIV effect, they nevertheless provide meaningful levels of suppression while they remain effective.

In discussing the replicative characteristics of HIV, Dr Saag related findings showing that more than 7 to 10 viral genotypes can develop in a patient within the first 2 to 3 weeks of infection. According to Dr Saag, RT exhibits a transcription error rate of approximately 1 per every 2000 to 3000 base pairs in the context of a viral genome that contains approximately 9000 base pairs, suggesting that several mutations may occur with each round of genome replication. Although the majority of these mutations are likely to be lethal to the virus, those that are not add to a growing 'library' of genotypes. Recombination between viral genotypes may also occur. Some mutants with drug resistance traits are subsequently selected for under antiretroviral therapy; some may be the syncytium-inducing HIV variants that are observed to gain prominence in many patients as infection advances. Dr Saag suggested that the evolution of genotypic diversity, as well as the progressive increase in viral burden, may in fact underlie the finding that isolation of zidovudine-resistant virus occurs markedly earlier after start of zidovudine treatment in patients with advanced disease than in those with relatively early disease. He also suggested that the rapid turnover and high mutation rate of the virus provides additional rationale for the use of combination therapy because it provides coverage of viral subpopulations not covered by a single agent. Such an approach theoretically would provide a more 'even' and consistent suppressive effect that might enable the immune system to recover or improve its functional abilities.

Recent combination studies

With regard to currently available treatment options, Dr Saag discussed findings in recent sequential or combination treatment trials. In Community Programs for Clinical Research on AIDS (CPCRA) protocol 002, patients with advanced disease who had failed on zidovudine monotherapy (intolerance or clinical progression) received either didanosine or zalcitabine; the two agents were found to have equivalent effects, although a potential survival advantage was associated with zalcitabine. In AIDS Clinical Trials Group (ACTG) protocol 155, patients with advanced disease who were receiving zidovudine continued on zidovudine therapy or were administered a zidovudine-zalcitabine combination; it was found that the combination was associated with a reduction in the incidence of clinical events among patients with CD4+ cell counts ≥150/μL but no additional benefit was found in patients with lower cell counts. As related by Dr Saag, a potential explanation for the lack of benefit of the combination in patients with more advanced disease is that benefit of such a combination may be restricted to earlier disease in association with the decreased overall viral replication occurring at earlier stages; in addition, he stated that since patients with CD4+ cell counts <50/μL who developed grade III toxicity were taken off treatment, many patients with advanced disease were not receiving therapy throughout the study, raising questions about the role of therapy in these patients. The patients with low CD4+ cell counts may have received therapy with zidovudine for a longer period and had more zidovudine-resistant virus at baseline. Dr Saag stated that, on balance, such findings indicate a benefit of switching treatments or initiating combination treatment when monotherapy begins to fail and maintained that his preference, while awaiting definitive data, is to institute combination treatment. He also suggested that in addition to being unable to produce profound suppression of viral replication and to maintain suppression for prolonged periods, the nucleoside analogues, when used as monotherapy, have diminishing effects in producing meaningful viral suppression as disease advances.

Table 1. Virologic markers in previously untreated patients receiving zidovudine for 6 weeks followed by a 1-week discontinuation

	HIV RNA (copies/mL)	HIV p24 antigen (pg/mL) ICD	HIV p24 antigen (pg/mL) Standard	Plasma culture (TCID/mL)
Patient 1				
Week 0: no zidovudine	84,900	0	0	0
Week 1: zidovudine	18,000	0	0	ND
Week 2: zidovudine	33,500	0	0	ND
Week 6: zidovudine	28,100	0	0	ND
Week 7: no zidovudine	72,700	0	0	0
Patient 2				
Week 0: no zidovudine	49,100	0	0	0
Week 1: zidovudine	7300	0	0	ND
Week 2: zidovudine	6500	0	0	ND
Week 6: zidovudine	11,200	0	0	ND
Week 7: no zidovudine	58,400	0	0	0
Patient 3				
Week 0: no zidovudine	173,600	79	0	0
Week 1: zidovudine	21,900	28	0	ND
Week 2: zidovudine	10,900	24	0	ND
Week 6: zidovudine	9200	31	0	ND
Week 7: no zidovudine	136,300	47	0	25

TCID = tissue culture infectious dose.

Adapted from Piatak et al, *Science*, 1993;259:1749-1754.

Nevirapine in combination and viral quantitative findings

With regard to the potential inclusion of non-nucleoside RTIs (NNRTIs) in combination therapy, Dr Saag related data from a study by his group showing that, after an impressive initial virologic response, resistance to the NNRTI L697,661 developed within 6 weeks after the start of high-dose monotherapy. Resistance was associated with mutation at RT codon 181, producing a change in susceptibility of as great as from 50 nM to >12,000 nM in isolates from some patients. According to Dr Saag, the emergence of resistance likely reflects selection of subpopulations of preexisting resistant mutants through the pressure of a strong antiviral effect on drug-susceptible subpopulations. In other studies, treatment with the NNRTI nevirapine has also been associated with emergence of resistance, although there are data to indicate that

some patients receiving high-dose monotherapy exhibit a sustained response despite development of resistance. According to Dr Saag, although current data suggest general unsuitability of NNRTIs for monotherapeutic use, there are some data indicating a prolonged beneficial effect in some patients when such agents are added to nucleoside RTI treatment.

Experience of Dr Saag's group with combination therapy has included an uncontrolled open-label extension of a pharmacokinetics study in which nevirapine (200 mg q12h) was added to treatment in a small group of patients who had received regimens of didanosine, zidovudine plus zalcitabine, or zidovudine plus didanosine for an average of 25 weeks. Monitoring of virologic response included use of quantitative competitive PCR and branched-DNA assessment of viral load and ICD p24 antigen testing. As related by Dr Saag, all patients demonstrated a substantial decrease in viral burden upon the addition of nevirapine. Yet, the long-term effects of adding nevirapine were variable. Although all patients exhibited initial CD4+ cell count increases and decreases in plasma viral RNA levels, time to return to baseline values varied from weeks to months. Dr Saag noted that even though rapid offset of effect of nevirapine was observed in some patients, it was heartening to find that additional suppressive effects could be obtained in patients already receiving RTI treatment. Figure 3 depicts the response in one patient. One case identified by Dr Saag as intriguing is that of the patient responding to zidovudine after rapid offset of effect achieved by the addition of nevirapine to didanosine. Consultation with this patient regarding potential alternative treatment revealed that the patient had been taking zidovudine but had discontinued it a month previously in order to be eligible for the study.

An important observation in the study is that the PCR and branched-DNA findings appear to sensitively reflect the replicative behavior of the virus during treatment, showing marked declines in viral levels with initial administration of a potent antiretroviral agent and increases with apparent offset of activity, while inversely correlating with CD4+ cell count changes. He stated that the viral quantitation techniques are likely to become extremely useful in the guidance of day-to-day management of patients in the future as a means of indicating when therapy should be altered and assessing the response to treatment. He suggested that agents with a greater ability to maintain significant suppression for prolonged periods may soon exist to provide better options in responding to data produced by these techniques. In the latter regard, he identified the NNRTI delavirdine, which currently is entering clinical evaluation, as a promising agent with potent in vitro anti-HIV effects. He placed particular emphasis on the potential utility of protease inhibitors, suggesting that some candidate agents could be available for use in novel treatment strategies within the coming year or two. ■

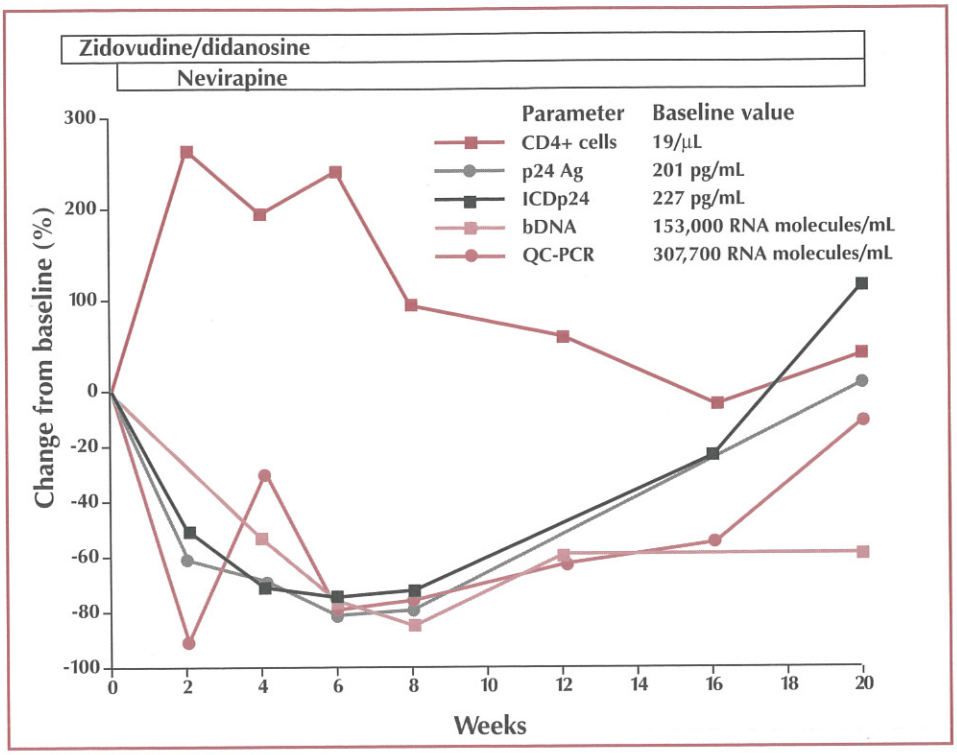

Figure 3. Virologic and CD4+ cell count response to addition of nevirapine to nucleoside analogue treatment in one patient. bDNA = branched-DNA. ICD p24 = immune complex-dissociated p24 antigen. QC-PCR = quantitative competitive PCR. p24 Ag = p24 antigen. Figure courtesy of Michael S. Saag, MD.

Antiretroviral Resistance

Aspects of HIV resistance to antiretroviral agents were discussed at the Atlanta meeting by Victoria A. Johnson, MD, from the University of Alabama at Birmingham, and at the Boston meeting by Clyde S. Crumpacker, MD, from Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts.

Factors in clinical drug failure

According to Dr Johnson, HIV resistance to antiretroviral agents is very likely unavoidable in the absence of complete suppression of viral replication, with the elements of chronic active infection, prolonged drug exposure, and underlying immunodeficiency combining to provide an ideal setting for development of resistance. She noted that virtually every agent that has been extensively evaluated has been associated with at least in vitro resistance. She also stressed, however, that clinical drug failure is multifactorial in nature. Although much attention has focused on resistance as a mechanism in failure, it is now evident that other factors contributing to disease progression during treatment include high and increasing viral load and conversion to SI phenotype, as well as potential cellular resistance to antiretroviral agents.

According to Dr Johnson, viral load may be considered the most fundamental determinant of progression, with optimal suppression of viral load forming the ideal objective of antiretroviral treatment. She suggested that the goal of suppressing viral load could be best achieved by early institution of treatment and use of combination regimens. The rationale for combination treatment is that it may provide more complete suppression of viral replication; limit emergence of drug-resistant virus by reducing replication; and provide treatment of established drug resistance, the latter on the view that viral populations in an individual harboring virus resistant to an agent are mixtures of susceptible and resistant viral strains. She also stated that better antiretroviral agents are needed. It is part of Dr Johnson's current practice to offer combination therapy to patients beginning

treatment after tolerance of monotherapy is established and to offer early treatment with the understanding that no clinical data currently are available to support the benefit of such treatment. According to Dr Johnson, one factor currently motivating the offering of early treatment is that phenotypic conversion to SI virus has been observed to occur in some patients with CD4+ cell counts >500/μL.

Clinical significance of zidovudine resistance

In discussing the clinical import of in vivo resistance, Dr Johnson related that development of zidovudine phenotypic resistance occurs in a progressive and step-wise manner in association with mutations at RT residues 41, 67, 70, 215, and 219; recent findings indicate that step-wise decreases in sensitivity are associated with sequential accumulation of mutations in isolated virus, with the identified order of accumulation, by codon mutation site, being: 70; 215; 215, 41; 215, 41, 70, 67; and 215, 41, 70, 67, 219. As noted by Dr Johnson, the viral population within a given individual is likely to consist of a mixture of susceptible and resistant strains, with resistant populations representing a mixture of resistance genotypes and phenotypes. This heterogeneity has a number of implications for clinical practice. According to Dr Johnson, one implication is that phenotypic assays for resistance, which indicate the overall susceptibility of all virus in a sample to a given agent, are more likely to provide useful information regarding clinical effect of the agent than are genotypic assays. Detection of particular point mutations on the latter may not provide an accurate idea of characteristics of the overall viral population; further, it has been observed that, for example, virus with the zidovudine resistance codon 215 mutation, typically associated with a major increase in phenotypic resistance, can exhibit increased zidovudine susceptibility in the presence of, for example, the RT codon 181 mutation conferring resistance to NNRTIs. Experience with the NNRTI nevirapine also has shown that high-dose monotherapy is capable of eliciting a sustained response in some patients, despite rapid in vivo selection of virus with particular RT point mutations associated with high-level resistance. Thus, in some cases, blood drug levels exceeding the resistance threshold associated with resistance mutations may be achieved. Another important implication of the viral heterogeneity is that the development of resistance to an agent used monotherapeutically does not entail the lack of clinical utility of the agent; the agent may still exert effect among remaining susceptible subpopulations of virus and can be used in combination with an agent having activity against resistant subpopulations.

Table 2. Zidovudine IC-50s of clinical isolates and percentage of isolates with zidovudine resistance, defined as IC-50 >1.0 μM, by duration of zidovudine therapy

Weeks of therapy	No. of isolates	Median IC-50 (μM)	Percentage of isolates exhibiting resistance
0	11	0.006	0
1-26	11	0.061	18
27-52	18	0.115	28
53-78	33	0.125	27
79-104	44	0.284	34
105-130	16	1.19	50
>130	9	0.724	44

Data are from Japour et al, *Antimicrob Agents Chemother*, 1993;37:1095-1101.

As discussed by both Dr Johnson and Dr Crumpacker, a virology study in patients from ACTG 116B/117 has demonstrated for the first time that zidovudine resistance is a significant independent predictor of clinical progression of disease. An earlier study by Kozal et al of genotypic resistance involving PCR detection of the codon 215 mutation in patients who had received ≥2 years of zidovudine treatment had shown that presence of the 215 mutants was associated with a 50% decline in CD4+ cell counts, whereas presence of wild type virus was associated with an 11% increase in count. In ACTG 116B/117, symptomatic patients with CD4+ cell counts ≤300/μL or asymptomatic patients with counts ≤200/μL who had received ≥16 weeks of prior zidovudine (mean, approximately fourteen months) were randomized to one of two dosages of didanosine or continued zidovudine. It was found that didanosine 500 mg/d was associated with significant delay of progression to an AIDS-defining event or death, although no survival differences among the three groups were noted. It was also found that the benefit of didanosine was not associated with duration of prior zidovudine therapy. In the virology study, involving a subpopulation of study patients, it was found that high-level phenotypic resistance to zidovudine at baseline, defined as a 50% inhibitory concentration (IC-50) of ≥1.0 μM, was strongly associated with progression to an AIDS-defining event or death and with progression to death regardless of treatment arm. Baseline CD4+ cell count, baseline SI phenotype, and baseline diagnosis of AIDS were also significant risk factors for progression and were found to be independent of zidovudine resistance at baseline. Findings included adjusted relative hazards for progression to AIDS or death and for progression to death of 1.7 and 2.8, respectively, for high-level resistance at baseline and 1.4 and 3.3, respectively, for SI phenotype at baseline. As stated by Dr Crumpacker, it was found that duration of prior zidovudine or cumulative zidovudine dose was predictive of values of high-level zidovudine resistance, although neither of the factors was predictive of clinical disease progression. No association between zidovudine IC-50 and SI phenotype was observed, with similar proportions of SI and NSI isolates being zidovudine-resistant and similar proportions being zidovudine-susceptible. As related by Dr Crumpacker, although no difference in clinical benefit of didanosine treatment was observed according to whether patients had zidovudine-sensitive or zidovudine-resistant isolates, the absence of a significant difference may have been due to small sample size. Dr Crumpacker reported that analysis of viral load in ACTG 116B/117 patients by branched-DNA assay showed that whereas plasma viral RNA level was significantly associated with stage of disease (AIDS, ARC, or asymptomatic), no association of viral load with level of resistance was observed (high-level, low-level, susceptible). The latter finding suggests that resistance, while itself a marker for disease progression, is not clearly associated with increased viral load.

Both Dr Crumpacker and Dr Johnson noted that many patients did not exhibit zidovudine resistance during the approximately 14 months of treatment prior to entry in ACTG 116B/117, with 15% of the approximately 150 patients exhibiting high-level resistance and 39% exhibiting IC-50s of >0.2 μM at baseline. In a prior study of patient isolates, it was found that up to 50% of isolates exhibited resistance during treatment ranging up to >130 weeks (Table 2). These findings contrast with earlier estimates of resistance rates, based on study of fewer isolates, that predicted greater frequency of resistance over such treatment periods. As stated by Dr John-

son, findings such as this, and the finding that prior duration of treatment is not predictive of clinical progression, suggests that individual evaluation of a patient's continuing response to treatment is in order, with there being no hard and fast rules regarding when zidovudine can be expected to have offset of beneficial effect due to resistance.

Resistance to other agents

In discussing resistance to other agents, Dr Crumpacker noted that a recent study has indicated a significant relationship between high-level zidovudine resistance in isolates from long-term zidovudine recipients and decreased susceptibility to didanosine and zalcitabine, with the clinical significance of these findings remaining unknown. Other investigators have not found such a relationship. Dr Crumpacker stated that cross-resistance within classes of agents is likely to be an increasing problem in both the clinical setting and in drug development. He cited the cross resistance among the NNRTIs as a clear example, it having been shown that virus developing resistance to L697,661 is also cross-resistant to nevirapine and the TIBO compound. He also stated that a potential exception in the case of the NNRTIs is the drug delavirdine, which is chemically distinct from and has thus far been found not to exhibit cross-resistance with the other compounds. Dr Crumpacker noted that the agent sensitizes HIV in vitro to the effects of the other agents, with delavirdine-resistant virus remaining susceptible to nevirapine and L697,661, for example. This agent, which exhibits synergistic activity in combination with zidovudine and other NNRTIs, is currently undergoing early clinical evaluation. In discussing potential resistance to protease inhibitors, Dr Crumpacker related recent findings with the Roche compound A77003 indicating that high-level resistance and cross-resistance to other protease inhibitors can be induced in early passages of virus. He also noted, however, that resistant virus exhibited reduced growth kinetics, raising the possibility that resistant strains selected under treatment might be less pathogenic.

Dr Johnson related that it has been difficult to document high-level resistance to didanosine and zalcitabine, with the 2- to 10-fold decreases in susceptibility observed with these agents standing in contrast to the much greater reductions observed with zidovudine, NNRTIs, and such other nucleoside analogues as 3TC and FTC. Specific mutations that have been associated with reduced sensitivity to didanosine include codon 74 mutation, which has been observed to be associated with reversion of zidovudine-resistant virus to susceptibility during didanosine treatment. Both the codon 74 mutation and another didanosine-resistance mutation at codon 184 have been reported to induce cross-resistance to zalcitabine. There has been one report of reduced zalcitabine susceptibility (>5-fold) in association with a codon 69 mutation. Dr Johnson speculated that a factor contributing to the apparently reduced frequency of high-level resistance to these agents may be that the didanosine and zalcitabine molecules may more closely resemble the normal RT substrates; however, in discussing the rapid emergence of drug-resistant populations that has been observed under 3TC treatment, she suggested that rapid selection of resistant mutants may also occur as a result of greater anti-HIV potency against susceptible strains. With regard to resistance to NNRTIs, she stated that the agents have not been abandoned despite rapid emergence of high-level resistance in clinical investigations because of: (1) the possibility of achieving serum drug levels exceeding the IC-50 of resistant virus, which appears to explain prolonged response to high-dose nevirapine therapy in some patients; (2) the synergistic effect exhibited with nucleoside analogue RTIs, suggesting potential benefit in combination treatment; and (3) the possibility of compensatory mutations—eg, the NNRTI resistance mutation at codon 181 that has been found to increase susceptibility to zidovudine of virus with the zidovudine-resistance 215 mutation. Cross resistance to multi-drug regimens may be a possibility and must be considered in patients receiving multi-drug therapy.

In closing her presentation, Dr Johnson presented combined data from a study at her institution in which patients with CD4+ cell counts of 50 to 400/μL had nevirapine added to existing tolerated nucleoside analogue RTI treatment (see 'Continuing Antiretroviral Therapy'). The group data were characterized by a rapid increase in CD4+ cell count and a decrease in viral load according to a number of quantitative measures, followed by a reversal of effect such that cell count and viral load on some measures had returned to near baseline levels by week 24. Dr Johnson noted the initial decrease in viral burden seen in these patients already receiving RT inhibitor treatment and stated that it is hoped that with better antiretroviral agents, greater and more persistent decreases could be achieved with combination treatment. ■

HIV Disease in Women

HIV disease in women was discussed at the Boston meeting by Deborah Cotton, MD, MPH, from Harvard Medical School and Massachusetts General Hospital in Boston.

Epidemiology

As related by Dr Cotton, HIV disease is now the fourth leading cause of death in women of childbearing age in the US. Statistics as of 1992 indicate that AIDS cases in women are clustered in cities on the Eastern seaboard and in such urban centers as Chicago, Houston, Los Angeles, and San Francisco. Although women currently account for approximately 12% of reported AIDS cases, the proportion of women in the total HIV-infected population is projected to be much greater and to be increasing, with steady increases in the proportion of AIDS cases in women thus being expected; as related by Dr Cotton, the proportion of AIDS cases in women in Massachusetts increased from 12% to 18% between 1989 and 1992. Currently, AIDS is disproportionately diagnosed in women of color; as noted by Dr Cotton, of newly diagnosed AIDS cases in children in 1993, almost exclusively reflecting perinatal transmission, 90% were in children born to

Table 3. Transmission category by race/ethnicity among US women with AIDS reported in 1992

	Number (%)		
	White	Black	Hispanic
Injecting drug use	617 (42)	1600 (47)	581 (43)
Heterosexual contact	535 (37)	1328 (39)	549 (41)
Transfusion/hemophilia	143 (10)	78 (2)	49 (4)
Other/risk not reported or identified	163 (11)	388 (11)	158 (12)
Total	1458	3394	1337

*Includes 66 women of unknown or other race/ethnicity.

Data are from CDC, AIDS Public Information Data Set.

women of color. Women newly diagnosed with AIDS are on average several years younger than their male counterparts.

Statistics as of 1992 indicate that 45% of women with AIDS contracted HIV infection through IV drug use, with 39% reporting heterosexual contact as route of transmission (Table 3); an additional 12% reported other/undetermined risk, which Dr Cotton suggested often reflects a past heterosexual contact with a partner whose infection status or risk factors were unknown. The proportion of women infected through heterosexual contact is expected to increase. As stated by Dr Cotton, given the large proportion of women infected through heterosexual contact, women are more likely than men to be unaware of placing themselves at risk for infection; Dr Cotton indicated that failure to acknowledge this has resulted in inadequate or inappropriate targeting of educational efforts for women.

Dr Cotton noted that most transmission of HIV worldwide is associated with vaginal intercourse, with infected males being the primary vectors; since concentrations of virus in semen are higher than those in vaginal and cervical secretions and since the skin of the penis provides relatively greater protection during intercourse, transmission of infection from an infected male is more likely than that from an infected female. According to Dr Cotton, risk of infection through vaginal intercourse for an uninfected female is currently believed to be on the order of 5 to 10 times greater than that for an uninfected male. Genital ulcers increase the risk of transmission for both genders, and passive anal intercourse is associated with greater risk than vaginal intercourse.

Disease characteristics

According to Dr Cotton, relatively little is known about natural history of HIV disease in women. Most funding for cohort studies was dedicated in the mid-1980s to setting up and following cohorts of at-risk gay men. When it became clear that the incidence of HIV disease in women was increasing, there were few available sources for funding. It is only within the past year, after persistent activism, that cohort studies of women have been initiated, with several being performed by the NIH and several by the CDC. Thus, solid epidemiologic data on transmission risk factors, surrogate markers, disease course, and female-specific manifestations of disease are not expected for a number of years. As noted by Dr Cotton, analyses of currently available data for gender-related differences in disease course are potentially confounded by a number of factors, including a different racial/ethnic distribution of cases and a high proportion of cases currently attributable to transmission via IV drug use among women and the possibility that women with infection may not be recognized at the same stage of disease as men.

Dr Cotton stated that concerns that infection characteristics in women were radically different from those in men may have been overstated. Data from the CDC for 1992 indicate that PCP was the most common AIDS-defining illness in women, being observed in 43% of cases, with wasting syndrome and esophageal candidiasis being the next most common defining illnesses (Table 4). It is currently believed that women may be more prone to the latter two illnesses, with the other difference according to gender being the relative absence of Kaposi's sarcoma in women. With regard to the other illnesses shown in Table 4, Dr Cotton stated that they probably occur with similar frequencies and presentations as in males and are amenable to the same diagnostic tests and treatments. Survival in women has been reported both to exceed and to be shorter than that in men. Dr Cotton noted that findings indicating that women have shorter survival than men have been found to reflect less access to and utilization of medical care, including use of antiretroviral therapy and PCP prophylaxis, among women and suggested that potential gender-related differences in survival in the absence of such factors remain undefined.

The currently proposed female-specific markers of HIV-disease include cervical dysplasia and neoplasia, vulvovaginal candidiasis, and pelvic inflammatory disease (PID). As related by Dr Cotton, HIV-infected women have been found to have a higher incidence of cervical abnormalities on routine screening and appear to be more likely to progress to cervical dysplasia and frank cervical carcinoma. Human papilloma virus (HPV), which has been implicated as a cause of cervical cancer, is found with increased frequency in women with HIV disease, with similarities in the acquisition risk profiles including multiple sexual partners and sexual activity beginning at an early age. Recent studies have indicated that women who are positive for both HIV and HPV have a greater risk of cervical dysplasia than do those who are HPV-negative and HIV-positive or those who are HPV-negative and HIV-negative, with one study in New York City showing respective rates of 52%, 18%, and 9%. Additional evidence indicates that cervical dysplasia is more rapidly progressive and, perhaps, multifocal in HIV-infected women, apparently in association with declining CD4+ cell count. Invasive cervical carcinoma became an AIDS-defining condition in 1993. With regard to the other female-specific markers, Dr Cotton noted that HIV-infected women have a high incidence of vaginal candidiasis, which tends to be recurrent and refractory to treatment and appears to precede oral candidiasis in onset; it may constitute the first presentation of symptomatic disease. Although vaginal candidiasis is very common in the HIV-uninfected population, Dr Cotton suggested that the threshold for recommendation for HIV screening be lowered for women presenting with chronic candidiasis in the absence of such explanatory factors as diabetes, pregnancy, or antibiotic use. PID also occurs with high incidence in HIV-infected women; as noted by Dr Cotton, this may also be influenced by convergence of risk factors. However, she stressed that HIV-infected women tend to have more severe and treatment-refractory disease.

Dr Cotton noted that results of one study have indicated that Pap smear is a relatively

Table 4. Most common AIDS-indicator diseases in US women in 1992

Rank	Diagnosis	Percentage of patients*
1	PCP	43
2	HIV wasting syndrome	21
3	Candidiasis, esophageal	21
4	HIV encephalopathy	6
5	Herpes simplex	6
6	Toxoplasmosis of the brain	6
7	MAC	6
8	Cryptococcosis, extrapulmonary	4
9	CMV disease	3
10	CMV retinitis	3

*Some women had multiple diagnoses.

Data are from CDC, AIDS Public Information Data Set.

insensitive method of diagnosis of cervical dysplasia in HIV-infected women when compared with colposcopy. She suggested that although a minority of gynecologists are recommending routine colposcopy instead of Pap smear in HIV-infected women, most believe that the latter should remain the routine screening procedure in the absence of further definitive data, with colposcopy being employed in cases in which any Pap smear abnormality is observed.

Pregnancy

Early findings in pregnant women indicated that those with CD4+ cell counts of <300/μL were more likely to experience HIV-associated illness during pregnancy. Pregnant HIV-infected women exhibit a greater CD4+ cell count decline during pregnancy than do women without HIV infection, with counts in the former not returning to prepregnancy levels as they do in uninfected women; Dr Cotton suggested that the overall declines in HIV-infected women likely represent declines that would have occurred in the absence of pregnancy and maintained that there currently is no evidence that pregnancy accelerates disease progression. Currently, she informs pregnant patients who intend to give birth who have CD4+ cell counts >200/μL that pregnancy is unlikely to have a deleterious impact on their health; the likelihood of the mother being severely ill while still caring for a young child is raised in discussion with patients with lower cell counts.

Early studies of risk of vertical transmission of HIV infection to infants indicated a risk of 50%. More recent US studies suggest a risk of 20% to 30%, with the recent ACTG 076 study of zidovudine treatment in pregnant women and their newborns finding a transmission rate of 25% in the placebo group. As stated by Dr Cotton, transmission may occur at various times: virus has been isolated from fetuses as early as 8 weeks of gestation; however, many infected infants exhibit a pattern of being first PCR-positive and then culture-positive, suggesting relatively later transmission; breast-feeding poses additional risk for transmission postpartum. Dr Cotton noted that the importance of intrapartum transmission has been underscored by twin studies showing that first borns had a much greater risk of acquiring infection than did second borns; in addition, there is some evidence that delivery via cesarean section may be associated with reduced risk of transmission compared with vaginal delivery. Other findings suggest that lower CD4+ cell count in the mother is a risk factor for transmission.

As recounted by Dr Cotton, ACTG 076 demonstrated that treatment with zidovudine in pregnancy, during delivery, and in the newborn was associated with a reduction in the rate of transmission from 25% to 8%, with the trial being stopped after interim analysis revealed this highly significant difference. In the trial, pregnant women between 14 and 34 weeks of gestation received placebo or zidovudine 600 mg/d orally in six divided doses and high-dose IV zidovudine during labor and delivery and for 24 hours postdelivery; newborns received oral zidovudine or placebo according to maternal treatment group for 6 weeks after birth. According to Dr Cotton, time to PCR- and culture-positive findings in infected treatment group infants parallels that in infected placebo group infants, suggesting that the effect of zidovudine was not merely that of delaying time to positive culture. In addition, in the subgroup of infants thus far followed to the time at which HIV antibody testing could be expected to be diagnostic, antibody testing findings have supported the dramatic reduction in transmission associated with zidovudine. Dr Cotton suggested that these results should prompt a concerted public health campaign targeting pregnant women.

As stated by Dr Cotton, overall experience with zidovudine in pregnancy suggests that the agent is not associated with a major risk of teratogenicity. At least three cases of intrauterine growth retardation have been reported; of two for which details were available, one occurred in the infant of a cocaine user and one in the infant of a woman with symptomatic HIV disease who was receiving multiple medications. One case of oligohydroamnios has been reported. As related by Dr Cotton, no significant problem with neonatal anemia was observed in ACTG 076, with a clinically nonsignificant decrease in hemoglobin levels being observed in treatment group infants.

With regard to women who have had prolonged exposure to zidovudine, have failed treatment, or are known to harbor resistant virus, Dr Cotton stated that there currently is very little information on the use of other nucleoside analogue RTIs in pregnancy. Didanosine appears to be metabolized by both placenta and fetus, and there is evidence that fetal and amniotic fluid drug levels are reduced; no data on potential fetal toxicities of didanosine or zalcitabine are available. Dr Cotton stated that in the absence of relevant data, the selection of an alternative agent is a highly individual decision. She suggested that given current skepticism on the part of some about the benefit of treating patients with asymptomatic infection, a reasonable strategy for HIV-infected women with CD4+ cell counts >200/μL who are considering pregnancy would be to delay zidovudine treatment until time of pregnancy in order to minimize chances of development of resistance. She also maintained, however, that decisions regarding timing of initiation of antiretroviral therapy and what course to take in terms of a possible future pregnancy are highly individual ones, to be made by the patient after appropriate consultation with the physician.

Dr Cotton stated that trimethoprim-sulfamethoxazole (TMP-SMX) is the preferred agent for PCP prophylaxis, with the most commonly used dosages being one double strength tablet qd or three times per week. Dr Cotton indicated that although TMP-SMX has been associated with theoretical risks of teratogenicity and neonatal kericterus, most obstetricians believe that actual risk is minimal and prefer use of TMP-SMX to aerosolized pentamidine. Concerns with the latter include decreased preventive efficacy compared with TMP-SMX, occasional systemic absorption, and questions about absorption of the agent into the lungs in pregnancy, particularly after elevation of the diaphragm in the second trimester. Although no animal pregnancy data on dapsone are available, the agent has been used in leprosy for many years without obvious teratogenic effects and, thus, constitutes an alternative. Dr Cotton maintained that use of steroids in treatment of PCP is indicated in pregnancy, using standard criteria.

With regard to other agents used in prophylaxis, Dr Cotton stated that fluconazole generally is avoided in pregnant women due to an antiestrogen effect; she also noted that the findings in ACTG 981—ie, significant effects of fluconazole in preventing fungal disease without an associated mortality benefit (see above)—do not provide clear guidance regarding clinical practice of fluconazole prophylaxis, with analysis of the benefits of prevention versus cost of treatment and potential for promoting resistance needing to be performed before specific recommendations can be made. Dr Cotton related that it is her practice to use amphotericin B in treatment of cryptococcal disease, both because of the antiestrogen effect of fluconazole and because there are data that suggest the latter may provide inferior results. She also stated that although there are no strong animal data suggesting a teratogenic effect of rifabutin, many practitioners are avoiding use of the agent in pregnant women in the absence of definitive evidence of a survival benefit or more compelling evidence of a marked delay in onset of disease with use of the agent in MAC infection prophylaxis. ■

Management of Fungal Infections

Management of fungal infections was discussed at the New York meeting by William G. Powderly, MD, from Washington University School of Medicine, St. Louis, Missouri.

Candidiasis

As related by Dr Powderly, candidiasis is ubiquitous in patients with advanced HIV disease, with oral infection being nearly universal, vaginal infection extremely common, and esophageal involvement occurring in some 10% to 20% of patients. Local (clotrimazole troches, nystatin) or systemic (fluconazole, ketoconazole) treatment of acute oral candidiasis and systemic treatment of acute esophageal infection are effective, with systemic treatment probably being associated with some increase in time to relapse. Relapse is quite common; virtually all HIV disease patients with a CD4+ cell count of 100/μL harbor oral *Candida* and it has become clear that neither acute antifungal therapy nor chronic suppressive therapy succeeds in eradicating the organism from the mouth, with chronic suppression being associated with changes in flora rather than eradication. Dr Powderly and colleagues have found that infection with a new strain of *C albicans* or a new species occurs in approximately 50% of patients with recurrence, with the frequency of novel isolates being associated with advanced immunosuppression, low CD4+ cell count, and use of azoles.

Such observations provide an explanation for the emerging problem of clinical resistance to fluconazole, which, according to Dr Powderly, is most likely to be seen in patients with CD4+ cell counts <50/μL who have had significant prior intermittent or continuous exposure to the agent. In one study cited by Dr Powderly, increased fluconazole minimal inhibitory concentrations (MICs) of colonizing organisms were found in patients on chronic azole prophylaxis, with approximately 10% having fluconazole-resistant strains and fluconazole resistance being observed in patients receiving other azoles (Figure 4). Although clinical resistance is being encountered sporadically, it is unclear what the frequency of the problem is in this country. According to Dr Powderly, some European investigators have cited resistance rates of 40% to 50%, although such rates could be associated with differences in treatment practices. Currently, it is unknown whether resistance is more likely to result from chronic drug exposure or multiple acute treatments; this issue currently is being examined in an ACTG study.

As related by Dr Powderly, although there are a number of options for treating fluconazole-resistant candidiasis, none has emerged as more effective than another. Typically, different approaches are attempted until the patient responds; in some, IV amphotericin B is required, with some of these patients subsequently failing therapy due to resistance to this agent. Higher-dose fluconazol—eg, up to 800 mg/d—may be used; Dr Powderly noted that doses of up to 2 g/d have been used in unsuccessful attempts to treat aspergillosis. Treatment with other azoles may be attempted, since not all fluconazole-resistant organisms are resistant to other agents. There are some data to indicate that 20% to 30% of resistant strains retain in vitro susceptibility to itraconazole. Oral suspension of nystatin constitutes another option. Oral amphotericin B is not available in this country. Flucytosine treatment may also be attempted. Dr Powderly related that he has observed some success with the combined use of flucytosine and fluconazole.

Cryptococcosis

Cryptococcosis is observed in 7% to 10% of patients with advanced HIV disease. There is continued debate over whether optimal initial treatment of cryptococcosis consists of amphotericin B or an azole, with there being an apparent trend toward use of the former. In two small comparative trials in cryptococcal meningitis, amphotericin B treatment with or without flucytosine was associated with a 100% response rate, whereas fluconazole and itraconazole were associated with response rates of 40% to 50%. However, in a larger ACTG trial in 194 patients, the response rate with amphotericin B treatment was 40% versus 34% with fluconazole (P = 0.39). According to Dr Powderly, the lower response rate with amphotericin B in this study may have been associated with suboptimal dosing or a lower frequency of concomitant use of flucytosine. Although there was little difference in response rate, it was found that cerebrospinal fluid (CSF) cultures tended to clear more rapidly in amphotericin B recipients (Figure 5) and that early mortality was decreased, albeit nonsignificantly, in these patients. According to Dr Powderly, these findings may have contributed to concern over the use of fluconazole in patients with adverse prognostic signs.

Factors associated with greater risk of mortality in the study were a decreased level of consciousness at diagnosis, which was the single most important factor; high CSF cryptococcal antigen titer (>1:1024); low CSF white cell count (<20); and younger age (<35 years). As related by Dr Powderly, in at least those patients with such signs, initial treatment currently is optimally begun with amphotericin B at relatively high doses (eg, 0.7 mg/kg/d) for 2 to 3 weeks, with the addition of flucytosine remaining a subject of study, followed by 10 weeks of fluconazole 400 mg/d, and maintenance therapy with fluconazole 200 mg/d. Although Dr Powderly maintained that his bias is to implement amphotericin B treatment in all patients, he suggested that it may be reasonable to consider initial treatment with fluconazole in patients without adverse prognostic signs. The approach of initial amphotericin B treatment followed by fluconazole currently is being evaluated in a large scale ACTG trial, results of which may be available later in the year.

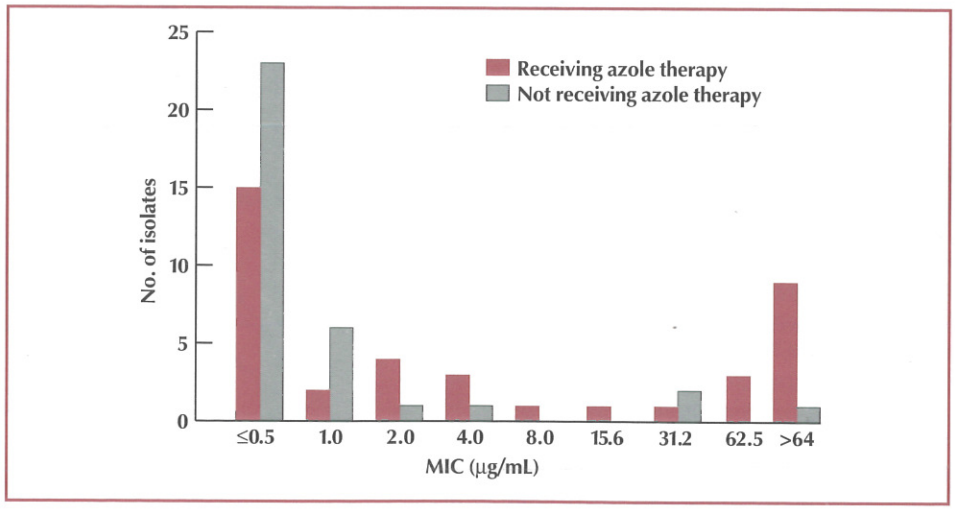

Figure 4. Correlation of* Candida *in vitro susceptibility to fluconazole with prior azole use. MIC = minimal inhibitory concentration. Data are adapted from Cameron et al. Antimicrob Agents Chemother. 1993;37:2449.

With regard to alternatives, one promising approach may be the combination of oral fluconazole and flucytosine in initial treatment. According to Dr Powderly, available data from an ongoing study of fluconazole 400 mg/d and flucytosine 150 mg/kg/d conducted by the California Collaborative Treatment Group indicate a mycologic response of 75% and a complete clinical response of 63% in 32 patients. The early findings suggest that dose-limiting flucytosine toxicity did not occur in the majority of patients over 2 to 3 weeks, with discontinuation being required in 28%. Other potential alternatives include itraconazole. Data from acute and maintenance treatment studies of the agent may be available by year end. In addition, liposomal formulations of amphotericin B are currently being investigated.

Dr Powderly stressed that mechanical management of intracranial pressure in patients with cryptococcal meningitis is an important adjunct of therapy, with much of the associated acute mortality being related to intracranial pressure rather than infection per se. According to Dr Powderly, removal of fluid can be accomplished as effectively with daily lumbar puncture as with placement of an intraventricular shunt. The role of steroids in this setting, which remains controversial, is being evaluated in an ongoing ACTG study.

Histoplasmosis

Histoplasmosis may be observed in 20% of patients in endemic areas, including the Mississippi River basin and regions of Latin America. The considerable number of cases of disseminated disease found in New York City represent reactivation infections, primarily occurring in hispanic patients harboring strains endemic to Puerto Rico or Latin America. Although no formal prospective studies of amphotericin B use in disseminated histoplasmosis have been performed, experience indicates a response rate of approximately 80%, with weekly or twice weekly maintenance therapy with this agent also being effective in preventing relapse. The relapse rate in the absence of maintenance therapy has been found to be 80% over 2 years. Recent findings suggest that itraconazole may be a viable alternative in maintenance or acute treatment. In ACTG 084, itraconazole suppression in patients who had received at least 500 mg of amphotericin B in acute treatment was successful in preventing relapse in 39 (93%) of 42 patients over median follow-up of 109 weeks; there were two cases of relapse, both in noncompliant patients, and one patient stopped treatment due to toxicity. Subsequently, acute itraconazole treatment was evaluated in patients with non-life-threatening disease (eg, excluding patients with meningitis or shock) in ACTG 120; treatment was associated with response in 83% of patients (43/52) with proven disseminated disease and each of seven with other disease. As related by Dr Powderly, a study of initial fluconazole treatment motivated by these findings showed that, whereas a dosage of 600 mg/d was not associated with substantial efficacy, treatment with 800 mg/d produced response in approximately 80% of patients. However, approximately one third of patients relapsed by 6 months, leading to termination of the study. Dr Powderly maintained that although the inferiority of fluconazole cannot be established on the basis of these noncomparative studies, the discrepant relapse findings in what were similar patient populations lead him to prefer itraconazole use.

Fluconazole prophylaxis study

Dr Powderly also presented available data from a large-scale ACTG study of primary antifungal prophylaxis. In ACTG 981, approximately 440 patients, a subpopulation of patients enrolled in *Pneumocystis carinii* pneumonia (PCP) primary prophylaxis study ACTG 081, were randomized to receive fluconazole 200 mg/d or clotrimazole troches 10 mg five times daily, with the active control being used to decrease what would be expected to be a high incidence of oral candidiasis in a placebo control group. The median duration of follow-up was 35 months. Invasive fungal infection was observed in 9 fluconazole patients and 23 clotrimazole patients (P=0.0063), with the CD4+ cell count-adjusted relative risk of invasive infection in clotrimazole patients being 3.25 times that in fluconazole patients. The significant difference was attributable to a highly significant difference in invasive cryptococcal disease, which was observed in 2 fluconazole recipients and 15 clotrimazole recipients (P=0.00095). Fluconazole was also associated with a significant effect in preventing esophageal candidiasis (3 vs 17 cases) and in preventing thrush or other superficial infections (P<0.0001; 10 vs 36 confirmed cases and 23 vs 64 presumed cases). The preventive benefit of fluconazole was greatest among patients with a baseline CD4+ cell count <50/μL, who accounted for nearly all invasive fungal infections observed. However, no significant difference between the two groups was observed with regard to mortality or the combined measure of time to first invasive fungal infection or death.

As stated by Dr Powderly, given the absence of mortality benefit despite the significant preventive effect of fluconazole prophylaxis, it is unclear how the findings of this study are to be translated into clinical practice. Although such prophylaxis could be expected to decrease morbidity and hospitalization due to cryptococcal disease and morbidity due to candidiasis, it may also be associated with increased cost and potential for drug interactions and would likely result in an increase in *Candida* resistance. Dr Powderly noted that resistance may have been operative in the breakthroughs of thrush on fluconazole treatment in the study. However, since clinical specimens were not preserved, no definitive information on development of resistance in the study patients will be forthcoming. ■

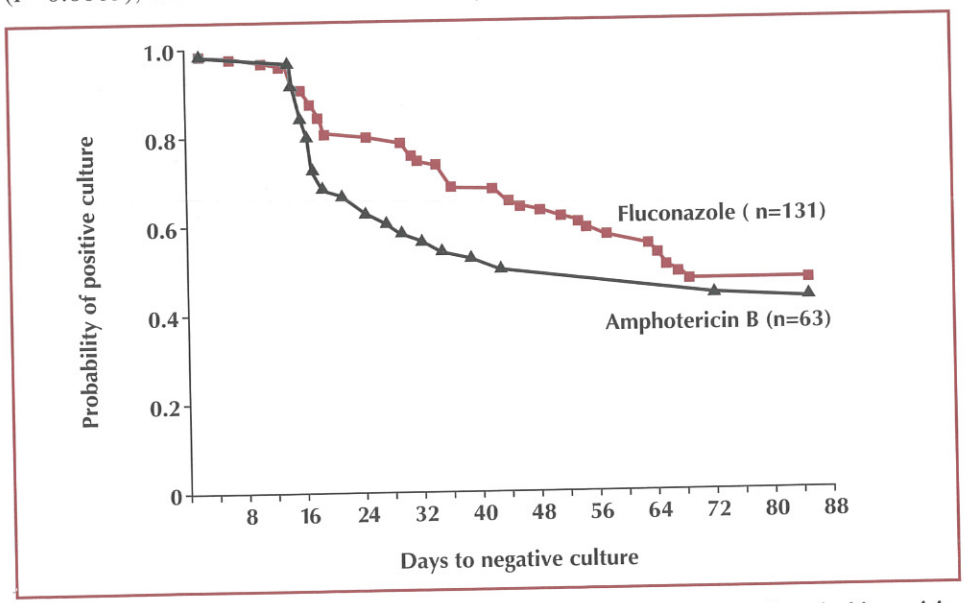

Figure 5. Time to conversion to negative culture among patients with cryptococcal meningitis receiving fluconazole or amphotericin B in ACTG-Mycoses Study Group. Data are from Saag et al. N Engl J Med. 1992;326:83-89.

Tuberculosis Management

The management of tuberculosis was discussed at the Atlanta meeting by Michael L. Tapper, MD, from Lenox Hill Hospital, New York, New York.

Between the mid-1980s and 1992, the number of reported tuberculosis (TB) cases in the US exceeded the projected case number by more than 50,000. The highest case rates and the largest increase in case rates over this period have been in black and hispanic individuals largely between the ages of 30 and 45 years (Figure 6). As observed by Dr Tapper, the increase in cases associated with the convergence of the HIV-infected and Mycobacterium tuberculosis (MTB)-infected populations in part reflects the failure of public health systems to adequately control TB, with this being particularly true in the large urban centers in which the disease is now epidemic. He intimated that preliminary epidemiologic data for 1993 are likely to reveal a decrease in case rates in association with recognition of this problem and reinvigorated public health measures, including directly observed therapy (DOT) at some locales. However, he also warned that abatement of vigilance in this regard would lead to resurgence of cases in epidemic areas and increased incidents in locales that have not yet witnessed significant changes in case rates.

Prevention and diagnosis

Centers for Disease Control and Prevention (CDC) estimates of an HIV-infected population of 1 million and latent MTB infection of approximately 10% in the general population indicate the potential for 100,000 cases of active TB in HIV-infected individuals. As related by Dr Tapper, the presence of AIDS and HIV infection increases risk for reactivation disease by 170-fold and 113-fold, respectively, over that associated with absence of known reactivation risk factors. He stressed that important objectives of TB management remain (1) prevention of cases through early identification of HIV infection, timely tuberculin skin testing, and timely institution of prophylaxis, and (2) improved detection and prompt treatment of disease. Factors contributing to difficulty in accurate diagnosis include: atypical pulmonary patterns; the high frequency of pulmonary disease caused by such other pathogens as *P carinii* and cytomegalovirus (CMV); the common presence of such other atypical mycobacteria as *M avium* complex (MAC); frequent occurrence of TB at extrapulmonary sites, which often constitutes the presenting form of disease; and anergy on skin testing. As noted by Dr Tapper, loss of reactivity to skin testing, which is relied upon heavily in diagnosis, becomes increasingly common with increasing immune suppression. Whereas false-negatives occur in approximately 10% of HIV-infected individuals with CD4+ cell counts >500/µL, a proportion similar to that among HIV-negative individuals, they are observed in approximately 80% of those with cell counts <50/µL. As related by Dr Tapper, it is important that a high clinical index of suspicion for TB be maintained in HIV-infected patients. He suggested that early identification of active disease can be facilitated by remembering that it can occur simultaneously with other pulmonary infection, by considering any acid-fast bacilli in respiratory specimens to be MTB until proven otherwise, and by utilizing such rapid laboratory diagnostic methods as fluorescent microscopy and radiometric culture and drug susceptibility testing.

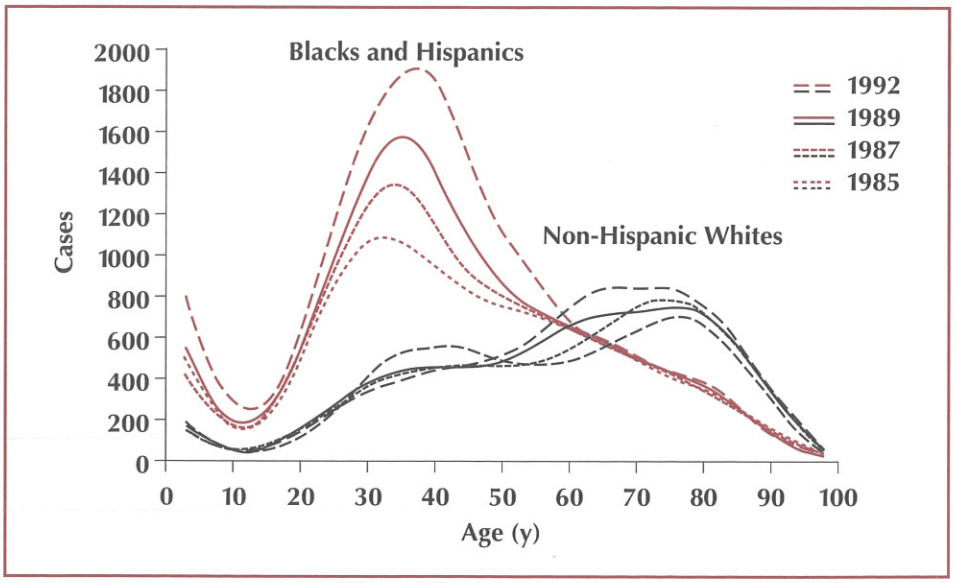

Figure 6. Number of TB cases by age among black or hispanic patients and among non-hispanic white patients in 1985, 1987, 1989, and 1992. Data are from CDC, Division of TB Elimination.

With regard to chemoprophylactic regimens, Dr Tapper stated that HIV-positive individuals who are tuberculin-skin-test positive should receive 1 year of isonaizid (INH) at a dose of 300 mg/d with appropriate monitoring of clinical symptoms and liver function tests. HIV-positive individuals who are anergic, but who are deemed at high-risk for TB exposure in the commmunity or in health care facilities, should also be evaluated for INH chemoprophylaxis. Consideration should be given to administering prophylaxis under direct observation to any individual judged likely to be noncompliant.

Dr Tapper noted that prophylaxis for individuals exposed to drug-resistant MTB is problematic. Rifampin prophylaxis is likely to be effective for persons exposed to INH-resistant, rifampin-sensitive strains of MTB. No data exist to recommend a prophylactic regimen for exposure to INH- and rifampin-resistant TB. In June 1992, the CDC published a decision analysis that offers the option of pyrazinamide (PZA) plus a quinolone or ethambutol for persons exposed to multi-drug-resistant TB (MDR-TB). At least one group has reported a high degree of intolerance to the quinolone (ofloxacin)/PZA regimen.

New York City epidemic

The contribution of public health system failures to the upsurge in TB is underscored by experience with the disease in central Harlem, New York City. As noted by Dr Tapper, TB rates in this area have long been several orders of magnitude greater than the national average, as well as markedly higher than citywide rates. After a period of marked decline from 1970 rates, case rates began to increase in the late 1970s, with a dramatic rise occurring over the next decade. According to Dr Tapper, the increase was facilitated by the deterioration of the public health infrastructure in New York City, including withdrawal of funds from TB treatment programs and the inability to access patients to begin and complete treatment. In a recent study reported by Brudney et al of more than 200 consecutive TB inpatients of an area hospital, 79% of whom were male and who had a mean age of 42.5 years, it was found that 53% were alcoholic, 45% homeless, 23% unstably housed, and 82% unemployed,

with 40% having advanced HIV disease. Of more than 175 discharged on TB treatment, 4% were cured, 6% remained on treatment, and 1% had died of HIV disease at the time of the report; the remaining 89% were noncompliant, with 56% having no follow-up treatment, 28% having <3 months of treatment, and 6% having ≥3 months of treatment. The high rate of incomplete treatment provides an explanation for the continuing community outbreak and hospital outbreaks, as well as the emergence of drug-resistant MTB.

On a model presented by Dr Tapper, increased numbers of patients with active disease represent increased sources of MTB infection; in the context of HIV infection, both morbidity and transmission of TB are amplified by (1) a high rate of reactivation disease among latently infected individuals who become HIV-infected and (2) by a high rate of active disease in previously MTB-naive HIV-infected individuals following acute MTB exposure and infection in association with severe immune deficiency, with the latter problem being particularly apparent in congregate settings. Dr Tapper also stated that he is inclined to the opinion that HIV-infected individuals are more likely to become infected following exposure.

Table 5. CDC draft guidelines for initial treatment of TB among children and adults

TB without HIV infection

Option 1

Administer daily INH, RIF, and PZA for 8 weeks followed by 16 weeks of INH and RIF daily or 2–3 times/week[1] in areas where the INH resistance rate is not documented to be less than 4%. EMB or SM should be added to the initial regimen until susceptibility to INH and RIF is demonstrated. Continue treatment for at least 6 months and 3 months beyond culture conversion. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

Option 2

Administer daily INH, RIF, PZA, and SM or EMB for 2 weeks followed by 2 times/week[1] administration of the same drugs for 6 weeks (by DOT[3]), and subsequently, with 2 times/week administration of INH and RIF for 16 weeks (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

Option 3

Treat by DOT, 3 times/week[1] with INH, RIF, PZA, and EMB or SM for 6 months.[2] Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.

TB with HIV infection

Options 1, 2, or 3 can be used, but treatment regimens should continue for a total of 9 months and at 6 months beyond culture conversion.

[1]*All regimens administered 2 times/week or 3 times/week should be monitored by DOT for the duration of therapy.*

[2]*The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 months. There is weaker evidence that SM can be discontinued after 4 months if the isolate is susceptible to all drugs. The evidence for stopping PZA before the end of 6 months is equivocal for the 3 times/week regimen, and there is no evidence on the effectiveness of this regimen with EMB for less than the full 6 months.*

[3]*DOT—Directly observed therapy.*

Adapted from: CDC *MMWR* 1993;42:1–8.

Nosocomial outbreaks

The numerous nosocomial outbreaks of MDR-TB in largely HIV-infected patients have been characterized by extremely high mortality rates and rapid progression to death. As related by Dr Tapper, factors contributing to these outbreaks include: delayed recognition of TB, with failure to consider the diagnosis in the presence of nonclassical radiographic findings; laboratory delays in specimen processing; delayed recognition of drug resistance; and delayed initiation of effective treatment, resulting in prolonged periods of infectiousness. As noted by Dr Tapper, an analysis by the CDC of patient characteristics in one outbreak showed that 14 (82%) of 17 patients presented with pulmonary and extrapulmonary infection sites, that only 69% had positive first sputum smears (with 94% eventually having positive smears), and that 82% had abnormal admission x-rays. Although infiltrates were common (13 of 14), other typical findings of pulmonary TB such as effusion (2 of 14), adenopathy (4 of 14), and miliary patterns (1 of 14) were largely absent. Another set of factors contributing to outbreaks consists of inadequate isolation procedures, including delayed initiation and inadequate duration of isolation, isolation lapses, inadequate ventilation, and inadequate precautions for cough-inducing procedures.

Treatment guidelines

According to statistics presented by Dr Tapper, initial resistance to at least one drug among TB cases increased from 8.9% nationally during 1982-1986 to 13.4% in 1991. Resistance to both INH and rifampin increased from 0.5% to 3.0% between the two periods. Patients with increased risk for drug-resistant TB include foreign-born persons from areas with high resistance rates (eg, Asia, Africa, and Latin America), residents of US areas with high prevalence of drug resistance, those who have previously been treated with anti-TB drugs, those with positive bacteriologic findings after 3 months of treatment, and those who are contacts of known drug-resistant cases. The 1993 CDC draft guidelines for initial treatment of TB are shown in Table 5. Four drugs are recommended for use in all areas in which the INH resistance rate is ≥4% or in which the prevalence of INH resistance rate is not known. Recommendations for HIV-infected and HIV-uninfected individuals differ only with regard to the current recommendation that HIV-infected patients should be treated for 9 months and at least 6 months after culture conversion rather than 6 months and at least 3 months after culture conversion. Dr Tapper stated that it is possible that newer recommendations will indicate that adequate treatment can be provided in HIV-infected patients with drug-susceptible TB by a 6-month course of therapy with a four-drug regimen. He stressed that the recent decline in TB rates has been the result of intensive effort on the part of health care workers and largely reflects the success of strict adherence to directly observed theory (DOT). On current recommendations, all treatment occurring on a twice or thrice weekly basis should be monitored by DOT for the duration of therapy.

Health care worker exposure

Widespread concern regarding exposure of health care workers to TB has also been addressed in CDC draft guidelines. According to statistics from MDR-TB outbreak hospitals related by Dr Tapper, 20 cases of MDR-TB among workers have been documented, and additional cases were seen outside these outbreaks. Cases have included physicians, nurses, dental

UPCOMING EVENTS

International Society for Sexually Transmitted Disease Research (ISSTDR) Meeting, New Orleans, Louisiana, USA, August 27-30, 1995. David H. Martin, MD, Chairman.

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staff, respiratory therapists, transportation and laboratory workers, and a prison guard. Eleven of the individuals were known to be HIV-infected. A total of seven have died, including five HIV-infected persons. Of the two deaths in noninfected persons, one was due to a drug overdose and one occurred in an individual undergoing cancer treatment. The skin test conversion rate in previously PPD-negative workers has been 20% to 50%.

In addition to specifying general standards for infection control, including negative pressure rooms, and supplemental approaches, such as HEPA filtration and ultraviolet irradiation, CDC draft guidelines for infection control indicate that the minimal acceptable level of respiratory protection for workers exposed to TB should be a HEPA filter respirator. The Occupational Safety and Health Administration (OSHA) has recently indicated that employers in a variety of health care settings are obligated to establish TB control programs and that the HEPA filter respirators will be considered the minimal acceptable standard of protection. As noted by Dr Tapper, the legal requirement of the use of these devices, which are difficult to wear and are associated with increased cost, has caused much controversy. Their necessity remains unclear, since institutions that had fully implemented earlier CDC guidelines recommending use of a dust-mist particulate respirator have generally reported success in terminating nosocomial transmission of TB infection.

Many other issues concerning health care worker exposure remain unresolved. One is the difficulty in compliance with both current OSHA requirements and elements of the Americans with Disability Act. As related by Dr Tapper, the questions arising in the context of TB exposure are whether an institution can accommodate a worker's handicapping condition if the condition is HIV infection and whether HIV-infected workers can reliably be protected from TB exposures. Other unresolved issues include the reliability of skin testing in monitoring nosocomial transmission, distinguishing between nosocomial- and community-related skin test conversions, and monitoring of exposure in anergic HIV-infected workers. In addition, there is no established prophylactic regimen for HIV-positive or HIV-negative workers exposed to MDR-TB. The utility of the current CDC-recommended combination of pyrazinamide and either ethambutol or a quinolone (ofloxacin or ciprofloxacin) remains largely unproven and in one study has been reported to be poorly tolerated. ■

Diarrhea Associated With HIV Disease

Diarrheal illness in patients with HIV disease was discussed at the New York meeting by Douglas T. Dieterich, MD, from the New York University School of Medicine in New York.

As related by Dr Dieterich, diarrheal illness has been observed to occur in approximately 60% of patients with AIDS. A recent study has shown that such illness has a profound economic and quality of life impact: the effect of chronic diarrhea vs no diarrhea among AIDS patients with CD4+ cell counts <200/μL was a reduction in function, global health, and fatigue quality of life measures, a doubling of annual cost of treatment ($24,567 vs $14,471), a doubling of disability days (131 vs 72), and a doubling of proportion of patients requiring home assistance (66% vs 35%), with all of these differences being statistically significant. Dr Dieterich stressed that while the lower end of the range of proportion of cases in which an etiologic diagnosis can be made is 50%, assiduous and repeated efforts at diagnosis can raise the diagnostic yield to 85%. Approximately 50% of pathogens currently are treatable. With regard to the potential role of HIV in diarrheal illness, Dr Dieterich noted that HIV can be found in rectal and small-bowel biopsies, that the GI tract (mouth and rectum) may be a portal of entry of HIV, and that local infection of GI tissues and mucosal inflammation caused by HIV may contribute to symptoms. He also noted that recent findings suggest that human herpesvirus 6, which is frequently found in the GI tract, may induce CD4 receptors in various tissue cells. However, he maintained that the role of HIV as a primary enteric pathogen remains unclear and emphasized that, although it is tempting to invoke HIV enteropathy when initial testing is unrevealing, it is highly probable that some other pathogen will be found if diagnostic efforts are continued or repeated and that pathogen-specific treatment is of greater benefit to the patient than symptomatic treatment. The approach to evaluation of diarrheal illness in HIV disease recommended by Dr Dieterich is shown in Figure 7.

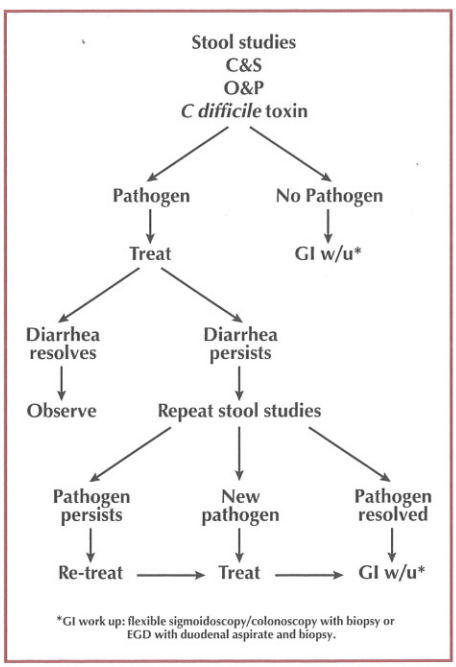

Figure 7. Evaluation of diarrhea in patients with HIV disease. C&S = culture and stain. O&P = ova and parasites. w/u = work-up. EGD = esophagogastroduodenoscopy. Figure courtesy of Douglas T. Dieterich, MD.

As stated by Dr Dieterich, the potential microbiologic causes of diarrhea are manifold. Bacterial causes include MAC, MTB, *Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and entero-adherent *Escherichia coli*. The *E coli*, which appear to adhere to colonic mucosa and which are similar to strains that have been found to infect children, have been described as pathogens only within the last year. They reside primarily in the right colon, and diagnosis requires electron microscopy of biopsy tissue. According to Dr Dieterich, the organisms are sensitive to ciprofloxacin, which many patients receive as empiric therapy for diarrhea. Parasitic causes include *Cryptosporidium*, *Isospora*, *Entamoeba histolytica*, *Giardia*, *Microsporidia*, and *Cyclospora*. Viral causes include CMV, herpes simplex virus, adenovirus, astrovirus, picobirnavirus, and calicivirus; the more recently identified viruses are difficult to isolate and have not as yet been found to respond to any known treatment. Although fungi generally are rare causes of diarrhea, *Histoplasma* has been found to cause GI symptoms in a significant proportion of patients in *Histoplasma*-endemic areas. Dr Dieterich noted that such illness can also be observed outside of endemic areas; among patients in New York City, he has observed a number of cases of *Histoplasma* colitis presenting as diarrhea with an unknown primary site of histoplasmosis.

Cryptosporidiosis

GI symptoms of cryptosporidiosis include profuse, watery diarrhea, malabsorption and weight loss, flatulence, abdominal pain, nausea and vomiting, and absence of fever. A notable exception to the usual finding of absence of fever are cases in

which infection of the biliary tree results in cholangitis with bacterial superinfection. Currently, there is no completely effective therapy for cryptosporidiosis, with more than 100 agents having been examined for potential use. Agents evaluated in recent investigations include macrolide/azalide agents, benzoacetonitrile derivatives, and the antiamebic aminoglycoside paromomycin. A study of IV and oral spiramycin by Dr Dieterich and colleagues failed to show activity of the agent. Another group has found some activity of oral azithromycin and currently is evaluating IV azithromycin, having noted that patients who achieved meaningful blood drug levels tended to respond better to treatment. Clarithromycin has not shown activity in in vitro models of infection. With regard to the benzoacetonitrile derivatives, a recent small-scale placebo-controlled trial of diclazuril by Dr Dieterich and colleagues revealed a low response rate and general failure to achieve blood drug levels. Subsequent evaluation of letrazuril, which is better absorbed than diclazuril, in placebo-controlled ACTG 192 has also suggested small beneficial effect. There has been one report of the combination of letrazuril and paromomycin resulting in successful treatment. Anecdotal reports suggest that high-dose paromomycin (1500 to 3000 mg/d in divided doses) may exhibit some activity, and the agent is currently being evaluated in an ACTG trial. Little effect has been observed with such other approaches as treatment with transfer factor, hyperimmune bovine colostrum, or interleukin-2.

Dr Dieterich stated that in addition to continuing efforts at development or identification of effective agents, future efforts are likely to focus on combinations of agents that show at least some activity. With regard to reports that antiretroviral treatment is of benefit in treatment of cryptosporidiosis, Dr Dieterich stated that the observations are likely explained by an effect of such treatment in increasing CD4+ cell counts, with it having been observed that patients with cryptosporidiosis with counts >150/μL tend to spontaneously resolve infection, whereas infection generally is progressive in those with lower counts.

In cryptosporidiosis cases, as in all other cases of chronic diarrhea that are not amenable or do not respond to specific treatment, supportive therapy is essential. Initial options among antimotility agents include loperamide and lomotil; opiates can be tried, including morphine, methadone, paregoric, and deodorized tincture of opium, and, finally, use of the synthetic somatostatin octreotide can be attempted. Enteral feedings and total parenteral nutrition are important components of supportive treatment.

Microsporidiosis

Typical symptoms of microsporidiosis are identical to those of cryptosporidiosis, with the exception that the former is not associated with the severe nausea and vomiting characteristic of the latter and that patients with microsporidiosis may have preserved appetite in apparent association with a relatively reduced tendency of infection to affect the upper GI tract; microsporidiosis may also be associated with fever in cases of cholangitis with bacterial superinfection. According to Dr Dieterich, the prevalence of this relatively recently discovered disease has been reported at 15% to 50% in patients with no other identifiable cause of diarrhea. Diagnosis is best made by electron microscopy of small bowel biopsy; stool tests are still being developed and are as yet unreliable. Albendazole is a promising agent for treatment of microsporidiosis; currently three double-blind placebo-controlled trials of the agent, including ACTG 207, are under way or about to begin. In an uncontrolled study recently reported by Dr Dieterich and colleagues, 29 homosexual men with a mean CD4+ cell count of 21/μL, mean time since AIDS diagnosis of 24 months, mean of seven bowel movements per day for 12 months, and mean weight loss of 17% of normal body weight who were infected with *Enterocytozoon bieneusi* were administered oral albendazole at dosages of 400 to 1600 mg bid. With treatment response assessed as good, partial, or poor for >50%, >25%, and <25% reduction in diarrhea, 50% of patients exhibited a good response and an additional 35% exhibited partial response. Experience of Dr Dieterich and colleagues with albendazole in patients with disseminated *Septata intestinalis*, the other microsporidial species thus far implicated in disease, has shown that this species is very sensitive to the agent, with patients invariably improving within 10 days of treatment; in Dr Dieterich's experience, this organism accounts for only approximately 10% of microsporidiosis cases.

Cyclospora

Cyclospora is another recently described pathogen that has been found to produce devastating diarrhea in AIDS patients. It closely resembles *Cryptosporidium*, and also results in positive acid-fast testing. It can be distinguished from *Cryptosporidium* on the basis of a distinctively shaped nucleus. Although there is no known proven treatment as yet, patients able to tolerate trimethoprim-sulfamethoxazole appear to respond to treatment with the agent.

CMV

Biopsy remains the sole method for definitive diagnosis of CMV GI infection. Cases of upper GI and lower GI infection appear to occur with similar frequency; CMV hepatitis is rare in AIDS patients compared with its incidence in transplant patients. In stressing the need to persevere in arriving at an etiologic diagnosis and the need to consider presence of multiple pathogens, Dr Dieterich recounted a case in which the finding of *C difficile* pseudomembranous colitis, which often is not present alone in AIDS patients, prompted him to biopsy tissue beneath the membranes, which subsequently revealed the presence of CMV, *Cryptosporidium*, and MAC.

As related by Dr Dieterich, CMV GI disease can be successfully treated. A placebo-controlled trial in patients with CMV colitis conducted by Dr Dieterich and colleagues showed that IV ganciclovir was associated with significant effects in treatment response (20/32 vs 11/30), clearance of viral culture (5/25 vs 17/26 positive), weight change, and incidence of extracolonic CMV disease (4 vs 7) during the 14-day study; Dr Dieterich stated that virtually all treated patients exhibited improvement and that although no significant improvement in diarrhea score was observed over the 14 days, all treated patients actually improved in this regard. He stressed that an important finding was that five of the placebo patients (compared with none of the ganciclovir patients) developed CMV retinitis during the 14 days, and urged that any patient suspected of CMV GI infection be referred for ophthalmologic examination. In a more recent study, Dr Dieterich and colleagues found that IV foscarnet treatment in patients with CMV GI infection failing ganciclovir treatment was associated with clinical and pathologic response in eight of ten patients with colonic disease and clinical response in six of nine and pathologic response in six of eight patients with esophageal disease (overall clinical and pathologic response rates of 74% and 67%, respectively), with the median survival in these patients being 5 months. In other recently reported experience, Dr Dieterich and colleagues made the surprising finding that nine of 10 patients failing both ganciclovir and foscarnet alone subsequently responded to combination treatment; the overall median survival in these patients after the start of

combination treatment was 175 days, with median survival among the five who died being 190 days and that among the five survivors being 166 days at last analysis. In a recent pilot/pharmacokinetics study, Dr Dieterich and colleagues found that twice daily foscarnet 90 mg/kg IV was associated with pathologic and endoscopic improvement in 90% of patients with CMV GI disease, with full resolution of symptoms occurring in 80% of patients and partial resolution occurring in 10%. Dr Dieterich noted that confirmation of such findings could have a financial impact, since the 90 mg/kg bid regimen can be administered at home, whereas the 60 mg/kg tid regimen must be administered in the hospital; he also related that the former regimen has been reported to be effective in treatment of CMV retinitis in European experience.

The role of maintenance therapy for CMV GI disease after initial treatment remains unclear. In a study scheduled to begin soon, patients with upper or lower CMV GI disease will receive foscarnet 90 mg/kg IV bid for 4 weeks followed by randomization to maintenance treatment or no maintenance treatment. In an ACTG study that is currently under way, a pharmacokinetic analysis of oral ganciclovir maintenance treatment is to be performed in patients with CMV colitis after 3 weeks of ganciclovir-induction therapy. ■

Developments in CMV Disease Treatment

Developments in CMV disease treatment were discussed at the Boston meeting by W. Lawrence Drew, MD, PhD, from the Mt Zion Medical Center of the University of California at San Francisco.

Diagnostics

As related by Dr Drew, advances in CMV diagnostics include wide availability of a novel CMV antigenemia assay, involving staining of peripheral blood samples with tagged monoclonal antibodies, that permits documentation of CMV viremia on a same-day basis. According to Dr Drew the antigen assay is also an effective means of documenting CMV central nervous system (CNS) disease. Although initial experience with the test in Dr Drew's laboratory suggested 60% to 70% accuracy compared with blood culture, continued use in their hands and at other laboratories has shown sensitivity approaching 90% to 100%. Dr Drew stated that the shell vial assay, which can provide results within 24 hours, has proven to also have high accuracy in detecting viremia according to blood culture standards. A particular virtue of the antigen assay is the ability to quantitate viremia. For example, it is possible that a correlation between degree of viral antigenemia and CMV wasting syndrome will be demonstrated. Another diagnostic development, the branched-DNA assay for measuring levels of CMV DNA in the blood, also provides quantitative results. Dr Drew presented an example in which a patient developed CMV retinitis 3 weeks after persistent increased viral DNA levels were initially detected on the assay, followed by levels falling below detection limits at 10 days after initiation of ganciclovir treatment. As related by Dr Drew, the branched-DNA assay may thus prove to be of value in predicting onset of disease, as well as providing a practical method for monitoring patients during treatment—eg, for documenting an antiviral effect and then its dimunition in association with resistance. Similar considerations apply to quantitative PCR techniques that are currently undergoing adaptation for routine clinical use.

Resistance

Studies performed by Dr Drew and colleagues several years ago indicate that CMV isolates resistant to ganciclovir can be isolated in approximately 10% of patients after 3 months of treatment. The majority of cases of resistance are due to mutation in the viral kinase required for initial phosphorylation of ganciclovir. Rare cases are attributable to mutation in cellular DNA polymerase, and double mutations may occasionally occur. As noted by Dr Drew, resistance is manifest by progressive increases in drug 50% effective doses (ED-50s) over time and appears to be the result of selection of preexisting mutants in the viral population. The viral kinase mutations that have been associated with resistance include substitutions at amino acid residues 460 and 595 in the UL97 or protein kinase gene. As stated by Dr Drew, given successful adaptation for routine clinical laboratory use, use of PCR to detect such mutations in clinical isolates may prove valuable in patient management, providing extremely rapid identification or prediction of resistance compared with current culture-based phenotypic assays. He noted that resistant genotypes are identified by PCR only when they constitute at least approximately 10% of the viral population in an individual sample and that this threshold level appears to correlate with initial increases in ED-50s. Thus, it is unlikely that detection of resistant genotypes by PCR would significantly antedate development of phenotypic resistance.

Development of resistance to foscarnet was expected to occur less frequently than ganciclovir resistance, given that foscarnet does not require phosphorylation to its active form. Studies at Dr Drew's laboratory have indicated that whereas all ganciclovir-sensitive CMV strains remain susceptible to foscarnet, approximately half of ganciclovir-resistant strains also exhibit reduced sensitivity to foscarnet. Dr Drew suggested that these isolates may exhibit DNA polymerase resistance mutations or double mutations. According to data from a Studies of the Ocular Complications of AIDS (SOCA) patient group presented by Dr Drew, there was an equivalent increase in the proportion of both ganciclovir-treated and foscarnet-treated patients becoming blood culture-positive over time on treatment after initial conversion to negative culture. This suggests a similar rate of resistance development in patients receiving the two drugs, but definitive interpretation will follow the results of antiviral resistance testing of all isolates. According to Dr Drew, information on the incidence of resistance in SOCA patient isolates and on the relationship of resistance to clinical events in these patients may be available before year end.

Oral ganciclovir

As related by Dr Drew, study of the effects of oral (1 to 3 g/d) and IV (5 mg/kg/d) ganciclovir on CMV titer in semen of infected patients over 28 days has shown that both forms of ganciclovir are associated with decreased titers in the majority of patients. Although the antiviral effect of the oral form is reduced compared with the IV drug, in association with poor bioavailability, the need for an oral agent for use in prophylaxis and maintenance and the documentation of meaningful antiviral activity by the oral agent have prompted performance of a number of trials of oral treatment. According to Dr Drew, preliminary data from a large-scale preventive study are expected by year end and enrollment of a community consortium prevention trial is nearly complete. Maintenance trials include one in which patients were randomized to oral or IV maintenance after IV induction therapy and one in which patients already on IV maintenance were offered the choice of continuing on IV or switching to oral maintenance. Data from

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more than 100 patients in the former maintenance study were presented by Dr Drew. Progression determined by funduscopic examination was found to be significantly delayed by IV ganciclovir at the standard maintenance dosages compared with oral ganciclovir at a dosage of 3 g/d, with the mean times to progression in the groups being 96 days and 68 days, respectively. However, there was no significant difference between IV and oral groups with regard to progression according to masked reading by ophthalmologists of retinal photographs taken at the time of funduscopic examination, with mean times to photographic progression being 62 days in the IV group and 57 days in the oral group. In addition, there was no difference between the two groups with regard to deterioration of visual acuity at any time point. There was no significant difference between proportions of IV and oral patients found to be culture positive during maintenance treatment. Dr Drew noted that oral ganciclovir can be given in dosages up to 6 g/d and that a trial examining this higher dosage in maintenance treatment is under way. No increased incidence of GI adverse effects was observed in oral patients, with the only notable difference in adverse events being a greater incidence of IV line sepsis and fever in the IV group.

HPMPC

The investigational anti-CMV agent HPMPC is a nucleotide analogue with the structure of a monophosphorylated drug, allowing the agent to bypass the step of phosphorylation via viral kinase. Cellular phosphorylation converts the agent to its active diphosphate form. In theory, HPMPC, like foscarnet, may be of greater prophylactic utility than ganciclovir, since it should be present in active form in CMV-uninfected cells. Similarly, like foscarnet, it may pose greater risk of overall cellular toxicity than ganciclovir, since its activity is not selective for infected cells. In an initial dose-escalating study, Dr Drew and colleagues have found both that the agent has significant nephrotoxic potential and that nephrotoxicity can be reduced by modification of the regimen. A modified regimen consisting of concomitant probenecid administration, hydration, dosing interval extension, and interruption for proteinuria appeared to be beneficial in this regard. As noted by Dr Drew, a feature of treatment with HPMPC of potentially great impact is that the agent can be given as induction therapy on a once-weekly basis and as maintenance therapy on a biweekly basis by 1 hour infusion; suppression of viral replication over between-dose intervals of up to 3 weeks has been observed.

CMV CNS infection

According to Dr Drew, polyradiculopathy in association with CMV infection is becoming an increasingly common problem, with presentation characterized by lower extremity pain and weakness and bladder incontinence. CSF abnormalities uncommon to viral infections, including polymorphonuclear pleocytosis, with an average WBC count of 400/μL, and moderately low glucose levels, are observed in patients with the condition in the absence of any other potential etiologic agent. Dr Drew stated that CMV culture of the CSF may be negative in one third to one half of cases, whereas branched-DNA and CMV antigen assays appear to provide accurate diagnosis. Data presented by Dr Drew showed that both of these assays proved positive in each of nine cases of polyradiculopathy while culture was positive in only six. There are data indicating that patients with CMV polyradiculopathy who are not treated have an average survival of 3 weeks, with none showing stabilization or improvement, and that treated patients have an average survival of 11 weeks, with approximately half showing stabilization or improvement. Dr Drew presented data showing progressive decreases in CSF CMV levels on branched-DNA testing in six of seven polyradiculopathy patients during treatment with ganciclovir and/or foscarnet. He suggested that the relatively poor outcome in treated patients is thus not due to absence of antiviral effect, but rather to the irreversible nature of CNS damage; it is thus imperative to make the diagnosis of CSF infection in a timely manner. He also noted the potential utility of techniques such as the CMV antigen and branched-DNA assays in rapidly indicating absence of antiviral effect in CSF, presenting data from one polyradiculopathy patient in whom CMV titers continued to increase during ganciclovir treatment, presumably in association with resistance to the agent.

Other treatment developments

Dr Drew related a number of other recent findings or developments in the area of treating CMV disease. Results of a small comparative study in CMV retinitis patients reported by Jacobson and colleagues indicate that foscarnet maintenance therapy with 120 mg/kg may be superior to the commonly used 90 mg/kg regimen; the higher dosage increased time to progression from 31 to 95 days and survival time from 5.1 months to 11.0 months compared with the lower dosage. In a study reported at the 1993 International Conference on AIDS in Berlin of approximately 50 patients with upper or lower GI CMV disease, Blanshard et al found foscarnet and ganciclovir to be comparable in effectiveness, producing similar rates of endoscopic improvement (81% vs 84%), histologic improvement (81% vs 95%), and symptomatic response (90% vs 90%), with adverse effects occurring in 31% of foscarnet patients and 24% of ganciclovir patients. More foscarnet patients had other GI pathogens (35% vs 12%). In a study by Tolpin et al, also reported at the 1993 International Conference on AIDS, biweekly IV administration of CMV monoclonal antibodies in combination with ganciclovir or foscarnet treatment in patients with CMV retinitis was associated with a median time to remission of >200 days. Prospective trials involving such combination treatment are planned. Dr Drew noted that another promising agent in early stages of development is cyclobut-G. This agent, which is similar to ganciclovir and is structurally described as deoxyguanosine with sugar replaced by a cyclobutyl ring, exhibits 40% oral bioavailability, a level greatly exceeding the bioavailability of oral ganciclovir.

Finally, Dr Drew described a sustained-release device that is capable of delivering drug into the vitreous of the eye for nearly 6 months. The device, which is sutured in place, is currently being evaluated in a trial in which CMV retinitis patients are receiving intravitreal ganciclovir alone or in combination with IV or oral drug. Dr Drew noted that despite the characteristic systemic nature of CMV disease, some retinitis patients who have received only intravitreal drug have responded remarkably well; he suggested that the device may have utility in patients without significant systemic disease or those incapable of tolerating systemic treatment. ■

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