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. ■

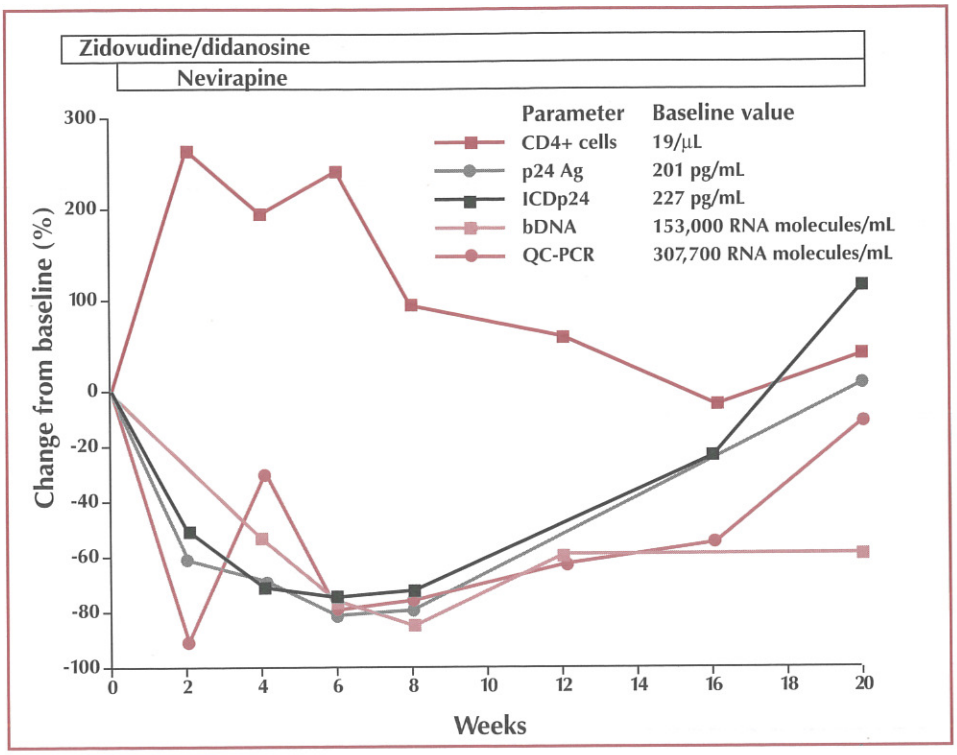

Figure 3. Virologic and CD4+ cell count response to addition of nevirapine to nucleoside analogue treatment in one patient. bDNA = branched-DNA. ICD p24 = immune complex-dissociated p24 antigen. QC-PCR = quantitative competitive PCR. p24 Ag = p24 antigen. Figure courtesy of Michael S. Saag, MD.

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.