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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

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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.

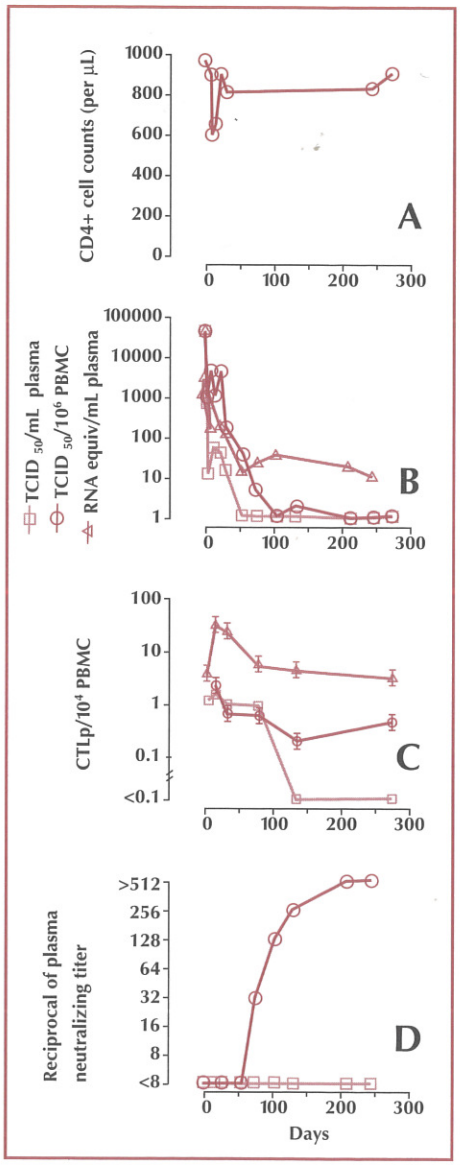

Figure 1. Viral load and immune response in patient during and after symptomatic acute infection. A, CD4+ cell count. B, HIV-1 in blood by plasma culture (□), PBMC culture (○), and branched-DNA (Δ) results. C, CTL precursor response to gag (○), pol (Δ), and env (□) viral epitopes. D, Serum neutralizing 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. ■

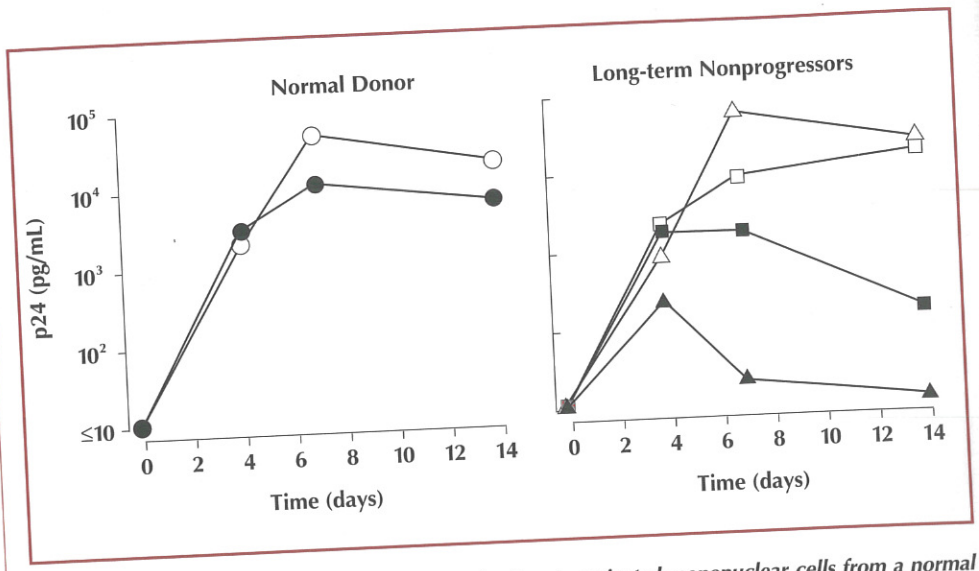

Figure 2. Viral growth, measured as antigen production, in activated mononuclear cells from a normal donor (left) and from two long-term nonprogressors (right). Closed symbols = growth in culture; open symbols = growth after CD8+ cell depletion.

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