A publication of the
International AIDS Society-USA

IMPROVING THE MANAGEMENT OF HIV DISEASE

IN THIS Issue – Recent Advances In
• Immunopathogenesis of HIV Infection
• In Vivo Dynamics of HIV
• Strategies for Continuing Antiretroviral Therapy
• Antiretroviral Resistance and HIV Dynamics

VOLUME 3 ISSUE 1 JUNE, 1995
This issue of Improving the Management of HIV Disease is the first in our publications derived from programs sponsored in 1995 by the International AIDS Society-USA. For the third consecutive year, IAS-USA has sponsored such educational programs nationwide for clinicians and practitioners under the title of “Improving the Management of HIV Disease: An Advanced Course in HIV Pathogenesis, Antiretrovirals, and Selected Populations with HIV.” This publication highlights selected presentations at IAS-USA-sponsored programs; this issue is derived from symposia in Atlanta and Los Angeles. The next two issues will highlight recent information on the status of new nucleoside and nonnucleoside reverse transcriptase inhibitors, protease inhibitors, HIV disease in women and in children, and gene therapy in HIV disease. In addition, IAS-USA has initiated a national educational effort on the management of symptomatic HIV disease. Future issues of this publication will summarize presentations from that program.

IAS-USA is a 501(c)(3) nonprofit organization committed to improving the treatment, care, and quality of life of persons with HIV disease by providing balanced and relevant information to physicians that is particularly intended to bridge clinical research and patient care.

Unrestricted educational grants, which support these programs, have been provided by Bristol-Myers Squibb, Burroughs Wellcome Co., and Roche Laboratories. These companies have shown a continued commitment to support independent, balanced, and scientifically rigorous educational programs on HIV/AIDS. IAS-USA is grateful for this support. IAS-USA is also grateful for the additional unrestricted grants from Abbott Laboratories for the Atlanta program and from Chiron Corporation for the Los Angeles program. None of the companies providing financial support have any input or control over the selection of speakers or the content of presentations.

**Program Faculty**

**Atlanta Program**

**Chairs**
Michael S. Saag, MD
University of Alabama at Birmingham
Melanie A. Thompson, MD
AIDS Research Consortium of Atlanta

**Faculty**
Victoria A. Johnson, MD
University of Alabama at Birmingham
Daniel R. Kuritzkes, MD
University of Colorado Health Sciences Center
H. Clifford Lane, MD
National Institutes of Health
Jeffrey Lennox, MD
Emory University School of Medicine
Kathleen E. Squires, MD
University of Alabama at Birmingham
Paul A. Volberding, MD
University of California San Francisco

**Los Angeles Program**

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University of California Los Angeles
Paul A. Volberding, MD
University of California San Francisco

**Faculty**
Yvonne J. Bryson, MD
University of California Los Angeles
Andrew H. Kaplan, MD
University of California Los Angeles
H. Clifford Lane, MD
National Institutes of Health
Alexandra M. Levine, MD
University of Southern California School of Medicine
Steven A. Miles, MD
University of California Los Angeles
Douglas D. Richman, MD
University of California San Diego
Robert T. Schooley, MD
University of Colorado School of Medicine
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IMMUNOPATHOGENESIS OF HIV INFECTION

The immunopathogenesis of HIV infection was discussed at both the Atlanta and Los Angeles meetings by H. Clifford Lane, MD, from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD.

As noted by Dr. Lane, the primary clinical problems associated with HIV infection are the opportunistic infections and neoplasms that occur as a result of the severe immunodeficiency that develops during the course of disease. The hallmark of this immunodeficiency is the decrease in quantity and function of CD4+ lymphocytes. As related by Dr. Lane, the relative immune function in an HIV-infected individual is the net result of three competing forces: (1) destruction of CD4+ lymphocytes by the virus; (2) the ability of the patient to mount an immune response in an attempt to contain infection; and (3) the ability of the immune system to regenerate and to replenish CD4+ cells. Dr. Lane’s presentation focused on the latter two components.

Immunologic Effector Mechanisms

Immunologic effector mechanisms important in the control of HIV infection include: (1) production of neutralizing antibody; (2) lysis of antibody coated cells; (3) induction of cytotoxic CD8+ T lymphocytes; (4) lysis of HIV-infected cells by natural killer (NK) cells; and (5) the activity of the helper/inducer CD4+ lymphocytes. The functioning of CD4+ lymphocytes is crucial for coordinating immune function and response. These cells also elaborate cytokines that facilitate much of the complex communication and interaction among the different cells of the immune system.

As explained by Dr. Lane, compared with healthy controls, alterations in patterns of cytokine production have been described in HIV-infected individuals and appear to be secondary to the destruction of CD4+ lymphocytes rather than a primary cause of HIV-related immunodeficiency. CD4+ lymphocytes may function in host defense against HIV infection by regulating CD8+ cell responses, antibody production, macrophage function, and NK cell function, much of which is mediated by cytokine production. Nonspecific immune responses to HIV infection may include two primitive elements of the immune system: complement, proteins that facilitate lysis of cell membranes and mediate leukocyte chemotaxis, and NK cells, which recognize and kill such altered cells as tumor cells and virus-infected cells. These immune mechanisms have relatively weak effects against HIV. CD8+ cells may also nonspecifically inhibit HIV replication through both cytotoxic and noncytotoxic effects.

HIV-Specific Immune Responses

Specific immune responses to HIV infection include HIV-specific cytotoxic (CD8+) T cells and HIV-specific antibody responses. That the immune system is at least partially effective in controlling HIV replication following primary infection is evidenced clinically by the long time between infection and disease and histologically by the containment of viral particles in the germinal centers of lymph nodes. It remains unclear which of the HIV-specific immune responses play the major role in controlling infection.

In general, the cytotoxic CD8+ cells play an important role in controlling viral infections and tumors. HIV-specific cytotoxic T cells recognize, bind to, and lyse HIV-infected cells. These functions are enhanced by interaction with CD4+ lymphocytes. Cytotoxic T cells also elaborate several cytokines important in HIV-specific immunity, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (INF-γ). As related by Dr. Lane, studies have shown that there are high levels of CD8+ cells in healthy homosexual men and in individuals with relatively early HIV infection compared with controls and lower levels of CD8+ cells in

![Graph showing percentage lysis of K562 target cells in vitro by lymphocytes from subjects without HIV infection or subjects with AIDS in the presence of interleukin-2. Adapted from Rook AH, et al. J Clin Inves 1983.](image-url)
individuals with much later stage infection (e.g., those with opportunistic infections). Dr. Lane presented data showing that T-cell specific killing of cytomegalovirus (CMV), as well as NK activity, are markedly reduced in patients with AIDS. In comparison between six bone marrow transplant recipients and seven AIDS patients with CMV infection, NK killing of CMV was reduced from 61.1% to 34.1%; more striking was the comparative reduction in T-cell specific killing of CMV, which was 26.6% in the controls and 0.5% in the AIDS patients. As explained by Dr. Lane, the lytic activity of the cytotoxic T cells from both healthy individuals and AIDS patients is enhanced by in vitro incubation of cells with interleukin 2 (Figure 1). The ability to increase this activity in cells from AIDS patients indicates the absence of an intrinsic defect in the cells and suggests that the diminished activity may be due to a defect in the ability of the host to induce cells to perform their normal effector functions. This induction would appear to occur through CD4+ lymphocyte-regulated cytokine elaboration. Thus, it may be the loss of the CD4+ cells that ultimately comprises the crucial defect in HIV-specific immunity.

HIV-specific antibodies, the other element of the specific immune response, bind to HIV and facilitate trapping of virus by follicular dendritic cells in the lymph nodes. These antibodies may directly neutralize virus and they also mediate antibody-dependent cellular cytotoxicity (ADCC), in which they bind virus or virally-infected cells that are subsequently killed by cells expressing Fc receptors.

As sketched by Dr. Lane, the current understanding of the immune response to HIV infection is as follows: After acute primary infection, there is brisk viral replication, prompting induction of cytotoxic T cells and antibody production. With mounting of this response, the level of circulating virus decreases. This decrease is associated with killing of HIV-infected cells by cytotoxic T cells and antibody binding and trapping of virus by the follicular dendritic cells of the germinal centers of the lymph nodes. In early infection, there is a heavy concentration of trapped virus. As viral replication continues, lymph node architecture begins to be lost and trapping of virus is decreased. Very little virus trapping is evident in late-stage disease (Figure 2). Concomitantly, in initial infection, there are very few HIV-infected cells in the lymph node. The concentration increases with progression of infection; this is also seen with regard to the proportion of infected cells in the peripheral circulation. Genotypic analysis of lymph node proviral DNA has shown that the sequences are much more closely related to sequences in plasma
than to the proviral DNA in circulating peripheral blood lymphocytes. This suggests that the lymph nodes are the site of ongoing active virus replication and the source of virus that eventually becomes evident in large quantities in the circulation (Figure 3).

**CD4+ Lymphocyte Deficiencies**

As stated by Dr. Lane, it is the lack of ability to contain infection that appears to lead to the progressive decline in CD4+ lymphocyte count and progressive immunosuppression in HIV infection. Precisely how HIV destroys CD4+ lymphocytes continues to be investigated. The primary factor appears to be cell death as a consequence of productive infection. Potential explanations for how this occurs include intracellular accumulation of nonintegrated viral DNA, toxic effects of viral proteins, and alterations in cell activation related, for example, to abnormalities in biochemical pathways that control the cell cycle. There is an increasing body of evidence that HIV infection causes cell death by triggering programmed cell death (apoptosis). The process can be understood as a suicide cascade of biochemical events leading to disintegration of the cell nucleus. This is a normal physiologic cellular pathway; it is used by the immune system in ontogeny to eliminate self-reactive clones and is important in tissue remodeling. According to Dr. Lane, the evidence that HIV invokes this pathway upon direct infection of CD4+ lymphocytes is much stronger than evidence that it can trigger the process without infection of the cell.

**Functional Characteristics of CD4+ Lymphocytes**

As explained by Dr. Lane, a number of interesting findings have been made regarding the functional capacities and the source of CD4+ lymphocytes in HIV-infected individuals. Normal functional characteristics of CD4+ helper/inducer T-lymphocytes include: (1) proliferation in response to mitogen, alloantigen, or protein antigen stimulation; (2) providing help to B lymphocytes; and (3) providing inductive signals for a variety of immunologic functions. Studies of the proliferative responses of T cells to mitogenic and antigenic stimulation have shown decreased activity in AIDS patients compared with controls. However, this deficiency is not an intrinsic deficiency of the T cells; see Figure 4. Studies with pokeweed mitogen stimulation have shown that the decreased proliferative response in unfractionated samples from AIDS patients is associated with an alteration in the ratio of CD4+ to CD8+ cells in these patients. Fractionated CD4+ and CD8+ cells respond to mitogen stimulation in a manner more comparable to those from control patients. Similarly, it was found that although response to alloantigen stimulation was decreased in unfractionated samples from AIDS patients, responses were actually comparable to control samples when correction was made for the relative decrease in CD4+ cell number. The decreased response to soluble protein or recall antigens, however, appears to be profoundly diminished and is not attributable to numerical or proportional CD4+ cell abnormalities alone. As shown in Figure 4, the deficient response to tetanus toxoid is present even when purified CD4+ lymphocytes are tested, thus indicating that the ability to recognize and respond to recall antigen is indeed lost in HIV infection. It appears that response to antigens that are present in relatively low frequency, such as tetanus toxoid, are lost relatively early in infection; responses to Pneumocystis or CMV antigens, however, to which a greater proportion

![Figure 4. Proliferation responses of normal and AIDS lymphocytes to (left) pokeweed mitogen, (center) alloantigen, and (right) tetanus toxoid when samples were un-fractionated (UF) or fractionated into CD4 and CD8 subsets. Adapted from Lane HC, et al. N Engl J Med 1985.](image-url)
of the T cell repertoire is devoted, are evident even in later stage disease.

Source of CD4+ Cell Replenishment

Investigations of the survival patterns of CD4+ cells and of the loss of antigen responsiveness by Dr. Lane and colleagues have yielded notable results. There is always turnover of T cells of the immune system. Studies of the rates of spontaneous T lymphocyte division have shown that rates for both CD4+ and CD8+ cells fractionated from peripheral blood are substantially higher in AIDS patients than in HIV-negative controls (Figure 5). This is due in part to the fact that the body is attempting to replace the CD4+ cells destroyed through HIV infection.

In a series of studies in identical twins discordant for HIV infection, Dr. Lane and colleagues have found that the source of the T cell replenishment appears to be division of existing mature T cells rather than stem cell differentiation—a finding that has implications for whether losses in T cell repertoire are reversible. In these studies, lymphocytes from the twin without HIV infection were tagged with a genetic marker and infused in the HIV-positive twin; consecutive samples were taken from the HIV-positive twin and analyzed by polymerase chain reaction (PCR) for the marker. It was expected that the proportion of marked cells would rapidly decrease with time as cells were destroyed and cell replacement occurred via stem cells differentiating through the thymus or a comparable extrathymic environment. However, it was found that responses were variable, with proportions of marked cells declining slowly in some individuals and remaining stable in others. The persistence of marked cells was observed for both CD4+ and CD8+ cells. Study of lymph node biopsies showed that the proportion of marked CD4+ cells in the peripheral circulation was similar to that in the lymph nodes in most cases. According to Dr. Lane, these findings indicate both that the T cells that are turning over are primarily the existing mature cells, with very little contribution from stem cell differentiation, and that there is a remarkable distribution of CD4+ cells between the peripheral blood and the lymphoid tissue. Dr. Lane stated that the findings raise some question regarding whether there is any significant stem cell differentiation to T cells in adults in general, regardless of HIV disease status.

A potential implication of these recent findings is that antigen-specific responses are lost from the T cell repertoire, they may not be able to be recovered. In the normal situation, there are different proportions of the T cells specific for particular antigens with small populations of antigens encountered relatively infrequently, such as tetanus, and greater populations for more ubiquitous antigens, such as Pneumocystis or CMV. Replenishment of the T cell pool as part of natural remodeling occurs through somatic cell division and perhaps through a thymic pathway, as well, with the continued division of the mature cells ensuring persistence of antigen-specific responses. In the case of HIV infection, with the increased rate of cell death, antigen-specific T cells present in low frequency may disappear entirely from the T cell pool. In the absence of entry of truly new cells through stem cell differentiation, numeric replenishment from somatic cell division will not keep pace with T cell destruction and the ability to mount certain antigen-specific responses may thus be lost. As stated by Dr. Lane, it may be that the gains in CD4+ cell count that occur with antiretroviral or immunologic therapy may not be accompanied by reconstitution of lost elements of the host’s antigen-specific repertoire. Whether such reconstitution can or does occur is the subject of ongoing investigation.

H. Clifford Lane is Clinical Director at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.
IN VIVO DYNAMICS OF HIV INFECTION

The dynamics of HIV in vivo was discussed at the Atlanta meeting by Michael S Saag, MD, from the University of Alabama at Birmingham.

As related by Dr Saag, the novel techniques for quantitating viral burden in plasma, including most prominently the quantitative PCR and branched-DNA (b-DNA) assays for plasma HIV RNA, have altered the frameworks both for understanding HIV dynamics in vivo and for developing and implementing treatment strategies. The relative inability to culture virus from the peripheral circulation and the finding of relatively low numbers of infectious virus in cultures taken after resolution of the viremia following acute primary infection encouraged the belief that viral infection was quiescent during the prolonged asymptomatic stage of disease. However, pathology studies showing high levels of ongoing viral replication in lymphoid tissue, and PCR and b-DNA assay findings showing that plasma HIV RNA remains high throughout the course of infection, have combined to change the view of HIV as an infection with a quiescent stage. The plasma RNA assays have shown that the viral load in plasma at the time of initial infection is extraordinarily high (10^6 to 10^7 virions/mL) and that there is a dramatic decrease in viral level with the onset of HIV-directed immune response. Viral load nevertheless remains at significant levels (10^5 to 10^6/mL) throughout the so called clinically latent period. In addition to demonstrating that viral replication is ongoing throughout infection, the assay findings indicate the potency of the initial immune response to infection.

As stated by Dr Saag, the plasma RNA PCR and b-DNA assays have been shown to have highly correlated results (Figure 6). The high degree of correlation indicates that the two assays are indeed providing an accurate measure of the same quantity, namely the HIV RNA present in plasma samples. Early blinded findings with one of the RNA PCR (QC-PCR method) assays showed that all HIV-negative controls were negative for HIV RNA in plasma and that different stages of infection, corresponding to acute seroconversion, ‘asymptomatic’ disease, AIDS-related complex, and AIDS, were characterized by different RNA levels. In this study, patients with acute infection had 1 million to 20 million RNA copies/mL, those with asymptomatic disease had levels approximately three logs (a factor of 1000) lower, and those with later stages had successively higher viral loads. As noted by Dr Saag, such findings have resulted in a reformulation of the proposed general immunologic and virologic course of HIV disease (Figure 7), with the revised scheme representing the potency of host immune response in curtailing viral replication and, at the same time, the persistently high level of replication as indicated by the high level of plasma viral RNA.

Rapidity of Viral Turnover Demonstrated with Antiretroviral Treatment

Recent studies have investigated the dynamics of HIV replication in vivo, including the effects of antiretroviral therapy. A study initiated in 1992 by Dr Saag and colleagues included assessment of virologic responses to zidovudine treatment using a variety of assays, including RNA PCR and b-DNA assays. Figure 8 shows the virologic response in 12 patients, many of whom had been receiving zidovudine previously and had undergone a drug-washout phase. The data show that there was a 75% reduction in plasma viral burden that persisted throughout the 6 weeks of treatment and that the viral burden returned to pretreatment level within 1 week of stopping treatment. According to Dr Saag, an implication of these findings, although it was not fully appreciated at the time of the study, is that the viral turnover in vivo is
diversity of the viral population and its rapid turnover rate, resistance appears to occur as a result of selection of preexisting mutants under antiretroviral pressure, with what is initially a minority quasispecies becoming the predominant species over time. He noted that this also implies that resistant mutants are in some sense at a competitive disadvantage to wild type virus. Since resistance is very rarely observed de novo in infected individuals, indicating that any preexist in resistant mutants represent a small minority of the viral population, wild type virus is likely more "fit" from a Darwinian perspective than is virus with resistance traits. Precisely how much less "fit" resistant mutants are could have important implications for therapy and requires further study.

Development of Resistant Mutant Population

Figure 9 shows the virologic response in one patient to the addition of nevirapine to zidovudine/didanosine treatment; plasma HIV RNA levels dropped 80% from 103,000 copies/mL at baseline within 14 days and then rapidly returned to the baseline level. Genotypic analyses in patients receiving nevirapine showed that specific mutations were associated with the development of phenotypic resistance and that resistant mutants could be found early after initiation of treatment. Use of an automated DNA sequencing device has permitted assessment of the proportion of isolates in a given sample that possess a particular mutation at different reverse transcriptase codons. Analysis by Dr Saag and colleagues of sequential samples from patients in whom nevirapine was added to existing antiretroviral treatment confirmed that a complete turnover of the plasma viral population to virus with a resistance mutation at a particular codon can occur in a few weeks after the addition of nevirapine.

Dr Saag described data on four patients who had nevirapine added to their regimen showing the proportion of functional clones retrieved from the patients and the proportions of nevirapine-sensitive and nevirapine-resistant clones in plasma and in peripheral blood mononuclear cells (PBMCs) over various

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Rapid Achievement of Genetic Diversity

Further evidence of the rapidity of viral turnover has come from genotypic analyses of virus in vivo. Findings made by Dr Saag’s group, as well as others, indicate that there is a rapid development of genotypic heterogeneity in the viral population following initial infection. Initially, viral isolates constitute a "cloud" of genetically distinct, highly related virions, which appear to arise from a common progenitor; over time, with replication and mutation, the population is characterized by quasispecies or "swarms" of genetically variant virions that change over time under selective pressure.

Dr Saag underlined the rapidity with which HIV develops variants with data from one patient studied by his group: in a patient presenting with symptomatic acute infection, all 44 peripheral blood clones of HIV obtained proved to be genetically identical, indicating a common progenitor; of 21 clones taken 3 weeks later, 11 were genetically distinct. The ability of the viral population to achieve such great genetic heterogeneity can be explained by high replication and mutation rates. According to Dr Saag, the virus makes on the order of two to three transcription errors per copy; many of these mutations are likely to represent terminal deletions or stop codons in the genetic material, rendering the virus replication-incompetent.

However, some mutations will result in viable virus. It is this ability of the virus to achieve genotypic diversity that appears to underlie the rapid appearance of resistance to some antiretroviral agents. As stated by Dr Saag, given the wide genetic

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The HIV population rapidly achieves genotypic diversity in vivo

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Figure 8. Virologic and CD4+ cell count response to initiation and withdrawal of zidovudine treatment. Zidovudine was administered to 12 patients for 6 weeks. Virologic response was assessed by standard p24 antigen assay, immune-complex dissociated (ICD) p24 assay, quantitative-competitive PCR plasma RNA assay, and b-DNA plasma RNA assay. Adapted from Cao Y, et al. AIDS Res Hum Retroviruses. 1995.

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Figure 9. CD4+ cell and plasma HIV RNA responses to addition of nevirapine to existing antiretroviral treatment in a single patient. Baseline CD4+ count was 106 cells/µL; baseline bDNA level was 103,000 RNA molecules/mL. Figure courtesy of Dr Saag.
durations of treatment. The proportion of isolates resistant to nevirapine increased quite rapidly and faster in plasma than in the PBMCs. For example, in one patient, nearly two thirds of clones from plasma were nevirapine-resistant by day 14, with 100% being resistant by day 28; for PBMC samples, no resistance was observed over the first 14 days of treatment, while half of the clones were resistant by day 28, and three-quarters were resistant by day 140. As explained by Dr Saag, the proportion of resistant clones in PBMCs has never been observed to reach 100%; this finding suggests that whereas virus in plasma would appear to be newly produced virus, the circulating PBMCs represent more of a reservoir of past generations of virus, with at least a proportion of surviving cells having been infected with and continuing to produce susceptible progeny.

**Rate of Viral Turnover**

Detailed kinetic studies of changes in viral load with initiation of nevirapine treatment performed by Dr Saag and colleagues have permitted estimates of the rate of viral turnover. As can be seen from Figure 10, 98% to 99% decreases in plasma viral burden occurred within a few weeks of beginning treatment. The kinetic analyses showed that the half-life of virus in the plasma is approximately two days, indicating that 30% of the virus detected in plasma at any given time was produced within the past 24 hours. As shown in Figure 11, similar findings were made in patients receiving protease inhibitor monotherapy. As noted by Dr Saag, currently used antiretrovirals act at the reverse transcription stage of replication and have no effect in chronically infected cells that constitutively produce virus. The 98% to 99% decrease in viral load indicates that it is precisely the newly produced virions that are being affected. If a greater proportion of virus was being constitutively produced by chronically infected cells, the drop in viral load in response to current agents would be more gradual.

**CD4+ Cell Kinetics in Infection**

Kinetic studies of changes in CD4+ lymphocyte counts have indicated that more than 1 billion new cells are produced each day in response to infection. Overall, at a given time, there is approximately one trillion lymphocytes in the lymphoid organs. It can be estimated that some significant proportion—e.g., 10% to 25%—are HIV-infected. Thus there are perhaps 100 billion covertly infected lymphocytes (i.e., if one tenth of the total are infected), with most being quiescently infected and with some proportion harboring deficient or replication-incompetent virus. Productively infected cells account for approximately 1 billion of the infected cells. It is speculated that the virus from these cells spills out from the lymphoid organs into the plasma, such that measurement of plasma viremia provides an indication of the level of uncontrolled viral replication in the lymphoid tissues. Further, changes in plasma viral levels during treatment provides an indication of the antiretroviral effect of the therapy on active replication.

As elaborated by Dr Saag, the picture that emerges is that of a titanic struggle between the immune system and the virus that begins on day 1 of infection and continues throughout the course of the infection.
of disease. The immune system creates a hostile environment that the virus attempts to overcome through sheer force of numbers. Dr Saag noted that although the goal of reducing viral production in plasma to zero has not been achieved with current antiretroviral therapies, reductions of from $10^6$ to $10^3$ copies/mL have been accomplished. Dr Saag suggested that the remaining virus represents production from the pool of cells that are chronically infected and constitutively producing virus, and noted that this component of the viral population will not be affected until drugs active against integrated provirus are available. He also stressed, however, that the ability to reduce viral burden from 1 million to 1000 virions/mL and to maintain it at this reduced level for years would constitute a significant therapeutic achievement.

The ability to assess viral burden and response to treatment may permit individualization of therapy.

**Treatment Implications**

Dr Saag maintained that the advances in understanding of viral dynamics in vivo motivate a shift in the paradigm of antiretroviral therapy to one of treatment being tailored to the individual patient. Clinical studies provide a good idea of drug safety and perhaps of the relative activity of different regimens, but they do not provide guidance on how the individual patient should be treated. Each patient is host to a unique population of viruses and exhibits a unique immune response. As an example of the failure of clinical trials to provide a good idea of how the individual is best treated, Dr Saag posited the administration of identical regimens to two patients for a 3 year period, with one patient developing resistant virus within weeks of beginning treatment and the other harboring virus that remains sensitive to the treatment for the entire course of the study. As related by Dr Saag, treatment in former is essentially equivalent to providing a patient with hypertension treatment for several weeks, after which the patient becomes refractory, and then following the patient for more than 2 years with essentially no treatment.

The ability to assess viral burden and effect of treatment on viral burden may allow individualization of therapy; Dr Saag identified the relating of viral load to clinical outcome as a primary research task in the coming year.

*Michael S. Saag is Associate Professor of Medicine and Director of the AIDS Outpatient Clinic at the University of Alabama at Birmingham, Birmingham, Alabama.*
STRATEGIES FOR CONTINUING BENEFIT FROM ANTIRETROVIRAL THERAPY

Strategies for continuing benefit from antiretroviral therapy were discussed at the Atlanta meeting by Daniel R. Kuritzkes, MD, from the University of Colorado Health Sciences Center in Denver.

Dr Kuritzkes’s presentation was largely devoted to a review of clinical trial data on available nucleoside analogues, with some discussion of how such data might affect treatment decisions in patients who have received initial therapy for a given duration and are doing well or who are considered to be failing initial treatment on the basis of virologic, immunologic, or clinical parameters. The discussion generally assumes that initial treatment consists of zidovudine monotherapy. Zidovudine has been found to be superior to other nucleoside analogues in head-to-head comparisons in previously untreated patients and is commonly used as first-line treatment. As noted by Dr Kuritzkes, however, a growing body of data suggests that combination treatment produces greater and more sustained immunologic and virologic effects than does monotherapy. Whether combination therapy will ultimately be considered first-line treatment depends on the results of ongoing study of whether the enhanced response to such therapy is associated with clinical or survival benefits.

Didanosine

In ACTG 116B/117, patients with CD4+ cell counts <300/μL who had received at least 16 weeks of zidovudine monotherapy were randomized to continued zidovudine 600 mg/d or didanosine at dosages of 500 or 750 mg/d. Patients had received an average of approximately 1 year of zidovudine therapy. It was found that: (1) the lower didanosine dosage was associated with fewer new AIDS-defining events or deaths compared with zidovudine treatment; (2) didanosine significantly delayed onset of AIDS or death in patients with AIDS-related complex or asymptomatic disease (Figure 12); (3) survival was equivalent in the three treatment groups; and (4) the duration of prior zidovudine treatment did not alter the benefit of didanosine treatment.

These findings were confirmed in a subsequent study by Spruance et al in patients progressing (continued decline in CD4+ cell count or recurrence of AIDS-defining illnesses) during zidovudine treatment; in this study, didanosine recipients exhibited delayed progression compared with patients who continued on zidovudine treatment (Figure 13). In another study (ACTG 116A), patients who had received zidovudine for 16 weeks or less received didanosine or continued zidovudine. Zidovudine was superior to didanosine in patients with no prior zidovudine treatment, the treatments were equivalent in patients who had received less than 8 weeks of prior zidovudine, and didanosine treatment was superior in those receiving 8 to 16 weeks of prior zidovudine. As noted by Dr Kuritzkes, the overall data indicate that patients who have been receiving zidovudine treatment may benefit from a change to didanosine treatment but do not provide guidelines for when such a switch should be made. Based on the hypothesis that the benefit of didanosine, which does not exhibit cross-resistance with zidovudine, was associated with the presence of zidovudine resistance, a virology study involving a subset of ACTG 116B/117 patients was performed to assess the impact of phenotypic and genotypic zidovudine resistance on treatment outcome. It was found that patients harboring virus with phenotypic resistance or zidovudine resistance mutations were more likely to progress irrespective of the treatment they received and that the benefit of switching to didanosine could not be accounted for solely on the basis of zidovudine resistance. According to Dr Kuritzkes, one conclusion of this study is that monitoring for zidovudine resistance may not be helpful for determining when alteration of treatment should occur.

The most common serious adverse event in patients taking didanosine is pancreatitis. The incidence of this adverse effect has ranged from 2.5% to 8% in different patient series. Approximately 6% of cases have been fatal, with the overall rate of fatality due to pancreatitis being approximately 0.3% in all treated patients.

Zalcitabine

In ACTG 114, zalcitabine was compared with zidovudine in previously untreated patients with CD4+ lymphocyte counts of less than 300/μL. It was found that zidovudine treatment was associated with a lower risk of clinical disease progression and increased survival. In CPRCA 002, patients who were either intolerant or who had failed zidovudine treatment were given either didanosine or zalcitabine. The patients had very advanced disease, as indicated by the median CD4+ cell count of 37/μL. No significant difference between treatments was observed regarding disease progression or death. According to Dr Kuritzkes, although the conclusion of the study was that the two agents were

![Figure 12. Probability of remaining free of new AIDS-defining event or death for asymptomatic patients or patients with AIDS-related complex among two didanosine dosage groups and continued zidovudine group in ACTG 116B/117. All patients had received ≥16 weeks of prior zidovudine treatment. Adapted from Kahn JO et al. N Engl J Med 1992.](image)
of equivalent efficacy in the patient population, it is possible that, given the advanced illness of the study patients, drug therapy was of little benefit in many patients. Two thirds of patients experienced adverse events. Peripheral neuropathy, the primary toxicity of zalcitabine, was significantly more frequent among zalcitabine recipients, whereas gastrointestinal events were more common in didanosine patients. Stomatitis occurred only in zalcitabine recipients and pancreatitis occurred only in didanosine recipients.

**Stavudine**

Stavudine has been granted provisional approval by the FDA on the basis of analysis of CD4+ cell count and p24 antigen responses in a study sponsored by Bristol-Myers Squibb (BMS 019) comparing stavudine with continued zidovudine in patients with 50 to 500 CD4+ cells/µL and less than 6 months of prior zidovudine therapy. Initial analysis showed that stavudine treatment was associated with a significant increase in CD4+ cell count and decreases in viral load as measured by p24 antigen levels and viral titers in PBMCs, with patients who continued on zidovudine exhibiting a progressive decline in CD4+ count. The differences in CD4+ cell counts and HIV viral load between the two treatments remained significant after 48 weeks of follow up. Subjects who received stavudine had a longer time to a protocol-defined treatment failure than subjects who received zidovudine ($P = 0.002$). Progression to AIDS and death also favored stavudine ($P = 0.007$); subjects who received stavudine had a longer survival time, but the difference was not significant ($P = 0.07$).

The primary toxicity of stavudine is peripheral neuropathy. In BMS 019, approximately 20% of patients exhibited some symptoms of peripheral neuropathy over 24 months of follow up. Another open-label study indicates that the incidence of neuropathy is dose-related. A low dose of stavudine is currently recommended for compassionate use. Study of a higher dose of stavudine continues, and the ultimate optimum dosage recommendations for this drug remains to be determined.

**Combination Therapy**

As stated by Dr Kuritzkes, there are a number of compelling reasons to add another agent to zidovudine treatment in patients who have clinical disease progression on zidovudine or who have received monotherapy for extended periods of time, to begin treatment with combination therapy. These reasons include the potential for additive or synergistic antiviral effects, prevention of emergence of resistance, and potentiation of the anti-HIV effect by attacking the virus at different stages of its life cycle. In vitro additive or synergistic effects in vitro have been observed for many combinations of antiretroviral agents against a number of HIV strains and including zidovudine-resistant virus. As noted by Dr Kuritzkes, the potential for limiting emergence of resistance has long held theoretical appeal but has been difficult to demonstrate. He stated that evidence of such an effect is beginning to emerge, particularly in the context of combination treatment with zidovudine and lamivudine (3TC). The potential for attacking the virus at different stages of its life cycle has begun to be realized with the advent of protease inhibitors as a potential combination treatment option.

Potential problems with combination therapy include overlapping toxicity, such adverse interactions as antiretroviral antagonism or pharmacokinetic opposition, difficulty with adherence, and cost. With regard to overlapping toxicity, Dr Kuritzkes stated that it may be unadvisable to combine stavudine and zalcitabine given the shared adverse effect of peripheral neuropathy. There are conflicting data concerning the potential antagonism of stavudine and zidovudine via competition for phosphorylation by intracellular kinases. To address this question, the combination is being tested in two ACTG trials.

Available data support the use of concomitant rather than alternating combination therapy, although a number of studies comparing the effects of the strategies continue. In a pilot study performed by Yarchoan and colleagues, patients received either zidovudine 300 mg/d plus didanosine 250 mg/d or alternating 3 week courses of zidovudine 600 mg/d and didanosine 500 mg/d. Mean changes in CD4+ cell counts in the concomitant and alternating treatment groups were +66/µL and +20/µL, respectively, at 18 weeks, +68/µL and +4/µL, respectively, at 27 weeks, and +75/µL and -12/µL, respectively at 54 weeks.

According to Dr Kuritzkes, there are now data from a number of small trials indicating superiority of combination therapy over monotherapy. In ACTG 106, patients receiving various dosages of zidovudine and zalcitabine in combination had significantly greater and more prolonged increases in CD4+ cell count than those receiving zidovudine monotherapy, although the monotherapeutic zidovudine dosage was much lower (i.e., 150 mg/d) than that currently used. In ACTG 143, symptomatic patients received didanosine alone or one of three zidovudine-didanosine combinations. Although increases in CD4+ cell count were similar among treatment groups, combination therapy patients exhibited a significantly greater reduction in viral load.

Similar results were observed in a pilot study of zidovudine plus zalcitabine. In a study comparing zidovudine monotherapy with zidovudine plus either zalcitabine or didanosine in patients with less than 300/µL CD4+ cells and less than 4 weeks of prior zidovudine, combination therapy patients had significantly greater increases in CD4+ cell count and reductions in viral load, as measured by plasma HIV RNA levels. Improvements in these

![Figure 13. Probability of clinical progression among patients who received either didanosine (ddI) or continued zidovudine (ZDV) after exhibiting clinical or immunologic progression on zidovudine monotherapy. Adapted from Spruance, et al. Ann Intern Med 1994.](image-url)
measures persisted for more than 1 year in the combination therapy group compared with 24 weeks in the zidovudine monotherapy group. Currently, there are data available from only one trial of combination therapy that included clinical end points. In ACTG 155, symptomatic patients with a CD4+ lymphocyte count ≤300/μL and asymptomatic patients with a count of ≤200/μL who had received at least 6 months of prior zidovudine received continued zidovudine, zalcitabine, or the combination of the two. The study as a whole did not show a benefit of combination therapy over monotherapy with regard to survival or disease progression. However, trend analysis showed a significant benefit of combination therapy compared with zidovudine monotherapy as pretreatment CD4+ cell count increased. In particular, it was found that combination therapy was associated with an improvement in clinical outcome compared with zidovudine monotherapy among patients with initial CD4+ cell counts ≥150/μL; combination treatment was also associated with a more sustained improvements in CD4+ cell count in this subgroup. Severe toxicities were less common in patients with higher CD4+ cell counts.

As related by Dr Kuritzkes, the treatment protocol in this study mandated that study medication be withdrawn in cases of toxicity, and toxicity was more common among combination therapy recipients who had both drugs withdrawn in cases of toxicity. Thus, particularly among patients with lower CD4+ cell counts, combination therapy patients received less cumulative drug therapy than did monotherapy patients, a factor that could at least in part account for the finding of no greater benefit of combination treatment in the lower CD4+ cell strata. Treatment protocols in subsequent, combination therapy studies have been designed to permit greater flexibility and discretion of clinical investigators in responding to toxicity, including the latitude to hold or discontinue only the drug believed to be responsible for the observed toxicity in a patient receiving combination treatment. Better information on toxicity management in the context of combination treatment can be expected from such studies. According to Dr Kuritzkes, a second large trial of combination therapy as either initial or subsequent treatment in patients with CD4+ cell counts of 200-500/μL (ACTG 175) is nearing completion.

**Lamivudine**

Dr Kuritzkes briefly reviewed some of the findings from trials with lamivudine (3TC), which is currently available from the manufacturer through an expanded access program. Rapid emergence of high-level resistance to lamivudine, associated with a mutation at codon 184 of the reverse transcriptase dampened the initial enthusiasm for this drug. However, it was subsequently found that although codon 184 mutants emerged within 4 weeks of treatment with lamivudine monotherapy, viral load remained at or below 50% of baseline values, suggesting a persistent antiviral effect despite the development of resistance. Other findings suggest the effectiveness of lamivudine-zidovudine combination treatment.

In two European studies assessing the combination of lamivudine-zidovudine, one in zidovudine-naive patients (NUCB 3001) and one in zidovudine-experienced patients (NUCB 3002), combination treatment resulted in significantly greater and more sustained elevations in CD4+ cell counts than did zidovudine monotherapy, with changes in viral load markers mirroring the CD4+ cell count responses. The emergence of zidovudine-resistant isolates appeared to be markedly delayed in patients receiving the combination regimen.

**Potential Strategies**

Dr Kuritzkes outlined potential strategies for continuing antiretroviral therapy in patients initially receiving zidovudine monotherapy. He indicated that alternative monotherapy might particularly be considered an option in asymptomatic patients with declining CD4+ cell counts that remain above 300/μL or who have been on zidovudine monotherapy for some time. In such cases, he suggested that didanosine or stavudine might be substituted for zidovudine. He indicated that lamivudine cannot yet be considered a rational choice for alternative monotherapy apart from its use in patients intolerant of the other nucleoside agents, given the concern about rapid emergence of resistance. He stated that although the available data indicate that lamivudine and zidovudine have roughly equivalent effects on viral load in zidovudine-naive patients when used as monotherapy, he would probably use stavudine or didanosine, as alternative monotherapy because of the data suggesting their clinical benefit, until further information on lamivudine becomes available.

Although alternative monotherapy is an option, it is his practice to add didanosine or zalcitabine to zidovudine in patients who appear to be progressing or who have been on zidovudine for some time. He suggested that zalcitabine may be better tolerated than didanosine in terms of compliance, given the problems with the palatability of the latter. Data comparing different combination regimes with monotherapy in terms of clinical outcome differences are expected from the analyses of ACTG 175 and CPCRA 007. The combination of zidovudine and stavudine is also being evaluated in a clinical trial, which should answer questions about antiretroviral antagonism. Lamivudine currently is available for use in patients progressing on zidovudine who have CD4+ cell counts less than 300/μL. As related by Dr Kuritzkes, the lamivudine compassionate-use program does not require that other antiretroviral treatment be discontinued. He predicted that, in light of the data suggesting a benefit of the lamivudine-zidovudine combination, many practitioners may begin to use this combination.

Finally, Dr Kuritzkes mentioned that a study in symptomatic pediatric patients comparing zidovudine, didanosine, and the combination of the two has been partly terminated. Although the trial is still partly blinded and analysis of the findings will not be completed until August 1995, it appears that the outcome in the zidovudine monotherapy arm was inferior to that in one of the other treatment arms, most likely the combination arm. Dr Kuritzkes stated that the final data from this trial may significantly influence thinking on whether therapy should begin with monotherapy or combination therapy.

Daniel R. Kuritzkes is Assistant Professor of Medicine, Microbiology, and Immunology at the University of Colorado Health Sciences Center, Denver, Colorado.
ANTIRETROVIRAL RESISTANCE AND HIV DYNAMICS

Douglas D. Richman, MD, from the University of California San Diego and the San Diego VA Medical Center, discussed aspects of HIV kinetics and antiretroviral resistance as part of a larger presentation on newer antiretroviral agents at the Los Angeles meeting. This portion of his talk is summarized herein.

Kinetics of Resistant Virus

As related by Dr Richman, with the introduction of an antiretroviral agent in a patient with relatively constant plasma viral RNA levels, there is no change in such levels for some 24 to 48 hours, during which viral replication in cells infected prior to treatment continues. Subsequently, there is a rapid reduction in viral load that is drug and dose dependent. For example, according to Dr Richman, with monotherapy the nucleoside analogues may produce a 0.5 to 1 log drop in viral load, the nonnucleoside reverse transcriptase inhibitors a decrease of approximately 1 to 1.5 logs, and the protease inhibitors a decrease of 0.5 to 2 to 3 logs, depending on the particular agent. The virus clearance rate can be calculated based on the rate of reduction in viral load. In cases in which viral load attains a constant level, it can be assumed that there is a dynamic equilibrium resulting in a steady-state level, with production rates matching clearance rates. When resistance emerges, such as in some cases of nevirapine resistance, the production of resistant virus may double every two days. The proportion of virus with resistance mutations can also be calculated. According to Dr Richman, in the case of the nonnucleoside reverse transcriptase inhibitors, this has been found to be approximately 1 to 2 per 1000 RNA copies circulating in the plasma; that is, a patient with 60,000 copies/mL plasma has approximately 100 copies/mL of resistant mutants prior to beginning treatment. Dr Richman stated that a similar scenario probably holds for all drug-resistance mutations.

A substantial proportion of HIV may have resistance mutations prior to patient exposure to drug treatment.

Implications of Viral Dynamics

The rapidity of the turnover of the viral population has several implications for pathogenesis and treatment of HIV disease. High levels of replication persist at all stages of infection, with the rate of replication appearing to be fairly constant throughout the course of the disease. Clearance of virus is also rapid and remains fairly constant throughout disease. It is only the steady-state levels of virus that appear to change, which is affected by the production rate of virus. Treatment can affect virus-steady-state levels by inhibiting production of virus. It is not clear if the rate of viral clearance can be increased. Chronically infected cells contribute only a negligible amount to the peripheral viral load, as is evidenced by the finding that although reverse transcriptase inhibitors do not impact viral production in such cells, treatment with such agents produces a remarkable reduction in viral load.

The implications of the presence of high levels of virus and high viral turnover for the assessment of antiretroviral drug activity are clear. With new techniques for quantitating plasma viral RNA, virtually all HIV-infected individuals can be evaluated for response to antiretroviral therapy. According to Dr Richman, a just-completed study of nevirapine in patients with CD4+ cell counts >500/µL showed that an effect on plasma viral RNA could be detected in every patient. Plasma HIV RNA assays can be used to determine whether a drug does or does not have a significant antiretroviral effect. Since maximal activity of antiretrovirals has been found to occur within a week of beginning treatment, such determinations can be made rapidly. It is likely that information about the relative activity of a drug or a dosage can be gained in short-term (eg, 2 week) studies in a relatively small number of patients (eg, 6 to 12). The ability to assess antiretroviral activity in this manner promises to have a major impact on the evaluation of new drugs.

Dr Richman noted that the long-term utility of agents or dosages shown to be active in the short term will still require longer follow-up, but that decisions regarding further development of candidate agents, optimal dosages, and optimal combinations can be made on the basis of these short-term studies. The quantitative assays also permit assessment of the magnitude and durability of antiretroviral effects. Dr Richman stressed that, in his opinion, the utility of plasma HIV RNA assays in evaluating antiretrovirals is a completely different issue from their use in patient management. He indicated that it is not yet known how to best use viral load information in making treatment decisions for the individual patient. Dr Richman noted that the high turnover of the viral population is reflected in a very accelerated turnover in CD4+ cells. The level of CD4+ cells in HIV infection is a function of the rates of CD4+ cell destruction and replacement. If approximately 1 billion CD4+ cells are being destroyed each day and patients' cell counts remain relatively unchanged from day to day, there is production of a huge amount of cells on a daily basis. Dr Richman stated that the ability to affect the course of HIV disease appears to reside in the ability to reduce the rate of destruction of CD4+ cells rather than to simply increase their number. He provided the analogy of the inadequacy of treating
chronic hemolytic anemia only with red blood cell transfusions (or treating idiopathic thrombocytopenia purpura with platelet transfusions) in suggesting that immune modulation alone in the face of high cell turnover would make little sense. Experience with the plasma HIV RNA assays has shown that there is a correlation between reduction of plasma RNA levels and CD4+ cell count increases and that the durability of CD4+ cell response is directly related to the durability of the plasma RNA response under treatment. Describing the view as being perhaps somewhat contentious, he asserted that restoration of immune function may be best achieved by antiviral or immunologic interventions that reduce HIV replication and resultant CD4+ cell destruction. Immune-based therapies may have promise only insofar as they affect virus production.

**Potential Mechanisms for Persistent Antiviral Effect Despite Drug Resistance**

It is reasonable to expect that resistant mutants will emerge to most antiretroviral compounds. Nucleoside analogues that closely resemble their physiologic nucleoside counterparts—e.g., didanosine, zalcitabine, and stavudine—appear to induce small or slowly occurring changes in susceptibility. High-level resistance has been observed with the nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and the nucleoside analogues with unusual sugars that may make them more easily distinguishable from physiologic nucleosides—e.g., zidovudine and lamivudine. As stated by Dr Richman, there are data demonstrating that development of resistance to some of these agents does not equal absence of antiretroviral effect in all cases.

According to Dr Richman, there are a number of potential mechanisms that may explain persistence of antiviral activity despite development of resistance. First, it is possible that plasma levels of drug can be generated that exceed the susceptibility of the resistant virus, a mechanism that is supported by data from patients receiving nevirapine. Second, drug resistance mutations may alter the replicative capacity of resistant virus rendering the mutant virus less fit than the wild type virus; according to Dr Richman, there are also some data to indicate that this does occur in some settings, such as the reverse transcriptase mutation at residue 184 that emerges with lamivudine therapy. Third, with combinations of drugs directed at a common target, the mutations induced by one of the drugs may increase susceptibility to the others or constrain the evolutionary options for acquiring resistance to the others; such a mechanism may be operative in the observed effects of the lamivudine-zidovudine combination as well as with combinations of protease inhibitors.

*Douglas D. Richman is Professor of Pathology and Medicine at the University of California San Diego, and San Diego VA Medical Center, San Diego, California.*
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