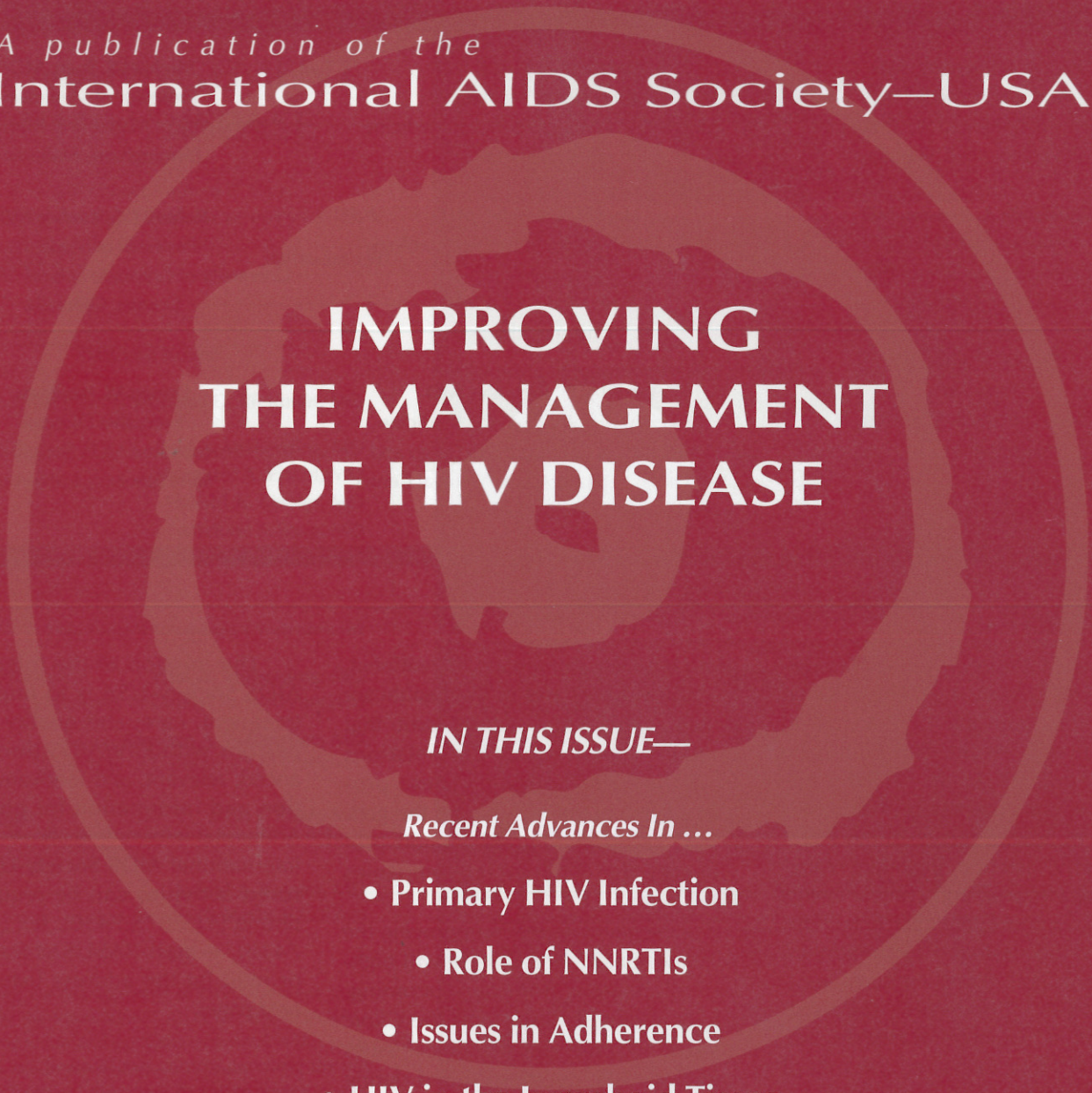


A publication of the
International AIDS Society—USA



**IMPROVING
THE MANAGEMENT
OF HIV DISEASE**

IN THIS ISSUE—

Recent Advances In ...

- Primary HIV Infection
 - Role of NNRTIs
- Issues in Adherence
- HIV in the Lymphoid Tissue



VOLUME 5 ISSUE 3

SEPTEMBER 1997

Paul A. Volberding, MD

Professor of Medicine
University of California San Francisco
San Francisco, California

Margaret A. Fischl, MD

Professor of Medicine
University of Miami School of Medicine
Miami, Florida

Michael S. Saag, MD

Professor of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Constance A. Benson, MD

Professor of Medicine
University of Colorado School of Medicine
Denver, Colorado

Harold A. Kessler, MD

Professor of Medicine and Immunology/
Microbiology
Rush Medical College
Chicago, Illinois

Robert T. Schooley, MD

Professor of Medicine
University of Colorado School of Medicine
Denver, Colorado

Peter C. Cassat, JD

Associate
Dow, Lohnes, & Albertson
Washington, DC

Douglas D. Richman, MD

Professor of Pathology and Medicine
University of California San Diego and
San Diego Veterans Affairs Medical Center
San Diego, California

Donna M. Jacobsen

Executive Director
International AIDS Society-USA
San Francisco, California

ABOUT THIS ISSUE...

This issue of *Improving the Management of HIV Disease* highlights selected presentations from the 1997 advanced CME courses. At the San Francisco course (April), Dr James O. Kahn discussed recent progress in the understanding of how to recognize and treat primary HIV infection, including recognizing the virologic and clinical events that occur immediately after initial HIV infection, the strategies for treatment, and recent data regarding early treatment studies. Concerning the treatment options available for HIV disease, Dr John P. Phair discussed the role of nonnucleoside reverse transcriptase inhibitors (NNRTIs) at the Chicago course (April), focusing on available clinical trial data and the role of NNRTIs in combination with protease inhibitors. At the San Francisco course, Dr Ashley T. Haase reviewed the kinetics of HIV and immune cell populations in the lymphoid tissue, where the bulk of viral replication is believed to occur, as well as the effects of antiretroviral treatment on HIV kinetics. Finally, there is a follow-up article to Dr Friedland's discussion of adherence to drug regimens in the last issue of *Improving the Management of HIV Disease*, this time highlighting Dr Margaret A. Chesney's review of adherence issues at the course in San Francisco. Dr Chesney reiterates that the complexity of drug regimens requires the patient to not only follow a

given regimen, but remain in treatment, in clinical trials, and in the healthcare system. This is the second issue that contains summaries of presentations from the 1997 courses. These programs were made possible by the generous, unrestricted grant support provided by the commercial companies listed below.

Subsequent issues of *Improving the Management of HIV Disease* will highlight discussions from our upcoming, newly designed *Cases from the Clinic* courses, wherein specific clinical issues and diagnostic questions raised during the everyday care of HIV-infected patients will be addressed by analyzing individual case studies. These cases, developed by a panel of 17 expert clinicians in the field of HIV disease, cover a wide array of issues that commonly arise in the treatment of HIV infection, including opportunistic infections, end-of-life issues, neurologic complications, and the role of antiretroviral therapy. Upcoming *Cases from the Clinic* courses are scheduled for September 26 in New York, October 4 in San Francisco, October 22 in Chicago, and November 4 in Los Angeles. These courses are intended to provide summaries of the most recent clinical and basic scientific findings, with the goal of bridging clinical research and patient care.

The mission of the International AIDS Society-USA is to improve the treatment, care, and quality of life of persons with HIV/AIDS through balanced, relevant, and innovative education and information for physicians. Additional information about upcoming International AIDS Society-USA-sponsored activities can be requested by phone (415-675-7430), fax (415-675-7438), e-mail (IASUSA1@aol.com), or mail (at the address listed on the next page).

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Editorial Board

Editor in Chief Douglas D. Richman, MD

Editorial Board Paul A. Volberding, MD
Margaret A. Fischl, MD
Harold A. Kessler, MD
Michael S. Saag, MD
Robert T. Schooley, MD

This Issue's Symposia Chairpersons

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

Stephen A. Follansbee, MD
University of California San Francisco

Chicago John P. Phair, MD
Northwestern University Medical School

Harold A. Kessler, MD
Rush Medical College

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© International AIDS Society—USA
353 Kearny Street
San Francisco, CA 94108
Phone: 415 675-7430 Fax: 415 675-7438
e-mail: IASUSA1@aol.com

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RECOGNITION AND TREATMENT OF PRIMARY HIV INFECTION

In the first decade of the AIDS epidemic, studies of the pathogenesis of HIV infection focused on the later stages of HIV disease. More recently, significant progress has been made in understanding the virologic and clinical events that occur immediately after the initial HIV infection, called primary HIV infection. At the San Francisco course James O. Kahn, MD, discussed this phase of HIV infection. He reviewed the definition of primary infection, how to recognize it clinically, and findings from studies evaluating treatment of this phase of the disease.

Definition of Primary HIV Infection

As with all infectious processes, infection with HIV starts when the uninfected and susceptible host receives an exposure to the pathogen sufficient to result in independent replication of the pathogen in the host tissues. Dr Kahn presented a definition for primary HIV infection incorporating two phases—phase I, or acute HIV infection, and phase II, or early HIV infection.

The distinction between primary infection and chronic infection, and between the two phases of primary infection (acute and early HIV infection), is based on the pathogenesis of HIV and the timing of the host immune response. Immediately after infection, rapid viral replication occurs in the tissues with a burst of viremia, measured as plasma viral RNA, that usually peaks within the first month (Figure 1). After this peak of virus replication the viremia decreases and then stabilizes. The peak in viremia coincides with the first appearance of an immune response, both humoral and cellular. There is delay of weeks to months between the ability to first detect virus in blood and tissues and the subsequent ability to detect antibodies. The time between the appearance of viral RNA and the appearance of antibodies is the period of acute HIV infection. Of note, neutralizing antibodies often do not appear for 6 months.

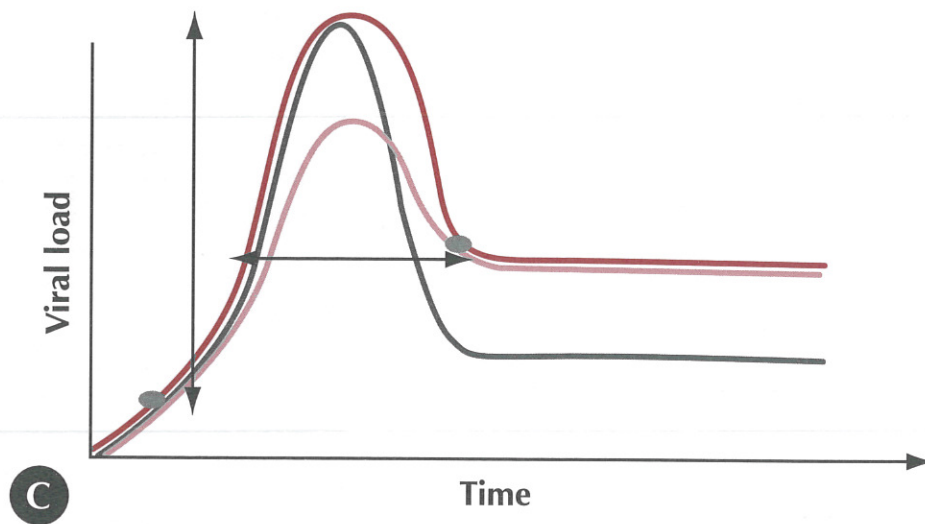


Figure 1. Model for the viral dynamics during primary HIV infection (see text).

Acute HIV Infection

The first phase of primary HIV infection, called acute HIV infection, constitutes approximately the first 30 days after the initial infection. According to Dr Kahn, acute infection can be further subdivided into three categories: A, B, and C (Table 1). In category A of acute infection the patient has evidence of viral replication (detectable HIV RNA by reverse transcriptase polymerase chain reaction [RT-PCR] or by branched DNA [bDNA]

assays) but there is no antibody measured by enzyme immunoassay (EIA) or by western blot analysis. In category B there is detection of viral RNA, the EIA assay can be positive or negative, and the western blot is indeterminate. Since about 5% of non-HIV infected individuals have an indeterminate western blot, the viral load measure may be able to distinguish true HIV infection from a false-positive serology. Category C acute infection is characterized by detectable HIV RNA in

Table 1. Defining and Characterizing Primary HIV Infection

Phase	Category	EIA	Western blot	Plasma HIV RNA
Acute HIV	A*	–	–	+
	B	+/-	Indeterm.	+
	C**	+/-	+	+
Early HIV†		+	+	+

* With evolution of antibody response or confirmation of HIV RNA.

** With a negative EIA or negative/indeterminant western blot in the previous 30 days.

† Within 12 months of a documented negative EIA.

plasma and evidence of antibodies by western blot, usually with an evolving pattern, but a known negative EIA or a negative or indeterminate western blot when tested within the prior 30 days.

Early HIV Infection

This subdivision of primary infection is similar to category C of acute infection, in that there is evidence of viral replication (detectable plasma HIV RNA) and antibodies by western blot, but the EIA serol-

The acute HIV syndrome mimics other, more benign viral infections, and is often not recognized as HIV in the primary care setting.

ogy has been negative within the prior 12 months. Detection of this category of infection follows the classic seroconversion technique used in diagnosing many viral diseases by obtaining two serum specimens, one collected before or during the onset of symptoms of acute infection, and one collected after the resolution of acute symptoms (the convalescent phase).

One caveat in using quantitative tests for viral RNA is that false-positive results occur in about 3% of cases. However, most false-positive values are low level, typically at or below 1,000 copies/mL, and such results should lead to a repeat test if serologic and clinical data are not definitive.

Recognition of Primary HIV Infection

In order to intervene in primary HIV infection, the clinician first must recognize the event that leads to the necessary laboratory tests. Currently there is inconsistent recognition and diagnosis of the clinical syndrome associated with primary infection, which occurs in approximately 80% of primary infections. In one evaluation of 23 laboratory-confirmed cases of acute infection, 20 patients (87%) had signs or symptoms at the time of infection. Of

these, 19 (95%) sought medical evaluation, but acute HIV infection was considered in only 5 of the 19 patients.

Table 2 shows the most common signs and symptoms associated with acute HIV infection, in order of frequency. Symptoms typically appear 1 to 4 weeks after the exposure to HIV. The acute retroviral syndrome mimics many other viral syndromes, except the common cold, since there are no rhinitis and coryza with acute HIV. Taking a detailed history, including recent sexual and injection drug practices, is an important part of the evaluation. A history of higher-risk behavior raises the index of suspicion and helps distinguish clinically other common viral infections from acute HIV infection.

Rationale for Treatment of Primary Infection

Theoretical Basis for Treatment of Primary Infection

Following the initial burst of viral replication and the peak of viremia, the plasma HIV RNA level decreases and then stabilizes to a level called the viral set point (light gray circle in Figure 1). The set point is the result of a number of factors, including the maximum or peak viral load, the duration of the viral burst, the viral replicative half-life, and the host immune response. Antiretroviral intervention could have several effects on the kinetics of the acute phase of infection. The peak viral load may be reduced without affecting the set point, as shown by the red curve, or, the peak viral load might not be affected, but the duration of the viral burst might be shortened, which would reduce the set point (pink curve).

The amount of replicating virus to which a person is exposed, conceptually the area-under-the-curve in Figure 1, may determine the damage done to the immune system and the later steady state viral load indicated by the set point. Theoretically with a lowered peak viral load there would be less seeding of the virus to the lymphoid and other tissues during the viral burst, which might reduce the overall body burden of HIV during the chronic infection. This might have important implications for "sanctuary sites" of HIV infection, such as the central nervous system. Additionally, the extent of the initial immune system damage may

Table 2. Signs and Symptoms of Acute HIV Infection

Sign or Symptom	Percent of Patients
Fever	87
Rash	68
Lymphadenopathy	55
Sore throat	48
Myalgia	42
Oral ulcers	40
Headache	39
Diarrhea	32
Genital ulcers	23
Perleche	6

Percentages are based on 30 patients with acute HIV infection.

From Kinloch-de Loës. Clin Infect Dis. 1993.

be lessened, reducing the level of immunocompromise during the chronic phase.

Lastly, according to Dr Kahn, the viral quasispecies (the spectrum of genetic variants) during the acute phase of infection is likely to be relatively more homogeneous than later in the infection. This is because virus produced during the early replicative cycles will be the progeny of a relatively limited genotypic repertoire of the small number of viral particles that initiated the infection. The rate at which HIV develops mutations that are resistant to antiretroviral drugs is proportional to

Treatment of primary HIV infection may be less likely to result in HIV resistance.

the genotypic heterogeneity of the viral population being treated. The more heterogeneous the genotypes the more likely that resistant mutants already exist in the population. Theoretically, patients with a more homogeneous infection would be less likely to develop resistance mutations, and there would be a better chance to eliminate all HIV replication with early treatment.

Primary Infection Studies

The NIAID announced the funding of an ambitious new program that focuses on innovative ways to study how HIV-1 causes disease in adults. Scientists at six research units will use interventions, such as highly active antiretroviral therapy given in the acute and early phases of infection, to increase the understanding of the mechanisms and course of HIV disease. They will also directly study the outcomes of these interventions.

The six *Acute Infection and Early Disease Research Program* principal investigators and their proposed research plans are:

- Lawrence Corey, MD, of the Fred Hutchinson Cancer Center in Seattle, will define the role of cytotoxic T-lymphocytes in controlling early infection and determine whether initial HIV-1 specific CD8+ T-cell responses are predictive of subsequent disease progression.
- David Ho, MD, of the Aaron Diamond AIDS Research Center in New York, will examine the effect of antiretroviral therapy on virus in the blood and lymphoid tissue on CTL response. His team also proposes to monitor B and T-cell responses.
- Jay Levy, MD, of the University of California San Francisco, will evaluate the effect of therapy on viral load, the rate at which the virus is produced, immune activation and CD8+ T-cell function.
- Joe Margolick, MD, of the Johns Hopkins University School of Medicine, will explore how the virus adapts to the host during early infection and determine whether treatment during acute infection allows the immune system to recover its function.
- Robert T. Schooley, MD, of the University of Colorado Health Sciences Center in Denver, proposes to examine the differences among virus in the lymph tissue and blood, and to determine the types of cells that are involved in active versus latent infection.
- George Shaw, MD, PhD, of the University of Alabama at Birmingham, will study where HIV is distributed and sequestered in the body and its form in various reservoirs, the dynamics of virus reproduction and the host immunogenetic profile.

NIAID press releases, fact sheets and other materials are available on the Internet via the NIAID home page at:

<http://www.niaid.nih.gov>.

Laboratory Data Supporting Treatment of Primary Infection

Dr Kahn reviewed a study performed at the University of Washington in Seattle in monkeys challenged with simian immunodeficiency virus (SIV). The monkeys were administered PMPA, an antiviral compound related to zidovudine, 48 hours before and 4 hours or 24 hours after challenge inoculation. In the control group of 10 monkeys all developed infection as determined by detection of viral RNA in plasma, SIV DNA in peripheral blood mononuclear cells (PBMC), development of SIV-specific antibodies, and SIV in lymph node tissue. None of the treated monkeys developed any evidence of SIV infection, including those treated 24 hours after the challenge inoculation.

Clinical Data Supporting Treatment of Primary Infection

Dr Kahn presented summaries from several epidemiologic or clinical studies in other settings of HIV infection (eg, post-exposure prophylaxis and maternal-fetal transmission) providing indirect pathogenetic support for the concept of early treatment in the setting of primary infection. The Centers for Disease Control and Prevention (CDC) conducted a multinational, case control study of healthcare workers exposed to HIV. Among 31 healthcare workers who had an occupational exposure to HIV, the use of zidovudine monotherapy soon after the exposure reduced the risk of HIV infection (odds ratio of 8.5). In the placebo-controlled ACTG 076 trial, zidovudine monotherapy given during both the prenatal and postnatal period (presumably during the time that primary infection of the child occurs) reduced the rate of infection in the infants at 18 months of age from 25.5% to 8.3% ($P < 0.001$). These data indirectly suggest that treatment during the time of initial HIV infection is likely to have clinical benefit and provides a rationale for treating people with primary HIV-infection.

Cautions About Early Treatment

According to Dr Kahn, there are also theoretical risks associated with early treatment. Modulating the infection

early, before the development of a full immunologic response to the virus, might result in an overall weaker immune response, manifested as lower levels of antibodies, or lower affinity antibodies, or a less vigorous cellular immune response. This may result in more rapid HIV progression later if the treatment is discontinued or if viral resistance develops. There are anecdotal reports of a clinical syndrome similar to that with acute HIV infection that occurs in some patients who discontinue treatment for primary HIV. As with any unproven therapy, the benefit to risk ratio may be lower for antiretroviral intervention during primary infection since the long-term benefits are not known but the toxicities of the drugs may still be considerable.

Preliminary Data on Treatment of Primary Infection

Reported Early Treatment Studies

Dr Kahn summarized a multicenter, double-blind, placebo-controlled study of zidovudine monotherapy 250 mg bid. A total of 77 patients with primary HIV infection were treated for 6 months, with a mean follow-up of 15 months. Among the 39 patients randomized to zidovudine, 1 patient had an early opportunistic infection (OI), and 7 of 38 patients on placebo had an OI, including herpes simplex infection, oral hairy leukoplakia, and candidiasis. Compared with the placebo group, the treated group experienced a rise in CD4+ cell counts that persisted for about 6 months, after which time the decline paralleled that of the placebo group, perhaps due to the fact that zidovudine was discontinued at that point.

In another report reviewed by Dr Kahn, a Vancouver group studied a combination of zidovudine/didanosine in patients who were HIV p24-antigen positive but HIV-antibody negative, or who had evidence of seroconversion within the prior 6 months. This was not a randomized study, as treatment was determined by patient choice. Seven of eight gay men and one of ten injection drug users accepted treatment. The 10 patients who declined treatment were followed as the control group. The

mean plasma HIV RNA level among all patients at entry was 350,000 copies/mL. Compared with the control group, combination treatment resulted in approximately a two log drop in HIV RNA, and

Preliminary clinical data show a marked reduction in HIV RNA following treatment of acute HIV infection.

by week 12 four of six treated patients had plasma HIV RNA levels less than 500 copies/mL.

Dr Kahn also summarized a study in which 12 patients were treated with zidovudine/lamivudine/ritonavir within 65 days of the onset of symptoms of acute HIV infection. At entry all patients had detectable plasma HIV RNA (mean 91,000 copies/mL), and the mean CD4+

cell count was 633/ μ L. Three patients reportedly withdrew, leaving nine who were followed up long term. From the first month of treatment, at least 75% of the patients had plasma HIV RNA levels below 500 copies/mL by bDNA assay (Figure 2). This antiviral effect appeared to have persisted for at least 9 months.

Initiation of treatment with antiretroviral drugs during primary infection results in marked decreases in HIV viral load. Based on the rationale for early treatment that Dr Kahn outlined above, these reductions in HIV load may translate into immunologic and clinical benefit, and clinical studies are under way to evaluate this possibility. However, at present there is no direct clinical evidence that early treatment provides long-term benefit.

Summary

Primary HIV infection is underdiagnosed, but can be confirmed by recognition of the acute HIV clinical syndrome followed by appropriate laboratory testing. There are compelling preliminary laboratory

and clinical data to suggest that antiretroviral intervention during primary HIV infection may alter the long-term outcome of the infection. Key to the laboratory diagnosis of primary infection is a combination of EIA and western blot serology and testing for plasma HIV RNA (or alternatively HIV p24 antigen). Early intervention should consist of combination antiretroviral treatment, preferably with potent antiretroviral drug regimens that include at least one protease inhibitor. There are risks associated with treatment during the primary phase of infection. Until well-designed clinical studies of early intervention are completed, the potential benefits and risks must be evaluated on an individual patient basis, or patients may be referred into one of these clinical trials.

James O. Kahn, MD, is Associate Professor of Medicine at the University of California San Francisco, San Francisco General Hospital.

Suggested Readings

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CURRENT STATUS OF NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) were discussed at the Chicago course by John P. Phair, MD, from Northwestern University Medical School. Dr Phair reviewed the characteristics of this class of compounds, summarized available clinical trial data, and discussed the use of NNRTIs in combination with protease inhibitors.

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) are the most recent class of antiretroviral drugs to become available for HIV treatment. The NNRTIs function by binding noncompetitively to the hydrophobic pocket close to the polymerase catalytic site of the reverse transcriptase (RT) and decreasing RT polymerizing activity. The NNRTIs are selectively active against HIV-1; these drugs are not effective for HIV-2 or for HIV-1 group O isolates, and they do not interfere with the function of human DNA polymerases.

The rapid development of viral resistance to the NNRTIs has historically been the significant obstacle to the development of these drugs. Resistance often

The NNRTIs are selectively active against HIV-1, but are not effective for HIV-2 or for HIV-1 group O isolates.

develops within weeks of administration of these drugs. In most cases, less susceptible isolates contain amino acid substitutions in the region of codons 179, 181, 188, and 190, and 98, 100, 103, 106, and 108 of the RT. In general, resistance to

NNRTIs does not alter the susceptibility of the virus to nucleoside reverse transcriptase inhibitors (nRTIs), and, conversely, resistance to NNRTIs usually does not reduce susceptibility to nRTIs. Cross-resistance with the protease inhibitors is unlikely due to the different enzyme targets involved. Cross-resistance within the NNRTI class is extensive. Two NNRTI-associated alterations, substitutions at codons 188 and 181, appear to suppress resistance to zidovudine when co-expressed with zidovudine-resistance-conferring mutations.

This rapid appearance of virus with increased resistance precludes the use of NNRTIs as monotherapy. Clinical trials evaluating these drugs as part of double- and triple-combination regimens with nRTIs and protease inhibitors are ongoing.

Delavirdine

In vitro studies have demonstrated that delavirdine blocks HIV-1 replication, including replication in HIV-1 isolates that are resistant to nRTIs or protease inhibitors. In tissue culture, delavirdine is synergistic with nRTIs, protease inhibitors, and immunomodulators. Steady-state pharmacokinetics for delavirdine are nonlinear; increased doses result in increased blood levels and decreased clearance. Delavirdine is metabolized primarily by the hepatic cytochrome P450 system. There is high interpatient variability in steady-state delavirdine concentrations that cannot be explained by demographic factors. Trough blood levels of delavirdine greater than 10 μM are easily achieved with the recommended dose of 400 mg tid. A summary of selected drug interactions with delavirdine is presented in Table 1.

The majority of clinical trials with delavirdine were conducted before protease inhibitors were available. One clinical trial comparing didanosine/delavirdine with didanosine monotherapy was stopped when no significant differences were found between the two arms of the study. A clinical

Table 1. Selected Delavirdine Drug Interactions

- Delavirdine is a weak base with very low solubility at pH above 3.0
- Administration of an antacid reduced delavirdine absorption and area-under-the-curve by approximately one third
- Ingestion of delavirdine with a high-fat meal or simultaneously with didanosine does not significantly alter delavirdine pharmacokinetics
- Concurrent use of fluconazole, clarithromycin, zidovudine, or trimethoprim/sulfamethoxazole does not significantly alter delavirdine pharmacokinetics
- Concurrent use of rifampin or rifabutin (strong inducers of the cytochrome P450 system) significantly increases the clearance of delavirdine

trial evaluating zidovudine/delavirdine has been modified to include lamivudine, and results are not yet available.

However, a proportional hazard regression analysis combining results from 1740 patients enrolled in Pharmacia & Upjohn protocols 0017 and 0021 revealed that in patients taking delavirdine/zidovudine or delavirdine/didanosine a 0.5 log decrease in plasma HIV RNA following therapy was associated with a 56% reduction in the clinical progression rate. An initial increase of 25 CD4+ cells/ μL or more was not associated with a reduction in clinical progression rate; however, sustained increases in CD4+ cell count of 25/ μL or more appeared to be a better predictor of clinical progression.

The most frequent and usually the first genotypic mutation observed with delavirdine monotherapy and combination therapy is at K103N. The Y181C

mutation is observed during monotherapy and delavirdine/didanosine therapy; the P236L mutation, alone or in combination with the K103 mutation, is observed during delavirdine/zidovudine therapy. In general, delavirdine phenotypic susceptibility decreases in the presence of Y181C ± K103N/T mutations > P236L + K103N > P236L > K103T > K103N mutations. A stepwise increase in delavirdine IC₅₀ is often observed with the emergence of a second mutation, and double mutations correlate with poorer surrogate marker response.

The major side effect associated with delavirdine is a diffuse pruritic maculopapular rash that usually occurs in the first month of therapy in approximately 33% of patients. The rash is not related to blood levels or doses of delavirdine and appears to be more common in patients with CD4+ counts below 300 cells/μL who are taking other medications. More than 85% of patients who develop a rash can continue therapy.

Nevirapine

Nevirapine, the first NNRTI approved by the US Food and Drug Administration, is rapidly absorbed and is associated with a dramatic decrease in viral load after initiation of therapy. Plasma concentrations exceed the IC₅₀ after the first dose. In addition, nevirapine penetrates the blood-brain barrier with a ratio of 1:1 unbound nevirapine in plasma to nevirapine in the cerebrospinal fluid (CSF). Although clinical trial data are not available, nevirapine may prove to be a useful drug for the management of HIV encephalopathy.

Nevirapine in combination has been shown to maintain suppression of viral replication in naive and advanced patients. In one study (Boehringer Ingelheim protocol 1046), antiretroviral naive patients (mean CD4+ count 375 cells/μL and mean plasma HIV RNA 25,740 copies/mL) were randomized to zidovudine/ nevirapine/ didanosine, zidovudine/nevirapine, or zidovudine/didanosine. Figure 1 shows the difference between the treatment arms at 28 weeks. Two-thirds of patients on triple-combination therapy had a sustained reduction in plasma HIV RNA below the level of detection for more than 52 weeks. In this study, nevirapine-associated resistance developed whether or not the indi-

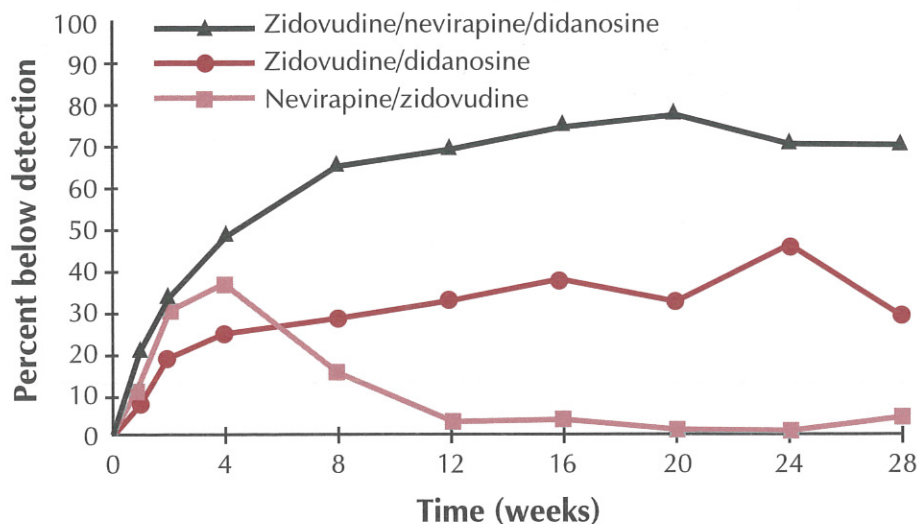


Figure 1. Percentage of patients below the limit of plasma HIV RNA detection (<200 copies/mL) through 28 weeks of treatment with nevirapine/zidovudine, zidovudine/didanosine, or zidovudine/didanosine/nevirapine. From the BI 1046 trial.

vidual adhered to the prescribed regimen as measured by pill counts, but individuals not adhering to the regimen were much more likely to develop resistance to nevirapine.

ACTG protocol 193A evaluated the nevirapine in patients with advanced HIV disease and extensive antiretroviral pretreatment (mean CD4+ 20 cells/μL; 18% of patients were antiretroviral naive). Patients were randomized to zidovudine/ alternating didanosine, zidovudine/ zalcitabine, zidovudine/didanosine, or zidovudine/didanosine/nevirapine. There

was a significant increase in median survival in patients taking the triple-combination regimen compared with patients taking zidovudine/alternating didanosine ($P = 0.012$) or zidovudine/ zalcitabine ($P = 0.009$).

As with delavirdine, rash is the most common side effect associated with the use of nevirapine. In an analysis combining patients from three comparative trials, rash occurred in 37% of 252 patients taking nevirapine, compared with 20% of 255 control patients ($P < 0.01$).

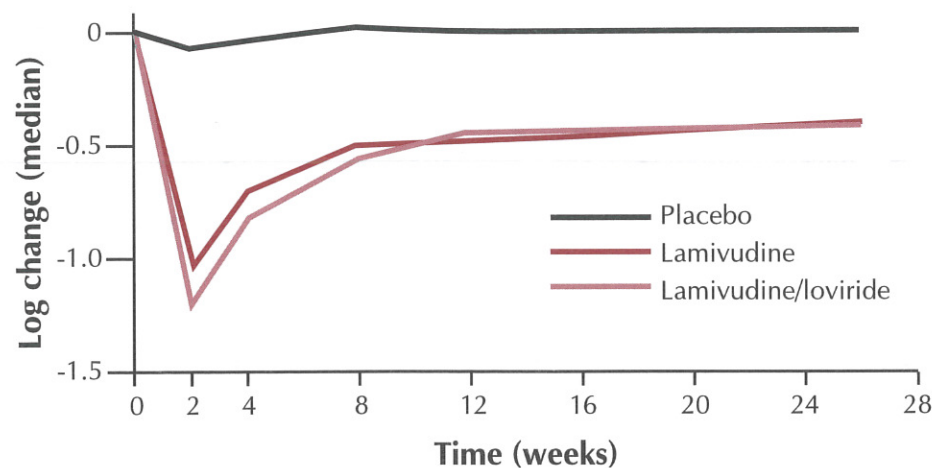


Figure 2. Median log change in plasma HIV RNA from baseline through 26 weeks in patients randomized to add placebo, lamivudine, or lamivudine/loviride to their existing treatment regimen. From the CAESAR trial.

Table 2. Effects of NNRTIs on the Metabolism of Selected Drugs.

Nevirapine	Induces cytochrome P450 Reduces levels of protease inhibitors, rifampin/rifabutin, oral contraceptives
Delavirdine	Inhibits cytochrome P450 Increases levels of protease inhibitors, rifampin/rifabutin, astemizole, loratidine, terfenadine, cyclosporin, estradiol, ketoconazole, itraconazole, macrolides, warfarin, progesterone, and testosterone
DMP-266	Induces cytochrome P450 Expected to have the same effects as nevirapine
Loviride	Appears to have no effect on metabolism of other drugs

Loviride

Loviride has been studied primarily in Europe. The current dose of 100 mg tid results in good plasma levels, and the drug does not appear to significantly alter hepatic enzyme functions. In the AVANTI-1 trial study, loviride was added to the combination of zidovudine and lamivudine in antiretroviral-naïve patients. The median maximal decrease in plasma HIV RNA from baseline (occurring at 4 weeks) was 2.1 log in the triple-combination group and 1.9 log in the zidovudine/lamivudine group. At week 52, the median decreases in viral load from baseline were 1.4 log and 1.3 log, respectively. The median maximal increases from baseline at 52 weeks in CD4+ cell counts were 127/ μ L and 69/ μ L, respectively.

In the CAESAR study, naïve and experienced patients with 25 to 250 CD4+ cells/ μ L were randomly assigned to add lamivudine (150 mg bid), lamivudine (150 mg bid)/loviride (100 mg bid), or placebo to their current treatment regimen. No further reduction in morbidity or mortality was observed with the addition of lamivudine/loviride compared with the addition of lamivudine alone (Figure 2). The role of loviride in potent antiretroviral regimens is unclear.

DMP-266

The investigational NNRTI, DMP-266, differs from other current NNRTIs in that viral resistance requires multiple mutations, and administration of the drug is not associated with a significant incidence of rash. DMP-266 has entered clinical trials in the United States.

The Use of NNRTIs with Protease Inhibitors

The NNRTIs are metabolized by the hepatic cytochrome P450 system and thus affect the metabolism of a number of other drugs (Table 2). The use of the NNRTIs in combination regimens that contain protease inhibitors requires careful evaluation of the potential interactions.

In small combination studies, use of nevirapine was associated with significant reductions in steady-state area-under-the-curve (AUC), C_{\min} , and C_{\max} of saquinavir and indinavir; there was no significant reduction in these measures when nevirapine was combined with ritonavir. The protease inhibitors had no effect on the concentration of nevirapine, and there was no loss in viral suppression after 120 days when indinavir and nevirapine were administered together.

Coadministration of delavirdine and saquinavir in non-HIV-infected persons was associated with an increase in concentrations of saquinavir compared with those achieved with the administration of saquinavir alone (Figure 3). The effects of delavirdine on ritonavir and indinavir concentrations were less marked than those observed on saquinavir concentration.

Summary

Despite the limitations created by their effects on hepatic metabolism, the NNRTIs offer options for prolonged aggressive antiretroviral therapy. In chronic HIV infection in adults, it is currently understood that the optimal use of the NNRTIs is in regimens that are intended to achieve maximal suppression in antiretroviral naïve patients who have low plasma HIV RNA levels. Nevirapine, in combination with two nRTIs, results in significant improvements in antiretroviral-naïve patients. In addition, the rapid reduction in viral load observed with initial NNRTI therapy may prove useful in specific clinical situations such as managing occupational exposure to HIV or preventing vertical transmission. According to Dr Phair, the ultimate therapeutic niche for the NNRTIs remains to be defined.

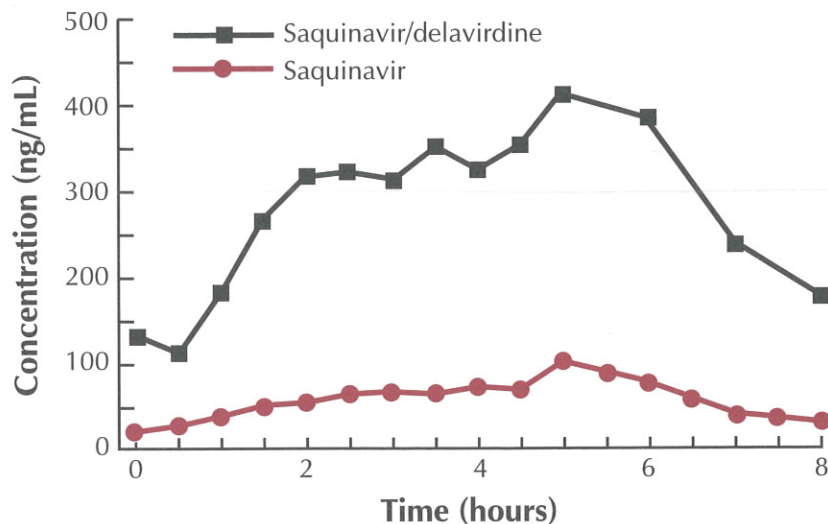


Figure 3. Mean steady-state plasma saquinavir concentrations in non-HIV-infected persons given saquinavir alone or saquinavir/delavirdine. From Protocol 0052.

John P. Phair is Professor of Medicine and Director of the Comprehensive AIDS Center at Northwestern University Medical School in Chicago, Illinois.

Suggested Readings

- Freimuth WW, Wong Y, Docci S, et al. Surrogate marker responses from an open-label extended use of delavirdine mesylate (DLV) treatment of triple combination (ZVD+DLV+DDI, or ZVD+DLV+DDC) for HIV-1 patients. Presented at the XIth International Conference on AIDS; July 7-11, 1996; Vancouver, British Columbia, Canada. Abstract MOB 1134.
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ADHERENCE TO DRUG REGIMENS: A LEARNED SKILL

The challenge of adhering to potent combination antiretroviral regimens was discussed at the San Francisco course by Margaret A. Chesney, PhD, from the University of California San Francisco. The following short review highlights some of Dr Chesney's remarks, focusing on practical strategies for helping patients learn the skills necessary to adhere to these complex therapeutic regimens.

To best achieve maximum efficacy and prevent or delay the development of viral resistance, antiretroviral therapy must be potent, continuous, and well tolerated. The most potent regimens available are, however, the most complex and demanding. In addition, missed doses or "drug holidays" allow viral replication and more rapid selection of drug-resistant variants. These factors underline the urgent need to help patients improve their ability to adhere to drug regimens.

Preliminary findings from an ongoing study at San Francisco General Hospital of patients taking regimens that include a protease inhibitor found that 12% (21/179), 11% (19/179), and 13% (22/179) had skipped at least one dose the day before the interview, two days before the interview, and three days before the interview, respectively. The most common reasons offered for skipping a dose were that the patient had forgot (40%), slept through dose time (37%), was away from home (34%), had a change in routine (27%), or was busy with other things (22%).

Other reasons include feeling too sick, experiencing side effects, or being depressed. Data from the AIDS Clinic Trials Group (ACTG) 175 protocol indicate that younger age, depressed mood, perceived stress, pessimism about HIV disease, and lower levels of coping are correlates of nonadherence.

Adherence to a drug regimen involves a sequence of complex cognitive factors and behavioral skills. Patients must be able to (1) understand the regimen and believe they can adhere to the regimen (self-efficacy); (2) remember to take the medications; (3) integrate the regimen into their lifestyle; and (4) problem-solve to accommodate changes in routine and schedules. Specific strategies to help patients learn to integrate these behaviors are listed in the Table.

As noted by Dr Chesney, adherence involves not only following a drug regimen, but remaining in treatment, in clinical trials, and in the healthcare system. The findings from innovative education efforts will ultimately help highly active antiretroviral therapy become not only efficacious, but an effective approach to the treatment of HIV disease.

Margaret A. Chesney is Professor of Medicine and Co-Director of the Center for AIDS Prevention Studies at the University of California San Francisco.

(See also Friedland GH. Adherence: The Achilles' heel of highly active antiretroviral therapy. IMHD. 1997; 5:13-15.)

Table. Strategies for Improving Adherence to Antiretroviral Therapy

Clarify the regimen

- Follow up with patients one or two days after their clinic appointment to confirm their understanding of the regimen
- Provide accessible educational materials
- Make sure that patients understand all the instructions for taking the drugs (ie, ritonavir should be taken with a high-fat meal—what constitutes a "high-fat" meal?)

Self-monitor adherence with a personalized diary

- Identify/develop a diary/daily recording system that is easy for patients to use

Tailor the regimen to individual lifestyles

- Identify daily activities that are consistently performed at medication intervals (ie, television shows, meals)
- Provide patients with extra pill bottles so that medications can be physically placed where these activities take place (ie, on the television, in a desk drawer)
- Plan ahead for vacations and holidays that disrupt daily routines

Facilitate interaction with clinic staff

- Encourage patient empathy for and communication with clinic staff
- Address frustration with medical care system by teaching clinic survival skills
- Encourage patients to ask questions by providing them with index cards
- Train frontline staff on helping patients integrate regimens into their daily lives

Identify and remove personal barriers to adherence

- Help patients find ways to take drugs with privacy
- Create special cues to help patients remember to take drugs

Refer patients with special needs

- Identify conditions such as stress, substance/alcohol abuse and/or depression and refer patients to specialized treatment/support services

Enhance self-efficacy

- Prescribe a regimen of vitamins to be taken at the same intervals and with the same restrictions as HAART; problem-solve the challenges that arise
- Provide guided practice on planning ahead for weekends
- Offer positive feedback for new skills
- Demonstrate problem-solving and ways to integrate the regimen into their lives

Create a social environment conducive to adherence

- Gain permission to contact patients outside the clinic; make counselor calls and leave reminder messages
- Enlist support from patients' social network
- Maintain support/involvement of the primary care physician
- Give patients copies of viral load records; teach them how these measures are used in clinical decision-making



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H. Clifford Lane, MD

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Melanie A. Thompson, MD

Approaches to the Prevention and Management of HAART Failure

Michael S. Saag, MD

Prevention and Treatment of CMV Infections

Kathleen Squires, MD

Prevention and Treatment of Fungal Infections in Patients with AIDS

William G. Powderly, MD

Strategies for the Prevention and Treatment of *Mycobacterium avium* Complex Disease

C. Robert Horsburgh, Jr., MD

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Results of Clinical Trials of New Anti-HIV Drugs and Combinations

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Clinical Considerations of Drug Resistance

Douglas D. Richman, MD

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Ashley T. Haase, MD
- Immune Reconstitution After Highly Active Antiretroviral Therapy (HAART)
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- Recent Results and Insights From Drug and Combination Trials
Julio S. G. Montaner, MD, FRCPC, FCCP
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THE IMPACT OF TREATMENT ON THE PRODUCTION AND STORAGE OF HIV IN LYMPHOID TISSUE

Clinicians who manage the care of HIV-infected individuals rely primarily on the peripheral CD4+ lymphocyte count and the level of plasma HIV RNA to monitor the effects of antiretroviral treatment. However, virus and CD4+ cells in the peripheral circulation represent only the tip of the iceberg. Most HIV viral replication and the resulting changes in the immune cell populations occur in the lymphoid tissues. At the San Francisco course Ashley T. Haase, MD, reviewed the research conducted in his laboratory of the kinetics of HIV and immune cell populations in the tissues of HIV-infected individuals before and after antiretroviral treatment.

Interactions Between HIV and Host Cells

Characteristics of Retrovirus Infection

Retroviruses are so named because during viral infection genetic information flows from RNA to DNA. The HIV genome is composed of RNA, and the viral-encoded enzyme reverse transcriptase catalyzes the production of DNA provirus from the viral RNA template. From the provirus stage there are two possible outcomes, integrated nonproductive infection and productive infection. In latent infection there are nearly undetectable amounts of RNA within the cell, but viral genetic information persists as proviral DNA integrates into the host genome. There is little if any viral gene expression. In productive infection there is extensive viral gene expression. The cell produces thousands of copies of viral RNA, millions of copies of viral capsid protein, and hundreds of HIV virions. Productive retrovirus infection is associated with disease as infected cells die by a number of mechanisms; latent infection is sub-clinical.

In the HIV-infected individual, many cells harbor provirus in a silent state.

These latently-infected cells can become productively-infected and produce large amounts of virus, or with limited gene expression can express sufficient viral protein that the cell becomes a target for cytotoxic lymphocytes. The cells that remain latently infected will eventually die, but this may take years. Latent infection may involve lymphocytes, macrophages, and perhaps other cell types.

The Storage Pool for HIV in Lymphoid Tissue

Another mechanism of persistence has been described based on in situ studies of lymphoid tissue. In the lymph node germinal centers the follicular dendritic cells (FDCs) continue to act as antigen repositories that activate B lymphocytes to develop and secrete antibodies. In the HIV-infected individual the FDCs contain large numbers of HIV virions coated with antibodies, including neutralizing antibodies, that essentially form immune

complexes. These virion-antibody complexes are attached in large numbers extracellularly to the FDCs processes by complement and complement receptors.

The FDCs with the attached HIV particle immune complexes constitute a large storage pool of virus. In addition, FDCs are themselves infected and have the capacity to reactivate a productive infection. Thus the germinal centers of lymph node is a large storage reservoir of HIV, as well as a source of productive HIV infection.

Kinetics of HIV Infection

Within the lymphoid tissue of the HIV-infected individual there is a virtual HIV factory (Figure 1). The main production of HIV occurs in productively-infected T-cells and macrophages. The source of these cells is the bone marrow/thymus progenitor pool and the peripheral precursor pool undergoing self-renewal. Some virus is derived from the latently-infected

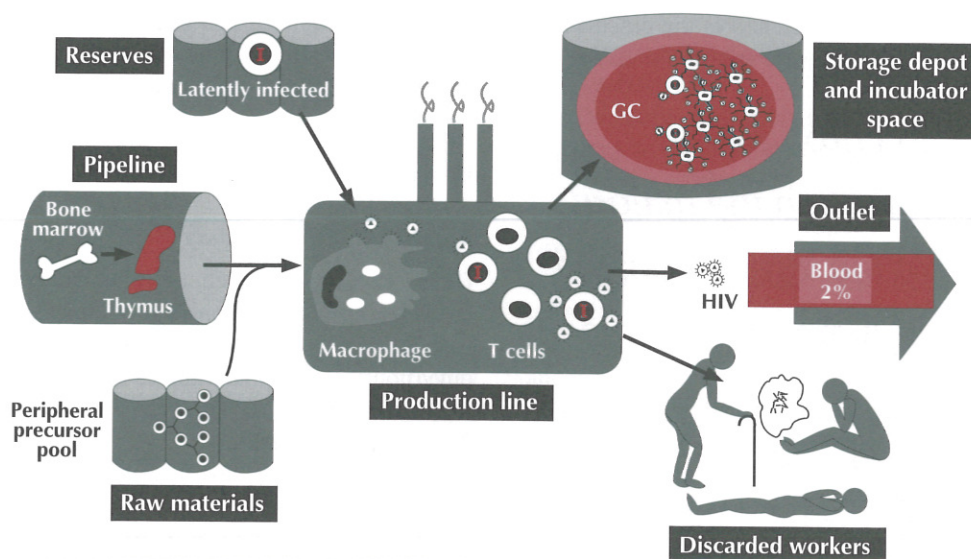


Figure 1. A schematic depicting the source of HIV and infected cell, and the eventual fate of virus and cells during HIV infection.

cell pool as these cells are activated and productively become infected. Mature HIV particles are stored in the FDCs and some move into the blood. A large number of infected cells die either directly as a consequence of HIV infection, or secondary to apoptosis.

In Situ Techniques

Considerable progress has been made in understanding the kinetics of HIV by using in situ hybridization. This technique involves a radioisotope-labeled probe, which has a sequence that is specific for the target RNA. Tissue sections are made using standard histologic techniques of thin slicing of tissue, and the tissue sections are reacted with the probe. A photographic emulsion is laid over the section and where probes have reacted with target RNA, the radioisotope which causes silver grains to form in the emulsion. When developed, the exposed grains overlying the target sequences are visible.

Immunohistochemistry involves a similar process wherein the probe consists of an antibody specific for an antigen such as the CD4 molecule on the cell membrane. The antibody is tagged with an enzyme or a fluorescent marker, and upon reacting the marker with substrates or light, those cells that have the target antigen are stained.

Distribution of HIV in Lymphoid Tissue

HIV particles attached to the processes of the FDC are quite spread out along the

In chronic HIV infection the majority of the virus is located in lymphoid germinal centers, associated with follicular dendritic cells.

surface of these large cells and so in autoradiographs show a diffuse pattern of hybridization signal. Productively-

infected cells produce large numbers of virions within the small area of one cell, resulting in a focal hybridization pattern. In the HIV-infected individual, lymphoid tissue stained with probe specific for HIV will show both of these patterns (Figure 2).

The number of copies of viral RNA can be quantified by counting the silver grains in an autoradiograph. A camera and a computer are used to count the grains and calculate the copies of RNA in a given area of tissue. By further calculation involving the volume of specific tissues, the number of HIV virions within a single lymph node or in the entire lymph system can be estimated.

Quantity of HIV in Infected Individuals

The lymphoid tissue carries approximately 98% of the viral burden. There are about 10^8 viral RNA copies per gram of lymph tissue or about 10^{11} copies in the entire body, most of which is associated with the FDCs. Only approximately 2×10^9 copies are found in the productively-infected mononuclear cell pool of macrophages and T-lymphocytes. Thus the vast majority of tissue-associated virus is HIV that is already produced and associated with FDCs in the germinal centers.

Effects of Antiretroviral Treatment on HIV Kinetics

Results of a Clinical Study

Dr Haase next described a clinical study involving antiretroviral naive HIV-infected individuals who started zidovudine/lamivudine/ritonavir. Tonsillar samples for biopsy were taken at baseline (pretreatment), day 2, week 3, and week 24.

Triple-therapy resulted in a rapid decline in plasma HIV RNA levels by more than 2 logs, and in many patients the plasma RNA levels fell below the detection limit of the assay. Figure 3 shows the changes seen in autoradiographs of tonsillar tissue sections taken at

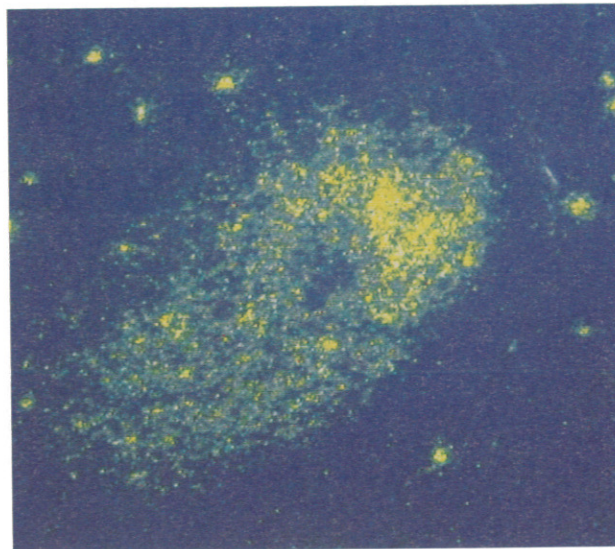


Figure 2. Autoradiograph of a section of lymph node from an individual chronically infected with HIV. The diffuse bright pattern on the right represents HIV virions stored in the follicular dendritic cells in the germinal center. The discrete bright patches on the left represent individual foci of productively infected cells.

baseline and at week 3 of treatment. Before treatment (Figure 3a) there is a large, diffuse pattern of grains representing the FDC-associated virus in the follicles, as well as areas of discrete, focal

Triple-therapy resulted in a rapid decline in plasma HIV RNA levels by more than 2 logs, and in many patients the plasma RNA levels fell below the detection limit of the assay.

signal in the interfollicular area representing productively-infected mononuclear cells. After 3 weeks of therapy there was a marked reduction in viral burden in the tonsil (Figure 3b). There was a reduction in the productively-infected mononuclear

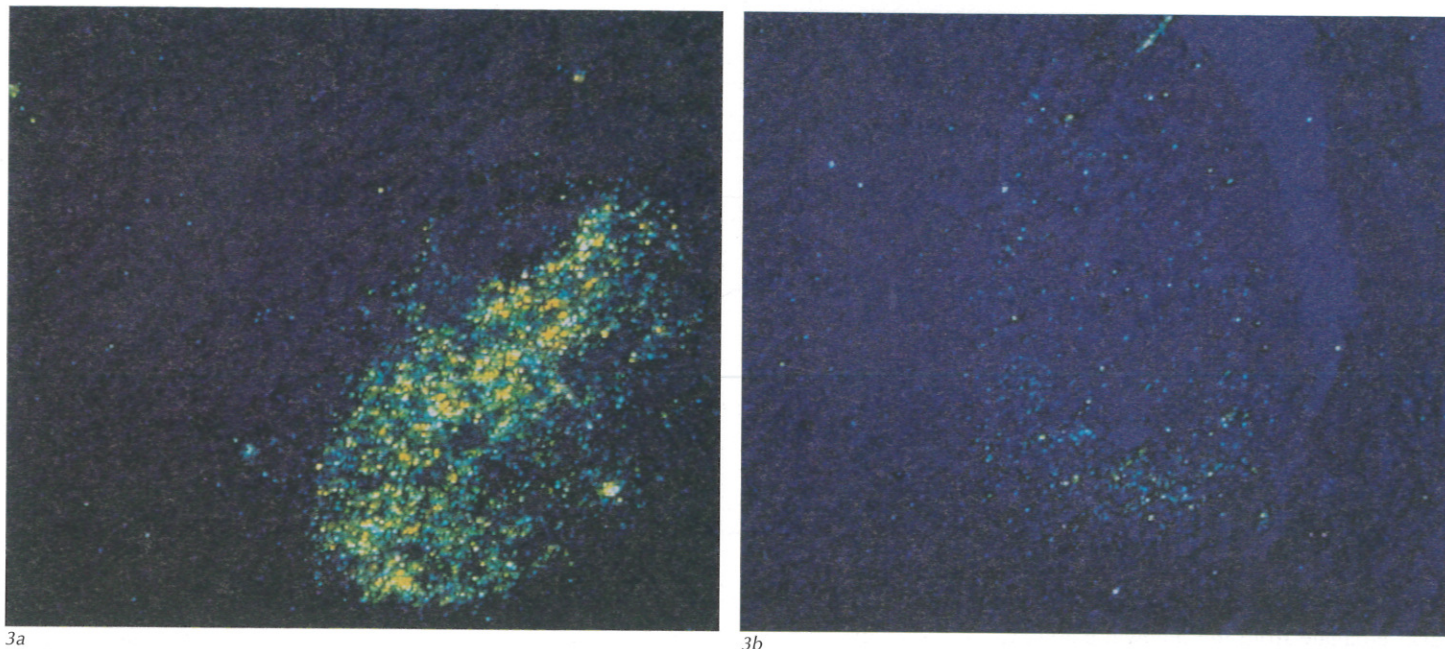


Figure 3. Autoradiograph of tonsillar tissue. 3a; HIV RNA stored in the germinal center of the tonsil prior to treatment. 3b; A germinal center of tonsil after 3 weeks of triple antiretroviral therapy. Reproduced with permission from Cavert W et al. Science. 1997. Copyright 1997 American Association for the Advancement of Science.

cell pool and a reduction in the virus associated with the FDCs.

Computer-aided photographic quantification of viral burden in the tonsillar sections revealed bi-phasic kinetics, (Figure 4). Between the baseline sample and day 2 there was a rapid decrease in HIV RNA load, with a half-life of about 1 day. A second phase with a half-life of about 14 to 15 days was seen between day 2 and week 3. The productively-infected mononuclear cell population lost about 1.0 log of virus by day 2, and another 0.5 log between day 2 and week 3. What was surprising, according to Dr Haase, was that the viral load in the FDC pool paralleled that seen in the productively-infected cell pool (Figure 4). The viral RNA levels associated with the FDC also showed a bi-phasic curve, with half-lives similar to those described for the productively-infected mononuclear cell pool.

After 6 months of treatment, the viral load in FDC was reduced from about 10^8 copies/gram of tissue to less than 10^4 copies/gram, the limit of detection of the assay, in 8 of the 10 patients. By increasing the sensitivity of the autoradiographic technique, it was shown that even after 6 months of treatment there was still HIV RNA associated with the FDCs of each germinal center in the lymph node. The

highly productive mononuclear cells producing 175 virions per cell were now gone, but there were mononuclear cells producing on average 2 to 5 virions per cell. These data show that after 6 months of continuous treatment with triple

After 6 months of antiretroviral treatment the viral load in tissue was reduced from about 10^8 copies/gram of tissue to less than 10^4 copies/gram.

antiretroviral therapy, between 10^7 and 10^8 virions still persist in the entire body. HIV DNA was also still detectable, suggesting that latently-infected cells persist after treatment.

Interpretation of the Post-Treatment Kinetic Data

These data suggest that there are two pools of cells producing virus. One pool

produces the largest number of virions with a rapid turnover and a half-life of about 1 day. The other pool has a longer half-life of about 14 days and produces considerably less virus. It is believed that this second pool consists of CD3+ cells, but the exact nature of these cells has not yet been elucidated. Calculations based on the above kinetic data collected from treated patients shows that the average productively-infected mononuclear cell produces 175 virions. The turnover of these mononuclear cells is about 8×10^7 cells each day.

Dr Haase summarized changes that occurred in the CD4+ cellular compartments after triple therapy. In the uninfected individual about 2% of CD4+ cells (or about 5×10^9 cells) are in the peripheral circulation and about 98% of CD4+ cells 2×10^{11} are in the lymphoid tissue. About 45% of the CD4+ cells are naive, and a small percentage undergo apoptosis or enter a self-renewal pool. During HIV infection, prior to the initiation of treatment, about 1% of CD4+ cells (10^9 cells) are in the blood and 99% (10^{11} cells) are in lymphoid tissue. The naive cell component decreases to about 24% of the CD4+ population and the rate of apoptosis and self-renewal increases 2- to 3-fold. In the infected patient there is an

additional loss of CD4+ cells due to HIV infection, estimated to be 8×10^7 cells per day.

After 6 months of treatment the peripheral CD4+ cell count increases as expected, doubling from 10^9 to 2×10^9 total cells. This yields an apparent rate of increase of about 10^9 cells per day, but in fact the actual measured replacement rate in lymphoid tissue is calculated to be 10^8 cells per day. This suggests that the increase in the CD4+ cell count in the blood is due primarily to redistribution of lymphocytes rather than new production. The proportion of naive CD4+ cells increases, and the apoptosis rate and the re-population rate decrease. These data suggest that most of the new cells produced after antiretroviral drug treatment emanate from the renewal pathway, that is the bone marrow and the thymus, and consist of naive CD4+ lymphocytes.

Even during the later stages of HIV infection the immune system may have the capacity to recover.

Thus during the chronic stage of HIV infection this source of new lymphocytes does not appear to be irreversibly damaged and there may be the capacity for the immune reactive cell populations

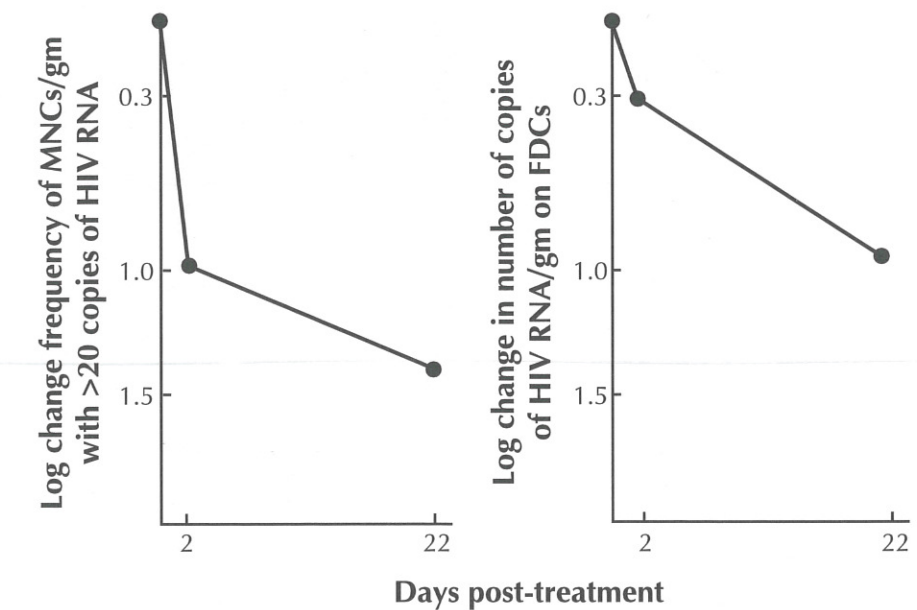


Figure 4. Changes in HIV-infected productive mononuclear cells (MNCs)/gram of tonsil tissue, and HIV RNA viral load/gram of tonsil tissue at 2 days and 3 weeks after the start of triple antiretroviral therapy. Adapted with permission from Cavert W et al. *Science*. 1997. Copyright 1997 American Association for the Advancement of Science.

to recover. This provides hope that significant immune reconstitution is possible even in the later stages of infection.

If the rate of production of naive CD4+ cells by the thymus and bone marrow is about 8×10^7 to 8×10^8 cells per day, and the rate of turnover of productively HIV-infected cells is the same, then during HIV infection the rate of cell death due directly to viral infection must equal the rate at which the cells can be replaced. Since there are other causes of CD4+ cell death in addition to that resulting directly from viral infection, the

total CD4+ cell population decreases, and this accounts for the immune depletion in HIV infection. At steady state HIV infection the cell renewal processes can just barely keep up with the rate of destruction of cells by HIV. The immune system is essentially running in place.

Ashley T. Haase, MD, is Professor and Head of the Department of Microbiology at the University of Minnesota, Minneapolis.

Suggested Readings

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