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# IMPROVING THE MANAGEMENT OF HIV DISEASE®

VOLUME 6 ISSUE 4 SEPTEMBER 1998

## IN THIS ISSUE

**Recent Advances In:**

Primary HIV Infection

Issues in Antiretroviral Therapy

Adherence Strategies

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### *ABOUT THIS ISSUE...*

This issue of *Improving the Management of HIV Disease* highlights talks given earlier this year as part of the annual antiretroviral therapy CME courses sponsored by the International AIDS Society–USA. Three topics of increasing importance in HIV disease management are addressed.

The review of the state of antiretroviral therapy in 1998 was presented by Dr Paul A. Volberding at the Los Angeles course in February. While antiretroviral treatment strategies have changed little in the past year, there has been increased experience with antiretroviral therapy with regard to virologic responses, drug failures, immunology, and the consequences of adherence and nonadherence.

The second article summarizes issues involving a specific area of HIV disease management—primary HIV infection—which was discussed by Dr Eric S. Daar at the Los Angeles course. Scientific, clinical, and social issues in the treatment of primary HIV infection are addressed, providing an overview of what is necessary to properly evaluate primary infection in order to better understand the immunopathogenesis of HIV and to define the optimal treatment of this stage.

Also included in this issue is a review of Dr Margaret A. Chesney's discussion of adherence at the Chicago course in April. The summary reviews recent data on adherence, and also suggests several strategies for enhancing this essential component of effective antiretroviral therapy in the clinical setting.


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# Primary HIV Infection: Recognition and Management

*At the Los Angeles course, Eric S. Daar, MD, discussed scientific, clinical, and social issues concerning primary HIV infection. Dr Daar presented an overview of diagnosis and management given the current understanding of the biology of HIV disease and of this initial stage of infection.*

Primary HIV infection offers unique insights into the pathogenesis of HIV disease and the immune response to HIV. The management of primary HIV infection requires consideration of almost every factor operating in HIV disease: virology, immunopathogenesis, transmission, treatment, and medication adherence. Unfortunately, primary HIV infection is often not identified, and thus, may represent a lost opportunity to impact the patient's disease at a crucial time. Furthermore, this under-identification has meant that the available data for primary infection are largely based on small nonrandomized studies, and often associations and anecdotes. Dr Daar stressed that there is a great need for state and national priorities to increase the recognition of primary HIV infection, to gain further knowledge about the immunopathogenesis of this disease state, and to define the optimal treatment.

> *The composition of the virus population is an important variable in primary HIV infection.*

## Virologic and Immunologic Aspects of Primary Infection

Primary infection refers to the period surrounding the time at which HIV first enters the body. During the first few weeks of infection (generally 3-6 weeks after exposure to the virus), a burst of viremia accompanies the acute syndrome and may go unnoticed. From 1 week to 3 months following infection, an HIV-specific immune response develops. Dr Daar noted that physicians commonly look for a humoral immune response in individuals suspected of recent HIV infection, but the cellular immune response may be a more important controlling factor in early viremia. As data from prospective studies accumulate on primary HIV infection (ie, from following individuals from the first few weeks after exposure), several relationships emerge:

- Individuals who are most symptomatic during primary infection have the highest plasma HIV RNA levels.
- Persons who are symptomatic during the primary infection period have more rapid disease progression than those who are asymptomatic during this time.
- The viral set point parallels clinical outcome, such that individuals with high plasma viral load set points (eg, >10,000 copies/mL), at approximately 6 months after seroconversion, are more likely to progress to AIDS in the first 5 years than individuals with lower plasma viral load set points (eg, <10,000 copies/mL).
- Primary infection results in seeding of virus into the lymphoid tissue and central nervous system (CNS).
- Potent CD8+ cytotoxic lymphocyte (CTL) responses after seroconversion are associated with greater decreases in viremia (after the initial burst) and slower CD4+ cell declines over a 2- to 3-year period.

The composition of the virus population is an important variable to consider during primary infection. According to Dr Daar, evidence suggests that the virus population at this time is relatively homogeneous; apparently there is preferential transmission of the nonsyncytium-inducing viral phenotype, now called R5 viruses (referring to the utilization of the chemokine receptor CCR5). With regard to the virus's resistance phenotype or genotype, the acquisition of resistant strains of HIV have been recognized with increasing frequency.

The immunology of primary HIV infection is also gradually being characterized. It has been shown that early immune damage does occur. Several factors negatively affect the immune responses to HIV infection, and other factors produce responses that are important for controlling HIV replication (Table 1).

## Recognizing Primary HIV Infection

Of the estimated 40,000 people in the United States who become infected with HIV each year, a poorly defined 30% to 80% may develop symptoms of primary infection, called the acute retroviral syndrome. The majority of these patients will not be diagnosed for several reasons. First, the patients themselves are often not aware of their exposure risk or the

### Table 1. Immunology of Primary HIV Infection

- **Possible immune damage**
  - Decline in lymphoproliferative responses to mitogens
  - Immune activation
  - Decline in CD4+ T-lymphocyte number
  - Decline in HIV-specific CD4+ cell responses
- **Potentially beneficial immune responses**
  - CD8+ cytotoxic T-lymphocytes
  - CD4+ helper cell responses
  - Humoral immune response

symptoms associated with the acute retroviral syndrome, and therefore do not seek medical care. When patients do present for care, HIV risk factors are often not disclosed and, in turn, the classic signs and symptoms of primary infection are not recognized and the appropriate evaluation is not performed.

Fever, adenopathy, and sore throat are the most frequent but very nonspecific signs and symptoms of primary HIV infection (Table 2). Thus, the original description of the syndrome was of an acute mononucleosis-like or flu-like illness. Rash is a more specific finding, but it can still be associated with several other illnesses. The presence of a rash often leads to diagnostic tests for syphilis; but suspecting syphilis should raise the index of suspicion for primary HIV infection as well. In addition to rash, patients with oral ulcerations resembling herpes or aphthous stomatitis should also be evaluated for primary HIV infection.

Diagnosing primary HIV infection requires a high index of suspicion for the clinical syndrome and a sound knowledge of the appropriate diagnostic tests to perform. Evidence of an immunologic response can be identified during the first few weeks after exposure. As the screening antibody tests have become more sensitive, the seronegative window period has narrowed. Virologic tests narrow this window further, as plasma viremia can be detected within days of infection. Dr Daar recommended that the diagnosis of primary HIV infection be made on the basis of HIV viremia rather than antibody testing alone, since early infection is characterized by low levels or the absence of antibodies to HIV. Determination of HIV p24 core antigen levels has been considered an insensitive assay for established HIV infection, but the test is often positive during symptomatic primary infection. The more commonly used tests (because they are more sensitive) are those that measure for plasma HIV RNA. Unfortunately, false-positive plasma HIV RNA results occasionally occur. However, Dr Daar noted that in this setting plasma HIV RNA levels are generally below 10,000 copies/mL, while those with primary HIV infection typically have levels in the range of 100,000 to greater than 1 million copies/mL.

Common laboratory abnormalities include leukopenia, anemia, thrombocytopenia, elevated transaminases, and atypical lymphocytosis. These signs, symptoms, and laboratory abnormalities should lead to a differential diagnosis that includes Epstein-Barr virus or cytomegalovirus mononucleosis, toxoplasmosis, secondary syphilis, rubella, viral hepatitis (in the presence of elevated transaminases), group A streptococcus infection or herpes simplex and other viral infections. All of these need to be addressed and evaluated for at the same time that the HIV tests (virologic and immunologic) are being performed.

## Table 2. Signs and Symptoms of Primary HIV Infection Among 365 Patients

| Sign or Symptom | Number of Patients (%) |
|---|---|
| Fever | 342 (94) |
| Adenopathy | 253 (69) |
| Sore throat | 241 (66) |
| Rash | 197 (54) |
| Myalgia/arthralgia | 175 (48) |
| Headache | 140 (39) |
| Diarrhea | 115 (32) |
| Nausea/vomiting | 105 (29) |

Adapted from Katsufrakis PJ and Daar ES. In: *Primary Care*. 1997.

## Clinical Issues Specific to Primary Infection

Patients who present with suspected primary HIV infection require a considerable amount of education and counseling. The risk of a false-negative or a false-positive result needs to be explained during the pre-test counseling. When the test results become available, appropriate post-test counseling will then be necessary. It is important to recognize that patients with primary infection are often quite ill and may think that being symptomatic with HIV disease means having AIDS, particularly given the prolonged duration of the syndrome (several weeks). The counseling after positive test results presents an opportunity to clarify the difference in these stages of HIV disease.

Individuals who are ill with primary infection are often asked to make immediate decisions related to complex aspects of treatment that often have long-range consequences. It is the clinician's responsibility to help the patient understand the rationale for and the goal of therapy, as well as the importance of medication adherence, before they initiate treatment. Physicians can play a critical role at this stage by spending time with patients upfront, thereby improving the odds that patients will continue on therapy and avoid creating an environment favorable to the development of drug-resistant virus.

## Therapy During Primary Infection

The question of when to initiate therapy for primary HIV infection remains an important one, but has yet to be answered. This issue is being addressed in several research programs, including a collaborative state project in California. In the interim, based on scientific rationale, Dr Daar believes it is reasonable to initiate antiretroviral therapy as early as possible in patients who are prepared to commit to the complex therapy required. Education and counseling about the various drugs and regimens and the requirements of antiretroviral therapy should be provided, after which time patients should be offered a potent antiretroviral regimen. It is not known which drug regimen is the most effective in this setting, but many

open label studies have resulted in maximal viral suppression with several different 3-drug regimens. The best antiretroviral regimen will be one that is most likely to be adhered to. Importantly, it must be explained to the patient that the therapy will most likely need to be continued for an extended period of time, and possibly for life.

In the context of therapy, the biologic and physiologic difference between the first few days and the first few months after exposure to HIV is just beginning to be studied. New research is being implemented to examine the virologic and immunologic status of primary infection in patients treated within days versus months of acquisition of HIV infection.

As with most issues surrounding antiretroviral therapy today there are potential advantages and disadvantages associated with treating primary HIV infection (Table 3). Treating primary infection as early as possible may have clinical, virologic, and immunologic effects. Two placebo-controlled clinical trials have demonstrated the benefits of early therapy during primary infection, although both utilized zidovudine monotherapy, which would not be considered today. In both trials, patients did better when treatment was instituted during primary HIV infection. In one study, the mean monthly change in CD4+ cell count was better and the development of HIV symptoms was less common in treated patients.

The potential virologic benefits associated with treatment of primary HIV infection include a reduction in plasma HIV RNA levels and a reduction in the seeding of virus to the lymphoid and CNS tissues. In addition, early treatment might decrease the long-lived viral reservoirs. A study by Finzi and colleagues evaluated patients with primary and chronic infection and suggested that HIV reservoirs are established extremely quickly, perhaps within the first days or weeks of infection.

The immunologic benefits are unknown at this time, although data from studies by Walker and coworkers suggest that early treatment is associated with persistent HIV-specific CD4+ cell responses, such as a lymphoproliferative response to HIV p24 antigen. Patients who received antiretroviral therapy during primary infection retained these proliferative responses, a benefit which is usually lost in chronically infected patients. More research is being devoted to the CTL response, and although scant, available data do suggest that an initially robust CTL response appears to wane in patients treated during primary infection. Thus, strategies to maintain or even bolster the immune response in patients treated during this stage of HIV disease seems to be an important approach for the future. Primary infection may also be the best stage at which to attempt to purge HIV reservoirs by cellular activation with cytokines. Several groups are designing trials that include immunomodulatory therapies in primary HIV infection for long-term control of viremia.

No antiretroviral therapies or regimens are specific for primary infection; the same HIV-suppressive regimens that are used for chronic infection (ie, those containing a protease inhibitor) are believed to be appropriate for primary infection. Eventually, phenotypic or genotypic analysis for drug resistance of an individual patient's viral isolates may help determine the best regimen for initial therapy. For now, epidemiologic surveys and clinical research need to be completed to determine the precise role of resistance testing in the treatment of primary infection. This is emphasized by the recent reports of increasingly resistant virus being acquired by newly infected individuals.

One trial (reported by Hoen and colleagues from France) studied the effects of zidovudine/lamivudine/ritonavir in 40 patients with primary infection. Among the 18 adherent patients, 17 (94%) had plasma HIV RNA levels below 50 copies/mL after 6 months of therapy. Although the reduction of plasma HIV RNA to below detectable levels in the adherent patients is hopeful, the number of patients lost to follow-up and the number of patients who could not maintain adherence to the complex regimen is worrisome.

ACTG 371 is evaluating a four-drug combination (zidovudine and lamivudine along with the investigational drugs abacavir and amprenavir) in primary infection. A substudy of ACTG 371, a collaborative effort by universities in California, will seek to address the following:

- The effect of early therapy on development and decay of HIV reservoirs in latently infected cells.
- The effect of timing of therapy during primary infection on development and maintenance of HIV-specific cellular immune responses (to determine whether initiating therapy within days versus weeks versus months of the acute syndrome affects virologic and immunologic parameters).

## Table 3. Rationale and Concerns in Treatment During Primary HIV Infection

| Rationale (possible advantages) | Concerns (possible disadvantages) |
|---|---|
| Therapy could blunt dissemination | Therapy could decrease the magnitude and potency of the initial immune response |
| Therapy could blunt early immune damage | Risk of long- and short-term adverse effects |
| Narrow target for therapy because of homogeneous viral population | Cost |
| Therapy could decrease viral set point | Adherence |
| Therapy could decrease viral reservoirs | Effect of therapy in body compartments outside of blood |

- The virologic determinants important to HIV transmission during the primary infection period.

Adherence is of central importance to the success of treatment for primary HIV infection. A patient's plasma viral load will gradually or abruptly rebound when therapy is interrupted. This observation alone underscores the fact that long-term therapy is crucial. Thus, patients who start antiretroviral therapy during primary infection need to understand that they are going to be on some form of therapy for an exceedingly long time, and possibly for life.

Although there are compelling reasons and an emerging scientific rationale for initiating antiretroviral therapy as early as possible in primary infection, there are also potential risks and many unanswered questions. The risks of adverse effects, for example, are important considerations. Individuals who are relatively healthy will be embarking on long-term treatment, and only now are some long-term toxic effects being recognized. These long-term abnormalities being reported in association with protease inhibitor use include glucose intolerance, fat redistribution, and hyperlipidemias. These alterations are added to the already well-known, short-term side effects. Additionally, the emergence of drug resistance possibly due to poor adherence or the transmission of resistant viruses is a key factor that will continue to influence the timing and choice of the initial therapeutic regimen. Epidemiologic monitoring of the prevalence of drug-resistant viruses in specific populations of newly infected individuals is essential to understanding the patterns of primary HIV resistance.

## Summary

Clearly, more prospective and long-term data are needed to provide both scientific and clinical rationales for initiating treatment for primary HIV infection as early as possible, and for continuing suppressive treatment indefinitely. As these data accumulate, information about the immunopathogenesis of HIV infection immediately following exposure may provide insights into immunologic strategies for controlling HIV.

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## Suggested Readings

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# HIV Drug Resistance and Resistance Testing Terminology

*The following was developed as a supplement to the recently published International AIDS Society–USA panel recommendations on the implications and uses of antiretroviral drug resistance testing in adults with HIV infection (Hirsch et al. JAMA. 1998). This glossary is intended to clarify some of the complex terminology involved in this relatively new aspect of HIV disease management.*

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**Amino acid abbreviations:** A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

**Amino acid residue:** that portion of an amino acid that is incorporated into a peptide or protein.

**Cleavage site:** one of nine sites (peptide bond) within the gag-pol polyprotein (peptide precursor) that is cleaved by HIV-1 protease to form functional subunits of gag (p17, p7, p24) and pol (protease, reverse transcriptase, integrase).

**Codon:** a three-nucleotide sequence of a mRNA specifying (coding for) an amino acid.

**Consensus sequence:** the expected predominant sequence determined from the aggregate sequences of a virus population.

**Cross-resistance:** failure of one drug to inhibit replication of a virus that is resistant to a second drug. When development of resistance to one drug also results in resistance to a second drug, there is cross-resistance between the two drugs.

**Dideoxynucleotide sequencing:** a DNA-sequencing method that utilizes the incorporation of labeled dideoxynucleotides to terminate DNA synthesis at specific bases (A, C, T, G), thereby identifying the base at each position in the DNA sequence.

**Fitness:** the ability of an individual virus to replicate successfully under defined conditions.

**Genetic mixtures:** a mixture of HIV variants with different nucleotide sequences.

**Genetic polymorphism:** a genetic variant not recognized to confer a change in drug susceptibility.

**Genotype:** the sequence of nucleotide bases that constitutes a gene.

**Hybridization:** binding of strands of DNA by nucleotide base pair between the strands (A:T and G:C).

**$IC_{50}$, $IC_{90}$, etc:** the concentration of drug that inhibits the replication of microorganisms by 50% ($IC_{50}$), 90% ($IC_{90}$), etc.

**Mutation:** a change in the nucleotide sequence of a gene that differs from the wild type.

**Nucleoside:** a purine or pyrimidine base linked to a pentose; the natural deoxyribonucleosides are deoxyadenosine (dA), deoxyguanosine (dG), (deoxy)thymidine (dT), and deoxycytidine (dC).

**Nucleotide:** a phosphate ester of a nucleoside.

**Phenotype:** a defined behavior; specifically drug susceptibility with regard to HIV-1 drug resistance.

**Polymerase chain reaction:** a method whereby a defined segment of nucleic acid (DNA, or RNA after reverse transcription to DNA) is replicated in a cyclical and exponential fashion with repetitive denaturation and renaturation of the DNA helix in the presence of a DNA polymerase and synthetic oligonucleotides complementary to the segment in question.

**Quasispecies:** a complex mixture of genetic variants of an RNA virus.

**Recombinant virus:** a virus constructed by combining parts of different viruses, usually by using recombinant DNA technology in vitro.

**Resistant:** an interpretation of whether inhibition of an isolate, considering its drug susceptibility, is unlikely to be achieved.

**Sensitive:** an interpretation of whether inhibition of an isolate, considering its drug susceptibility, is likely to be achieved.

**Substitution:** replacement of one amino acid residue or nucleotide by another. Usually used to denote replacement of wild type by a mutation at a specific locus.

**Susceptibility:** the degree of inhibition of virus replication at a given concentration of drug.

**Wild type:** a genotype or phenotype circulating prior to selection of drug resistance.

# Issues in Antiretroviral Therapy in 1998

*At the Los Angeles course in February, Paul A. Volberding, MD, discussed current strategies for the use of antiretroviral drugs for the treatment of HIV infection, as well as the rationale underlying these strategies. Dr Volberding emphasized that although dramatic changes in treatment strategies have not occurred in the last year, increased experience with combination antiretroviral therapy has yielded practical knowledge about virologic responses and drug failures, immunologic responses and nonresponses, and the consequences of medication adherence and nonadherence.*

The overall goal of antiretroviral therapy remains largely unchanged in 1998 from that in 1997. Potent antiretroviral regimens are used to effect sustained maximal suppression of HIV replication. Such suppression is considered important to prevent the emergence of drug-resistant viral variants and to allow the recovery of immune function. While the goal of antiretroviral therapy has remained straightforward, the clinical management of HIV-infected patients has become more complex as an increasing number of drug combinations are evaluated and found potent. In addition, identifying practical strategies for attaining durable virologic responses and defining and managing treatment failure remain significant challenges.

## General Issues

Accumulating data continue to support treatment strategies, such as the early initiation of potent antiretroviral therapy. It is critical to choose the drugs used in initial therapy carefully, and newer studies are broadening the available options (Table 1). Considerations for the selection of a particular regimen include potency, tolerability, convenience, potential side effects, and the available therapeutic options should the initial regimen fail. Potent antiretroviral regimens are defined as those that achieve sustained maximal viral suppression. However, there is no clear consensus on the relative potencies of the numerous available regimens, and long-term, comparative clinical trial data are needed.

As noted, tolerance and convenience of the drugs and drug regimens are two considerations that are essential for the long-term success of antiretroviral therapy. Because tolerability and convenience vary by drug as well as from patient to patient, the clinician's role has expanded to include assisting patients to identify daily living strategies that can best support long-term medication adherence. Preliminary data suggest that patients who understand the rationale for adherence and the consequences of nonadherence are more likely to remain committed to their prescribed regimen (ie, with regard to dosing schedules and food restrictions). The possible consequences of nonadherence include emergence of drug-resistant viral variants, including cross-resistant and multi-drug-resistant virus strains, as well as transmission of drug-resistant viruses. Already, several cases of patients newly infected with HIV that is resistant to multiple antiretroviral agents have been reported.

**Table 1. Examples of Potent Antiretroviral Regimens in Clinical Use or Under Investigation**

- **nRTI + nRTI + PI**
- **nRTI + nRTI + NNRTI**
- **nRTI + nRTI + PI + PI**
- **PI + PI**
- **NNRTI + PI**
- **nRTI + nRTI + nRTI**
- **nRTI + hydroxyurea + PI**

*nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.*

Short-term as well as long-term adverse effects of the drugs must be considered in the choice of the initial regimen. There is a growing body of information about the long-term metabolic sequelae of antiretroviral therapy, particularly with the use of protease inhibitors. These include abnormal fat distribution, glucose intolerance, and hyperlipidemias. The natural history, frequency, and clinical impact of these changes are still being elucidated, and concern about these complications do affect treatment decisions.

Data published in the past year show that, contrary to initial hopes, eradication of HIV in patients with established HIV infection is unlikely with the currently available drugs even after 2 to 3 years of potent therapy. Thus, it is crucial to ensure that patients are fully prepared to commit to the possibly life-long and complex therapeutic regimens before therapy is initiated. In fact, the optimum time to begin treatment may be more determined by the patient's ability to commit to long-term medication than by an arbitrary CD4+ cell or plasma HIV RNA threshold. The surprising degree of immune recovery following antiretroviral therapy may allow for a period of safe deferral of treatment. During this interval, treatment options can be carefully weighed against better knowledge of the patient's motivation and lifestyle.

When selecting an initial antiretroviral regimen, it is important to anticipate incomplete suppression or eventual virologic failure. The initial treatment strategy should take into account the resistance profiles of the currently available drugs to leave one or more subsequent therapeutic

options available. Ongoing clinical trials are providing sobering information on cross-resistance, particularly among the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs).

## Recent Preliminary Findings on Antiretroviral Therapy

Data relating to the virologic and immunologic effects of potent antiretroviral therapy are accumulating, and can be used to guide the use of antiretroviral treatment. New data are particularly encouraging regarding the role of the NNRTIs as components of potent regimens.

### *Predicting Virologic Responses*

Data from the ACTG 320 study, reported by Hammer and colleagues, indicate that the virologic response at weeks 4 or 8 to the triple-drug regimen indinavir/zidovudine (or stavudine)/lamivudine is predictive of the virologic response at 6 months. Among the patients who had not achieved plasma HIV RNA levels below the assay detection limit (500 copies/mL in this study) by week 4 or 8, only 31% had a virologic response at 6 months. Conversely, of those patients who had plasma HIV RNA levels below 500 copies/mL at both weeks 4 and 8, 85% had plasma HIV RNA levels below 500 copies/mL at 6 months.

Definitive recommendations cannot be made based on these limited data, but they may provide some direction. For example, Dr Volberding suggested that if a patient has low but still detectable (>500 copies/mL) levels of plasma HIV RNA 8 weeks after starting therapy, it may be reasonable to attempt to intensify the regimen by adding another drug, especially if that patient is tolerating the initial regimen. Some clinicians may be inclined to change the entire regimen in such a scenario. At present, either approach seems more appropriate than waiting until the patient's viral load rebounds toward baseline levels. It should be noted, however, that an addition of a drug to the regimen must be made before the plasma HIV RNA level begins to rebound, because the addition of a single drug in the setting of virologic failure would be considered the equivalent of sequential monotherapy.

The correlation between magnitude of plasma viral load reduction and the duration of virologic response was assessed in the INCAS trial (which evaluated zidovudine/didanosine/nevirapine) and in the AVANTI 3 trial (which evaluated zidovudine/lamivudine/nelfinavir). Patients in whom plasma HIV RNA levels were below 500 copies/mL, but not below the detection limit of more sensitive assays (ie, <20-50 copies/mL), had shorter durations of virologic response than patients who had plasma HIV RNA levels that were reduced to below the 20 to 50 copies/mL threshold. In the AVANTI 3 trial, no durable responses occurred in patients who had plasma HIV RNA levels below 500 but greater than 50 copies/mL. Together, these findings suggest that the more sensitive plasma HIV RNA assays have clinical value for assessing the response to antiretroviral therapy. However, with the more sensitive assays, it may take longer (16 weeks or more in some trials) to reach a nadir or virus level below the detection limit after initiating therapy, depending on the patient's pretreatment plasma viral load.

The CD4+ cell count remains an important independent predictor of prognosis in HIV infection and cannot be replaced in patient management. Recent data from the Merck 028 study underscore the point that CD4+ counts are a more direct predictor of clinical progression risk than plasma viral load. Investigators assessed the last known CD4+ count plotted against the last known viral RNA measurement among treated subjects and distinguished between those who did or did not experience an opportunistic illness or death. Patients who had clinical events had a wide range of plasma viral loads, but almost all had CD4+ counts below 300 cells/μL, and most of these were below 100 cells/μL.

### *Predicting Virologic Failures*

Growing experience with potent antiretroviral combinations is beginning to reveal factors that are predictive of treatment failure. One of the strongest predictors of virologic failure is nonadherence, and the best marker of nonadherence is patient self-reporting of this when questioned. Virologic failures due to nonadherence (assuming the patient is taking at least a substantial portion of prescribed doses) are usually due to the selection of drug-resistant viral variants. Ample evidence now exists supporting the hypothesis that incomplete suppression of HIV replication, as predicted with frequent missed drug doses, creates an environment that favors the emergence of drug-resistant viral variants. Other factors identified as independent predictors of virologic failure in patients with established infection include very high pretreatment plasma viral loads (eg, >50,000 copies/mL), very low pretreatment CD4+ counts (eg, <100 cells/μL), and the addition of a single drug to an existing failing drug regimen.

*The CD4+ cell count remains an important independent predictor of prognosis.*

Virologic failure and virologic rebound signal the need for replacing several and possibly all of the drugs in a patient's existing antiretroviral regimen. The specific drugs to be added or replaced depend on the individual clinical situation, including the patient's previous treatment history, as well as past and current plasma viral load, CD4+ cell count, and clinical status. Other important considerations include what the patient can tolerate and whether the patient is chronically nonadherent. Drug resistance or susceptibility assays (genotype or phenotype) may well add information although the role of this information for treatment decisions remains an important research question.

### *Virology and Treatment Decisions*

The potential role of viral genotype data in clinical management is receiving increased attention. The presence of some specific resistance mutations does not necessarily predict or correspond with treatment failure. Much more in vivo re-

sistance data, especially with regard to the protease inhibitors, are needed before it becomes possible to understand which mutations actually confer resistance, which are natural polymorphisms, and which are compensatory or insignificant mutations. The issues surrounding the interpretation and use of viral genotyping are complex and confusing (see Hirsch et al. *JAMA*. 1998).

Technologic development of viral phenotyping assays for clinical isolates, including automation of these assays, may make virologic phenotyping more integral to the design of antiretroviral therapy regimens in the future. Dr Volberding noted that one assay in development may be able to provide results in 8 to 10 days, compared with the current 4 to 8 week turnaround time for phenotyping test results.

*It is difficult to compare different dual protease inhibitor regimens because of the differences in patient populations in the different trials.*

Phenotype data may be more easily interpreted by the clinician than genotype data. As recently described by Mellors, a phenotypic assay was used to determine the probability that a clinical isolate known to be at least 10-fold less susceptible to one protease inhibitor will be at least 4-fold less susceptible to all other approved drugs in this class.

### *Dual Protease Inhibitor Therapy*

In an attempt to identify more-potent antiretroviral regimens using currently available drugs, several dual protease inhibitor combinations are being investigated.

In most cases, dual protease inhibitor combinations achieve high potency by one protease inhibitor positively influencing the pharmacokinetics of the second protease inhibitor (Table 2). Ritonavir/saquinavir is the best-studied combination at this time. Ritonavir is a strong inhibitor of the cytochrome P450 system and it raises the plasma drug concentration of saquinavir by about 20-fold when the two drugs are combined, which significantly increases the potency of saquinavir. There are insufficient data to identify which dual protease inhibitor combinations are superior in potency, tolerability, and durability of response. Dr Volberding noted that it is difficult to compare different combinations based on current data because of differences in the study populations as well as in the regimens used. For example, ritonavir/saquinavir trials actually involve regimens of these two drugs plus NNRTIs. Furthermore, completed or ongoing clinical trials evaluating dual protease inhibitor therapy for individual patients often have drugs added or changes made to the regimens throughout the course of the studies.

One question at this time is whether it is best to combine protease inhibitors that have similar resistance mutation patterns or those that have dissimilar resistance mutation patterns. It could be argued that the combination of ritonavir/indinavir, 2 drugs with numerous overlapping mutations, may provide potency while preserving future salvage therapy options. The opposite argument, using 2 protease inhibitors with a low frequency of overlapping mutations, such as nelfinavir/indinavir, may provide more sustained viral suppression given a broader genetic resistance profile. Clearly, long-term and comparative data from large studies are needed to answer this question.

### *Management of Protease Inhibitor Failure*

At present, the potential for success of salvage therapy after a protease inhibitor-containing therapy fails is not very encouraging, and few large trials comparing different salvage regimens have yet been completed. However, there are some data to suggest that dual protease inhibitor therapy as an element of salvage therapy may be acceptable, or at least better than continuing with a failing regimen or discontinuing all therapies. A small trial evaluated stavudine/lamivudine/ritonavir/saquinavir as salvage therapy for zidovudine/lamivudine/nelfinavir failure in 26 patients who had received nelfinavir for a mean duration of 55 weeks. After 6 months of the 4-drug regimen, 68% of patients had plasma HIV RNA levels below 500 copies/mL, and 40% had below 50 copies/mL. Although these are short-term results, they suggest that ritonavir/saquinavir may be a potentially viable salvage strategy for patients heavily pretreated with nelfinavir. Longer-term data and additional studies evaluating various salvage regimens for patients in whom

## Table 2. Dual Protease Inhibitor Combinations Under Investigation

| Dual Protease Inhibitor Regimen | Primary Pharmacokinetic Effect |
|---|---|
| Ritonavir/saquinavir | ↑ saquinavir concentration (20-fold) |
| Ritonavir/indinavir | ↑ indinavir concentration (5-fold) |
| Indinavir/nelfinavir | ↑ nelfinavir concentration (1.8-fold) |
| Nelfinavir/saquinavir | ↑ saquinavir concentration (5-fold) |
| Ritonavir/ABT-378* | ↑ ABT-378* concentration (200-fold) |

* Investigational protease inhibitor

different initial protease inhibitor therapies have failed are needed.

### *Twice Daily Regimens for Protease Inhibitors*

Medication adherence is directly related to the convenience of the antiretroviral regimen. Twice-daily-dosing schedules are easier to follow and more convenient than thrice-daily-dosing schedules. As such, lower-frequency schedules are expected to facilitate adherence.

The thrice-daily-dosing schedules for 3 of the 4 currently approved protease inhibitors were determined based on pharmacokinetics, or specifically, the peak and trough plasma concentrations and time to peak concentrations of each drug. Preliminary data indicate that higher doses of indinavir or nelfinavir, each taken on a twice-daily-dosing schedule, may result in similar or higher proportions of patients with plasma viral loads that decrease to below assay detection limits, compared with those achieved by the standard dose on a three-times-daily schedule. An obvious question that arises is whether the more convenient dosing schedule plays a role in these improved responses. However, it is also not yet known whether the higher doses of these drugs will result in a higher risk (for some) of adverse effects.

## Induction-Maintenance Regimens

The strategy of starting with an aggressive regimen (termed "induction") and following up with a less intense regimen (termed "maintenance") is attractive for several obvious reasons. However, initial trial data are not supportive at this time. In the ACTG 343 study, patients began a 3-drug regimen of zidovudine/lamivudine/indinavir; patients in whom plasma HIV RNA levels were below the assay detection limits at 6 months were asked to participate in a randomization in which they would either continue on their regimen, receive indinavir monotherapy, or receive zidovudine/lamivudine. Patients had plasma HIV RNA levels below the detection limit at 6 months and most elected to participate in the randomization. Patients who received indinavir monotherapy or zidovudine/lamivudine experienced rapid viral rebound. Another trial, conducted by Raffi and colleagues in France, showed similar results with a different 2-drug maintenance regimen. The ADAM study was recently reported in which maintenance including a dual protease also failed rapidly.

> *Twice-daily-dosing schedules are easier to follow and more convenient than thrice-daily-dosing schedules and are expected to facilitate adherence.*

When some of the extremely aggressive, 5- or 6-drug regimens are used as induction for established infection, it may still be possible to retreat to a potent 3-drug regimen. The underlying rationale for such a strategy is that patients may not tolerate these extremely aggressive regimens very well or for very long. A Dutch study of an aggressive regimen for patients with advanced HIV disease, reported at the 5th Retrovirus Conference in Chicago, cited 40% of patients withdrawing from the study because of intolerability of the medications.

## Summary

As in 1997, the current strategies for antiretroviral therapy are based on preventing or delaying viral resistance to the drug, which is believed necessary to delay virologic rebound. Indeed, the "hit hard, hit early" maxim is rooted in the belief that maximal suppression of HIV for as long as possible creates the least favorable environment for drug-resistant viral variants to emerge and propagate. Initiation or intensification of antiretroviral therapy requires a scientifically sound strategy, one that takes into account the potential for cross-resistance among the reverse transcriptase inhibitors or among the protease inhibitors.

Maximal and sustained suppression of virus is the primary goal of treating HIV infection; however, it is important to consider future therapeutic options for patients in whom the virologic response wanes with the initial potent regimen. Accumulating data suggest that in some situations it is possible to provide effective alternative regimens for patients in whom potent protease inhibitor-containing regimens have failed. Increased experience with potent antiretroviral regimens and with the patients taking them has created an evolving knowledge base about the various combinations of drugs, including such critical information as predictors of virologic response or failure.

*Paul A. Volberding, MD, is Professor of Medicine at the University of California San Francisco and Director of the AIDS Program at San Francisco General Hospital.*

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# New Antiretroviral Therapies: Adherence Challenges and Strategies

*At the April International AIDS Society–USA course in Chicago, Margaret A. Chesney, PhD, from the University of California San Francisco, reviewed the available data on adherence and suggested some strategies that can be used to enhance adherence in the clinical setting.*

Nonadherence to prescribed medication is not a new issue in medicine, nor is it one that is unique to HIV disease. Much of the research available on adherence is from the field of hypertension. In general, studies have estimated that only 50% of individuals take more than 80% of their anti-hypertension medications. Two early studies of subjects infected with HIV indicated that 63% and 67% of the subjects were taking more than 80% of prescribed zidovudine monotherapy. As Dr Chesney noted, the 80% figure has been quoted historically as a cutoff for "adequate" adherence, but there is no evidence that "80%" is specifically related to a satisfactory effect (ie, appropriate viral suppression) with any particular drug regimen.

Adherence decreases as the number of medications, doses, and side effects increase, as well as when the frequency of interference with daily routines increases. The complexity and duration of potent antiretroviral therapy is unprecedented in the ambulatory care setting. Dr Chesney noted that a variety of leading experts in HIV are underscoring the importance of adherence; for example, recommendations for antiretroviral therapy published by the International AIDS Society–USA and ones developed by the Department of Health and Human Services both stress that excellent and consistent adherence is necessary to prevent viral breakthrough and the evolution of drug-resistant strains of HIV.

*At least 25% of patients may be at risk of viral breakthrough resulting from nonadherence.*

## Prevalence of Nonadherence Among Patients Taking Combination HIV Therapy

To date, there have been two surveys conducted on adherence to combination HIV therapy. The first study, conducted by the Recruitment, Adherence, and Retention Subcommittee of the AIDS Clinical Trials Group (ACTG), included 76 patients from 10 sites who were enrolled in a clinical trial and were taking a protease inhibitor. In the study, almost 20% of patients reported missing at least one dose in the 2 days prior to the interview.

A study of patients at San Francisco General Hospital found very similar results and also showed a significant association between the patients' plasma HIV RNA levels and the reported degrees of adherence. These and other data suggest that at least 25% of patients are at risk for viral breakthrough as a result of nonadherence.

Among the commonly reported reasons for missing medications are that patients just forgot, fell asleep, were too busy, or were depressed. Ironically, many of the reasons, such as being away from home or changes in routine, involve returning to an active lifestyle that is due in part to the success of the combination antiretroviral drug therapy. A significant percentage of patients reported feeling sick as the reason for missing medication. This finding underscores the need to proactively discuss and manage side effects. It also points to an important research question: what are the effects of vomiting on drug levels in the blood? Few data are available, and the issue of whether to take another pill after vomiting is a commonly asked question from patients.

## Predictors of Nonadherence

In adherence studies, stress/depression is the only variable that predicts nonadherence across disease categories. Gender, age, ethnic, or educational differences have not been identified as consistent predictors of nonadherence.

In a recent study, patients were categorized as having reported taking all of their medications in the past 2 weeks and having reported skipping at least one dose. Nonadherent patients had statistically higher monthly rates of alcohol consumption than adherent patients. In addition, a higher percentage of nonadherent patients were working outside the home.

## The Role of the Clinician in Improving Adherence

In order to ensure optimal adherence, it is essential for clinicians to (1) give patients a clear rationale for the need for strict adherence; (2) provide clear instructions, including the exact timing of doses, the number of pills, and specific dietary restrictions; (3) proactively manage side effects; and (4) create a partnership with patients based on honesty and trust. Selected strategies for working with patients on these issues are listed in the Table 1.

From the initial interaction, the goals of treatment should be discussed with patients to ensure that they understand that decreasing and maintaining viral load to below detectable levels is the primary objective of therapy. In addition to remembering to take each dose, patients need to understand the specific instructions asso-

## Table 1. Improving Adherence: Strategies for the Clinician

**• Manage side effects proactively.**

- Educate patient about the potential for different side effects.
- Provide patients with the medications they may need to relieve potential side effects.
- Ask patients to contact you (by phoning the office) if they experience any side effects so you have a record of it.

**• Call the drug whatever the patient calls the drug, unless the name is wrong.**

- If a patient refers to a drug as "the little white capsule," ask how many little white capsules he or she is taking and when he or she is taking them.

**• Ask patients about daily routine activities that can serve as cues to take the pills. Use reminder cards or other tools to plan an individual schedule.**

- Establish cues for the first and subsequent pills of the day (examples of cues may be going to the bathroom first thing in the morning, watching a specific TV show, or feeding a pet, etc). Emphasize that the medications should be taken before the routine activity. Continue to identify activities throughout the day. If the second dose of a drug is scheduled for 3:00 PM, ask what he or she does everyday at 3:00 PM.
- Think of activities in patients' lives rather than meals, since many of us skip or are irregular about eating meals.
- Suggest using an inexpensive watch with a timer that can be set for a given time of day.

**• Use nonjudgmental questions to ask how patients are doing.**

- Avoid saying, "Are you taking your medications the way you are supposed to?"
- Create an environment in which the patient feels comfortable talking candidly. Use language such as, "Taking these medications regularly can be a real challenge. A lot of people are having trouble remembering. What I need you to tell me is how you are really doing. Don't tell me what you think I want to hear. Let's look at yesterday. Did you miss any of your doses? How many?"

**• Anticipate problems.**

- Every time medication is changed, adherence is likely to be problematic. Reemphasize the adherence issues and make sure patients understand the new regimen.
- Plan for schedule changes such as holidays, weekends, and vacations. At holidays, send patients a holiday card reminding them to take their medications.

**• Troubleshoot problems and involve patients in problem-solving.**

- Ask patients:

  What is the reason they missed taking the medication?

  What would have worked instead?

  How might they have remembered to carry the medications with them?

  Do they need extra vials so that they can keep medications at their desk or other places?
- Keep a supply of snack-size baggies at the clinic. Show patients how to open one up, reach in, and remove the drugs from a pocket. Ask them to demonstrate how they will do the same.

**• Reinforce patients' efforts to adhere to medications, even if they are having trouble.**

- If a patient tells you that he or she missed taking the medication yesterday, respond: "I am so glad that you told me that. Always tell me what is really going on." Reinforce whatever it is that a patient is doing right and build from there.

ciated with each drug. Thus, it is important to avoid the use of confusing names for the drugs (eg, using trade names and generic names for the drugs interchangeably) or confusing medical abbreviations (eg, "bid" and "tid"). If a physician's schedule does not allow sufficient time for explanations, the patient should be referred to a designated person on the health care team for follow-up and additional questions.

Patients must also be prepared for potential side effects and their management. Discussing side effects will not create the effects. In fact, patients who are not prepared for side effects frequently discontinue the medication, or they may try to self-manage the side effects (such as diarrhea) on their own by experimenting with different dosage schedules.

It is essential to help patients tailor the medication to their lifestyle rather than tailoring their lives to the drugs. Identifying regular activities to serve as cues can help patients remember to take their drugs. Generally, they will already have consistent daily activities that can direct the medication intervals. Patients with symptoms of stress or depression should be referred for services or treatment. Similarly, it is necessary to help patients manage drug and alcohol use through appropriate referrals, as increased alcohol or substance use may indicate depression. Such measures focus on the whole patient and address issues of adherence on a realistic basis.

By acknowledging from the beginning that adherence will be a challenge, but that the clinical team will work with the patient, clinicians can establish a trusting relationship that increases the likelihood that the patient will report honestly about his or her adherence. Nonjudgmental questions, a willingness to problem-solve with patients, and accessibility of a staff member for questions and follow-up are key factors in building a trusting relationship.

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

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# Upcoming International AIDS Society–USA CME Courses

## *Annual Fall Series*

***Current Challenges in HIV Disease: A Case-based, Advanced Course in Clinical HIV Management***

This is the fourth year of the fall series, which focuses on recent data and new information in the clinical management of HIV disease. The advances in the field are presented through a mix of clinically relevant cases and didactic lectures.

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| October 9, 1998 | New York, NY |
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This series reviews the most recent developments in the field of HIV disease pathogenesis and antiretroviral management. Expert faculty will speak on timely and clinically relevant issues in the management of HIV disease.

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| March 27-31, 1999 | Snowmass Village, CO |

For more information on any of these courses, please call the International AIDS Society–USA symposium voice mail at (415) 561-6725; fax at (415) 561-6740; or e-mail at cme@iasusa.org.

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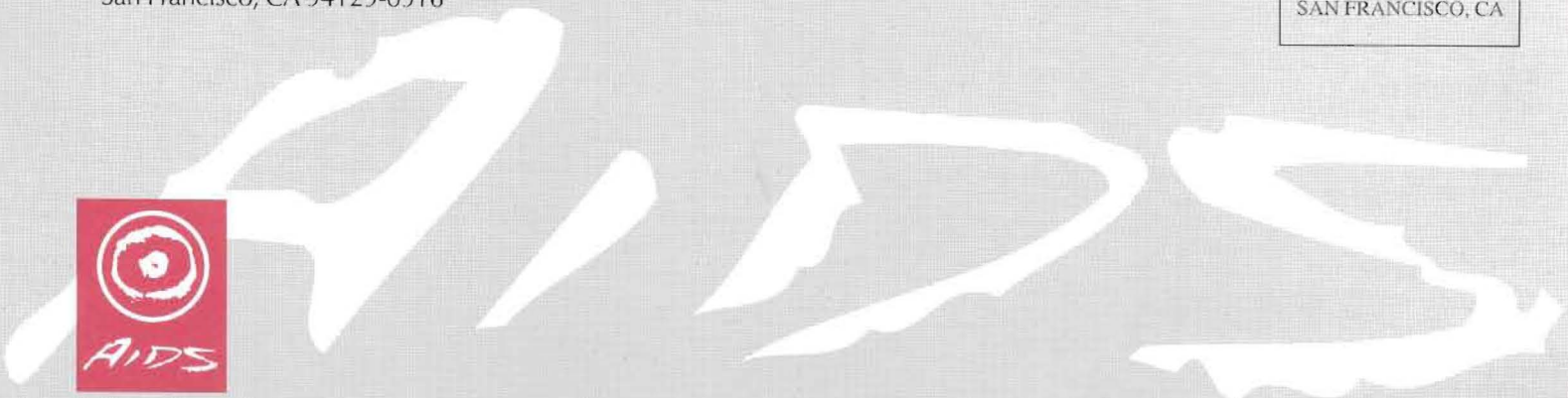
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