Major advances during the past 2 years have resulted in an unprecedented optimism regarding the perception of human immunodeficiency virus (HIV) infection. An improved understanding of the pathogenesis of HIV infection coupled with the availability of assays to measure HIV-1 RNA and the approval of new antiretroviral drugs has led to the development of new approaches to the management of HIV infection. In this article, we discuss these advances and their implications in the care of HIV-infected patients. In addition, we present the guidelines for the use of antiretroviral therapy for HIV infection.


AIDS = acquired immunodeficiency syndrome; FDA = Food and Drug Administration; HIV = human immunodeficiency virus; NNRTIs = nonnucleoside reverse transcriptase inhibitors

The advances in the management of human immunodeficiency virus (HIV) infection that have occurred during the past 2 years have led to a new perception of the disease and the establishment of new treatment paradigms. These advances include (1) an improved understanding of the pathogenesis of HIV infection; (2) the development of reliable assays to detect and quantify HIV-1 RNA (viral load); (3) the availability of new and potent drugs to treat HIV infection; and (4) the results of recently completed trials of combination antiretroviral therapy that demonstrate reductions in the risk of progression to the acquired immunodeficiency syndrome (AIDS) and death.

PATHOGENESIS
Contrary to previously held beliefs, HIV is not dormant during the so-called clinical latency period. Studies of lymph node biopsy specimens from HIV-infected patients in which nucleic acid hybridization techniques were used have demonstrated active virus replication at all stages of disease.1,2 On the basis of studies of HIV replication kinetics, an estimated 10 billion viral particles are produced and cleared daily throughout all stages of disease in an HIV-infected person. The half-life of HIV in plasma is approximately 6 hours. Productively infected CD4 cells have an estimated half-life of less than 2 days.3,5 Approximately 140 generations of viral particles are produced in 1 year, and 1,400 generations are produced during the course of 10 years. Thus, an extremely large number of genetic variants may be responsible for the presence of preexisting drug resistance and the development of drug resistance under selective drug pressure. These genetic variants may also allow the virus to escape immune surveillance activity. This active replication of HIV is accompanied by a rapid turnover of CD4+ lymphocyte cells; however, the rate of this T-cell replenishment cannot offset the rate of cell destruction due to HIV, and immunologic decline progresses.

QUANTITATIVE PLASMA HIV RNA
The ability to quantify plasma HIV RNA represents a major advance that facilitates individualized management of HIV-infected persons.6,7 Three assays are currently available for measurement of viral load: reverse transcriptase polymerase chain reaction, branched DNA, and nucleic acid sequence-based amplification. The methodologies used to perform these assays differ, but all three assays are thought to be reliable and reproducible. The assays also differ in their sensitivity in detecting HIV strains that are different from the subtype B strains common in North America and western Europe. Because there is no uniform standard between these assays, the same assay should be used to monitor the progress of each patient. Of the three assays, reverse transcriptase polymerase chain reaction is the only one that has been approved by the Food and Drug Administration (FDA) for use in clinical practice, but all three are available through commercial laboratories.

Several studies have confirmed the utility of viral load as a prognostic indicator of the risk of death or disease progres-
sion in HIV-infected persons. In the study by Mellors and colleagues of 1,601 men from the Multicenter AIDS Cohort Study, the baseline HIV RNA was highly predictive of disease progression and survival. The CD4 cell count was useful as a prognostic indicator only in those with the lowest CD4 cell counts. Viral load has also become a useful tool for assessing and monitoring the efficacy of antiretroviral therapy. Virologic analysis performed within the context of several antiretroviral therapy clinical trials has confirmed the relationship between changes in viral load and treatment benefit. These studies have shown that a decrease in HIV RNA is associated with a reduction in the risk of disease progression and death independent of the baseline CD4 count or the increase in the CD4 count due to treatment. In one study, a 90% reduction in the risk of disease progression was associated with a 10-fold decrease in viral load between baseline and week 56 of follow-up. Guidelines for the clinical use of viral load to manage antiretroviral therapy have recently been published. These guidelines recommend the use of viral load as the standard practice in the care of all HIV-infected persons. An increasing viral load while a patient is receiving therapy suggests treatment failure and should trigger consideration of a change in or a modification of the current regimen if other causes of increases in viral load, such as an intercurrent illness, have been ruled out.

NEW ANTIRETROVIRAL DRUGS

Until November 1995, the antiretroviral drugs available and approved for clinical use in the United States consisted of only four nucleoside analogue reverse transcriptase inhibitors: zidovudine (Retrovir, ZDV, AZT), didanosine (Videx, ddI), didanosine (Zidovudine, d4T). Since then, two new classes of agents and seven new agents have been approved; thus, the number of available antiretroviral drugs has almost tripled.

Nucleoside Analogue Reverse Transcriptase Inhibitors.—Nucleoside analogue reverse transcriptase inhibitors are structurally similar to the building blocks of nucleic acids (RNA and DNA) and compete with those same building blocks to act as chain terminators in the synthesis of proviral DNA. The newest addition to this group is lamivudine. Lamivudine (Epivir, 3TC), a cytosine analogue reverse transcriptase inhibitor, was approved by the FDA in November 1995 for use in combination with zidovudine in the treatment of HIV infection. It has a favorable toxicity profile. The most common side effect is mild headache. Other adverse events include gastrointestinal symptoms, insomnia, and fatigue. Pancreatitis has been reported in pediatric patients. Although lamivudine-resistant mutants appear rapidly during treatment, the mutation seems to prevent emergence of resistance to zidovudine or restore susceptibility to zidovudine if resistance is already present. Results from the multinational CAESAR (Canada, Australia, Europe, and South Africa) trial indicate a significant clinical benefit with use of lamivudine in combination regimens.

Nonnucleoside Reverse Transcriptase Inhibitors.—Nonnucleoside reverse transcriptase inhibitors (NNRTIs) bind directly to the enzyme reverse transcriptase and block DNA polymerase activity. Unlike nucleoside analogues, NNRTIs do not compete with nucleoside triphosphates and are inactive against HIV-2. The two NNRTIs currently approved for clinical use are nevirapine and delavirdine.

Nevirapine.—Nevirapine (Viramune), the first agent from this new class of NNRTIs, was approved by the FDA in June 1996 for use in combination with nucleoside analogues in the treatment of adults with HIV-1 infection who have experienced clinical or immunologic deterioration (or both). When nevirapine is used as a single agent, resistance emerges rapidly. A rash is the most severe side effect, and thus nevirapine is administered at half the regular dose (200 mg daily) for the first 2 weeks.

Delavirdine.—Delavirdine (Rescriptor) is a potent NNRTI that was approved by the FDA in April 1997. Rapid emergence of resistance to delavirdine has been noted when it is used as monotherapy. Cross-resistance to nevirapine and other NNRTIs is possible. As with nevirapine, rash is the most severe side effect. The recommended dosage of delavirdine is 400 mg (four 100-mg tablets) three times daily.

Protease Inhibitors.—The protease enzyme is vital during the final stage of the HIV life cycle. It is responsible for the cleavage of large polypeptide chains into smaller functional proteins, thus allowing maturation of the HIV virion. Inhibition of the protease enzyme results in the release of structurally disorganized and noninfectious viral particles. Currently, four protease inhibitors are approved and available for the treatment of HIV infection. Other protease inhibitors are at various stages of development. An overview of the general characteristics of currently approved protease inhibitors is presented in Table 1.

Saquinavir.—Saquinavir (Invirase) was the first protease inhibitor to be approved (December 1995). It has poor oral bioavailability (approximately 4%) but otherwise is well tolerated. It is available as 200-mg capsules. The standard dosage is 600 mg three times daily and should be taken with meals for increased absorption. The most common side effects are gastrointestinal. A new soft gel formulation of the drug with better bioavailability (and, hopefully, increased potency) is currently in development.

Ritonavir.—Ritonavir (Norvir), which was approved by the FDA in March 1996, is a very potent antiretroviral drug. It is available as 100-mg capsules and should be refrigerated. The standard dosage is 600 mg twice a day with meals. Significant gastrointestinal side effects are common, espe-
Table 1.—General Characteristics of Currently Available Protease Inhibitors*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Bioavailability (%)</th>
<th>Adverse effects</th>
<th>Administrationudo</th>
<th>Cytochrome P-450 enzyme inhibitor†</th>
<th>Cost/yr‡ ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>600 mg t.i.d.</td>
<td>4</td>
<td>Gastrointestinal</td>
<td>Take with fatty snacks or a full meal</td>
<td>+</td>
<td>6,957</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>600 mg b.i.d.</td>
<td>70</td>
<td>Gastrointestinal, hypertriglyceridemia, paresthesia</td>
<td>Take with meals</td>
<td>++++</td>
<td>8,118</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg every 8 h</td>
<td>60</td>
<td>Nephrolithiasis, hyperbilirubinemia</td>
<td>Take on an empty stomach or with light snack, with 6-8 oz of water</td>
<td>++</td>
<td>4,380</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg t.i.d.</td>
<td>20-80</td>
<td>Diarrhea</td>
<td>Take with meals</td>
<td>++</td>
<td>6,782</td>
</tr>
</tbody>
</table>

*b.i.d. = twice a day; t.i.d. = three times a day.
†Relative inhibitory potency.
‡Based on average wholesale price.

During the first 2 weeks because of increased drug levels before hepatic enzyme induction responsible for the metabolism of ritonavir. Thus, the manufacturer recommends starting with a lower dose and gradually increasing it over a period of up to 2 weeks until the full recommended dose is achieved. The side effects usually improve after the first 2 weeks. Ritonavir is a potent inhibitor of the cytochrome P-450 enzyme system and thereby inhibits the metabolism of substances that use this system. This leads to increased plasma concentrations of these substances and may result in serious adverse effects. The drugs that should not be administered concomitantly with ritonavir include terfenadine (Seldane), astemizole (Hismanal), and the rifamycins (rifampin and rifabutin), as well as numerous antiarrhythmics, analgesics, calcium channel blockers, and gastrointestinal and psychotropic agents. Before ritonavir is added to a patient's regimen, the physician should review the medications the patient is already taking in order to avoid possible drug interactions.

**Indinavir.**—Indinavir (Crixivan) is a potent protease inhibitor that was also approved by the FDA in March 1996. It has good oral bioavailability. Indinavir is available in two strengths—200- and 400-mg capsules. The recommended dosage is 800 mg every 8 hours, and the drug should be taken at least 2 hours after or 1 hour before eating. If indinavir is administered with didanosine, there should be at least a 1-hour interval between administration of the two drugs. Like ritonavir, indinavir also inhibits the cytochrome P-450 enzyme system but to a lesser degree. The following medications are contraindicated in concurrent administration with indinavir: terfenadine, astemizole, cisapride (Propulsid), triazolam (Halcion), midazolam (Versed), and rifampin (Rifadin, Rifamate, Rifater, Rimactane). The dose of rifabutin (Mycobutin) should be halved when this drug is used concomitantly with indinavir. Because of possible drug interactions, the physician should be aware of the drugs the patient is already taking before indinavir is prescribed.

**Nelfinavir.**—Nelfinavir (Viracept) is another protease inhibitor with potent antiretroviral activity. It was approved by the FDA in March 1997. Double-blind controlled studies of nelfinavir in combination with zidovudine and lamivudine showed a significant decrease in viral load with a concomitant increase in CD4 cell counts. Nelfinavir has been found to be safe and well tolerated; mild diarrhea is the most severe side effect. Nelfinavir is also a cytochrome P-450 enzyme system inhibitor and has drug interactions similar to indinavir.

**ANTIRETROVIRAL TREATMENT TRIALS**

When antiretroviral therapy was first available, the use of single drugs was the standard practice; single drugs were sequentially substituted when clinical failure or adverse reactions occurred. This monotherapeutic approach resulted in weak suppression of HIV replication, rapid development of drug resistance, and a brief clinical benefit. Since then, several clinical trials using a combination of two antiretroviral drugs have clearly demonstrated that such regimens are superior to monotherapy and are associated with greater decreases in viral replication and significant clinical benefits as measured by a delay in progression to AIDS and a reduction in the risk of death. Although a combination of two antiretroviral drugs is superior to monotherapy, suppression of HIV is still incomplete and unsustainable. Most recently, reductions in mortality and disease progression rates have been reported in clinical trials involving a regimen of three antiretroviral drugs, one of which is a protease inhibitor. Such regimens have resulted in the potent suppression of viral replication, reduced development of drug resistance, and increased CD4 cell count for a longer period. This results in a decrease in the number of opportunistic infec-

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tions and an improvement in the quality of life of HIV-infected patients.

GUIDELINES ON THE USE OF ANTIRETROVIRAL THERAPY FOR HIV INFECTION

Because of the recent advances in the management of HIV infection, previous state-of-the-art guidelines and recommendations have become obsolete. Thus, an international panel of leading AIDS specialists convened under the auspices of the International AIDS Society, United States of America, to develop recommendations for the clinical management of HIV-infected persons. These guidelines recommend initiation of treatment to all HIV-infected persons who have symptoms due to HIV infection, a rapidly declining CD4 cell count, a CD4 count lower than 500 cells/mm³, or a viral load greater than 5,000 to 10,000 RNA copies/mL, regardless of the CD4 cell count. Antiretroviral therapy should also be considered for all HIV-infected persons with detectable plasma HIV RNA levels who request such therapy and are committed to lifelong adherence to the necessary treatment. The preferred antiretroviral regimen is one that is most likely to reduce and maintain plasma HIV RNA levels below the level of detection when the most sensitive assays available are used. Currently, such a regimen would consist of a combination of two nucleoside analogue reverse transcriptase inhibitors and a protease inhibitor. The guidelines also identified three settings that necessitate special considerations relative to antiretroviral treatment: primary HIV infection, postexposure prophylaxis, and maternal-to-fetal (vertical) transmission.

Primary HIV Infection.—Primary HIV infection, also known as the acute retroviral syndrome, refers to the 4- to 7-week period after exposure to HIV. The most potent combination therapy available is recommended in an attempt to intervene before the HIV infection is fully established, when the viral population is relatively homogeneous and the host immune system is relatively intact. Studies exploring the possibility of eradication of HIV in patients during this time frame in which potent triple and quadruple antiretroviral drug regimens are being used are currently under way.

Postexposure Prophylaxis.—In a recent case-control study, prophylaxis with zidovudine reduced the risk of transmission from a needle stick by 79%. Prophylaxis is recommended for all workers after occupational exposures associated with a risk of HIV transmission unless their exposure is deemed negligible. The combination of zidovudine, lamivudine, and indinavir has been suggested as the regimen of choice for persons with the highest risk of HIV transmission. Factors that may ultimately influence the choice of antiretroviral therapy include the probable antiretroviral drug-resistance profile of HIV from the source patient, current drug therapy, and local availability of drugs. Prophylaxis should be initiated within 1 to 2 hours after exposure and administered for 4 weeks.

Maternal-To-Fetal Transmission.—When zidovudine is administered to the mother during the antepartum and intrapartum periods and to the newborn during the first 6 weeks of life, it has been shown to reduce the transmission of HIV from an HIV-infected mother to her newborn by 66%. Perinatal prophylaxis with zidovudine (in conjunction with appropriate counseling) is recommended for all HIV-infected pregnant women and their newborns. The safety and efficacy of other antiretroviral drugs as well as combination regimens in this setting are under active investigation.

Newer Recommendations.—Of importance, these recommendations were based on the information available at the time they were developed. Currently, experts under the auspices of the United States Public Health Service are finalizing new guidelines for the treatment of HIV infection. Although the final drafts of the recommendations are still being reviewed, preliminary reports indicate that the paradigm shift toward earlier and aggressive treatment with combination antiretroviral agents continues. The goal of treatment is complete suppression of the virus as long as possible, by using the most potent combinations of available antiretroviral agents and quantitative HIV RNA assays to monitor therapeutic response.

CONCLUSION

The important advances in the understanding and management of HIV infection have given investigators hope that HIV will soon become a chronic manageable disease like hypertension and diabetes. Previously unthinkable issues such as whether HIV infection could be eradicated are being seriously considered and actively investigated. Despite these developments, however, several unanswered questions and concerns must still be addressed. The best approach for using quantitative HIV RNA assays and the frequency of use remain uncertain. Further studies are needed to determine the optimal use of combination regimens, to clarify the virologic goals of antiretroviral treatment, and to validate the long-term efficacy and tolerability of currently advocated aggressive treatment strategies. The issue of payment for these combination treatments that cost more than $10,000 per person annually has not yet been completely addressed. An additional concern is that the improved outlook regarding HIV infection may breed complacency and lead to a decrease in educational and preventive efforts. Of importance, the aforementioned advances are applicable only to HIV-infected persons in developed countries and are neither available nor feasible in developing countries with limited resources where the effect of the HIV pandemic is the highest. In these countries, current efforts are dir-
ected toward (with some success) prevention of HIV infec-

tion by promoting behavioral modification, safer sexual
practices, and improved management of sexually transmited

diseases.25

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Questions About Management of HIV Infection
(See article, pages 854 to 858)

1. Which one of the following human immunodeficiency virus (HIV) surrogate markers is the **single best** predictor of progression to the acquired immunodeficiency syndrome (AIDS) or AIDS-related death?
   a. Helper cell count (CD4)
   b. Suppressor cell count (CD8)
   c. P24 antigen
   d. Clinical thrush or wasting disease
   e. Plasma HIV viral load

2. Which one of the following is **incorrect** regarding antiretroviral therapy?
   a. Combination treatment regimens reduce progression to AIDS
   b. Increased suppression of HIV replication results in a lower rate of development of drug resistance
   c. Treatment with a single antiretroviral agent leads to weak suppression of viral replication and short-lived clinical benefit
   d. No difference is noted in the rate of AIDS-related deaths between single agent and combination antiretroviral regimens
   e. Use of potent triple antiretroviral regimens that include protease inhibitors has resulted in a reduction in mortality and progression to AIDS

3. Which one of the following is **not true** about HIV pathogenesis?
   a. About 10 billion new HIV particles are produced daily
   b. About 2 billion CD4 lymphocytes are produced daily
   c. A large number of genetic variants are produced because of rapid turnover of HIV
   d. Drug resistance can occur only after a drug has been administered
   e. HIV is actively replicating during the clinically silent period

4. Which one of the following is not a proven advantage of current combination antiretroviral regimens?
   a. Decreased viral load burden
   b. Decreased transmission from infected mother to child
   c. Improvement in immunologic function
   d. Eradication of HIV infection
   e. Delay in progression of disease resulting in increased survival

5. Which one of the following is the **primary** treatment goal of HIV?
   a. Lowest cost
   b. Complete suppression of HIV replication for as long as possible
   c. Relief of symptoms
   d. Nontoxic treatment
   e. Drug regimen that promotes patient compliance

Correct answers:
1. e, 2. d, 3. d, 4. d, 5. b