Current Report – HIV

Antiretroviral Strategies

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Antiretroviral therapy against the human immunodeficiency virus (HIV) can delay the progression of HIV disease.[1-3] Although it is agreed that all patients should be offered antiretroviral therapy, considerable disagreement remains about the optimal time to initiate treatment and the choice of drug(s). Because of the paucity of head-to-head studies using clinical endpoints (as opposed to laboratory surrogate markers), no single treatment regimen can be recommended as superior. Furthermore, it has yet to be established that antiretroviral therapy prolongs life for patients with asymptomatic disease.[4]

Although the absence of a single treatment of choice presents difficulties for both the patient and the physician, the opportunity to offer different regimens is helpful in the primary care of HIV disease. The choice of therapy remains more a matter of strategy than of science. In this *Current Report – HIV* we discuss some of the data now available on the nucleoside analogs and strategies for antiretroviral therapy.

HIV Disease Progression

The natural course of HIV disease results in a progressive decline of CD4+ (T-helper) lymphocyte counts and the development of opportunistic infections, malignancies, and other HIV-related illnesses. The normal reference range of CD4+ lymphocytes is broad and variable. CD4+ cell counts are usually near 1000/μL, but for some persons and some laboratories normal can be fewer than 500/μL. With HIV infection CD4+ cell counts decline by about 50 – 85/μL per year. Early clinical manifestations of HIV disease, such as oral candidiasis and hairy leukoplakia, usually precede the development of acquired immunodeficiency syndrome (AIDS). AIDS-defining conditions generally occur after CD4+ lymphocyte counts decline to fewer than 200/μL. AIDS-related mortality is usually associated with CD4+ cell counts fewer than 50/μL.

Reverse Transcriptase Inhibitors

Information about antiretroviral treatment comes from clinical drug trials and epidemiologic studies. Antiretroviral therapy is effective in delaying and decreasing clinical endpoints (i.e., opportunistic infections and malignancies) and improving laboratory surrogate markers (i.e., CD4+ lymphocyte counts, p24 antigenemia). Studies that compare surrogate markers as measures of efficacy are difficult to interpret because modest increases in CD4+ cell counts for short periods of time do not necessarily indicate clinical benefit. Some epidemiologic studies suggest, but do not establish, survival benefit of antiretroviral therapy.[5-7]

Three nucleoside analogs, zidovudine, didanosine, and zalcitabine, have been approved by the Food and Drug Administration (FDA). All act by inhibiting reverse transcriptase, an enzyme essential to HIV replication.

Zidovudine (AZT, Retrovir), the first agent approved, is the antiretroviral drug against which others are measured. Zidovudine delays the development of opportunistic infections and other manifestations of AIDS and might decrease mortality in persons with AIDS.[1-4] In addition, zidovudine has promoted weight gain and improved neuropsychiatric function in some patients. The duration of zidovudine's clinical effectiveness is uncertain.

Didanosine (ddI, Videx) treatment results in modest improvements in laboratory surrogate markers that are roughly equivalent to those

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seen with zidovudine therapy.[8-10] In one study of patients with a median CD4+ count of 98 cells /μL, changing to didanosine after approximately 1 year of zidovudine therapy resulted in fewer AIDS-defining events.[11] This advantage was observed only in patients who did not already have AIDS; no survival benefit was evident in any group studied.

Zalcitabine (ddC, HIVID) administration also results in modest improvement in surrogate markers of disease progression.[12] Monotherapy with zalcitabine does not appear to be as effective as zidovudine for initial therapy.

The emergence of viral resistance to reverse transcriptase inhibitors is of concern. Data from in vitro studies suggest that zidovudine resistance occurs in the first year of treatment. The clinical importance of this observation, however, is uncertain because the pathogenicity of resistant viruses is poorly understood. Zidovudine-resistant viral isolates appear to retain sensitivity to both didanosine and zalcitabine. Whether alternating or combining drugs will decrease the development of resistance remains to be established.

Combination therapy with zidovudine plus didanosine or zalcitabine is under investigation. No clinical endpoint data are available. Zalcitabine has been given conditional approval for use in combination with zidovudine for patients with fewer than 300 CD4+ cells /μL based on short-term studies showing improvement in laboratory surrogate markers. Studies of sequential regimens (alternating one agent with another for periods of days, weeks, or months) are in progress. Sequential therapy has the theoretical advantage of reducing both toxicity and the emergence of drug resistance. All the nucleoside analogs, however, have the same basic mechanism of action, so their usefulness in combination might be limited.

A fourth nucleoside analog, stavudine (d4T), has improved laboratory surrogate markers in Phase I studies. Although not yet FDA-approved, stavudine is available from the manufacturer through a Parallel Track (research) protocol.

Strategies of Antiretroviral Therapy

The initiation of antiretroviral therapy marks a milestone in the life of an HIV-infected person. At this time a person living with HIV infection becomes a patient receiving lifelong treatment for a chronic disease. Many patients are understandably reluctant to make this change. Nevertheless, antiretroviral therapy is recommended to delay progression to AIDS, a key goal of HIV primary care.

Provider and Patient Variables

In clinical medicine the absence of scientific conclusions leads to strong opinions. With a serious problem, such as HIV disease, opinions are especially strong — from both the provider and patient-family perspective. Joint decision making requires consideration of some key variables. For the physician these variables include interpretation of the medical literature, recommendations by consensus panels,[13] the influence of local and regional experts, the influence of pharmaceutical company representatives, community standards, and the physician's philosophical approach. This last variable deserves more comment. Some physicians prefer to begin treatment as early as possible. They might believe that it is wrong to withhold potentially helpful therapies or that early antiretroviral treatment is most effective when the viral load is small. Being able to intervene can be important to the physician-patient relationship. Other physicians prefer delaying antiretroviral therapy to save drugs whose effectiveness appears time-limited and to avoid unnecessary drug toxicities.

Patients and families also balance many variables. Some want an aggressive pharmacological attack on HIV using any potentially helpful medication. Others choose to delay or avoid treatment, perceiving it as more of a burden than a benefit. Some patients avoid antiretroviral therapy because it forces them to confront HIV disease on a daily basis, or they have known partners, friends, or family members who have done poorly while receiving antiretroviral therapy. Others want to maximize their health through "natural" means. Physicians must recognize that medical care is only one of many things patients must consider. Antiretroviral therapy is often less important than such survival issues as food and lodging, substance use, and family and social problems.

Range of Approaches

The physician should choose an antiretroviral strategy that is consistent with acceptable

medical practice and the patient's wishes. A broad range of options is available. At one extreme, multiple antiretroviral and nonapproved drugs are used as soon as HIV seropositivity is diagnosed, even while CD4+ lymphocyte counts are greater than 500/μL. The more common aggressive approach uses multidrug therapy as soon as CD4+ lymphocyte counts are fewer than 500/μL. Available data neither support nor contraindicate such an approach. Most physicians in the United States initiate zidovudine monotherapy when CD4+ lymphocyte counts are consistently fewer than 500/μL. Alternative regimens to zidovudine monotherapy are used when recurrent illnesses or toxicity occur. At the other extreme, antiretroviral therapy is avoided altogether because of the belief that evidence of efficacy is not strong enough to warrant potential toxicity.

Recommendations

Because studies have not established the optimal time to initiate or change therapies, the appropriate strategy is one that is most consistent with the patient and physician variables mentioned above. The patient should be allowed flexibility in selecting strategies that might be of equivalent efficacy. A regimen that is unlikely to cause serious toxicity or interfere with the ability to administer other essential treatments is preferred. Table 1 shows toxicity profiles.

We recommend a relatively conservative approach. Initiation of antiretroviral therapy can be *offered* when the CD4+ count falls to fewer than 500 cells/μL on at least two separate occasions. For those who choose not to begin therapy at this threshold, antiretroviral treatment should be *encouraged* when CD4+ counts are fewer than 400 cells/μL. Because AIDS-defining diseases usually occur at CD4+ lymphocyte

Table 1. Approved Antiretroviral Medications.

Drug	Common Adverse Effects	Drug Interactions	Comments
Zidovudine (AZT, Retrovir) 100 mg po 5 times a day or 200 mg po tid	Malaise, headache, myalgias, insomnia (often diminish after 4 – 6 weeks of continuous use); anemia, granulocytopenia, thrombocytopenia; toxic myopathy with long-term use; blue to black discoloration of nails and skin in pigmented races	Careful monitoring required when used with other myelosuppressive drugs (trimethoprim-sulfamethoxazole, ganiclovir, dapsone, and pyrimethamine). Acetaminophen (Tylenol) does not increase zidovudine toxicity. Probenecid increases serum levels of zidovudine	Can decrease dosage to 100 mg tid for nausea, anemia, or neutropenia. 60% of plasma drug concentration crosses to cerebral spinal fluid (CSF)
Didanosine (ddI, Videx) tablets 200 mg po bid for patients >60 kg, 125 mg po bid for patients <60 kg	Pancreatitis; dosage-related painful peripheral neuropathy; rash; nausea, abdominal cramps, diarrhea; hyperglycemia, hyperuricemia; hepatitis; headache, insomnia, seizures; elevated triglyceride and amylase levels	Needs to be administered 2 hours before or after administration of dapsone, ketoconazole, and quinolone antibiotics because of decreased absorption of these drugs caused by the buffer in didanosine. Careful monitoring required when used with drugs that can cause peripheral neuropathy (isoniazid, metronidazole, vincristine). Do not use concomitantly with intravenous pentamidine because of increased risk of pancreatitis	Two tablets must be taken with each dose to provide enough buffer for absorption. Tablets must be chewed thoroughly or crushed. Take only with apple juice or water. Dosages of 300 mg bid are used for patients weighing more than 75 kg. 20% of plasma concentration crosses to CSF
Zalcitabine (ddC, HIVID) 0.75 mg po tid	Painful peripheral neuropathy; pancreatitis; oral and esophageal ulcers; rash; nausea; hepatitis; seizures	Careful monitoring required when used with other drugs that can cause peripheral neuropathy (isoniazid, metronidazole, vincristine)	Can decrease dosage to 0.375 mg tid for intolerance or for cachectic patients. 15% of plasma concentration crosses to CSF

counts fewer than 200/μL, all patients should receive antiretroviral therapy in advance of this threshold.

Single-agent treatment with zidovudine at 500 – 600 mg/d is recommended as initial therapy. Zidovudine has been studied more and its clinical efficacy is better established than other antiretroviral drugs. Patients who cannot tolerate zidovudine or prefer an alternative drug are offered didanosine. Combination therapy (zidovudine and didanosine or zidovudine and zalcitabine) can be substituted for monotherapy if desired, but it does not have a clear advantage and is more expensive, complicated, and potentially more toxic than monotherapy. Combination therapy with didanosine and zalcitabine is not recommended because the toxicity profiles of the two drugs are similar.

Deciding when a regimen is no longer effective can be very difficult. Guidelines defining antiretroviral treatment failure have not been established. Indications that a regimen is no longer effective include the development of new or recurrent opportunistic infections or malignancies; disabling clinical symptoms such as weight loss, diarrhea, or unexplained fevers; or a sustained decline in the absolute number and percentage of CD4+ lymphocytes by 50 percent or more. Increasingly frequent and severe clinical problems, occurring despite prolonged treatment with an antiretroviral regimen favor changing to an alternate agent or combination therapy. Selecting a different antiretroviral regimen that causes toxicity or drug interactions, however, can be more harmful than continuing the same drug.

Additional Considerations

Drug therapy for HIV disease is expensive. Before offering treatment options, it is important to assess the reimbursement mechanisms available through the patient's insurance or state funding mechanisms. It is counterproductive to decide upon one of many equivalent regimens if the cost is prohibitive.

Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) when indicated (for patients with fewer than 200 CD4+ cells/μL, past episodes of PCP, or advanced symptomatic disease) and careful management of opportunistic infections are essential components of HIV care. Because of the progressive natural history of HIV disease, clinical complications will continue to occur. When severe immunodeficiency develops (e.g., CD4+ cell counts fewer than 50/μL), multiple simultaneous complications are the rule. At this stage careful medical management of opportunistic infections and other complications with complex drug regimens can be crucial. The antiretroviral agent least likely to cause drug interactions with other necessary drugs is the most appropriate choice. At times, drug interactions and drug toxicity prohibit antiretroviral therapy.

Conclusion

Until well-controlled long-term studies are completed, the information now available permits wide latitude in selecting antiretroviral strategies. Because patients and their medical providers have a broad range of approaches to HIV disease, treatment should be individualized. When to initiate or change therapy and which agents to use are collaborative decisions to be made by the physician and patient. Antiretroviral drug toxicity should not interfere with the ability to treat opportunistic infections, nor should it severely decrease the patient's quality of life. At the same time, no patient should progress to severe life-threatening opportunistic infections, malignancies, or other advanced diseases without having been offered antiretroviral therapy.

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