Current Report—HIV

Antiretroviral Strategies Revisited

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For the primary care provider, making recommendations about antiretroviral therapy for human immunodeficiency virus (HIV) disease is an important yet controversial component of HIV care. Decisions about when to initiate treatment, whether to use monotherapy or combination therapy, and when to change regimens are extremely important for patients and their families. These decisions are especially relevant at this time because of the uncertainty and controversy that now surround antiretroviral therapy. Expectations of antiretroviral drug benefits, which ran high only a few years ago, unfortunately have been replaced by the hope that these drugs eventually will be combined with or superceded by more effective agents.

HIV infection causes a chronic disease with an average latency period of about one decade between infection and the development of the acquired immunodeficiency syndrome (AIDS). The latency period varies considerably. Some persons progress to AIDS within a few years while others remain stable after 10 or 15 years (long-term nonprogressors). The reasons for this variable expression of HIV infection remain uncertain; studies of long-term nonprogressors to help discover new approaches in HIV treatment are ongoing.

Current Report—HIV has addressed antiretroviral therapy periodically since 1990.[1-5] With each new development we have made minor changes in our recommendations. In the initial "Antiretroviral Strategies,"[3] the overview of antiretroviral therapy addressed clinical studies in the broader context of patient care. Our article in this issue provides updated information and recommendations consistent with previous Current Report — HIV articles and with published guidelines[6] and includes new information regarding zidovudine use to decrease perinatal transmission.

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Studies of Nucleoside Analogs

Considerable information is now available about the principal nucleoside analogs (Table 1), zidovudine (AZT, Retrovir), didanosine (ddI, Videx), zalcitabine (ddC, Hivid), and stavudine (d4T, Zerit).[6-9] Most studies have compared short-term changes in surrogate markers of HIV disease progression, such as CD4+ (T-helper) lymphocyte counts, p24 antigen and β_2-microglobulin levels, and viral titers. Although these studies can indicate drug effect, changes in surrogate markers do not necessarily translate into clinical benefit. In fact, a lack of correlation has been demonstrated between changes in the most commonly used surrogate marker, the CD4+ cell count, and long-term clinical endpoints.[10]

The most meaningful studies to primary care providers and patients, however, are ones that evaluate clinical outcomes, such as opportunistic infections and malignancies, mortality, and quality of life. These studies require long-term follow-up, with close adherence to defined protocols and few confounding variables. After nearly a decade of antiretroviral drug research, only a few studies have met these criteria, in part because of the inherent difficulty of performing trials in a chronic disease where clinical endpoints occur late and in part because of the early termination of trials when promising, but inconclusive, findings were noted.

Monotherapy

The two most important studies of initial antiretroviral therapy are the ACTG O19 zidovudine trial in the United States and the Concorde zidovudine trial in Great Britain and France. ACTG O19[11] was a study of 1434 asymptomatic patients

Table 1. Antiretroviral Drugs

Drug Regimen	Dosage Form	Adverse Effects/ Drug Interactions	Comments
Zidovudine (AZT, Retrovir) 200 mg po tid; lower dosages (e.g., 100 mg 3–5 times daily) for patients unable to tolerate higher dosages and patients with end-stage renal disease or cirrhosis	Available as 100-mg capsules; syrup 10 mg/mL; injection 10 mg/mL	Malaise, headache, nausea, insomnia, seizures, myalgias. Anemia, granulocytopenia, thrombocytopenia; macrocytosis is an expected effect of zidovudine therapy and requires no intervention. Toxic myopathy (with elevated creatine phosphokinase [CPK]) with long-term use. Lactic acidosis. Hepatomegaly with steatosis; aminotransferase elevations (alanine transaminase [ALT], aspartate transaminase [AST]). Blue to black discoloration of nails and skin in pigmented races Drug interactions: prn acetaminophen (Tylenol) administration does not increase zidovudine toxicity. Careful monitoring required when used with other myelosuppressive drugs (i.e., trimethoprim-sulfamethoxazole, ganciclovir). Probenecid can increase levels of zidovudine	Ideal time to initiate antiretroviral treatment uncertain. Recommend treatment for all symptomatic patients and asymptomatic patients with repeated CD4+ lymphocyte counts <200 cells/μL; can be offered to patients with CD4+ counts as high as 500 cells/μL. Zidovudine is the usual first-choice antiretroviral agent Monitor for signs of zidovudine toxicity and reduce dosage if required. Transfusions or erythropoietin (if endogenous erythropoietin level <500 IU/L) therapy can be used if anemia (e.g., hemoglobin <8.0 g/dL) occurs in patients who require zidovudine therapy. Decrease dosage or interrupt for absolute neutrophil count (ANC) <500 cells/μL; consider granulocyte colony-stimulating factor (G-CSF). Transfusions and erythropoietin and G-CSF therapies are expensive; changing to alternate agent preferred Thrombocytopenia and HIV dementia have been reported to respond at times to zidovudine therapy. High-dosage (1200 mg po qd) zidovudine therapy can be considered for HIV dementia. Didanosine and zalcitabine do not penetrate the blood-brain barrier as well as zidovudine Change to alternate agent if unable to tolerate or marked progression of disease
OR			
Didanosine (ddI, Videx) 200-mg tablet po or 250-mg powder bid for patients >60 kg; 125-mg tablet or 167-mg powder po bid for <60 kg. Consider dosage reduction (i.e., 200 mg/d) in end-stage renal disease	Available as 25-, 50-, 100-, and 150-mg chewable or crushable tablets and in 45-, 67-, 100-, 167-, 250-, and 375-mg foil packets of buffered powder	Pancreatitis; painful peripheral neuropathy (dosage related, reversible); nausea, abdominal cramps, diarrhea related to antacid in formulation; rash; hyperglycemia; hyperuricemia; aminotransferase elevations; headache, insomnia, seizures; elevated triglyceride and amylase levels; thrombocytopenia; retinal atrophy	Can be used in combination with zidovudine or as monotherapy in patients who fail or are intolerant to zidovudine. Monitor for signs of neuropathy. Two tablets must be given per dose to provide adequate buffer for absorption. Can be difficult to chew; tablets do not dissolve readily in water, can be crushed manually

Table 1. Continued.

Drug Regimen	Dosage Form	Adverse Effects/ Drug Interactions	Comments
Didanosine (cont.) OR		Drug interactions: Concomitant administration of H_2 antagonists, antacids, and omeprazole (Prilosec) can increase didanosine absorption, resulting in additional toxicity. Avoid alcohol and other pancreatic toxins (e.g., systemic pentamidine). Avoid concomitant neurotoxic drugs (e.g., zalcitabine, stavudine, isoniazid, vinca alkaloids, oral ganciclovir). Decreases absorption of drugs (e.g., dapsone, ketoconazole, itraconazole, tetracyclines, quinolone antibiotics) whose absorption is impaired by buffered products	Administer didanosine on empty stomach 2 hours apart from antacids, H_2 antagonists, and drugs (e.g., dapsone, ketoconazole, itraconazole, tetracyclines, quinolone antibiotics) whose absorption is impaired by buffered products; breakthrough episodes of *Pneumocystis carinii* pneumonia (PCP) have been reported in patients receiving concomitant didanosine therapy and dapsone PCP prophylaxis
Zalcitabine (ddC, Hivid) 0.75 mg po tid; 0.375 mg po tid for patients <30 kg. Consider dosage reduction in end-stage renal disease OR	Available as 0.75- and 0.375-mg tablets	Painful peripheral neuropathy (dosage related, reversible); rash; stomatitis, aphthous ulcers; pancreatitis; esophageal ulceration; seizures; aminotransferase elevations; cardiomyopathy Drug interactions: Avoid alcohol and other pancreatic toxins (e.g., systemic pentamidine). Avoid concomitant neurotoxic drugs (e.g., didanosine, stavudine, isoniazid, vinca alkaloids)	Can be used in combination with zidovudine or as monotherapy in patients who fail or are intolerant to zidovudine. Not as effective as zidovudine for monotherapy. Neurotoxicity can improve with zalcitabine "rest periods"
Stavudine (d4T, Zerit) 20 mg po bid for patients >60 kg; 15 mg po bid for patients 40-60 kg; reduce dosage for patients <40 kg and patients with renal failure OR	Available as 15-, 20-, 30-, and 40-mg capsules	Painful peripheral neuropathy. Aminotransferase elevations. Anemia, macrocytosis. Psychological disturbances: insomnia, anxiety, panic attacks Drug interactions: Avoid concomitant use of drugs that can cause neurotoxicity (including didanosine and zalcitabine) or pancreatic toxicity. See didanosine	Consider for patients intolerant to zidovudine, didanosine, and zalcitabine. Dosages listed in this table are lower than the original Food and Drug Administration (FDA)-approved dosages. Studies suggest that these lower dosages are associated with equivalent efficacy and a lower incidence of peripheral neuropathy than current FDA-approved dosages
Combination therapy (zidovudine plus didanosine or zidovudine plus zalcitabine). Didanosine plus zalcitabine or combinations of stavudine plus zidovudine, didanosine, or zalcitabine are not recomsmended		Additive toxicities can complicate management, especially for patients with late-stage disease and patients receiving multiple other medications	No clear evidence of added benefit from combination therapy or from sequential therapy (alternating regimens of zidovudine and didanosine or zalcitabine). Unclear whether combination of zidovudine plus acyclovir provides additional antiretroviral benefit

with CD4+ cell counts fewer than 500/μL. This triple-arm study compared placebo with two different dosages of zidovudine. A small but statistically significant decrease in disease progression was noted during the 1.1 year mean follow-up period. Based on these findings and the hopes that this short-term delay in disease progression would translate into long-term benefit, zidovudine was approved for patients with fewer than 500 CD4+ cells shortly after the trial ended in 1989. Most authorities subsequently recommended starting zidovudine when the CD4+ lymphocyte count decreased to fewer than 500 cells/μL. Longer follow-up of ACTG O19 trial subjects, however, demonstrated no significant difference in disease progression or mortality at a mean of 2.6 years.[12]

The Concorde trial[10] was a 3.3-year study that began in 1988. This study enrolled 1749 asymptomatic persons with any level of CD4+ cells. The Concorde trial demonstrated a decrease in disease progression during the first year, as did ACTG 019. This effect, however, was transient. Overall, no significant difference in disease progression or mortality was noted for patients who were randomized to receive immediate versus deferred zidovudine treatment. An important finding of this study was that a sustained increase of approximately 30 CD4+ cells/μL occurred in the immediate treatment group and lasted throughout the trial period, but did not correlate with decreased disease progression.

Other zidovudine trials, such as the Veterans' Affairs Cooperative Study[13] and the European-Australian Collaborative Group study,[14] provided additional information about clinical experience with zidovudine therapy but did not have stronger clinical endpoint data than the ACTG 019 or Concorde trials.

With the information available to date, it is generally concluded that zidovudine use delays disease progression for asymptomatic persons. This effect, however, is time-limited for a period of about 1 year or perhaps longer. No survival benefit can be demonstrated for starting treatment earlier rather than later in the course of asymptomatic disease. Quality-of-life studies that compare side-effects of zidovudine with morbidity from HIV disease progression remain inconclusive, showing neither net benefit nor harm.

Unpublished studies suggest that initial zidovudine monotherapy is more effective than initial monotherapy with didanosine or zalcitabine. Most clinical studies of didanosine and zalcitabine therapy are in the setting of previous zidovudine administration (including zidovudine "failure"). Modest short-term improvements in laboratory surrogate markers[9,15-19] and some clinical endpoints[18,19] have been observed after changing from zidovudine to didanosine or zalcitabine. There is no evidence of better outcomes from regimens that alternate drugs (e.g., weekly or monthly).

Combination Therapy

Because monotherapy does not offer impressive long-term benefits, the focus of antiretroviral therapy has shifted to the use of drugs in combination.[20] This approach is based on the success of synergistic antibiotic therapy in treating some bacterial and mycobacterial infections and the use of multiple chemotherapeutic agents to increase efficacy and decrease toxicity in cancer treatment. Although theoretically appealing, this approach remains clinically unproved in antiretroviral therapy. Studies of combination therapy to date have analyzed laboratory surrogate marker changes and some short-term clinical endpoints. Although these studies indicate possible advantages of combination therapy, no long-term clinical endpoint studies have been performed to show benefit from combinations of the antiretroviral agents currently available.[20]

Strategies of Care

When choosing antiretroviral treatment options, factors other than the scientific data must be considered. Individual patient and provider variables can help guide choices within the wide range of acceptable approaches.

Patient, Family, and Provider Variables

Patients, families, and their providers weigh many variables when making treatment choices.[3] For patients and families these variables include an understanding of medical information, financial and social considerations, and the knowledge of others' personal experiences (both positive and negative) with antiretroviral therapies. Providers must consider the medical literature, consensus statements, the opinions of local and regional experts, community standards, pharmaceutical company information, and cost.

Both patients and providers should recognize that their personal attitudes and philosophical ap-

proaches to disease and treatment influence decision making. In many ways the decisions about initiating or changing antiretroviral therapies are similar to decisions made in other chronic diseases. Some patients wish to have frequent physician visits and monitoring and intensive medication regimens, whereas other patients prefer infrequent visits, less intense monitoring, and fewer drugs and interventions. Similarly, some physicians strongly encourage intensive monitoring and treatment, whereas others prefer a less directive approach.

Primary care providers should be aware that many patients and their families are extremely knowledgeable about HIV disease treatment. Some have lost considerable confidence in the medical community of clinicians and researchers. Many recognize that previous claims and assumptions about the benefit of early antiretroviral treatment were overly optimistic. The disappointment, frustration, and anger that accompany this new understanding can be directed at the primary care provider. It will be essential for practitioners to recognize that scientific credibility has been eroded, and patient confidence in our advice must be regained. Frank discussions about the value of antiretroviral therapy and the various approaches available must be at the core of HIV primary care.

Aggressive and Conservative Approaches to Antiretroviral Treatment

Depending on patient and provider preferences, a range of approaches, from aggressive to conservative, can be taken. An aggressive approach would include early treatment (closer to the CD4+ cell count of 500/μL threshold) with combination therapies. Theoretical rationales supporting this approach are that early treatment might decrease the viral load and result in fewer newly infected cells, that drugs used in combination might act synergistically, and that new drugs might be available when the usefulness of current regimens has been exhausted. Because the aggressive approach is proactive, it appeals to many patients and providers.

A conservative approach would be to initiate monotherapy at a later time, namely, when the patient's CD4+ cell count decreases to fewer than 200/μL or when symptomatic disease occurs. The rationale for this approach is to avoid multiple and cumulative drug toxicities while saving drugs for later use when disease progression occurs.

Initiating Antiretroviral Therapy

Ideally clinical trials and experience would guide decisions about when to initiate antiretroviral therapy, which drugs to use, and whether to use monotherapy or combination therapy. Available data, unfortunately, do not support definitive answers to these dilemmas, so the optimal time to initiate therapy remains uncertain. Guidelines using a series of clinical scenarios have been published[6] and provide guidance for most clinical situations. Table 2, which is consistent with national guidelines, gives our recommendations for strategies of antiretroviral treatment.

Antiretroviral therapy is not recommended for asymptomatic patients who have more than 500 CD4+ cells/μL. Studies of patients with this early stage of infection have not demonstrated benefit.[21] Because clinical endpoints generally occur after many years of infection, the results of this study are not surprising.

For asymptomatic patients who have between 200 and 500 CD4+ cells/μL, deciding when to initiate antiretroviral therapy remains most problematic. When patients and their providers agree on an aggressive approach, antiretroviral therapy can be started at or near 500 CD4+ cells/μL. When there is agreement to pursue a more conservative approach, therapy could be initiated closer to 200 CD4+ cells/μL. If the patient is unable to decide, the primary provider must make recommendations. Current Report — HIV has recommended a conservative approach for the past 5 years. We continue to favor this strategy. We believe that initiating antiretroviral therapy closer to the 200 CD4+ cells/μL threshold rather than the 500 cells/μL threshold is preferred for

Table 2. Initiation of Antiretroviral Therapy.

Clinical Status	CD4+ Lymphocyte Count (Cells/μL)	Recommendation
Asymptomatic	>500	No treatment
Asymptomatic	200–500	Treatment depends on patient and provider preferences. See text
Asymptomatic	<200	Treat
Symptomatic	0–500	Treat

asymptomatic patients who do not request earlier treatment. Given the chronicity of HIV infection, it can be years before symptomatic disease and AIDS develop. We are concerned that the benefits of therapy might be lost before actual disease occurs, leaving only experimental and investigational antiretroviral options. Disappointing early results demonstrating drug resistance with newer agents, including protease inhibitors, indicate that effective alternative drugs might not be available soon.

For symptomatic patients at any stage of HIV disease, antiretroviral therapy should be offered. Because no clear definition of symptomatic disease exists, the patient and provider have latitude in deciding when to initiate therapy. Persistent constitutional symptoms and signs, unexplained weight loss, oral candidiasis, frequent herpes simplex or zoster outbreaks, and oral hairy leukoplakia are among the conditions generally considered to indicate symptomatic disease. Lymphadenopathy and thrombocytopenia, which can occur very early in HIV disease and do not predict imminent progression, are not indications for treatment. Although zidovudine therapy can increase platelet counts, treatment is not required unless platelet counts are dangerously low or bleeding occurs.

All patients with Centers for Disease Control and Prevention (CDC)-defined AIDS should be offered antiretroviral therapy. Special attention must be given to the potential for interactions with other required medications. At times antiretroviral treatment is discontinued to avoid additive drug toxicity with medications for opportunistic infections or malignancies.

Monotherapy with zidovudine is recommended for initial treatment. For patients who are unable to take zidovudine or are reluctant to use it (usually because they know others who have had adverse experiences with it), didanosine is usually the first alternative. Combination therapy with zidovudine plus didanosine or zidovudine plus zalcitabine are the regimens most often used when combination therapy is agreed upon.

Changing Antiretroviral Therapy

Thresholds for changing antiretroviral therapy are arbitrary. Factors to consider include the length of time the drug has been taken, drug toxicities, and the severity of progressive disease. When new episodes of opportunistic infections or other AIDS-defining conditions occur, changing to another antiretroviral agent, alone or in combination with zidovudine, is reasonable. It has also been recommended to change therapy when the CD4+ cell count decreases to fewer than 300 cells/μL,[6] which appears to be based on the assumption that antiretroviral therapy had been started at a considerably higher CD4+ cell count, presumably at or near 500 cells/μL. We recommend changing antiretroviral therapy or adding additional antiretroviral agents when the CD4+ cell count has decreased to 50 percent of the initial threshold chosen. Other thresholds, which are just as arbitrary, are a CD4+ cell count fewer than 100 or 50 cells/μL. Continued antiretroviral therapy is not required in the face of progressive end-stage disease, such as multiple AIDS-defined conditions, extremely low CD4+ cell counts, or poor functional status.

Antiretroviral Therapy for Pregnant Women

For HIV-infected pregnant women strong recommendations can be made. The findings of a large clinical trial, ACTG O76, have been reported at meetings and in the medical literature.[22] Pregnant women whose CD4+ cell count was 200/μL or more and who had not previously received zidovudine therapy during pregnancy were given zidovudine 100 mg orally five times daily beginning at 14 to 34 weeks' gestation. They also received intravenous zidovudine (a 1-hour loading dose of 2 mg/kg, followed by 1 mg/kg/h infusion) during labor. Their infants were given oral zidovudine syrup every 6 hours for the first 6 weeks of life. Transmission of HIV to the infants occurred in 8.3 percent of the zidovudine-treated group compared with 25.5 percent of the control group. This difference was highly statistically significant and has led to the recommendation that most pregnant women be offered zidovudine therapy after the first trimester. It has not been established that these results apply to women with different base-line characteristics (prior zidovudine use, a CD4+ cell count of 200/μL or less). Although treatment was well tolerated by the mothers and their infants, the long-term safety of zidovudine therapy in pregnancy has not been established. This uncertainty, along with an understanding of psychosocial and cultural factors, must be taken into consideration when recommending zidovudine therapy for pregnant women.

Conclusion

The challenge to the family physician and other providers of HIV primary care is to deliver comprehensive care to patients with this serious chronic disease in the setting of a long-term physician-patient-family relationship. This care, in addition to providing antiretroviral therapy, includes health care maintenance, preventing opportunistic infections, diagnosing complications, treating acute diseases, and ensuring appropriate palliative care.

The goals of antiretroviral therapy for HIV disease are similar to patient goals in other chronic diseases: prolonging life, improving the quality of life, and providing a bridge to further therapies and interventions. Although antiretroviral therapy does not offer a cure for HIV disease, it appears that disease progression can be delayed and prolongation of life can occur.

For both patients and providers, important clinical decisions about antiretroviral therapy must be made on the basis of relatively weak scientific data. When data are weak, opinions can be strong. With the wide range of acceptable options in antiretroviral therapy, listening to the patient's opinions is one of the provider's most important tools. Treatment decisions must be individualized, with careful consideration given to patient and family concerns and wishes. When patients and families do not indicate strong preferences, we recommend a conservative approach. Regardless of the strategy selected, it is the process of deciding on treatment strategies that underscores the value of the primary care approach to this chronic disease.

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