HIV Frontline

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A Newsletter for Professionals Who Counsel People Living With HIV

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Initiating Antiretroviral Therapy

Significant advances in the field of antiretroviral therapy have so improved the outlook for persons who have HIV infection that it is now regarded by many as a treatable chronic disease, although one usually necessitating lifelong medical management to maintain suppression of the virus and prevent coinfections. Because many persons infected with HIV can now live longer, healthier lives than ever before, counselors need to discuss treatment options with their clients at early stages of the disease and help motivate them to actively participate in decision making related to their care.

Clients in whom HIV infection or AIDS has been diagnosed and who are committed to taking charge of their lives and their health have taken a critical first step in controlling the disease. By becoming and staying involved in the management of their disease, they will increase their sense of control over their condition, their satisfaction with their medical care, and their chances of survival.

The ultimate goal of antiretroviral therapy for HIV infection and AIDS—to eradicate the virus from the body—may soon be achievable as increasingly effective treatment strategies become available. At present, the goals of therapy are as follows:

- To achieve maximal and durable suppression of viral load (VL)
- To restore and/or preserve immunologic function
- To improve quality of life (QOL)
- To reduce HIV-related morbidity and mortality

The tools at hand to achieve these goals are strict adherence to antiretroviral therapy, use of rational drug sequencing, preservation of future treatment options, and use of resistance testing in selected clinical settings.

Benefits and Risks of Early Antiretroviral Therapy

Antiretroviral therapy is clearly beneficial for patients with advanced disease and significant immune dysfunction, but whether the benefits of antiretroviral therapy for asymptomatic clients outweigh the risks is the subject of considerable debate. Initiating antiretroviral therapy early, before symptoms have developed, has several potential benefits. One of them is the probability that antiretroviral therapy has a greater chance of success in newly infected persons, because their viral populations are more likely to be homogeneous and less likely to contain high levels of drug-resistant variants.

According to guidelines that were developed by a panel convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation, there are 6 potential benefits of early initiation of antiretroviral therapy in asymptomatic HIV-infected patients. Early antiretroviral therapy helps control viral replication and mutation, as well as reduce VL. It prevents progressive immunodeficiency and, thus, offers the potential of preserving or restoring normal immune function. It may delay the development of AIDS, thereby prolonging life. Early antiretroviral therapy decreases the risk of selection of resistant virus. It decreases the risk of drug toxicity. And, finally, it may decrease the risk of viral transmission from the HIV-infected person to others.

Six potential risks of early antiretroviral therapy in asymptomatic patients were also identified by the panel convened by the DHHS and the Kaiser Foundation. Adverse drug effects and the inconvenience of the highly suppressive regimens in use today may reduce QOL. Drug resistance has the potential to develop earlier, and drug-resistant virus may be transmitted. Future antiretroviral therapy options will be narrowed in the event of treatment failure or the development of resistance. The long-term toxicity of antiretroviral therapy is unknown. The durability of the efficacy of currently used antiretroviral therapy regimens has not been established.

When Clients Should Start Antiretroviral Therapy

Before a client begins antiretroviral therapy, his or her counselor needs to assess whether the person is ready to make a lifelong commitment to following the prescribed treatment.

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Initiating ART

Adherence is a problem, and, therefore, treatment failure is inevitable, unless the client is ready to assume the responsibilities and make the effort that adherence entails.

Before assessing the client's readiness to begin antiretroviral therapy, the counselor needs to take the client's medical history, inquiring in particular about the person's use of alcohol, chemicals, and medications and about the presence of any psychiatric problems, especially depression. Tobacco, alcohol, caffeine, and other drugs may further damage an already compromised immune system. In addition, use of mood-altering drugs and depression may weaken the person's resolve to adhere to therapy and practice safe sex. For clients who are not sure whether their use of alcohol or other substances constitutes abuse, the counselor can suggest that they ask themselves such questions as

- Is my use of this substance causing me or those close to me any problems?
- How is it affecting me physically, mentally, emotionally, and spiritually?
- Does my use of the substance detract from my ability to function or to get along with other people?
- Does using the substance make me feel that I am losing my sense of values?

Using a nonjudgmental tone of voice and choice of language, counselors may need to point out to clients that denial is an important psychological component of alcohol and drug addiction. Therefore, clients who strongly deny being substance abusers in spite of evidence to the contrary may need to come to terms with the possibility that they have an addiction.

Clients who acknowledge a substance abuse problem and are willing to seek treatment for it can be advised to obtain individual counseling, join support groups or 12-step programs, or enter programs at specialized addiction treatment centers, either as inpatients or outpatients. Clients' physicians or local AIDS service organizations should be able to provide referrals. Similarly, clients who are clinically depressed should be referred for treatment.

For clients who are committed to antiretroviral therapy and willing to adhere to complex regimens in spite of being asymptomatic, treatment is generally recommended when their plasma HIV RNA levels are above 30,000 copies/mL, regardless of their CD4 cell counts, or when their CD4 counts are below 350 cells/μL, regardless of their HIV RNA levels. Some would recommend initiating treatment when plasma HIV RNA levels are above 10,000 copies/mL. Treatment is also advised for clients whose CD4 counts are 350 to 500 cells/μL if their plasma HIV RNA levels are at least 5000 copies/mL. Treatment is usually deferred in patients with CD4 counts higher than 500 cells/μL and plasma HIV RNA levels below 5000 copies/mL, because they are at low risk of clinical progression of their disease within 3 years. These guidelines are somewhat arbitrary, and physicians and their patients will need to make decisions on the timing of antiretroviral therapy on an individual basis.

Recommended Initial Antiretroviral Therapy Regimens

Among the overall considerations in choosing an initial regimen for

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treatment-naive clients (those who have never received antiretroviral therapy) are whether to use a highly potent regimen, one that has the best chance of achieving maximal suppression of plasma VL below the limits of detection and minimizing the development of resistance. The initial treatment regimen represents the best opportunity to attain these goals, because antiretroviral therapy options for treatment-experienced patients become increasingly limited.

Because adherence is essential to the success of antiretroviral therapy, it is important to plan a simple and convenient regimen, one that entails taking as few pills as possible as infrequently as possible every day. Adherence will also be more likely if the regimen does not require many storage and food restrictions. The regimen should be associated with a low incidence of side effects and toxicities, and it should not consist of drugs that may interact with other medications the client may be taking.

The following table lists antiretroviral therapy combinations that are generally recommended for initial treatment of HIV infection and their advantages and disadvantages.

Initial Antiretroviral Therapy Regimens

Combination regimens	Advantages/ disadvantages	Regimen examples
2 NRTIs + 1 PI	Experience greatest with this first-choice regimen; applicable to all VLs. Pill burden high; strict adherence crucial; durability of effect uncertain; long-term toxicity	**Lamivudine + zidovudine + indinavir**
2 NRTIs + 1 NNRTI	Good alternative to preceding regimen; permits deferral of PI; low pill burden. Strict adherence crucial; durability of effect uncertain; potency compared to that of PI-containing regimens uncertain, however, data suggest it may be equivalent to PI-based regimen; compromises future NNRTI regimens	**Stavudine + didanosine + nevirapine**
2 PIs ± 1 or 2 NRTIs	Exploits pharmacokinetic interactions; high potency; convenient dosing. Potential for broad PI resistance; high pill burden with some regimens; long-term toxicities unknown	**Ritonavir + indinavir + abacavir**

NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NNRTI = nonnucleoside RTI.

An effective alternative basic regimen consists of 3 NRTIs, such as abacavir, zidovudine, and lamivudine. Advantages of this triple-combination regimen are deferral of the use of PIs and NNRTIs and a low pill burden, especially when a single triple-combination NRTI tablet is used. Although this tablet is not available yet, a study by G. Yuen and colleagues, presented at the 7th CROI (Conference on Retroviruses and Opportunistic Infections), abstract 98, that enrolled 24 healthy volunteers showed that a single tablet containing abacavir, zidovudine, and lamivudine was bioequivalent to a sequential regimen in which the 3 NRTIs were administered separately. That same study demonstrated that no food restrictions were necessary with the triple-combination tablet. One concern about to triple-NRTI regimens is whether they will compromise the future use of other NRTI regimens. In addition, triple-NRTI regimens may be less effective in patients who have higher VLs.

Investigators compared the antiretroviral effect and CD4 response of a triple-NRTI regimen consisting of abacavir plus lamivudine/zidovudine single-tablet formulation with that of a triple regimen consisting of the PI indinavir plus lamivudine/zidovudine single-tablet formulation. A 48-week, randomized, double-blind international study (CNA 3005) in which 562 treatment-naive subjects were enrolled showed the 2 regimens to be comparable with respect to their effects on VL and CD4 cell counts, except in subjects with VLs above 100,000 copies/mL at the beginning of treatment. Other investigators found the 2 regimens comparable in their ability to support immune restoration. Results were reported by Staszewski and colleagues at the 39th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy), abstract 505, and by Demarest and colleagues at the 7th CROI, abstract 331.

Lower total pill count has been associated with VL efficacy in one meta-analysis that examined triple therapy with 2 NRTIs plus either a PI, an NNRTI, or a third NRTI. Pill count was correlated with VL response in this analysis, while the study saw comparable effectiveness in all 3 types of regimens.

Strategies to Promote Adherence and Minimize Resistance

Once a client is committed to receiving antiretroviral therapy, the counselor, along with the physician and other members of the healthcare team, have key roles to play in helping the person adhere to the prescribed treatment regimen. Strict adherence is the most critical challenge in the treatment of HIV, and adherence to a potent initial antiretroviral therapy regimen represents the client's best chance of achieving durable suppression of HIV infection. In a study of PI-containing regimens, investigators found that adherence exceeding 95% was associated with virologic success and that failure rates rose sharply with decreasing degrees of adherence. Yet estimates of antiretroviral therapy nonadherence rates range from 15% to 93%, depending on how adherence is defined. The importance of adherence was also supported by a study of 84 subjects that compared the results of directly observed therapy and self-administered therapy in clinical trials. Although subjects in the directly observed therapy group had lower CD4 cell counts and higher VLs than those in the self-administered therapy group, the former experienced a faster and greater overall decline in VLs during treatment, along with a greater increase in CD4 cell count and less serious toxicities.

The problem of adherence is closely related to the problem of resistance. Resistance mutations are more likely to develop when a client's VL is not maintained below the limits of detection. This, in turn, is often due to lack of adherence to therapy.

Results of several recent studies suggest that amprenavir and saquinavir may pose fewer resistance problems than other PIs. For example, in a study of plasma samples from 108 patients in whom initial PI-containing regimens failed, investigators found that the frequency of phenotypic resistance to amprenavir was lower than that to other PIs that the subjects had received. Also, a PI phenotypic susceptibility study of 96 patients whose first PI-containing regimen had failed showed that they retained susceptibility most often to amprenavir and saquinavir (82%), less often to indinavir and ritonavir (67% to 68%), and least often to nelfinavir (28%). Similarly, phenotypic resistance to amprenavir was less than 4-fold in 90% of the subjects enrolled in an antiretroviral response study and 10-fold or less in the remaining subjects. Resistance to saquinavir was less than 4-fold in approximately 85% of the subjects, less than 10-fold in about 8%, and greater than 10-fold in the rest. At the time of enrollment, 53% of the subjects had previously taken nelfinavir and 36%, indinavir. Thus, in the majority of cases, the subjects remained sensitive to amprenavir and saquinavir.

Typical reasons that clients give for missing antiretroviral therapy doses are forgetting to take their medication, being too busy, being away from home, being asleep, feeling depressed, feeling too ill, or having adverse drug reactions. The underlying reasons for lack of adherence can be classified into logistical barriers, psychological barriers, and environmental barriers. Examples of logistical barriers include inconvenient dosing schedules, regimens with high pill counts, and food restrictions. Psychological barriers include resentment about dependence on medication, emotional stress, and flagging motivation because of active use of drugs or alcohol or adverse effects of medication. Potential environmental barriers include financial stress, difficulty balancing self-care with family responsibilities, and poor access to healthcare.

Strategies that can eliminate some of the barriers to adherence include informing clients about what to expect from antiretroviral therapy, anticipating problems they may encounter, reducing and treating drug interactions and side effects, and, if possible, reducing pill numbers and dosing frequency.

In helping a client adhere to antiretroviral therapy, the counselor needs to work with other members of the healthcare team, such as nurses, pharmacists, peer educators, and physician assistants, in reinforcing the message of adherence. Medication-related strategies include designing a treatment plan that is as simple and tolerable as possible and that has manageable restrictions. Otherwise, the plan is unlikely to succeed, especially if the client is living on the street, in a shelter, or in a correctional or residential drug-treatment facility. Clients in those settings have limited control over logistical and environmental barriers and may be more hindered by psychological barriers than persons who have stable housing and the support of family and friends.

Among the client-related strategies that the counselor should implement are

- Negotiating a treatment plan, rather than trying to impose one
- Providing a written medication schedule, pictures of the drugs to be taken, and mechanical aids such as pill organizers, pagers, and alarm clocks
- Taking enough time and scheduling enough visits with the client to explain the goals of therapy, reinforcing the importance of adherence, keeping the client motivated, and resolving problems as they arise
- Reassuring the client that some adverse drug effects will be mild or temporary and that alternative regimens can be tried if side effects become a deterrent to adherence
- Addressing the issues around the client's disclosure of his or her disease status
- Recruiting family and friends to support the treatment plan
- Referring clients to support groups, peer educators and advocates, and case managers, as appropriate
- Considering "pill trials" using jelly beans

Communication is a key element in adherence. The counselor needs to assess adherence at each visit in a nonthreatening way, such as by asking the patient to fill out a questionnaire on recent medication use or to answer nonjudgmental questions about adherence, such as "Which doses do you find hardest to remember?" The client must know whom to call to discuss problems, including troublesome side effects, missed doses, or confusion about dosing instructions. The client must also feel confident that the person to be called when problems arise will be supportive and available to talk.

Drug Interactions

Drug interactions are a potential complication of antiretroviral therapy of which clients need to be aware. For example, the NNRTI efavirenz is known to interact with the PI amprenavir, reducing its area under the curve by about 40%. However, recently investigators found that the addition of either low-dose (subtherapeutic) ritonavir or full-dose nelfinavir to an amprenavir/efavirenz combination regimen eliminated the interaction of the 2 drugs and increased the serum concentration of amprenavir. Similarly, concomitant administration of ritonavir with saquinavir and rifampin enables therapeutic plasma concentrations of saquinavir to be reached. The addition of ritonavir to the regimen eliminates the drug interaction that causes a dramatic decline in the concentration of saquinavir when it is administered with rifampin alone. The triple regimen of ritonavir/saquinavir/rifampin thus permits patients who are coinfected with HIV-1 and *Mycobacterium tuberculosis* to receive effective treatment.

Antiretroviral Therapy Reference Guide: Initial Therapy

Recommended combination regimens
• 2 NRTIs + 1 PI • 2 NRTIs + 1 NNRTI • 2 PIs + 1 NRTI • 2 PIs + 2 NRTIs

continued on page 8

Self-assessment Test

For CE certification, circle the letter that corresponds to the correct answer for each test question. Return this completed form by March 1, 2001 (August 31, 2001 for those seeking CME credit from the AAPA) via fax or mail to

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Select the best answer to each question below.

1. Which is not a benefit of early antiretroviral therapy?
   a. Control of viral replication and mutation, as well as reduction in viral load
   b. Patient knowledge of the sequence of medications
   c. Delay of onset of AIDS
   d. Decrease in the risk of drug toxicity

2. Which is not considered a risk in early antiretroviral treatment?
   a. Adverse drug effects and inconvenience may reduce quality of life.
   b. Future antiretroviral therapy options will be narrowed in the event of treatment failure or the development of resistance.
   c. Long-term toxicity of antiretroviral therapy is unknown.
   d. Patients may develop an indifference to taking medication.

3. Before assessing the client's readiness to begin antiretroviral therapy, a counselor should
   a. Take client's full medical history
   b. Give client a psychological exam
   c. Assess client's complete sexual history
   d. All of the above

4. What is the most critical challenge of treating HIV?
   a. The client's nutritional habits
   b. Monitoring the client's viral load and CD4 cell counts
   c. The client's strict adherence to taking medication
   d. None of the above

5. All are considered underlying reasons for lack of adherence in taking medication, except
   a. Logistical barriers
   b. Psychological barriers
   c. Environmental barriers
   d. Physical barriers

6. Which of the following is not a manifestation of mitochondrial toxicity?
   a. Peripheral neuropathy
   b. Cardiomyopathy
   c. Lactic acidosis
   d. Brain swelling

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practitioner/consultant in Austin, Texas ***IV Frontline*** *Editorial Advisory Board.*

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Evaluation Form

You must complete and return this page along with your CE self-assessment test answer form to receive CEUs/credit. There is no fee to participate in this activity. Please fill in the requested information on the answer form and return by fax to **(212) 481-8532** or by mail to **Frontline Editor, World Health Communications Inc., 41 Madison Avenue, 40th Floor, New York, NY 10010**, no later than March 1, 2001 (August 31, 2001 for those seeking CME credit from the AAPA). A certificate will be faxed to you in approximately 4-6 weeks.

5 = Excellent 4 = Very good 3 = Good 2 = Fair 1 = Poor

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	Educational value	Clarity
Feature article	5 4 3 2 1	5 4 3 2 1
Counselor-to-counselor	5 4 3 2 1	5 4 3 2 1
HIV News Briefs	5 4 3 2 1	5 4 3 2 1

2. Do you think that ***HIV Frontline*** helps you in your work? Why or why not?

3. What topics should ***HIV Frontline*** address in the future?

4. How can ***HIV Frontline*** be more useful to you?

The Decision-Making Process

Sue Gallego, MSSW, LMSW-ACP

There are many milestones along the continuum of HIV infection that people with HIV disease and those serving clients who are HIV positive must prepare for and anticipate. We often read and talk about the reactions people may experience when they first find out that they are HIV positive. Many emotions and feelings may come up when someone is diagnosed with their first opportunistic infection. The client's process of deciding what to do about his or her HIV disease, when to initiate treatment, and whether or not to follow the medical recommendations to begin treatment medications is an important, and sometimes minimized, issue. This is an area in which counselors can provide significant insight and support.

Counselor -to- Counselor

The decision-making process can take a great deal of the client's, counselor's, and medical care team's time and energy. For clients, it is a process that begins when they are first told they are HIV positive.

I was recently asked to fill in for a counselor who was on leave for a few days, and I met with a client who was clearly trying to decide on treatment for his HIV disease. Frank, a 28-year-old African American man, has been in recovery (ex–intravenous drug user) for the past 3 years. Frank's physician met with him, and after reviewing his lab work and medical history, recommended that he begin combination therapy.

Frank began by telling me that he did not want anyone in his family to know he was HIV positive. He had never been sick much before he was HIV positive, and he really did not feel very sick now. He also told me that he had some friends that had tried these "cocktails" and had gotten extremely ill. He questioned whether the medicines would work and if someday in the future, research would show that the medications hurt more than they helped. He also told me he knew someone who had been on some medications for HIV disease, which had made the man deaf until he stopped taking them. After listening to Frank for about 15 minutes, it was clear to me that Frank and I would benefit from more information and time.

It is important for counselors to recognize that while knowledge about HIV treatments can help some people feel more in control of their lives and disease, others may feel overwhelmed. It is key for the counselor to focus on helping the client move, one step at a time, from a sense of powerlessness or confusion to feeling that, "there are some things I can do."

There are also many urban myths about HIV medications, which are created out of fear and perpetuated by people with "big names" who are not involved in the field of HIV disease, but want to create confusion. So, when Frank asked me if combination therapy worked on African Americans, it opened the door for providing him with further information, but more importantly, it allowed me to listen to his thoughts, fears, and possible feelings of mistrust.

Clients need to hear that the information we currently have about HIV treatment is what we know now. They need to know that we are learning new things about HIV treatment all the time and that research is ongoing.

We must also be mindful of our cultural experiences. We should be aware of how our cultures define illness, what is considered healthcare treatment, and what our history with "the establishment" is. HIV disease and treatments for HIV have often challenged our beliefs and sensibilities.

Counselors understand that the commitment to adherence and the individual's sense of personal responsibility related to his or her healthcare usually involves many biopsychosocial and spiritual issues. The decision of whether or not to begin HIV treatment is difficult, and clearly it is a process in which clients and counselors can take an active role.

Sue Gallego is a private practitioner/consultant in Austin, Texas and a member of the ***HIV Frontline*** *Editorial Advisory Board.*

Long-term Complications of Antiretroviral Therapy

Although the use of potent antiretroviral therapy regimens containing at least 3 drugs has led to significant improvements in the medical condition of patients infected with HIV and, for many of them, prolonged life expectancy, these regimens have also been associated with certain complications. We are well aware of short-term side effects that appear when a regimen is begun, such as diarrhea, nausea, vomiting, blurred vision, dizziness, insomnia, fatigue, and skin rashes. However, counselors of HIV-infected patients need to be familiar with the signs and symptoms of *long-term* complications so that they can alert patients to them and make sure that patients in whom these complications develop receive proper medical attention, including, if necessary, a change in drug regimen. Close monitoring by counselors and patients for adverse effects to antiretroviral therapy is the first step in managing complications and preventing nonadherence to antiretroviral drug regimens. The following discussion will cover some of the major complications of antiretroviral therapy.

Nucleoside Reverse Transcriptase Inhibitors

Mitochondria, or organelles, are components of cell cytoplasm. They are the main source of energy for cells and are essential for normal functioning of body systems. Damage to these structures, which is due to mitochondrial toxicity, can cause reversible or irreversible dysfunction of affected organs and occasionally even death. The mechanisms that underlie mitochondrial toxicity are not fully understood, but nucleoside reverse transcriptase inhibitors (NRTIs) and HIV infection are known causes. Both factors may inhibit DNA polymerase, the sole enzyme responsible for mitochondrial DNA replication.

Signs and symptoms of mitochondrial toxicity are not evident in some patients until they have been taking NRTIs for several months. In other patients, however, toxicity develops after a short time, suggesting that they may be genetically predisposed to this complication. The adverse effects of mitochondrial toxicity vary from patient to patient, from one organ or body system to another, and with the particular NRTI administered. One report cited female gender, obesity, and early HIV disease as possible risk factors for mitochondrial toxicity. Older age has also been suggested as a factor in susceptibility.

Mitochondrial toxicity may be manifest as one or more diseases of the liver, heart, pancreas, skeletal muscles, nervous system, bone marrow, kidneys, inner ears, or eyes. Specifically, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, or lactic acidosis may occur. The usual symptom of myopathy, which may be due to long-term therapy with zidovudine or to HIV infection, is weakness in the neck and limbs. The histologic sign of zidovudine-induced myopathy is the presence of ragged-red fibers (a proliferation of certain abnormal mitochondria). Discontinuation of zidovudine therapy appears to reverse this condition. This was first seen in patients on very high doses of zidovudine monotherapy.

Cardiomyopathy, or primary noninflammatory disease of the heart muscle, has been associated with zidovudine, zalcitabine, and didanosine therapy, but additional studies are needed to clarify the risks posed by each drug and the effects of discontinuing treatment. HIV infection can also cause cardiomyopathy.

Peripheral neuropathy is typically manifest as pain, numbness, or tingling in the arms, legs, or toes. Stavudine, zalcitabine, and didanosine have all been implicated in this condition. Peripheral neuropathy can become worse over time, so close monitoring of patients who are taking any of these agents for several weeks or months, particularly older patients, is important to prevent serious damage. The finding in one study that zalcitabine-induced neuropathy became worse when a patient was switched to didanosine therapy suggests that zalcitabine and didanosine have synergistic effects.

Symptoms of pancreatitis (inflammation of the pancreas) include nausea, vomiting, and abdominal pain. Elevated serum amylase and lipase levels are also suggestive of the disease. In HIV-infected patients, the use of NRTIs or other medications, such as pentamidine, as well as infections affecting the pancreas (eg, cytomegalovirus) can cause pancreatitis. Zidovudine, zalcitabine, and stavudine therapy have all caused pancreatitis in some patients.

Lactic acidosis, which occurs when dysfunctional mitochondria force cells to rely on the method of producing energy known as glycolysis, refers to highly elevated levels of lactate in the blood. Typically, symptoms of this rare disorder are vague and nonspecific. They often include nausea, vomiting, abdominal pain, weight loss, malaise, and shortness of breath. Lactic acidosis has developed in patients who were taking only one NRTI, as well as in patients taking a combination of 2 NRTIs. Among the known risk factors are Caucasian race, female gender, obesity, prolonged use of NRTIs (for several months), and occurrence of other NRTI-related side effects. Vitamin deficiencies, specifically L-carnitine and riboflavin, have also been linked. Lactic acidosis is often accompanied by hepatic steatosis (accumulation of fat in the liver). The combination of hepatic steatosis and severe lactic acidosis has led to some deaths among patients who were taking NRTIs on a long-term basis.

Nonnucleoside Reverse Transcriptase Inhibitors

The nonnucleoside RTI (NNRTI) efavirenz appears to be associated with increased triglyceride and fatty-acid levels in patients infected with HIV. Moyle and colleagues found that triglyceride and fatty-acid levels rose in patients who were taking a combination of efavirenz and NRTIs. The increase occurred more often in patients who had previously taken protease inhibitors (PIs). In a second study, Moyle and colleagues corroborated the association between prior PI therapy and metabolic changes in patients who were taking efavirenz. In that study, the investigators noted changes in visceral adipose tissue and blood-lipid levels. These changes may be caused by efavirenz-induced alterations in the expression of genes in adipose and liver tissue, according to the results of a study of the effects of efavirenz on obesity-prone mice.

Preliminary results in an ongoing international multicenter trial (DuPont Study 006) comparing 3 different antiretroviral therapy regimens in treatment-naive HIV-infected patients indicated that fewer patients who were receiving the triple combination of efavirenz/zidovudine/lamivudine discontinued treatment because of lack of efficacy or adverse effects than patients who were receiving either efavirenz plus indinavir or indinavir/zidovudine/lamivudine. Furthermore, the triple regimen containing efavirenz had a better and more durable antiretroviral effect than the other 2 treatments. If long-term monitoring and follow-up show that these findings are sustained, the triple-therapy regimen with efavirenz could be promising for patients with HIV infection, in terms of both efficacy and avoidance of long-term complications.

Protease Inhibitors

The first recognized complication of highly active antiretroviral therapy (HAART) containing PIs was lipodystrophy. This disorder encompasses various abnormalities in the metabolism of fat. Later it was noted that these abnormalities are often associated with certain metabolic disturbances, such as insulin resistance and hyperglycemia, that can also occur in patients who are not taking antiretroviral therapy. Carr and colleagues described a syndrome of peripheral fat wasting, hyperlipidemia, and insulin resistance in HIV-infected patients who were taking PIs. The syndrome was more frequent and severe in those patients who were taking ritonavir/saquinavir than in those who were taking indinavir.

The various signs and symptoms of metabolic abnormalities related to PI therapy may be classified as shown in Table 1.

Adverse metabolic effects of HAART were once thought solely to be caused by PIs, but evidence is emerging that NRTIs may also play a role in one type of lipodystrophy—loss of body fat. The results of one small study of HIV-infected patients suggest that fat accumulation in the form of buffalo hump is not unique to patients taking PIs but may occur in patients taking other antiretroviral agents as well.

Results of a study of clinical factors related to lipodystrophy in HIV outpatients showed that the likelihood of fat redistribution was most strongly associated with increasing patient age. In addition, use of the NRTI stavudine and of the PI indinavir were associated with moderate-to-severe fat redistribution. Ritonavir is apparently the most likely of the PIs to cause adverse metabolic effects, whether used alone or in combination with another PI. Single-agent therapy with indinavir, nelfinavir, or saquinavir may also cause adverse metabolic effects, according to preliminary data. Whether amprenavir has this potential has yet to be determined.

Another potential adverse effect of PI therapy is hepatotoxicity. In one study, the relative risk of severe hepatotoxicity was found to be nearly 5 times greater (4.8) in patients who were taking ritonavir than in patients who were taking dual NRTIs. The combination of ritonavir plus saquinavir carried an even higher relative risk (5.6).

TABLE 1

SELECTED MANIFESTATIONS OF LIPODYSTROPHY

Category	Signs and Symptoms
Loss of fat	Sunken cheeks, eyes; thin, prominent arm veins; skinny or bony legs; loose skin folds on buttocks; loss of fat or muscularity of trunk
Fat accumulation	Increased abdominal girth; enlarged breasts; dorsocervical fat pad formation ("buffalo hump"); double chin
Lipid disturbances	Significant increases in triglyceride levels after eating; abnormally high serum triglyceride and total cholesterol levels after overnight fast
Glucose disturbances	Abnormal fasting blood glucose or fasting serum insulin levels; emergence of diabetes mellitus

Conclusions

Some of the long-term complications associated with HAART discussed here, specifically, increased triglyceride and fatty-acid levels, decreased high-density lipoprotein cholesterol, decreased insulin resistance, and decreased body fat, are associated with HIV disease. Hereditary and environmental factors (eg, diet and exercise) may also predispose certain patients to these complications. The presentations of metabolic abnormalities differ between men and women, and among different antiretroviral agents. More studies are needed to identify all the various risk factors for these and other long-term complications of potent antiretroviral therapy regimens and to determine how they interact to cause toxicities. The safety profiles of each antiretroviral agent in a given regimen must be differentiated when complications arise so that appropriate steps can be taken to properly manage side effects.

Initiating ART

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Recommended Antiretroviral Therapy for Initial Treatment of Established HIV Infection

The following table is a guide to available treatment regimens for persons with little or no prior experience with HIV therapy. The information appearing below was updated in January, 2000 by the Department of Health and Human Services' Panel on Clinical Practices for Treatment of HIV Infection. Priority is given to regimens that, according to clinical trial data, appear to provide sustained suppression of VLs, especially in patients with high baseline VLs; sustained increases in CD4 cell counts (usually over 48 weeks); and favorable clinical outcomes—that is, delayed progression of AIDS and death. Regimens that meet these criteria and that are superior to other regimens with respect to pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interactions are included in the "strongly recommended" category. However, all antiretroviral agents have the potential to cause serious toxic and adverse events. Initial antiretroviral therapy consists of one choice each from column A and column B. Drugs are listed in alphabetical, not priority order.

	Column A	Column B
Strongly recommended	Efavirenz Indinavir Nelfinavir Ritonavir + saquinavir (SGC or HGC)	Stavudine + lamivudine Stavudine + didanosine Zidovudine + lamivudine Zidovudine + didanosine
Recommended alternative	Abacavir Amprenavir Delavirdine Nelfinavir + saquinavir.SGC Nevirapine Ritonavir Saquinavir.SGC	Didanosine + lamivudine Zidovudine + zalcitabine
*No recommendation; insufficient data**	Hydroxyurea in combination with other antiretroviral agents Ritonavir + indinavir Ritonavir + nelfinavir Ritonavir + amprenavir	
Not recommended all monotherapies†	Saquinavir.HGC‡	Stavudine + zidovudine Zalcitabine + lamivudine Zalcitabine + stavudine Zalcitabine + didanosine

SGC = soft-gel capsule; HGC = hard-gel capsule.
Reprinted from DHHS Guidelines, "The Living Document," January 28, 2000.

* This category includes drugs or drug combinations for which information is too limited to permit a recommendation for or against use.

† Zidovudine monotherapy may be considered for prophylaxis in pregnant women with low VLs and high CD4 cell counts to prevent perinatal transmission.

‡ Use of saquinavir.HGC is not recommended, except in combination with ritonavir.

HIV News Briefs

Clinton Plan Could Expand Federal Benefits to HIV-Infected Persons

The *Boston Globe* reported that a 5-year demonstration program approved by the Clinton administration will permit the state of Maine to issue Medicaid payments to HIV-infected residents who do not yet have AIDS. In addition to being Maine residents, recipients must earn less than $25,000 per year. The purpose of the program is to expand the number of people with HIV infection who are helped before they become ill and disabled due to AIDS. Among the benefits that these HIV-positive persons will receive are drug therapy, office visits, lab services, and other therapy services. This new program will allow approximately 300 people in Maine to receive treatment for HIV infection who cannot afford to pay for it.

Minority and Young Women at Continuing High Risk for HIV/AIDS

The Centers for Disease Control and Prevention (CDC) estimate that 120,000 to 160,000 women and adolescent girls in the United States are living with HIV infection, including those who have AIDS. In 1992, 13.8% of US residents living with AIDS were women; by 1997, that percentage had grown to 19.1%. Between 1985 and 1998, the proportion of all AIDS cases reported among women and adolescent girls rose from 7% to 23%. Although African American and Hispanic women represent less than 25% of all women in this country, they account for 77% of AIDS cases reported to date among women in the United States. In spite of recent advances in treatment, HIV infection and AIDS remains one of the leading causes of death among women aged 25 to 44 in the United States. In 1998, the most common cause of AIDS among women was heterosexual exposure to HIV, followed by the use of injection drugs. A large percentage of women who became infected heterosexually did so through sexual contact with injection-drug users. For this reason, reducing the HIV infection rate among women will require combating substance abuse as well as reducing HIV risk behaviors.

Possible Impact of New Combination Therapies for HIV/AIDS on High-Risk Behaviors

According to the CDC, research suggests that the availability of potent new combination regimens to treat HIV/AIDS may be making some people less worried about becoming infected with HIV and, thus, more inclined to engage in high-risk sexual behaviors and drug use. In addition, some people may erroneously think that the virus cannot be transmitted by HIV-positive persons who take PIs. The CDC is also concerned that the transmission of resistant viral strains could undermine recent gains made in the control of HIV disease and AIDS.

To add your name to the mailing list for this publication, please send your request to **HIV Frontline**, World Health CME, 41 Madison Avenue, New York, NY 10010-2202. **HIV Frontline** is also available on the World Wide Web, through the HIV Information Network℠ at http://www.HIVLine.com.