SWITCHING ANTIRETROVIRAL THERAPY

Liz Highleyman

A DECADE AGO, at the dawn of the HAART era, many people with HIV considered it a victory to find an antiretroviral regimen that reduced their viral loads to an undetectable level and raised their CD4 cell counts out of the danger zone—even if that meant putting up with agonizing side effects and difficult dosing schedules.

Today, given an improved understanding of HIV treatment and an array of new agents, it is often possible to devise regimens that both suppress HIV and are relatively easy to live with. Treatment veterans may see treatment-naive individuals starting therapy with simpler, less toxic regimens—like the newly approved one-pill, once-daily Atripla (tenofovir/ emtricitabine/efavirenz)—and wonder: Is it time for me to switch?

While treatment-experienced individuals typically have fewer options than those starting therapy for the first time, many can still benefit from revising their treatment plans. This article will examine motivations for changing therapy and recent innovations in antiretroviral treatment. It will review some of the switch studies that support changing regimens—and also look at why, in some cases, it may make sense to stick with what's already working.

Reasons for Switching

People with HIV may be motivated to switch drugs for a variety of reasons, including:

- Inadequate virological control
- Intolerable or bothersome side effects
- Metabolic and mitochondrial abnormalities
- Inconvenience and poor adherence

At the XV International AIDS Conference in 2004, Brian Boyle, MD, and colleagues presented the results of a survey of 357 readers of a publication for HIV positive people (*POZ* magazine) asking about their interest in and experience with switching antiretroviral therapy. Switching was common, with 40% saying they had changed their regimen during the past year, and 20% saying they had made two or more changes. The most frequent reasons for wanting to switch were to reduce side effects (44%), improve potency (27%), and enhance convenience (20%).

Inadequate Potency

The most urgent reason for changing therapy—and one few doctors or patients will argue with—is poor virological control. The goal of antiretroviral therapy is to suppress HIV viral load to an undetectable level, ideally below 50 copies/mL. When even low-level viral replication continues in the presence of a drug, resistance mutations can emerge. This not only may reduce HIV's susceptibility to current drugs, but can also confer cross-resistance to similar agents—in the worst case rendering an entire class of drugs ineffective.

With the selection of antiretroviral agents now available, most HIV positive people—even those with some prior treatment experience—have a good chance of keeping the virus in check. According to Ronald Mitsuyasu, MD, of the University of California at Los Angeles Medical Center, patients starting their second or third regimen typically should achieve full HIV suppression within three months or so. Individuals with more extensive prior treatment histories may not achieve complete virological suppression, but still should see some improvement.

In addition to suppressing viral load, a potent antiretroviral regimen typically also raises CD4 cell counts out of the danger zone—below 200 cells/mm^3—where the risk of opportunistic illnesses begins to rise. According to the current U.S. federal HIV treatment guidelines, 350 cells/mm^3 is an acceptable level, though recent studies suggest that the risk of disease progression is lower if antiretroviral therapy is started early and CD4 count is maintained at a higher level (see "News Briefs" on page 8). After initiating therapy, it is not uncommon for CD4 counts to increase more slowly than viral load declines; some patients, especially those with a low CD4 nadir (lowest-ever level), may have difficulty reaching an optimal level.

If viral load does not fall or CD4 cell count does not rise within a reasonable period of time (about 3–6 months), further testing is indicated to determine the reason. As a rule, the sooner such problems are detected, the easier they are to fix. However, viral load "blips" (transient spikes) are common, and most research suggests they are harmless; in addition, various factors can temporarily alter CD4 counts. Therefore, many experts prefer to wait until a patient has had at least two consecutive tests showing a trend of increasing viral load and/or declining CD4 count before changing therapy.

If treatment is failing to suppress HIV, the cause may be low drug levels in the body, perhaps due to suboptimal adherence or individual variations in how drugs are processed. Therapeutic drug monitoring (TDM) can show whether this is the case.

Another possibility is that drug resistance has developed; even people who have never used antiretroviral therapy may have been infected with a drug-resistant strain of HIV. Resistance testing can show if this is why certain drugs are not working, and what might be the best options for a switch. Standard genotypic testing involves analyzing HIV genetic material for known resistance mutations. In the more expensive phenotypic assay, an individual's virus is exposed to a drug in a test tube to determine how well that agent works against that particular strain of HIV.

People who started treatment in the pre-HAART era may have a history of suboptimal therapy with nucleoside reverse transcriptase inhibitor (NRTI) monotherapy or dual-NRTI therapy and may have developed resistance to multiple drugs. For these individuals, decisions about switching therapy are more complex—and there is less room for error if they have advanced HIV disease and low CD4 cell counts. (See the Winter 2003 issue of *BETA* for an in-depth discussion of "salvage" therapy for heavily treatment-experienced patients.)

Side Effects and Toxicities

Drug-related toxicity is one of the most common reasons for modifying antiretroviral therapy. In Boyle's survey, adverse events were the most frequently cited reason for wanting to change drugs. (Some of the most common and most worrisome antiretroviral side effects are listed in the sidebar on page 19.)

Most medications can cause some side effects in some people, especially when they are first introduced. Some of the typical symptoms associated with antiretroviral therapy—nausea and vomiting, diarrhea, fatigue—often go away as the body adjusts to a drug. Therefore, it is important not to give up on a new regimen too soon. According to Mitsuyasu, most side effects of this sort should dissipate within several weeks. If they persist longer than a couple of months, it may be time to think about making a switch. (Note: In rare cases, common

SIDE EFFECT	MOST COMMONLY ASSOCIATED DRUGS
Nausea and vomiting	all drug classes
Diarrhea	NRTIs; PIs, especially nelfinavir (Viracept), lopinavir/ritonavir (Kaletra), tipranavir (Aptivus)
Malaise (flu-like feeling)	all drug classes
Fatigue	all drug classes
Headache	all drug classes; T-20 (Fuzeon)
Anemia	AZT (Retrovir)
Myopathy (muscle damage)	AZT
Mitochondrial toxicity/lactic acidosis	NRTIs, especially d4T (Zerit) and ddI (Videx EC)
Peripheral neuropathy	ddI, d4T
Pancreatitis	ddI
Hypersensitivity reaction	abacavir (Ziagen); NNRTIs, especially nevirapine (Viramune)
Skin rash	NNRTIs, especially nevirapine; tipranavir; T-20 (injection site reaction)
Liver toxicity/elevated liver enzymes	NNRTIs, especially nevirapine; PIs, especially full-dose ritonavir (Norvir), lopinavir/ritonavir, tipranavir
Enlarged fatty liver (hepatomegaly with steatosis)	NRTIs, especially d4T and ddI
Elevated bilirubin/jaundice	atazanavir (Reyataz); indinavir (Crixivan)
Kidney toxicity	tenofovir (Viread); indinavir (kidney stones)
Lipoatrophy (peripheral fat loss)	NRTIs, especially d4T and ddI (particularly in combination)
Lipodystrophy (body shape changes)	PIs
Elevated blood fats (cholesterol, triglycerides)	PIs
Insulin resistance/diabetes	PIs
Central nervous system symptoms (unusual dreams, depression)	efavirenz (Sustiva) (Note: See "News Briefs," page 7, for more information.)

NRTIs: *nucleoside/nucleotide reverse transcriptase inhibitors*
NNRTIs: *non-nucleoside reverse transcriptase inhibitors*
PIs: *protease inhibitors*

mild-to-moderate side effects—especially occurring in certain clusters—may be signs of a more serious hypersensitivity reaction; individuals taking abacavir [Ziagen] or nevirapine [Viramune] should familiarize themselves with hypersensitivity symptoms and report these to a health-care provider without delay. See "News Briefs," page 10, for information about an abacavir hypersensitivity test currently in development.)

The respondents in Boyle's survey differed in terms of what side effects they found most difficult to live with: 75% said diarrhea, followed by nausea (49%), fatigue (47%), body shape changes (45%), peripheral neuropathy (41%), headaches (25%), and elevated cholesterol (12%). And side effects need not be severe to interfere with quality of life. Michael Saag, MD, of the University of Alabama at Birmingham Center for AIDS Research notes that patients sometimes neglect to tell their physicians about "subtle toxicities" such as persistent loose stool, mild headaches, or general malaise, but these, too, might improve with a well-considered switch.

Because there is no "one size fits all" regimen that is optimal for everyone, HIV positive people should work with their providers to find an individually tailored combination that offers the best balance of potency and tolerability.

Metabolic and Mitochondrial Manifestations

While "garden variety" side effects such as gastrointestinal symptoms and fatigue often improve over time, some more worrisome long-term manifestations associated with antiretroviral therapy have emerged since effective treatment has allowed HIV positive people to live longer. These fall into two broad categories:

- ***Metabolic manifestations:*** lipodystrophy (body shape changes), hyperlipidemia (elevated blood cholesterol and triglycerides), blood glucose abnormalities (insulin resistance, diabetes mellitus)
- ***Mitochondrial toxicity and associated conditions:*** lactic acidosis, lipoatrophy (loss of fat in the face, limbs, and buttocks), hepatomegaly with steatosis (enlarged fatty liver), peripheral neuropathy, pancreatitis

Metabolic manifestations are most often associated with the protease inhibitor (PI) class, while mitochondrial toxicity is linked with NRTIs, especially ddI (didanosine, Videx EC), d4T (stavudine, Zerit), and AZT (zidovudine, Retrovir). Both sets of conditions are poorly understood, however, and have also been observed in HIV positive individuals who have never taken antiretroviral therapy.

Body shape changes—whether abdominal fat accumulation associated with PIs or peripheral fat loss linked to NRTIs—are among the most distressing side effects of antiretroviral drugs, and are commonly cited reasons for switching therapy. And it's not all about vanity: visceral fat accumulation, elevated blood lipids, and insulin resistance are all associated with increased risk of cardiovascular disease. And, though rare, lactic acidosis and liver failure related to mitochondrial toxicity can be life-threatening.

Convenience and Adherence

Given that so many people with HIV have struggled over the years merely to find a regimen that keeps the virus under control and prevents immune system decline, convenience may seem like a trivial reason for switching.

But ease of use is a crucial factor contributing to good adherence. Research has shown that near-perfect adherence is necessary to maintain virological suppression and prevent the emergence of drug-resistant virus. And studies have found that simpler regimens do indeed promote better adherence. For example, a study by Tracy Glass and colleagues reported in the March 2006 *Journal of Acquired Immune Deficiency Syndromes* (*JAIDS*) showed that complex therapy—in particular, use of a boosted PI regimen—was associated with poorer adherence.

Saag is among the experts who believe that if a patient is having difficulty sticking to a regimen, it's better to "nip the problem in the bud" by switching to an easier combination before treatment failure occurs.

Individuals who have been on antiretroviral therapy for many years remember the challenges of the earliest anti-HIV regimens. When AZT was first introduced, it had to be taken six times daily. The discontinued unboosted formulation of saquinavir (Fortovase) required eight capsules at a time, twice daily. Unboosted indinavir (Crixivan) had to be taken every eight hours. It was not uncommon for an individual's regimen to include some drugs that had to be taken with food, while others had to be taken on an empty stomach. Ritonavir (Norvir) and the old formulation of lopinavir/ritonavir (Kaletra) required refrigeration—a serious drawback in much of the developing world, but bad enough for people who take their medications during the workday.

While most antiretroviral combinations no longer consist of handfuls of pills, and HIV positive people typically no longer require several additional medications to prevent or treat opportunistic illnesses, high "pill burden" remains a common complaint. Along with their anti-HIV drugs, many people also take adjunct medications—such as lipid-lowering agents and antidepressants—to manage treatment side effects, as well as complementary therapies such as vitamins and supplements. Thus, many patients and physicians feel, the fewer pills in an antiretroviral regimen, the better.

In addition to reduced pill burden, several newer antiretroviral agents can be taken just once daily, and it is now possible to construct a few complete once-daily regimens.

As is the case with side effects, convenience is also in the eye of the beholder. Nearly two-thirds of Boyle's survey respondents said that they would prefer a simpler regimen, assuming it could control HIV equally well. But simplicity meant different things to different people: about half said they would rather take three or four pills at a time once daily, while 40% preferred one or two pills at a time twice daily. Here again, HIV positive people should work with their providers to devise an individualized regimen that is convenient and promotes optimal adherence, without sacrificing antiretroviral potency.

Evolution of Antiretroviral Therapy

Over the past decade, several innovations have made antiretroviral therapy not only more effective, but also easier to tolerate and simpler to fit into one's life:

- New antiretroviral agents
- Reformulations of older drugs
- Fixed-dose combination pills
- Once-daily regimens
- Protease inhibitor boosting
- Class-sparing regimens
- Improved treatment strategies

Numerous switch studies have compared older drugs and treatment strategies with newer ones that researchers hoped would offer better or more durable virological suppression, fewer side effects, and greater convenience. Many such studies include participants who have achieved good virological control on an existing regimen, with the aim of examining other aspects of therapy—typically simplified dosing or reduced long-term toxicity.

When dramatic treatment advances occur—such as the use of ritonavir to boost levels of other PIs—most HIV specialists will review their patients' existing regimens and suggest appropriate changes. But practitioners who have less experience in the field may find it difficult to keep up with incremental changes; therefore, it may be helpful for patients to gather information explaining the potential benefits and risks of switching.

Some HIV positive people, following the "if it ain't broke, don't fix it" principle, have chosen to stay on the same regimens for years. As discussed below, the urge to stick with the "tried and true" is often reasonable, since there is no guarantee that switching will prove advantageous for any specific individual. But in many cases, patients may be needlessly missing out on the latest innovations in antiretroviral therapy.

New Agents, and More to Come

While the drug development process often seems agonizingly slow to people who need new medications now to construct viable antiretroviral regimens, the HIV treatment field has actually progressed remarkably rapidly. A total of 22 antiretroviral agents have been approved since the appearance of AZT in 1987, although two—ddC (zalcitabine, Hivid) and amprenavir (Agenerase)—have since been pulled off the market following the development of superior alternatives.

While new agents in existing drug classes are continually working their way through the development pipeline (for example, the experimental NNRTI TMC-125), novel agents that attack HIV by entirely different mechanisms hold the most promise, especially for people with extensive resistance to current drugs. Some of the agents in novel classes now moving through the pipeline include CCR5 coreceptor antagonists such as maraviroc, other types of entry inhibitors, integrase inhibitors such as MK-0518 and GS-9137 (see "Drug Watch" on page 13), and the viral maturation inhibitor bevirimat (PA-457).

New Formulations

Along with novel agents, manufacturers have also developed new formulations of drugs. For example, the original version of ddI (Videx), discontinued earlier this year, contained a buffering agent that restricted which other drugs could be taken at the same time; the new formulation, Videx EC, is not affected by stomach acid. Some drugs have been reformulated to contain larger doses, allowing for a lower pill burden; for example, people used to have to take five of the old 250-mg nelfinavir (Viracept) tablets at a time to get the same amount of medicine they can now get in two 625-mg tablets.

Saquinavir—the first PI on the market, approved in 1995—has come full circle. The original hard-gel tablet (Invirase) was poorly absorbed, and thus less potent in suppressing HIV. A new soft-gel capsule (Fortovase), released two years later, was better absorbed, but required six pills three times daily. With the discovery that ritonavir could be used to boost saquinavir levels in the blood, Invirase made a comeback. Today, the standard dose is two 500-mg Invirase tablets plus one 100-mg ritonavir capsule twice daily; Fortovase was recently taken off the market.

Amprenavir (Agenerase), a less potent PI that was usually taken eight pills at a time, was replaced with its more powerful pro-drug, fosamprenavir (Lexiva); the original amprenavir formulation, too, was recently discontinued. A new formulation of the Kaletra lopinavir/ritonavir combination pill allows patients to take fewer pills per day, has no food restrictions, and no longer requires refrigeration—which will be a boon in resource-limited settings.

Substituting a new formulation of an older drug is one of the most conservative switch strategies. Since people already have an idea how well the drug works for them and whether they can tolerate its side effects, benefits such as simplified dosing may be achieved with minimal risk.

Fixed-Dose Combination Pills

Using a fixed-dose coformulation that contains two or more drugs in a single pill is perhaps the easiest way to reduce pill burden, and changing from two or three separate medications to a coformulation is one of the most popular and low-risk switch strategies. In order to gain Food and Drug Administration (FDA) approval, studies must show that a combination pill is "bioequivalent" to the separate drugs used together—that is, it is processed the same way in the body and works equally well. As an added benefit, most insurance companies consider fixed-dose combinations as a single medication requiring just one copayment.

So far, most fixed-dose coformulations contain only NRTIs (see sidebar at right). The first, Combivir (AZT/3TC), was released in 1997, and there are now four all-NRTI combinations on the market. Because of its once-daily dosing schedule and good side effects profile, the Truvada (tenofovir/emtricitabine) combination pill is now the most frequently prescribed medication for patients starting first-line antiretroviral therapy. The Kaletra pill contains the PI lopinavir plus a boosting dose of ritonavir.

The newest fixed-dose combination, approved on July 12, is Atripla, a three-in-one coformulation containing Gilead Science's tenofovir (Viread) and emtricitabine (Emtriva) plus Bristol-Myers Squibb's efavirenz (Sustiva). Atripla is the first-ever complete one-pill, once-daily antiretroviral regimen.

In wealthy countries, the development of coformulations has been limited by patent issues. Typically, brand-name combination pills contain drugs manufactured by a single pharmaceutical company. For example, Abbott Laboratories holds the patent on ritonavir, allowing the company to produce the Kaletra coformulation, while PIs produced by other manufacturers must be taken with a separate dose of ritonavir.

Some foreign generic drug-makers have produced fixed-dose combination pills containing agents patented by multiple companies—for example, Triomune, manufactured by Cipla in India, contains Glaxo's 3TC, Bristol-Myers Squibb's d4T, and Boehringer Ingelheim's nevirapine. The FDA recently approved a three-in-one, twice-daily AZT/3TC/nevirapine coformulation, produced by India's Aurobindo, for use in developing countries. The Gilead/Bristol-Myers Squibb effort to develop Atripla is the first successful cooperative venture among drug manufacturers in the HIV field, and the first multiclass coformulation available in the United States.

Once-Daily Dosing

While the approval of Atripla has generated considerable excitement, it was already possible to put together complete regimens that require as few as two to four pills once daily (see sidebar on page 23). Once-daily dosing is feasible if a drug has a long enough half-life (the amount of time it takes for the concentration of an agent to be reduced by one-half in the body) to remain potent for 24 hours.

NRTIs were the first once-daily drugs to come on the market. Some agents that were originally prescribed twice daily, such as 3TC and abacavir, were later shown to work equally well when taken once daily. The NNRTI efavirenz may also be taken once per day. Atazanavir (Reyataz) was the first approved once-daily PI, and boosting with ritonavir also allows some older PIs to be taken once per day. With some drugs, however, once-daily dosing is recommended only for people starting antiretroviral therapy for the first time, while treatment-experienced patients should take them more often.

In Boyle's survey, more than 80% of respondents expressed interest in a once-daily regimen. Among the reasons they gave for preferring less frequent dosing: getting their pill-taking out of the way so they don't have to think about HIV for the rest of the day; concern about forgetting doses later in the day; ease of fitting pills into their daily schedule; and greater privacy—for example, not having to take drugs at work.

Studies have shown that such self-reported preferences translate into improved adherence and more effective therapy. For example, at the 2005 Interscience Conference on Antimicrobal Agents and Chemotherapy (ICAAC), Edwin DeJesus, MD, and colleagues presented preliminary data from COMET (Combination of Efavirenz and Truvada), a Phase IV post-marketing study that included 411 patients with suppressed HIV who switched from

Fixed-Dose Antiretroviral Coformulations

Combination	Contains	Approved
Combivir	AZT/3TC	1997
Trizivir	AZT/3TC/abacavir	2000
Kaletra	lopinavir/ritonavir	2000
Epzicom (Kivexa)	3TC/abacavir	2004
Truvada	tenofovir/emtricitabine	2004
Atripla	tenofovir/emtricitabine/efavirenz	2006

Once-Daily Antiretroviral Drugs

Drug	Class
3TC (Epivir)	NRTI
abacavir (Ziagen)	NRTI
ddI (Videx EC)	NRTI
emtricitabine (Emtriva)	NRTI
tenofovir (Viread)	NRTI
3TC/abacavir (Epzicom)	NRTI coformulation
tenofovir/emtricitabine (Truvada)	NRTI coformulation
efavirenz (Sustiva)	NNRTI
tenofovir/emtricitabine/efavirenz (Atripla)	NRTI/NNRTI coformulation
atazanavir (Reyataz)	PI
fosamprenavir (Lexiva); boosted	PI
lopinavir/ritonavir (Kaletra); treatment-naive only	PI coformulation

Some once-daily regimens	Pill burden
Atripla	one pill
efavirenz plus Truvada	two pills
efavirenz plus ddI plus 3TC	three pills
atazanavir plus ritonavir plus Truvada	four pills

twice-daily Combivir to once-daily Truvada while remaining on efavirenz; 86% said they switched for regimen simplification, 6% hoped for reduced toxicity, and 8% cited both reasons. After 24 weeks, significantly more patients who switched maintained virological suppression; participants also experienced fewer side effects and reported increased convenience and greater overall satisfaction with the Truvada regimen.

In Abbott's open-label study M02-418, presented by Richard Rode, PhD, and colleagues at the same conference, 190 treatment-naive participants were randomly assigned to receive either 800/200 mg once-daily or 400/100 mg twice-daily lopinavir/ritonavir plus once-daily tenofovir and emtricitabine. After 96 weeks, efficacy was similar in both groups. However, patients in the once-daily arm achieved better adherence, assessed using pill bottles with electronic monitors; furthermore, the difference in adherence widened over time, falling from 97% to 93% in the once-daily arm, but from 92% to 81% in the twice-daily arm.

Data from another PI switch study were presented by Jose Gatell, MD, at the 2005 European AIDS Clinical Society (EACS) conference. In the open-label Phase III SWAN study, 419 participants with undetectable viral load were randomly assigned to remain on their current boosted or unboosted PI-based regimen—which contained at least three pills taken twice daily or more—or switch to a once-daily atazanavir-based regimen. After 48 weeks, 16% in the continued regimen arm experienced virological rebound, compared with 7% in the atazanavir switch arm.

Overall, these and other studies suggest that switching to once-daily regimens—especially those with reduced side effects—improves adherence, resulting in higher rates of treatment success. The drawback to once-daily dosing is that near-perfect adherence and correct timing (taking medications at the same time every day) becomes even more important. Once-daily drugs are typically less "forgiving" because the virus potentially has a whole day, rather than 8–12 hours, to begin replicating if a dose is missed.

Protease Inhibitor Boosting

One of the most beneficial advances in antiretroviral therapy was the realization that small doses of ritonavir could be used to boost blood levels of other PIs. This approach takes advantage of ritonavir's action as an inhibitor of the CYP3A4 enzyme, which processes many drugs

in the liver. This causes ritonavir to interact with several classes of medications—sometimes dangerously raising their levels in the body—but it also means co-administration of ritonavir can raise blood levels of other PIs, conferring increased potency and allowing fewer pills to be taken less often. For example, unboosted indinavir required four capsules three times daily on an empty stomach, while boosted indinavir can be taken two pills at a time twice daily with or without food.

Numerous studies have demonstrated the advantages of boosted PI regimens. In the SWAN study, for example, most cases of treatment failure occurred among patients taking unboosted PIs. In a meta-analysis of 64 studies with more than 10,000 treatment-naive patients taking nearly 100 different HAART regimens, John Bartlett, MD, and colleagues found that virological suppression was achieved more often with triple combinations that included a boosted PI (64%) or an NNRTI (63%) than with regimens that included an unboosted PI (44%) or three NRTIs (51%).

Managing Metabolic Problems

The quest to manage metabolic abnormalities such as lipodystrophy, elevated LDL ("bad") cholesterol, and elevated triglycerides has driven many switch studies. Although research to date has produced conflicting data about whether HIV positive people who experience visceral fat accumulation and/or elevated blood lipid levels while taking antiretroviral therapy have a greater likelihood of developing cardiovascular disease, most patients and providers would prefer to minimize the risk.

However, switching to a protease-sparing regimen may not produce as rapid an improvement as lipid-lowering medications. At the 2005 Conference on Retroviruses and Opportunistic Infections, Leonardo Calza, MD, and colleagues reported data from a study in which 142 patients on stable HAART with well-controlled HIV were randomly assigned to either switch from their PI-based regimen to nevirapine or efavirenz, or to stay on their current regimen and add pravastatin (Pravachol) or bezafibrate (not available in the U.S.). After 12 months, triglyceride reductions in the NNRTI arms (25% for nevirapine, 9% for efavirenz) were significantly lower than those seen in the adjunct therapy arms (41% for pravastatin, 46% for bezafibrate); the corresponding reductions in total cholesterol were 27% and 10% for the two NNRTIs, and 46% and 38% for the lipid-lowering drugs.

Even if switching does not bring blood lipids down to normal levels, any decrease is likely to be beneficial in terms of reducing cardiovascular risk, and may decrease the required dose of lipid-lowering medications. Yet while switching regimens and adding adjunct medications can help manage metabolic side effects, it is best to avoid the most problematic drugs and combinations from the outset, if possible, since it is often easier to prevent these conditions than to fix them later.

Protease-Sparing Regimens

The most straightforward method of addressing metabolic toxicities is to stop the offending drug(s). Because most PIs are associated with metabolic abnormalities, researchers began exploring "protease-sparing" regimens consisting of either an NNRTI plus at least two NRTIs or NRTI-only combinations. Overall, NNRTI-based regimens perform about as well as boosted PI-based regimens with fewer toxicities; however, individuals taking NNRTIs with suboptimal adherence appear to develop resistance more rapidly than those taking PIs.

In the July 1, 2001 issue of *JAIDS*, L. Ruiz and colleagues reported data from a prospective open-label simplification study in Spain in which 106 patients with lipodystrophy and suppressed HIV were randomly assigned to either remain on their current PI or switch to nevirapine. After 48 weeks, similar proportions (72% and 74%, respectively) maintained undetectable viral load, and CD4 cell counts increased in both arms. Total cholesterol and triglyceride levels decreased in the switch arm, but were not significantly different at the end of the study; there also were no significant differences in body shape changes. Nevertheless, participants in the switch arm reported higher quality of life, in part due to the simpler dosing schedule.

More recently, in the French ALIZE-ANRS 099 trial, reported in the March 15, 2005 *Journal of Infectious Diseases* and presented by Jean-Michel Molina, MD, and colleagues at the 2005 ICAAC, 355 patients with well-controlled HIV were randomly assigned to either continue their current PI-based regimen or switch to a simplified once-daily combination of ddI, emtricitabine, and efavirenz. After 48 weeks, both regimens similarly suppressed HIV (88% vs 91%, respectively); after 36 months, 95% of patients in the protease-sparing arm still had viral loads below 400 copies/mL.

All-NRTI Regimens

Several studies have explored switching from PI- or NNRTI-based regimens to ones that contain only NRTIs. This may be done because an individual has already developed resistance to NNRTIs or in order to preserve that class for later use. While such studies typically find that patients switching to NRTI-only regimens experience improvement in blood lipid profiles, data are mixed in terms of virological efficacy.

Some individuals evidently can do well on NRTI-only combinations. In the open-label TRIZAL study, reported by Christine Katlama, MD,

and colleagues in the August 15, 2003 issue of *AIDS,* 40 participants with well-controlled HIV were randomly assigned to continue their NNRTI-based combination or switch to an all-NRTI regimen using the Trizivir (AZT/3TC/abacavir) combination pill. After 48 weeks, virological suppression was similar in the two arms, but total cholesterol levels improved significantly in the switch group.

Esteban Martinez, MD, and colleagues reported 12-month results from the Nevirapine, Efavirenz, Abacavir (NEFA) trial in the September 11, 2003 *New England Journal of Medicine* (*NEJM*) and presented the final 36-month data at this year's Retrovirus conference. In this simplification study, 460 participants with well-controlled HIV on stable regimens containing a PI plus at least two NRTIs were randomly assigned to replace the PI with nevirapine, efavirenz, or abacavir. Patients who switched to abacavir were more likely to experience virological failure, progression to AIDS, or death than those who substituted nevirapine or efavirenz (23%, 11%, and 15%, respectively). But adverse events leading to discontinuation were more common in the nevirapine and efavirenz arms compared with the abacavir arm (19%, 25%, 9%, respectively), so overall treatment success rates were similar.

Certain individuals require the more potent activity of an NNRTI or PI, especially those with higher HIV viral loads, relatively more treatment experience, and a history of prior suboptimal therapy. Recall that in Bartlett's 2005 meta-analysis, regimens that included a boosted PI (64%) or an NNRTI (63%) suppressed HIV better than those containing three NRTIs (51%). The ACTG 5095 study, reported by Roy Gulick, MD, and colleagues in the April 29, 2004 *NEJM,* found that even among treatment-naive patients, the AZT/3TC/abacavir combination was less effective than efavirenz-containing regimens.

A study by Alessandro Cozzi-Lepri and colleagues published in the July 1, 2006 *Journal of Infectious Diseases* showed that individuals taking an all-NRTI regimen containing abacavir instead of an NNRTI or PI were 85% more likely to experience virological rebound, even if their viral load was undetectable when they started this regimen; the authors suggested that it may be prudent for such patients to switch to a more potent combination, even if their viral load is currently suppressed.

Studies have also shown that regimens combining ddI plus tenofovir may lead to early virological failure and immunological decline. Current U.S. treatment guidelines list AZT/3TC/abacavir as an alternative regimen only if PI- or NNRTI-based regimens "cannot or should not be used," and caution against the use of NRTI-only regimens that contain tenofovir.

Some research indicates that, far from correcting metabolic abnormalities, some NRTIs contribute to the problem; the thymidine analogs—AZT and d4T—are most commonly implicated. In the COMET study, patients who switched from Combivir to Truvada while remaining on efavirenz experienced reduced LDL cholesterol and triglyceride levels. Likewise, the RAVE study, described below, found that switching from d4T to tenofovir improved lipid levels.

Switching to Atazanavir

For treatment-experienced patients who need a more potent regimen, substituting the newer PI atazanavir may be a good option. Atazanavir is less likely than other drugs in its class to cause elevated LDL cholesterol and triglycerides; some studies suggest it may also raise HDL ("good") cholesterol, which is protective against cardiovascular disease. In the SWAN study, patients who switched from regimens that included other boosted or unboosted PIs to atazanavir experienced significant reductions in total cholesterol, LDL cholesterol, and triglyceride levels.

While SWAN was primarily intended to assess virological efficacy, the AI424067 trial was designed as a switch study with the aim of managing hyperlipidemia in patients with well-controlled HIV; Michael Sension, MD, and colleagues presented preliminary data at the 2005 Retrovirus conference. A total of 246 participants on stable HAART with undetectable viral load and elevated LDL cholesterol were randomly assigned to either continue their current PI-based regimen or switch to unboosted atazanavir while remaining on the same NRTIs. After 12 weeks, patients in the atazanavir arm maintained virological suppression while experiencing a 35% decrease in triglycerides, a 15% reduction in LDL cholesterol, an 18% drop in total cholesterol, and increased HDL cholesterol (they also had significantly higher bilirubin levels).

Importantly, since atazanavir, fosamprenavir, and the newest PI, darunavir (Prezista), were approved more recently, their long-term side effects in terms of body shape changes are not yet known. Another fairly new PI, tipranavir (Aptivus), has been linked with lipodystrophy even with relatively short-term use, so it is not a good candidate for switching to minimize metabolic toxicity.

Managing Mitochondrial Toxicity

While body shape "redistribution" associated with antiretroviral therapy was initially blamed on PIs, it later became apparent that central fat accumulation and peripheral fat loss (lipoatrophy) are two distinct phenomena, and that the latter is linked with certain NRTIs.

Many researchers also came to suspect that lipoatrophy and other NRTI-associated side effects—including lactic acidosis, enlarged fatty liver (hepatomegaly with steatosis), peripheral

neuropathy, and pancreatitis—were manifestations of drug-induced damage to the mitochondria, energy-producing structures within the cells.

Switching NRTIs

Much research suggests that mitochondrial toxicity is most strongly associated with the dideoxynucleotides, or "d drugs": d4T, ddI, and the now-discontinued ddC (zalcitabine, Hivid). Other experts believe that the thymidine analogs—d4T and AZT—are the primary culprits. Either way, d4T is clearly problematic, and the d4T/ddI combination even more so. For this reason, current U.S. treatment guidelines now recommend against using these two drugs together.

Several studies have shown that switching from d4T and/or ddI to other NRTIs leads to gradual restoration of mitochondrial DNA in cells and improvements in hyperlactatemia (elevated lactic acid in the blood), lipoatrophy, and peripheral neuropathy. As noted above, switching from AZT or d4T may also improve blood lipid profiles.

Graeme Moyle, MD, and colleagues presented data at both the 2005 Retrovirus conference and ICAAC from the RAVE study, in which more than 100 individuals with moderate-to-severe lipoatrophy were randomly assigned to switch from d4T or AZT to abacavir or tenofovir. After 48 weeks, DEXA and computed tomography (CT) scans showed that those who switched experienced modest gains in subcutaneous limb fat. Tenofovir was associated with fewer overall side effects and modest reductions in triglycerides and total and LDL cholesterol; lipid decreases were mainly seen among patients who switched from d4T.

In the January 15, 2004 issue of *Clinical Infectious Diseases,* Grace McComsey, MD, and colleagues reported data from the open-label TARHEEL study, in which 118 patients with lipoatrophy and well-controlled HIV switched from d4T to either AZT or abacavir. After 48 weeks, DEXA scans showed increases in arm fat (median 35%), leg fat (12%), and trunk fat (18%) in the patients who switched; participants also reported that they noticed fat gains in their limbs, buttocks, and face.

Likewise, Esteban Ribera and colleagues reported at the 2005 Retrovirus conference that in the Spanish LIPOTEST study, in which 53 subjects with well-controlled HIV and lipoatrophy switched from d4T to tenofovir, facial fat thickness increased significantly, triglycerides decreased significantly, and cholesterol decreased slightly after 18 months; in addition, lactic acid levels fell significantly and mitochondrial DNA in peripheral blood mononuclear cells showed a slight increase.

Some NRTI side effects, such as peripheral neuropathy, resolve relatively quickly after the offending drugs are stopped, but lipoatrophy improves very slowly. In the MITOX study by Andrew Carr, MD, and colleagues, reported in the July 10, 2002 *Journal of the American Medical Association,* 111 patients with moderate to severe lipoatrophy were randomly assigned to continue their current regimen or switch from d4T or AZT to abacavir. Patients who switched experienced a significant increase in subcutaneous limb fat as determined by DEXA and CT scans, although the change was too small for them to notice. The authors concluded that at the rate of increase observed, fat loss "may take years to resolve." It is not yet clear whether some degree of peripheral neuropathy, lipoatrophy, and other manifestations of mitochondrial damage may be irreversible.

NRTI-Sparing Regimens

While some researchers have studied NRTI-only regimens as a strategy for avoiding PI-related side effects, others have taken the opposite tack, testing regimens that contain no NRTIs.

At the 2005 Retrovirus conference, Margaret Fischl, MD, and colleagues presented data from ACTG 5116, an open-label simplification study that included 236 individuals with well-controlled HIV (although they previously had advanced disease) and no evidence of drug resistance. Participants were randomly assigned to switch from their initial three- or four-drug PI- or NNRTI-based HAART regimen to either efavirenz plus two NRTIs (78% AZT/3TC, 19% ddI/d4T) or an NRTI-sparing regimen of efavirenz plus lopinavir/ritonavir. After 110 weeks, 66% of subjects who switched to lopinavir/ritonavir had viral loads below 50 copies/mL, compared with 74% who stayed on NRTI-containing regimens. Participants in the NRTI-sparing arm showed a trend toward reduced virological suppression and were three times more likely to discontinue therapy due to adverse events, mainly triglyceride elevation.

These results suggest that NRTI-containing regimens are superior, but toxicity profiles tell a somewhat different story. Pablo Tebas, MD, and colleagues presented data from ACTG 5125s, a substudy of ACTG 5116, at the same conference. In an analysis of 62 patients, limb fat increased significantly in the NRTI-sparing arm after 48 weeks, but decreased further in those who stayed on NRTIs. Among a subset of 46 subjects followed for an average of 104 weeks, those in the NRTI-sparing arm continued to gain limb fat, while those in the NRTI-containing arm continued to lose it.

Results of another NRTI-sparing trial were presented at the same meeting by Robert Murphy, MD, and colleagues. In the ACTG 5110 study, 101 participants with lipoatrophy and well-controlled HIV were randomly assigned to either replace the thymidine analog in their regimen (24% AZT, 76% d4T) with abacavir, or else switch to an NRTI-free regimen of lopinavir/ritonavir plus nevirapine. After 24 weeks, subjects in both arms

maintained virological suppression. DEXA and CT scans showed that patients in both the thymidine-sparing and NRTI-free arms experienced increased subcutaneous abdominal fat and decreased visceral abdominal fat; however, thigh fat increased only in the NRTI-free arm.

These data suggest that decisions about whether to switch to an NRTI-sparing regimen should be made on an individualized basis, taking into account body weight, fat distribution, and cardiovascular risk factors.

The New Monotherapy

In an attempt to simplify antiretroviral regimens as much as possible, a few researchers have taken a second look at "monotherapy"—which in this context refers to a single PI boosted with a small dose of ritonavir—either as first-line treatment for selected patients or as a maintenance strategy once virological control has been established.

At the XV International AIDS Conference in 2004, Joseph Gathe, MD, presented a case series of 30 patients at an inner-city clinic who were treated with lopinavir/ritonavir alone in an effort to improve adherence and reduce the cost of therapy; after 48 weeks, 67% had viral loads below 400 copies/mL.

In the open-label OK (Only Kaletra) pilot study, reported by Jose Arribas, MD, and colleagues in the November 1, 2005 issue of *JAIDS,* 42 patients with undetectable viral load were randomly assigned to either continue on lopinavir/ritonavir plus two NRTIs, or to stop taking the NRTIs. After 48 weeks, 81% of patients in the monotherapy arm maintained undetectable viral loads, compared with 95% in the triple-therapy arm (a non-significant difference). There was no evidence of lopinavir/ritonavir resistance and patients regained virological control once their previous NRTIs were reintroduced.

At the 2006 British HIV Association (BHIVA) conference this March, Laura Waters, MD, and colleagues presented an analysis of data from 35 heavily treatment-experienced patients with a median viral load of nearly 55,000 copies/mL and a median CD4 count of about 250 cells/mm^3 who switched from their current HAART regimens to lopinavir/ritonavir monotherapy outside a clinical trial setting. After 12 months, half achieved undetectable HIV RNA and 73% experienced at least a 1-log reduction in viral load. During the one-year follow-up period, eight patients switched again, mostly due to virological failure or immunological decline.

At the XV International HIV Drug Resistance Workshop in June, however, two teams of researchers from Abbott Laboratories reported that some clinical trial participants developed resistance while using lopinavir/ritonavir monotherapy either as first-line treatment or as part of a simplified maintenance regimen; detailed data are expected to be presented later this year.

Susan Swindells, MD, and colleagues presented data from a study of boosted atazanavir monotherapy at this year's Retrovirus conference. The 36 patients in the open-label ACTG 5201 pilot study had no history of virological failure and had undetectable viral loads while taking regimens consisting of a PI plus two NRTIs. Subjects first switched to ritonavir-boosted atazanavir plus two NRTIs for six weeks, then discontinued the NRTIs if they still had undetectable viral load. In a planned analysis 24 weeks after NRTI discontinuation, three out of 33 patients (9%) experienced virological failure (two had no detectable atazanavir in their blood, suggesting poor adherence). No evidence of genotypic resistance to atazanavir was observed, and two patients regained virological control after they received adherence counseling or their previous NRTIs were reintroduced.

While results from studies to date appear promising, monotherapy remains an experimental—and controversial—switch strategy. The risks and benefits of this approach are discussed in "Revisiting Monotherapy: Heresy or Revised Orthodoxy?" in the Winter 2006 issue of *BETA*.

Sequencing

Along with new agents and class-sparing regimens, a better understanding of the natural history of HIV disease and how drugs work against the virus has led to the evolution of improved treatment strategies. One of these is sequencing, which involves thinking ahead when starting a new regimen about what might be used next should the current combination fail and, if possible, preserving future treatment options. Both the U.S. and European HIV treatment guidelines recognize that sequencing is an important factor to consider when choosing therapy.

At this year's BHIVA meeting, S. Mandilia and colleagues reported on an analysis of more than 22,000 individuals seen at 27 HIV clinics in the United Kingdom. Between 1996—the beginning of the HAART era—and 2002, patients stayed on their first combination regimen for an average of 6.7 years. The average time on the second regimen was 4.3 years, and the third regimen lasted about the same duration, 4.2 years. About 40% of patients changed their first-line regimen due to virological failure, immunological decline, or clinical disease progression, as was the case for about 50% of those changing second or third regimens. This suggests that at least half of treatment discontinuations are due to factors other than inadequate potency, such as intolerable side effects or difficult dosing schedules.

While an expanded armamentarium of drugs has increased the prospects for finding an appropriate regimen to switch to in case of treatment failure or lack of tolerance, it remains important to select the best possible first-line regimen, because it

is easier to fully suppress HIV when a person is not yet resistant to any drugs.

It is difficult to make direct comparisons among different regimen sequences—in part because antiretroviral therapy evolves so rapidly—but it is clear that advances in therapy have benefited people with HIV. According to a retrospective observational study of nearly 4000 patients by Fiona Lampe, PhD, and colleagues, published in the March 13, 2006 *Archives of Internal Medicine,* the rate of treatment failure with initial regimens fell by more than half between 1996 and 2002, with virological failure rates dropping from 28% to 12%. The authors attributed this increasing success to better drugs, a change in emphasis towards maximal viral suppression, and a general increase in adherence thanks to "accumulating clinical experience, more effective clinical management, and perhaps an increase in patients' knowledge about treatment."

In another "big picture" analysis, Bartlett and colleagues reported in the March 2006 issue of *JAIDS* the results of an overview of 15 randomized clinical trials assessing genotypic resistance after virological failure during first-line therapy. The combined data showed that virological success rates were highest when starting with boosted PI regimens (55%–79% success) or NNRTI-based regimens (51%–76% success) that also contained NRTIs. Patients who experienced treatment failure while taking boosted PIs developed drug resistance more slowly—and thus retained more future treatment options—than individuals on failing NNRTI-based regimens.

Reasons Not to Switch

While advances in antiretroviral therapy have consistently produced regimens that are more potent, less toxic, and generally easier to live with, this does not suggest that everyone should switch each time something new emerges from the pipeline. There is considerable wisdom to the "if it ain't broke, don't fix it" principle, which was the major reason Boyle's survey respondents gave for sticking with their current regimens.

If an individual's existing regimen keeps his or her viral load fully suppressed and the CD4 cell count within a safe range, does not cause unmanageable side effects, and is easy to adhere to, there's no need to change therapy. And indeed, switching does not always prove advantageous. According to Boyle, "there's no guarantee that virological breakthrough or immune failure won't occur" with a new regimen. And many patients have switched to a supposedly superior regimen, only to develop side effects they find harder to live with. In addition, there's always a risk when switching to the newest drugs that rare or long-term toxicities or unforeseen drug interactions that were not detected in clinical trials could crop up later—as was the case with PI-related lipodystrophy.

Mitsuyasu says it's important that patients and physicians discuss the reason for a proposed switch. He is likely to agree that a switch is a good idea if "the new drug is cheaper, easier to access, less cumbersome to use, or has fewer side effects," provided there are "no contraindications such as adverse interactions with other medications the patient is taking, or the patient is likely to be resistant due to prior therapy, or is likely to have more rather than fewer side effects than with the old drugs."

Some people with HIV—and some physicians—are reluctant to switch to simpler and more tolerable regimens for fear that this will limit or "use up" future treatment options. For example, some believe it's preferable to start with an NNRTI-based regimen in order to preserve the more potent PI class for later. However, as Bartlett's 2006 analysis illustrates, the general rule is that the better HIV is controlled at the outset, the longer a regimen will last before treatment failure occurs. Furthermore, the drug development pipeline is relatively full, and there is a good chance that new agents that work by novel mechanisms will become available within the next few years.

Conclusion

With the array of antiretroviral agents available today, many people—even those with prior treatment experience—can find a regimen that suppresses HIV, does not cause unmanageable side effects, and is fairly easy to fit into a daily schedule. For others, the available medications still leave much to be desired in terms of potency, toxicity, and simplicity. Switching to more convenient reformulations of drugs in a current regimen, or fixed-dose combination pills that contain the same agents, is a nearly risk-free strategy. Today, well-considered regimen switches are more attractive than ever, since a proposed alternative approach to alleviating toxicity and "treatment fatigue"—structured treatment interruptions or "drug holidays"—increasingly appears to be a risky strategy (see "Structured Treatment Interruptions: After SMART" on page 30).

Once patients and physicians decide that a switch is the way to go, it is important to ensure that it's the right one. Here, prior treatment history and drug-resistance testing can help determine whether a new medication is likely to work well for a specific person. Other individual characteristics, including cardiovascular risk factors and increased susceptibility to other toxicities, should also be taken into account. Once again, no antiretroviral regimen is "one size fits all," so it is important for HIV positive people to tell their providers which features of a regimen they find most desirable and most bothersome.

After making a switch, regular monitoring is crucial, both to ensure that HIV remains under control and CD4 counts are stable or rising, and

to check for toxicities such as liver inflammation, elevated blood lipids, and blood cell deficiencies.

If a switch proves less than satisfactory, it is often possible to revert back to an older regimen. This is particularly true if the change was made to reduce toxicity. If a switch introduces side effects that prove more difficult to tolerate, an individual can usually safely switch back to the previous combination if viral load has remained suppressed. (Note: An exception is abacavir hypersensitivity; if abacavir was stopped for this reason, it should not be restarted, as this could cause a life-threatening reaction.) It may also be possible to regain lost virological control by re-intensifying a simplified regimen, especially if using a boosted PI.

If an individual's current regimen does not measure up, a switch could be the key to improved quality of life. If future advances in antiretroviral therapy continue at the same pace as they have in the past decade, people with HIV will soon have even more options for constructing regimens that provide an optimal balance of efficacy, safety, tolerability, and ease of use.

Liz Highleyman is a freelance medical writer and editor based in San Francisco.

Selected Sources

Bartlett, J.A. and others. An updated meta-analysis of triple combination therapy in antretroviral-naive HIV-infected adults. 12th Conference on Retroviruses and Opportunistic Infections (CROI). Boston. February 22–25, 2006. Abstract 586.

Bartlett, J.A. and others. Minimizing resistance consequences after virologic failure on initial combination therapy: a systematic overview. *Journal of Acquired Immune Deficiency Syndromes* 41(3):323–31. March 2006.

Boyle, B. and others. Patients prefer simplified and well-tolerated antiretroviral regimens. XV International AIDS Conference. Bangkok. July 11–16, 2004. Abstract 5815.

Calza, L. and others. Comparison between switching therapy from protease inhibitors to an NNRTI and lipid-lowering therapy with pravastatin or bezafibrate for the management of HAART-related dyslipidemia. 12th CROI. Abstract 859.

Carr, A. and others. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. *Journal of the American Medical Association* 288(2):207–15. July 10, 2002.

Cozzie-Lepri, A. and others. A comparison between abacavir and efavirenz as the third drug used in combination with a background therapy regimen of 2 nucleoside reverse-transcriptase inhibitors in patients with initially suppressed viral loads. *Journal of Infectious Diseases* 194(1):20–28. July 1, 2006.

DeJesus, E. and others. Effects of switching from fixed dose zidovudine/lamivudine (CBV) to fixed dose tenofovir DF/emtricitabine (TVD): maintenance of virologic suppression and other benefits. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). Washington, DC. December 16–19, 2005. Abstract H-517.

Fischl, M. and others. Randomized, controlled trial of lopinavir/ritonavir + efavirenz vs efavirenz + 2 nucleoside reverse transcriptase inhibitors following a first suppressive 3- or 4-drug regimen in advanced HIV disease. 12th CROI. Abstract 162

Gatell, J.M. and others. Efficacy and safety of atazanavir (ATV) based HAART in patients switched from a stable boosted/unboosted protease-inhibitor (PI) treatment: the SWAN study. 10th European AIDS Conference (EACS). Dublin. November 17–20, 2005. Abstract PS1/1.

Glass, T.R. and others. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: The Swiss HIV Cohort Study. *Journal of Acquired Immune Deficiency Syndromes* 41(3):385–92. March 2006.

Katlama, C. and others. Comparison of metabolic abnormalities 48 weeks after switching from highly active antiretroviral therapy containing a non-nucleoside reverse transcriptase inhibitor to Trizivir versus continued highly active antiretroviral therapy. *AIDS*.17(12): 1855–56. August 15, 2003.

Lampe, F.C. and others. Changes over time in risks of initial virological failure of combination antiretroviral therapy. *Archives of Internal Medicine* 166(5):521–28. March 13, 2006.

Martinez, E. and others. 3-year final results of a simplification trial with nevirapine, efavirenz, or abacavir as substitutes of protease inhibitors in patients with HIV infection (the NEFA Study). 13th CROI. Denver. February 5–8, 2006. Abstract 521.

McComsey, G.A. and others. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clinical Infectious Diseases* 38(2):263–70. January 15, 2004.

Molina, J.-M. and others. Simplification therapy with once-daily emtricitabine, didanosine, and efavirenz in HIV-1-infected adults with viral suppression receiving a protease inhibitor-based regimen: a randomized trial. *Journal of Infectious Diseases* 191(6):830–39. March 15, 2005.

Murphy, R. and others. Switching to a thymidine analog-sparing or a nucleoside-sparing regimen improves lipoatrophy: 24-week results of a prospective randomized clinical trial, AACTG 5110. 12th CROI. Abstract 45LB.

Ribera, E. and others. Improvement of subcutaneous fat, lipid profile, and parameters of mitochondrial toxicity in patients with peripheral lipoatrophy when stavudine is switched to tenofovir. The LIPOTEST Study. 12th CROI. Abstract 860.

Sension, M. and others. AI424067: improvement in lipid profiles after 12 weeks of switching to atazanavir from boosted or unboosted protease inhibitors in patients with no previous PI virologic failure and hyperlipidemia at baseline. 12th CROI. Abstract 858.

Swindells, S. and others. A prospective, open-label, pilot trial of regimen simplification to atazanavir/ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression (ACTG 5201). 13th CROI. Abstract 108LB.

Waters, L. and others. Kaletra monotherapy—a real-life experience. *HIV Medicine* 7 (supplement 1):13. April 2006. Abstract P9.

SAN FRANCISCO AIDS FOUNDATION

BILINGUAL HOTLINE

(English/Spanish)
415-863-AIDS

Toll-Free in California
800-367-AIDS

The California AIDS Hotline volunteers provide support and confidential, comprehensive information about HIV transmission, test sites, prevention, and treatment in English and Spanish. A TDD line is also available for the hearing-impaired. The Hotline operates from 9:00 am to 5:00 pm Monday through Friday, and Tuesdays 9:00 am to 9:00 pm.

In California, call toll-free
800-367-2437
In San Francisco or out of state, call
415-863-2437
The TDD line in California is
888-225-2437