New treatment options present people with HIV disease with exciting opportunities as well as unanticipated challenges. Recent data support the commonly held belief that strict adherence is crucial in order to achieve long-term viral suppression and, presumably, durable clinical effectiveness. Other studies suggest that viral eradication and a cure are most likely unattainable with the currently available classes of antivirals. While data are limited about the long-term efficacy of treatment initiated at any stage of HIV infection—including very early infection—many researchers and providers believe that patients with acute HIV infection should initiate antiviral therapy as soon as possible. Finally, HIV antiviral drugs have significant short-term, and unknown potentially long-term, side effects. Complex treatment decisions must therefore be driven by personal preference, common sense, rapidly accumulating data, changes in community prescribing patterns, and, perhaps most important, a comfort with uncertainty. This article reviews the factors clients might consider when making treatment decisions, focusing on issues of adherence and duration of effect.

Deciding to Initiate Therapy: Efficacy

The decision to initiate therapy should be based on an understanding of the risks (for example, toxicity and effects on lifestyle) and benefits (for example, improved survival and quality of life) of a specific treatment option. Published guidelines provide a useful framework for considering these risks and benefits, but each individual will value and weigh these issues in unique ways. The guidelines regarding the initiation of antiviral therapy rely on increasing data that suggest that there is virologic (decreased viral load), immunologic (increased CD4+ cell counts), and morbidity and mortality benefits associated with antiviral combinations that include two nucleoside analogues and a potent protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI). The duration of this positive effect, however, is not known.

Efficacy can be evaluated on several levels. For patients with early HIV infection, long-term efficacy will be most important. For those with advanced disease, shorter-term goals may be more relevant. For most people, improved quality of life and extended life span are the explicit hopes. However, for many others, an unspoken goal may be total viral eradication and cure.

Recent data from three different laboratories show that even with prolonged suppression of detectable virus in the blood, there remain latently infected resting CD4+ cells (non-replicating; not producing virus). These cells, when activated, are capable of producing infectious virus, thus serving as a reservoir of infection even in those who have had no detectable virus in their blood for up to 30 months. The bottom line is that people using currently available combinations will likely need to continue treatment indefinitely in order to keep the virus in check. While cure with the currently available drugs is not a realistic goal, it is still possible that people will live long enough to try newer drugs that may eventually achieve this goal.

Toxicity, Side Effects and Quality of Life

Patients also experience medication toxicities in unique ways. Considering the side effect profile of a given combination...
Editorial: Bucking the Norm
Robert Marks, Editor

The newest AIDS buzzwords are "treatment adherence." Everywhere you listen people are talking about the hope for viral eradication and the fear of viral resistance, and the bottom line is always adherence. The media does pay lip service to the idea that combination therapy is a pill-popping challenge. But, as it becomes clear that strict adherence is essential, it becomes clearer still that strict or even consistent adherence is not merely a challenge, it is abnormal.

I was talking to Gail, the mother of a woman with HIV about her daughter's reactions to her drug regimen and the difficulties of both tolerating side effects and adhering perfectly to her treatment schedule. The day before, someone had told me about new data and anecdotal evidence that suggest that for some people with HIV, missing even a few doses can result in rapid increases in viral load and drug resistance.

When I told Gail about these studies, her immediate reaction was anger. Gail has been an active advocate for HIV funding, going to Washington each year to lobby Congress, and her otherwise mild manner becomes animated when she talks about AIDS.

The press, she said, would have a field day with this news: they would blame people with HIV for not adhering and label them failures. But how many of those reporters, or the doctors for that matter, were getting up in the wee hours to pop a dose of Crizivan, she demanded? I replied, wait! (her passion required an exclamation to interrupt): If the study findings stood the test of time, wouldn't it be important for people on these drug combinations to know that only a few missed doses might lead to resistance?

Dose-Difficult Experiences

Gail eventually agreed that the information itself was not the problem; it was the tired perception that somehow people who become infected, or fail to adhere to their regimens, or choose not to try the regimens at all somehow deserve their fate. It's not a position that most people will voice when talking about an individual—a friend, a son, a partner—but it's a simple one to express when talking about those "other" people who, if they just took their pills, could "get on with their lives."

In this month's issue of FOCUS, Michelle Roland is particularly effective in presenting the scientific data about drug adherence, the real challenges to adherence posed by everyday living, and the shared responsibility of provider and client to design attainable treatment plans. And in our second article, our anonymous author is poetic in his evocation of "dose-difficult" experiences—too many pills too often—with which we can all empathize, HIV-positive or not.

It's easy to exhort people to be responsible—to take their meds and be thankful for the opportunities they have—easier still to blame them for the opportunities they might seem to be squandering. But, think about living with HIV and dealing with all the challenges that we've written about in these pages for the past 13 years, and then add the prospect of popping those pills at all hours without exception for the rest of your life. Doesn't the issue seem to go way beyond the science of treatment adherence?

I hold out hope for a time when the doses are fewer and the consequences of missing one are less dire. Until then, moments of empathy, encouragement, and supportive problem-solving would be more appropriate than the befuddlement or indignation that appear to be the more fashionable response.

References

is important, as the possibility of certain side effects may direct specific treatment choices. For example, the possibility of side effects such as fatigue, nausea, diarrhea, or headache may be unacceptable to some. Still, patients may tolerate common side effects more easily when warned about them in advance.

Some undesirable consequences of highly active antiviral therapy (HAART; that is, the use of potent drug combinations) may, ironically, result from improved immune function. These include: rapidly progressive hepatitis B or C (liver destruction is largely immune mediated) and worsening immune thrombocytopenia purpura (ITP; immune mediated destruction of platelets). Body composition changes, including buffalo humps (fat collections in the upper back) and abnormal fat collections around the torso, as well as a number of endocrinologic changes, including hypertriglyceridemia (elevated lipid subset) and possibly diabetes mellitus, are less well understood.

Some of these side effects can be life-threatening. Others can be disfiguring. The long-term effects of hypertriglyceridemia for example, heart disease or pancreatitis) are unknown, and it is possible that serious long-term side effects may develop for those who live for many years.

Other issues may affect quality of life while taking these antiviral medications.
Patients must be seen and monitored regularly with laboratory studies. They must be especially vigilant not to run out of medications. Those with insurance or AIDS Drug Assistance Program (ADAP) restrictions may leave the pharmacy empty-handed if they attempt to get refills early or if there are paper work problems.

Taking into account an individual's lifestyle is extremely important when recommending a potential combination. Some medications need to be taken with meals while others are only absorbed on an empty stomach. One drug must be refrigerated; the others should not be. Some can be taken three times a day during waking hours, while another must be taken every eight hours.

Although protease inhibitors are generally more potent than the non-nucleoside reverse transcriptase inhibitors, in some cases starting with an NNRTI might be a good choice. In a motivated patient with a history of adherence problems, adherence can be assessed with an NNRTI-containing regimen. The advantage of this approach is that if the patient is not able to adhere to the regimen and develops a detectable viral load, he or she will not have developed protease inhibitor resistance. If the patient is able to stabilize and restart medications in the future, the protease inhibitors will still be an option.

There are even circumstances when using two nucleoside analogues alone might be a reasonable choice. Although destined to "fail" eventually as HIV becomes resistant to the double combination, this approach can slow disease progression and diminish adherence problems and pill burden.

Finally, several once-a-day drugs are currently in clinical trials. For those who are doing relatively well clinically, waiting a few more months for a once-a-day regimen may be a reasonable alternative. Close monitoring of the CD4+ count and viral load is important if patients and providers choose this option.

A Commitment to Adherence

One of the reasons for viral breakthroughs is non-adherence. Because adherence studies are limited at this time, it is not clear how many doses an individual may miss in a given time period before resistance will develop to one or more of the drugs. Such studies have shown an association between an increase in a person's viral load and notes in his or her medical records suggesting non-adherence; a direct relationship between the likelihood of developing a detectable viral load and delays in refilling medications; and an increase in viral load in individuals who have missed three days of medication. Cross-resistance is common within both the protease inhibitors and the NNRTI classes, which means that resistance to one drug is likely to confer resistance to other drugs in that class.

Because taking these medications requires such a tremendous commitment, it's crucial to take the time to be sure the decision to begin treatment is the right one.

Clinicians and patients may attempt to maximize adherence by discussing cues to remember to take medications, anticipating changes in daily patterns, and reviewing medications in the clinic prior to starting them.


More Urgent Treatment Decisions

There are a few situations when starting therapy may be more urgent. Patients with very high or rising viral loads (or both) and falling CD4+ cell counts or rapid disease progression are likely to benefit from prompt initiation of therapy. For a very ill patient with advanced disease, whose only hope of extended life is near-immediate antiviral therapy, the decision to begin must be made in the context of the importance of quality versus quantity of life; and any decision to start therapy should be seen as flexible and reversible.

The other circumstance in which there may be a sense of urgency is for the patient with acute HIV infection, a condition defined by a detectable viral load plus a negative or indeterminant antibody test result. It is not yet known if the very early treatment of acute HIV will achieve the goals of preserving immune function, preventing infection of sanctuary tissue sites such as the central nervous system, lowering viral load and increasing longevity, and achieving long-term viral suppression. Nor is it known if this very early treatment might have the potentially negative consequence of reducing the natural effective immune response to early HIV infection. However, many clinicians and researchers believe that the theoretical reasons to treat people with acute HIV as soon as possible are compelling.

When someone is diagnosed with acute HIV infection, they are likely to feel overwhelmed. They may remember the event that exposed them to HIV and feel guilt, shame, or anger related to that exposure. They will have to deal with the impact of a life-threatening diagnosis. And then they may be presented with a very complex, "high tech" treatment decision, perhaps after never having had any significant experience with the health care system. The language that providers and long-term patients have become familiar with, for example, viral load, T-cell counts, and antivirals, may be completely foreign.

In most other cases, there is no urgency to start medications immediately. It is most important to start them at the right moment for each individual, taking the time to counsel carefully, select the right medications, and provide the necessary resources to maximize adherence.

Conclusions

While the encouraging results of ongoing clinical trials and HAART-related decreases in HIV morbidity suggest that a subset of people with HIV can and are benefiting from treatment advances, recent data on viral latency and the importance of adherence may be discouraging to some clients. Unfortunately, there are no data available to inform people about exactly how adherent they must be.

The task of health care and mental health providers is to help individuals explore all of the complex issues related to the decision to use these medications and to support strict adherence as best we can—without creating an unbearable burden for patients. This counseling must occur in the context of the knowledge that, for now, therapy must be indefinite. Advances in the understanding of the basic science of HIV, while discouraging at the moment, will enable scientists to construct rational approaches to the ongoing control of HIV infection. And, while we know that some cells remain latently infected with HIV, as long as the virus is suppressed by adequate levels of potent antivirals, this latent infection is not likely to pose a problem.

Clearinghouse: HIV Drug Adherence

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Popping Pills for Life
Anonymous

My prized pill collection is shrinking. Two years ago, I maintained the usual arsenal of a person with HIV: a couple antivirals—but hoards of antifungals and antibiotics, a hodgepodge of cold sore compounds, diarrhea fighters, and pills, potions, and creams to combat various itches, rashes, and scratches. Don’t forget about the necessary selection of sedatives and antidepressants to help me cope with it all.

The good news is that these days, I have little need for anything but two nukes (aka nucleoside analogue reverse transcriptase inhibitors) and a protease inhibitor. My labs are good. I feel great. The pressure’s off.

So I go get this new job and it’s really demanding. I’m trying to eat better, sleep more, and work out three times a week. My off-hours are spent dealing with health insurance, taxes, credit ratings, and student loans, along with the simple tasks of washing dishes and buying groceries. If I’m lucky, I have time to go on a date once in awhile. I’m starting to feel like a normal person.

On Being Superman

The problem is that normal people, generally, don’t take a handfull of pills two or three times a day. They don’t have food restrictions. They don’t secretly stash medicine bottles in the refrigerator. You never see a normal guy chewing big chalky tablets, toting pillboxes, or searching his pockets to separate non-nucleoside reverse transcriptase inhibitors NNRTIs from lint balls.

Although I’m swallowing fewer pills in number, the timing and food restrictions for the remaining few is a real ball-buster. Was that take two tablets two hours after eating or take two tablets two hours before eating? Do I take the white ones three times a day and the red and triangle ones only twice a day, or the other way around? Did I even take my pills this morning?

I definitely remember the first time I swallowed my Crixivan. At first it was a breeze. Taking those capsules every eight hours was no problem—for about a week. Then it hit me: a wave of nausea while on the bus headed to work. The scent of coffee gave me the dry heaves. I felt toxic. For two weeks straight, my mouth tasted like I was sucking on a dirty penny. The whites of my eyes became yellows. Finally, I called my doctor and said I can’t take it! I can’t live like this forever.

His response: Your T-cells have doubled and your viral load is below the limits of detection. Who could argue with that payoff? I pressed on, and with time the side effects subsided.

Now if I remember to bring my “candy” with me to work, it’s not the side effects that get me, but the dosing schedule. I’m not about to pop a protease snack in the middle of a staff meeting. Try timing medicine and food restrictions around an eggnog toast at a Thanksgiving dinner. Imagine landing in Peru for work while your luggage (and meds) land in Colombia. I’m a fairly organized guy, but I’m no Superman.

Meanwhile, I keep hearing the buzz about how strict adherence is absolutely, unquestionably, necessary. If I miss just one dose, they say, viral resistance will...
The Adherence Enforcer

On one hand, I know that treatment adherence is important. On the other hand, the everyday boring task of living a productive life is no cakewalk. I get tired. Sometimes I'm lazy. I forget little stuff here and there.

A while back, my doctor asked if I missed doses of medicine. I said "yes." He looked disappointed, wrote something in my chart, and then delivered a four-minute speech that left me with anxiety and guilt.

Now when my doc asks the same question, I think for a moment. Do I want the speech or not? I'm sure I miss a dose about once every two weeks, but I don't admit to it. It's just easier.

An acquaintance of mine pleads the Fifth at every doctor visit. Not only does he miss meds for the usual reasons, but he occasionally takes these extended drug and alcohol getaways. He's a party boy; loves those circuit parties where it's easy to buy underground drugs such as cocaine, Special K, Ecstasy, or crystal (methamphetamine). At some point, the guy heard it's bad to mix HIV meds with street drugs. He opts for the street drugs and lies to his doctor.

Another friend of a friend is this earthy-crunchy type. Wears open-toed sandals. He's big into vitamins, herbs, and visualization. He's always talking about pharmaceutical propaganda, toxic buildup, and the need to "purify" at times. So he takes "drug holidays." He stops all his meds and does herbal tea for several days. He claims it makes him feel better.

I once heard this story about how the executives of a pharmaceutical company were instructed to eat M&Ms three times during a day to simulate the experience of the typical "AIDS patient." Clever. Perhaps a more realistic experience is vomiting in public. Or getting a surprise attack of diarrhea in a car during rush hour.

I'm not demeaning the pharmaceutical companies. To the contrary, they saved my life. Believe me, I'm grateful. In a relatively short period, they brought to market some amazing therapies. I love hearing stories of empty hospital beds. I was granted the good fortune to witness a renaissance in HIV treatment. I thank God every eight hours, one hour before a meal or two hours after. Or as needed.

It's just the whole pill thing. Sometimes it's hard to connect the abstract adherence messages with the indigestion-causing pills in my pocket. It's not impossible, it's just hard.

Somewhere under my stacks of late bills is a shiny brochure about adherence. I glanced at it once: it described something or other about the importance of taking your medicine on time. I really should read it. Sometimes, my pharmacist brings up the topic of adherence: blah, blah, blah. In one ear, out the other. (Between you and me, I'm far more honest with my friends than with my pharmacist or my doctor. In that order.)

The Memory of Dread

I don't talk much with my regular shrink about adherence. He doesn't ask and I don't tell. These days, we talk most about my destructive lifestyle habits, stress levels, and my mom. There was a time when our 50-minute hour was spent dealing with the day-in-day-out, gun-to-your-head terror of dying from AIDS.

Sometimes I remember the dread. That's the best reminder for me to take my pills.

It also helps to sit down about once a week and organize my pills in these cheap color-coded containers. What's left over from the previous week determines if I've been good or bad. Then I stash tablets in matchboxes, small aspirin containers, and packs of cigarettes. I hide them in my gym bag, the glove compartment of my car, and the bottom drawer of my desk at work. I hand over mini-supplies (along with apartment and car keys) to my closest friends. I tend to lock myself out of things.

What works for me, probably won't work for someone else. But it works for me. For now. I'd love to stay and debate the most effective strategy for promoting adherence among patients, but I have to run. It's that time of the day. I have to take a few pills.

Authors

The author of this article, who prefers to remain anonymous, has had HIV for 12 years. He is a firm believer that—through self-education, self-empowerment, and persistence—patients have far more control over their own health than conventional wisdom would predict.

Comments and Submissions

We invite readers to send letters responding to articles published in FOCUS or dealing with current AIDS research and counseling issues. We also encourage readers to submit article proposals, including a summary of the idea and a detailed outline of the article. Send correspondence to:

Editor, FOCUS
UCSF AIDS Health Project, Box 0884
San Francisco, CA 94143-0884
The advent of potent antiviral combinations heightens the negative consequences of missing doses, taking doses improperly with respect to eating, and varying the time period between doses, according to a review of new studies on treatment adherence.

Antiviral drugs place “selection pressure” on HIV to mutate, giving new drug-resistant virus an advantage over original, non-resistant strains. Only replicating virus can mutate, and no regimen has yet been proven to suppress viral growth completely. Weaker regimens, comprised of only nucleoside analogue reverse transcriptase drugs—for example, zidovudine (ZDV; AZT) or didanosine (ddI)—exert weaker selection pressure than stronger regimens containing a protease inhibitor as a component of a three-or-more-drug combination. If blood levels of drugs in these potent combinations fall temporarily, allowing more viral production, resistant strains can emerge and overtake the original strains.

Adherence is particularly important for another reason related to the way in which protease inhibitors and non-nucleoside analogue reverse transcriptase inhibitors (NNRTI) are metabolized by the body. The less potent nucleoside analogue drugs require the addition of phosphate molecules to activate them. These “tri-phosphate” drugs remain in HIV-infected cells for much longer periods of time than do the newer drugs, which can diffuse easily in and out of cells and whose levels, therefore, may quickly change and vary over time.

Several recent studies offer compelling support for strict adherence. Defining adherence as taking at least 60 percent to 85 percent of prescribed doses, these studies show that those participants who adhered to dosing instructions were more likely to achieve and maintain viral loads below detectable levels and less likely to develop resistant virus. Although there were individual exceptions within these studies, indicating that non-adherence is not the only factor that can undermine a regimen, these results reinforce the importance for both patients and providers of understanding the instructions for taking prescribed medications. This is even more significant because of the possibility of a person developing not only resistance to a single drug, but also cross-resistance to similar drugs not yet taken.

Latent HIV in People with Low Viral Load

A 30-month-long study of 22 patients found “compartments” of replication-competent latent HIV in the resting CD4+ cells of patients on triple or quadruple combination therapy. Notably, the recovered HIV did not demonstrate mutations that would indicate resistance to the HIV medications used in the treatment combinations.

Researchers do not know whether such latent HIV can be reactivated, however, the existence of a stable reservoir of latently infected cells should be a consideration in deciding whether to continue, reduce, or even stop antiviral treatment in people with no other evidence of persistent virus.

Subjects were selected according to very specific criteria: both patient- and physician-reported strict adherence to aggressive highly active antiretroviral therapy (HAART) regimens, rapid decline in viral load to less than 200 copies per milliliter, and continued undetectable viral load levels on several measurements throughout the duration of the study. In all of the research subjects, long-term suppression of viral replication to undetectable levels was achieved. Additionally, as a result of treatment, CD4+ counts in most patients increased, and there was a lack of viral mutation.

The number of CD4+ cells harboring replication-competent HIV was low, and, compared to other study populations, lower than the number in patients not on HAART. The fact that this number did not decrease over the course of treatment suggests that the HIV reservoir has a slow decay rate.

Surveying Adherence
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Two national studies—one of people with HIV disease, the other of physicians—found strikingly high rates of non-adherence to antiviral regimens and concerns about the number of doses per day and the number of pills per dose in these regimens.

Conducted by telephone by pharmaceutical company DuPont Merck, the first study surveyed 665 patients who were taking at least two antiretroviral medications; the
The literature suggests approaches to adherence including supervised therapy and case management; the establishment of trust, acceptance, and good communication; individualized treatment; and cultural competence. In terms of patient education, flexible short-term goals, patient reminders, and outreach may all help achieve adherence. Health care providers who are more proactive and optimistic about their ability to help clients are generally more effective in improving adherence: approaching care with the constellation of attitudes that comprise an “I can” versus an “I can’t” position will facilitate this strategy.

Finally, directly observed therapy (DOT), used primarily in the treatment of tuberculosis (TB), has regained popularity in recent years as a means for improving compliance. However, because HIV treatment is more complicated, requires medication throughout the day and night, and can last a lifetime, DOT may not be a cost-effective option. One form of DOT may offer some lessons; by employing a surrogate family model and including field trips, hot meals, support groups, and clinic and home visits, providers achieved high rates of adherence.

### Compliance and HIV Disease


Supervised therapy, a strong nurse-client relationship, and conscientious patient education all play important roles in adherence to HIV antiviral therapy, according to a review of the literature.

Among the psychosocial factors that influence adherence are trust, communication, internal conflict or stress, paternalistic provider behavior, mental health problems, and control. One study found that four medication-related attitudes affected adherence: degree of skepticism about the treatment, degree of concern about HIV disease, perceived severity of illness, and barriers to taking medication.

Ethnocultural factors also affect adherence. Among these are: language and literacy barriers, the motivation of some ethnic groups to please or distrust authority, and the “locus of control,” that is, whether a person believe control comes from within themselves or is determined by external forces. Many providers make the assumption that people with external loci of control are “hard to reach” or “non-compliant” and that people of color are likely to be fatalistic; however, research reveals that many people of color actively participate in their health care, and that health care worker attitudes can sabotage this participation.
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