The House Is Burning: An HIV Clinician’s View after 20 Years
Stephen Follansbee, MD

The recent release of updated guidelines for the initiation of antiviral treatment do more than present a new “recipe” for clinicians.1 By recommending a more conservative treatment algorithm, shifting the “start point” for initiation from a CD4+ cell count of 500 to 350, they force each clinician to reevaluate his or her fundamental treatment model. These guidelines may undermine the confidence of some clinicians in their treatment decisions. This article reviews 20 years of HIV treatment from the perspective of an HIV practitioner and discusses the potential impact of the new guidelines on the practitioner’s perspective of care and interactions with patients.

The first cases of Kaposi’s sarcoma and Pneumocystis carinii pneumonia in men who have sex with men alerted the medical community to the emergence of a new syndrome of immunodeficiency.2 In the six years between 1981 and 1987—in the absence of any antiviral treatment for HIV infection itself—the management of HIV disease involved five primary approaches:

• Identifying infected people;
• Attempting the early recognition of opportunistic infections and malignancies;
• Treating diagnosed opportunistic conditions;
• Prescribing prophylactic treatments for those infections, when available;
• Mitigating pain.

While these approaches did extend life, clinicians were frustrated by their lack of ability to impact the progression of HIV disease itself, and a sixth approach was necessary: easing the transition to disability and death, the number of which rose each year.

With the isolation of HIV came the recognition of the reverse transcriptase enzyme as a possible “Achilles’ heel” of the virus, and the development and marketing of zidovudine (ZDV; AZT; Retrovir). In retrospect, treatment doses of zidovudine at 1200 milligrams per day were too high. Yet, ZDV, the first nucleoside reverse transcriptase inhibitor (NRTI), was and remains a proven medication.

This era saw the appearance of several NRTI analogues, including zalcitabine (dDC; Hivid), didanosine (ddI; Videx), lamivudine (3TC; Epivir), and stavudine (d4T; Zerit). Each brought with it variable potency, new toxicities, and the promise of new treatment options. Soon, the first recommendation for initiating antiviral treatment at a CD4+ cell count of 200 was revised, raising the level to 500. Clinicians, initially at the urging of their patients, often combined two or three NRTI agents, attempting to increase potency. The NRTI era, with the promise of more antiviral agents in the pipeline, was encouraging. Although the impact on disease course was modest, it was measurable, and both clinicians and people with HIV were comforted by the fact that there were treatment options. This era saw little shift in the growing death rate.

The release of data in 1996 at the 4th National Conference on Retroviruses marked the beginning of the highly active antiretroviral treatment (HAART) era. The addition of the protease inhibitor ritonavir to therapy of NRTI medications resulted in a significant rise in CD4+ cell counts. More impressively, the study found that among patients with advanced disease and baseline CD4+ cell counts of less than 100, there was a statistically significant survival benefit.3 The rapid availability of several
Editorial: The Hidden Patient
Robert Marks, Editor

Two weeks ago, I got hit in the face by a softball. Nothing major: bashed teeth, a deviated septum, a boggled eye, a momentary blackout. I’ve had to visit my primary care physician, an ophthalmologist, dentist, endodontist, and ear, nose, and throat specialist. Why is all this relevant to an issue of *FOCUS* about adjusting to changes in HIV antiviral treatment guidelines?

Seeing five doctors in two weeks, some more than once, gave me a crash course in patient behavior, admittedly a non-controlled study with an n of 1. Here I am, a relatively competent, clear-thinking, articulate individual knowledgeable about medical practice, who upon entering the consultation room becomes overwhelmed, passive, even shy. And this is no life-threatening illness.

At the endodontist, I learned that the nerves in both top front teeth were dead, likely the result not of my softball fumble, but of some trauma 10 years earlier. Both root canals were atypical, and the endodontist said that while she recommended root canal procedures for each, neither was a sure thing. Faced with uncertainty, I clutched at her recommendation. I realized that despite being an informed consumer, I did not want to make the decision: if we waited I could lose the teeth, if we went ahead, I might still lose the teeth (and a significant amount of cash).

The experience has made me think a lot about the articles in this issue of *FOCUS*, in which Stephen Follansbee talks about the delicate balance of the provider-patient relationship, and Dale Brashers discusses the importance of self-advocacy in dealing with uncertainty. Follansbee makes the point that each interaction is individual. This must be true; but what I discovered this month is that the way I present myself to my doctors is just the tip of the iceberg. The slow unfolding of personality is normal in psychotherapy where the relationship grows over time. But medical relationships don’t usually operate this way—especially when they are caught in the vise of managed care—and what lies beneath the surface of my calm exterior can undermine preventive care, treatment decision making, and adherence, unless my medical provider knows me well enough to sense my unstated, often carefully hidden, concerns.

Recent research suggests that medical providers may be the most important link in the HIV chain, not only in terms of treatment decisions, but also in the context of adherence and HIV prevention. Medical providers cannot be clairvoyant, but they can borrow from their mental health colleagues the counseling skills that can help them uncover their patients’ fears and desires, revealing the hidden patient and the key to influencing individual health behaviors. The “clinical dialogue” that Follansbee identifies and the “negotiated treatments” that Brashers suggests form the foundation for this crucial relationship.
I tell patients that if we had the perfect treatment, which eradicated HIV in a single dose without significant side effects, we would not discuss CD4+ cell counts or viral loads at all.

The shift in treatment guidelines may also seem to fuel the arguments of AIDS denialists, who have suggested that antiviral treatment regimens, not HIV, are one cause of AIDS. In fact, the change in guidelines are part of an evolution toward more effective and less toxic HIV treatment protocols that have resulted in extended life and dramatically improved quality of life.

The Post-HAART Era: 2001–????

The new guidelines for initiating antiviral treatment, released in February 2001, are based on several observations. First, antiviral combinations work better than predicted. They clearly lead to a measurable and effective immune "reconstitution," usually about three months after beginning treatment. Second, these drugs are associated with viral resistance. There are a growing number of people with HIV who have exhausted all or nearly all currently available treatment options, often before any complications of HIV disease have become apparent, because their HIV has become resistant to treatment regimens. Third, while there is new drug development on several fronts—including existing classes of antiviral agents, new HIV targets, for example, integrase inhibitors and fusion inhibitors, and immunomodulator therapy—the progress of drug development is unpredictable. Finally, with long-term antiviral medication use, there is an emerging list of risks and toxicities, including metabolic complications such as body appearance changes, diabetes mellitus, lipid disorders, liver toxicity, kidney toxicity, bone loss, emotional and psychological challenges, and skin changes. Some of these are not easily treated or reversed.

The new guidelines temper the "hit early, hit hard" approach. Extending the burning house analogy, the guidelines suggest that calling the fire department too soon might cause more damage then letting the fire burn a little more: it might be better to wait until there is better firefighting equipment and better-trained firefighters. Perhaps new fire fighting approaches would be less damaging to the rest of the house that is still free of fire.

Clearly this shift in approach is unsettling. For clinicians and patients, the guidelines mandate a review of the indications for treatment and require revisiting the decision whether to continue treatment for some individuals: should treatment be interrupted, and what will be available when it is time to reinitiate therapy? Up to now, antiviral treatment has offered the relative assurance that every skin rash, sore throat, cough, episode of diarrhea, or fever is not somehow the beginning of a new HIV-related problem. Treatment has been equated with "doing something," a perception bolstered by viral load testing, which has enabled clinicians and patients to "measure" the effects of treatment even in the absence of symptoms. A measurable drop in the viral load, regardless of any indication of immunodeficiency, has become equated with "good."

The new guidelines raise the question: having emphasized viral load measurements for so long as the key indicator for treatment decisions, how do we refocus on CD4+ cell counts, generally considered indicators of "immunologic health"? Although clinicians have always relied on CD4+ cell counts to help identify HIV-related complications, they have not used these tests since the advent of HAART as indicators of early HIV drug failure or predictors of when to change HIV medications. In addition, the rate of CD4+ cell decline may be unpredictable, requiring monthly or bimonthly blood draws instead of quarterly ones. With each blood draw, people with HIV may experience a period of uncertainty and stress.

Reviewing the Doctor-Patient Relationship

The change in guidelines forces a review of the relationship between each provider and patient and may undermine the patient's trust. Providers must acknowledge the confusion over treatment indications and advice at each encounter. I often ask patients if they are considering treatment interruptions even when I do not think this approach is indicated. This helps to establish the dialogue. It puts into practice the notion that the treatment plan should be reassessed and renegotiated at each encounter. It is more difficult to discuss...
delays or interrupting antiviral treatment when the patient wants treatment yet the practitioner questions the benefit early in the course of infection. Like practitioners, patients see treatment as “doing something.” The strategy I have adopted is to expand the concept of the treatment plan—the overall disease management—to include laboratory monitoring, risk reduction, and health maintenance, as well as the potential for prescribing antiviral medications at the right time. In this way, not prescribing medications is also “doing something,” and is part of an active treatment plan.

But the shift in definition of the “right time” can threaten this approach. If the practitioner recommends discontinuing therapy because the CD4+ cell count has never been low, the patient may question the practitioner’s integrity: “Is he or she just trying to save the insurance company some money?” The apparent switch in strategy may lead patients to question whether practitioners know what they are doing: “Last month, they told me to take my meds and not miss any doses. This month they tell me not to take them at all.” Many patients have been reluctant to undertake combination treatment, but up to now have followed the advice of their practitioners. As a result, they have experienced bodily changes, peripheral neuropathy, and other challenges. The new guidelines raise the question: should patients ever have distrusted their own instincts about treatment (or trusted their practitioners’ recommendations)?

For practitioners, the shift in treatment strategy appears temporary. Trained to “hit early, hit hard” in other infections, most clinicians are awaiting better drugs and better treatment strategies. I still tell patients that if we had the perfect drug—one that eradicated HIV in a single dose without significant side effects—we would not discuss CD4+ cell counts or viral load levels at all. We would just treat, and follow treatment with the admonishment to “never catch HIV again.” In other words, we would put the fire out right away and then remove the matches. For now, it seems we are going to let the house burn a little, but not forever.*

Conclusion
The release of new, more conservative guidelines for initiation of antiviral treatment appears to undermine a settled treatment model, and this can be disturbing to both practitioners and patients. Presented as a reversal of current treatment strategies, the new guidelines can threaten the practitioner-patient relationship. But, it is important to realize that the new guidelines do not reverse the basic goal of HIV treatment; instead they reaffirm the challenges of adjusting treatment in the face of rapidly evolving research and developments in medications and monitoring.

Early in the dialogue regarding treatment initiation or discontinuation, I assure the patient that it is not necessary to make a decision immediately; the decision is rarely an “emergency.” This seems to decompress the interaction and allow patients enough time to consider their options: to get further information from other practitioners, their friends, and web sites or other lay resources. I make certain that patients know that I will support their informed decisions, even if that means starting treatment sooner than the guidelines suggest.

By addressing these issues at each encounter, patients and practitioners can use the clinical dialogue as an opportunity to reevaluate strategies and reaffirm goals. These treatment changes and this ongoing dialogue encourage us to acknowledge that eventually there will be better treatments, initiated earlier in the course of infection. The fact remains that HIV treatment continues to successfully extend life for many, anticipating what might one day be a cure.

References
HIV and Uncertainty: Managing Treatment Decision Making
Dale E. Brashers, PhD

The changes to standards represented in the February 2001 federal HIV antiretroviral treatment guidelines highlight the uncertainty that accompanies HIV medical care. These guidelines include delaying therapy until the disease is more advanced, except when treating an acute HIV infection. This is a dramatic change from previous recommendations that highly active antiretroviral therapy (HAART) be used to keep HIV under control throughout all of the stages of the disease. The rationale for delayed treatment includes such considerations as the complexity of treatment regimens, the possibility of major side effects, the potential for nonadherence, and the devastating consequences of viral resistance associated with nonadherence or suboptimal levels of antiviral drugs.

Of course, treatment uncertainty is nothing new for people living with HIV. Questions about the safety and efficacy of treatments have been raised since the first clinical trials of zidovudine (ZDV; AZT) concluded around 1989. Many refused treatment with ZDV because they believed it had toxic side effects—especially at the very high doses recommended at the time. Since then, treatment uncertainty has been constant, recently heightened by a much wider range of options as well as the identification of side effects such as lipodystrophy (abnormal fat accumulation in the back and abdomen combined with wasting syndrome in the face), hyperlipidaemia (elevation of fats in the bloodstream), insulin resistance, and peripheral neuropathy.

Current sources of HIV uncertainty influence at least three major HIV treatment decisions: when to start medication, which medications to take, and when to switch medications. Managing this uncertainty can help clients feel better equipped to handle treatment decision making and more committed to decisions that they make. Even for those not currently taking antiviral medications, uncertainty management may be important to help them cope with media coverage of treatment advances and questions about starting or delaying treatment.

Self-Advocacy as a Coping Mechanism

The challenges of treatment decision making can be managed by a number of cognitive and behavioral coping strategies. For example, people can learn self-advocacy skills that will help them participate in decisions about their health care, including educating themselves about treatments; learning to be assertive, for example, by asking questions in their interactions with health care providers; and rejecting treatments that seem inappropriate for their circumstances. HIV physicians have become accustomed to patients who are well-educated about treatment options and who engage in collaborative decision making. To facilitate their participation in such interactions, people living with HIV can educate themselves through their health care providers, through comprehensive HIV information web sites, and through HIV treatment publications. Additionally, peer support opportunities (formally through support groups or peer mentoring; informally through networks of friends) can be

Self-advocacy must be prescribed cautiously. Not everyone is ready or willing to seek information on his or her own.

References


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See also references cited in articles in this issue.
good sources of information sharing. All of these resources might be useful to answer important questions: “How do these drugs fight HIV? What side effects are associated with which medications? Is it ‘safe’ to take a ‘drug holiday’ (that is, a structured treatment interruption)? How do physicians use such diagnostic tools as viral load and CD4+ cell count to determine when to start medications or when to switch to an alternative regimen?”

The right health care provider also increases comfort with treatment decision making. Two criteria help determine the best physician for an individual: a provider who is competent in HIV care and one who is interpersonally compatible with the person seeking care. Studies have shown that people fare better—and live longer—if they have HIV-experienced physicians. In one case, an inexperienced physician prescribed ZDV monotherapy in 1998, long after combination treatment had become the standard of care.

Dilemmas of Self-Advocacy

Despite its benefits, self-advocacy must be prescribed cautiously. Not everyone is ready or willing to seek information on his or her own. In a study of uncertainty management, some people reported that they needed a break from HIV-related information, either because it was too negative, and therefore anxiety producing, or because the volume of information was overwhelming. Similarly, providers should not assume that all people have easy access to accurate sources of information or that they will be able to easily translate and apply the complex language of virology, pharmacology, or medicine. Another study found that self-advocacy was highest among people with higher education. A risk in elevating the importance of self-advocacy is that people who are not able to negotiate HIV-related information may be marginalized or stigmatized as uncooperative or “hard to reach.”

People who have problems advocating for themselves, either because of anxiety or because of difficulty finding and interpreting information, may need a support person to help them. One study participant said that she was so stressed that she cried during every visit with her physician for the first year after her diagnosis. She began taking a friend to her appointments when she realized that she was missing most of what her physician told her. Other participants said they relied heavily on their social networks of HIV-positive friends for treatment advice and emotional comfort.

Finally, the complexity of treatments is only one of many sources of uncertainty for people living with HIV. Uncertainty may also occur because of the diversity and unpredictability of symptoms, unstable personal relationships, and unclear financial consequences of the disease. Even when people experience dramatic improvements in health, they often still are uncertain about the long-term safety and efficacy of treatments and the need to return to work. These circumstances require people with HIV to adapt to chronic uncertainty, perhaps learning to accept it as a “natural rhythm to life.” Participants in the uncertainty management study said that they learned to cope with chronic HIV-related uncertainty by changing their orientation toward uncertainty, focusing on day-to-day activities, and redefining decision-making tasks. One participant noted that people living with HIV have to be “more willing to live in the moment and suspend the need for concrete answers that aren’t forthcoming.” Others said they benefited by focusing on manageable short-term goals and projects with immediate consequences, which allowed them to feel productive despite an uncertain future.

Stress management interventions also help clients manage anxiety if troublesome uncertainty cannot be reduced. A number of such interventions that might be useful—for example, aerobic exercise—have been tested recently for people with HIV.

Conclusion

The most recent HIV treatment guidelines noted that “patient education and involvement in therapeutic decisions is important for all medical conditions, but is considered especially critical for HIV infection and its treatment.” Negotiated treatments, in which both physician and patient are relatively comfortable with decisions about the drugs and their methods and schedules of delivery, are increasingly important.

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. Send correspondence to rmarks@itsa.ucsf.edu or to Editor, FOCUS, UCSF AIDS Health Project, Box 0884, San Francisco, CA 94143-0884.
Recent Reports

Reassessing Treatment Success and Failure

According to an editorial in the Journal of the American Medical Association, two studies suggest that the "hit hard" approach to HIV antiviral treatment and its goal of complete viral suppression may not be necessary for durable treatment benefits.

The first study (by Hermankova and colleagues) found that while HIV continues to replicate in people whose viral load is below the level of detection, this level of replication appears to be insufficient to cause drug resistance. The second study (by Havlir and colleagues) found, despite predictions to the contrary, similar rates of treatment failure in two groups of patients: those whose plasma viral load remained consistently below the level of detection and those whose viral load levels were "transiently detectable," that is, rising above 50 and then falling below 50 (the level of detection).

These studies raise the question: is there a level of viral replication below which viral turnover still occurs but is insufficient to allow for the establishment of a drug-resistant and replication-competent variant? If such a "viral threshold" exists, it opens the way for an alternative to the current treatment philosophy of complete HIV suppression. Regimens that achieve the goal of reducing viral load to below this threshold, are well-tolerated, and preserve future medication options may be preferable to more potent but less well-tolerated regimens that reduce viral load to below the level of detection. Such a change may, in fact, lead to four treatment alternatives for patients with low-level HIV infection: continue current regimens with close observation; label current regimens as failures and switch to new regimens ("salvage therapy"); add a drug to current regimens ("intensification"); or stop therapy altogether and reassess therapy at a future date. It is unclear, however, when "continuing the current regimen with close observation" will be an insufficient response.

There are limitations to both these studies, including the fact that they were not prospective and long-term and focused only on protease inhibitor regimens. But they suggest that categorizing the response to therapy as a dichotomy—undetectable or detectable; success or failure—may be misleading.

Ethical Considerations for HIV Care

Providers have an ethical responsibility to do everything possible to see that patients who might benefit from HIV treatment have an opportunity to do so, according to a commentary by the New York State AIDS Advisory Council's Workgroup on Ethical Issues in Access to HIV Treatment. The workgroup formulated a "new paradigm of provider-patient interaction" that combines traditional values of trust in the provider and beliefs in the benefits of therapy with new strategies for patient education and therapeutic partnerships.

The paradigm consists of three components: treatment readiness, treatment maintenance (the term preferred over "compliance" or "adherence"), and support services. It is characterized by three assumptions: that the provider-patient relationship is necessarily collaborative and ongoing, that the process is patient-centered, and that trained providers must work as a team to provide effective treatment.

Treatment readiness encompasses education of patients about treatment options and includes ensuring that patients understand and commit to the requirements of an appropriate regimen. It builds on the premise that every patient should have access to HIV medications when that person would most likely benefit from them. A physician who decides that it is best to temporarily withhold treatment from a patient would be obligated to reassess the patient's status regularly and to continue to encourage treatment readiness.

Treatment maintenance requires effective integration of a realistic medication schedule into a patient’s life. The workgroup's conclusions were consistent with the literature: "Physicians should not auto-
A Model of HIV Treatment Timing


Applying a statistical modeling process to a hypothetical population of people with HIV suggests—although it does not "prove"—that delaying HIV antiretroviral treatment may lead to better outcomes in terms of viral load and less likely development of multidrug resistance.

Researchers used “Markov modeling and decision analysis” to track the effects of two HIV antiretroviral treatment initiation strategies over the course of 10 years in a hypothetical population of 10,000 seropositive people. A Markov model describes a finite series of “states” that evolve at discrete time intervals. In this case, the states are either treatment naïve or treated, and either undetectable or detectable. A patient who becomes detectable is presumed to have experienced “failure.” The model allows for three instances of failure before an individual is considered multidrug-resistant.

The model uses current statistical knowledge regarding treatment. Among the statistical probabilities that were integrated into the model are: success after an initial regimen and the durability of an undetectable response over time; success of a second regimen after failure and its durability; and the model does not take into account clinical outcomes, only virologic ones. In addition, it assumes that the response rate to a given regimen remains constant over time and that no adverse clinical events delay therapy. However, it also assumes that in carefully followed patients, those at high risk of clinical progression could be identified using CD4+ cell and viral load testing and started on therapy before adverse clinical events occur.

The modeling described six scenarios: all 10,000 people begin a regimen at the start of year 1; and each year, either 5 percent, 10 percent, 15 percent, 20 percent, or 30 percent begin therapy (until all individuals are treated or the 10 years elapse). In the case where therapy was started immediately for all 10,000 patients, the model predicts that after 10 years, 57 percent would be undetectable and 38 percent would have detectable multidrug-resistant virus. In contrast, the model predicts that in the group that initiates treatment at a rate of 10 percent a year, 64 percent would be undetectable and 24 percent would have detectable multidrug-resistant virus.

While the model does not prove these outcomes and is based on short-term clinical trials, it provides a theoretical foundation for questioning the aggressive, early use of HIV treatment.

Next Month

For many African American gay and bisexual men, the church has been a central institution. But churches have been slow to address HIV, and the rejection by churches further alienates men already stigmatized by attitudes toward same-sex behavior. In the September issue of FOCUS, Robert L. Miller, Jr., PhD, CSW, Assistant Professor of Social Welfare at the State University of New York, Albany, describes the social and psychological difficulties African American gay and bisexual men face in the context of this alienation.

Also in the September issue, Yvette A. Flunder, MA, DMin, Executive Director of Ark of Refuge in San Francisco and Co-Chair of the National African American Church Caucus on AIDS, discusses a program that equips faith leaders with HIV-related information and scriptural tools, as well as practical suggestions, guidance, and resources for developing AIDS ministries.
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