Antiviral treatment failure is common among people with HIV, even in an age of more effective combination regimens. A recent study found that rates of treatment failure were 50 percent for people initiating antiviral treatment for the first time and that it rose to 70 percent and 80 percent, respectively, for people attempting second and third courses. This article examines some of the cultural, psychological, and social issues related to treatment failure. It focuses in particular on the population of clients at an outpatient HIV social services agency in urban Los Angeles.

Defining Treatment Failure

A treatment regimen generally is considered to have failed if any of the following occur: viral load consistently rises, CD4+ cell count consistently falls, an opportunistic infection occurs, or HIV-related symptoms increase. The decision to abandon a regimen as failed must be considered as part of a trend and not based on an isolated “bad” lab test. Treatment failure can occur in the initial regimens of treatment-naïve patients or at any time in the course of treatment.

According to the Centers for Disease Control and Prevention (CDC), of the many factors that may contribute to treatment failure, some of the most common are: nonadherence; initial viral resistance to one or more medications in a regimen; medication absorption or metabolism problems; multidrug interactions that affect medication levels; contraindications with other medications or even herbs; substance abuse; or other psychosocial stressors that negatively impact treatment. Of these, nonadherence appears to be the most significant, but it is also one to which many other factors contribute. (See “The Causes of HIV Antiviral Treatment Failure,” page 5 of this issue of FOCUS.)

An individual’s psychological response to treatment failure may vary based on demographic factors such as risk group, gender, ethnicity, and culture. People experiencing treatment failure represent a subgroup within the already stigmatized and isolated population of people living with HIV; they are a “minority within a minority” that faces unique challenges and can experience a variety of reactions that can exacerbate any pre-existing feelings of isolation, stigma, fear, hopelessness, vulnerability, and confusion that HIV often already brings.

Treatment failure is usually identified by an increase in viral load. In responding medically, the health care provider and the patient must reconsider the current regimen and strategize together about new regimens most likely to be effective, relatively easy to adhere to, and well-tolerated. If a patient has used only a few antiviral drugs in the past, the provider may change the regimen with little fear of pervasive viral resistance. But if the individual is a veteran of treatment, only creative or “salvage” regimens may be available as options. Salvage regimens might combine multiple drugs from the same drug classification, for example, two different protease inhibitors, or might use a greater number of drugs, for instance, four or five, instead of three, in an attempt to “hit the virus population from all sides” and to achieve at least partial clinical benefit.

Culture and the Response to Failure

The emotional response to treatment failure may include any combination of reactions. Among these are: confusion; disappointment; hopelessness; shame, guilt, and feelings of inadequacy; powerlessness and vulnerability; feelings of abandonment and isolation; fear of
Editorial: Between Failure and Success?
Robert Marks, Editor

It is rare for anyone to talk about HIV treatment success without qualifying his or her enthusiasm by mentioning treatment failure. For those who experience failure, I imagine there are not enough words to describe the disappointment that follows the hope invested in combination regimens. For those whose regimens are successful, talk of failure may seem an unnecessary evocation of the worst, the dark lining of an optimistic future.

Today, it seems hard to know what is treatment failure and what is treatment success. In this issue of FOCUS, Kathleen Clanon establishes the criteria for virologic failure; it is clear when and, to a large extent, why a treatment regimen fails to achieve a significant drop in viral load and what this means for a person’s health.

But success, itself, is fraught with uncertainty: it straddles the border between tolerable and intolerable side effects; it hovers as viral load and CD4+ cell counts rise and fall and rise again over time; and it dissolves as drug resistance develops. How many people riding the HIV roller coaster actually feel the confidence that we attribute to the words “treatment success,” words that imply a permanent state rather than a moment of balance before the car plunges down the track?

Resignation or Confrontation
Failure or success gets defined as much by attitude—and the ability to hope—as by the hard numbers that Clanon outlines. I don’t imagine that hope is ever independent of those numbers. But the qualities of hope and fear filter all the ups and downs of living with HIV and influence whether a person perceives treatment as a success or a failure—whether he or she tends, in the face of challenges, toward resignation or confrontation.

As Ken Howard discusses in this issue, there are a variety of cultural and historical experiences that affect a person’s response to treatment failure and the place of both hope and fear in that person’s life. Understanding these experiences may help providers understand a client’s response to the hard numbers of viral load and CD4+ cell count and the ways in which he or she copes with the daily triumphs and drawbacks of antiviral treatment and living with HIV.

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As Ken Howard discusses in this issue, there are a variety of cultural and historical experiences that affect a person’s response to treatment failure and the place of both hope and fear in that person’s life. Understanding these experiences may help providers understand a client’s response to the hard numbers of viral load and CD4+ cell count and the ways in which he or she copes with the daily triumphs and drawbacks of antiviral treatment and living with HIV.

incapacity, illness, pain, or death; and loss of faith in medical treatment. An individual may cope with these responses in maladaptive ways, including engaging in compulsive sex, alcohol or drug bingeing, overspending, and self-isolation. Further, the experience of treatment failure may negatively reinforce attempts at treatment adherence, which can undermine future treatment endeavors. Individual responses may vary based on the experience of HIV-related loss, the number and complexity of treatment regimens a person has undergone, history of side effects, the occurrence of non-HIV-related health conditions, and the length of time on any one regimen before failure.

While generalizations about subpopulations may result in stereotyping, there are common cultural experiences that may mitigate or exacerbate these emotional responses. For example, many gay men experience treatment failure in the context of a long history of HIV-related disappointments, loss and unresolved grief, and the devaluation that may result from pervasive cultural stigma. Treatment failure becomes yet another in a series of events that contributes to a diminished self-concept, and for the first time in the epidemic, treatment failure may increase isolation by estranging gay men for whom treatments are failing not only from HIV-negative gay men but also from HIV-positive gay men for whom treatments are working. Cultural identity extends beyond sexual orientation. A middle-class, White gay man raised in an affluent suburb with a lifelong history of consistent and effective health care may experience treatment failure differently from an African American gay man, a White gay man who grew up in poverty, or a Latino immigrant. In these examples, it may be the “pampered” middle- to upper-middle-class gay man who has the hardest time dealing with treatment failure, precisely because of his history of privilege: people who have never had much do not expect as much, while those who are accustomed to access to resources may experience more distress in response to disappointments. Nonetheless, gay men who also are men of color may face additional stress because of real or perceived lack of cultural support during medical difficulty.

In addition to sexual orientation and social class, ethnicity affects the emotional interpretation of treatment failure. While Latino culture is not unified—representing
Treatment failure can challenge the Latino cultural value of dignidad (worthiness), undermining a sense of self and personal or cultural pride. For HIV-positive Latinos who also are undocumented immigrants, dignidad may already be compromised, and treatment failure can further symbolize the barriers to resources in the United States that these individuals face. For Latino people who speak English as a second language, the complexity of medical jargon becomes another barrier.

While individuals who identify as African American may be as culturally varied in their influences as Latino people, common cultural influences affect their reactions to treatment failure. For African Americans, news of treatment failure could exacerbate a historical cultural mistrust of medical institutions; however, it may be a myth itself that African Americans are forever distrustful of medical institutions in the wake of abuses such as the Tuskegee syphilis experiments. While treatment failure does little to inspire confidence in medical institutions, treatment failure among African Americans, at least at the SPECTRUM clinic in Los Angeles, occurs frequently as a result of nonadherence, not as a result of basic distrust.

Further, treatment adherence can be particularly poor in populations such as impoverished African Americans who have not traditionally had access to preventive medicine. In this case, nonadherence and treatment failure are related to socioeconomic conditions and the stresses of poverty. Impoverished African Americans tend to respond reactively, rather than proactively, in terms of medical self-care, so they have little frame of reference for taking medications when they simply do not feel sick. For such clients, treatment failure becomes a warning sign to improve adherence so that the next treatment regimen can be successful in controlling HIV to achieve improved health and quality of life.

For African Americans, in particular, treatment is not simply a medical issue. Treatment failure may be the result of a combination of social forces that includes poverty, discrimination, stigma regarding men who have sex with men, and stigma related to HIV. Stigma may lead to nonadherence, as clients “hide” medications at home to prevent family members from associating the client with high-risk-group behaviors, including bisexuality, homosexuality, injection drug use, or HIV serostatus itself. To avoid treatment failure, providers and clients must address issues of disclosure. This dynamic may also occur among African American women, who may believe that their HIV exposure has resulted from sexual contact with men they had assumed to be heterosexual but who were secretly gay or bisexual.

Recent focus groups at the SPECTRUM clinic revealed that regardless of race or ethnicity, long-term societal disenfranchisement of women may make it more likely that they would personalize or accept blame for the failure of a treatment regimen, while men may be more able to externalize responsibility to health care providers or medications. Women may also yield to pressures and expectations to put the needs of children or significant others above their own self-care (for example, missing medical appointments in order to care for children), raising the likelihood of treatment failure.

The focus groups also found that alcohol or other substance abuse can undermine treatment adherence and trigger failure; likewise for people in recovery from substance abuse, treatment failure can trigger relapse. Untreated depression can also contribute to nonadherence, resulting in a self-fulfilling prophesy that medication regimens inevitably will fail. Significant, uncomfortable side effects such as chronic nausea or diarrhea can further exacerbate depression and nonadherence.

**Effective Responses to Treatment Failure**

Effective responses to treatment failure involve a synergistic collaboration among client, medical providers, other social service providers, and cultural and community supports. Clients in communities with increased access to care, community support resources, and a history with the epidemic may be able to minimize the physical and psychological harm of treatment failure by building a support system into the fabric of the community.
social support may result in a more aggressive response to side effects that may persist until regimens are tolerable and effective. The positive effects of social support were seen with gay male communities earlier in the epidemic and are emerging now in African American church communities that have AIDS ministries. Such resources can increase awareness of and access to treatment options, including salvage regimens, alternative therapies, and emotional support.

The role of the multidisciplinary team of providers is to minimize factors that contribute to negative coping with treatment failure and maximize the client’s individual strengths. Treatment success seems to be most often associated with a comprehensive, holistic approach, specifically, helping to mobilize a client’s system of personal support. Further, the psychosocial support team—including mental health providers, treatment educators, advocates, peer counselors, case managers, peer support groups, and even pharmacists—augments and supports the functions of traditional medical providers by assisting patients to tolerate uncertainty and anxiety, cope with loss, regain hope, build confidence in new antiviral regimens, incorporate a new medication regimen’s demands, and enhance medication adherence. Behavioral intervention techniques borrowed from the harm reduction model may also help clients accept the value of partial progress versus an all-or-nothing approach that defines anything short of absolute adherence as failure.

Since treatment success is a full-time job for people with HIV, it is facilitated by support from the broader institutions of society. Many church congregations—particularly in the African American community—are recognizing the vital role of the faith community not only in HIV prevention but also in support for HIV-positive people. When leaders of these organizations talk about HIV, they encourage others to reduce stigma, promote treatment access, encourage adherence, provide support for managing difficult regimens and side effects, and provide emotional solace in the face of treatment failure. Similarly, since the primary public gathering place for most people is the workplace, businesses can do much to promote HIV sensitivity, and provide not only reasonable accommodation for HIV-related absences, but also a supportive atmosphere for undertaking the physical and logistical struggles of HIV treatment. Finally, for treatment efforts to be maximized, civic groups and clubs must do their part to increase HIV awareness, reduce stigma, and promote well-being for all members of the community.

**Conclusion**

Language has always played an important role in convincing society to respond to the epidemic and to modulate prejudice and ostracization. This remains true when discussing treatment: medications “fail” the person; people do not “fail” treatment. This is not just a semantic nicety; there is no justification for blaming a person for the failure of treatment that requires frequent dosing, difficult scheduling, intolerable side effects, and drug toxicity, and which is often accompanied by hopelessness and exhaustion. Unfortunately, while the rate of treatment failure can be reduced through a combination of provider assistance, community response, and improved drug formulations, it is not likely to be eliminated entirely. Treatment changes are inevitable, but effective and culturally appropriate support systems from all portions of society can ease the blow and pave the road for future treatment success.

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**Clearinghouse: Treatment Failure**

**References**


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The Causes of HIV Antiviral Treatment Failure
Kathleen Clanon, MD

Highly active antiretroviral therapy (HAART) has extended life and improved health for millions in the industrialized world. In spite of this record, five years into the miracle age, the honeymoon with HAART is over and the difficulties of life spent married to these drugs are apparent. One of the most frustrating aspects of antiviral treatment is how often and how quickly regimens fail.

The phrase “treatment failure” has an ominous tone, suggesting that failing health is soon to follow. Generally when clinicians use the term treatment failure, they mean virologic failure, the increase of viral load after a period of effective viral suppression. Failing health—for example, a new opportunistic infection or a new diagnosis of AIDS—is referred to as clinical failure. There is no predictable progression from virologic to clinical failure. Although neither is good news, there is generally a considerable lag (more than a year) between the reappearance of virus and a measurable impact on health. Virologic failure should trigger a review of what could be contributing to viral reappearance and consideration of a change in treatment to prevent clinical decline.

The actual viral load number that should cause concern is the topic of heated discussion among clinicians, and often confusion and distress for patients. The January 2000 version of U.S. Department of Health and Human Services (DHHS) treatment guidelines took the fundamentalist position that any viral load over 50 should trigger a change in treatment. In practice, to avoid “churning” drug regimens—switching again and again from one new regimen to another—clinicians often use a viral load of between 1,000 and 5,000 as the marker. The newest version of the guidelines, released in February 2001, acknowledges this clinical reality and includes a revised recommendation for switching regimens, tying this decision to a three-fold or greater increase in viral load and a persistent decline in CD4+ cell count.

Treatment failure may not be inevitable—there are people enrolled in triple combination trials who are still on the same regimen more than five years later—but it is common. In a study done on San Francisco General Hospital’s AIDS ward, only 50 percent of patients had viral loads below the level of detection 48 weeks into therapy. Treatment failure is nearly always multifactorial, with the factors falling into four areas: the provider, the pills, the patient, or the pathogen.

Provider Problems

The medical provider generally picks the regimen, and this choice can make failure more or less likely. If the provider prescribes a low potency regimen—for example, two nucleoside reverse transcriptase inhibitors alone—or reuses HIV antiviral drugs that have already failed in an individual, the new regimen is doomed. Providers who fail to think ahead to the next regimen may back themselves and their patients into an avoidable corner, being forced to reuse medications when better planning could have preserved the variety of medications and the option of a better regimen.

Medical providers play an important role in preventing adherence difficulties and underdosing by carefully teaching patients...
about their regimens, including scheduling and side effects, and then checking back to help identify and solve problems early. Prescription and pharmacy errors are probably more frequent than we know. In the past year, three clients of an Oakland, California HIV clinic have brought in medication bottles with incorrect dosing directions printed on the label; in each case, the client was underdosed for days or weeks. If providers do not question patients about their medications, these errors probably will not be caught. Finally, the provider sets the tone for talking about adherence and can either encourage or discourage frank answers depending on how he or she asks questions.

Pill Problems

If an individual has an inadequate serum level of even one drug in a medication “cocktail,” the regimen will eventually fail. Nonadherence is often the culprit when this happens, but pharmacological issues may be at fault more often than we think. Among these issues are:

- Underdosing resulting from single strength, standardized doses that cannot be adjusted for body mass or metabolism;
- Unpredictable absorption rates resulting from individual biochemistry, the presence of short-term digestive problems, or even stomach contents from a prior meal;
- Drug interactions, which become unsolvable when a person is taking seven or eight other medications in addition to HIV antiviral drugs;
- Side effects, which can be intolerable.

Low drug levels will be easier to identify and address when the technology to measure serum and intracellular drug levels becomes more available in clinical settings. Some of these assays can already be ordered from clinical labs, but not enough is known yet about how to interpret the results to make them clinically useful.

Patient Problems

Nonadherence is the most common reason for development of drug resistance and for regimen failure. Patient factors that predict poor adherence include depression, some forms of substance abuse, and an individual’s belief in his or her inability to be effective in adherence.

Adherence challenges aside, people with HIV who feel ambivalent about the safety or efficacy of a prescribed medication may be reluctant to discuss their doubts with their provider. In particular, individuals who have little reason to trust the medical establishment may throw away prescriptions or leave the pills on a shelf. Patients are often more likely to confess this situation to ancillary staff, peers, or nurses than to the prescribing physician. Finally, other diseases—including hepatitis B and C, diabetes, hypertension, and renal failure—may undermine treatment efficacy.

Pathogen Problems

Drug resistance is the biggest challenge posed by HIV, the pathogen. Resistance may occur when a virus successfully reproduces even in the presence of an antiviral drug, usually because there is an inadequate level of the drug in the patient’s system. Other factors also predispose to the development of resistance, including high viral loads or severe immune compromise (CD4+ cell counts lower than 100) when therapy is started, and prior use of antiviral drugs.

More recently, there has been concern that drug resistant virus may be transmitted: newly infected people who have never taken antiviral drugs may acquire resistance from the person from whom they acquired HIV. Drug susceptibility assays are helpful in identifying when resistance is playing a role in treatment failure. These tests remain difficult to interpret and prone to vary from one lab to another, but they have been proven to result in better treatment outcomes.

Conclusion

Many of the causes of HIV treatment failure are preventable with the education of people with HIV and their providers, the use of laboratory tools such as resistance testing, and improvements in drug pharmacology. At the start of a regimen and at the point of failure, providers should consider all possible contributing factors in order to prevent problems with the next regimen. Communication between people with HIV and their providers is crucial and is the best resource to minimize failure.

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

Depression and HIV Treatment Failure

According to a study of seropositive men and women on triple combination treatment regimens, participants experiencing debilitating side effects or suboptimal treatment responses often reported feelings of depression and pessimism. Depression adversely affects antiviral treatment adherence, and people who become depressed due to lack of early response to HIV treatment regimens may become less adherent and further jeopardize potential treatment benefit.

Researchers recruited 44 outpatients attending an HIV clinic at the Medical College of Wisconsin, interviewed them two or three times, and coded their responses and subjected these to a qualitative analysis. The interviews covered a range of topics for both treatment successful and unsuccessful participants, including changes in life view as a result of treatment, work, disability, living conditions, romantic relationships, and other relationships. Eighty-four percent of the participants were men, and the average age of the sample was 39 years. Fifty percent of the participants were African American, 43 percent were White, 5 percent were Hispanic, and 2 percent were Native American. Nurses rated 34 percent as "very poor" compliers with the prescribed HIV medication regimen, 32 percent as "average" compliers, and 34 percent as "very good" compliers.

While participants who were responding well to treatment held optimistic views for their future, those who maintained detectable viral loads or who were not able to tolerate medication side effects expressed feelings of depression and hopelessness. Some spoke of struggling with depression their entire lives, while others specifically related depression to the perceived ineffectiveness of the medication or to their decreased quality of life because of side effects. These participants focused on the meaning of the laboratory tests as central in determining their treatment response. They interpreted a detectable viral load to mean that their disease continued to progress despite their efforts to adhere to the medication regimen.

Participants who were tired of taking the medications, who experienced severe side effects, or who felt their daily lives were structured around taking medications also felt depressed and pessimistic about the future. These respondents reported that treatment decreased quality of life, and they wondered whether the costs of treatment outweighed the potential health benefits.

Racial Differences in Treatment Attitudes

A New York study of 38 seropositive men found that African American participants expressed significantly more doubt than White participants regarding their ability to utilize protease inhibitors and adhere to treatment regimens. These racial differences may be important for creating patient education and adherence strategies.

Study participants completed a short battery of self-administered measures of psychosocial adjustment and an interviewer-administered questionnaire. Study participants were between the ages of 50 and 67. Fifteen of the 38 participants were African American and 23 were non-Hispanic White. Researchers compared differences between the two groups with regard to perceptions of medication efficacy, self-efficacy, physician competence, quality of life, side effects, skipping medication doses, and timing of treatment initiation.

White participants felt a greater level of self-efficacy than African American participants regarding their ability to adhere to treatment regimens. African American participants reported more negative attitudes related to their physician’s knowledge and the prescribing behavior of physicians in general than did White participants. They also worried more than White participants about the possible side effects of protease

Some participants related depression to the perceived ineffectiveness of medication or to decreased quality of life. They interpreted a detectable viral load to mean that disease continued to progress despite efforts to adhere.
inhibitor therapy. There were no significant differences between the two groups in their beliefs about medication efficacy, quality of life benefits, or the consequences of skipping doses.

Seventy-seven percent of White participants believed that they began protease inhibitor therapy at the appropriate time, compared to only 40 percent of African Americans. Thirteen percent of the African American men were uncertain about the appropriateness of the timing and another 13 percent felt they started protease inhibitors too late, while none of the White participants reported feeling uncertain or that they started too late. There were participants in both groups who felt they began drug therapy too soon (33 percent of African American men, and 23 percent of White men).

**Indicators of HIV Treatment Failure**


A review of literature on HIV antiviral treatment success and failure concluded that a low baseline CD4+ cell count and high baseline viral load are independent predictors of treatment failure with a combination antiviral treatment regimen. Once therapy is initiated, factors that influence the exposure of drug to the virus, such as adherence and drug metabolism, also have significant effects on virological responses to treatment.

In a large clinical trial of 577 study participants who were initially randomized to receive triple combination treatment, the outcome was successful—defined as viral load of less than 500 at weeks 24 and 40—for 51 percent of participants. But the outcome was successful for only 39 percent of participants who had baseline CD4+ cell counts of less than 50, compared with 58 percent of those with baseline CD4+ cell counts between 51 and 200. An observational study conducted at San Francisco General Hospital found that only 50 percent of 337 participants had a viral load below the level of detection after 48 weeks of therapy and that the risk of failure increased incrementally as the baseline viral load increased.

Research also indicates that the response to triple combination therapy improves when all three drugs are initiated simultaneously rather than sequentially. One clinical trial found that among 32 participants treated simultaneously with zidovudine (ZDV; AZT), lamivudine (3TC), and indinavir, 78 percent achieved viral loads below the level of detection. In contrast, among the 33 participants who began therapy with ZDV and 3TC and then added indinavir 24 weeks to 52 weeks later, only 33 percent achieved viral loads below the level of detection. Several cohort studies have demonstrated that resistance to antiviral drug therapy can exist in treatment-naïve patients, usually at a prevalence rate of 5 percent. Researchers speculate that these cases of drug resistance reflect naturally occurring HIV mutations or are a result of drug-resistant HIV transmitted during primary infection.

Lack of adherence to medication regimens is also a predictor of treatment failure. In a study of marginally housed seropositive adults on protease inhibitor therapy, the absolute viral load doubled for every 10 percent decrease in adherence as measured by pill count. Participants in a San Francisco study reported various reasons for non-adherence: 40 percent forgot, 37 percent slept through the dosing time, 27 percent reported a change in routine, 22 percent were too busy, 13 percent were too sick, 10 percent found the side effects intolerable, and 9 percent were too depressed.

**Next Month**

Two concepts in prevention are receiving a great deal of attention: the belief that the ethos of "treatment optimism" undermines the willingness of people to sustain safer behaviors; and the focus on responsibility for others in the creation of interventions targeting people with HIV. In the July issue of *FOCUS*, Jonathan Elford, PhD, Graham Bolding, MSc, and Lorraine Sherr, PhD, all from the Royal Free and University College Medical School in London, review the literature on treatment optimism—essentially, the belief that HIV is curable—and conclude that it hinders risk reduction among only a small number of people.

Also in the July issue, Les Pappas, Principal and Creative Director of Better World Advertising in San Francisco and formerly with the San Francisco AIDS Foundation, discusses the role of altruism in prevention interventions focused on people with HIV. He discusses, in particular the development of the media campaign, HIV STOPS WITH ME.
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