With the advent of potent HIV antiviral therapy, the medical prognosis for people with HIV has markedly improved. Frequency of hospitalization, complex home care, and death have all decreased, as combination treatment has ushered in an era of chronic, but incurable, illness.1,2

This article offers non-medical providers an overview of the medical challenges that confront HIV-positive people whose immunodeficiency is stabilized. These medical issues include: “outlier syndromes,” that is, disease symptoms that worsen or fail to improve despite low viral loads and rising or stable CD4+ cell counts; medication side effects; and coexisting conditions—for example, hepatitis B or C—whose symptoms or treatment side effects overlap with those of HIV disease.

In discussing quality of life, it is important to state several caveats. First, different people have different priorities and these influence their quality of life concerns. Second, providers must attend to a person’s symptoms and side effects even when, after applying quantitative criteria, treatment seems to be successful. The easiest mistake a medical caregiver may make in the new era of HIV treatment is to falsely assume that improving viral load and CD4+ cell readings translate into feelings of day-to-day well-being. Third, since side effects are one of the principal saboteurs of medication adherence, clinicians must monitor their patients’ perceptions of whether medications are causing side effects, the impact of these side effects on day-to-day life, and the reversibility of these side effects. Finally, while HIV is no longer a routinely terminal disease, the long-term prognosis of people for whom treatment is working remains unclear.

**Outlier Symptoms and Syndromes**

A substantial minority of seropositive people who have undetectable viral loads and stable or rising CD4+ cell counts nonetheless experience functional symptoms related to HIV disease. Most commonly these untreated or residual outlier symptoms include fatigue, cognitive impairment, and chronic pain. For some, these symptoms are manageable and require only minor accommodations; for others, these symptoms are disabling in both their work and personal lives. For the purpose of documenting disability, it is critical that medical caregivers chart these outlier symptoms, even if they are poorly understood or not treatable.

HIV-associated fatigue is typically variable and sporadic. People experiencing fatigue may get extremely frustrated by this unpredictability, which may undermine efforts to return to work even when they are able to function well much of the time. The etiology of this fatigue is unclear. In the context of HIV disease, some experts speculate that fatigue reflects neuropsychiatric effects of autoimmune processes that are not fully controlled with HIV suppression. Fatigue may also be due to low testosterone levels, depression, anemia, and medication-induced hepatitis or chronic viral hepatitis—all of which are treatable. Many people with fatigue benefit from stimulants, which should be prescribed on a trial basis.3,4

Severe HIV-associated cognitive impairment is much less commonly seen today than it was before combination antiviral treatment. However, many people for whom antiviral treatment is effective experience persistent, even new-onset, mild cognitive impairment. This is characterized by word-finding problems and occa-
Editorial: Symptoms of Living with HIV
Robert Marks, Editor

Is the cure worse than the disease? HIV antiviral drugs are powerful chemotherapy, which, in limiting HIV replication, can cause unpleasant, even disabling, side effects. When we first asked Lisa Capaldini to write for FOCUS, this was the topic she was going to cover. But Capaldini wisely took a broader view, discussing the range of symptoms, some caused by side effects, others by HIV itself, that materialize when HIV disease becomes chronic—when antiviral treatment is successful.

As combination treatment extends life, some people with HIV may exchange a threat to life for insults to the quality of life as the debilitating but sustainable symptoms of antiviral treatment, non-life-threatening “outlier syndromes,” and co-existing conditions undermine feelings of health.

To respond to these symptoms, many of which are treatable, it is crucial to distinguish among them, for example, to understand when fatigue is a side effect of a particular antiviral regimen versus a symptom of hepatitis C versus a condition of HIV itself. In addition, as Linda Grinberg outlines in her article on structured treatment interruption, researchers are exploring approaches to HIV treatment that may both reduce the severity of side effects and improve treatment outcomes.

While research suggests that a lot of people without HIV minimize the severity of HIV disease in light of successful treatment, no one I know with HIV underestimates the daily challenge of side effects and other symptoms of HIV. Likewise, no one I know takes the idea of treatment interruption lightly. For most people with HIV, treatment is serious, treatment success is vulnerable, and changes in treatment are undertaken with care, hope, and fear.

For many, living with successfully treated HIV does not mean living without physical symptoms, and the psychological distress from symptoms may be all the more acute because of the expectation for “normal” lives that successful treatment engenders. Ironically, this expectation is as much imposed on people with HIV by a society weary of the epidemic as it is on each individual by his or her own desire for health.

Clients and providers may fail to recognize the fragility of improved spirit and may minimize, even yearn to minimize, the physical challenges of renewed health. Yet, this is one of the most important roles of the therapist: to create a setting in which clients can speak those thoughts that ordinarily remain unspoken—to open a forum for validation and support, two factors that are crucial for sustaining the perseverance required by antiviral therapy.

Medication Side Effects

Over the past four years, HIV clinicians have come to understand that it is oversimplistic to suggest that all people with HIV should be treated with combination antiviral therapy: the choice of beginning or continuing treatment must be individualized for each person, balancing the benefits of controlling the virus and stabilizing the immune system with the risk and signifi-

sionally by sleep disorders. Causes of cognitive impairment may include direct HIV infection of the brain, depression, low testosterone levels, substance use, and the side effects of prescription medications.

HIV-related chronic pain is extremely common. In some cases, it stems from specific conditions like antiviral-induced peripheral neuropathy. In many cases, however, the cause of pain is undeterminable, and it is especially in these cases that chronic pain is likely to be underdiagnosed and undertreated: it is second only to fatigue as an overlooked complication of HIV disease. Patients at particularly high risk for the underdiagnosis and undertreatment of pain include women and people of color (who are less likely to report symptoms), and both people with psychiatric conditions and people with past or current substance use histories (about whom providers are more likely to be biased in terms of pain management). In addition to the obvious drawbacks of untreated pain, it can also lead to depression, which, itself, can lead to medication non-adherence.

Some clinicians are reluctant to treat pain in people with HIV because of concerns about problematic interactions between pain medications and HIV antiviral drugs. With three exceptions, there are probably no clinically significant interactions between HIV antivirals and standard analgesic treatments. First, the antiviral medications ritonavir (Norvir) and delavirdine (Rescriptor) may impair the metabolism of narcotics by the liver. Second, reports suggest that some HIV antiviral medications may either raise or lower methadone levels, but no clear guidelines have emerged from these variable reports. Finally, anticonvulsant drugs, which are commonly used to palliate peripheral neuropathy and other pain syndromes, may lead to some interactions, but gabapentin (Neurontin), a newer agent, has no drug interactions with HIV antiviral medications.
For many people with HIV, treatment success has raised expectations, and this can be unsettling for clinicians.

References
ing HIV and hepatitis treatment or deferring treatment of one or the other condition. Many people who are co-infected with hepatitis and HIV may also be dealing with other issues, for example, drug abuse or depression, that may complicate treatment.

Depression is commonly seen with HIV disease, although it remains controversial whether it is more common in people with HIV than in the general population. Many experts believe that depressive symptoms may not represent a primary depressive disorder but are often due to HIV disease, itself, or to other associated conditions.

There are two obstacles to diagnosing depression in people with HIV. First, many symptoms of depression overlap symptoms of HIV disease making it easy to miss an underlying depression: impaired libido, impaired concentration, fatigue, chronic pain, and disturbed sleep.8 In addition, clinicians may be inappropriately empathetic, characterizing depressive symptoms as “normal” coping responses to being HIV-infected, rather than as signs of a separate depressive disorder. Second, clinicians may be overly concerned about drug interactions between antidepressant medications and HIV antiviral drugs: in most cases, potential interactions are not clinically significant. When using ritonavir or delavirdine, some antidepressants need to be started at reduced doses, increased judiciously, and monitored for blood levels of the drug. St. John’s Wort, an herbal remedy for depression, reduces indinavir levels enough to cause drug failure.

An increasing proportion of people who receive HIV care either currently use drugs or have a history of drug use. Studies have shown that individuals in drug recovery are able to adhere to HIV medication regimens, while those who actively use recreational drugs may have problems adhering. In addition, people with recreational drug-induced brain damage are more prone to the neuropsychiatric side effects of medications. These individuals, at greater risk for adherence problems, may benefit from more structured treatment protocols or more regular visits. Finally, HIV antiviral treatments have variable effects on methadone levels, and data suggest that all non-nucleoside reverse transcriptase inhibitors and all protease inhibitors can unpredictably affect methadone levels.

**Conclusion**

For many people with HIV, treatment success has naturally raised the bar of expectations, and this can be unsettling for clinicians. Four years ago when people with HIV were relieved not to be dying or hospitalized, medication side effects were a welcome exchange for longer lives. Now, as they extend over the long term, side effects have become less tolerable. Many people with HIV have unexpectedly tasted the possibility of normal lives and are reacting to the limitations of diarrhea, peripheral neuropathy, and fatigue. Some clinicians have responded to this with impatience, even disdain: side effects are a small price to pay for being alive. In some cases, this response stems from clinicians’ feelings of powerlessness, in others, from a fear that altering a successful regimen might compromise an individual’s HIV prognosis.

Historically, modern Western medical practitioners have been reluctant to acknowledge conditions or symptoms they could not diagnose or fix. Today, effective care requires HIV clinicians to inquire about symptoms that are difficult to define and treat, to accurately distinguish among outlier syndromes, medication side effects, and coexisting conditions, and to help patients respond to them. Clinicians also need to remind themselves that people with HIV can benefit from clinical care especially when the role of healer involves attentive listening and active witnessing.

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**Clearinghouse: Chronic Illness Effects**

**References**


Mitochondrial toxicity, lipoatrophy, neuropathy, and fatigue. Some clinicians have responded to this with impatience, even disdain: side effects are a small price to pay for being alive. In some cases, this response stems from clinicians’ feelings of powerlessness, in others, from a fear that altering a successful regimen might compromise an individual’s HIV prognosis.

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HAART Breaks: Structured Treatment Interruptions

Linda Grinberg

References


The hottest buzz in HIV circles is structured treatment interruptions (STI). Hopes for eradication were dashed when researchers discovered replication-competent viral reservoirs, capable of persisting for more than 60 years. Despite immeasurable HIV in the bloodstream, these hidden sanctuaries harbor virus impervious to highly active antiretroviral treatment (HAART). The dreary prospect of a lifetime of pill-popping and potentially intolerable side effects has lent a sense of urgency to finding innovative treatment approaches.

One rationale for STIs is that the very success of HAART, ironically, may be its flaw. HAART decreases HIV-specific cellular immunity by lowering the amount of HIV antigen. A treatment interruption, allowing a controlled amount of virus to be reintroduced to the immune system might, theoretically, provide sufficient antigen stimulation to trigger stronger HIV-specific CD4+ and CD8+ cell responses.

The Berlin and Washington Patients

The initial excitement began with Franco Lori’s report of the famous “Berlin patient,” who cycled on and off treatment twice, prompting HIV to re-emerge, and then subsequently resuppressed it with treatment. After the last interruption, the Berlin patient’s virus became undetectable and has remained so for nearly three years, without treatment. Because replication-competent virus can still be found in his latent cells, the Berlin patient is not considered “cured.”

Lori and colleagues then theorized that exposing the immune system to HIV in a highly controlled way might stimulate the body’s innate ability to fight back. To test this, they attempted to replicate the process in three treatment-naïve individuals. After a second interruption, the first patient’s viral load remained below 5,000 for six months. A second patient’s viral load quickly rebounded with each interruption. But in the third patient—now known as “the Washingtonian”—the period before viral rebound became increasingly prolonged. After the last treatment interruption, he went 150 days before resuming treatment.

A Walk on the Wild Side

Veronica Miller of J.W. Goethe-Universitat in Frankfurt dazzled participants at the 1999 Salvage Therapy Workshop with her presentation on a chronically infected, multi-drug resistant cohort of 39 patients on “megaHAART” (including five to nine drugs). Using phenotypic testing to check baseline resistance, Miller found that two-thirds had shifted toward a more drug-sensitive HIV, also known as “wild type” virus, following a treatment interruption.

Steven Deeks and colleagues at the University of California San Francisco confirmed and expanded upon Miller’s observations. Patients whose protease inhibitor-based regimen was failing were randomized into two groups: 18 patients underwent a 12-week treatment interruption; the others remained on failing regimens. After eight weeks, 16 of the 17 STI patients who could be evaluated underwent a shift from drug-resistant to protease inhibitor-sensitive virus.

Cellular Immunity

In Bruce Walker’s Massachusetts General Hospital acute infection study, seven patients underwent treatment interruptions and weekly tracking of viral load, CD4+ cell counts, and T-lymphocyte proliferation. After the first interruption, all three measures improved. After the second interruption, viral levels remained at...
and frequency of CTL responses after structured therapy interruptions in individuals treated with HAART during acute HIV-1 infection. Presentation from the 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, January 2000.


Author
Linda Grinberg, President of the Foundation for AIDS and Immune Research (FAIR) in Los Angeles, was a sponsor of the 1st STI Workshop in July 1999 and is organizing the 2nd STI workshop for Fall 2000. She is also on the Board of Directors of Project Inform.

Largest and Longest Studies
Preliminary results of the largest STI study to date suggests that responses are highly variable. At the XIII World AIDS Conference in Durban, Bernard Hirschel reported preliminary results of a study involving 122 patients who underwent four STI cycles, consisting of eight weeks on treatment and two weeks off, or until viral load reached 5,000. Hirschel detected no consistent pattern in the 56 patients who completed four treatment interruptions. Nineteen patients failed to get their viral loads below 50 after therapy resumption, though researchers suspected that poor adherence might be a factor. One patient showed evidence of resistance to two drugs in the study regimen, an apparent first in STI research. Experts suggest that a two-week treatment interruption may be too short to elicit adequate immune responses.

Studies at the National Institutes of Health under Mark Dybul and Anthony Fauci seek to determine whether the benefits of HAART can be preserved, while minimizing side effects and reducing costs. The following strategies are being studied: two months on treatment/one month off; one week on/one week off; and two days on/five days off. Reporting on the longest trial to date at the World AIDS Conference in Durban—the two-months on/one month off regimen—Dybul reported that nine of 70 recruits made it through either two or three STI cycles. While the first nine experienced viral rebounds with each interruption, virus was subsequently resuppressed with treatment. Three of the nine had smaller rebounds during the second interruption, while one had a higher rebound. During the first STI, CD4+ cells counts decreased by almost 20 percent, but after the initial dip, they remained stable. The third strategy was ineffective and abandoned. While it is too early to evaluate whether the first two strategies will be successful, without loss of viral control or seriously reduced CD4+ cell counts, such approaches could dramatically cut the cost of treatment for developing nations.

Caution and Hope
In the past, treatment interruptions raised fears that reemerging virus would mutate into drug-resistant forms. Such worries have been partially allayed, since only one documented case of resistance attributable to a treatment interruption has been reported and non-adherence was suspected as its cause. Since half-lives of antiviral drugs vary, clinicians must stagger cycling off particular drugs. Unanswered questions remain: how long will drug-resistant viruses persist at low levels or as “archived” virus in long-lived cells, and will recombinant virus emerge during STIs?

A year after presenting her initial results, Veronica Miller presented a sobering update, underscoring inherent risks of stopping therapy in the setting of virologic failure. Almost three-quarters of her original cohort eventually experienced virologic rebound and one-quarter failed to recover pre-STI CD4+ counts. In an expanded cohort of 165 patients, Miller also documented 17 new opportunistic infections. Without a non-STI comparison arm, the impact on disease progression remains unclear; however, if treatment failure can be delayed, this might prove beneficial in advanced disease.

While STIs may hold promise, the data are inconclusive. The answers may be variable and ultimately hinge on immune status, host and viral factors. Numerous “proof of concept” studies are underway, covering virtually every patient population, addressing safety, efficacy, optimal on/off schedules, and which markers may be predictive of outcome.

As eradication has all but evaporated into yesterday’s elusive dream, scientists face an age of treatment uncertainties, a global pandemic, and the inescapable reality that growing numbers of patients are stopping therapy. We must confront the fact that lifelong treatment, as we know it, appears untenable. Exploring innovative strategies, which harness the power of the immune system in tandem with effective antiretrovirals, appear crucial.
Lipodystrophy and Antiviral Medications


Current literature suggests a link between lipodystrophy and protease inhibitor therapy and, more recently, to nucleoside reverse transcriptase inhibitors and duration of HIV infection. “Lipodystrophy” describes physical and metabolic characteristics, including fat redistribution, pancreatitis, insulin resistance, and diabetes.

A two-year study found that 83 percent of participants receiving protease inhibitors developed lipodystrophy, compared to only 4 percent of participants not receiving protease inhibitors. Among participants receiving protease inhibitor therapy, lipodystrophy was mild in 42 percent, moderate in 30 percent, and severe in 11 percent. In a similar study, 64 percent of participants receiving protease inhibitors experienced fat wasting in the face, arms, and legs; only 3 percent of participants not taking protease inhibitors experienced these side effects.

A study of 42 HIV-positive women on antiviral treatment found that half of the participants experienced lipodystrophy. In a subset of 12 participants with fat redistribution, common side effects included elevated cholesterol levels, increased abdomen size, weight gain, fat wasting in the arms, legs, face, and buttocks, and development of “buffalo hump.” Risk of fat redistribution significantly increased with duration of antiviral therapy. Research also suggests that persistent lipid abnormalities may increase the risk of cardiovascular disease.

Several studies suggest that replacing protease inhibitors with non-nucleoside reverse transcriptase inhibitors can reverse the abnormalities associated with lipodystrophy, but doing so may increase viral load. In one study, 23 participants with lipodystrophy and a viral load of less than 200 switched from a protease inhibitor to nevirapine. Viral load increased in only one participant and overall, there were significant improvements in cholesterol, triglyceride, and glucose levels.

Adverse Effects of Protease Inhibitors


Thirty-six percent of participants in a large Italian study experienced adverse reactions to protease inhibitor therapy, and 10 percent had at least one serious adverse effect. In response, 15 percent of participants interrupted their treatment regimens, and each case led to a failed treatment regimen.

The two-year study monitored 880 men and 327 women from the time they began protease inhibitor therapy. The average age of participants was 37 years. Twenty-five percent of the study group had been diagnosed with AIDS, and 23 percent had hepatitis.

Women and participants with hepatitis experienced a significantly greater number of adverse events compared to other participants. Researchers grouped possible protease inhibitor side effects into six categories: gastrointestinal toxicity, hepatic (liver-related) toxicity, neurologic toxicity, metabolic alteration, allergic reaction, and renal toxicity.

Ritonavir was associated with the largest number of adverse reactions, which usually appeared during the first few months of treatment, while saquinavir hard-gel and nelfinavir were the best tolerated. Gastrointestinal side effects such as nausea, vomiting, and diarrhea frequently occurred in participants treated with either ritonavir alone or in combination with either saquinavir hard-gel or nelfinavir. Among participants treated with ritonavir, other side effects included: hepatic toxicity; neurologic toxicity such as headache, nerve disorders, and taste alteration; and metabolic complications such as lipodystrophy, weight gain, cholesterol increase, and diabetes.

Participants on indinavir presented with the highest incidence of renal toxicity, including kidney stones, discharge of blood in the urine, and acute kidney
failure. Participants on nelfinavir commonly experienced allergic reactions such as swelling, rash, and itching.

Alternate Strategies for Antiviral Treatment


Contrary to the widely accepted HIV treatment strategy that calls for suppressing viral load as quickly as possible, a University of Minnesota physician argues that some clients may benefit from patient-focused alternative strategies such as delayed initiation of therapy, drug regimens that exclude protease inhibitors, planned drug interruptions, and immune-based therapy.

Early aggressive therapy often prematurely exposes individuals to medication-related side effects and potential drug resistance. Persistent, though mild, side effects are common and can negatively affect quality of life. Metabolic problems, hepatitis, pancreatitis, nerve disorders, gastrointestinal symptoms, bone problems, and renal disorders have replaced AIDS-related illnesses for many HIV-positive patients.

Standard guidelines suggest that therapy should change when a regimen ceases to suppress viral load. However, recent data suggest that during a 12- to 18-month period, viral load may rise to detectable levels without any noticeable damage to the immune system. Further, viral load resurgence in people receiving antiviral therapy may reflect development of resistance to only one of the drugs in the regimen. Because of the risk of drug resistance, it may be prudent to reserve potent antiviral treatments for use later in the course of HIV disease at a time when there is a greater risk for developing AIDS-related illnesses.

Clarification

The May issue of FOCUS included an article entitled “HIV, AIDS, and the Distortion of Science,” by Martin Delaney. Delaney refers several times to Christine Maggiore, the author of What if Everything You Thought You Knew about AIDS Was Wrong? Maggiore takes exception to his statements.

In response to Delaney’s statement, which can be read to mean that Maggiore relies only on her personal experience to support her assertions that the HIV test is flawed, Maggiore says, “I offer referenced data raising questions about the test’s cross-reactivity, its inability to specifically identify HIV antibodies, and the lack of a gold standard of virus isolation.”

In response to Delaney’s statement that “Maggiore’s book seems to indicate that repeated testing in her case confirmed that she was not HIV-positive in the first place,” Maggiore says, “Following the mention of my experience of testing HIV-positive, -indeterminate, -positive, -negative, and -positive, my book states, ‘Although my HIV status has been decidedly positive for the past five years, I enjoy abundant good health and live without pharmaceutical treatments or fear of AIDS.”

Finally, in response to Delaney’s statement that “Maggiore conceded she had no idea why people died ‘of AIDS’ before antiviral drugs were available,” Maggiore adds that she has hypothesized in two articles about alternative causes of AIDS, including treatment with experimental HIV-related chemotherapy, recreational drug use, and antibiotic treatment, which combined with improper sleep and nourishment to create immunodeficiency. “Ultimately, without knowing the unique health history and lifestyle of the people who died, it’s impossible to come up with a definitive answer that would explain these unfortunate deaths.”

Next Month

The XIII World AIDS Conference took place in Durban, South Africa, in July. In the October issue of FOCUS, David Miller, PhD, Rachel Baggaley, MB, BS, and Bita George, MD, all of whom work with HIV in the developing world, review conference presentations and other sources to provide a perspective on the psychosocial implications of the epidemic in Africa. They focus, in particular, on the relevance of formal mental health and counseling programs in areas where such approaches are not as common as they are in more westernized societies.

Also in the October issue, Nancy Geshke, MSW, former Executive Director of LA Shanti, reviews conference presentations covering the prevention and care challenges of people with HIV.
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