

Successful HIV Treatment: Lessons Learned

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ABSTRACT

OBJECTIVE: To review current insights concerning treatment of human immunodeficiency virus (HIV).

SUMMARY: The range of antiretroviral agents available for treating patients who have HIV/AIDS (acquired immunodeficiency syndrome) has expanded to 20 medications since the first, zidovudine, was approved in 1987. While the exact choice of drugs to use in treatment must be tailored to the patient, depending on safety and tolerance, the ultimate goal is durable suppression of the HIV virus. Highly active antiretroviral treatment (HAART) is the current standard of care and involves treating the patient with a combination of antiretrovirals. First-line regimens usually contain a combination of 2 nucleoside reverse transcriptase inhibitors plus either one nonnucleoside or protease inhibitor. Differences in side effects have become more important than differences in efficacy in determining the choice of the initial antiretroviral regimen. To prevent the development of viral resistance to treatment, it is essential to begin treatment with all medications simultaneously, rather than sequentially. If the initial HAART regimen fails, more complex regimens that involve adding at least 2 new antiretrovirals can often reestablish control, even in patients with extensive pretreatment and in whom there was the development of viral resistance.

CONCLUSION: For patients with HIV/AIDS embarking on treatment today, the durability of HIV suppression in optimal regimens suggests that a normal lifespan is now a realistic outcome of HIV treatment.

KEYWORDS: Human immunodeficiency virus (HIV), Acquired immunodeficiency syndrome (AIDS), Highly active antiretroviral therapy (HAART), Antiretroviral drugs, HIV resistance, Protease inhibitor

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Treatment for human immunodeficiency virus (HIV) has progressed substantially since the introduction of zidovudine (traditionally referred to as AZT) 2 decades ago. Since then, the therapeutic arsenal for HIV/AIDS (acquired immunodeficiency syndrome) has expanded to include 20 different antiretroviral drugs (Table 1). The lifelong nature of HIV and the critical importance of long-term patient adherence to their antiretroviral regimen underscore the importance of individualizing therapy to the patient's needs and tolerance. Providers are continually challenged to combine available antiretroviral agents into a regimen that will best control the disease, while minimizing adverse events.

Goal of HIV Treatment

The primary goal of antiretroviral therapy is to suppress viral replication. Early research showed that suppressing or preventing HIV viral replication would control infection, significantly reducing damage to the immune system, and allow the immune system to recover from the damage done from uncontrolled HIV replication.

HIV specifically recognizes a key cell type of the human immune system, the CD4+ T lymphocyte. Once HIV enters the CD4+ cell, HIV integrates its RNA into the host cell's genetic processes for viral replication. At the end of the HIV life cycle, the immune cell is destroyed, while approximately 100 new virions are produced and released. These new virions infect and replicate in other CD4+ cells. Effective antiretroviral therapy suppresses this viral replication, causing the number of HIV RNA copies, or viral load, to decrease, and the CD4+ count to increase. A rise in CD4+ count indicates that the patient's immune status is improving given historic demonstrations that these higher CD4+ counts are protective against opportunistic infections.

The plasma HIV RNA level and CD4+ cell count are useful surrogate markers for measuring virologic and immunologic changes, respectively, in HIV-infected patients. These markers continue to be used to monitor the progression of HIV disease and the effectiveness of treatment.

TABLE 1 Available Antiretroviral Drugs

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
Abacavir	Lamivudine	Zidovudine
Didanosine	Stavudine	
Emtricitabine	Tenofovir	
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Delavirdine	Efavirenz	Nevirapine
Protease inhibitors (PIs)		
Atazanavir	Indinavir	Ritonavir
Darunavir	Lopinavir	Saquinavir
Fosamprenavir	Nelfinavir	Tipranavir
Entry Inhibitor		
Enfuvirtide		

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Early Treatment Approaches: Trial and Error

Until 1991, the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine was the only approved antiretroviral drug available for treating HIV infection. However, zidovudine appeared to be effective: many patients responded to monotherapy with a transient decrease in viral load (or, more commonly measured at that time, a decline in the p24 antigen level) and a transient increase in CD4+ count (Figure 1). As research continued, investigators began testing the effects of treatment with a combination of zidovudine plus an investigational NRTI, didanosine. Results were favorable and superior to what was observed with monotherapy, and once didanosine was approved in 1991, combination therapy became the new standard of care for patients with HIV/AIDS.

One problem, as illustrated in Figure 1, was that the effectiveness of NRTI therapy—whether given as monotherapy or combination therapy—was often not sustained. Eventually, patients became viremic since viral suppression was not durable, and as the viral load rebounded, the CD4+ count declined. Better treatment was needed to overcome this problem of resistance to mono or dual NRTI therapy.

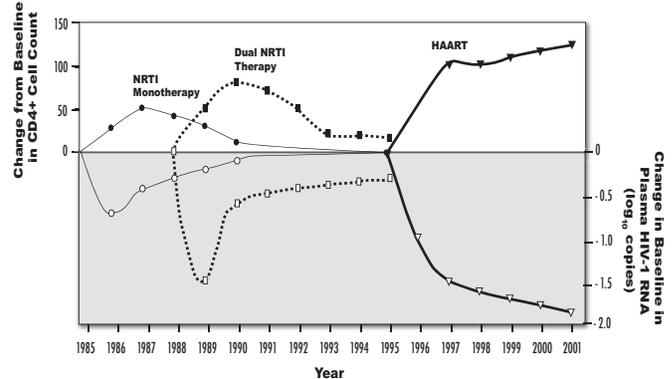
The Era of Highly Active Antiretroviral Therapy (HAART)

Studies involving a new class of antiretroviral drugs—HIV protease inhibitors (PIs)—showed that PI-containing 3-drug regimens were more potent than dual NRTI therapy in suppressing viral replication. The potent suppression led to more durable suppression as well, lasting years instead of months as was previously the case (Figure 1). The approval of several PIs in 1995 and 1996 ushered in the era of what became known as highly active antiretroviral therapy (HAART).

During the early days of HAART, most patients who had started treatment with zidovudine monotherapy had new drugs sequentially added to their regimen as they became available. This type of sequential therapy, even in the HAART era, led to a substantially lower response compared with a regimen involving simultaneous administration of the same drugs (Figure 2).¹ The lessons learned from this observation engendered a new standard of HIV/AIDS care, in which treatment-naïve patients are simultaneously started on a HAART regimen consisting of a dual NRTI backbone plus a PI or a nonnucleoside reverse transcriptase inhibitor (NNRTI). High levels of viral suppression can be achieved by combination of 1, 2, or even 3 classes of antiretrovirals. The current standard of care for initial HAART, which has been defined based on the results from numerous randomized studies, consists of 2 NRTIs and either an NNRTI or a ritonavir-boosted PI (i.e., a PI that is simultaneously given with low-dose ritonavir). Boosting is done to increase the exposure to the drug (increased trough and/or area under the curve), which results in greater antiviral activity than that with an unboosted PI, as well as a simplified dosing schedule.

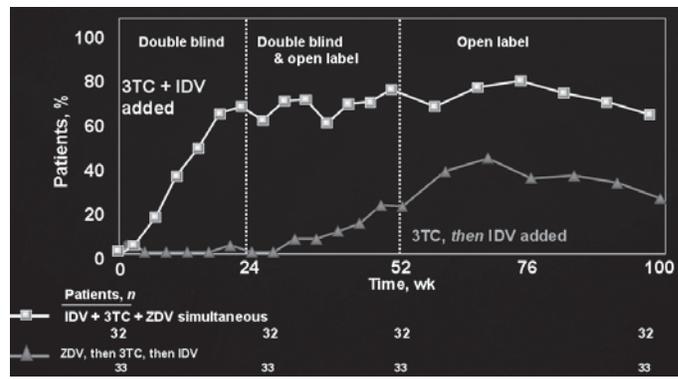
Incomplete suppression of viral replication still occurs and is problematic. On an individual level, it leads to treatment failure and, with the loss of CD4+ cell counts, a higher risk of disease

FIGURE 1 Typical Virologic and Immunologic Responses Over the 3 Antiretroviral Treatment Eras



The 3 antiretroviral treatment eras: monotherapy with a single nucleoside reverse transcriptase inhibitor (NRTI), dual NRTI therapy, and highly active antiretroviral therapy (HAART). Schematic compares the typical virologic (plasma HIV-1 RNA level) and immunologic (CD4+ cell count) responses over time with each regimen. HIV=human immunodeficiency virus.

FIGURE 2 IDV + 3TC Simultaneously vs. Sequentially



Difference in patient response to a highly active triple-drug regimen when patients are exposed to antiretroviral medications simultaneously versus sequentially. Patient response to treatment was defined as achieving an HIV RNA level below 50 copies/mL. Data from the Merck 035 study, which evaluated the use of a triple-drug regimen comprising the protease inhibitor indinavir (IDV) plus the nucleoside reverse transcriptase inhibitors zidovudine (AZT) and lamivudine (3TC). Adapted from Gulick et al., JAMA 1998;280:35.¹ HIV=human immunodeficiency virus.

progression. On a broader scale, incomplete suppression leads to the following undesirable scenarios:

- *Partial or complete loss of drug activity.* Ongoing viral replication during treatment usually results in a mutated HIV strain that is resistant to the antiviral effects of one or more of the drugs in the patient's antiretroviral regimen.

CASE STUDY Managing Triple Resistance to HIV

JH was a 53-year-old man who was diagnosed with human immunodeficiency virus (HIV) in 1995. His initial CD4+ count was 259; HIV viral load was nearly 40,000 copies/mL. These values were similar on repeat determination. JH was willing to start treatment but did not want any “experimental” or “cocktail” therapies. At the time, the recommended treatment consisted of 2 drugs, such as zidovudine and lamivudine.

JH responded fairly well to this treatment. Within 2 months, his viral load dropped below 400 copies/mL, and his CD4+ count increased to 360. However, the treatment did not offer durable protection, and by month 12, his viral load had increased to around 4,000 copies/mL. JH’s CD4+ count remained stable.

JH was treated with a series of PIs, all of which involved cumbersome regimens that were not well tolerated. Because of cross-resistance, the next regimen—ritonavir-boosted lopinavir with amprenavir, supplemented with lamivudine and abacavir—was not completely suppressive and again was poorly tolerated. JH stopped treatment and, ultimately, this led to a CD4+ count of 10 and a viral load exceeding 1,000,000 copies/mL.

Resistance testing showed that JH had become resistant to all then-available PIs. The only drugs with some hint of activity against HIV were some of the nucleosides, one of which was tenofovir. Some new medications had become available since JH had first presented, among them were tipranavir and enfuvirtide.

The addition of enfuvirtide rounded out JH’s treatment program to zidovudine, lamivudine, tenofovir, lopinavir (the only PI that JH could tolerate), and enfuvirtide. The viral load dropped by 3 logs in the first month of treatment, then came up by about 1 log in the second month, ending at 10,000 copies/mL. JH maintained this 2-log drop in HIV count for more than 1 year. The next year, his CD4+ increased from 10 to more than 320.

JH has done well. His CD4+ count has stabilized at 320, and he is very adherent with treatment and follow-up.

- *Development of cross-resistance.* Certain viral mutations can result in the development of drug-resistant viruses that will be less susceptible to other antiretroviral agents that have not yet been used (that is, cross-resistance).

The Need for Multiple Drug Regimens

Any antiretroviral drug can select for resistance when given as monotherapy, which is why physicians now prescribe combination treatment. With multiple drugs from various classes on board, the virus is less likely to develop resistance to a single antiretroviral drug since the other medications reduce the ability of the mutant virus to replicate.

Clinicians soon discovered, however, that it was not enough to just add a third drug to a failing 2-drug combination. Doing so would lead to resistance against the third medication if HIV had already selected for resistance to the first one or two antivirals because of incomplete suppression. As a result, many treatment options were lost through resistance. Today, several thousand patients in the United States have triple-class resistance to HIV, meaning they have some degree of resistance to 3 classes of antiviral medications. Controlling viremia is very difficult in these patients (see Case Study: Managing Triple Resistance to HIV).

CD4+ Response

The phenomenon of CD4+ stability despite ongoing HIV replication while on treatment has become the focus of intensive research. A study by Deeks and colleagues examined changes in CD4+ cell count and in HIV RNA that occur over time in persons receiving HIV treatment (Figure 3).² This study showed that patients achieving viral suppression to “undetectable levels” have the best increase in their CD4+ cell counts, often as much as 200 cells by the end of a year.

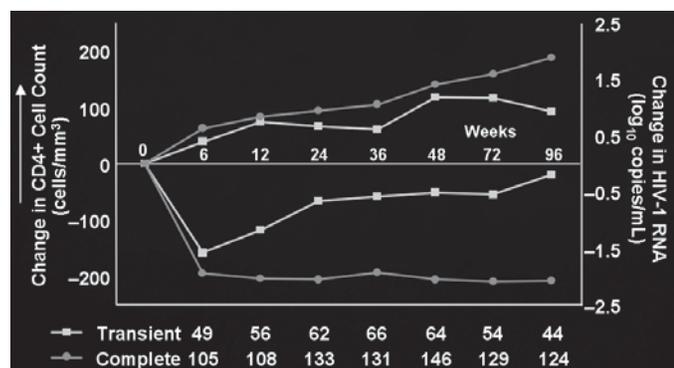
Under conditions of partial viral suppression, the CD4+ count still does well, increasing by about 100 cells and then remaining stable for about 3 years; this trajectory in the presence of viremia was understood to have multiple determinants, one of which was the degree of partial suppression conferred despite some degree of HIV resistance to treatment. Early on, physicians and patients alike were satisfied if the CD4+ count simply increased, regardless of complete viral suppression.

Importance of Complete Suppression

If the patient’s CD4+ count has gone up and his or her risk of opportunistic infection has declined, why care about complete viral suppression? Some medications will lose complete activity as the result of development of drug resistance over time.

An example of this has been demonstrated in an early study of nevirapine.³ In this study, persons who were on a stable regimen of zidovudine monotherapy had nevirapine added to their treatment. In response, the viral load declined about 1.5 logs but returned to baseline within 2 weeks. Thus, adding nevirapine to a stable regimen of zidovudine provides a benefit that lasts only

FIGURE 3 CD4+ Stability Despite Ongoing Viremia



CD4+ response with durable versus transient suppression of HIV replication. When viral suppression is significant, the CD4+ count can increase. After a year, the count may have risen by 100 to 200 cells. Adapted from Deeks et al. *J Infect Dis* 2000;181:946.²
HIV=human immunodeficiency virus.

about 2 weeks; after which, HIV changes its genetic structure so that a mutated form can once again flourish—this time in the presence of nevirapine.

Sometimes, HIV does pay a price to become resistant to other antiretroviral drugs. One example is lamivudine. Adding lamivudine to the treatment plan causes an initial 1.5 log decline in HIV viral load.⁴ Even though HIV can develop resistance to lamivudine, the viral load does not return to baseline in the face of continued lamivudine therapy but is durably suppressed by about 0.5 logs.

Drug Resistance and Cross-Resistance

Partial suppression is not a desirable outcome of HIV treatment, in part due to the potential for cross-resistance. A state of partial HIV suppression compromises the efficacy of medications the patient is taking—both now and in the future—because the more the virus replicates, the greater the likelihood of mutations being introduced. In turn, with more mutations occurring, the greater the chance is that these mutations will allow the virus to become resistant not only to the antiretroviral effects of the drugs to which it is being exposed but also to other drugs not yet used from the therapeutic arsenal (referred to as cross-resistance). In short, drug resistance undermines the ability to achieve life-long HIV suppression.

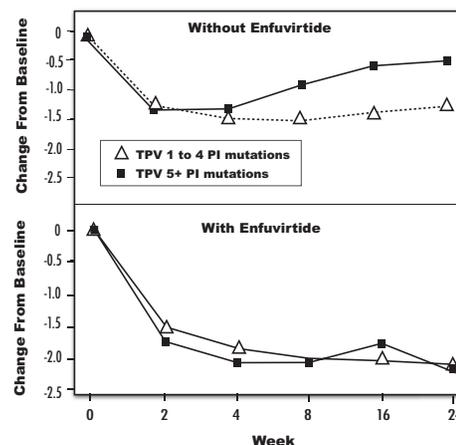
Melby and colleagues⁵ reported the effects of partial viral suppression over time in patients taking a coformulation of zidovudine, lamivudine, and abacavir. Patients who did not achieve complete suppression usually had a rebound in their viral load, with viral isolates initially showing only a single mutation associated with NNRTI drug resistance but soon developing other resistance mutations. With drug therapy that provides only partial suppression of viral replication, HIV will augment the number of mutations conferring resistance. This will have 2 implications:

- The viral load of HIV will increase toward its original level, and partial suppression will typically be lost over time.
- HIV mutations resulting from partial suppression lead to resistance to currently used medications and, potentially, cross-resistance to other medications of that class. In the Melby study, the mutations selected by zidovudine, lamivudine, and abacavir can confer resistance to the entire class of NRTIs. Thus, a single failing regimen may render an entire class of drugs less useful in a matter of a few years if there is ongoing viremia.

Possible Solutions

In the early days of HIV treatment, physicians would simply add or switch to another drug when they felt that the patient's current medication was failing. Physicians have since discovered that the success of changing medication depends on the approach used. Gulick and colleagues compared the outcomes achieved when indinavir and lamivudine were added sequentially versus simultaneously while patients were viremic during treatment with zidovudine.¹ They discovered that the key to success was not in the number of drugs given but in how those drugs were started

FIGURE 4 RESIST Trials: Change in Viral Load With and Without Enfuvirtide



Median viral load change from baseline by the number of baseline protease inhibitor (PI) mutations in the tipranavir (TPV) RESIST (Randomized Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir) studies when enfuvirtide was added and withheld. Adapted from the U.S. Food and Drug Administration, 2005.⁷

(Figure 2). Adding 2 new drugs simultaneously, rather than sequentially, produced a higher percentage of patients with an HIV count of <50 copies/mL. By treating with a sufficient number of effective drugs concomitantly, the physician can reestablish control and maintain suppression of HIV in the majority, rather than minority, of patients.

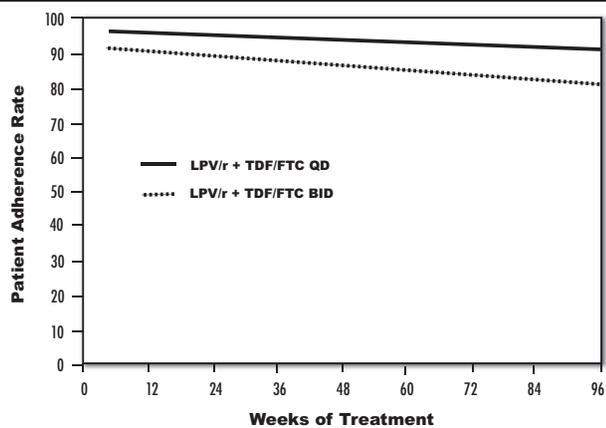
New Medications

Treatment options for persons with HIV/AIDS have recently expanded with the introduction of new PIs like darunavir and tipranavir and the first entry inhibitor enfuvirtide. Tipranavir was developed specifically for protease-resistant HIV. Enfuvirtide, an injectable antiviral, is in its own new class of drugs so there is no cross-resistance from the use of other antiretroviral medications.

Cahn and colleagues studied tipranavir in an optimized background of other antivirals versus other approved PIs in about 1,000 patients worldwide who were infected with highly PI-resistant viruses.⁶ Tipranavir was about 2.5 times more successful at controlling HIV than any of the other comparator PIs.

As with all antiretrovirals, tipranavir data show that patients with fewer PI mutations respond better to tipranavir than those with many such mutations (Figure 4).⁷ Whatever greater activity tipranavir may initially have, however, can be lost when it is used in a highly PI-resistant population unless the rest of the regimen has some activity as well. Giving tipranavir with a second fully active drug—enfuvirtide, for instance—significantly improves results (Figure 4).⁷ The combination of tipranavir and enfuvirtide produces a stable, durable 2-log drop in HIV count that can main-

FIGURE 5 Effect of Once- Versus Twice-Daily Dosing on Adherence



Effect of once-daily (QD) versus twice-daily (BID) dosing on patient adherence to antiretroviral treatment. In this study, both groups received a regimen of tenofovir (TDF) and emtricitabine (FTC) given QD plus lopinavir/ritonavir (LPV/r) given QD or BID. Patient adherence was determined through the use of Medication Event Monitoring System (MEMS) caps. Adapted from Rode et al., 2005.¹⁶

tain suppression in most patients.

New medications from existing and new antiretroviral classes (that is, CCR5 inhibitors and integrase inhibitors) are being developed, some that will probably become available to clinicians within the next 12 months.

Cost Concerns

The medications we have today are effective for most patients, but they are also very expensive. Enfuvirtide is probably the most expensive, costing about between \$15,000 and \$20,000 a year. Tipranavir is similarly expensive at more than \$10,000 per year.

Is treatment that includes such antiretrovirals worth the cost? Evidence indicates that treatment with enfuvirtide is still cost effective, when it successfully interferes with HIV replication.⁸ In so doing, antiretrovirals minimize the risk of comorbid illnesses that contribute to significant morbidity and therefore decrease the overall cost of care by decreasing hospitalization rates.

Approach to Treatment

While the specific choice of medications is subject to debate, the 3-drug regimens used for initial treatment are also favorable from a cost perspective. Based on a recent randomized study of initial therapy, there is clear evidence that 3 drugs are sufficient and that adding a fourth drug to a combination of 2 nucleosides and a third drug (for example adding a third NRTI to a combination containing 2 NRTIs and 1 NNRTI) does not add any demonstrable benefit.⁹

In the time since this presentation was given, a single tablet containing a combination of 2 nucleosides and 1 nonnucleoside

taken once a day has become available. The single tablet contains tenofovir, emtricitabine, and efavirenz—a combination that has been validated from an ongoing randomized study¹⁰ and supported by a previous study containing lamivudine instead of emtricitabine,¹¹ drugs understood to be largely interchangeable. This combination has been shown to be among the best first-line regimens in terms of efficacy and safety criteria. As a result of this further reduction in pill burden, it is reasonable to expect this treatment to be among the most successful for HIV infection in those starting therapy.

The number of people with virologic failure continues to decline. Evidence now demonstrates sustained virologic response 4 years into treatment with tenofovir, lamivudine, and efavirenz.¹²⁻¹⁴ It is reasonable to assume that if HIV resistance has not been observed after 4 years of treatment, resistance is unlikely as long as “adequate” patient adherence to treatment is preserved over time. It should be noted that there is considerable ambiguity with regard to the degree of adherence that is required to maintain suppression, and a goal of ongoing research is to define the minimum adherence patterns that maintain suppression of HIV replication with current regimens.

Studies involving the ritonavir-boosted PI approach, where patients also receive 2 nucleosides, show a similar very high response rate and good tolerance. When patients tolerate the treatment well initially, medications are likely to work effectively for a long period given good adherence to therapy.

Adherence

The other key focus of care is making sure the patient can and does take all medications. Mannheimer and colleagues examined the issue of whether adherence can be altered.¹⁵ Two interventions were tested: a nurse trained in adherence counseling and an automated beeper/pill reminder. Some patients were randomized to counseling by the nurse, some to the beeper, and some to both. The control group patients were given no adherence aids. Incidence of virologic failure was lowest (28%) in patients who received counseling by the nurse and highest (42%) in patients who received only the beeper. Thirty percent of the study participants who received no help and 33% of those who got both the nurse and the beeper had virologic failure in the first year. Therefore, the beeper/pill reminder actually detracted from adherence.

One insight into issues of adherence comes from a study done by Rode and colleagues.¹⁶ The team looked at adherence with once- versus twice-daily treatment with the same HAART regimen over a period of 2 years. The adherence with twice-daily treatment had declined to 81% by study end. Once-daily adherence remained greater than 90% after 2 years. This occurred despite a higher incidence of diarrhea on the once-daily regimen, strongly suggesting that once-daily treatment is simpler to adhere to.

Simpler Antiretroviral Regimens

Clinical studies reporting high response rates with potent drug regimens that are less complex and better tolerated suggest that

such regimens are allowing patients to better adhere to and remain on their treatment (Figure 5). One randomized study examined the difference between zidovudine plus lamivudine versus tenofovir plus emtricitabine in efavirenz-containing regimens.¹⁷ Tenofovir/emtricitabine was found to be superior to zidovudine/lamivudine primarily because it caused less toxicity.

Safety differences also are a concern when choosing a drug, especially considering that HIV/AIDS treatment is now so prolonged. In this study, tenofovir caused less elevation in cholesterol levels than did zidovudine.

This study¹⁷ also examined the incidence of lipodystrophy, which is a cosmetically disfiguring side effect. People with lipodystrophy or lipodystrophy may look ill since there can be fat loss in the face or limbs, suggesting a wasting-like illness. Using dual-energy X-ray absorptiometry, which is a rigorous method for measuring limb fat, those on tenofovir/emtricitabine showed a greater amount of limb fat after 1 year compared with those taking zidovudine/lamivudine.

Summary

There has been continued evolution in the number of HIV treatments available for use. However, the lessons learned as result of treatment have been intact for the past decade. Effective and durable suppression can be achieved in a majority of patients when at least 2 active antiretrovirals are initiated simultaneously and patient adherence is maintained. When virus replication is suppressed on a well-tolerated combination to “undetectable” levels, the observations of years of improved health associated with the control of HIV replication can confidently be anticipated to translate to decades of a healthy life despite HIV infection.

DISCLOSURES

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