



AIDS update 1999: Viral reservoirs and immune-based therapies

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■ ABSTRACT

The advent of highly active antiretroviral therapy (HAART) has brought about a dramatic decline in opportunistic infections, hospitalizations, and mortality in AIDS patients. However, the recent discovery that HIV can lay dormant in quiescent T cells and other tissues even in the face of HAART therapy has dampened optimism for a cure for AIDS, though it suggests new avenues of research.

TWO FACTS about human immunodeficiency virus (HIV) that have only recently been understood have changed our thinking about the treatment of HIV infection:

- HIV replicates throughout the course of infection.¹ (An earlier theory held that the virus entered a latency period soon after infection.)
- HIV can persist in quiescent T cells, macrophages, follicular dendritic cells, and other reservoirs during treatment with even our best drugs.²

This paper explores the ramifications of these findings in light of the development of highly active antiretroviral therapy (HAART), along with current recommendations for treating HIV infection.

■ HIV LATENCY A MISNOMER

Almost since the appearance of HIV, we have described the infection as going through three clinical phases:

- Primary infection, ie, the first 3 to 6 weeks after exposure, when the virus reproduces rapidly and is detectable in the blood. During this time, the patient may experience a syndrome that resembles infectious mononucleosis.

- A so-called latent period, lasting months to years, during which the patient feels well and HIV cannot be detected in the blood, but the number of CD4⁺ T cells declines progressively.

- Clinical disease, when the CD4⁺ count declines to less than 200/ μ L, and the patient becomes susceptible to opportunistic infections, AIDS-related cancers, and other complications.

However, we now know that “latent infection” was a misnomer. In fact, from the moment of initial infection, the virus replicates as fast as it can, but is held in check with variable success by the immune system. Even if the CD4⁺ count is normal, more than 10 billion new virus particles are produced each day. Most of these are quickly destroyed—their half-life is about 6 hours. However, some go on to infect new CD4⁺ cells, and infected CD4⁺ cells also have a short half-life, about 1.5 days. Therefore, the immune system sustains progressive damage from loss of CD4⁺ cells, although the rate of decline varies from patient to patient.

■ CURRENT RECOMMENDATIONS: TREAT EARLY, TREAT HARD

These new insights about HIV infection have changed our approach to treatment. Early in the epidemic, treatment with antiviral drugs was often reserved until late in the infection. Now the guiding principle is to “treat early, treat hard.”

**Even with
therapy, HIV
can persist for
years in
memory T cells**

TABLE 1

Antiretroviral drugs**Nucleoside reverse transcriptase inhibitors**

Zidovudine (ZDV, azidothymidine, AZT)
 Dideoxyinosine (ddI, didanosine)
 Stavudine (d4T)
 Dideoxycytidine (ddC, zalcitabine)
 Lamivudine (3TC)
 Abacavir

Nonnucleoside reverse transcriptase inhibitors

Nevirapine
 Delavirdine
 Efavirenz

Nucleotide inhibitors

Adefovir (currently in expanded-access trials)

Protease inhibitors

Saquinavir
 Ritonavir
 Indinavir
 Nelfinavir
 Amprenavir (in clinical trials)

TABLE 2

Initial treatment regimens for HIV infection**Give one of the following**

Indinavir
 Nelfinavir
 Ritonavir
 Saquinavir (soft gel cap formulation)
 Ritonavir plus saquinavir
 Nevirapine or delavirdine (may be less likely to provide sustained suppression than the above choices)

Plus one of the following

Zidovudine plus dideoxyinosine
 Stavudine plus dideoxyinosine
 Zidovudine plus dideoxycytidine
 Zidovudine plus lamivudine
 Stavudine plus lamivudine

Combinations to avoid

Two nucleoside reverse transcriptase inhibitors alone
 Two nucleoside reverse transcriptase inhibitors plus saquinavir in hard gel cap formulation
 Stavudine plus zidovudine
 Dideoxycytidine plus dideoxyinosine
 Dideoxycytidine plus stavudine
 Dideoxycytidine plus lamivudine
 All monotherapies (except in pregnancy)

Tell patients the virus will return if they stop their medication

Treat early. Antiviral therapy should be started if the patient has any of the following:

- Symptoms of HIV infection such as thrush, AIDS, or unexplained fever
- A CD4⁺ count less than 500/ μ L
- An HIV RNA level greater than 20,000/mL by polymerase chain reaction (PCR) testing.

In addition, some experts believe *any* person with HIV should start treatment, even if asymptomatic and with a CD4⁺ count greater than 500/ μ L and an HIV RNA level less than 20,000/mL. However, the value of antiretroviral therapy in this group remains controversial.

Treat hard. The goal is to suppress HIV below levels of detection as long as possible.

Treat for life. Initiating therapy is a life-long commitment. Patients should be aware that if they go off their regimen, the virus is likely to return forcefully.

Always use combination therapy to maximize viral suppression and avoid development of resistant mutants. The 1998 NIH consensus panel³ recommends using a combination of a

protease inhibitor plus two reverse transcriptase inhibitors (TABLES 1 AND 2).

This therapy is not easy. Many of the drugs have multiple interactions with other drugs, as well as toxic effects. The dosing schedules are complicated. If a treatment regimen fails because of noncompliance, drug-resistant viral strains are likely to emerge, seriously limiting the patient's future treatment options. For these reasons, some physicians may wish to consider referring patients with HIV to teams with experience in this field.

Do not add a single agent to a failing regimen. Doing so only promotes the emergence of treatment-resistant strains of HIV.

■ WHERE HIV CAN HIDE FROM THERAPY

Only a few years ago, when protease inhibitors were first introduced, we hoped that if viral levels could be suppressed below detectable limits and kept there for 2 to 3 years, patients

could be cured of HIV infection as viral reproduction was stopped and infected cells died off.

This was wishful thinking. A series of recent clinical observations demonstrated that viral levels rapidly return to pretreatment concentrations even after prolonged and profound inhibition of viral replication. The reason: antiviral drugs inhibit HIV replication within CD4⁺ cells, but HIV replicates only when the CD4⁺ cell is activated. A subpopulation of CD4⁺ cells, termed "memory" cells, can live for years or even decades in a quiescent state, and HIV, integrated into the genome of these cells, can persist almost indefinitely. (Macrophages and follicular dendritic cells can also harbor HIV, but are much shorter-lived.)

How can we get at the HIV in these cells? Several strategies have been proposed, but are yet unproved. These include:

- "Debulking" or reducing the number of the infected cells, using agents traditionally used for chemotherapy. (This strategy has a major disadvantage of further weakening the patient's immune system.)
- Flushing out viral reservoirs by activating the memory cells. The HIV within them would then start to replicate, but it would also become vulnerable to antiviral therapy. A promising way to activate memory cells is by giving interleukin 2.
- Immune restoration, using a therapeutic vaccine.

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CME ANSWERS

Answers to the CREDIT TEST on page 319 of this issue

1 B 2 C 3 B 4 D 5 C 6 E 7 C 8 B 9 B 10 A
11 E 12 C

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