CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

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/μL, 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.

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

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."

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/μL
- 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/μL 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 lifelong 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 panel[3] 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.

REFERENCES

1. **Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M.** Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995; 373:123–126.
2. **Schrager LK, D'Souza MP.** Cellular and anatomical reservoirs of HIV-1 in patients receiving potent antiretroviral combination therapy. JAMA 1988; 280:67–71.
3. **Feinberg MB, Carpenter C, Fauci AS, et al.** Report of the NIH panel to define principles of therapy of HIV infection and guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Ann Intern Med 1998; 128:1057–1100.

CME ANSWERS

CME 2 CREDIT HOURS

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**