LEONARD H. CALABRESE, DO
R.J. Fasenmyer Chair of Clinical Immunology,
Department of Rheumatic and Immunologic
Diseases, Cleveland Clinic

Using viral load, CD4+ levels, and clinical response to guide antiviral therapy for HIV

ABSTRACT

The decision to start or modify antiviral therapy in patients with human immunodeficiency virus (HIV) infection is not based on any single factor. Although HIV RNA levels are the primary guide to therapy, the CD4+ count and clinical response are also important.

KEY POINTS

The primary virologic goal is to reduce the plasma viral load to an undetectable level, ie, an HIV RNA level of less than 50 copies per mL.

Changes in the CD4+ count often do not correlate well with changes in the HIV RNA level, and the CD4+ count is therefore problematic to use as a basis for modifying therapy.

Often, treatment failure is due to nonadherence to the regimen rather than to viral resistance.

TO HELP GUIDE PHYSICIANS through the profoundly complex treatment and monitoring options, the International AIDS Society-USA Panel[1] recently updated its recommendations on antiviral therapy for human immunodeficiency virus (HIV).

We now have 14 antiretroviral drugs, with several thousand different potential combinations available to treat patients infected with HIV. In addition, laboratory monitoring for CD4+ levels, viral load, and antiviral resistance testing have advanced, giving clinicians an array of tools to monitor therapy. However, drug toxicities and complex regimens make patient compliance very difficult.

This article summarizes recent recommendations for clinicians to individualize therapy, using the different monitoring tools to guide therapy, detect treatment failure, and cope with the problems of compliance.

WHEN TO START HIV THERAPY

Guidelines for when to start antiretroviral therapy have changed often in the past few years and were updated most recently in January 2000.[1] The new recommendations from the International AIDS Society-USA Panel (TABLE 1) take into account the documented potential benefits of highly active antiretroviral therapy (HAART) and issues such as patient compliance and the emerging long-term complications of therapy.

Nonetheless, these guidelines remain controversial, and some experts advocate starting treatment earlier in the disease process to preserve cellular immunity.[1,2]

WHAT DRUGS TO USE

Which combination of drugs to use is beyond the scope of this paper. Interested readers can consult the published guidelines.[1,2]

WHEN TO CHANGE THERAPY

Once antiretroviral therapy has been started, one should use both laboratory tests and clinical factors to monitor its efficacy and to decide whether to change it. Although the matrix of decision-making is complex in patients with HIV disease, the indications for changing therapy can be reduced to two basic situations:

- When the therapy stops working
- When the therapy causes toxicity or difficulty with administration or adherence.

MONITORING THERAPY

Two laboratory tests that are essential in monitoring therapy are the HIV RNA level and the CD4+ cell count.

The HIV RNA level

HIV RNA assays are used to measure viral load, and can now detect as few as 50 copies / mL. Because plasma HIV RNA levels tend to fluctuate, it is advisable to obtain two HIV RNA measurements to determine a baseline level before starting therapy.

The primary virologic goal of therapy is to reduce the amount of HIV RNA in the plasma to undetectable levels (ie, < 50 copies / mL).[1] The rationale for such a goal is that the virus is less likely to become resistant to therapy if its replication is kept to a minimum. Viral resistance occurs less frequently when HIV RNA levels are maintained at less than 50 copies per mL than even at levels between 50 and 500 copies per mL.[3]

The HIV RNA level should decrease rapidly after therapy is started. A decline of 1.5 to 2.0 log (eg, from 100,000 copies/mL to 1,000 copies/mL) is expected by approximately 4 weeks. Undetectable levels usually take longer to achieve—as long as 16 to 24 weeks in patients with high baseline HIV RNA levels (ie, > 100,000 copies/mL).[1]

If the HIV RNA does not decrease to an undetectable level, the regimen has failed to some extent, and the clinician should consider altering it, although HIV RNA levels may fluctuate intermittently. Therefore, before changing the regimen, one should obtain two separate measurements of HIV RNA, and both should show that the viral load is rebounding.[1]

A goal of HIV RNA at undetectable levels may not be realistic for all patients, however. Other variables that must be weighed in the decision to intensify (ie, add one or more drugs) or change the regimen include the degree of immune reconstitution (ie, the CD4+ count), the acceptability and adherence to the present therapy, and the number of treatment options left to offer.

Obtain two HIV RNA levels before starting therapy

For example, suppose a patient has a very high baseline HIV RNA level—eg, 1 million/mL—and achieves a level of 5,000/mL. This submaximal response may be acceptable if he or she is tolerating the regimen well, has a sustained increase in the CD4+ count, and continues to do well clinically. In fact, some experts[4] argue that to plan therapy for the long term (ie, 20 years or more), we may need to accept higher HIV RNA levels and lower CD4+ counts than the published targets,[1] with the goals of preserving therapeutic options and minimizing toxicity and the emergence of drug resistance. This hypothesis deserves serious consideration and clinical study.

Frank virologic failure, in which the HIV RNA level rebounds to pretreatment levels or higher, should always prompt modifications in the treatment if other options are available.

TABLE 1

International AIDS Society: When to start therapy in adults

CD4+ CELL COUNT ($\times 10^9$/L)	PLASMA HIV RNA LEVEL (COPIES/ML)		
	< 5,000	5,000–30,000	> 30,000
< 350	Start	Start	Start
350–500	Consider	Start	Start
> 500	Defer	Consider	Start

ADAPTED FROM CARPENTER C, COOPER D, FISCHEL M, ET AL. ANTIRETROVIRAL THERAPY IN ADULTS: UPDATED RECOMMENDATIONS OF THE INTERNATIONAL AIDS SOCIETY—USA PANEL. JAMA 2000; 283:381–390.

The CD4+ count

After antiretroviral therapy is started, CD4+ counts increase. At first the increase is mainly due to redistribution of CD4+ cells from the lymphoid tissues to the circulation.[5,6] Later, new ("naive") CD4+ cells appear, believed to be primarily of thymic origin.[7]

If the patient achieves an undetectable HIV RNA level with therapy, the CD4+ count should increase by about 150 cells per mL.[8] Individual patients vary greatly, however, in how well their CD4+ counts recover.

In addition, some patients have a discordance between their HIV RNA response and CD4+ count.[9,10] The most common discordance is an increase or stabilization of the CD4+ count without optimal HIV RNA control. Others achieve excellent HIV RNA control, but their CD4+ counts increase very little. Progressive loss of CD4+ cells is of grave concern in any situation, but if the HIV RNA level remains undetectable, clinicians have few options for raising the CD4+ count aside from experimental immune-based therapies.

Thus, using the CD4+ cell count by itself as a guide to modifying therapy is more problematic than using the HIV RNA level.

Long-term therapy may require us to accept higher HIV RNA levels and lower CD4+ counts

DRUG TOXICITY

Drug toxicity is always a potential indication for changing the antiretroviral regimen. The toxicity associated with antiretroviral drugs varies from drug to drug and from patient to patient, and may be mild to severe. Potential long-term adverse effects of aggressive (primarily protease-based) therapies[4] include hyperlipidemia,[11] lipodystrophy,[11,12] diabetes,[11] wasting,[13] and osteopenia.[14,15] Whether any of these complications improve if the regimen is changed from a protease-based to a non–protease-based regimen is not known.

Some clinicians and patients are willing to put up with mild degrees of toxicity (eg, intermittent diarrhea) if the HIV disease remains under excellent control. However, severe or even life-threatening reactions such as Stevens-Johnson syndrome or lactic acidosis demand an immediate change in the regimen. The decision should be made independently of the CD4+ cell count or HIV RNA level.

ASSESSING TREATMENT FAILURE

Drug failure is generally defined as any of the following:

- Inadequate viral suppression—either failure to reach the target viral load or rebound of the viral load after reaching the initial goal
- Unsatisfactory increases in the CD4+ count
- Clinical progression.

Reasons for treatment failure

When therapy fails, our first thought is often that the virus is becoming resistant to the drugs. Other reasons often account for treatment failure, however.

Nonadherence to the regimen. The initial approach to virologic failure is to assess adherence. Failure to take drugs at appropriate intervals or missing doses will lead to loss of potency of the regimen. A study showed that after only 12 weeks, 95% adherence was associated with a success rate of 80% in achieving targeted suppression of the HIV viral load, but 80% adherence was associated with a success rate of just 50%![16] Some patients simply cannot adhere to a highly complex regimen, and thus may have to take simpler and at times suboptimal combinations.

Inadequate blood levels of the drug. Inadequate drug levels can affect antiviral potency. The fault may lie in drug interactions or malabsorption. Therapeutic drug level monitoring is not currently readily available nor a standard of care, but likely will be.[1]

What are the options in treatment failure?

Once the clinician concludes that the treatment is failing, he or she has several options that range from intensifying the regimen by adding a single drug to changing the entire treatment plan. In general, adding a single drug to a failing regimen is considered suboptimal unless guided by specific resistance data. These options have recently been reviewed in great detail.[2]

CHANGING TREATMENT IN THE ABSENCE OF VIROLOGIC FAILURE

Aside from the laboratory findings or even toxicity, patients often need to have their regimens modified on the basis of individual preferences leading to difficulties with compliance. Selection of drug programs has to be highly individualized, taking into account lifestyle (eg, living situation, travel schedule, and eating habits) and financial resources.[1,2] Recent advances in drug design have allowed twice-a-day regimens using as little as four pills a day for some people. Once-daily dosing regimens are now in active clinical trials. Unfortunately, these inviting options will continue to be limited by drug tolerance and resistance patterns.

WHO SHOULD TREAT HIV DISEASE?

There is no specific credentialing in HIV care. While infectious-disease specialists undertake most of the care of HIV patients, there is no restriction based on specialty training.

Early in the HIV epidemic, there were calls for all primary care physicians to participate in its care. Now, however, as the disease and its treatment have become more complex, the pendulum has swung the other way, with calls for care to be limited to those with sufficient training and experience. Recent studies found that HIV patients had higher survival rates if they received care from physicians with more experience in HIV disease.[17,18]

To provide optimal care, clinicians need:

- Hands-on experience gained in managing many patients
- Access to and experience in using state-of-the-art diagnostic tests and immune system monitoring
- Skilled ancillary workers such as case managers, social workers, and nutritionists.

In addition, given the many questions remaining about HIV treatment, all patients should have the option of participating in clinical trials when appropriate.

Ideally, a partnership between the primary care physician and the HIV treatment team would provide the best care.

REFERENCES

1. **Carpenter C, Cooper D, Fischel M, et al.** Antiretroviral therapy in adults: Updated recommendations of the International AIDS Society—USA panel. JAMA 2000; 283:381–390.
2. Guidelines for the use of antiretroviral agents in adults and adolescents. Department of Health and Human Services and Henry J. Kaiser Family Foundation. January 28, 2000. http://www.hivatis.org.
3. **Raboud JM, Montaner JS, Conway B, et al.** Suppression of plasma viral load below 20 copies/mL is required to achieve a long-term response to therapy. AIDS 1998; 12:1619–1624.
4. **Henry K.** The case for more cautious patient focused antiretroviral therapy. Ann Intern Med 2000; 132:306–311.
5. **Rosenberg ES, Billingsley JM, Caliendo AM, et al.** Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. Science 1997; 278:1447–1450.
6. **Bucy RP, Rockett RD, Derdeyn CA, et al.** Initial increase in blood CD4(+) lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues. J Clin Invest 1999; 103:1391–1398.
7. **Autran B, Carcelain G, Tubiana R, et al.** Effects of antiretroviral therapy on immune reconstitution [abstract]. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract S44.
8. **Deeks SG, Hecht FM, Swanson M, et al.** HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic. AIDS 1999; 13:F35–F43.
9. **Deeks S, Barbour J, Swanson M, et al.** Sustained CD4 T cell response after virologic failure of protease inhibitor based regimens [abstract]. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 494.
10. **Kaufmann D, Pantaleo G, Sudre P, et al.** CD4+ cell count in HIV-1 infected individuals remaining viraemic with highly active antiretroviral therapy (HAART). Lancet 1998; 351:723–724.
11. **Carr A, Samaras K, Burton S, Law M, et al.** A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12:F51–F58.
12. **Henry K, Melroe H, Huebesch J, et al.** Severe premature coronary artery disease with protease inhibitors. Lancet 1998; 351:1328.
13. **Brinkman K, ter Hofstede HJ, Burger DM, et al.** Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. AIDS 1998; 12:1735–1744.
14. **Scribner AN, Skiest DJ, Marcantonio D, et al.** A case control study of osteonecrosis in HIV [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy. 1999:1311.
15. **Hodak SP, Fluhme D, Kumar P, et al.** Avascular necrosis and protease exposure [abstract]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy 1999:1312.
16. **Paterson D, Swindells S, Mohr J, et al.** How much adherence is enough? A prospective study of adherence to protease inhibitor therapy using MEMS caps [abstract]. Sixth Conference on Retroviruses and Opportunistic Infections. 1999:92.
17. **Kitahata MM, Koepsell TD, Deyo RA, et al.** Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. N Eng J Med 1996; 334:701–706.
18. **Laine C, Markson LE, McKee LJ, et al.** The relationship of clinic experience with advanced HIV and survival of women with AIDS. AIDS 1998; 12:417–424.

ADDRESS: *Leonard H. Calabrese DO, Department of Rheumatic and Immunologic Diseases, A50, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195; e-mail calabrl@ccf.org.*