Viral Load in Clinical Trials

Recent findings on plasma viral load and the practical aspects of using viral load data in the clinical setting were discussed at the Los Angeles course by Steven A. Miles, MD, from the University of California Los Angeles.

The Use of Viral Load Measurements as Prognostic and Therapeutic Markers

In the last year, the use of viral load assays to measure HIV RNA in plasma has become recognized as an essential part of clinical management for patients with HIV disease. One viral load test, a quantitative reverse transcriptase polymerase chain reaction (RT PCR) test can dependably detect 500 or more copies of HIV RNA/mL of plasma and has been approved by the FDA for diagnostic and prognostic use. Two other tests, branch DNA (bDNA) and nucleic acid sequence-based amplification assay (NASBA) have comparable sensitivities but are not yet FDA-approved.

Viral load measurements have become an essential part of HIV disease management.

Several studies have now demonstrated the correlation between higher viral load and more-rapid disease progression and death in HIV-infected adults and children. The risk of progression and death grows steadily with increasing viral load. Plasma HIV RNA levels and CD4+ cell counts are independent markers of disease progression, and they should be used in conjunction to monitor disease status and manage antiretroviral therapy.

Ongoing investigations have clarified the prognostic value of viral load measurements in early disease. In a prospective longitudinal study of 74 patients with primary and very early infection, median plasma HIV RNA levels were 235,000 copies/mL at 30 days and 46,000, 52,000, 36,000, and 19,000 copies/mL at 60, 90, 120, and 180 days, respectively. Considerable intersubject variation was observed at all time points. In patients from whom samples were obtained within 6 months of seroconversion, clinical and immunologic progression was not related to the plasma HIV RNA level. After approximately 6 months a steady state "set point" appears to be established. In one study, the plasma HIV RNA level at the post-seroconversion set point level (>6 months after seroconversion) was highly predictive of clinical progression and was related to the risk of death.

Viral load measurements are also valuable in measuring the kinetics of viral and T-cell replication in response to antiretroviral therapy. There is a two-phase viral decay slope, with a 90% to 99% reduction in plasma viral load in the first two weeks of therapy, and a slower second-phase decline to undetectable levels over the next 12 to 24 weeks. This second phase reflects the slower clearance of chronically infected T cells or macrophages.

With potent combination therapies, many patients achieve a level of plasma viral RNA below the limit of detection of the available assays. Newer generation bDNA and RT PCR research assays, which can detect as little as 20 to 50 copies of HIV RNA/mL of plasma have confirmed that "undetectable" does not necessarily indicate "no viral replication." Further, while the virus may be undetectable in the plasma, it may be present in the central nervous system, the lymph nodes, the bone marrow, and other body compartments.

The limits of currently available assays in detecting low levels of plasma HIV RNA complicates the ability to completely assess the effectiveness of antiretroviral regimens and to identify initial failure. The "duration of maximal viral suppression," a term borrowed from oncology, is defined as the time between the trough value for the plasma HIV RNA level and two subsequent values (measured at least four weeks apart) that are at least 0.3 log greater than the trough value. In the studies of ritonavir, the durability of the HIV RNA level response was predicted by the trough value, not by the magnitude or rate of the plasma HIV RNA decline. Thus, with the protease inhibitors, the minimum plasma HIV RNA value achieved with therapy may serve as a prognostic indicator for time to eventual viral rebound.

Clearly, viral load assays are important and powerful tools, but many questions remain about optimal clinical use. Understanding the value and limitations of the assays will help to avoid premature discontinuation of still-effective antiretroviral regimens. Familiarity with logarithms,

Table 1. Decimal, Exponent, and Logarithms

Decimal Number	Exponential Form	Log_{10} Value
100,000,000	10^8	8
10,000,000	10^7	7
1,000,000	10^6	6
100,000	10^5	5
10,000	10^4	4
1,000	10^3	3
100	10^2	2

Each number is a tenfold change from the previous

knowledge of factors that effect plasma viral load, and the ability to assess clinical trial data critically all contribute to optimal use of these assays.

Clinical Use of Viral Load Measurements

Interpreting Logarithmic Data

Several general strategies can simplify the use of viral load data. Table 1 lists decimal numbers, the exponential forms, and the logarithmic equivalents. To calculate a 1-log increase or decrease, add or remove, respectively, the last digit (eg, 1-log decrease from a value of 10,000 is a decrease to 1000). To determine if two plasma HIV RNA values are significantly different, calculate whether there is a threefold difference between them (eg, 150 copies/mL to 50 copies/mL represents a significant decline). While these strategies may help in comparing serial viral load measurements, it is important to emphasize that the target viral load value is unequivocally zero.

Factors That Influence Viral Load Measurements

A number of immunologic stimuli, including secondary viral infections such as reactivation of herpes simplex virus; opportunistic infections; influenza; and vaccinations may increase viral load and confound viral load measurements. Suppressing opportunistic or other infections, with the resulting decline in cytokine levels, decreases plasma HIV RNA levels. Other factors that are known to increase viral replication are blood transfusions and poor patient adherence to the drug regimen. One plasma HIV RNA value at any given point in time is difficult to interpret; the ability to assess a patient's response to a drug regimen requires multiple sequential measurements. According to Dr Miles, if a laboratory value indicates increased viral replication, particularly a modest increase of 0.5 to 0.7 log, it is important to consider laboratory error, a transient intervening influence such as a secondary infection, and poor patient adherence before changing the antiretroviral regimen.

One common clinical question is the value of influenza vaccine for patients with HIV. According to Dr Miles, while the vaccine is likely to increase HIV replication, an episode of influenza is likely to cause a greater increase. Thus, if a patient is likely to be exposed to influenza, the vaccine is recommended.

Evaluating Virologic Response Data From Clinical Trials

Interpreting virologic response data from clinical trials of antiretroviral therapy is challenging due to the number of factors that can be incorporated into, or not be included in, any particular analysis. According to Dr Miles, four pieces of information are critical: 1) the sensitivity of the assay (eg, what is the limit of detection of the method used); 2) the pretreatment viral load; 3) the median decrease in plasma HIV RNA; and 4) the number of patients at each measurement interval (see Table 2).

Table 2. Questions to Consider in Evaluating Virologic Response Data From Clinical Trials of Antiretroviral Therapy

- What is the sensitivity of the assay used?
- What is the baseline (pretreatment) viral load of the population?
- What is the mean change in the plasma HIV RNA level?
- How many patients were evaluated at each observation interval?
- What is the maximum response that could be achieved?
- How many patients achieved the maximum response?
- What was the HIV disease stage and prior antiretroviral drug history of the population?

Conclusions

New generations of viral load tests with greater sensitivity will enable providers and patients to more accurately assess the viral burden and the potency of various antiretroviral therapies. In the near future, proviral DNA assays, which can determine the level of integrative virus, may be used for viral testing in patients with undetectable levels of plasma HIV RNA. At present, however, the available assays provide invaluable markers of disease progression and response to antiretroviral therapy.

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Suggested Readings

Brown TM, Steketee RW, Abrams EJ, et al. Early diagnosis of perinatal HIV infection comparing DNA-polymerase chain reaction and plasma viral amplification. Presented at the XI International Conference on AIDS; July 7-11, 1996; Vancouver, BC, Canada. Abstract Tu.B. 2374.

Busch M, Schumacher RT, Stramer S, et al. Consistent sequential detection of RNA, antigen and antibody in early HIV infection: assessment of the window period. Presented at the XI International Conference on AIDS; July 7-11, 1996; Vancouver, BC, Canada. Abstract Tu.A. 153.

Cavert W, Staskus K, Zupancic M, et al. Quantitative in situ hybridization (ISH) measurement of HIV-1 RNA clearance kinetics from lymphoid tissue (LT) cellular compartments during triple-drug therapy. Presented at the 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract LB9.

Hubert JB, Meyer L, Dussaix E, et al and the SEROCO Study Group. Prognostic value of early HIV-1 RNA levels on disease progression in 363 patients with a known date of infection. Presented at the 4th

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Suggested Readings *(continued)*

Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 478.

Kempf D, Molla A, Sun E, et al. The duration of viral suppression is predicted by viral load during protease inhibitor therapy. Presented at the 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 603.

Kotler DP, Shimada T, Clayton F. Effect of combination antiretroviral therapy upon mucosal viral RNA burden and apoptosis. Presented at the 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract LB11.

Lederman M, Connick E, Landay A, et al. Partial immune reconstitution after 12 weeks of HAART (AZT, 3TC, ritonavir): preliminary results of ACTG 315. Presented at the 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract LB13.

Mellors JW. The contribution of viral load measurements. Presented at the XI International Conference on AIDS; July 7-11, 1996; Vancouver, BC, Canada. Abstract Mo.B. 533.

Mellors JW, Kingsley LA, Rinaldo CR, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med.* 1995;122:573-597.

Mellors JW, Rinaldo CR, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science.* 1996; 272:1167-1170.

Schacker T, Hughes J, Shea T, et al. Viral load in acute and very early HIV infection does not correlate with disease progression. Presented at the 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 475.

Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in human immunodeficiency virus type-1 infection. *Nature.* 1995;373:117-122.

Weverling GH, Keet IPM, de Jong MD, et al. HIV-1 RNA level is set early in the HIV infection and predicts clinical outcome. Presented at the XI International Conference on AIDS; July 7-11, 1996; Vancouver, BC, Canada. Abstract Th.B. 4330.

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new pathophysiologic and clinical trial data and how they revise the recommendations; its updated report may be available soon. A reprint of the report will be included in the next issue of this publication.

Clinical Dilemmas in HIV Disease Management: An Advanced CME Course

Until this year, the International AIDS Society–USA Fall CME program has presented a full day of lectures on the prevention and management of the opportunistic diseases and other manifestations of advanced-stage HIV disease. The format and the agenda have changed substantially this year.

The revised program will use specific case presentations to illustrate current clinical dilemmas and their management. The cases will cover issues in the clinical management of HIV disease that range from antiretroviral management to the treatment of specific opportunistic infections. Common themes throughout the case presentations will include drug-drug interactions, issues of viral resistance to drugs, toxicity management, and others.

The cases are being developed for presentation by an expert panel of 18 clinicians and investigators. Symposia will be scheduled for the fall of this year (September and October); program brochures and schedules will be available in July.

HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management: Sixth Annual Advanced Course Series

The 1998 program agenda for the sixth annual course series will be developed shortly. In general, new insights in HIV pathogenesis, recent data from clinical trials that evaluate new antiretroviral drugs and combinations, discussions of the appropriate strategies for initiating and changing antiretroviral treatments, and updates on the management of specific opportunistic infections will be discussed at the programs.

The CME courses will be held in Los Angeles, Atlanta, New York, Chicago, San Francisco, and other cities, and will be scheduled between February and May 1998.

National Course on HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management

Next year, in addition to the full-day CME programs described above, a four-day, national meeting will be held as part of the sixth annual course series. The course will cover relevant new research results and their applications to clinical practice. The course is tentatively scheduled for March 25-29, 1998, in Colorado.

Registry for Physicians Who are Actively Involved in HIV/AIDS Care

A Registry of HIV-treating physicians is being developed. Please refer to the information on the back page of this issue for more information.

Recommendations for Treatment for CMV Diseases

A 17-member expert panel has been convened by the International AIDS Society–USA to develop guidelines for the treatment of CMV end organ diseases. The panel met in April of this year, and is preparing its report. A reprint of the report will be sent to subscribers of this publication.

Improving the Management of HIV Disease

This publication will continue to provide reviews of clinically-relevant topics, special articles, and new features. If you wish to continue your complimentary subscription this year, please complete and return the form on the back page of this issue.