Viral counts count in HIV infection.

by David D. Ho

Research supports the view that measuring the amount of HIV in the blood can indicate the prognosis of the patient and the effectiveness of therapies. One study found a relative death hazard of 1.55 for each threefold increase in blood viremia.

What does this virologic setpoint mean, and why is it so important prognostically? During steady state, HIV-1 clearance is balanced by its production, or $cV = [\text{differential}]T^*N$ (2), where $c$ is the rate constant for virion clearance, $V$ is the virion concentration, $N$ is the number of virions made per infected cell (burst size), $T^*$ is the number of virus-producing cells, and $a$ is the rate constant for the loss of $T^*$.

Because the values for $c$ and $a$ do not vary significantly among patients (2), $V$ [difference] $N T^*$, measuring the viral load yields clear information about the total number of productively infected cells and their average burst size. A static measurement of viral load provides a kinetic view of viral production, which in turn drives a fixed rate of CD4 lymphocyte destruction. Thus, it should not be surprising that viral load is a good surrogate marker for clinical outcome in HIV-1 infection. It is, indeed, a disease marker.

If high viral loads lead to poor clinical outcome, then lowering viral loads with antiviral drugs should result in improved prognosis. Does the evidence support this assertion? In several clinical trials of relatively weak antiretroviral regimens (9, 10), consistent clinical benefits were observed in conjunction with modest reductions in plasma viremia. For example, in the AIDS Clinical Trials Group Protocol 175, a tenfold reduction in HIV-1 RNA concentration in plasma was associated with an [difference]50% decrease in the relative hazard of death (10). Recently, administration of a potent protease inhibitor, ritonavir, to patients in advanced stages of HIV-1 infection reduced viral loads by a factor of 3 to 16 for 16 weeks, which corresponded to [difference]45% lower risk of death (11). However, much more impressive antiviral effects are now regularly seen with certain combination therapies. One notable example is the use of indinavir, zidovudine, and lamivudine. which together reduced the viral load to less than 1%; indeed, 85% of these subjects had undetectable plasma viremia after 24 weeks of treatment (12). A decline in viremia of this magnitude should result in substantial clinical improvement (3, 7, 9-11), but the precise benefit awaits documentation. Nevertheless, many of the patients on potent combination therapies now have viral loads below those of long-term...

When the acquired immunodeficiency syndrome (AIDS) first appeared, its pathogenesis was frustratingly elusive because the disease does not appear immediately upon infection with the human immunodeficiency virus (HIV).

There is a variable period of time during which the patient remains healthy but exhibits viremia (the virus can be detected in the patient’s blood). Recent work shows that this viremia is sustained by continuous rounds of viral replication and reinfestation of blood cells (1, 2), dispelling the notion that HIV has a true latent period. It follows that measuring the amount of virus in the blood (viral load) should be useful in determining the prognosis of the infected individual and in monitoring the effectiveness of therapies. Among a number of reports in support of this simple view is the elegant study in this issue by Mellors et al. (3), who show that a single measurement of plasma viral load can predict the subsequent risk of AIDS or death.

Since 1989, researchers have consistently shown that patients in advanced stages of HIV-1 infection have higher concentrations of virus in their blood (4). Moreover, the viral load after seroconversion (appearance of antibodies to HIV in the blood) predicts the likelihood of developing AIDS later (5). The authors of the new study (3) use a commercial amplification assay (6) to correlate the concentration of HIV-1 RNA in plasma with the clinical course of AIDS in a cohort of infected gay men, monitored since 1984. The findings are truly striking. For example, only 8% of patients with less than 4350 copies of RNA per milliliter of blood plasma progressed to AIDS 5 years after entering the study, whereas 62% of those with viral loads greater than 36,270 copies developed AIDS (see the figure). Individuals with intermediate viral loads had progression rates of 26 to 49%. A relative hazard of death of 1.55 was noted for each threefold increase in plasma viremia. Similar results have been observed in a recent study of infected hemophiliacs (7). The prognostic utility of measuring plasma viral load in HIV-1 infection is now unequivocal.

When HIV-1 enters a new host, there is typically a burst of viremia, which is then inhibited by the onset of immune responses (8) (see the figure). The subsequent level of plasma virus is a reflection of the equilibrium reached between the virus and the host after the initial battle and is generally maintained for years. This steady-state level varies from individual to individual and is predictive of the long-term clinical outcome (3, 5, 7).

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nonprogressors (13). Thus, if this dramatic suppression of HIV-1 is sustainable, these patients on combination treatment will present a unique opportunity to define the viral threshold below which disease progression does not occur. Imagine, as well, the future possibilities when additional potent agents are incorporated into these already powerful regimens.

There is little doubt that viral load determinations will become useful tools, along with CD4 lymphocyte counts, in the clinical management of HIV-1-infected patients. Both measurements provide important insights into the disease process. To borrow a crude but illustrative analogy from a prominent retrovirologist, John Coffin: The development of AIDS can be likened to an impending train wreck, where the viral load indicates the speed with which the train is headed for catastrophe and the CD4 cell count marks the distance from the site of doom. The means of slowing the train are now available, but ways of stopping and reversing the locomotive must be found.

References

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(11.) J. M. Leonard et al., ibid (abstr. LB6), p. 162.


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