HIV PATHOGENESIS

HIV pathogenesis was discussed at the New York course by David D. Ho, MD, from the Aaron Diamond AIDS Research Center in New York.

The notion that viral replication is an ongoing and dynamic process during the period of clinical latency of HIV infection has been established over the past several years by findings from sensitive assays for viral RNA and histologic studies of lymphoid tissue. It has become increasingly clear that relatively steady levels of viral load are maintained for months to years during clinical latency but differ widely in individual patients. Maintenance of a relative steady state suggests that during these periods, viral replication approximates viral clearance. Dr Ho and colleagues recently performed a number of studies in which viral replication was abruptly curtailed by administration of a potent antiretroviral to determine viral clearance and, thus, replication rates.

HIV Kinetics In Vivo

These studies used the protease inhibitor ritonavir in 20 patients followed during acute treatment with a sensitive branched-DNA (bDNA) assay for plasma HIV RNA. In these patients plasma HIV RNA levels dropped rapidly for the first several weeks, with a first-order exponential decrease in plasma HIV RNA levels following the initiation of treatment (Figure 1). Measuring the slope of decay allowed determination of viral half-life, estimated at approximately 2 days. This estimation, how-
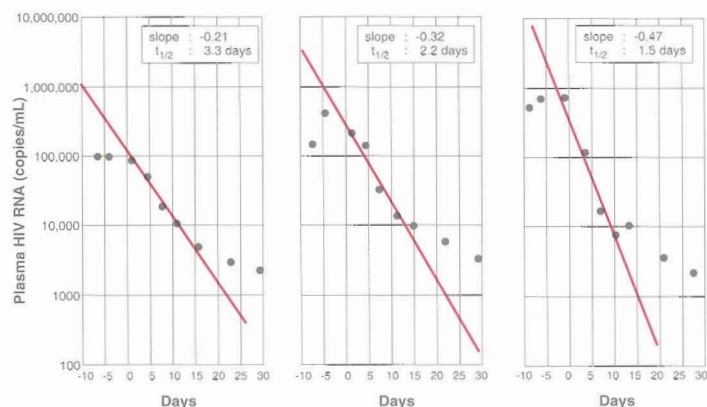

Figure 1. Plasma HIV RNA levels by duration of treatment in three patients. Adapted from Ho DD et al. Nature. 1995.

ever, is a composite of the half-life of the decay of free viral particles in the extracellular fluid space compartment and of the productively infected host cells (cellular compartment). A schematic summary of the kinetics of HIV infection in vivo in these compartments based on the findings in these initial studies is shown in Figure 2. Even with use of potent regimens, there is a residual viremia of approximately 0.1% to 1% of pretreatment levels, which indicates contribution to the viral pool by compartments that are as yet poorly understood.

Clearance of Plasma Virion and Productively Infected Cells

A subsequent study was performed in five patients to differentiate the free virion and infected cell clearance rates, with more frequent plasma HIV RNA measurements made to permit more detailed kinetic assessment. Mathematical modeling of these data showed that the half-life of free virus is 6 hours. This value was confirmed by an assay specific for infectious virus. Figure 3 compares findings from this assay with those measuring viral
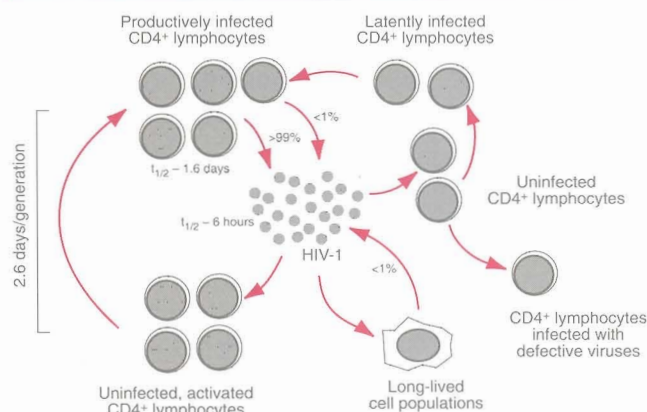

Figure 2. Schematic summary of HIV infection dynamics in vivo. The cell-free virion population sampled by plasma HIV RNA assays is shown in the center. Adapted from Perelson AS et al. Science. 1996.

particles in plasma. The decay of infectious particles is more rapid, although there is still a lag of several hours before decay is observed; Dr Ho believes that this delay is related to drug pharmacokinetics, with the effect on infectious virus being observed only after absorption and distribution of the drug into the intracellular compartment. Protease inhibitors act to prevent infectiousness of progeny virus. The noninfectious particles produced are counted in the plasma HIV RNA assay, but not in the infectious particle assay. Thus, clearance of only those infectious particles produced before drug administration is theoretically measured by the level of infectivity, reflecting what is believed to be the true viral clearance rate. Findings from this assay suggest that the half-life of virus particles in the extracellular fluid compartment is approximately 6 hours. On mathematical modeling, the decay half-life of infected cells actively producing virus is approximately 1.55 days, implying a prodigious turnover rate of susceptible host cells.

Rate of daily viral turnover. Using the body weight of the five subjects to derive plasma volume and extracellular fluid volume, the number of viral particles produced each day to maintain the quasi–steady state was calculated to be approximately 10 billion (10^{10}). This figure is a minimum estimate since the calculated decay rate for the free virus reflects a minimum rate; moreover, this estimate reflects only those viral particles that are released into the extracellular fluid compartment (and are thus available for measurement), and not those virions produced within and never released from tissue. The number of particles

produced may be a few-fold or as many as 10- or even 100-fold higher. As noted, the viral levels during quasi–steady state differ in individual patients; recent data on the prognostic utility of plasma HIV RNA levels have shown a significant association between viral load and survival.

Implications for Genetic Variabilty

In the quasi–steady-state condition, there are successive generations of viral progeny, with each generation following the next by about 2.6 days. Approximately 140 generations of virions are produced over the course of a year and 1400 generations over the course of 10 years, allowing production of an extraordinary number of genetic variants. Some variants can provide preexisting drug-resistant forms or enable rapid development of resistance under drug pressure, and some enable the viral population to escape immune activity. The viral pool is estimated to be a minimum of 10^{10} particles. It is known from experimental data that
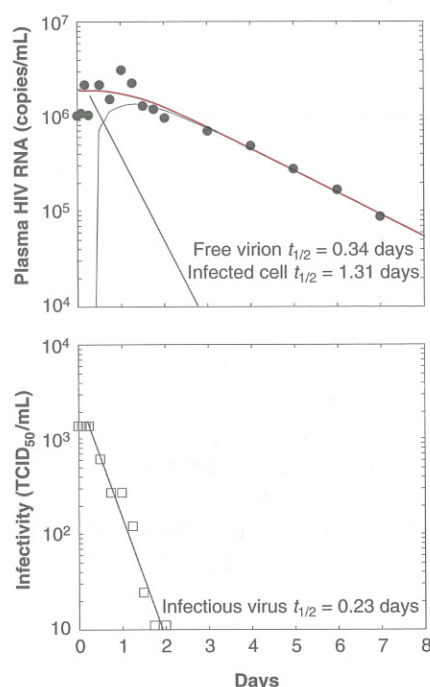

Figure 3. Assay of plasma viral particles **(top)** compared with assay of infectious virus **(bottom)**. Adapted from Perelson AS et al. Science. 1996.

only 1 in 1000 particles is infectious, so the infectious viral pool may be on the order of 10^7 particles. At the reverse transcription stage, errors are made at the rate of 3×10^{-5} per nucleotide per cycle. With a genome of approximately 10^4 nucleotides, there is potential for generation of at least 10 million variants daily, ensuring that mutations will occur at every genome position on a daily basis.

Implications for Treatment

These findings have important implications for treatment. First, treatment should be initiated at a very early point in HIV disease to prevent the generation of genetic variants. Second, the data on the ability of the viral pool to develop mutations argue for the use of combination drug therapy rather than monotherapy. It is difficult for the virus to develop four or five mutations in a single genomic background simultaneously, and it thus makes sense to place the virus under pressure to do so by using a combination of drugs. Dr Ho and colleagues have recently begun to explore these implications clinically, by identifying acute seroconverters and either following them through the initial viremic phase or beginning aggressive treatment with combinations of protease inhibitors, zidovudine, and lamivudine. Although the data are very preliminary, they found that such treatment was capable of essentially eliminating the virus from the bloodstream in every patient who had been treated for at least 6 weeks. However, the 2- to 3-log decreases in viral load that have been observed with combination treatment do not account for all of the virus present in an individual patient; there is a limit to the nadir achieved under treatment. This low-level residual viremia, as previously noted, may come from a number of different compartments. One potential source is latently infected CD4+ lymphocytes carrying infectious provirus; once activated, such cells become productively infected and the particles produced can be measured by quantitative assays. In addition, there may be cells that live for prolonged periods despite infection and that continuously produce measurable particles; such particles would be rendered noninfectious by protease inhibitor treatment (since these drugs act at the posttranscription stage) but would nevertheless be detected and measured by quantitative assays.

It is important for future studies to define the characteristics of decay in these viral compartments as well as in others that are less understood or have yet to be identified. Determination of the viral kinetics in these compartments is important because this virus appears to constitute the "embers" of infection, and can reignite robust replication if an antiretroviral regimen is withdrawn or becomes ineffective.

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Suggested Readings

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