
ANTIRETROVIRAL RESISTANCE AND HIV DYNAMICS

Douglas D. Richman, MD, from the University of California San Diego and the San Diego VA Medical Center, discussed aspects of HIV kinetics and antiretroviral resistance as part of a larger presentation on newer antiretroviral agents at the Los Angeles meeting. This portion of his talk is summarized herein.

Kinetics of Resistant Virus

As related by Dr Richman, with the introduction of an antiretroviral agent in a patient with relatively constant plasma viral RNA levels, there is no change in such levels for some 24 to 48 hours, during which viral replication in cells infected prior to treatment continues. Subsequently, there is a rapid reduction in viral load that is drug and dose dependent. For example, according to Dr Richman, with monotherapy the nucleoside analogues may produce a 0.5 to 1 log drop in viral load, the nonnucleoside reverse transcriptase inhibitors a decrease of approximately 1 to 1.5 logs, and the protease in-

hibitors a decrease of 0.5 to 2 to 3 logs, depending on the particular agent. The virus clearance rate can be calculated based on the rate of reduction in viral load. In cases in which viral load attains a constant level, it can be assumed that there is a

A substantial proportion of HIV may have resistance mutations prior to patient exposure to drug treatment.

dynamic equilibrium resulting in a steady-state level, with production rates matching clearance rates. When resistance emerges, such as in some cases of nevirapine resistance, the production of resistant virus may double every two days. The proportion of virus with resistance mutations can also be calculated. According to Dr Richman, in the case of the nonnucleoside reverse transcriptase inhibitors, this has been found to be approximately 1 to 2 per 1000 RNA copies circulating in the plasma; that is, a patient with 60,000 copies/mL plasma has approximately 100 copies/mL of resistant mutants prior to beginning treatment. Dr Richman stated that a similar scenario probably holds for all drug-resistance mutations.

Implications of Viral Dynamics

The rapidity of the turnover of the viral population has several implications for pathogenesis and treatment of HIV disease. High levels of replication persist at all stages of infection, with the rate of replication appearing to be fairly constant throughout the course of the disease. Clearance of virus is also rapid and remains fairly constant throughout disease. It is only the steady-state levels of virus that appear to change, which is

affected by the production rate of virus. Treatment can affect virus-steady-state levels by inhibiting production of virus. It is not clear if the rate of viral clearance can be increased. Chronically infected cells contribute only a negligible amount to the peripheral viral load, as is evidenced by the finding that although reverse transcriptase inhibitors do not impact viral production in such cells, treatment with such agents produces a remarkable reduction in viral load.

The implications of the presence of high levels of virus and high viral turnover for the assessment of antiretroviral drug activity are clear. With new techniques for quantitating plasma viral RNA, virtually all HIV-infected individuals can be evaluated for response to antiretroviral therapy. According to Dr Richman, a just-completed study of nevirapine in patients with CD4+ cell counts >500/ μ L showed that an effect on plasma viral RNA could be detected in every patient. Plasma HIV RNA assays can be used to determine whether a drug does or does not have a significant antiretroviral effect. Since maximal activity of antiretrovirals has been found to occur within a week of beginning treatment, such determinations can be made rapidly. It is likely that information about the relative activity of a drug or a dosage can be gained in short-term (eg, 2 week) studies in a relatively small number of patients (eg, 6 to 12). The ability to assess antiretroviral activity in this manner promises to have a major impact on the evaluation of new drugs.

Dr Richman noted that the long-term utility of agents or dosages shown to be active in the short term will still require longer follow-up, but that decisions regarding further development of candidate agents, optimal dosages, and optimal combinations can be made on the basis of these short-term studies. The quantitative assays also permit assessment of the magnitude and durability of antiretroviral effects. Dr Richman stressed that, in his opinion, the utility of plasma HIV RNA assays in evaluating antiretrovirals is a completely different issue from their use in patient management. He indicated that it is not yet known how to best use viral load information in making treatment decisions for the individual patient. Dr Richman noted that the high turnover of the viral population is reflected in a very accelerated turnover in CD4+ cells. The level of CD4+ cells in HIV infection is a function of the rates of CD4+ cell destruction and replacement. If approximately 1 billion CD4+ cells are being destroyed each day and patients' cell counts remain relatively unchanged from day to day, there is production of a huge amount of cells on a daily basis. Dr Richman stated that the ability to affect the course of HIV disease appears to reside in the ability to reduce the rate of destruction of CD4+ cells rather than to simply increase their number. He provided the analogy of the inadequacy of treating

chronic hemolytic anemia only with red blood cell transfusions (or treating idiopathic thrombocytopenia purpura with platelet transfusions) in suggesting that immune modulation alone in the face of high cell turnover would make little sense. Experience with the plasma HIV RNA assays has shown that there is a correlation between reduction of plasma RNA levels and CD4+ cell count increases and that the durability of CD4+ cell response is

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directly related to the durability of the plasma RNA response under treatment. Describing the view as being perhaps somewhat contentious, he asserted that restoration of immune function may be best achieved by antiviral or

immunologic interventions that reduce HIV replication and resultant CD4+ cell destruction. Immune-based therapies may have promise only insofar as they affect virus production.

Potential Mechanisms for Persistent Antiviral Effect Despite Drug Resistance

It is reasonable to expect that resistant mutants will emerge to most antiretroviral compounds. Nucleoside analogues that closely resemble their physiologic nucleoside counterparts—eg, didanosine, zalcitabine, and stavudine—appear to induce small or slowly occurring changes in susceptibility. High-level resistance has been observed with the nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and the nucleoside analogues with unusual sugars that may make them more easily distinguishable from physiologic nucleosides—eg, zidovudine and lamivudine. As stated by Dr Richman, there are data demonstrating that development of resistance to some of these agents does not equal absence of antiretroviral effect in all cases.

According to Dr Richman, there are a number of potential mechanisms that may explain persistence of antiviral activity despite development of resistance. First, it is possible that plasma levels of drug can be generated that exceed the susceptibility of the resistant virus, a mechanism that is supported by data from patients receiving nevirapine. Second, drug resistance mutations may alter the replicative capacity of resistant virus rendering the mutant virus less fit than the wild type virus; according to Dr Richman, there are also some data to indicate that this does occur in some settings, such as the reverse transcriptase mutation at residue 184 that emerges with lamivudine therapy. Third, with combinations of drugs directed at a common target, the mutations induced by one of the drugs may increase susceptibility to the others or constrain the evolutionary options for acquiring resistance to the others; such a mechanism may be operative in the observed effects of the lamivudine-zidovudine combination as well as with combinations of protease inhibitors.

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