Discordant Responses to Antiretroviral Therapy

Responses to potent antiretroviral therapy in the form of increases and stabilization in CD4+ cell count may occur in spite of persistent viremia. Potential biologic explanations and clinical implications of these discordant responses were discussed at the Boston course by Amalio Telenti, MD.

Clinicians have been confronted with a diversity of responses to potent antiretroviral therapy. As shown in Figure 1, these responses include not only the optimal suppression of HIV-1 viremia and continuous increase of CD4+ cell count, but also various manifestations of treatment failure. Treatment failure may present with depletion of CD4+ cells following rebound of viremia. However, the diversity of responses also includes a paradoxical failure to reconstitute the immune system despite successful suppression of viremia, and instances of increase and stability of CD4+ cell count in spite of significant viremia. The latter form of discordant response occurs more frequently than the former and may constitute a common response in a substantial number of patients in whom potent antiretroviral therapy is considered to be failing.

The most frequent discordant response is increase and stability of CD4+ cell count in spite of significant viremia

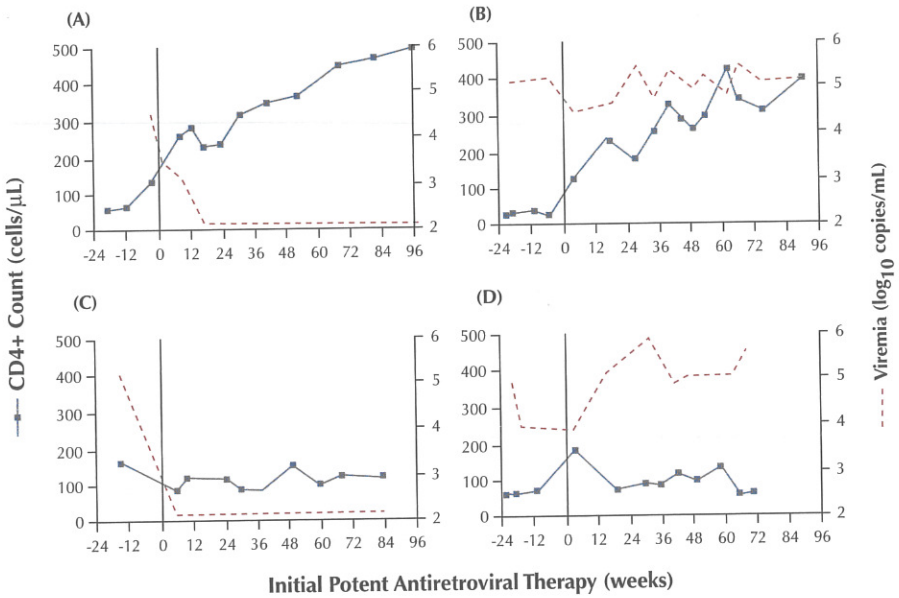

Figure 1. *Patterns of virologic and immunologic response after initiation of potent antiretroviral therapy. (A) Optimal response, with viral load maintained below assay detection limits and continuous increase in CD4+ cell count. (B) Discordant response of persistent viremia and increase in CD4+ cell count. (C) Discordant response of suppression of viremia and absence of change in CD4+ cell count. (D) Advanced treatment failure. Adapted from Perrin L, Telenti A.* Science. *1998;280:1871–1873.*

Recent data from the Swiss HIV Cohort Study indicate that antiretroviral therapy produces immunologic and clinical benefit in many patients despite the absence of optimal control of viremia. Laboratory data are providing information on the virologic and immunologic basis for this benefit. Precisely how these combined findings are to influence management of patients with suboptimal control of viremia remains to be determined.

POSSIBLE MECHANISMS FOR THE DISSOCIATED CD4+/VIREMIA RESPONSE

Reduction in Level of Viremia, Mutations, and Viral Fitness

One potential explanation for the immunologic benefit despite lack of control of viremia is the moderate reduction in viral load observed in patients failing therapy. Explaining this "residual" activity of therapy requires an understanding of changes in the replication kinetics of multidrug-resistant virus. Viral isolates from patients with persistent viremia on potent therapy typically exhibit multiple mutations in the protease and reverse transcriptase (RT) enzymes, and these viruses may exhibit replication defects associated with most of the major primary mutations (Figure 2). In the presence of primary mutations (those appearing early during the development of resistance, and generally involving the active site of the enzyme), the adaptive effort of the virus will include development of secondary mutations that may contribute to improved function of the mutated enzyme. However, secondary, compensatory mutations may not restore full replicative capacity of the virus. Mammano and colleagues have demonstrated, for example, that efficiency of