

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

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

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.

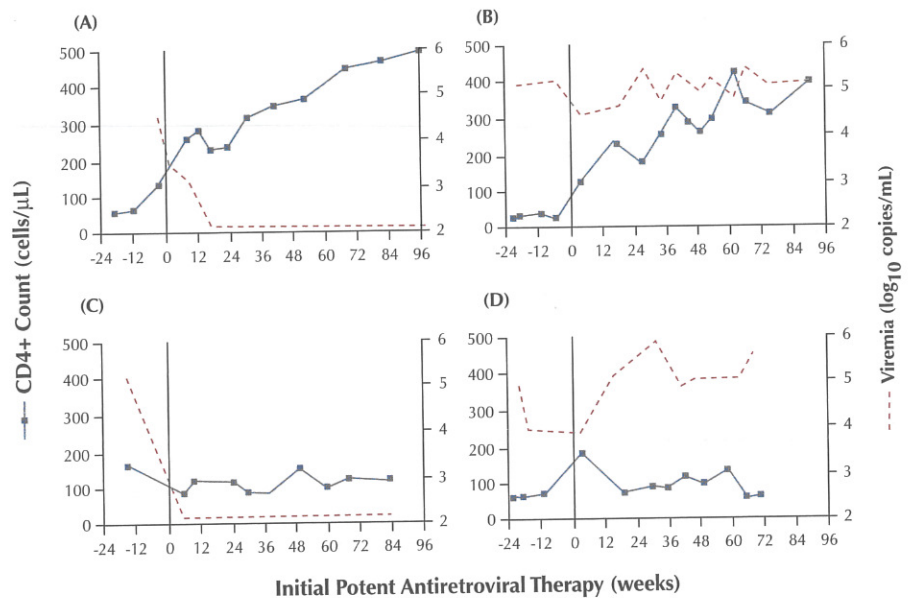


Figure 1. Patterns of virologic and immunologic response after initiation of potent antiretroviral therapy. (A) Optimal response, with viral load maintained below assay detection limits and continuous increase in CD4+ cell count. (B) Discordant response of persistent viremia and increase in CD4+ cell 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

HIV-1 protease in processing Gag viral protein is decreased in vitro despite compensatory secondary mutations in the enzyme Gag cleavage site, resulting in production of immature virions. Similarly, Back and Berkhout have demonstrated that replicative efficiency is markedly reduced in virus with the RT M184I mutation that precedes the characteristic M184V mutation conferring resistance to the nucleoside reverse transcriptase inhibitor (nRTI) lamivudine. The latter mutation is associated with increased RT function compared with the former, but reduced RT function compared with wild-type virus. (It is noteworthy that this defect is more pronounced in the presence of low intracellular deoxynucleoside triphosphate (dNTP) concentrations, a factor that may explain the observed activity of hydroxyurea in increasing the antiretroviral activity of purine nRTIs in the context of antiretroviral resistance.) Research by Dr Telenti and colleagues indicates that most RT and protease mutations have been associated with measurable changes in viral fitness. Changes in viral infectivity, replicative efficiency, and pathogenicity may affect the relationship of CD4+ cell destruction and production in HIV-1 infection.

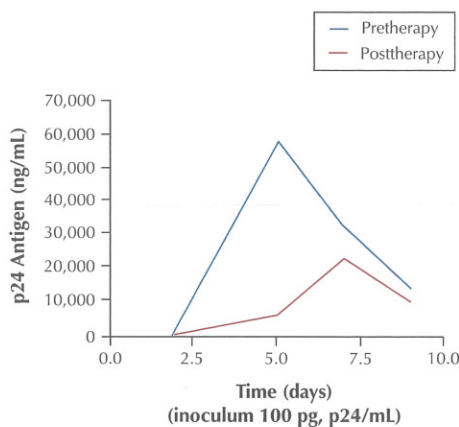


Figure 2. Replication kinetics in peripheral blood mononuclear cells of an isolate obtained prior to potent antiretroviral therapy (pre) and a multidrug-resistant isolate obtained from the same patient during therapy (post). Courtesy of A Telenti, MD.

TABLE 1. CD4+ CELL RECOVERY IN 2 PATIENTS WITH AND WITHOUT MULTIDRUG-RESISTANT HIV

	Patient 1: Wild-Type HIV-1	Patient 2: Multidrug-Resistant HIV-1
Baseline CD4+ Count (cells/ μ L)	69	28
Current CD4+ Count (cells/ μ L)	536	424
Current Viremia (copies HIV-1 RNA/mL)	<100	70,600
Memory CD4+ (RO+)	56%	26%
Naive CD4+ (RA+)	41%	59%
Cells in Cycle (CD4+ Ki67+)	2.1%	1.3%

Altered Cellular Tropism

An alternative hypothesis for the discordant response is the reduced ability of multiresistant viruses to inhibit T-cell regeneration. Stoddart and colleagues have demonstrated that while both wild-type and resistant viruses are capable of depleting mature CD4+ cells in vitro, they display a different pathogenic potential on thymic precursors. In a SCID-hu mouse (a mouse containing human thymic tissue), only the wild-type virus caused productive infection and depletion of CD4+ cells.

Apart from the decreased damage to thymus implants in animal models, additional evidence from research by Deeks and colleagues demonstrates a prolonged survival of CD4+ cells generated under conditions of persistent viremia under treatment, compared with CD4+ cells in patients with similar degrees of viremia who are not taking a protease inhibitor-containing regimen. In addition, it has been demonstrated that the CD4+ cell count increases observed in patients with multidrug-resistant virus and persistent viremia include increases in CD4+ cells of naive phenotype, irrespective of level

Maintaining a discordant response of sustained CD4+ cell count and persistent viremia may be the sole alternative for some patients

of viremia. This finding indicates the potential for immune reconstitution. As illustrated in Table 1, comparison of a patient with controlled viremia and wild-type virus with a patient with significant viremia and multidrug-resistant virus shows comparable percentages of naive CD4+ cells and cells in cycle (Ki67+) in

the context of comparable increases in overall CD4+ cell count.

Other Potential Mechanisms

Protease inhibitors may induce a sustained CD4+ T-cell response through mechanisms independent of their direct antiviral activity. A recent study by André and colleagues suggests that protease inhibitors may inhibit HIV-specific cytotoxic T-lymphocyte (CTL) activity. In the study, ritonavir, and to a lesser extent saquinavir, reduced major histocompatibility complex-1^{*}-restricted antigen presentation in mice infected with the lymphocytic choriomeningitis virus, and thus diminished CTL-mediated antiviral response. No direct effect of aspartyl protease inhibitors on apoptosis pathways (cysteiny-l-aspartic proteases) has been shown.

CLINICAL CONSEQUENCES OF DISCORDANT RESPONSES

Data from the Swiss HIV Cohort Study indicate a beneficial effect on CD4+ cell counts and clinical progression in patients on potent antiretroviral therapy with persistent viremia. Figure 3 shows changes in CD4+ cell count and plasma HIV-1 RNA level in patients from this

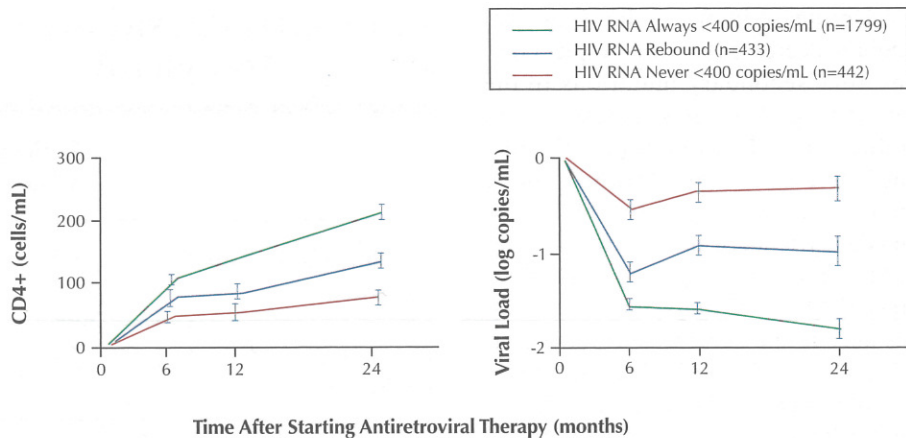


Figure 3. Changes in CD4+ cell count and plasma viremia (mean, 95% confidence interval) according to prior magnitude of control of viremia in patients receiving potent antiretroviral therapy in the Swiss cohort. Courtesy of A Telenti, MD for the Swiss HIV Cohort Study.

cohort who have either (1) maintained plasma HIV-1 RNA level below 400 copies/mL; (2) achieved plasma RNA levels below 400 copies/mL but experienced viral rebound; or (3) never had viremia reduced to below limits of detection (whether as a result of documented resistance or as a result of other factors such as lack of adherence). A 24-month increase in CD4+ cell count of approximately 70/ μ L occurred in the third group in spite of the relatively small effect on viral load and presumed poor adherence

to treatment in an undefined proportion of patients. As shown in Figure 4, data on clinical progression in these groups of patients show degrees of clinical benefit that correspond with the CD4+ cell increases and that are greater for each group than for similar historical comparison groups that were treated prior to the era of potent antiretroviral therapy.

After initiation of potent antiretroviral therapy, a rise in CD4+ cell count by 50/ μ L or more by 6 months reduced the risk of opportunistic events by 68%.

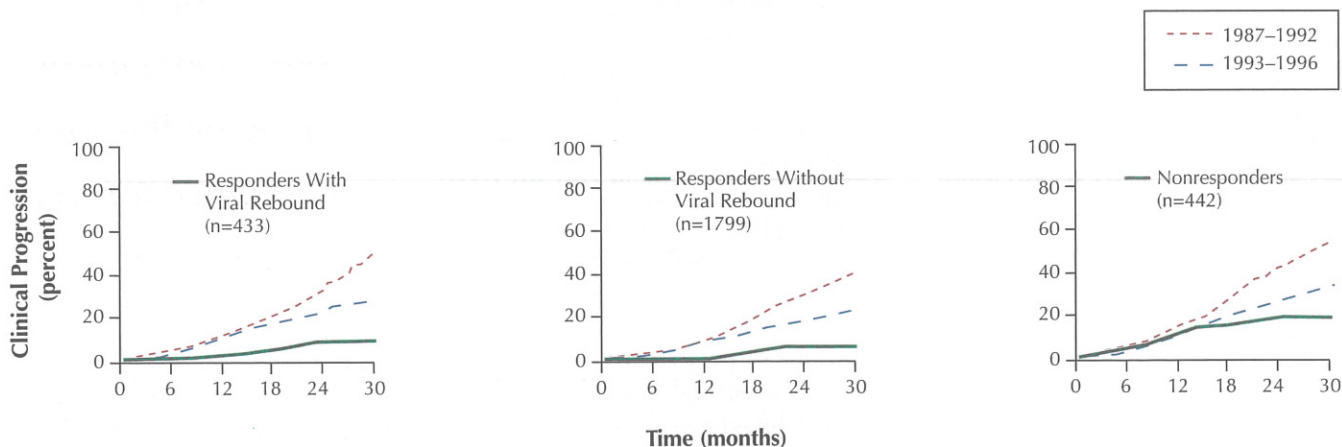


Figure 4. Rates of progression to death or opportunistic disease according to prior control of viremia in the Swiss cohort compared with rates in patients with similar control of viremia treated in years prior to availability of protease inhibitors and use of potent antiretroviral regimens. Adapted from Ledergerber B, et al. Lancet. 1999;353(9156):863-868.

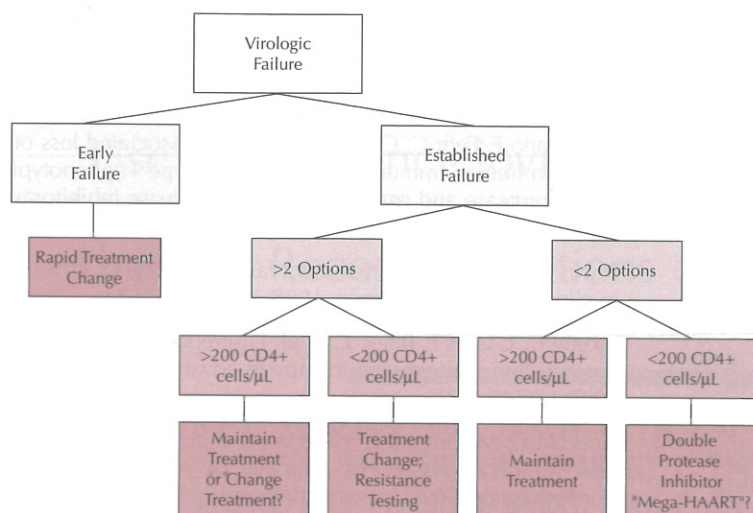


Figure 5. Proposed algorithm for management of treatment failure. Managing failure requires analysis of 2 factors: whether the failure is early (first record of rebound of viremia) or established, and the number of treatment options available. Courtesy of A Telenti, MD.

Achieving a CD4+ cell count of 200/ μ L during treatment is also associated with a dramatic protective benefit, with a less than 5% risk of an opportunistic event occurring over 18 to 24 months in such patients.

MANAGEMENT OF DISCORDANT RESPONSES

How the observation of immunologic and clinical benefit under potent antiretroviral therapy despite persistent viremia impacts clinical management remains unclear (Figure 5). For example, in cases of established virologic failure (as opposed to early treatment failure), should patients with CD4+ cell counts greater than 200/ μ L with several drug options still available be maintained on the current regimen (perhaps increasing the number of mutations and further improving viral fitness) or should their treatment be altered at the potential expense of losing future treatment options?

Alternately, maintaining a discordant response of sustained CD4+ cell count and persistent viremia may be the sole choice for patients with extensive exposure to antiretrovirals and few remaining treatment options. Switching to a dual-protease inhibitor-containing regimen from a single protease inhibitor-containing regimen in patients with CD4+ cell

counts below 200/ μ L constitutes a treatment option that may produce a protective increase in CD4+ cell count and/or increase of the CD4+ cell count to greater than 200/ μ L irrespective of whether viremia can be controlled. Data from the Swiss cohort indicate that such a switch in patients with persistent viremia has been associated with additional CD4+ cell count gains of approximately 50/ μ L. Additional support for maintaining patients with few or no treatment options on potent antiretroviral therapy despite persistent viremia may

be provided by the observation of marked increases in viremia and declines in CD4+ cell count when the regimen is withdrawn. Dr Telenti and colleagues have consistently observed such a response to withdrawal of these regimens irrespective of prior degree of control of viremia under treatment (Figure 6).

CONCLUSIONS

Discordant responses to potent antiretroviral therapy are not uncommon, particularly the response of increased and then stabilized CD4+ cell count despite persistent viremia. Continuing antiretroviral therapy may represent the only remaining alternative for patients with extensive exposure to antiretrovirals and limited additional options. Such continued treatment may maintain evolutionary pressure on the virus and thus potentially maintain its relatively reduced fitness. In such cases, it is important that adherence to the antiretroviral regimen is maintained, since immunologic progression is characteristic of withdrawal of treatment. When to switch antiretroviral therapy remains a complex issue.

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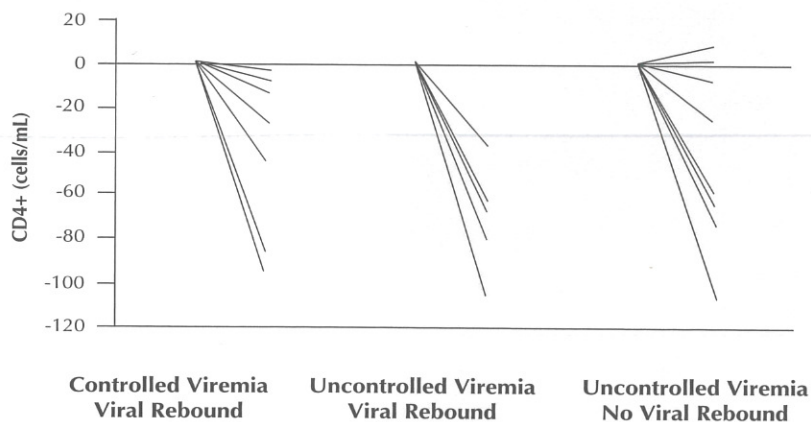


Figure 6. Effect on CD4+ cell count of interruption of potent antiretroviral therapy in patients with initially controlled viremia and viral rebound, uncontrolled viremia and viral rebound, or uncontrolled viremia and no viral rebound. Adapted from Kaufmann DK, et al. *Lancet*. 1998;351:723-724.

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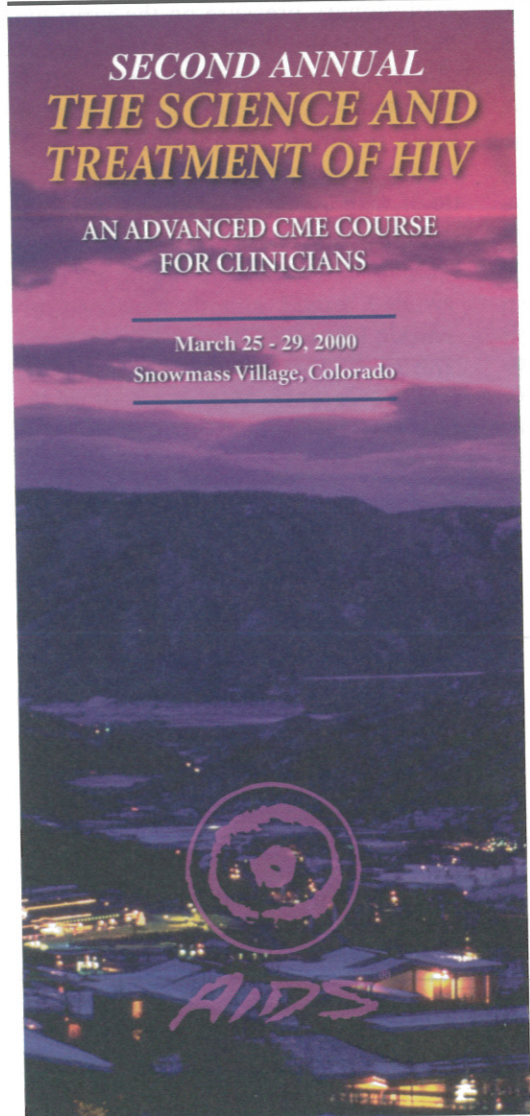
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