Cellular Immune Response in HIV-1 Infection and Effects of Therapy on Immunologic Parameters

The role of the cellular immune response in HIV-1 infection in patients with long-term nonprogression of infection and the effects of potent antiretroviral therapy during early infection on immune function were discussed by Bruce D. Walker, MD.

HIV-1 infection is associated with progressive destruction of the immune system in the majority of patients. Some patients, however, exhibit no detectable viremia in available assays and no progression of disease over long-term follow-up in the absence of antiretroviral therapy. Attenuated virus and host genetic factors (eg, chemokine receptor polymorphisms) account for only a minority of cases of such long-term nonprogression. Accumulating data suggest that host cellular immune response plays a major role in containing HIV-1 infection in long-term nonprogressors, a mechanism characteristic of long-term control of infection with a number of other human viruses (eg, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus). Recent data suggest a crucial role of HIV-1-specific T-helper cells in regulating effective immune response to HIV-1, including specific cytolytic CD8+ T-cell (CTL) activity, and indicate that this response can be preserved by early institution of potent antiretroviral therapy.

Recent data suggest that HIV-1-specific T-helper cell response can be preserved by early institution of potent antiretroviral therapy

IMMUNE RESPONSE TO HIV-1 INFECTION

Both humoral and cellular responses to HIV-1 have been detected in infected persons. Studies in long-term slow progressors have demonstrated that HIV-1-specific neutralizing antibody may be present in low levels to levels below the limits of detection, suggesting absence of a primary role of this mechanism in viral containment. However, a number of studies have now shown that CTL activity and number are associated with control of HIV-1 viremia and have suggested a central role for virus-specific CD4+ T-helper cells in regulating CTL response and activity.

CTLs kill infected cells via T-cell-receptor mediated recognition of processed viral protein presented in the context of MHC class I molecules on the surface of an infected cell (Figure 1). Studies of HIV-1 dynamics in vivo suggest a span of 2.6 days between new cell infection and budding of progeny virus; CTLs can identify and kill such cells during this period, thus preventing production of new virions, if the CTLs are present in sufficient number and in an appropriate activation state. In infected humans, CTLs are present at the earliest stages of acute infection, but decline in most individuals as infection progresses. Studies have been conducted to characterize the comparative activity of CTLs in rapid progressors versus nonprogressors by measuring lysis of cells expressing

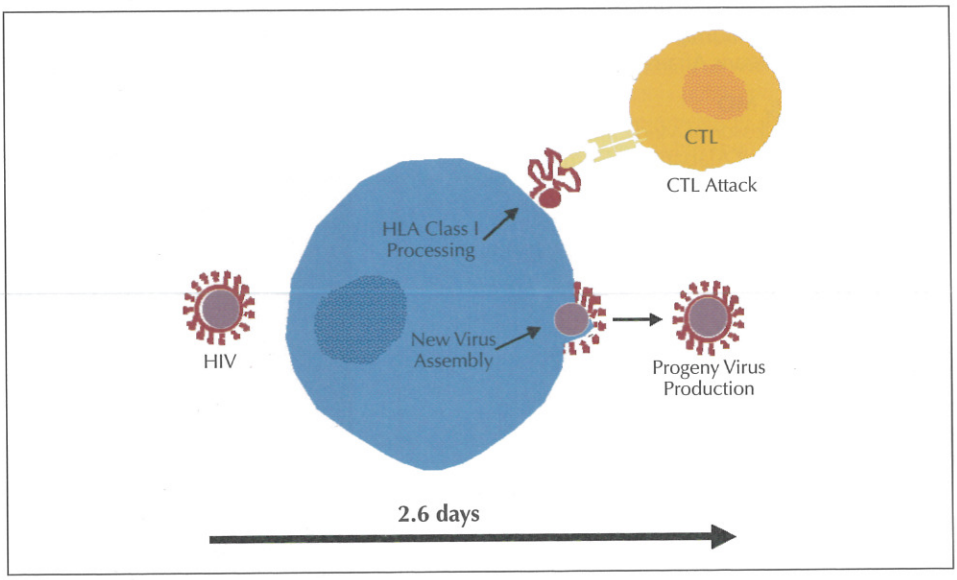


Figure 1. *CTLs recognize processed viral proteins expressed on the host cell surface. Rate of CTL activation and response may determine rate of virion production from newly infected cells and thus contribute to determination of viral set point in infected individuals.*

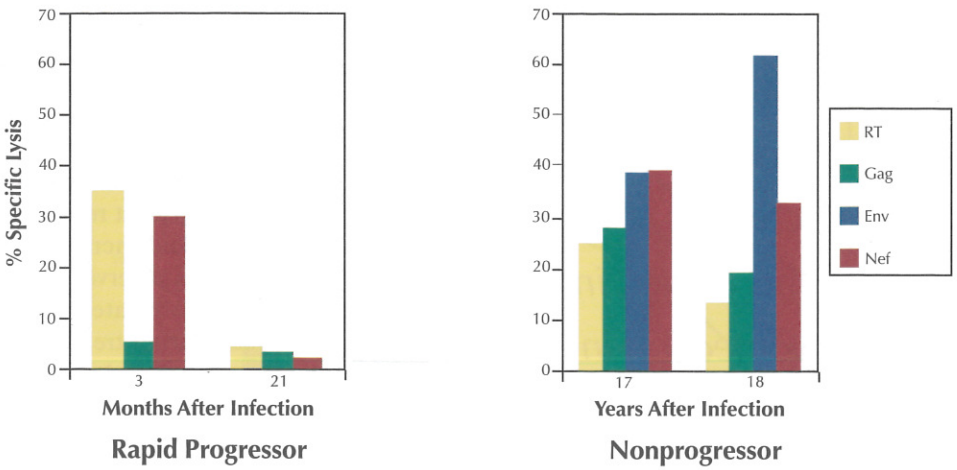


Figure 2. *HIV-1-specific CTL responses in rapid progressor and long-term nonprogressor. The rapid progressor exhibited a rapid CD4+ count decline and developed AIDS at 13 months with a consistently high plasma viral load (>300,000 copies/mL of HIV-1 RNA). The nonprogressor remains well at 19 years with a CD4+ cell count greater than 1000/μL and viral load less than 400 HIV-1 RNA copies/mL. Figure shows percent lysis by CTLs specific for HIV-1 reverse transcriptase (RT), Gag, Env, and Nef proteins.*

HIV-1 proteins. They have shown that although CTL response occurs in both after the acute infection period, this response appears to dissipate shortly thereafter in rapid progressors, while nonprogressors maintain a strong response broadly directed against multiple viral proteins (Figure 2). Additional studies have demonstrated that infected cells can be lysed prior to production of progeny virus. These studies have shown that addition of single CTL clones specific for single HIV-1 proteins in infected CD4+ cells in culture results in a 10,000-fold decrease in virion production compared with control experiments. The potential critical role of CTLs in controlling viremia has been supported by the recent finding that in vivo CD8+ cell depletion resulted in a dramatic increase in viremia in macaques infected with simian immunodeficiency virus. Attempts to restore CTL response in patients with chronic infection via infusion of HIV-1-specific CTLs have met with limited success; however, this finding is probably due to inability of the cells to achieve the appropriate activation state in vivo.

Findings showing a negative correlation between viral load and CTL activity have suggested a mechanism by which such activity might determine the viral set point in infected individuals. In brief, prompt CTL activation and response might prevent production of new virions, with progressively slower recognition and activation resulting in progressively higher rates of production and thus higher levels of viremia. A prime candidate for regulation of the activation of CTLs and magnitude of CTL response is the activity of CD4+ T-helper cells. These cells recognize antigen on cell surfaces via the T-cell receptor and the CD4 molecule on the helper cell surface, with the interaction stimulating lymphokine secretion and cell-cell interactions that regulate CTL activity, B cell function, antibody production, natural killer cell function, cytokine production, and antigen-presenting cell function (Figure 3). (Although it was generally believed that T-helper cells directly activated CTLs, it has recently been shown that activation of CTLs occurs through interaction with activated antigen-presenting cells. These latter cells are activated by contact with T-helper cells that have been activated by contact with the inactive antigen-presenting cells.) The crucial role of T-helper cells in maintaining effective immune responses in viral infection has been demonstrated in a number of models. For example, in the murine lymphocytic choriomeningitis virus infection model, viremia is controlled in association with a strong CTL response; however, in CD4+ cell-depleted or -knockout animals, CTL response wanes, and high-level viremia ensues after initial response.

HIV-1-specific T-helper cell responses appear to occur early in infection, to be lost shortly thereafter in the majority of patients, and to not recover when they are lost. Studies of cell proliferation induced by HIV-1 antigen stimulation of peripheral blood lymphocytes from rapid progressors and long-term slow progressors have shown that specific T-helper cell responses to the

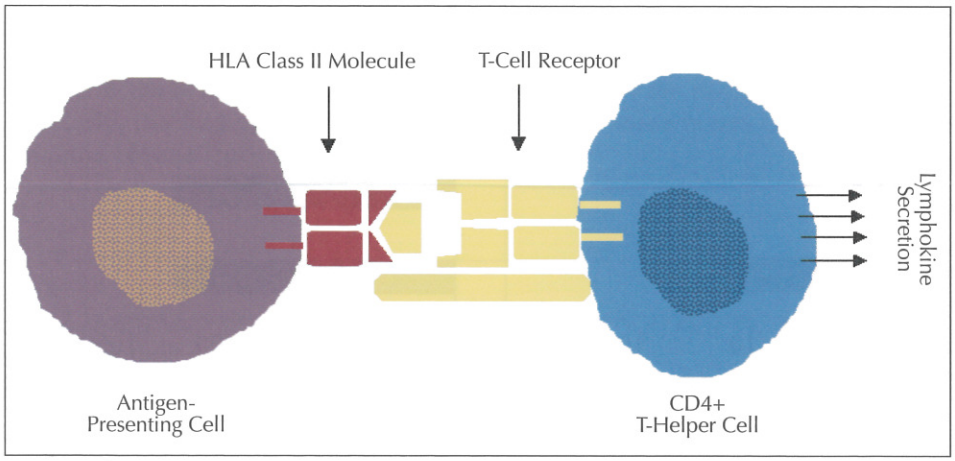


Figure 3. *Direct interaction of antigen-presenting cells and CD4+ T-helper cells results in T-helper cell lymphokine secretion and cell-cell interactions that regulate a variety of immunologic functions, including CTL activity and antigen-presenting cell function.*

viral proteins are lacking in the former, whereas the latter exhibit responses of large magnitude (Figure 4). Subsequently, it was shown in a group of treatment-naive patients with a wide range of viral load values (<400 to 300,000 plasma HIV-1 RNA copies/mL) that p24-specific T-helper cell responses were highly negatively correlated with level of viremia. Further, it was demonstrated that CTL response to HIV-1 Gag protein was significantly correlated with the level of HIV-1-specific T-helper cell activity. These findings indicate that HIV-1-specific T-helper cell response is associated with control of viremia and suggest both that loss of this response is associated with lack of CTL response in progressive disease and that preservation of response is associated with maintained control of viremia.

POTENTIAL EFFECT OF THERAPY ON IMMUNE FUNCTION

It is possible that HIV-1-specific T-helper cell response is lost in the earliest stages of acute infection due to activation of these CD4+ cells as part of initial immune response to infection—ie, activation of these cells serves to make them preferential targets of HIV-1 infection. Indeed, it has been observed that T-helper cells specific for such pathogens as cytomegalovirus are present when those specific for HIV-1 are absent in patients assessed in the early asymptomatic phase of chronic infection. The notion that loss of HIV-1-specific T-helper cells results from the dynamics of early infection has suggested the hypothesis that rapid initiation of potent antiretroviral therapy after initial infection might serve to protect developing T-helper cells and permit maturation of an effective immune response.

A strong T-helper cell response has been characteristic of the patients treated in early infection in initial studies

In ongoing studies, Dr Walker's group has identified persons with acute HIV-1 infection prior to seroconversion and instituted immediate treatment with triple drug potent antiretroviral therapy that includes a protease inhibitor, comparing p24-specific T-helper cell responses in these patients with those in untreated control patients with acute infection and with patients initiating potent antiretroviral therapy during chronic infection. Figure 5 shows the p24-specific response in one patient receiving early treatment; a marked increase in proliferative response was observed, with this increase being correlated with decreasing viral load during treatment. The development of a T-helper cell response has been characteristic of the patients treated in early infection; 11 of 12 patients studied have maintained a stimulation index response of greater than 10 over 6 months. In contrast, there is a minimal p24-specific T-helper cell response in patients with untreated acute infection over the course of 6 to 12 months. Restoration of the T-helper cell response has not been observed in patients given potent antiretroviral therapy for at least 12 months during chronic infection, whereas these responses remain detectable and elevated in the patients with very early initiation of treatment.

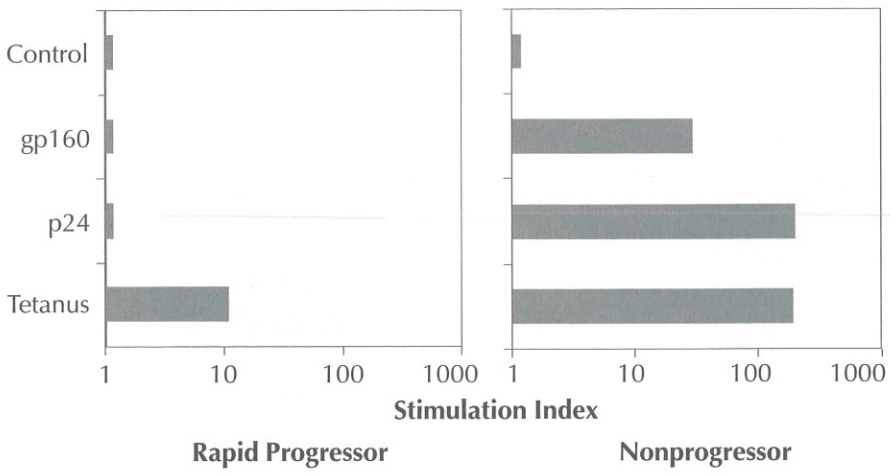
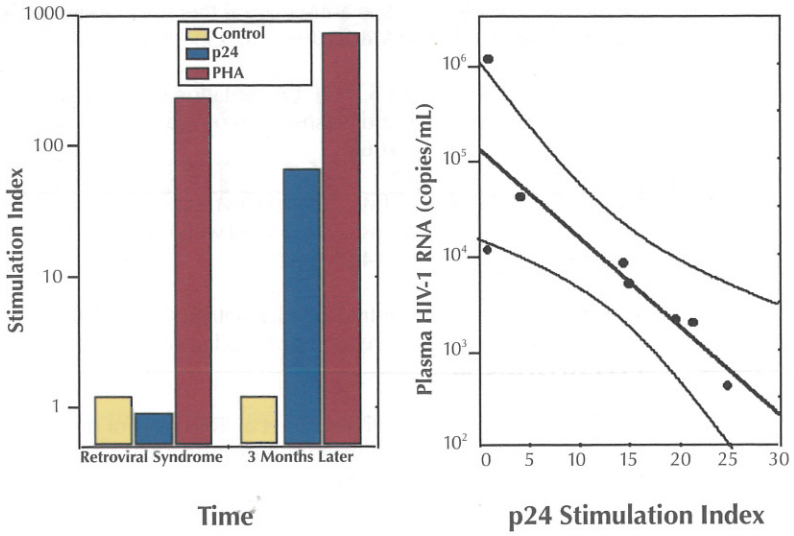


Figure 4. *HIV-1-specific T-helper cell response in rapid progressor and long-term nonprogressor (see Figure 2). Figure shows stimulation index as measure of proliferation of T-helper cells specific for HIV-1 gp160 and p24 compared with response in control condition and specific response to tetanus antigen.*

CAN THERAPY BE DISCONTINUED AFTER TREATMENT OF ACUTE INFECTION?

The apparent ability to preserve T-helper cell response with early potent antiretroviral therapy raises the questions of whether an effective immune response has been generated such that (1) viremia would remain controlled if therapy was withdrawn or (2) a rebound in viremia might prime effective immune response that subsequently controls the virus. A small number of cases have now been reported in which patients treated early in infection have maintained viral load below limits of detection or exhibited delayed return of viremia when treatment was stopped. In an ongoing controlled study, Dr Walker's group is assessing responses to stopping therapy in patients with viral loads below levels of detection who initiated potent antiretroviral therapy early in infection or during chronic infection. These studies will examine whether HIV-1-specific immune response can be boosted under selective conditions and



Emerging data indicate that the cellular immune response plays a critical role in containing HIV-1 replication, and case reports have indicated that immune containment of HIV-1 is an achievable goal

Figure 5. *HIV-1 p24-specific T-helper cell response in patient treated with early potent antiretroviral therapy in whom plasma viral load was reduced to levels below detection limits. Left: The p24-specific proliferative response compared with control condition and response to PHA (phytohemagglutinin) during acute retroviral syndrome and after 3 months. Right: Correlation of increased p24-specific response with decreasing plasma viral load. Curved top and bottom lines show 95% confidence intervals. Adapted from Rosenberg ES, et al.* Science. *1997;278:1447–1450.*

whether efforts should be undertaken to investigate this strategy with well-controlled, systematic studies.

CONCLUSIONS

Emerging data indicate that the cellular immune response plays a critical role in containing HIV-1 replication, and case reports have indicated that immune containment of HIV-1 is an achievable goal. Recent findings have indicated that HIV-1-specific T-helper cell response is inversely correlated with viral load, and that HIV-1 can induce strong virus-specific T-helper cell responses in individuals controlling viremia in the absence of antiretroviral therapy. These responses appear to be preserved in patients treated with potent antiretroviral therapy during acute infection but are not restored in the short term in patients treated during chronic infection. However, it should be noted that other recent evidence indicates that immune reconstitution may occur with continued therapy over the long term in patients with chronic infection. Data may suggest that the immune system can be harnessed more effectively in control of infection. Similarly, the findings indicating that immune reconstitution may occur in chronically infected patients suggest the opportunity for immunotherapeutic intervention to improve the ability of such patients to control infection.

Bruce D. Walker, MD, is Associate Professor of Medicine at Harvard Medical School and Director of the Partners AIDS Research Center at Massachusetts General Hospital in Boston.

SUGGESTED READING

Autran B, Carcelain G, Li TS, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science.* 1997;277(5322):112–116.

Brodie S, Lewinsohn DA, Patterson BK, et al. In vivo migration and function of transferred HIV-1-specific cytotoxic T cells. *Nat Med.* 1999;5(1):34–42.

Cao Y, Qin L, Zhang L, et al. Virologic and immunologic characterization of long-term survivors of human immunodeficiency virus type 1 infection [see comments]. *N Engl J Med.* 332(4):201–208.

Connors M, Kovacs JA, Krevat S, et al. HIV infection induces changes in CD4+ T-cell phenotype and depletions within the CD4+ T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. *Nat Med.* 1997;3(5):533–540.

Douek DC, McFarland RD, Kelser PH, et al. Changes in thymic function with age and during the treatment of HIV infection. *Nature.* 1998;396:690–694.

(continued)

Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science.* 1997;278:1295–1298.

Harrer T, Harrer E, Kalams SA, et al. Strong cytotoxic T cell and weak neutralizing antibody responses in subset of persons with stable nonprogressing HIV type 1 infection. *AIDS Res & Hum Retroviruses.* 1996;12(7):585–592.

Kahn JO, Walker BD. Acute HIV-1 infection. *N Engl J Med.* 1998;339(1):33–39.

Kelleher AD, Carr A, Zaunders J, et al. Alterations in the immune response of human immunodeficiency virus (HIV)-infected subjects treated with an HIV-specific protease inhibitor, ritonavir. *J Inf Dis.* 1996;173(2):321–329.

Klein MR, van Baalen CA, Holwerda AM, et al. Kinetics of Gag-specific cytotoxic T-lymphocyte responses during the clinical course of HIV-1 infection: a longitudinal analysis of rapid progressors and long-term asymptomatics. *J Exp Med.* 1995;181(4):1365–1372.

Komanduri KV, Viswanathan MN, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med.* 1998;4(8):953–956.

Ogg GS, Jin X, Bonhoeffer S, et al. Quantitation of HIV-1-specific cytotoxic T-lymphocytes and plasma load of viral RNA. *Science.* 1998;279(5359):2103–2106.

Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. *Science.* 1997;278(5342):1447–1450.

Schmitz JE, Kuroda MJ, Santra S, et al. Control of viremia in simian immunodeficiency virus infection by CD8 lymphocytes. *Science.* 1999;283:852–858.

Wong JK, Hezareh M, Gunthard HF, et al. Recovery of replication-competent HIV despite prolonged suppression of plasma viremia. *Science.* 1997;278:1291–1295.

Yang OO, Kalams SA, Trocha A, et al. Suppression of human immunodeficiency virus type 1 replication by CD8+ cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. *J Virol.* 1997;71(4):3120–3128.