
Immune Reconstitution in HIV-1-Infected Individuals Treated with Potent Antiretroviral Therapy

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Potent combination antiretroviral therapy that was introduced in the mid-1990s for treatment of HIV-1 infection has resulted in unprecedented decreases in HIV-1 replication and increases in CD4+ T cell counts in many individuals. Coincident with the introduction of potent combination antiretroviral therapy, substantial declines in AIDS-related morbidity and mortality have been observed. Although these declines strongly suggest that significant immune reconstitution is occurring, increasing evidence suggests that immune reconstitution is neither uniform nor complete in all treated individuals. Clinical data suggest that some HIV-1-associated malignancies have not declined despite the new therapies, and that not all treated individuals reconstitute CD4+ T cell numbers to normal values.

Laboratory studies reveal that immune responses to ubiquitous antigens are reconstituted, but that responses to rarely encountered antigens, such as tetanus, are not reconstituted without repeat vaccination. Many questions remain concerning the extent and clinical significance of the immune reconstitution that occurs in the setting of antiretroviral drug therapy. A better understanding of the nature of the immune reconstitution that results from potent antiretroviral therapy is critical to the optimal clinical management of HIV-1-infected individuals, and may provide important insights into the immunopathogenesis of HIV-1 infection as well. **Key words:** antiretroviral therapy/CD4+ T lymphocytes/HIV-1/immune reconstitution. *Journal of Investigative Dermatology Symposium Proceedings* 6:212–218, 2001

Infection with the human immunodeficiency virus type 1 (HIV-1) results in the progressive loss of CD4+ T lymphocytes and a variety of immune functions. In the absence of therapy, most infected individuals eventually develop opportunistic infections (OI) and ultimately die prematurely. The introduction of potent antiretroviral therapy for HIV-1 infection in the past 5 y has led to dramatic increases in CD4+ T cell numbers, decreases in OI, and improvements in survival, suggesting that immune reconstitution is occurring in treated individuals; however, the nature and extent of this immune reconstitution is not fully understood. A better understanding of the immune reconstitution that occurs in the setting of potent antiretroviral therapy is critical to the optimal treatment of HIV-1-infected individuals.

IMPACT OF POTENT ANTIRETROVIRAL THERAPY ON AIDS-RELATED MORBIDITY AND MORTALITY

Prior to the mid-1990s, the standard of care for treatment of HIV-1 infection consisted of monotherapy and dual therapy with HIV-1 nucleoside analog reverse transcriptase inhibitors. These therapies were shown to produce modest increases in

CD4+ T cell counts and some improvements in survival (Delta Coordinating Committee, 1996; Hammer *et al*, 1996; Katzenstein *et al*, 1996; Marschner *et al*, 1998). With the introduction of protease inhibitors in the mid-1990s and their use in combination with other antiviral drugs, much more profound and sustained viral suppression and larger increases in CD4+ T cell counts were observed than ever before. The first widely used potent combination antiretroviral therapies for HIV-1 infection consisted of an HIV-1 protease inhibitor and two nucleoside analog reverse transcriptase inhibitors (Collier *et al*, 1996; Gulick *et al*, 1997; Hammer *et al*, 1997). Over the past 5 y, a variety of combinations of antiviral drugs have been shown to be equally if not more potent in suppressing HIV-1 replication (D'Aquila *et al*, 1996; Murphy *et al*, 1999; Staszewski *et al*, 1999; Gulick *et al*, 2001). These various combinations of potent antiviral medications, frequently referred to as highly active antiretroviral therapy (HAART), have become the standard of care for HIV-1 infection (Carpenter *et al*, 2000).

Commensurate with the introduction of HAART, there has been a dramatic decline in mortality and morbidity from HIV-1 disease in the U.S.A. and other industrialized countries. In the U.S.A., AIDS-related deaths in adults have steadily declined from a peak of 50,610 in 1995 to 16,273 in 1999 (Centers for Disease Control and Prevention, 1999a). Profound decreases in the incidence of many OI, such as *Pneumocystis carinii* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV) retinitis, have been reported over the same period of time (Brodt *et al*, 1997; Egger *et al*, 1997; Correll *et al*, 1998; Hogg *et al*, 1998; Holtzer *et al*, 1998; Mocroft *et al*, 1998; Palella *et al*, 1998; Jones *et al*, 1999a; Paul *et al*, 1999; Pezzotti *et al*, 1999; Kaplan *et al*, 2000). These

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Abbreviations: AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; MAC, *Mycobacterium avium* complex; OI, opportunistic infection; PCP, *Pneumocystis carinii* pneumonia.

declines in OI cannot be explained by increases in prophylactic measures to prevent them (Palella *et al*, 1998; Jones *et al*, 1999a). Randomized trials of potent combination antiretroviral therapy compared with less potent regimens have demonstrated that it is the superior control of HIV-1 replication and the increase in CD4+ T lymphocyte counts induced by potent regimens that are associated with the reduced incidence of OI (Cameron *et al*, 1997; Hammer *et al*, 1997; Hirsch *et al*, 1999).

Further evidence to suggest that HAART results in immune reconstitution comes from numerous case reports of the resolution of OI after initiation of therapy. Progressive multifocal leukoencephalopathy (PML) (Baldeweg and Catalan, 1997; Baqi *et al*, 1997; Domingo *et al*, 1997; Elliot *et al*, 1997; Power *et al*, 1997; Albrecht *et al*, 1998; Cinque *et al*, 1998), diarrhea due to cryptosporidia and microsporidia (Goguel *et al*, 1997; Carr *et al*, 1998), treatment-refractory oral candidiasis (Zingman, 1996; Valdez *et al*, 1998), molluscum contagiosum (Hicks *et al*, 1997; Hurni *et al*, 1997), and Kaposi's sarcoma (Conant *et al*, 1997; Murphy *et al*, 1997; Parra *et al*, 1998) have been reported to regress after the initiation of potent combination antiretroviral therapy. Individuals with a history of CMV retinitis, which in the absence of CMV-specific therapy usually progresses within a few weeks, have had primary anti-CMV therapy withdrawn without disease recurrence after receiving HAART (Uthayakumar *et al*, 1997; Jabs *et al*, 1998). Similarly, disseminated MAC infection, which previously required lifelong therapy for containment, has failed to recur in individuals despite cessation of primary therapy after a good response to HAART (Aberg *et al*, 1998). Prophylactic PCP therapy has been safely withdrawn in subjects previously at risk for PCP due to a low CD4+ T cell count after they had achieved sustained increases in CD4+ T cell counts (Furrer *et al*, 1999; Schneider *et al*, 1999; Weverling *et al*, 1999).¹ These data suggest that the decrease in OI seen with potent antiretroviral therapy is due not only to a halt in the progression of HIV-1-induced immune deficiency, but also to reconstituted immunity that allows individuals to contain infections immunologically that previously they were unable to control. As a result of these data, official recommendations regarding prophylaxis of OI have been modified to allow for the discontinuation of primary PCP and MAC prophylaxis in individuals with sustained elevations in CD4+ T cell counts above threshold levels in the setting of HAART (Centers for Disease Control and Prevention, 1999b).

Further clinical evidence that HAART results in immune reconstitution comes from an increasing number of observations of immune inflammatory syndromes in the setting of initiation of HAART. These syndromes, which consist of severe and sometimes unusual clinical manifestations of OI shortly after the introduction of HAART, are believed to be due to reconstitution of immunity to pre-existing, but clinically occult OI. Severe CMV retinitis, including the more unusual presentation of vitritis associated with retinitis, has been reported to occur in patients recently initiated on HAART (Gilquin *et al*, 1997; Jacobson *et al*, 1997). PML, including one atypical case in which contrast enhancing lesions developed 2 mo after presentation (Kotecha *et al*, 1998; Mayo *et al*, 1998), has also been observed to develop shortly after initiation of HAART. Focal lymphadenitis and other unusual clinical manifestations of MAC, other atypical mycobacteria, and *Mycobacterium tuberculosis* (MTB) (Chien and Johnson, 1998; Race *et al*, 1998; Foudraire *et al*, 1999), have been reported in individuals who had recently started HAART. Similar immunopathology has been suggested

as the cause for elevations in liver function tests in patients with chronic hepatitis B or C infection following initiation of HAART (Carr *et al*, 1997; Vento *et al*, 1998). An association has been described between initiation of HAART and serious and sometimes fatal cases of Castleman's disease, which is believed to be caused by human herpesvirus-8 (HHV-8) infection (Zietz *et al*, 1999). Thus, the immune reconstitution brought about by initiation of potent antiretroviral therapy can in some instances be paradoxically deleterious to treated individuals. In general, with the continuation of HAART and, in some instances, treatment with steroids, these immune inflammatory syndromes have resolved.

Although many lines of evidence suggest that substantial immune reconstitution occurs in individuals treated with HAART, clinical data suggest that this immune reconstitution is not necessarily uniform or complete in every treated individual. Despite evidence that prophylaxis against CMV and PCP can be safely discontinued when CD4+ T cell counts rise above the traditional threshold values for prophylaxis, several studies have reported the presentation of these and other OI at higher CD4+ T cell counts than was usually seen in the past (Law *et al*, 1999; Pezzotti *et al*, 1999). The CD4+ T cell nadir has been shown to be a significant risk factor for AIDS-defining illnesses or death even after CD4+ T cell increases on HAART have occurred (Ledgergerber *et al*, 1999; Miller *et al*, 1999). A few case reports, such as recurrent CMV retinitis in an individual treated with HAART for over 1 y and with a CD4+ T cell count over 400 cells per mm³ (Johnson, 2001), suggest that some individuals may have persistent immunologic lacunae despite sustained increases in CD4+ T cell numbers.

Further evidence that immune reconstitution in the setting of HAART may not be complete comes from the observation that not all HIV-1-associated illnesses have been found to decline. HIV-1-associated malignancies in particular have had quite variable responses to HAART. Declines in the incidence of Kaposi's sarcoma (Jacobson *et al*, 1999; Jones *et al*, 1999b; Rabkin *et al*, 1999; Sparano *et al*, 1999), as well as primary brain lymphoma (Jones *et al*, 1999b), have been reported since the introduction of HAART; however, the incidence of other HIV-1-associated malignancies, including immunoblastic lymphoma, invasive cervical cancer, Hodgkin's lymphoma, and Burkitt's lymphoma, have not declined or have declined more slowly than Kaposi's sarcoma over the same time interval (Grulich, 1999; Jacobson *et al*, 1999; Jones *et al*, 1999b; Rabkin *et al*, 1999). It may be that it takes longer for HAART to reverse the oncogenic diathesis induced by HIV-1 infection than the susceptibility to OI. Alternatively, or in addition, there may be a persistent oncogenic risk induced by HIV-1 infection that cannot be eliminated by the immune restoration induced by HAART. Studies that examine the clinical outcomes of individuals treated with HAART over the long term are needed to assess more fully the immune reconstitution induced by HAART.

NUMERICAL AND FUNCTIONAL CHANGES IN CD4+ T LYMPHOCYTES IN THE CONTEXT OF HAART

Progressive loss of CD4+ T cell numbers and functions is the hallmark of HIV-1 infection. During the course of untreated disease, CD4+ T cell counts drop from normal values, which are usually over 800 cells per mm³, to less than 200 CD4+ T cells per mm³, which in and of itself constitutes a diagnosis of AIDS. Historically, CD4+ T cell counts have been used to guide clinical decisions as to when to start antiretroviral therapy or prophylaxis for OI because they are highly predictive of the risk of OI and death (Dolan *et al*, 1995). In the setting of HAART, dramatic increases in CD4+ T lymphocyte counts have been observed. An average increase of 150 CD4+ cells per mm³ in the first year of therapy has been seen in individuals with moderately advanced disease (Collier *et al*, 1996; Gulick

¹Dworkin M, Hanson D, Jones J, *et al*: The risk for *Pneumocystis carinii* pneumonia (PCP) and disseminated nontuberculous mycobacteriosis (Dmb) after an antiretroviral therapy (ART) associated increase in the CD4+ T lymphocyte count. In: *Abstracts of the 6th Conference on Retroviruses and Opportunistic Infections, Chicago, IL, January 31-February 4*. Alexandria, VA: Foundation for Retrovirology and Human Health, 1999 (abstr. 692)

et al, 1997; Hammer *et al*, 1997; Connick *et al*, 2000). The magnitude of CD4+ T cell increases has been shown to be directly correlated with the magnitude of virus suppression, although there is substantial variability among patients (Collier *et al*, 1996; Gulick *et al*, 1997; Hammer *et al*, 1997; Connick *et al*, 2000). A critical clinical question is whether CD4+ T cell counts in individuals treated with HAART can be interpreted in the same way as those in untreated individuals.

Peripheral blood CD4+ T cell increases in the setting of potent antiretroviral therapy occur in two phases (Autran *et al*, 1997; Pakker *et al*, 1997; Bisset *et al*, 1998; Giorgi *et al*, 1998; Gray *et al*, 1998; Li *et al*, 1998; Pakker *et al*, 1998; Connick *et al*, 2000). The first phase increase, which occurs over the first 8 wk of therapy, tends to be more precipitous than the second, and consists primarily of CD4+ T cells with a memory phenotype. Several lines of evidence suggest that the first phase increase primarily reflects redistribution of CD4+ T cells out of lymphoid tissues, perhaps due to downregulation of adhesion molecules in these tissues coincident with suppression of HIV-1 replication (Bucy *et al*, 1999). The T cell receptor (TCR) repertoires of the cells of the first phase increase are similar to the pre-existing repertoire, which is often aberrant (Connors *et al*, 1997; Gorochov *et al*, 1998; Lederman *et al*, 1998). The first phase increase in CD4+ T lymphocyte numbers observed in peripheral blood has not been found in lymphoid tissues (Zhang *et al*, 1998); instead, very little or no increase has been observed in lymphoid tissues during the first 2 mo of HAART. As the vast majority of lymphocytes are found in lymphoid tissues, the absence of increases in CD4+ T cells in lymphoid tissues supports the theory that the first phase primarily represents redistribution of CD4+ T cells into the peripheral blood.

The second phase increase, which occurs after the first 8 wk of therapy, is usually slower than the first (Autran *et al*, 1997; Pakker *et al*, 1997; Bisset *et al*, 1998; Giorgi *et al*, 1998; Gray *et al*, 1998; Li *et al*, 1998; Pakker *et al*, 1998; Connick *et al*, 2000), but similar in tempo to what has been observed in cancer patients treated with chemotherapy (Hakim *et al*, 1997). The second phase increase consists primarily of CD4+ T cells with a naïve phenotype. Phenotypically naïve cells are not necessarily newly synthesized, as reversion of cells from a memory to a naïve phenotype has been reported (Bell *et al*, 1990; Walker *et al*, 1998). Studies of lymphoid tissues, however, have demonstrated CD4+ T cell increases during the second phase of CD4+ T cell increases, suggesting that these represent true increases in total body CD4+ T cells (Zhang *et al*, 1998). The TCR repertoires of the second phase increases have been less extensively studied, but several studies suggest that they may be trending towards a more normal repertoire than that prior to HAART (Gorochov *et al*, 1998; Kostense *et al*, 1998), further bolstering the theory that HAART results in new CD4+ T cell synthesis. A novel method of identifying thymically derived cells using T cell receptor excision circles (TREC) that are a byproduct of TCR rearrangement in the thymus as a marker, has demonstrated increases in TREC in the naïve pool of peripheral blood cells in HIV-1-infected individuals following initiation of HAART (Douek *et al*, 1998), suggesting that new CD4+ T cells are being generated by the thymus. The number of phenotypically naïve cells in HAART-treated individuals has been correlated with the abundance of thymic tissue determined by CT scan, further suggesting that the thymus may be an important source of newly synthesized cells in patients on HAART (McCune *et al*, 2000). It has been argued, however, that the increase in TREC-containing cells observed in the setting of HAART may be the result of diminished proliferation in the naïve CD4+ T cell pool and not necessarily due to synthesis of naïve cells in the thymus (Hazenbergh *et al*, 2000). Thus, the origin of the second phase increases in CD4+ T cells, whether from thymically or peripherally derived T cells, remains unclear.

Increasing evidence suggests that there may be a third or plateau phase when CD4+ T cell reconstitution stops. Although some treated individuals achieve and maintain normal CD4+ T cell counts, many others, particularly those with moderately advanced

HIV-1 infection, do not fully reconstitute their CD4+ T cells to normal numbers (Notermans *et al*, 1999).² The determinants of the long-term ability to reconstitute CD4+ T cell numbers have not been defined. Whether this could represent an HIV-1-induced defect in the generation of CD34+ bone marrow precursors or in thymic regeneration is unclear. The clinical consequences of incomplete CD4+ T cell regeneration are also unknown. The failure to reconstitute any CD4+ T cells has been shown to be associated with a worse outcome among individuals with moderately advanced HIV-1 infection (Grabar *et al*, 2000), but it is unknown what the implications of partial CD4+ T cell reconstitution are.

In addition to increases in CD4+ T cell numbers, several studies have demonstrated improved CD4+ T cell function in individuals treated with HAART. The sequential loss of T lymphocyte proliferative responses to antigens, alloantigens, and mitogens, as well as delayed type hypersensitivity skin test responses, are well described in HIV-1 infection, and have been found to be prognostic of disease progression (Clerici *et al*, 1989; Blatt *et al*, 1993; Dolan *et al*, 1995). The recovery of T lymphocyte proliferative responses to antigens such as CMV, MAC, Candida, and MTB, and DTH responses to Candida following initiation of HAART, has been reported by several groups (Autran *et al*, 1997; Komanduri *et al*, 1998; Pontesilli *et al*, 1999; Rinaldo *et al*, 1999; Wendland *et al*, 1999; Connick *et al*, 2000). The development of new mycobacteria-specific T cell lymphoproliferative responses has been correlated with immune inflammatory reactions in patients with unusual clinical manifestations of mycobacterial infections following the initiation of HAART (Foudraire *et al*, 1999). In general, the restoration of these responses has occurred rapidly, within the first 3 mo of therapy.

T lymphocyte proliferative and DTH responses do not appear to be unilaterally reconstituted in the setting of HAART. Despite two reports of recovery of tetanus-specific lymphocyte proliferative responses in small numbers of patients (Pontesilli *et al*, 1999; Rinaldo *et al*, 1999), a much larger study did not reveal reconstitution of tetanus-specific lymphocyte proliferative responses after 1 y of HAART therapy (Connick *et al*, 2000). The selective failure of tetanus responses to increase most likely is due to the infrequency of exposure to tetanus compared with Candida, CMV, MAC, and MTB, to which individuals are likely re-exposed endogenously. Indeed, a tetanus booster vaccination given to subjects after 1 y of HAART therapy, resulted in reconstitution of tetanus-specific lymphocyte proliferative responses (Valdez *et al*, 2000), suggesting that antigen-specific precursors had not been completely eliminated in these subjects, but only depleted. Similarly, in the first year of this same study Candida DTH responses were recovered after 12 wk of therapy, whereas new mumps DTH responses did not appear until tested for at week 48 (Connick *et al*, 2000). The early recovery of Candida DTH responses was believed to be due to endogenous re-exposure to this antigen. The later recovery of mumps responses was believed to be due to reconstitution of the booster phenomenon such that skin tests at week 12 boosted the numbers of mumps-specific cells so that these responses became detectable at 48 wk. These findings suggest that HAART improves the immune system's ability to respond to antigen on exposure, but that HAART does not reconstitute pre-existing responses in the absence of re-exposure. Thus, the rejuvenated immune system on HAART is not identical to the one prior to HIV-1 infection.

²Valdez H, Connick E, Lederman M, *et al*: T-lymphocyte changes after 3 years of controlled viral replication. *8th Conference on Retroviruses and Opportunistic Infections, Chicago, February 4-8, Alexandria, VA: Foundation for Retrovirology and Human Health 2001 (abstr. 372)*

THE IMPACT OF HAART ON HIV-1-SPECIFIC IMMUNE RESPONSES

It is not fully understood why most HIV-1-infected individuals are unable to mount an immune response that is capable of controlling and eradicating HIV-1 replication. A variety of mechanisms of immune evasion have been described in HIV-1 infection, including rapid selection of virus isolates that contain mutations within cellular and humoral epitopes that confer resistance (Wrin *et al*, 1994; Nowak *et al*, 1995; Borrow *et al*, 1997; Goulder *et al*, 1997), and downregulation of MHC class I molecules on virus-producing cells (Collins *et al*, 1998). Loss of HIV-1-specific CD4+ T lymphocyte proliferative responses, which usually occur quite early in infection (Wahren *et al*, 1987; Berzofsky *et al*, 1988; Krowka *et al*, 1989), has been hypothesized to be critical to the immunopathogenesis of HIV-1 infection as well. The finding that these responses are preserved in long-term nonprogressors (Schwartz *et al*, 1994; Rosenberg *et al*, 1997), who have low levels of virus replication, has been interpreted as evidence that HIV-1-specific CD4+ T cell functions are essential for immunologic control of the virus. A critical question is whether HAART may reverse defects in HIV-1-specific immune responses, and thereby enhance immunologic control in infected individuals.

Studies of HAART in chronically infected individuals have shown that HIV-1-specific CD4+ lymphocyte proliferative responses are rarely reconstituted (Autran *et al*, 1997; Plana *et al*, 1998; Pontesilli *et al*, 1999; Connick *et al*, 2000). Reconstitution of these responses has been reported in some individuals in early stages of disease (Al-Harhi *et al*, 2000). It has also been reported to occur in individuals with transient interruptions of HAART (Haslett *et al*, 2000; Ruiz *et al*, 2000), suggesting that re-exposure to HIV-1 antigens may reconstitute these responses. HIV-1-specific CD4+ T cells have been detected in untreated individuals using more sensitive flow cytometric studies of antigen-induced interferon- γ production (Pitcher *et al*, 1999). Long-term administration of HAART to chronically infected individuals results in a decrease in HIV-1-specific CD4+ lymphocytes detected by these flow cytometric assays (Pitcher *et al*, 1999).

Other HIV-1-specific immune responses appear to decline in the setting of HAART as well, presumably due to decreased antigen concentration. HIV-1-specific CD8+ cytotoxic T lymphocyte (CTL) memory and effector responses decline in chronically infected individuals treated with HAART (Gray *et al*, 1999; Kalams *et al*, 1999; Ogg *et al*, 1999). Humoral immune responses to HIV-1 also decline in chronically infected individuals treated with HAART. HIV-1 gp120-specific antibody secreting cells rapidly decline in number with the institution of HAART, and anti-gp120 titers fall more gradually (Morris *et al*, 1998).

Treatment of acute seroconverters with HAART appears to have different immune consequences than treatment of chronically infected individuals. Institution of HAART during or shortly after seroconversion has been reported to result in preservation of HIV-1-specific lymphocyte proliferative responses (Rosenberg *et al*, 2000). In addition, treatment of acute seroconverters has been reported to result in strong HIV-1-specific neutralizing antibodies (Barassi *et al*, 2000), which are distinctly unusual in chronic HIV-1 infection (Wrin *et al*, 1994). HIV-1-specific CTL responses in seroconverters who receive HAART appear to be affected in the same way as those in chronically infected individuals treated with HAART, in that they decline in subjects with maximal virus suppression, but are maintained or increase in those in whom viral suppression is incomplete (Dalod *et al*, 1998; Markowitz *et al*, 1999).

Because virus-specific responses could potentially synergize with HAART and enhance control of viral replication (Rosenberg and Walker, 1998), a number of strategies are currently under investigation to bolster HIV-1-specific CD4+ and CD8+ T cell responses. Based on the observations that interruption of HAART can result in augmentation of both CD4+ and CD8+ HIV-1-specific responses, studies of the immunologic and virologic effects

of intermittent withdrawal of antiretroviral therapy have been undertaken. Preliminary results suggest that interruption of treatment in subjects treated during acute HIV-1 seroconversion may result in enhanced virologic control (Rosenberg *et al*, 2000), perhaps through preservation of HIV-1-specific CD4+ T cell responses. Multiple interruptions in therapy have been suggested to be important in augmenting virologic control, perhaps through additional stimulation of HIV-1-specific cellular responses (Rosenberg *et al*, 2000). Interruption of therapy in chronically infected individuals, on the other hand, has not yielded much evidence of enhanced virologic control thus far (Neuman *et al*, 1999; Ortiz *et al*, 1999; Ruiz *et al*, 2000). Further studies are needed to determine if these strategies are safe or successful in inducing HIV-1-specific immune responses, and if these immune responses are associated with more effective elimination of virus or more sustained viral suppression.

Therapeutic vaccination is another approach currently under investigation to augment HIV-1-specific immunity in HAART-treated individuals. SIV-infected macaques who were treated with HAART 15 d after experimental infection and then subsequently vaccinated, have demonstrated enhanced virologic control upon discontinuation of antiretroviral therapy compared with animals who received antiretroviral therapy alone (Hel *et al*, 2000). Similar studies in humans are ongoing, but there are no definitive results to date.

SUMMARY AND CONCLUSIONS

Immune reconstitution in the setting of potent combination antiretroviral chemotherapy has resulted in remarkable decreases in morbidity and mortality from HIV-1 infection over the past 5 y. Both clinical and laboratory data suggest that HAART restores the ability of the immune system to respond to antigens upon re-exposure. Nevertheless, immune reconstitution is neither uniform nor complete in all treated individuals. Some HIV-1-associated malignancies have not declined in frequency, and the long-term impact of HAART on these and other HIV-1-associated illnesses remains to be determined. CD4+ T cell counts do not normalize in all treated individuals and CD4+ T cell functional studies suggest that many HIV-1-infected individuals treated with HAART continue to have selected defects. The clinical implications of subnormal CD4+ T cell numbers and incomplete immune restoration are unknown.

Although HAART has revolutionized the treatment of HIV-1 infection, it is not the solution for this disease. A small fraction of individuals are absolutely intolerant of the medications and therefore unable to take them. Many others suffer side-effects, but continue to use them with substantial impairments in their quality of life (Lucas *et al*, 1999). As many as two-thirds of treated individuals do not achieve or maintain complete virologic suppression (Lucas *et al*, 1999). Although partial suppression of virus has been shown to result in clinical benefits, ultimately individuals with incomplete virologic suppression will develop resistant viruses and then lose the immune benefits that they have achieved with HAART. Transmission of resistant virus is increasing (Little *et al*, 1999), and limits the medications that individuals infected with resistant strains may receive. Lastly, the majority of HIV-1-infected people in the world currently do not have access to HAART, and therefore do not benefit from it at all. A better understanding of the immunopathogenesis of HIV-1 infection that has been brought about by HAART may ultimately lead to better therapies for this infection, and possibly decrease or eliminate the need for antiretroviral drug therapy in the future.

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