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Pathogenesis of HIV infection: implications for treatment and prevention

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The immune systems of patients with HIV infection are characterized by an immunodeficiency that develops in the setting of a global immune activation and a complex array of HIV-specific immune responses. The immunodeficiency of HIV infection is the result of a decrease in both memory and naïve CD4+ T cells. Imaging studies of the total body CD4+ T cell pool reveal global depletion within all lymphoid tissues. Antiretroviral therapy leads to increases in all CD4+ T cell subsets but may not fully replete the CD4+ T cell repertoire. Expansions within the naïve and central memory pools of CD4+ T cells can be enhanced with the use of the T cell derived cytokine IL-2. The clinical significance of these changes is being studied in two phase III trials. Cytokines signalling through pathways similar to IL-2, namely IL-7 and IL-15, are currently being studied as well. The mechanisms underlying the global immune activation seen in patients with HIV infection remain to be fully elucidated. Immune activation in patients with untreated HIV infection leads to qualitative defects in the functions of CD8+ as well as CD4+ T cells, elevations in IL-6 and D-dimer and is likely at least partially responsible for the increased incidence of cardiovascular disease recently identified as being a direct consequence of HIV infection. The immune activation in the CD4+ T cell subset is correlated with both the level of CD4+ T cell depletion and the viral load while the CD8+ T cell activation is most tightly correlated to the viral load. Efforts to block immune activation by interventions other than antiretroviral therapy have yet to be clinically successful. Immediately following the initiation of antiretroviral therapy one may see another form of immune activation, namely the immune reconstitution inflammatory syndrome. This syndrome represents an exaggerated immune response to existing opportunistic diseases following the rapid improvement in immune function that occurs with the initiation of therapy. Lowering the antigenic burden of opportunistic diseases prior to initiation of antiretroviral therapy may mitigate this, at times fatal, complication of treatment. A series of humoral and cellular immune responses have been described in patients with HIV infection. It is not clear at present, which, if any, of these reflect host control of HIV, and would thus be the appropriate surrogate marker for an HIV preventive vaccine or a therapeutic immune based intervention.