virus and appear after approximately 12 weeks of infection. Due to its high rate of mutation the virus is usually able to quickly escape these (and subsequent) neutralizing antibodies. One important mechanism of immune escape is the addition of N-linked glycosylation sites, forming a glycan shield that interferes with envelope recognition by these initial antibodies.

A number of broad and potent HIV-neutralizing envelope-specific antibodies have been isolated from HIV-infected individuals in studies designed to better understand the host response to HIV infection. Approximately 20% of patients develop antibodies capable of neutralizing highly diverse strains. These studies have revealed at least five major sites within the HIV envelope that are able to elicit broadly-neutralizing antibodies. These sites include antibodies directed toward the CD4 binding site (CD4bs) of gp120, those binding glycan-dependent epitopes in the V1/V2 region of gp120, those near the base of the V3 region of gp120, those binding to the gp120/gp41 bridge, and those binding to the membrane-proximal region of gp41 **(Fig. 226-28)**. Several of these antibodies contain unique features including high levels of somatic hypermutation, selective germline gene usage (especially for CD4bs antibodies) and long heavy chain complementary determining regions (especially CDRH3). Of note, while these antibodies are broadly neutralizing in vitro, their precise in vivo significance is unclear and the patients from whom they were derived demonstrate evidence of ongoing viral replication unless treated with cART.

The other major class of protective antibodies are those that participate in ADCC, a form of cell-mediated immunity **(Chap. 372e)** in which NK cells that bear Fc receptors are armed with specific anti-HIV antibodies that bind to the NK cells via their Fc portion. These armed NK cells then bind to and destroy cells expressing HIV antigens. The levels of anti-envelope antibodies capable of mediating ADCC are highest in the earlier stages of HIV infection. Antibodies to both gp120 and gp41 have been shown to participate in ADCC-mediated killing of HIV-infected cells. In vitro, IL-2 can augment ADCC-mediated killing.

In addition to playing a role in host defense, HIV-specific antibodies have also been implicated in disease pathogenesis. Antibodies directed to gp41, when present in low titer, have been shown in vitro to be capable of facilitating infection of cells through an Fc receptor–mediated mechanism known as *antibody enhancement*. Thus, the same regions of the envelope protein of HIV that give rise to antibodies capable of mediating ADCC can also elicit the production of antibodies that can facilitate infection of cells in vitro. In addition, it has been postulated that anti-gp120 antibodies that participate in the ADCC killing of HIV-infected cells might also kill uninfected CD4+ T cells if the uninfected cells had bound free gp120, a phenomenon referred to as *bystander killing*.

One of the most primitive components of the humoral immune system is the complement system **(Chap. 372e)**. This element of innate immunity consists of ~30 proteins that are found circulating in blood or associated with cell membranes. While HIV alone is capable of directly activating the complement cascade, the resulting lysis is weak due to the presence of host cell regulatory proteins captured in the virion envelope during budding. It is possible that complement-opsonized HIV virions have increased infectivity in a manner analogous to antibody-mediated enhancement.

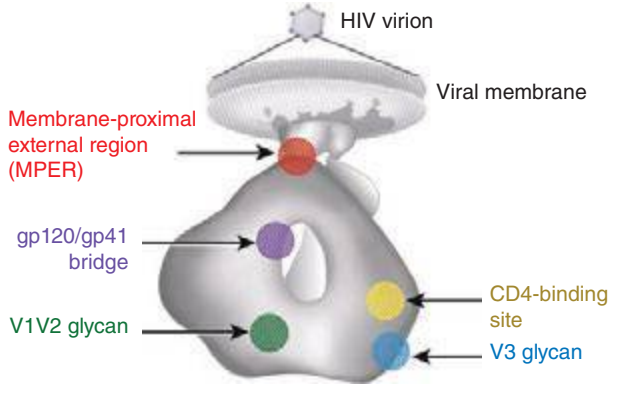


**FIGURE 226-28 Known targets of broadly neutralizing antibodies against HIV-1.** *(Adapted from PD Kwong, JR Mascola: Immunity 37:412, 2012.)*

## CELLULAR IMMUNE RESPONSE

Given that T cell–mediated immunity is known to play a major role in host defense against most viral infections **(Chap. 372e)**, it is generally thought to be an important component of the host immune response to HIV. T cell immunity can be divided into two major categories: that mediated by *helper/inducer CD4+ T cells* and that mediated by *cytotoxic/immunoregulatory CD8+ T cells*.

HIV-specific CD4+ T cells can be detected in the majority of HIV-infected patients through the use of flow cytometry to measure intracellular cytokine production in response to MHC class II tetramers pulsed with HIV peptides or through lymphocyte proliferation assays utilizing HIV antigens such as p24. These cells likely play a critical role in the orchestration of the immune response to HIV by providing help to HIV-specific B cells and CD8+ T cells. They may also be capable of directly killing HIV-infected cells. HIV-specific CD4+ T cells may be preferential targets of HIV infection by HIV-infected antigen-presenting cells during the generation of an immune response to HIV (Fig. 226-26). However, they also are likely to undergo clonal expansions in response to HIV antigens and thus survive as a population of cells. No clear correlations exist between levels of HIV-specific CD4+ T lymphocytes and plasma HIV RNA levels; however, in the setting of high viral loads, CD4+ T cell responses to HIV antigens appear to shift from one of proliferation and IL-2 production to one of IFN-γ production. Thus, while a reverse correlation exists between the level of p24-specific proliferation and levels of plasma HIV viremia, the nature of the causal relationship between these parameters is unclear.

MHC class I–restricted, HIV-specific CD8+ T cells have been identified in the peripheral blood of patients with HIV-1 infection. These cells include CTLs that produce perforins and T cells that can be induced by HIV antigens to express an array of cytokines such as IFN-γ, IL-2, MIP-1β, and TNF-α. CTLs have been identified in the peripheral blood of patients within weeks of HIV infection and prior to the appearance of plasma virus. The selective pressure they exert on the evolution of the population of circulating viruses reflects their potential role in control of HIV infection. These CD8+ T lymphocytes, through their HIV-specific antigen receptors, bind to and cause the lytic destruction of target cells bearing autologous MHC class I molecules presenting HIV antigens. Two types of CTL activity can be demonstrated in the peripheral blood or lymph node mononuclear cells of HIV-infected individuals. The first type directly lyses appropriate target cells in culture without prior in vitro stimulation (*spontaneous CTL activity*). The other type of CTL activity reflects the *precursor frequency of CTLs* (CTLp); this type of CTL activity can be demonstrated by stimulation of CD8+ T cells in vitro with a mitogen such as phytohemagglutinin or anti-CD3 antibody.

In addition to CTLs, CD8+ T cells capable of being induced by HIV antigens to express cytokines such as IFN-γ also appear in the setting of HIV-1 infection. It is not clear whether these are the same or different effector pools compared with those cells mediating cytotoxicity; in addition, the relative roles of each in host defense against HIV are not fully understood. It does appear that these CD8+ T cells are driven to in vivo expansion by HIV antigen. There is a direct correlation between levels of CD8+ T cells capable of producing IFN-γ in response to HIV antigens and plasma levels of HIV-1 RNA. Thus, while these cells are clearly induced by HIV-1 infection, their overall ability to control infection remains unclear. Multiple HIV antigens, including Gag, Env, Pol, Tat, Rev, and Nef, can elicit CD8+ T cell responses. Among patients who control viral replication in the absence of antiretroviral drugs are a subset of patients referred to as elite nonprogressors (see "Long-Term Survivors and Long-Term Nonprogressors," above) whose peripheral blood contains a population of CD8+ T cells that undergo substantial proliferation and perforin expression in response to HIV antigens. It is possible that these cells play an important role in HIV-specific host defense.