TABLE 226-7 ELEMENTS OF THE IMMUNE RESPONSE TO HIV

Humoral immunity
Binding antibodies
Neutralizing antibodies
Type specific
Group specific
Broadly neutralizing
Antibodies participating in antibody-dependent cellular cytotoxicity (ADCC)
Protective
Pathogenic (bystander killing)
Enhancing antibodies
Complement
Cell-mediated immunity
Helper CD4+ T lymphocytes
Class I MHC–restricted cytotoxic CD8+ T lymphocytes
CD8+ T cell–mediated inhibition (noncytolytic)
ADCC
Natural killer cells

Abbreviation: MHC, major histocompatibility complex.

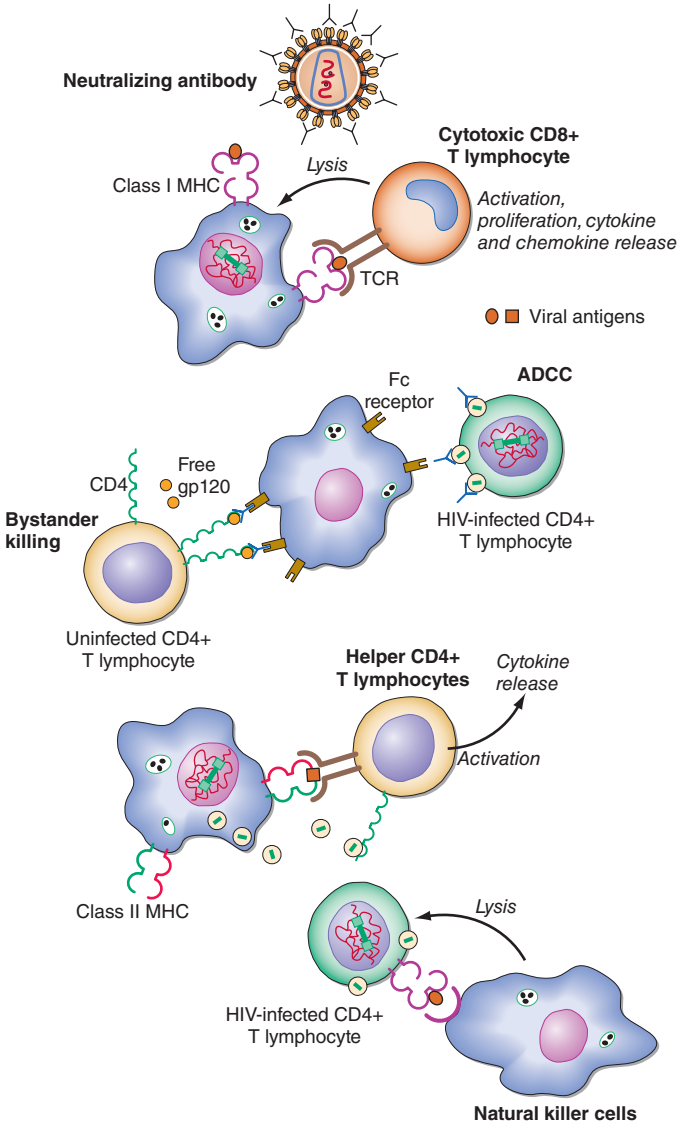

FIGURE 226-26 Schematic representation of the different immunologic effector mechanisms thought to be active in the setting of HIV infection. Detailed descriptions are given in the text. ADCC, antibody-dependent cellular cytotoxicity; MHC, major histocompatibility complex; TCR, T cell receptor.

well as against viral proteins expressed on the surface of infected cells. Ironically, those CD4+ T cells with T cell receptors specific for HIV are theoretically those CD4+ T cells most likely to be activated—and thus to serve as early targets for productive HIV infection and the cell death or dysfunction associated with infection. Thus, an early consequence of HIV infection is interference with and decrease of the helper T cell population needed to generate an effective immune response.

Although a great deal of investigation has been directed toward delineating and better understanding the components of this immune response, it remains unclear which immunologic effector mechanisms are most important in delaying progression of infection and which, if any, play a role in the pathogenesis of HIV disease. This lack of knowledge has also hampered the ability to develop an effective vaccine for HIV disease.

HUMORAL IMMUNE RESPONSE

Antibodies to HIV usually appear within 3–6 weeks and almost invariably within 12 weeks of primary infection (Fig. 226-27); rare exceptions are in individuals who have defects in the ability to produce HIV-specific antibodies. Detection of these antibodies forms the basis of most diagnostic screening tests for HIV infection. The appearance of HIV-binding antibodies detected by ELISA and Western blot assays occurs prior to the appearance of neutralizing antibodies; the latter generally appear following the initial decreases in plasma viremia and are more closely related to the appearance of HIV-specific CD8+ T lymphocytes. The first antibodies detected are those directed against the immunodominant region of the envelope gp41, followed by the appearance of antibodies to the structural or gag protein p24 and the gag precursor p55. Antibodies to p24 gag are followed by the appearance of antibodies to the outer envelope glycoprotein (gp120), the gag protein p17, and the products of the *pol* gene (p31 and p66). In addition, one may see antibodies to the low-molecular-weight regulatory proteins encoded by the HIV genes *vpr*, *vpu*, *vif*, *rev*, *tat*, and *nef*. On rare occasion, levels of HIV-specific antibodies may decline during treatment of acute HIV infection.

While antibodies to multiple antigens of HIV are produced, the precise functional significance of these different antibodies is unclear. The only viral proteins that elicit neutralizing antibodies are the envelope proteins gp120 and gp41. Antibodies directed toward the envelope proteins of HIV have been characterized both as being protective and as possibly contributing to the pathogenesis of HIV disease. Among the protective antibodies are those that function to neutralize HIV directly and prevent the spread of infection to additional cells, as well as those that participate in ADCC. The first neutralizing antibodies are directed against the autologous infecting

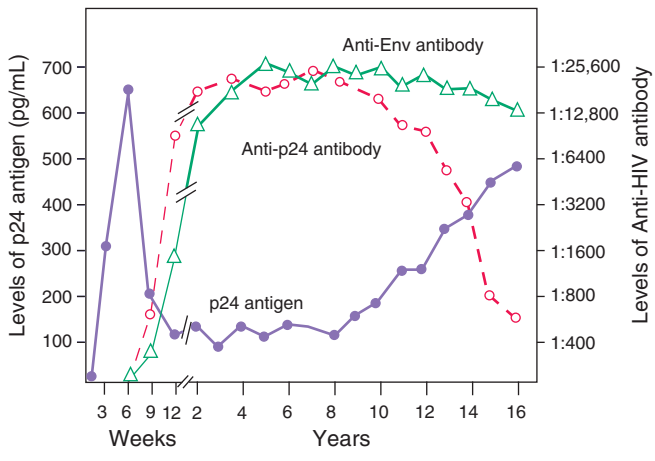

FIGURE 226-27 Relationship between antigenemia and the development of antibodies to HIV. Levels of plasma HIV parallel those of p24 antigen. Antibodies to HIV proteins are generally seen 6–12 weeks following infection and 3–6 weeks after the development of plasma viremia. Late in the course of illness, antibody levels to p24 decline, generally in association with a rising titer of p24 antigen.