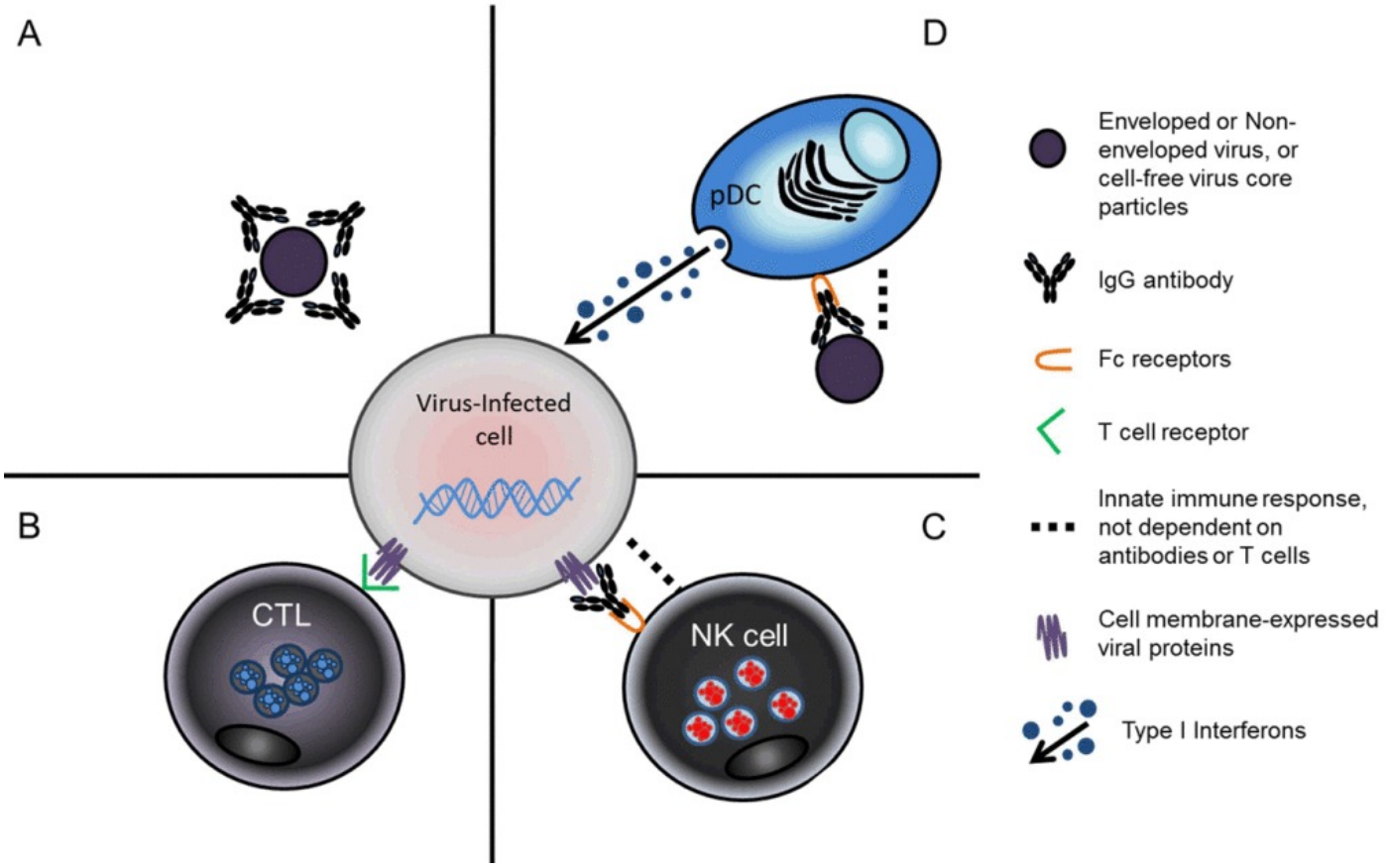
What type of immune responses are needed to control HIV infection?

Human immunodeficiency virus-1 (HIV-1) infection can be controlled by antiretroviral therapy (ART) for long periods of time, preventing the development of HIV-induced immunodeficiency and AIDS. However, HIV-1 infection cannot be eradicated from immune cells by ART and cure of the infection in this way is not possible. Consequently, life-long uninterrupted ART is essential. Strategies for curing HIV-1 infection are therefore under investigation around the world. These strategies will likely include the use of therapeutic HIV vaccines to boost immune responses that will clear the body of cells infected by HIV-1. It is therefore crucial to understand more about immune responses that have been associated with control of HIV-1 infection so that they can be targeted by therapeutic HIV vaccines.



Immune responses preventing the infection of cells by viruses and/or destroying cells that have become infected by viruses. [A] neutralising antibodies, [B] cytolytic T cells, [C] NK cell-activating antibodies (also known as antibody-dependant cell-mediated cytotoxicity [ADCC]), and [D] plasmacytoid dendritic cell-reactive opsonophagocytic antibodies.

The immune system produces several types of immune response that are particularly effective in preventing infection of cells by viruses and/or in killing cells that have become infected by viruses (Figure). These immune responses include antibodies that bind to and neutralise viruses before they can infect cells (neutralising antibodies) [A], lymphocytes that react with viral proteins expressed on the surface of cells infected by viruses resulting in cell lysis, particularly cytolytic T cells (CTLs) [B] and natural killer (NK) cells [C], and plasmacytoid dendritic cells (pDCs), which produce type 1 interferons that increase production of multiple anti-viral proteins and enhance NK cell function [D]. Both NK cells and pDCs can be activated directly by the virus (an innate immune response) or by antibodies to viral proteins as part of an adaptive immune response. Antibodies may bind to proteins expressed by whole virus or cell-free virus core particles.

Control of HIV-1 infection without ART is associated with a greater abundance and/or function of CTLs and antibodies reacting with proteins of the HIV-1 core (known as Gag proteins because they are encoded by the Gag gene of HIV-1), and a greater abundance and/or function of NK cells and pDCs. Gag proteins are particularly effective targets for CTL or antibody responses because their antigenic structure is more conserved than other HIV-1 proteins, such as envelope proteins, which are very prone to variation in antigenic structure and ‘escape’ from immune responses.

The number of circulating HIV-1-specific CTLs can be increased by vaccination but this does not control (or prevent) HIV-1 infection. Antibodies to HIV-1 envelope proteins that activate NK cells can also be induced by vaccination and do exert some effect in preventing HIV infection, but it is unclear if this type of antibody response would be effective in controlling or eradicating established HIV infection. Finally, an immune response that eradicates simian immunodeficiency virus (SIV) infection can be induced by a cytomegalovirus-vectored SIV vaccine in macaques but it is not known if this vaccination strategy will be feasible in humans. Antibodies that bind (opsonise) HIV-1 Gag proteins expressed by core particles and induce internalisation (phagocytosis) of the particles by pDCs (referred to as pDC-reactive opsonophagocytic antibodies) might provide an additional immune response to HIV-1 Gag-specific CTL responses that could be enhanced by a therapeutic HIV vaccine.

Studies of HIV-1 Gag-specific pDC-reactive opsonophagocytic IgG antibody responses undertaken so far indicate that they are associated with control of HIV-1 replication and that the antibody response may be more effective if it has characteristics of a response that has undergone a maturation process in areas of lymphoid tissue (lymph nodes, spleen etc) known as germinal centres. Mounting evidence indicates that HIV infection causes inflammation, fibrosis and dysfunction in germinal centres, which impairs antibody responses and persists in patients receiving ART.

Future studies will assess if therapeutic HIV vaccines strategies should include stimulation of both cellular (CTL) and humoral (IgG antibody) responses against HIV-1 Gag proteins and if B cells producing HIV-1 Gag-specific IgG antibody responses should undergo a germinal centre-type maturation process to enhance production of a pDC-reactive opsonophagocytic antibody response.

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Publication

Viremic HIV Controllers Exhibit High Plasmacytoid Dendritic Cell-Reactive Opsonophagocytic IgG Antibody Responses against HIV-1 p24 Associated with Greater Antibody Isotype Diversification.
Tjiam MC, Taylor JP, Morshidi MA, Sariputra L, Burrows S, Martin JN, Deeks SG, Tan DB, Lee S, Fernandez S, French MA
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