Basic Immunology of HIV

The human immunodeficiency virus (HIV), classified as a retrovirus, belongs to the genus Lentivirus within the family of Retroviridae. It is the causative agent of **acquired immunodeficiency syndrome** (**AIDS**). It invades various immune cells such as the **CD4$^+$ T cells** and **monocytes**. A decline in CD4$^+$ T cell numbers below the critical level leads to loss of cell-mediated immunity. Consequently, the body becomes progressively more susceptible to opportunistic infections and cancer.

HIV invasion of immune cells

- CCR5 and CXCR4 are expressed on the surface of host immune cells and act as coreceptors for HIV entry into human cells.
- HIV infects T cells via high-affinity interaction between the virion envelope glycoprotein (**gp120**) and the CD4 molecule.
- Infection of T cells is assisted by the **T-cell co-receptor, CXCR4** while HIV infects monocytes by interacting with **CCR5 co-receptor** (**Figure 1**). During the early stages of HIV infection, viral isolates tend to use CCR5 for viral entry, while later isolates tend to use CXCR4.
- As shown in Figure 2, after gp120 binds to CD4 on the T cell (**1**), nucleocapsids containing viral genome and enzymes enters the target cell (**2**).
- Following the release of viral genome and enzymes from the core protein, viral reverse transcriptase catalyses reverse transcription of ssRNA to form RNA-DNA hybrids (**3**).
- The viral RNA template is partially degraded by

ribonuclease H and the second DNA strand is synthesized (**4**).
- The viral dsDNA is translocated into the nucleus and integrated into the host genome by the viral integrase enzyme (**5**).
- Transcription factors transcribe the proviral DNA into genomic ssRNA (**6**), which is exported to cytoplasm (**7**).
- In the cytoplasm, host-cell ribosomes catalyse synthesis of viral precursor proteins (**8**).
- The viral precursor proteins are cleaved into viral proteins by viral proteases (**9**).
- HIV ssRNA and proteins assemble beneath the host-cell plasma membrane (**10**) forming virion buds from it (**11**).
- Maturation occurs either in the forming buds or after budding from the host cell (**12**).
- During maturation, HIV proteases cleave the poly-proteins into individual functional HIV proteins.
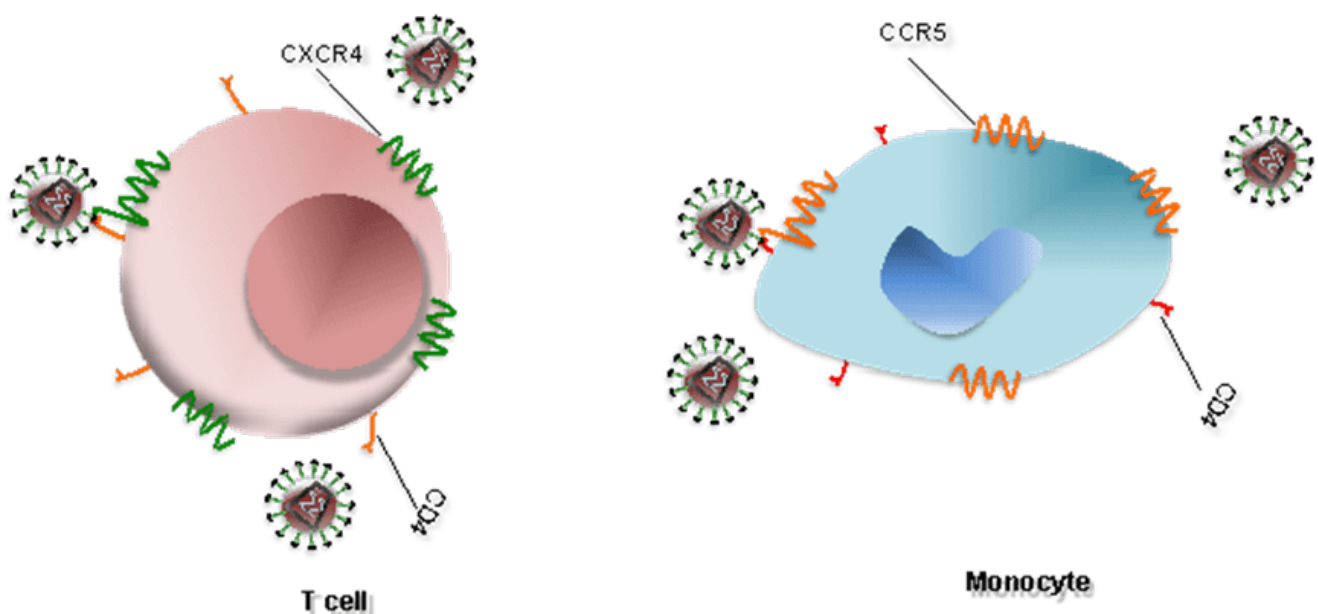- The mature virions are able to infect another host cell.

Figure 1. Interaction between HIV and coreceptors of a T cell and a monocyte [Alouani, N. and Berrezouga, P. L. (2021) "Oral HPV and HIV: A case report with analysis of the recent literature." Unpublished. doi: 10.13140/RG.2.2.15621.17120.]
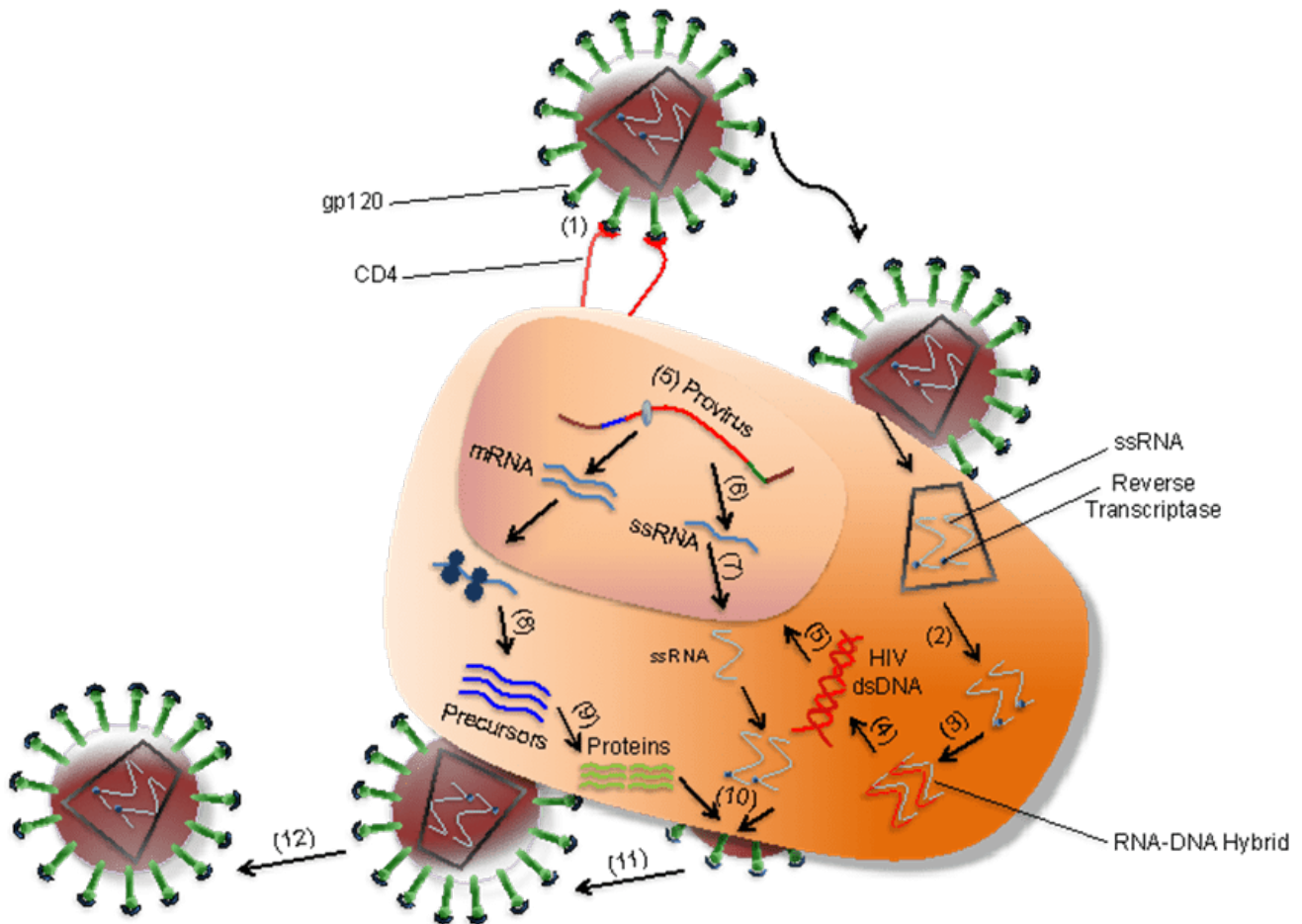
Figure 2. Overview of HIV infection of a target cell (e.g. T cell) [Alouani, N. and Berrezouga, P. L. (2021) "Oral HPV and HIV: A case report with analysis of the recent literature." Unpublished. doi: 10.13140/RG.2.2.15621.17120.]

Innate immune response to HIV

- Innate immune cells (e.g., dendritic cells and natural killer cells) are the first line of defense which HIV encounters upon entry to the body.

Macrophages

- Tissue macrophages are one of the target cells for HIV.
- They harbour the virus and are known to be the source of viral proteins.

Dendritic cells (DCs)

- DCs are large cells with dendritic cytoplasmic extensions.
- These cells present processed antigens to T lymphocytes in lymph nodes.
- Epidermal DCs, are probably among the first immune cells to combat HIV at the mucosal surfaces.
- These cells transport HIV from the site of infection to lymphoid tissue.
- The follicular DCs, found in lymphoid tissue, are also key antigen-presenting cells that trap and present antigens on their cell surfaces.
- In the lymph node follicles, DCs provide signals for the activation of B lymphocytes.

Natural killer (NK) cells.

- NK cells have lytic activity against cells that have diminished expression of **major histocompatibility complex** (**MHC**) **I**
- Because the presence of MHC class I is required for peptide presentation to T cell receptors, NK cells are an important line of defense when HIV escapes the cellular immune response.
- NK cells proliferate in response to **type 1 interferon** secreted by DCs.
- These stimulated NK cells release cytokines such as interferon γ (**IFN-γ**), tumour necrosis factor α (**TNF-α**), and chemokines to activate T-cell proliferation (cellular immune response).
- NK cells also inhibit viral replication by releasing IFN-γ.

Adaptive immune response to HIV

Cellular immune response to HIV

- This is induced upon the entry of HIV into the target cells (e.g., T cells) and synthesis of viral proteins (**Figure 1**).
- MHC class I on the cell surface displays the intracellularly degraded HIV peptide fragments for recognition by **T-cell receptors** (TCR) on **CD8+ T cells** (**Figure 3**).
- CD8+ T cells lyse HIV infected cells and secrete cytokines, i.e. interferon-γ (IFN-γ), tumor necrosis factor α (TNF-α), and chemokines, i.e. **MIP-1 α**, **MIP β** and **RANTES**, that inhibit virus replication and block viral entry into CD4+ T cells.
- Development of CD8+ T cells is crucial for control of HIV replication.
- This results in declining viraemia after primary infection. In the early stages of infection, CD4+ T cells lose their proliferative capacity and therefore their contribution to viral control is minor. However, during chronic infection CD4+T cells are present and secrete **interleukin-2(IL-2)** or cytokines, such as IFN-γ, to control viraemia.

Humoral response to HIV

- Occurs later in infection (**Figure 4**); therefore, the level of antibodies during the acute infection is very low.
- Non-neutralising antibodies to structural proteins (i.e. P17 and P24) are first to appear and generally do not persist.
- Later, neutralising antibodies specific to proteins involved in the entry of the virus into the cells, will be generated.
- These antibodies are specific to: (1) the variable

region of gp120 (V3); (2) CD4 binding sites and chemokine receptors (i.e., CXCR4 and CCR5); (3) the transmembrane protein gp41.

- Potent neutralizing antibodies have been shown to play a major role in controlling HIV infection in a few symptom-free HIV+ individuals who maintain high level of CD4+ T cells and low viral load.

A summary of the Immune Response to HIV is available as a wallchart — https://www.stemcell.com/media/files/wallchart/10000011477-Immune_Response_HIV.pdf
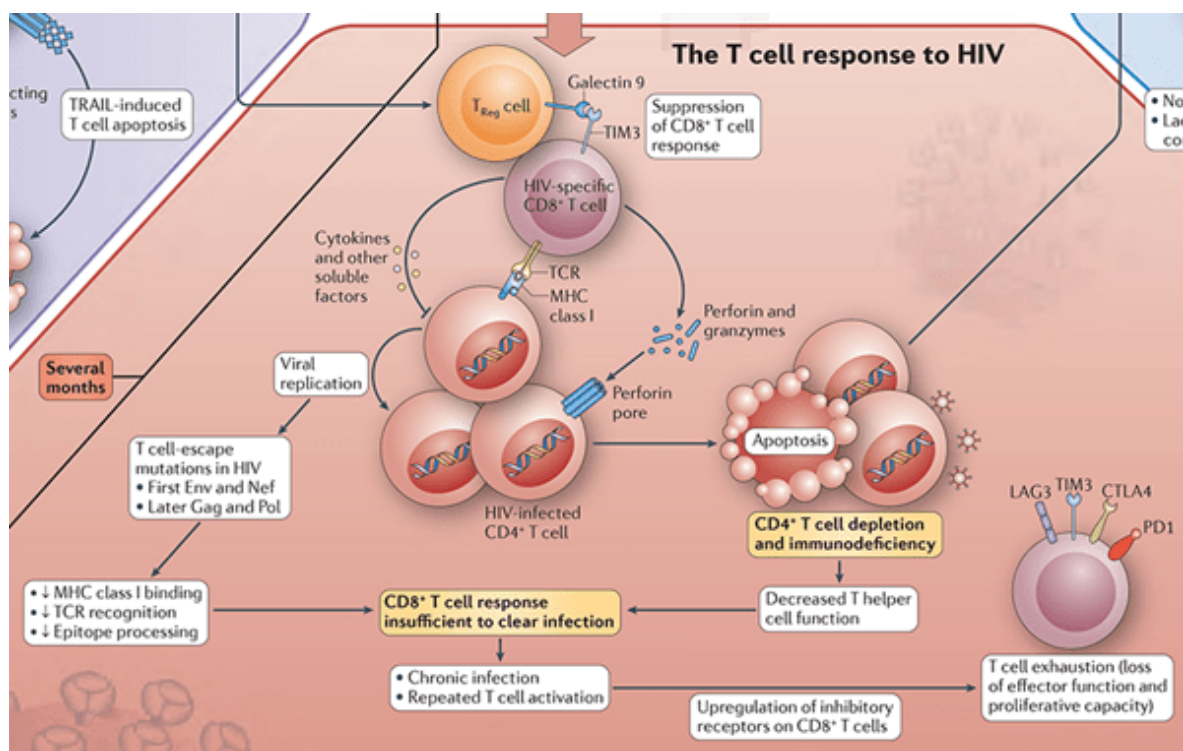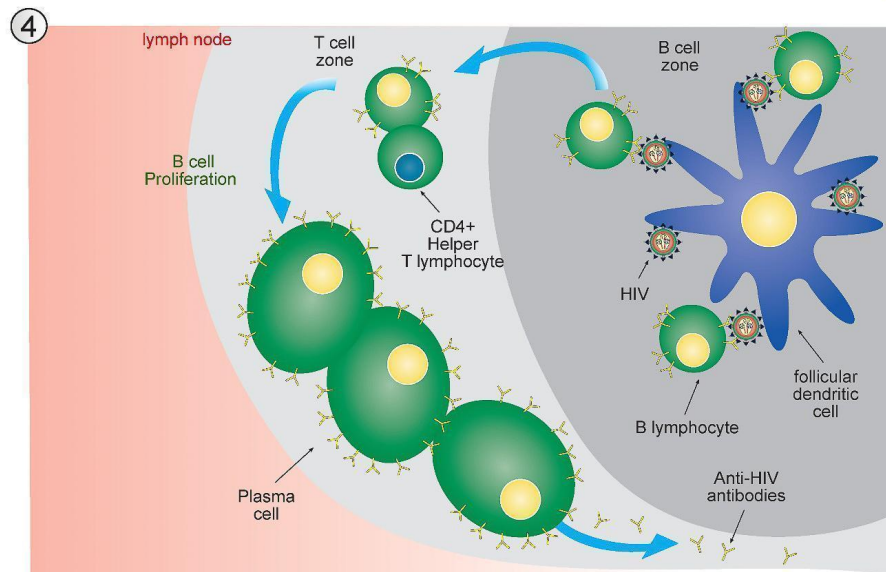

Figure 3: The T Cell Response to HIV [Adapted from the Immune Response to HIV wallchart, created by Nature Reviews Immunology in partnership with STEMCELL Technologies. Stemcell.com. https://www.stemcell.com/immunology-features/immune-response-to-hiv (Accessed: Oct 25, 2022)]

Antibodies to HIV begin to appear in peripheral blood a few weeks after infection (seroconversion). In order for HIV-specific antibodies to be generated there must be sufficient presentation of HIV antigens to B lymphocytes. This is done by capture of viral particles and proteins on the surface of follicular dendritic cells located in the germinal centre (B cell zone) of the lymph node. In addition, HIV-specific CD4+ Helper T lymphocytes are required to provide activation signals for B lymphocytes to differentiate into plasma cells.

Figure 4: Immune events leading to antibody production and seroconversion. [Shaan (2016) Immunity to HIV, Immunopaedia | Advancing global immunology education. Immunopaedia]

Insights into HIV vaccine design efforts

- The development of an effective HIV-1 vaccine is particularly challenging owing to the exceptional and increasing genetic diversity of the HIV-1 lentivirus. Some of this results from its complex mechanisms of immune evasion and the ability of HIV-1 to integrate into host immune cells to become resistant to host immunity and treatment regimens.
- The first generation of vaccines tested in clinical trials utilized gp120 as an antigen for eliciting neutralizing antibodies, whereas more recent trials tested vaccines designed to elicit CD8+ T cell responses and non-neutralizing antibodies.
- Out of eight HIV-1 vaccine efficacy trials completed so far, only one trial showed that high levels of

antibodies binding to the HIV-1 variable loop 2 (V2) and low levels of IgA specific for the envelope (Env) protein correlated with decreased transmission and guided the design of subsequent clinical trials.

- However, of two phase IIb/III clinical trials designed to improve on the RV144 trial — HIV-1 Vaccine Trials Network (HVTN) 702 (NCT02968849) and HVTN 705 (NCT03060629) — neither showed significant efficacy, suggesting that the RV144 trial may not have been a harbinger of vaccine success.
- An ongoing phase III trial is further exploring the concept of inducing high titres of non-neutralizing antibodies (HVTN 706, NCT03964415)
- Thus, for HIV-1, the induction of antibodies that broadly protect against heterologous HIV-1 strains (called broadly neutralizing antibodies (bnAbs) is a prime goal of HIV-1 vaccine development

HIV and Cancer

People infected with HIV have a substantially higher risk of some types of cancers compared to uninfected people of the same age. The general term for these cancers is "HIV-associated cancers."

Three different viruses are known to be causes of these cancers known as "acquired immunodeficiency syndrome (AIDs)-defining cancers" or "AIDS-defining malignancies";

- Kaposi sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), which causes Kaposi sarcoma and some subtypes of lymphoma
- Epstein-Barr virus (EBV), which causes some subtypes of non-Hodgkin and Hodgkin lymphoma
- Human papillomaviruses (HPV), which cause cervical cancer, most anal cancers,

and oropharyngeal, penile, vaginal, and vulvar cancer

Other viruses that are most likely to cause cancer in people with HIV are Hepatitis B virus (HBV) and hepatitis C virus (HCV), which both cause liver cancer. A diagnosis of any of these aforementioned cancers in someone infected with HIV confirms a diagnosis of AIDS.

Infection with HIV weakens the immune system and reduces the body's ability to fight viral infections that may lead to cancer. Also, because people infected with HIV have compromised immune systems, both immunosuppression and inflammation may have direct or indirect roles in the development of some cancers that are elevated in people infected with HIV.

The poorer cancer survival of HIV-infected people may result, at least in part, from the weakened immune system in such individuals. HIV infection is therefore associated with an increased risk of dying from cancer.

The introduction of highly active antiretroviral therapy (HAART), also called combination antiretroviral therapy (cART), starting in the mid-1990s, greatly reduced the incidence of certain cancers in HIV-infected patients, especially Kaposi's sarcoma and non-Hodgkin's lymphoma.

Although the risk of these AIDS-defining cancers among people infected with HIV is lower than in the past, it is still much higher than what it seen in the general population. This persistently high risk may reflect the fact that cART does not completely restore immune system functioning.

Quiz

Download these Resources:

[CD8 lymphocytes mitigate HIV-1 persistence](#)

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[Differential localization and limited cytotoxic potential of duodenal CD8+ T cells](#)

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