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THE IMMUNE RESPONSE TO HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT

Human Immunodeficiency Virus (HIV) is an infectious agent that disrupts the immune system by destroying CD4+ T lymphocytes, thereby triggering a decline in immune function and the development of Acquired Immunodeficiency Syndrome (AIDS). HIV employs a complex infection mechanism, including binding to host cell receptors, integration of genetic material, and modulation of the immune system to evade detection. The immune response to HIV involves the innate immune system, such as the activation of macrophages and dendritic cells through pattern recognition receptors, as well as the adaptive immune system through the activity of cytotoxic T cells and antibody production by B cells. However, HIV utilizes various strategies to evade immune responses, including rapid mutation and down-regulation of immune molecule expression. Antiretroviral therapy (ART) is the primary strategy for inhibiting HIV replication and maintaining immune system function, and it has been proven effective in reducing the morbidity and mortality associated with HIV infection, although a curative therapy has yet to be discovered.

Keywords: ART, CD4 T lymphocytes, HIV, immune response, immunodeficiency

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INTRODUCTION

Human Immunodeficiency Virus (HIV) is one of the leading causes of immunodeficiency in humans, a condition in which the immune system loses its ability to effectively combat infections and diseases. HIV infection results in the progressive destruction of CD4+ T lymphocytes, which play a central role in coordinating immune responses. Consequently, this infection may progress to Acquired Immunodeficiency Syndrome (AIDS), a condition that significantly increases the risk of opportunistic infections and mortality. According to the latest data from UNAIDS, in 2022,

approximately 39 million people were living with HIV worldwide, with around 630,000 deaths attributed to AIDS. These figures underscore the critical need for a comprehensive understanding of the immune response mechanisms to HIV infection. This article aims to examine the infection mechanism of HIV, the involvement of both innate and adaptive immune responses, and the current therapeutic approaches employed in the management of HIV infection.

METHODS : LITERATURE REVIEW

This literature review was conducted systematically through several stages, namely identification, screening, and inclusion. The identification process involved searching for scientific literature using major databases such as PubMed and Google Scholar, employing keywords such as “HIV”, “immune response”, “innate immunity”, “adaptive immunity”, and “antiretroviral therapy”. Selected articles met the inclusion criteria, which consisted of: publication within the period of 2015–2025, written in either English or Indonesian, and possessing at minimum a complete abstract structure.

The screening phase involved the removal of duplicate articles and those deemed irrelevant to the topic. Articles were further analyzed based on their relevance to the discussion and the credibility of their sources (e.g., peer-reviewed journals). Additionally, backward citation tracking was conducted by reviewing the reference lists of relevant articles to supplement information not obtained in the initial search.

The use of general search engines such as Google was limited to locating supporting documents or official publications from reputable health institutions and was not considered a primary source. This selection process was implemented to ensure that all included references in this review possessed sufficient scientific validity.

Definition

Human Immunodeficiency Virus (HIV) is an RNA virus classified within the family Retroviridae and the subfamily Lentivirinae. It is one of the etiological agents of Acquired Immunodeficiency Syndrome (AIDS), a condition characterized by the failure of the immune system to function properly (Pagaya & Que, 2017). HIV primarily infects immune cells, particularly CD4+ T lymphocytes, leading to their dysfunction and the progressive impairment of immune competence.

Infection Mechanism

The life cycle of HIV begins with the infection of host cells, followed by the production of a DNA copy from its RNA genome, which is subsequently integrated into the host cell’s genome. Initially, HIV initiates infection through its surface glycoprotein, gp120, which is located on the viral envelope. This glycoprotein binds to the CD4 receptor and the co-receptors CXCR4 and CCR5 (Shaw & Hunter, 2012). The primary target cells susceptible to HIV infection include dendritic cells, macrophages, and CD4+ T lymphocytes.

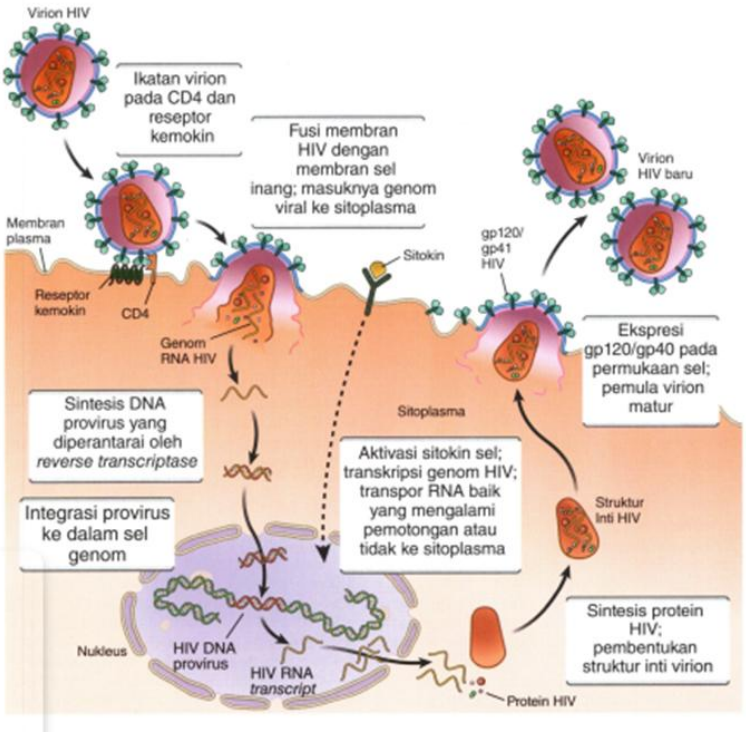

Figure 1. Infection Mechanism

The Human Immunodeficiency Virus (HIV) binds to the host cell receptor, CD4, followed by fusion with the host cell cytoplasm (Hazra A and Stoszek SK, 2011). Once inside the cytoplasm, the virus sheds its envelope and releases viral RNA into the host cell nucleus. The viral RNA is then reverse transcribed into proviral DNA mediated by the reverse transcriptase enzyme carried by HIV. Subsequently, the proviral DNA integrates into the host cell DNA with the assistance of the integrase enzyme. Following successful integration, HIV replicates by hijacking the transcriptional machinery of the infected cell. The virus forms a core structure that migrates to the cell membrane, assembles the viral envelope, and is released as an infectious viral particle capable of infecting other cells within the body. This replication process continues persistently until HIV dominates the host organism. If this infection persists over an extended period, HIV induces cell death, especially of lymphocytes, which ultimately leads to Acquired Immunodeficiency Syndrome (AIDS).

Immune System Response to HIV Infection

The immune response against HIV infection begins with the recognition of pathogen-associated molecular patterns (PAMPs) of the virus by pattern recognition receptors (PRRs) on host cells. The following are the PAMPs and corresponding sensors/PRRs involved in the innate sensing of HIV infection (Yin X, et al., 2020).

Table 1. PAMPs and PRRs involved in the innate sensing of HIV infection

Infected Process	Host Cell Type	PAMP	PRR	Effector Response
Entry, Uncoating	Macrophages	Single-stranded RNA (ssRNA)	RIG-I / MDA5	Inflammatory cytokines and Type I IFN
	Plasmacytoid Dendritic Cells	Single-stranded RNA (ssRNA)	TLR7 / TLR8	Inflammatory cytokines and Type I IFN
Reverse Transcription	Dendritic Cells, Macrophages, CD4+ T cells	Double-stranded DNA (dsDNA)	cGAS	Inflammatory cytokines and IFN
	Quiescent CD4+ T cells	Double-stranded DNA (dsDNA)	IFI16	Pyroptosis activation, Caspase-1
	Macrophages, Activated CD4+ T cells	Double-stranded DNA (dsDNA)	IFI16	Interferon (IFN)

Based on the table, host proteins identified as PRRs for HIV PAMPs during the uncoating stage include Toll-Like Receptors (TLRs), RIG-I-like receptors, and Melanoma Differentiation-Associated Protein 5 (MDA5), which recognize the presence of infection through the viral single-stranded RNA (ssRNA) (Yin X, et al., 2020). Activation of the TLR7 sensor subsequently stimulates the production of pro-inflammatory cytokines and chemokines. Meanwhile, RIG-I and MDA5 are localized in the cytoplasm. These receptors activate the production of type I and type III interferons (IFNs), as well as pro-inflammatory cytokines and chemokines that activate innate immune cells including macrophages, natural killer (NK) cells, and dendritic cells to control viral spread, and also activate and modulate adaptive immune responses (Altfeld & Gale, 2015).

In addition, intracellular PRRs such as Interferon Inducible Protein 16 (IFI16) and Cyclic GMP-AMP Synthase (cGAS) recognize viral reverse transcription products early in the viral replication cycle. The effector response involves the activation of IFN production, caspase-1, and IL-1β cytokines, which trigger pyroptosis (Yin X, et al., 2020). Pyroptosis is a form of programmed cell death caused by pathogen infection. This process further activates the cascade of innate immune signaling pathways leading to the induction of host antiviral responses.

To evade immune surveillance and response, HIV has developed certain strategies. HIV-1 can manipulate antiviral immune responses by shielding its encoded PAMPs, disrupting PAMP recognition signaling pathways, deactivating innate immune regulators, and modulating the transcription of innate immune effector genes (Altfeld & Gale, 2015).

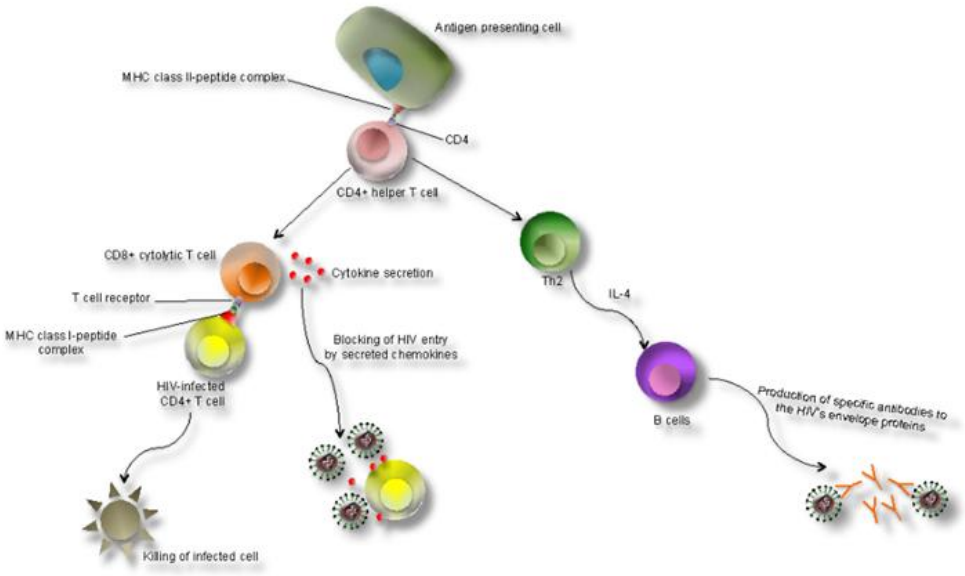

Figure 2. Adaptive Immune Response to HIV Infection

When the virus successfully evades the innate immune defenses, the adaptive immune response is activated. After transmission and replication, HIV and the debris resulting from pyroptosis are captured by dendritic cells (DCs). DCs act as antigen-presenting cells (APCs) that transport the antigen to lymphoid organs and present it to CD4+ T lymphocytes. This process is mediated by the expression of MHC class I and class II molecules on the surface of DCs. Upon transporting HIV to the lymph nodes, DCs also stimulate naïve T lymphocytes. These naïve T cells differentiate into cytotoxic T cells (CD8+) and helper T cells (CD4+). Cytotoxic T cells migrate into the bloodstream and attempt to eliminate all infected cells. Meanwhile, helper T cells activate B cells to differentiate into antibody-producing plasma cells and memory cells.

Immunodeficiency

At the early stage of HIV infection, the body is still able to compensate for the damage to immune system components. However, the rapid replication of the virus and destruction of CD4+ cells outpace the production of healthy immune cells, resulting in the failure of both cellular and humoral immune responses (Pagaya and Que, 2017). Several factors contribute to this condition, including:

- The high mutation rate of HIV allows continuous alteration of its virulence features, enabling it to evade detection by T cells or antibodies.

- HIV-infected cells down-regulate the expression of MHC class I molecules (HLA-A and HLA-B), helping the virus to avoid CD8+ T cell responses.
- HIV infection can increase the expression of Th2-specific cells, which produce cytokines that inhibit cellular immunity.

Due to these factors, the body gradually loses its ability to fight HIV, leading to immunodeficiency.

Antiretroviral Therapy

When HIV successfully dominates the body and disables its defense system, the condition progresses to Acquired Immunodeficiency Syndrome (AIDS). AIDS makes the body highly susceptible to various infections due to a weakened immune system, compromising its defense mechanisms. Complete recovery from this condition is extremely difficult. However, antiretroviral therapy (ART) is currently available to help reduce the effects of HIV infection. ART is the standard treatment for HIV patients today. It consists of a combination of drugs that work through various mechanisms to inhibit HIV replication and preserve the immune system (Günthard et al., 2016).

The antiretroviral drugs used in ART inhibit enzymes and proteins essential for HIV replication and entry into host cells. These drugs include reverse transcriptase inhibitors (RT inhibitors), protease inhibitors (PI), integrase inhibitors (INI), CCR5 binding inhibitors, and attachment inhibitors. HIV treatment typically involves a combination of three different classes of antiretroviral drugs to slow viral progression and minimize the risk of drug resistance (Günthard et al., 2016).

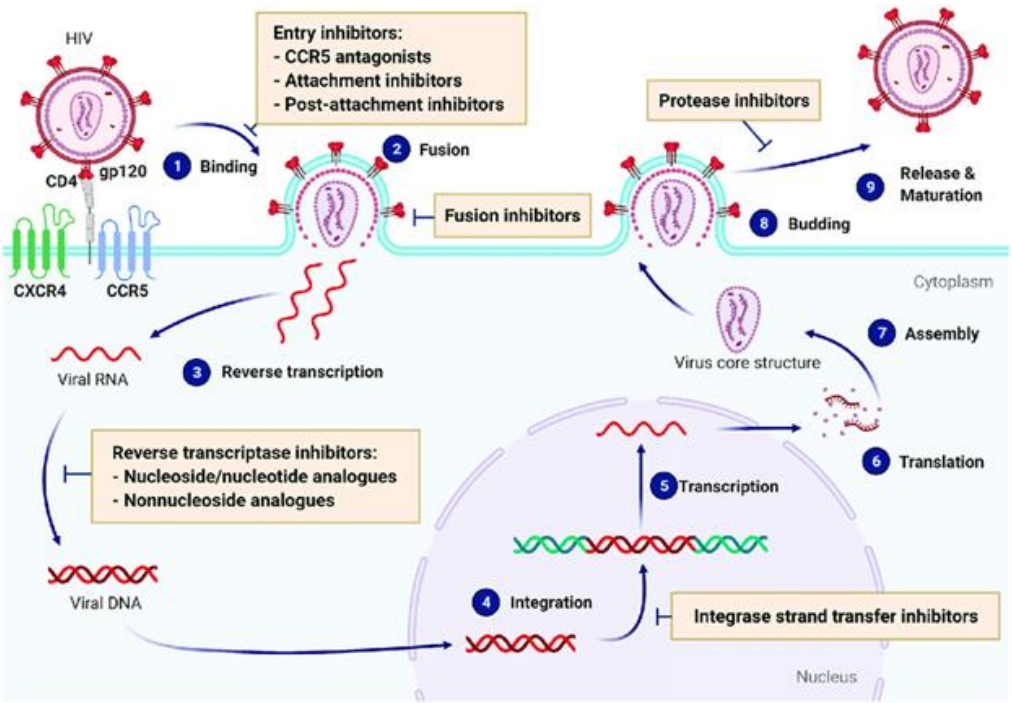

Figure 3. Mechanism of Inhibitors in Antiretroviral Therapy

In addition to ART, HIV patients may also undergo other treatment therapies such as prophylaxis for opportunistic infections and immunomodulatory therapy (Günthard et al., 2016). Prophylactic therapy involves administering drugs to prevent opportunistic infections in patients with weakened immune systems. Meanwhile, immunomodulatory therapy aims to enhance immune responses and reduce inflammation caused by HIV infection.

Proper HIV care can maintain patient health and slow disease progression. However, HIV treatment must always be supervised by qualified physicians and pharmacists. Patients should also routinely undergo blood tests to ensure viral load and CD4 cell counts remain controlled and to monitor for any serious side effects from medication use.

Recent Advances in Immune-Based Therapies

Advances in immune-based therapies for HIV show promising potential, especially in efforts to reduce long-term dependence on antiretroviral therapy (ART) and move toward curative strategies. A notable approach is the development of mRNA-based HIV vaccines, which utilize similar technology to COVID-19 vaccines. These vaccines are designed to induce broadly neutralizing antibody (bNAb) responses by targeting conserved epitopes on the HIV gp120 and gp41 glycoproteins. Preclinical studies have shown that mRNA vaccines can stimulate the formation of germinal center B cells and follicular helper T cells (Tfh), which are critical for generating strong and durable antibody responses (Pardi et al., 2018).

Besides vaccines, passive administration of bNAbs is also under evaluation both as standalone therapy and as prophylaxis. Several antibodies, such as VRC01 and 3BNC117, have demonstrated significant viral load reduction in HIV-infected individuals and protective effects in animal models. However, a major challenge is the rapid mutation rate of HIV, leading to resistance against single antibodies; thus, combination approaches involving multiple bNAbs are considered more promising (Sok & Burton, 2018).

Chimeric Antigen Receptor T cell (CAR-T) therapy for HIV is an emerging and promising field. In this approach, patient T cells are genetically engineered to express receptors specific to HIV antigens, allowing them to recognize and kill infected cells. Early studies suggest that CAR-T cells persist longer in the body and can target host cells harboring latent virus reservoirs, an important advantage over ART which is ineffective against latent reservoirs (Zhen et al., 2015). Although still in early stages, combining CAR-T therapy with bNAbs has the potential to become the backbone of future immuno-curative therapies.

CONCLUSION

HIV infection disrupts the immune system through destruction of CD4+ cells, leading to failure of both innate and adaptive immune responses. Complex viral evasion mechanisms, such as rapid mutation and downregulation of immune molecules, exacerbate progressive immunodeficiency. Currently, antiretroviral therapy (ART) is the most effective strategy to control HIV replication and preserve immune function, but it does not provide a complete cure.

This review underscores the importance of a deep understanding of HIV-immune system interactions as the foundation for developing new therapeutic strategies. The development of immune-based therapies, such as HIV vaccines and immune cell therapies, represents a promising direction to improve infection control in the future. Further research on HIV immune evasion mechanisms is essential to open opportunities for more specific, targeted, and sustainable therapeutic innovations.

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