Deciphering HIV Pathogenesis: A Deep Dive into Viral Entry, Immune Evasion, and Host Responses in HIV infection and novel aspects of AI/ML in HIV research

Corresponding Author: Mandana Daraei Fathabad

Abstract

This comprehensive literature review provides an overview on the variety mechanisms of HIV-1 pathogenesis, focusing on viral entry, immune evasion strategies, and the host immune responses. This review presents a summary of HIV initial invasion processes, detailing how HIV utilizes CD4+ T cells, macrophages, and dendritic cells, and the critical roles of co-receptors CCR5 and CXCR4 in mediating viral entry. The review dissects the sophisticated mechanisms of virus to evade immune system, including the formation of viral reservoirs, mutations, and induction of immune exhaustion, highlighting the persistent challenge of HIV latency and implications for cure strategies.

This review explores the dynamic of immune responses towards HIV infection, including the activation and depletion of CD4+ T cells, the compensatory mechanisms of CD8+ T cell responses, and the paradoxical effects of chronic immune activation on disease progression. Diving in to recent findings, to identify the gaps in our understanding of the long-term effects of HIV on the immune system, underscoring the need for innovative therapeutic interventions to disrupt viral reservoirs and counteract immune dysfunction.

A novel aspect of this review is the exploration of artificial intelligence (AI) and machine learning (ML) as transformative tools in HIV research. How AI/ML techniques are being applied to predict viral evolution, identify new therapeutic targets, and optimize treatment regimens. The potential of AI/ML to personalize patient treatment and interpret complex data from clinical trials is highlighted, offering promising avenues for enhancing the efficacy of antiretroviral therapy and advancing towards the ultimate goal of an HIV cure.

This review aims to provide a thorough review of current knowledge on HIV pathogenesis, immune response challenges, and the groundbreaking potential of AI and ML in paving new directions for research and therapy in the fight against HIV/AIDS.

Keywords: AI, ML, CART-cells, HIV Replication, HIV Evasion, bNAbs, HIV Letancy, TLRs and Cytokines in HIV-1

Introduction

Historical investigations on origin of the Human Immunodeficiency Virus HIV-1 pandemic have traced back to Kinshasa in the Democratic Republic of Congo in the 1920s, marking where the virus likely started to spread and disseminate among human populations(1). These foundational insights contextualize the viral epidemic within a broader temporal framework and enhance our comprehension of its initial human spreading. Since early 1980s when the Human Immunodeficiency Virus was identified as the cause of AIDS, HIV has remained as a global health challenge. Despite advancements in our understanding of HIV/AIDS, still the complete treatment and vaccine development continue to necessitate investing in HIV research.

Early studies to understand HIV in 80s was pivotal to identify HIV virus as the AIDS causation. Barré-Sinoussi in 1983 isolated HIV-1 for the first time which was a significant achievement in basic and clinical research science. Dalgleish in 1984 identified CD4+ T cells as the primary receptor for HIV and Koenig in 1986 described the crucial ability of HIV to infect cells like macrophages, suggesting its integration in to host genome and subsequent latency (2–4).
followed by years of research until Feng in 1996 to discover the CCR5 and CXCR4 as coreceptors for HIV entry and Wyatt in 1998 provided insights into the structure of the HIV envelope glycoprotein and its role in mediating viral entry into host cells (5).
The goal of this review is to cover HIV integration into the host genome, viral reservoir establishment and maintenance, and the impact of HIV latency on treatment and cure strategies. To discuss the long-term effects of HIV on the immune system, including evasion, mutation, immune exhaustion, and how chronic infection affects the immune system, particularly CD4+ T cells depletion CD8+ T cells and the role of immune activation and inflammation in disease progression. In this review my aim is to synthesize key findings from various studies, highlighting significant discoveries and consensus in HIV research and the potential of AI and ML in studying HIV and cure development.

Molecular Interplay in HIV-1 Invasion and Replication

The interaction of HIV-1 with monocytes, macrophages and CD4+ T cells, while known to be different, is not fully understood yet.
The crucial temporal cascade which is followed within HIV-1 entry, with critical replication steps occur within the initial 24 hours post-infection and detectable viral progeny production by approximately 40 hours ((1). Recent advancements in virology research have elucidated the role of dendritic cells and the Siglec-1 protein during initial HIV-1 infection stages. Dendritic cells, at the interface with the external environment, are suggested to be the primary cellular entity which HIV-1 encounters during sexual transmission. Siglec-1 has been identified as a pivotal receptor in mediating to capture the virus and subsequent transmission to T-cells(6). The dynamics of Siglec-1 nanoclusters, governed by the actin cytoskeleton and modulated by RhoA activity, offer new insights into the early cellular mechanisms of HIV-1 infection and represent potential targets for therapeutic interventions(6–9).

Macrophages are central to the immune response, capturing foreign entities and presenting antigens to T cells, and are characterized by their longevity and communication with CD4+ T cells and also chemokine receptors, which are particularly susceptible to HIV-1 infection. Macrophage express pattern-recognition receptors (PRRs) for pathogen phagocytosis. Post-phagocytosis proteins are presented on MHC class II to activate CD4+ T lymphocytes, while

exogenous proteins, such as viral proteins, are presented on MHC class I to CD8+ T lymphocytes. The secretion of interferons (IFNs) reduce spreading of HIV-1 infection with following the recognition of pathogen-associated molecular patterns (PAMPs) by PRRs. IFNs induce the expression of interferon-stimulated genes (ISGs) like sterile alpha motif (SAM), histidine/aspartate (HD) domain-containing protein 1 (SAMHD1), APOBEC3(apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G), MX2, tetherin, SERINC, and Siglec-1, which are known to restrict HIV-1 replication (10).

Monocytes/macrophages and CD4+ T cells are the central players to pathogen clearance, and paradoxically exploited by HIV-1 for replication. When the HIV-1 envelope protein (Env) binds to the CD4-receptors on the surface of these cells, prompting a cascade of structural changes that expose the V3 loop to Env-gp120. This event facilitates the binding of the chemokine receptors CXCR4(X4) or CCR5(R5-), leading to the fusion of viral Env-gp41 with the cell membrane and the subsequent entry of the viral capsid into the host cell (10).

CCR5 (R5-) and dual-tropic strains of HIV-1 predominantly infect macrophages and memory-type CD4+ T lymphocytes via the CCR5 co-receptor, while X4-tropic viruses, which later emerge, primarily target CD4+ T lymphocytes through the CXCR4 co-receptor. The switch in co-receptor usage from CCR5 to CXCR4 is associated with disease progression from acute to chronic stages in approximately half of AIDS patients, although the R5-tropic virus remains dominant in the rest (10)(11)

In a longitudinal cohort study on HIV-1B infected individuals, researchers found that 36.6% of patients experienced a switch from R5- to X4-tropic virus with a median of 1410 days post-seroconversion. This tropism shift, observed in a cohort of 82 ART-naive male seroconverters, correlated with accelerated CD4+ T-lymphocyte depletion and increased AIDS risk. Cross-sectional and longitudinal analyses revealed a negative association between X4-tropism and CD4+ T cells count, and a positive correlation with cellular immune activation markers like %HLA-DR+ CD4+ T-cells. The study highlights the predictive value of immune activation markers for a switch to X4-tropism, underscoring their roles in HIV disease progression(11).

The Crucial Role of TLRs and Cytokines in HIV-1 Disease Modulation

Toll-Like Receptors (TLRs) represent a family of pattern recognition receptors, which are crucial for detecting viral components and initiating of immune response (Martinsen et al., 2020). Among the TLR family, TLR7 and TLR8 are particularly crucial for recognizing HIV-1 RNA, triggering downstream signaling cascades that lead to production of type I interferons and pro-inflammatory cytokines(12). These cytokines are essential for inhibiting viral replication and priming the immune cells for an effective anti-HIV response. TLR agonists have been identified to enhance HIV-specific T cell responses, particularly those mediated by plasmacytoid dendritic cells. This interaction influences the disease progression in diverse HIV-1 phenotypes, underscoring the critical role of TLRs in modulating both innate and adaptive immunity(13) (12) (14).

TLR2 and TLR4 on the surface of mucosal epithelial cells can recognize the HIV envelope glycoprotein gp120(15).

Roles of Interferons and Cytokines in HIV-1 infection

The interplay between cytokines and HIV-1 is sophisticated; Type I interferons, especially IFNα subtypes and IFNβ, applying a dual role in the infection process. While they are key in controlling viral replication, their systemic immune activation is a paradoxical challenge(16). IFNβ, IFNε, IFNκ, and IFNω, and their overall effect on HIV progression is a subject of ongoing debate. The complex nature of cytokine during HIV-1 infection is characterized by decreasing in T-helper type 1 (Th1) cytokines, such as interleukin (IL)-2, and antiviral interferon (IFN) __critical for antiviral defense__ in contrast with an increasig in T-helper type 2 (Th2) and pro-inflammatory cytokines, that contribute to the chronic inflammation which are typical in HIV-1 infection(17).
The production of Th2 cytokines (IL-4, IL-10), proinflammatory cytokines (IL-1, IL-6, IL-8), and tumor necrosis factor (TNF)-α are increased, could contribute to the chronic inflammation observed in HIV-infected individuals(18) (19).

The magnitude of the cytokine response in the early phase of HIV-1 infection is significant and exceeds the response which can be seen in acute hepatitis B and C; suggesting that a systemic cytokine response is a distinctive feature of acute HIV-1 infection. This cytokine storm can contribute to both the control of the virus and the pathogenesis of the disease, without causing harm to the host(19).

Cytotoxic T Lymphocyte CTLs have been recognized for their pivotal role in mediating long-term control of HIV infection. Notably, HIV immune response among who manage to suppress viral replication without ART, demonstrate the functional role of CTLs in durable HIV control. The HLA class I-mediated antigen presenting and TCR cross-recognizing enhance CTL responses, which update vaccine design strategies aimed at eliciting robust CTL-mediated HIV control(20,21).

Innate Immune Detection Versus HIV-1 Evasion Strategies

Innate immune sensors play a crucial role in the defense mechanisms of the body to recognize HIV. Early responses to HIV are characterized by the emergence of acute-phase proteins, an initial cytokine storm, and the activation of natural killer (NK) cells. However, this response can be a double-edged sword, potentially contributing to the depletion of CD4+ T cells and fueling chronic immune activation, a hallmark of HIV-1 disease progression(19).
Proteins such as interferon inducible protein 16 (IFI16) have been identified as a key player to recognize DNA forms of the lentiviral replication cycle, subsequently controlling HIV-1 replication. The IFI16 DNA sensor indicates its significant role in early detection and response, while it is crucial for the apoptosis of lymphoid CD4+ T cells infected with HIV. This sensor also plays a role in the transcriptional regulation of type I interferons and other interferon-stimulated genes, which are vital in the immune response to DNA and RNA viruses. The cGAS-cGAMP signaling pathway is crucial for activating the type I interferon pathway, an integral part of the innate immune response to viral infections(15).
HIV-1 employs multiple evasion strategies to avoid innate immune recognition such as undergoes mutation and employs various mechanisms to escape the host immune system. For instance, HIV-1 accessory proteins are crucial for the survival of virus by modulating and evading host immune responses(22).

This variety of tactics to suppress or evade the host immune defenses, largely mediated by its accessory proteins, such as Vif, Vpr, Vpu, and Nef(23). These proteins perform multiple functions that disrupt the host immune defense mechanisms. For example, Vif can target APOBEC3G for degradation which is host restriction factor that potently inhibits HIV-1 infection. Nef can down-regulate the expression of certain receptors on the surface of infected cells to prevent recognition by immune cells, and Vpu can neutralize tetherin (bone marrow stromal antigen2), CD317, or HM1.2, which is the newest host restriction factor identified by Neil and Bieniasz. Tetherin inhibits HIV infection by preventing the virus from releasing mature virions to the cell surface(23).

Additionally, the virus has developed tactics to suppress these host cellular responses actively. The functional diversity of these proteins indicates the ability of virus to adapt and counter the host immune strategies. For instance, HIV-1 can evade host restriction factors, which are components of the innate immune system. These include APOBEC3G, a molecule that can mutate and thereby inactivate viral DNA; TRIM5α (tripartite motif 5-α) which recognizes viral capsids and targets them for destruction; tetherin, which prevents the release of the virus from infected cells; and SAMHD1, which degrades the viral RNA(24).

Impacts of HIV Infection on B Cell Functionality and Antibody Responses

HIV infection effects B cell and CD4+ T cell populations, which leads to functional impairments. HIV targets CD4+ T cells for infection and destruction, which result progressive depletion and dysfunction. This depletion disrupts the normal helper functions of CD4+ T cells, which are crucial for the activation and regulation of B cell responses. Subsequently, B cells dysfunction cause alteration of subpopulations in the blood, including over-represented immature B cells and exhausted B cells. These changes lead to decreased in B cells, reduced proliferative and effector properties, and impaired antibody responses against both T-cell-dependent and T-cell-independent antigens. The immune evasion strategies of HIV, which directly and indirectly affect B cell function, pose a significant challenge for the treatment of HIV and the development of effective vaccines(25).

The Role of bNAbs and T Cell Dynamics in HIV Defense and Persistence

The broadly neutralizing antibodies bNAbs target five epitopes on the HIV envelope (Env); the CD4-binding site, V3- and V1/V2-glycans on gp120, the gp120-gp41 interface, and the gp41 membrane-proximal external region (MPER) (26). Notably, the capability of bNAbs in reducing and interfering with the establishment of HIV reservoirs was demonstrated in humanized mouse models(27)

The presence of plasma bNAbs in HIV-infected infants was evaluated and revealed their effectiveness against diverse autologous circulating viruses in cases of multivariant HIV-1 infection, indicating a potential role in early intervention strategies(28).

Despite these advancements, still challenges persist, and HIV is able to evade antibody immune response by altering variable epitopes, leading to neutralization escape. Moreover,

modifications in the HIV envelope protein conformation and variations in glycan abundance can obscure conserved epitopes, thus facilitating HIV immune escape(29).

The adaptive immune response is further compromised by disturbances in CD8+ T cell function, with metabolic reprogramming being a hallmark of HIV-1 infection. A correlation between elevated plasma glutamate levels in people living with HIV on ART and the amount of the viral reservoir have been identified. This metabolic imbalance, particularly through the mTORC1 pathway, suggests a novel target for therapeutic intervention to rejuvenate CD8+ T cell function and reduce viral persistence(30).
The alteration in glutamate level and metabolism have been associated with sex-based differences in HIV-1 reservoirs, which shows that female patients may have fewer CD4+ T cells harboring replication-competent HIV. The interaction between glutamate metabolism and HIV-1 persistence requires further study, particularly to understand its role in these observed sex-based differences. The inhibitory effects of glutamate on CD8+ T cell function, although not fully understood, but underscore the complexity of HIV impact on the immune system(30,31).

CD8+ T Cell Effector Functions and Regulatory Challenges in HIV Infection

HIV-specific CD8+ T cells target HIV-infected cells through HLA class I molecule recognition, with employing cytotoxic mechanisms like perforin and granzyme secretion, and by engaging in Fas/Fas-ligand and TRAIL/TRAIL-R pathways(32).

The release of cytokines such as IFN-γ, TNF-α, CCL5, and macrophage inflammatory proteins further empower the antiviral effects. However, the effectiveness of CD8+ T cells, particularly cytotoxic T lymphocytes (CTLs), in targeting HIV reservoirs and their limitations in controlling proviruses are the remaining areas of investigation. The CD8+ T cells antiviral efficacy extends beyond cytotoxicity. The non-HIV-specific TCR-activated non-cytolytic $CD8^+$ T cells suppress HIV transcription through a virus- and MHC-independent immunoregulatory mechanism which also regulates $CD4^+$ T cell proliferation and activation. $CD8^+$ T cell-mediated effect promotes the survival of infected $CD4^+$ T cells harboring integrated, inducible virus. This activity, coupled with the release of CD8+ T cell antiviral factor (CAF) (33).
However, the full potential of CD8+ T cells in eradicating HIV reservoirs is not yet fully understood. Challenges such as HIV immune escape, CD8+ T cell exhaustion, and HIV latency hinder the efficacy of CD8+ T cells(34). Understanding these dynamics is vital for developing effective HIV/AIDS treatment and prevention strategies.

The chronic HIV infection leads to change in the homeostatic regulation of CD4+ and CD8+ T cell pools. Proliferation of CD4+ T cells is tightly controlled by the number of CD4+ T cells, whereas CD8+ T cell proliferation is more influenced by the level of HIV RNA, which reflect the impact of virus on these cells. HIV-induced lymphopenia, naive CD4+ T cells are mainly recruited into the proliferating pool in response to CD4+ T cell depletion, which is vital for host surveillance. On the other hand, naive CD8+ T cell proliferation is primarily driven by level of HIV RNA. This imbalance affects the communication and coordination between CD4+ and CD8+ T cells, which is critical for effectiveness of immune response(35).

HIV Reverse Transcription

HIV reverse transcription is a crucial step which the virus single-stranded RNA genome is converted into double-stranded DNA. This process is catalyzed by the enzyme reverse transcriptase (RT), which starts the conversion using host tRNA Lys3 as a primer. The viral capsid protein (CA) is vital in this process, particularly for stabilizing the transformation. The small molecule IP6 has been found to enhance reverse transcription by stabilizing the viral capsid. Host factors, such as translation elongation factors eEF1A and eEF1G, also play a significant role in small molecule IP6 has been found to enhance reverse transcription by stabilizing the viral capsid. Host factors, such as translation elongation factors eEF1A and eEF1G by binding to RT (Figure 1). The addition of IP6 is crucial for the efficiency and reduces RT dissociation from HIV-1 cores, highlighting the importance of both viral components and host factors in HIV replication(36–38)

HIV Integration and Latency

The capsid protein of HIV-1 orchestrates the nuclear import of viral DNA by interacting with host cell proteins such as nucleoporins Nup358, Nup153, and CPSF6. These interactions are critical for the virus to access to the nuclear compartment and consequentially influence the selection of the integration site within the host chromosomes(39).
Proteins like RANBP2 and Transportin 3 (TNPO3) alongside CPSF6 are critical for import of viral DNA into the nucleus, preceding the crucial step of viral integration (Figure 1). CPSF6 is particularly involved in determining the efficiency of nuclear import as well as the subsequent invasion of post-nuclear reverse transcription complexes (RTCs)(40).
HIV-1 Integrase, which is essential for viral integration, catalyzes two key enzymatic reactions: a) the processing of the viral DNA 3′-end and transferring the strand, b) then embedding the viral genome into cellular chromatin. The integrase tetramers association with viral DNA results the formation of the functional integrase-viral DNA complex, known as the intasome(41).
LEDGF/p75 is a host cell protein which interacts with the viral integrase and is pivotal in directing the integration of viral DNA into gene, in particular within transcriptionally active regions of the host genome (Figure 1). This interaction facilitates the favorable integration of HIV-1 into regions beneficial for viral transcription(42). The HIV-1 integrase is effective in identifying changes in the shape and nucleotide sequences of targeted DNA. It precisely cuts phosphodiester bonds in the DNA at the points where integration occurs(42).
The activity of the integrated HIV virus (provirus) within DNA of host cells largely depends on the surrounding chromatin structure and the nuclear environment of the cells. When the virus integrates into chromatin areas that are open and active, it tends to start immediate transcription. However, when it integrates into areas of the DNA that are not actively transcribed, it often leads to the creation of latent viral reservoirs. These reservoirs, where the virus remains inactive but present, pose a significant challenge to completely eradicating HIV-1(42).
HIV evade strategies from the host immune response display significant obstacles to developing effective therapeutics and vaccines. The virus has remarkable genetic diversity and employs sophisticated strategies to suppress immune pathways. Chronic HIV infection significantly impacts the immune system, notably affecting CD4+ T cells, which are vital for coordinating immune responses. These cells experience both a decline in numbers and a

reduction in functional quality. There is a clear but yet to be definitively proven link between continuous immune activation and the depletion of CD4+ T cells. The chronic inflammation persists even in the presence of ART, underscoring the necessity for interventions that target immune modulation as part of comprehensive HIV treatment strategies(43,44).

The dynamic between the immune system mechanisms against HIV and the virus evasion strategies is complex. Policicchio found that CD8+ T cells can initially control SIV (a virus similar to HIV in primitive), by killing infected cells and stopping the virus from multiplying, but this only works in early stage of infection(45). The researchers observed that CD8+ T cell responses can select viral adaptations prior to full antibody seroconversion and found that these adaptations tend to be retained over time in a non-selective immune environment, reflecting the increasing proportion of pre-adapted HIV strains within the Western Australian population over an approximate 30-year period (46).

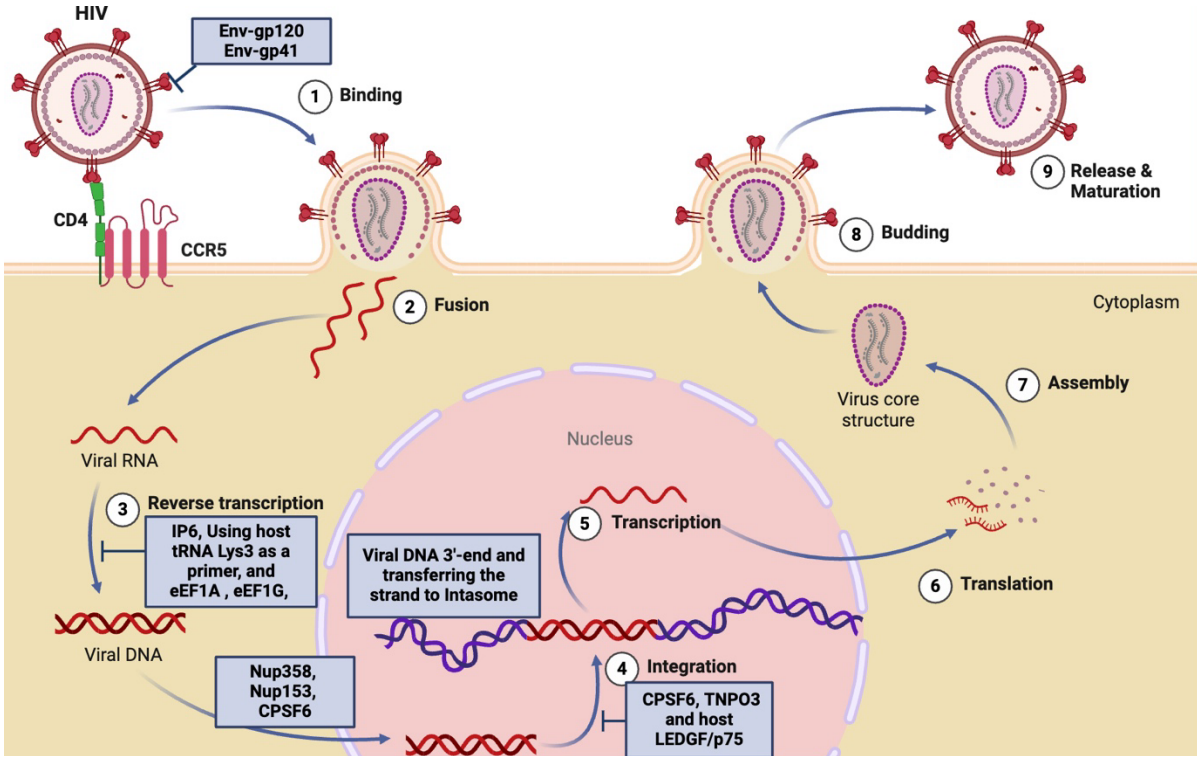

Figure 1: Overview of HIV Entry, Reverse Transcription, and Integration within a Host Cell. This figure illustrates a simplified sequential stages of HIV infection in a host cell, highlighting key molecular interactions. Stage 1 depicts the binding of HIV to a CD4+ T cell, facilitated by the viral envelope proteins Env-gp120 and Env-gp41 interacting with the CD4 receptor and CCR5 co-receptor. Stage 2 shows the fusion of the viral membrane with the host cell membrane, allowing the virus to enter the cell. The process of reverse transcription is detailed in stage 3, where the viral RNA is converted into DNA with the help of host cell factors like IP6 and tRNA Lys3; small molecule IP6 enhance reverse transcription by stabilizing the viral capsid. Host factors, such as translation elongation factors eEF1A and eEF1G bind to RT to facilitate reverse transcription. This viral DNA is then transported into the nucleus with the help of host cell proteins such as nucleoporins Nup358, Nup153, and CPSF6 , as shown in stage 4, where it integrates into the host genome with the assistance of viral integrase and host proteins such as CPSF6 and LEDGF/p75. Transcription of the integrated viral DNA into mRNA occurs in stage 5, followed by translation of viral proteins in the cytoplasm in stage 6. Stage 7 and 8 illustrate the assembly of new viral particles at the cell membrane and their subsequent budding out of the cell. Finally, stage 9 shows the release and maturation of new infectious HIV particles ready to infect additional cells. This figure encapsulates the critical steps of HIV's life cycle within a cell, providing a simplified visual summary for the detailed mechanisms discussed in the literature review.

Immunotherapeutic Interventions

The trispecific antibodies was used for targeting the HIV envelope and T cell antigens CD3 and CD28. N6/αCD3-αCD28 targets the HIV envelope, T cell antigen CD3, and co-stimulatory molecule CD28. This antibody has shown promising result in activation and elimination of latently infected cells, both in vitro and in vivo settings. This innovative approach offers a potential target for therapeutic interventions to eradicate the latent HIV(47). In a clinical study, it was demonstrated the ability of nanoparticle vaccine to expand the production of rare B cells that are precursors to those capable of producing bnAbs necessary for protection against diverse HIV variants. In the same study, it was highlighted the effectiveness of vaccine in producing broad helper T cell responses that support B cell development and bnAb production (48).

Various immunotherapeutic interventions are being investigated to enhance the adaptive immune response to HIV. These include "shock and kill" strategies to re-activate latent HIV, innate immunity-based interventions such as using TLR7 agonists to re-awaken HIV-infected cells, and T cell-based interventions like CTL-mediated immunotherapy and CAR-T cells that target HIV reservoir cells for elimination(49). The potential of chimeric antigen receptor (CAR)-T cell therapy in HIV cure strategies has gained notable attention, particularly due to the robust and prolonged T cell response these cells can obtain. Researchers have indicated that HIV-specific CAR-modified CD4+ T cells can effectively suppress HIV replication in vitro and target virus-infected cells for elimination. A pivotal study by Maldini introduced dual CD4-based CAR-T cells with different designed domains, enhancing the effectiveness of HIV-specific CAR-T cell therapy. This advancement demonstrated significant suppression of HIV, reducing both viremia and tissue viral load in a BLT humanized mouse model (50,51).

Despite these promising developments, CAR-T cell therapy for HIV faces critical challenges. A key limitation is the requirement for target epitopes to be highly expressed on cell surfaces, while current CAR T cells mainly target the highly variable envelope glycoproteins of HIV. The development of safe and effective latency-reversing agents (LRAs) remains a crucial step before CAR-T cell therapies can be tested in people living with HIV (PLWH). Overcoming these obstacles is essential for the successful implementation of CAR-T cell therapy in HIV treatment(49).

Discussion

The complex interplay between the Human Immunodeficiency Virus (HIV) and the host immune system, as detailed in this review, emphasize the sophisticated nature of viral entry, replication, and evasion strategies. Despite significant scientific advancements since the discovery of HIV _the virus that causes AIDS and dependency to daily medication intake_ HIV continues to pose a challenge and burden worldwide and especially low-income countries. Due to HIV ability to adapt, evade, and persist within the host cells, researchers yet to reach the cure and effective vaccines for HIV. The persistence of HIV reservoirs, evasion from immune system mechanisms, and causing chronic inflammation highlight areas which our current understanding is incomplete and where the future research should be directed.

Further research is required, not only to understand the complex mechanisms of HIV latency and immune escape but also to develop more effective therapeutic interventions and vaccines.

This emphasizes the need for innovative approaches to disrupt viral reservoirs and overcome the obstacles of immune exhaustion and systemic inflammation that contribute to disease progression.

Artificial Intelligence (AI) stands at the forefront of this quest, offering amazing new tools and methodologies to accelerate research and development. AI and machine learning (ML) capability to analyze vast datasets and identify patterns that are imperceptible to researchers can lead to the discovery of novel biomarkers, potential drug targets, and therapeutic strategies. Machine learning algorithms can predict viral evolution and help in the designing of vaccines. Another potential in HIV research is in applying of AI/ML to personalize patient treatment and interpreting the data generated in trials. Researchers can use the beneficial power of ML also to stimulate the effects of potential drugs or treatment strategies and refining them. AI/ML can be used to optimize drug regimens for patients, potentially improving the efficacy of antiretroviral therapy (ART) while minimizing side effects.

Despite these promising avenues, the application of AI/ML in HIV research is not without challenges. ML requires high-quality, comprehensive datasets to train algorithms effectively, which can be difficult to obtain in the field of biology and also for HIV. Although many data banks have been developed in the past few years, but still using available open access data in biology field is a challenge. From ethical point of view, the data privacy and the potential for algorithmic bias, should also be addressed.

In conclusion, in this literature review, I provide a fundamental understanding of HIV pathogenesis which can be a springboard for future research. The integration of AI into HIV research represents a transformative approach that may redefine our strategies to approach research to understand virus influence on immune system and cell to cell interactions. This approach can hold promise not just for improving our understanding of HIV infection but also for advancing towards the ultimate goal of cure.

List of abbreviations

Abbreviation	**Definition**
AIDS	Acquired immunodeficiency syndrome
AL	Artificial inteligent
APOBEC3	Apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G
bnAb	Broadly neutralizing HIV-1 antibodies
CAR-T cells	chimeric antigen receptor (CAR)-T cell
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
cGAS-cGAMP signaling pathway	Cyclic guanosine monophosphate (GMP)–adenosine monophosphate (AMP) synthase (cGAS) signaling pathway
CPSF6	Cleavage and polyadenylation specificity factor subunit 6
CTL	Cytotoxic T Lymphocyte
CXCR4	G-protein-coupled chemokine receptor
eEF1A and eEF1G	Elongation factor
Env	Envelope

HIV	Human immunodeficiency virus
IFI16	Interferon inducible protein 16
IFNs	Interferons
IL	Interlukine
ISGs	Interferon-stimulated genes
Lys	Lysine
ML	Machine learning
PAMPs	Pathogen-associated molecular patterns
PLWH	People living with HIV
PRRs	pattern-recognition receptors
SAMHD1	Sterile alpha motif (SAM), histidine/aspartate (HD) domain-containing protein 1
TLR	Toll Like Receptor
TNPO3	Transportin 3
TRIM5α	Tripartite motif 5-α
tRNA	Transferase RNA
ART	Anti-viral therapy

Fund Declaration:
This literature review was conducted without any funding.

Author Declaration:
This literature review titled ' Deciphering HIV Pathogenesis: A Deep Dive into Viral Entry, Immune Evasion, and Host Responses in HIV infection and novel aspects of AI/ML in HIV research' is my original work, conducted independently without any institutional affiliation or external support. All sources have been duly cited.

References

1. Bejarano DA, Puertas MC, Börner K, Martinez-Picado J, Müller B, Kräusslich HG. Detailed Characterization of Early HIV-1 Replication Dynamics in Primary Human Macrophages. Viruses [Internet]. 2018 Nov 10 [cited 2023 Nov 23];10(11). Available from: /pmc/articles/PMC6266216/
2. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science (1979). 1983;220(4599):868–71.
3. Dalgleish AG, Beverley PCL, Clapham PR, Crawford DH, Greaves MF, Weiss RA. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984 312:5996 [Internet]. 1984 [cited 2024 Jan 6];312(5996):763–7. Available from: https://www.nature.com/articles/312763a0
4. Koenig S, Gendelman HE, Orenstein JM, Dal Canto MC, Pezeshkpour GH, Yungbluth M, et al. Detection of AIDS Virus in Macrophages in Brain Tissue from AIDS Patients with Encephalopathy. Science (1979) [Internet]. 1986 [cited 2024 Jan

9];233(4768):1089–93. Available from: https://www.science.org/doi/10.1126/science.3016903
5. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 Entry Cofactor: Functional cDNA Cloning of a Seven-Transmembrane, G Protein-Coupled Receptor. Science (1979) [Internet]. 1996 [cited 2024 Jan 6];272(5263):872–7. Available from: https://www.science.org/doi/10.1126/science.272.5263.872
6. Gutiérrez-Martínez E, Garrabé SB, Mateos N, Erkizia I, Nieto-Garai JA, Lorizate M, et al. Actin-regulated Siglec-1 nanoclustering influences HIV-1 capture and virus-containing compartment formation in dendritic cells. Elife [Internet]. 2023 Mar 1 [cited 2023 Nov 23];12. Available from: https://medicalxpress.com/news/2023-04-insights-early-stages-hiv-infection.html
7. Espinar-Buitrago M, Muñoz-Fernández MA. New Approaches to Dendritic Cell-Based Therapeutic Vaccines Against HIV-1 Infection. Front Immunol. 2022 Jan 4;12.
8. Wang SF, Hung YH, Tsao CH, Chiang CY, Teoh PG, Chiang ML, et al. Galectin-3 facilitates cell-to-cell HIV-1 transmission by altering the composition of membrane lipid rafts in CD4 T cells. Glycobiology [Internet]. 2022 Aug 18 [cited 2023 Dec 31];32(9):760–77. Available from: https://dx.doi.org/10.1093/glycob/cwac040
9. Bayliss R, Wheeldon J, Caucheteux SM, Niessen CM, Piguet V. Identification of Host Trafficking Genes Required for HIV-1 Virological Synapse Formation in Dendritic Cells. J Virol [Internet]. 2020 Apr 16 [cited 2023 Dec 31];94(9). Available from: https://journals.asm.org/doi/10.1128/jvi.01597-19
10. Sukegawa S, Takeuchi H. Toward the unveiling of HIV-1 dynamics: Involvement of monocytes/macrophages in HIV-1 infection. Frontiers in Virology. 2022 Jul 25;2:934892.
11. Connell BJ, Hermans LE, Wensing AMJ, Schellens I, Schipper PJ, van Ham PM, et al. Immune activation correlates with and predicts CXCR4 co-receptor tropism switch in HIV-1 infection. Scientific Reports 2020 10:1 [Internet]. 2020 Sep 28 [cited 2023 Nov 23];10(1):1–10. Available from: https://www.nature.com/articles/s41598-020-71699-z
12. Rozman M, Zidovec-Lepej S, Jambrosic K, Babić M, Drmić Hofman I. Role of TLRs in HIV-1 Infection and Potential of TLR Agonists in HIV-1 Vaccine Development and Treatment Strategies. Pathogens [Internet]. 2023 Jan 1 [cited 2023 Nov 23];12(1). Available from: /pmc/articles/PMC9866513/
13. Martinsen JT, Gunst JD, Højen JF, Tolstrup M, Søgaard OS. The Use of Toll-Like Receptor Agonists in HIV-1 Cure Strategies. Front Immunol. 2020 Jun 11;11:519691.
14. Jimenez-Leon MR, Gasca-Capote C, Tarancon-Diez L, Dominguez-Molina B, Lopez-Verdugo M, Ritraj R, et al. Toll-like receptor agonists enhance HIV-specific T cell response mediated by plasmacytoid dendritic cells in diverse HIV-1 disease progression phenotypes [Internet]. 2023. Available from: www.thelancet.com
15. Altfeld M, Gale M. Innate immunity against HIV-1 infection. Nature Immunology 2015 16:6 [Internet]. 2015 May 19 [cited 2023 Nov 23];16(6):554–62. Available from: https://www.nature.com/articles/ni.3157
16. Utay NS, Douek DC. Interferons and HIV Infection: The Good, the Bad, and the Ugly. Pathog Immun [Internet]. 2016 [cited 2023 Nov 23];1(1):107. Available from: /pmc/articles/PMC4972494/
17. Kedzierska K, Crowe SM. Cytokines and HIV-1: Interactions and clinical implications. Antivir Chem Chemother. 2001;12(3):133–50.
18. Roff SR, Noon-Song EN, Yamamoto JK. The Significance of Interferon-γ in HIV-1 Pathogenesis, Therapy, and Prophylaxis. Front Immunol [Internet]. 2013 [cited 2023 Nov 23];4(DEC). Available from: /pmc/articles/PMC3888948/

19. McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. Nature Reviews Immunology 2009 10:1 [Internet]. 2009 Dec 11 [cited 2023 Nov 23];10(1):11–23. Available from: https://www.nature.com/articles/nri2674
20. Collins DR, Gaiha GD, Walker BD. CD8+ T cells in HIV control, cure and prevention. Nature Reviews Immunology 2020 20:8 [Internet]. 2020 Feb 12 [cited 2023 Nov 23];20(8):471–82. Available from: https://www.nature.com/articles/s41577-020-0274-9
21. Li X, Singh NK, Collins DR, Ng R, Zhang A, Lamothe-Molina PA, et al. Molecular basis of differential HLA class I-restricted T cell recognition of a highly networked HIV peptide. Nature Communications 2023 14:1 [Internet]. 2023 May 22 [cited 2023 Nov 23];14(1):1–15. Available from: https://www.nature.com/articles/s41467-023-38573-8
22. Li L, Li HS, Pauza CD, Bukrinsky M, Zhao RY. Roles of HIV-1 auxiliary proteins in viral pathogenesis and host-pathogen interactions. Cell Res [Internet]. 2005 [cited 2023 Nov 23];15(11–12):923–34. Available from: https://pubmed.ncbi.nlm.nih.gov/16354571/
23. Lu L, Yu F, Du LY, Xu W, Jiang SB. Tactics used by HIV-1 to evade host innate, adaptive, and intrinsic immunities. Chin Med J (Engl) [Internet]. 2013 [cited 2023 Dec 27];126(12):2374–9. Available from: https://pubmed.ncbi.nlm.nih.gov/23786957/
24. Sauter D, Kirchhoff F. Multilayered and versatile inhibition of cellular antiviral factors by HIV and SIV accessory proteins. Cytokine Growth Factor Rev. 2018 Apr 1;40:3–12.
25. Moir S, Fauci AS. B cells in HIV infection and disease. Nature Reviews Immunology 2009 9:4 [Internet]. 2009 Apr [cited 2023 Nov 23];9(4):235–45. Available from: https://www.nature.com/articles/nri2524
26. Haynes BF, Wiehe K, Borrow P, Saunders KO, Korber B, Wagh K, et al. Author Correction: Strategies for HIV-1 vaccines that induce broadly neutralizing antibodies. Nat Rev Immunol [Internet]. 2023 Apr 1 [cited 2023 Dec 27];23(4):265. Available from: http://www.ncbi.nlm.nih.gov/pubmed/36859597
27. Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bournazos S, Nogueira L, et al. Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. Cell [Internet]. 2014 Aug 28 [cited 2024 Jan 21];158(5):989–99. Available from: https://pubmed.ncbi.nlm.nih.gov/25131989/
28. Mishra N, Sharma S, Dobhal A, Kumar S, Chawla H, Singh R, et al. Broadly neutralizing plasma antibodies effective against autologous circulating viruses in infants with multivariant HIV-1 infection. Nature Communications 2020 11:1 [Internet]. 2020 Sep 2 [cited 2024 Jan 21];11(1):1–11. Available from: https://www.nature.com/articles/s41467-020-18225-x
29. Behrens AJ, Vasiljevic S, Pritchard LK, Harvey DJ, Andev RS, Krumm SA, et al. Composition and Antigenic Effects of Individual Glycan Sites of a Trimeric HIV-1 Envelope Glycoprotein. Cell Rep [Internet]. 2016 Mar 22 [cited 2024 Jan 21];14(11):2695–706. Available from: https://pubmed.ncbi.nlm.nih.gov/26972002/
30. Wang YY, Zhen C, Hu W, Huang HH, Li YJ, Zhou MJ, et al. Elevated glutamate impedes anti-HIV-1 CD8 + T cell responses in HIV-1-infected individuals on antiretroviral therapy. Communications Biology 2023 6:1 [Internet]. 2023 Jul 7 [cited 2023 Nov 23];6(1):1–12. Available from: https://www.nature.com/articles/s42003-023-04975-z
31. Qian G, Zhang Y, Liu Y, Li M, Xin B, Jiang W, et al. Glutamylation of an HIV-1 protein inhibits the immune response by hijacking STING. Cell Rep [Internet]. 2023

May 30 [cited 2023 Dec 27];42(5). Available from: https://pubmed.ncbi.nlm.nih.gov/37099423/
32. Morvan MG, Teque FC, Locher CP, Levy JA. The CD8 + T Cell Noncytotoxic Antiviral Responses . Microbiology and Molecular Biology Reviews [Internet]. 2021 May 19 [cited 2024 Jan 21];85(2). Available from: https://doi.org/10.1128/MMBR
33. Zanoni M, Palesch D, Pinacchio C, Statzu M, Tharp GK, Paiardini M, et al. Innate, non-cytolytic CD8+ T cell-mediated suppression of HIV replication by MHC-independent inhibition of virus transcription. PLoS Pathog [Internet]. 2020 Sep 1 [cited 2024 Jan 9];16(9):e1008821. Available from: https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1008821
34. Rowland-Jones S, Andrews SM. Recent advances in understanding HIV evolution. F1000Res [Internet]. 2017 [cited 2023 Nov 27];6:597. Available from: /pmc/articles/PMC5414815/
35. Catalfamo M, Wilhelm C, Tcheung L, Proschan M, Friesen T, Park JH, et al. CD4 and CD8 T Cell Immune Activation during Chronic HIV Infection: Roles of Homeostasis, HIV, Type I IFN, and IL-7. The Journal of Immunology [Internet]. 2011 Feb 15 [cited 2023 Nov 23];186(4):2106–16. Available from: https://dx.doi.org/10.4049/jimmunol.1002000
36. Aiken C, Rousso I. The HIV-1 capsid and reverse transcription. Retrovirology [Internet]. 2021 Dec 1 [cited 2024 Jan 9];18(1):1–9. Available from: https://retrovirology.biomedcentral.com/articles/10.1186/s12977-021-00566-0
37. Krupkin M, Jackson LN, Ha B, Puglisi EV. Advances in understanding the initiation of HIV-1 reverse transcription. Curr Opin Struct Biol [Internet]. 2020 Dec 1 [cited 2024 Jan 9];65:175. Available from: /pmc/articles/PMC9973426/
38. Ha B, Larsen KP, Zhang J, Fu Z, Montabana E, Jackson LN, et al. High-resolution view of HIV-1 reverse transcriptase initiation complexes and inhibition by NNRTI drugs. Nature Communications 2021 12:1 [Internet]. 2021 May 4 [cited 2024 Jan 9];12(1):1–11. Available from: https://www.nature.com/articles/s41467-021-22628-9
39. Engelman AN. HIV Capsid and Integration Targeting. Viruses [Internet]. 2021 Jan 1 [cited 2023 Dec 21];13(1). Available from: /pmc/articles/PMC7830116/
40. Lusic M, Siliciano RF. Nuclear landscape of HIV-1 infection and integration. Nature Reviews Microbiology 2016 15:2 [Internet]. 2016 Dec 12 [cited 2023 Dec 21];15(2):69–82. Available from: https://www.nature.com/articles/nrmicro.2016.162
41. Craigie R. The molecular biology of HIV integrase. Future Virol [Internet]. 2012 Jul [cited 2023 Dec 21];7(7):679. Available from: /pmc/articles/PMC3458710/
42. Engelman AN, Singh PK. Cellular and molecular mechanisms of HIV-1 integration targeting. Cell Mol Life Sci [Internet]. 2018 Jul 1 [cited 2023 Dec 21];75(14):2491. Available from: /pmc/articles/PMC6004233/
43. Mazzuti L, Turriziani O, Mezzaroma I. The Many Faces of Immune Activation in HIV-1 Infection: A Multifactorial Interconnection. Biomedicines [Internet]. 2023 Jan 1 [cited 2023 Dec 27];11(1). Available from: /pmc/articles/PMC9856151/
44. Lv T, Cao W, Li T. HIV-Related Immune Activation and Inflammation: Current Understanding and Strategies. J Immunol Res [Internet]. 2021 [cited 2023 Dec 27];2021. Available from: /pmc/articles/PMC8494587/
45. Policicchio BB, Cardozo-Ojeda EF, Xu C, Ma D, He T, Raehtz KD, et al. CD8+ T cells control SIV infection using both cytolytic effects and non-cytolytic suppression of virus production. Nature Communications 2023 14:1 [Internet]. 2023 Oct 20 [cited 2023 Nov 23];14(1):1–13. Available from: https://www.nature.com/articles/s41467-023-42435-8

46. Alves E, Al-Kaabi M, Keane NM, Leary S, Almeida CAM, Deshpande P, et al. Adaptation to HLA-associated immune pressure over the course of HIV infection and in circulating HIV-1 strains. PLoS Pathog [Internet]. 2022 Dec 1 [cited 2024 Jan 9];18(12). Available from: /pmc/articles/PMC9803285/
47. Promsote W, Xu L, Hataye J, Fabozzi G, March K, Almasri CG, et al. Trispecific antibody targeting HIV-1 and T cells activates and eliminates latently-infected cells in HIV/SHIV infections. Nature Communications 2023 14:1 [Internet]. 2023 Jun 22 [cited 2023 Nov 23];14(1):1–13. Available from: https://www.nature.com/articles/s41467-023-39265-z
48. Cohen KW, De Rosa SC, Fulp WJ, deCamp AC, Fiore-Gartland A, Mahoney CR, et al. A first-in-human germline-targeting HIV nanoparticle vaccine induced broad and publicly targeted helper T cell responses. Sci Transl Med [Internet]. 2023 May 24 [cited 2024 Jan 8];15(697). Available from: https://www.science.org/doi/10.1126/scitranslmed.adf3309
49. Li S, Moog C, Zhang T, Su B. HIV reservoir: antiviral immune responses and immune interventions for curing HIV infection. Chin Med J (Engl) [Internet]. 2022 Nov 11 [cited 2023 Nov 23];135(22):2667. Available from: /pmc/articles/PMC9943973/
50. Maldini CR, Ellis GI, Riley JL. CAR T cells for infection, autoimmunity and allotransplantation. Nature Reviews Immunology 2018 18:10 [Internet]. 2018 Jul 25 [cited 2024 Jan 21];18(10):605–16. Available from: https://www.nature.com/articles/s41577-018-0042-2
51. Maldini CR, Gayout K, Leibman RS, Dopkin DL, Mills JP, Shan X, et al. HIV-Resistant and HIV-Specific CAR-Modified CD4+ T Cells Mitigate HIV Disease Progression and Confer CD4+ T Cell Help In Vivo. Molecular Therapy [Internet]. 2020 Jul 8 [cited 2024 Jan 21];28(7):1585–99. Available from: http://www.cell.com/article/S152500162030246X/fulltext