# Human Immunodeficiency Virus: Pathogenesis, Transmission and Preventive Interventions

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**Abstract.** Human immunodeficiency virus (HIV) remains a major global public health challenge despite considerable advances in prevention and treatment. Understanding its biological characteristics and pathogenic mechanisms is fundamental to improving prevention and disease management. This review summarizes the classification, structural characteristics, replication cycle, and pathogenic mechanisms of HIV, with particular emphasis on viral infection, immune evasion, and the progressive depletion of $CD4^+$ T lymphocytes. It also reviews the major routes of HIV transmission and evaluates current prevention strategies, including behavioral interventions, antiretroviral therapy, pre-exposure prophylaxis (PrEP), treatment as prevention (TasP), and vaccine development. Current evidence demonstrates that integrated prevention and treatment approaches have substantially improved HIV control and reduced disease burden. Nevertheless, the high genetic variability of HIV, limited access to healthcare resources in some regions, and the absence of a licensed preventive vaccine remain major obstacles to global HIV elimination. Future research should prioritize the development of broadly protective vaccines, long-acting preventive therapies, and more accessible, personalized prevention strategies to further strengthen global HIV control.

**Keywords:** HIV, Pathogenesis, $CD4^+$ T lymphocyte, HIV transmission, Antiretroviral therapy.

## 1. Introduction

Acquired immunodeficiency syndrome (AIDS) has been one of the most severe public health problems in the 21st century since the discovery of the human immunodeficiency virus (HIV) in the early 1980s. Although there has been progress in reducing the spread of AIDS by 2030, HIV infections globally have dropped by 40% between 2010 and 2024; however, according to the World Health Statistics 2026 report from the WHO [1], there were still 1.3 million new cases in 2024. HIV transmission in the WHO African Region has dropped by 70%, but the number of new HIV infections is still rising in Eastern Europe and Central Asia, the Middle East, North Africa and Latin America [1]. More than 38 million people around the world are living with HIV today [1], and there is still a need for continuous scientific research and public health efforts to fight the virus.

In the past decade, considerable progress has been made in learning about the molecular mechanisms of HIV infection and the pathogenesis of HIV. HIV is a Lentivirus that belongs to the retrovirus family and has the ability to integrate into the genome of host cells to form a latent (chronic) infection. Viral capsids are made up of CA proteins and serve to evade the immune system and bind to chromatin. It has preserved the fragility of metastability, is stable enough to ensure the protection of viral genome DNA during transport in the cell, but flexible enough to dissociate in the nucleus for genome integration. Due to the high mutation rate of HIV, it can change rapidly; therefore, the immune system fails to recognise it and it is also resistant to drugs. One of the most significant achievements in the field of HIV persistence is that HIV can exist as latent reservoirs of integrated proviral DNA, mainly in resting memory CD4+ T cells, which are transcriptionally silent and protected from antiretroviral therapy (ART) and immune clearance. A recent 2026 study has shown that the TGF-β/SMAD signalling pathway suppresses the host's antiviral response by employing histone deacetylases to reduce the accessibility of chromatin for immune regulatory proteins and thus maintain viral latency.

At the same time, new treatments and prevention methods for HIV reservoirs and transmission are also being developed. Anti-PD-1 immunotherapies may reduce the latent reservoir of HIV in cancer

patients, but this has not been verified. Latency-reversing agents (LRAs) are needed to realise a "kick-and-kill" curative strategy, but most of the available LRAs lack sufficient potency and specificity, and combination regimens with pro-apoptotic agents have shown limited therapeutic effects. New tools for genome editing, such as CRISPR-Cas9 and next-generation sequencing, have also achieved good results in the quest for cures, but problems in safe delivery still exist. Prevention targets 95-95-95 are helping to expand ART coverage, and long-acting injectable lenacapavir provides excellent pre-exposure prophylaxis. However, vaccine research has also encountered many failures, such as the poorly designed trial of HVTN706 mosaic vaccine. Fortunately, several new vaccine candidates have shown good results so far; the Tiantan vaccinia-vector vaccine developed in China is a typical example.

Convergence of viral molecular biology, pathogenesis and prevention offers support for dealing with the incurable nature of HIV and enhancing epidemic control. This review will first introduce the classification and structural biology of HIV, then describe the replication cycle of HIV and its pathogenic pathways and routes of transmission, and finally present current prevention and treatment measures, including ART, PrEP, vaccine research, innovative cure studies, etc. This paper will provide a general overview of the basic reasons and ongoing problems in our knowledge of HIV/AIDS around the world by considering fundamental viral biology in the context of epidemic control and clinical treatment.

## 2. Viral Classification and Structure

### 2.1. Classification

Human Immunodeficiency Virus (HIV) is a lentivirus belonging to the family Retroviridae that establishes a latent infection and is therefore unable to cause symptoms of disease for an extended period after initial infection. The two varieties of the HIV virus are HIV-1 and HIV-2. In 1983, HIV-1 was isolated and is responsible for most of the infections around the world; HIV-2 is restricted to West Africa, is less virulent and less contagious. HIV-2 is about 60% similar to HIV-1 in genomic nucleotide sequence and is much less virulent. Since the beginning of the pandemic, there have been 10 subtypes of HIV-1 (A-D, F-H, and J-L). A large-scale molecular epidemiology study of nearly 1.4 million HIV-1 samples from 154 countries showed that subtype C was the most common globally (48.7%, 95% CI: 48.3-49.1) between 2020-2024 and was prevalent in Southern Africa and South Asia. Subtype A accounted for 12%, and subtype B, which is widespread in the Americas and Western Europe, made up only 10% of the world's cases. In 2024, it is estimated that 40.8 million people were living with HIV, an additional 1.3 million new infections occurred that year, and an estimated 630,000 deaths from AIDS-related illnesses took place in 2024 [1].

### 2.2. Viral Structure

HIV-1 is a roughly spherical, enveloped particle of about 120 nm in diameter. The outer layer is a lipid membrane that is pinched off from the host cell at the time of budding, and it contains two viral surface glycoproteins: gp120 and gp41. The gp120 protein extends outwards and has a high affinity (K~D~ ~3nM) for the CD4 receptor on target T cells, and gp41 is an integral protein that is embedded in the lipid bilayer to mediate membrane fusion. Under the envelope is the matrix layer, and within it are about 2,500 copies of the matrix protein p17. A cone-shaped protein shell in the matrix is called a capsid, and it is composed of approximately 1,000-1,500 copies (some sources report as many as 2,000 or more) of the p24 capsid protein. The two identical copies of the single-stranded positive-sense RNA genome are contained within the capsid and are approximately 9.8 kilobases (kb) long. The three main genes of the HIV-1 genome are gag, pol and env; there are six minor genes encoding single proteins, and two long terminal repeat (LTR) sequences. Gag gene codes for the matrix protein (p17), capsid protein (p24) and nucleocapsid proteins (p6 and p7). The pol gene is to encode three enzymes that are necessary: reverse transcriptase, integrase and protease. Approximately 120 Gag-

Pol polyproteins are contained within each virion. A total of about 15 viral proteins are encoded by the HIV-1 genome.

### 2.3. Replication Cycle

The HIV replication cycle begins when gp120 binds to the CD4 receptor on the surface of a host cell, then binds to a co-receptor (CCR5 or CXCR4), and finally, gp41 binds to the host cell membrane and causes fusion of the gp120 envelope with the host cell membrane. The viral capsid enters the cell and is then uncoats in the cytoplasm. Reverse transcriptase then produces double-stranded DNA from single-stranded viral RNA, and in vivo, this takes about 33 hours, about three times longer than the in vitro period. The error rate of reverse transcription is about $3.4 \times 10^{-5}$ mutations per base pair per replication cycle, and a large number of such mutations have arisen to cause immune evasion and drug resistance. The newly synthesized viral DNA and integrase form a pre-integration complex that moves to the nucleus, and then integrase randomly inserts the viral DNA as a provirus into the host genome. Integration for the production of new virions takes about 7 hours. The time from the release of a generation of virions to the release of the next is about 52 hours in vivo; this is called the viral generation time. The half-life of virion-producing $CD4^+$ T cells is estimated to be around 0.7 days (≈ 17 hours) and the half-life of free plasma virions is estimated to be around 5 minutes.

## 3. Pathogenic Mechanisms

### 3.1. $CD4^+$ T cell Depletion

The primary cause of the spread of HIV is a continuous drop in the number of CD4+ T-lymphocytes required by the immune system. The gastrointestinal lamina propria is a site of reduced CD4+ T cells by more than 50% during acute infection. Early loss of $CD4^+$ T cells is due to direct viral infection and lysis, and continuous loss is caused by activation-induced cell death of CD4 T cells and ongoing infection of susceptible cells. The daily numbers are alarming: in untreated HIV infection, 50-100 cells/μL of CD4+ T cells are lost each year due to HIV killing about one billion immune cells per day, and the body can replace only about 500 million. In the latent stage of HIV infection, there is a slow but continuous decline in peripheral blood CD4+ T cells without any symptoms. If the level of $CD4^+$ T cells drops to 200 cells/$mm^3$ or lower, then it is diagnosed as acquired immunodeficiency syndrome (AIDS).

### 3.2. The dynamics and progression of disease caused by viruses

Untreated HIV infection will present with a particular set of changes. The plasma viral load is relatively high after acute infection and generally exceeds 10^6 copies/mL. Viremia is then reduced to a set point (usually $1 \times 10^4$ - $1 \times 10^5$ copies/mL) by the immune system. The set-point viral load (SPVL) is a relatively poor prognostic factor; people with SPVL ≥ 5 $\log_{10}$ copies/mL had a median time of 5.32 years to reach a CD4 count of ≤200 cells/$mm^3$, while those with SPVL < 4 $\log_{10}$ copies/mL took 11.53 years. About 20% of the untreated infected people developed AIDS within 5 years of infection, and about 5% did not experience any significant reduction in CD4+ T cells after more than 10 years of infection.

The half-life of virus-producing CD4+ T cells was accurately measured to be 0.7 days, but the generation time of HIV-1 in vivo was around 2 days. Approximately 93-99% of the virus production occurs in actively infected CD4+ T lymphocytes, and these cells have a half-life of one day. A small fraction (1-7%) of infected macrophages are secreted with a half-life of 14.4 days, and less than 1% of these are released by latently infected T cells with a half-life of 8.5 days. The latent reservoir (integrated provirus in resting memory CD4+ T cells) is a serious barrier to a cure because it can persist for many years after effective antiretroviral therapy (ART). These chronically infected individuals have reached a stable low level of viremia of <50 copies/mL under suppressive therapy, but viral rebound is inevitable because of the latent reservoir.

### 3.3. Opportunistic Infections and Immunopathogenesis

Other forms of HIV injury include prolonged immune activation, altered organisation of lymphocytes and progressive immunodeficiency, in addition to direct cell damage. A reduction in the number of CD4+ T cells leads to impaired cellular and antibody-mediated immunity, and opportunistic infections that are normally controlled by a healthy immune system can then occur. Opportunistic infections are activated at a certain level of CD4+ T cells. If the count of CD4+ T cells is less than 200 cells/mm³, then AIDS-defining illnesses such as opportunistic infections and cancer may occur. Recently, the CARD8 inflammasome has been identified as a mechanism for the rapid detection of HIV-1 particles and CD4+ T cell depletion; thus, more components in the host-pathogen interaction network of HIV disease have been discovered.

## 4. Transmission Routes

### 4.1. Global Transmission Patterns

HIV can be spread in three ways: through sexual contact, from a mother to her child (such as during pregnancy, childbirth and breastfeeding), and by using contaminated needles. Each route will have a different share of the total based on the area and population. Most of the world's new HIV cases are transmitted through sexual contact. By 2025, it is expected that 1.2 million new HIV cases will be diagnosed worldwide [1], and in 2024, key populations (sex workers, men who have sex with men (MSM), transgender people, and people who inject drugs) accounted for 49% of all new HIV infections globally, an increase from 44% in 2010 [2]. The burden is not distributed evenly; therefore, this area has been relatively affected by the epidemic and needs to strengthen preventative measures.

### 4.2. Patterns of HIV Transmission in China

China's transmission environment is a typical case of how the mode of transmission for HIV has changed to sexual transmission. By June 30, 2025, there had been 1,387,471 new HIV/AIDS cases and 506,664 deaths due to HIV/AIDS in China so far, and an additional 47,054 new infections/AIDS cases were reported in the first half of 2025 [3,4]. Transmission route distribution shows that the proportion of sexual transmission via transmission routes is relatively high; 34,368 cases (73.0%) were caused by heterosexual sexual contact, and 11,653 cases (24.8%) occurred through homosexual sexual contact, primarily among men who have sex with men. Sexual transmission accounted for 97.8% of new cases, combined. Injection drug use accounted for only 61 cases (0.1%) and mother-to-child transmission for only 32 cases (0.07%), respectively, compared to other reasons [3]. The problem of injection drug use has gradually shifted to sexual transmission over time due to effective harm reduction programmes and changes in the course of the epidemic in the 1990s.

### 4.3. Mother-to-Child Transmission

Many improvements have been made to date; however, mother-to-child transmission still occurs. Untreated MTCT can be as high as 15-45%. If access to ART is provided during pregnancy and delivery, the risk will be less than 5%, and in 2025, 87% of pregnant women with HIV will be able to take antiretroviral drugs to prevent transmission of HIV to their children [2]. The world has made good progress in this area, and new HIV infections among children have dropped by 69% between 2010 and 2025, from 300,000 to 94,000 [2,5]. In July 2025, the World Health Organization released its first guidance on the triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B, and thus strengthened the integration of maternal and child health programmes. By 2025, a small number of nations have reached the leading benchmark for triple elimination of mother-to-child transmission.

## 5. Prevention and Control

### 5.1. Behavioural and Biomedical Prevention

Generally speaking, the three kinds of HIV prevention are behavioural modification, biomedical interventions and structural adjustments. Although the funds for condoms in some countries dropped by more than 90% in 2025, condom promotion is still needed for behaviour prevention.

The other is a new method for preventing diseases. PrEP is a daily HIV preventive medication for individuals who have not been infected with HIV but want to reduce their risk of acquiring it, so it needs to be taken regularly. With good compliance, PrEP with tenofovir/emtricitabine (POUm) can be taken once a day and has a prevention rate of more than 90% for HIV [2,6]. Models show that by offering organised, long-acting PrEP options with cabotegravir, up to one-third of HIV deaths over 10 years can be prevented. In July 2025, the World Health Organization (WHO) added injectable lenacapavir to the list of additional PrEP options and recommended administering it twice a year. This long-acting form is also a new kind of HIV prevention method that can solve the problem of adherence to daily oral PrEP medication. There are also issues of access; the number of people using PrEP dropped by 38% from 2024 to 2025 in the 62 countries reported to by UNAIDS.

The other kind of biomedical prevention is treatment as prevention (TasP). Under antiretroviral therapy (ART), a person has an undetectable viral load and is therefore not infectious through sexual contact (U=U: Undetectable = Untransmissible). In 2025, 32.1 million people were accessing ART, up from 7.7 million in 2010 [2,7]. The UNAIDS 95-95-95 goals are to have 95% of all people living with HIV know their HIV status, 95% of people who have been diagnosed are under treatment, and 95% of those under treatment are virally suppressed [2,8]. In 2025, 88% of the people living with HIV knew their status and 78% were under treatment for HIV and virally suppressed [2, 8]. Although there has been progress, there are still many deficiencies, and especially among children: only 54% of children aged 0-14 years living with HIV are under treatment, and about 1.3 million children have not been able to access ART [2, 9]. Treatment gaps are also sex-disaggregated; 84% of women have received treatment, and only 74% of men have done so [2,10].

### 5.2. Vaccine Development

More than 40 years after the start of the HIV epidemic, an effective preventive vaccine has still not been developed; thus far, none have been approved for use. As of now, the RV144 trial in Thailand is the only clinical trial to have shown some level of protection at three years (31.2%). Other trials, such as the HVTN 505 phase IIb trial, did not meet the efficacy criteria set out in the trials. HVTN 505 also found immunological associations of a reduced risk, such as vaccine-induced anti-HIV-1 Env glycoprotein IgG3 antibodies and antibody-dependent phagocytosis. New Strategies for Vaccination against HIV are on the horizon, and mRNA-based HIV vaccine candidates have shown strong immune responses in early-stage clinical trials; 80% of the subjects in these trials produced antibodies to viral proteins [6]. Although vaccine development still faces many scientific challenges, such as the extremely high genetic diversity of HIV, which makes it difficult to develop a vaccine; its ability to integrate with the host genome and the absence of clear correlates of protection, new platforms have brought new hope.

In summary, sexual transmission is the main way of transmission around the world and in China, accounting for 97.8% of new cases [3]. ART scale-up, PrEP expansion and MTCT prevention have achieved good results in prevention, and globally, new infections have dropped by 65% since 1995, while AIDS-related deaths have fallen by 74% since 2004. However, the following problems still exist: 1.2 million new infections in 2025, cuts to funds for prevention services, and no safe and effective vaccine has been developed yet. Lenacapavir is a long-acting injectable that the WHO recommended for use in 2025 [4, 5], and mRNA vaccine trials are the next step in the fight against AIDS around the world.

## 6. Conclusion

HIV is a complex lentivirus with sophisticated structural and replicative machinery. It exhibits inherent clinical latency characteristic of the Lentivirus genus. Owing to the error-prone activity of reverse transcriptase (mutation rate: approximately $3.4 \times 10^{-5}$ per base per replication cycle), HIV readily achieves immune escape and drug resistance, creating great obstacles to clinical treatment and vaccine development. Progressive depletion of $CD4^+$ T lymphocytes constitutes the core pathological feature of HIV infection, which arises from direct viral lysis, T cell activation-induced death and persistent chronic immune activation. Once peripheral $CD4^+$ T cell counts drop below 200 cells/$mm^3$, patients will develop severe immunodeficiency. Notably, integrated proviral latent reservoirs within resting memory $CD4^+$ T cells serve as a fundamental barrier to complete HIV cure, a critical mechanism elaborated in preceding chapters.

Over the past thirty years, the dominant transmission patterns of HIV have undergone dramatic shifts. In the early stage of the epidemic, injection drug use and exposure to contaminated blood products were the major transmission routes, whereas sexual contact has become the predominant transmission pathway nowadays. In China, sexual transmission accounts for 97.8% of all newly reported HIV cases, consisting of 73.0% heterosexual transmission and 24.8% transmission among men who have sex with men. Targeted behavioral and biomedical interventions should be delivered to key vulnerable populations. In 2024, these groups contributed 49% of global new HIV infections.

Global HIV prevention and treatment have yielded remarkable achievements in recent decades. By 2025, 32.1 million people worldwide have received antiretroviral therapy (ART), a substantial increase from 7.7 million in 2010. Effective ART leads to an undetectable viral load, which translates to non-transmissible status under the U=U principle and reshapes clinical management and public awareness of HIV. Pre-exposure prophylaxis (PrEP) has become a vital biomedical preventive tool, and the twice-yearly injectable lenacapavir newly recommended by WHO represents a major breakthrough in long-acting HIV prevention. ART coverage for HIV-positive pregnant women has reached 87% in 2025, cutting new paediatric HIV infections by 69% between 2010 and 2025. However, prominent inequities persist in global treatment access: only 78% of people living with HIV receive ART, with an obvious gender gap (84% coverage among women versus 74% among men), and merely 54% of HIV-positive children aged 0–14 can obtain antiretroviral drugs.

Despite 40 years of research efforts, no fully licensed preventive HIV vaccine has been developed to date. The RV144 trial remains the only study demonstrating partial protective efficacy of 31.2%. New mRNA-based HIV vaccine platforms show encouraging performance in early clinical trials: 80 per cent of vaccine recipients produced autologous tier 2 serum neutralizing antibodies against membrane-anchored viral envelope trimers. Combined with long-acting PrEP formulations, these novel immunization technologies bring new hope for attaining UNAIDS' target of ending the AIDS epidemic by 2030. Meanwhile, funding cuts pose severe threats to existing anti-AIDS systems; in some regions, PrEP uptake has declined by 38% and condom-related funding has been reduced by over 90%, erasing decades of accumulated prevention gains. Establishing comprehensive, evidence-based intervention systems that translate scientific findings into real-world practice remains a long-term undertaking to curb HIV transmission and reduce AIDS-related mortality.

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