Human Immunodeficiency Virus (HIV)

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🧍 Overview

- Causative agent of AIDS (Acquired Immunodeficiency Syndrome)
- Two types:
  - HIV-1 → Found worldwide 🌍 (main cause of AIDS globally)
  - HIV-2 → Found mainly in West Africa 🌍
- This section mainly refers to HIV-1 unless specified otherwise.

🧬 Important Properties

🔷 Family and Subgroup

- Member of Retroviridae family, genus Lentivirus ("slow viruses")

- Characterized by long incubation periods and chronic progressive disease

 Tropism & Target Cells

- Primary target: $CD4^+$ Helper T-lymphocytes

- Also infects: Macrophages and Monocytes (express CD4 receptors)

- Mechanism:

  → Virus binds to CD4 receptor on host cell
  → Entry facilitated by co-receptors (CCR5 or CXCR4)
  → Leads to loss of cell-mediated immunity
  → Host becomes highly susceptible to opportunistic infections and certain cancers (e.g., Kaposi sarcoma, lymphomas)

 Viral Structure

- Shape: Enveloped virus with a cylindrical (type D) core

- Envelope glycoproteins:

  - gp120 → Mediates attachment to CD4 receptors
  - gp41 → Mediates fusion of viral and host cell

membranes

- Genome:
    - Diploid — contains two identical single-stranded (+) RNA molecules
    - NOT double-stranded RNA (important distinction!)

🧩 Main Enzymes within the Nucleocapsid

Enzyme	Function
Reverse Transcriptase	RNA-dependent DNA polymerase → synthesizes DNA from RNA template; also has ribonuclease H activity to degrade RNA from RNA-DNA hybrid
Integrase	Integrates proviral DNA into host genome 🧬
Protease	Cleaves precursor polyproteins into functional viral proteins

🧠 Mnemonic: *RIP* → Reverse transcriptase, Integrase, Protease

🔬 Genomic Organization

HIV genome is complex, consisting of:

- 3 structural genes: *gag, pol, env*
- 2 essential regulatory genes: *tat, rev*
- 4 accessory (non-essential) genes: *nef, vif, vpr, vpu*

⚙ Functions of Major Genes

Category	Gene	Protein(s) Produced	Function
Structural genes	gag	p24, p7 (nucleocapsid); p17 (matrix)	Structural core proteins; p24 used in diagnostic tests 🧪
	pol	Reverse transcriptase, Protease, Integrase	Enzymes for replication and integration
	env	gp120, gp41	gp120 = attachment; gp41 = fusion
Essential regulatory genes	tat	Tat	Activates transcription of viral genes; enhances replication
	rev	Rev	Transports late mRNA from nucleus → cytoplasm
Accessory genes	nef	Nef	Decreases CD4 & class I MHC expression → evades cytotoxic T-cells; induces death of uninfected cytotoxic T-cells
	vif	Vif	Inhibits APOBEC3G enzyme (which normally causes lethal hypermutation in viral DNA) → enhances infectivity

vpr	Vpr	Transports viral core into nucleus (even in non-dividing cells)
vpu	Vpu	Enhances virion release from infected cells

🧠 Clinical & Diagnostic Relevance of Key Proteins

- p24 antigen → first viral protein detected in blood; used in ELISA screening tests
- gp120/gp41 antibodies → used in confirmatory tests (Western blot)
- Reverse transcriptase → target for antiretroviral drugs (e.g., AZT)

🧩 Mechanism of Reverse Transcription & Integration (Flowchart)

Viral RNA

↓

🧬 Reverse Transcriptase → Synthesizes complementary cDNA

↓

Ribonuclease H → Degrades viral RNA strand

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DNA Polymerase Activity → Converts cDNA → Double-stranded proviral DNA

↓

Integrase → Inserts proviral DNA into host genome

↓

 Host transcription machinery → Produces viral mRNA & viral proteins

↓

Protease → Cleaves viral polyproteins into functional units

↓

Assembly of mature virions → Budding from host cell membrane

↓

 Destruction of $CD4^+$ T-cell

↓

↓ Immunity weakened

↓

😀 Opportunistic infections develop

🧬 Genetic Variability (Clades)

- Based on gp120 gene sequence differences
- HIV-1 subdivided into clades (subtypes) of group M (Major)
    - Clade B: Common in North America — transmitted mainly via anal sex; infects mononuclear cells
    - Clade E: Common in Southeast Asia — transmitted mainly via vaginal sex; infects female genital tract cells

🧠 Exam Pearl 💡

- p24 = diagnostic antigen
- gp120 & gp41 = envelope glycoproteins (for attachment & fusion)

- Reverse transcriptase = hallmark enzyme of retroviruses
- tat & rev = essential regulatory genes
- nef, vif, vpr, vpu = accessory genes (enhance infectivity & pathogenesis)

 Major Antigens of HIV

1 Envelope Glycoproteins — gp120 & gp41

- gp120 → Projects from the viral surface and binds to:
  - CD4 receptor on host cell 🎯
  - Chemokine co-receptor (either CCR5 or CXCR4)
- gp41 → Embedded in the viral envelope; mediates fusion of viral and cell membranes
- Antigenic variation:
  - gp120 gene mutates rapidly due to lack of

proofreading by reverse transcriptase
    - Results in numerous antigenic variants → complicates vaccine development 💉

- Most immunogenic region: V3 loop of gp120 (major site of antigenic variation)

- Neutralizing antibodies form against gp120 but lose efficacy as new variants arise.

📝 Summary:

gp120 → attachment

gp41 → fusion → Rapid mutation → immune evasion → vaccine difficulty

2️⃣ Core Antigen — p24

- Located in the nucleocapsid (core)

- Highly conserved (non-variable)

- Non-neutralizing, but:

- Serves as a key diagnostic marker (detected in early infection via ELISA)
- Indicates active viral replication

🧍 Natural Host Range & Origin

- Natural host: Humans only
- No endogenous HIV sequences in human DNA → virus entered humans *recently* in evolution
- Origin evidence:
  - Chimpanzees (SIVcpz) in West Africa are believed to be the source of HIV-1 🐒
  - Cross-species transmission → "jumping the species barrier"

🧩 Related Retroviruses

🧬 1. HIV-2

- Discovered in West Africa (1986)

- Proteins share ~40% similarity with HIV-1
- Localized mainly to West Africa, less transmissible, and slower disease progression
- Closely related to SIVsmm (Simian Immunodeficiency Virus of *sooty mangabey*)
- Thought to arise from accidental human infection with SIVsmm.

🧬 2. Simian Immunodeficiency Viruses (SIVs)

- Found in monkeys and chimpanzees (e.g., *SIVcpz*)
- Cause persistent, often asymptomatic infection in nonhuman primates
- Source of human HIV-1 and HIV-2 via cross-species exposure (e.g., hunting or blood contact)
- Occasionally cause AIDS-like illness in some chimpanzees 🐒

🔁 Replication Cycle of HIV (Step-by-Step Flowchart)

🔷 1. Attachment

gp120 binds to CD4 receptor on T-helper cells and macrophages

gp120 also binds to co-receptor (chemokine receptor):

- CCR5 → macrophage-tropic strains
- CXCR4 → T-cell-tropic strains

🧠 Genetic protection:

- Mutation in CCR5 gene (Δ32 mutation) →
  → Homozygotes (1%) completely resistant to HIV infection 🛡️
  → Heterozygotes (10–15%) → slower progression to AIDS

🔷 2. Fusion & Entry

gp41 mediates fusion of viral envelope with host membrane

Viral core (RNA + enzymes) released into cytoplasm

🔷 3. Reverse Transcription

Reverse transcriptase converts single-stranded viral RNA → double-stranded DNA

Ribonuclease H activity degrades RNA strand of RNA-DNA hybrid

Forms proviral DNA 🧬

◈ 4. Integration

Integrase enzyme inserts proviral DNA into host cell genome

Provirus remains latent or transcriptionally active

◈ 5. Transcription & Translation

Host RNA polymerase II (aided by Tat protein) transcribes proviral DNA → viral mRNA

mRNA translated into polyproteins:

- Gag polyprotein → structural proteins (p24, p17, etc.)
- Pol polyprotein → reverse transcriptase, integrase,

protease

- Env polyprotein → gp160 (later cleaved into gp120 + gp41)

🔷 6. Assembly

Immature virions form in cytoplasm

Env glycoproteins transported to host membrane

Nucleocapsid assembled beneath membrane

🔷 7. Budding & Maturation

Virus buds through host membrane → acquires lipid envelope

Viral protease cleaves precursor polyproteins → functional proteins

Mature, infectious virion released 🌍

⚙️ Host Cell Proteins Involved

- CD4, CCR5, CXCR4 → viral entry
- Actin & Tubulin → transport of viral DNA to nucleus
- Cyclin T1 + Tat protein → transcription of viral mRNA
- Cellular proteases → cleave Env precursor (gp160 → gp120 + gp41)
- Host budding machinery → virion release

🧠 Exam Pearls 💡

- gp120 → CD4 attachment, gp41 → fusion

- p24 → diagnostic core antigen
- Δ32 CCR5 mutation → natural resistance
- Reverse transcriptase → hallmark enzyme of retroviruses
- Integrase → enables viral DNA integration
- Protease inhibitors → block virion maturation (used in ART therapy)

🧬 Transmission & Epidemiology of HIV

🔁 Modes of Transmission

HIV is transmitted primarily through:

- Sexual contact (most common route)
- Transfer of infected blood
- Perinatal transmission from mother to child:

- Across the placenta
- During birth
- Via breast milk

Note: More than 50% of neonatal infections occur at delivery, while the rest are roughly equally divided between transplacental and breastfeeding transmission.

There is no evidence for:

- Airborne
- Waterborne
- Insect-borne transmission of HIV

Mechanism of Infection

HIV transmission occurs through:

- HIV-infected cells or

- Free virus particles (not cell-associated)

Although small amounts of virus are found in saliva and tears, these do not play a significant role in transmission.

⚖️ Comparison with HBV Transmission

- Follows a similar pattern to hepatitis B virus (HBV).
- Less efficient transmission — a much higher viral dose of HIV is required for infection.

🧩 Risk Factors Increasing Susceptibility

- Pre-existing sexually transmitted diseases, especially ulcerative lesions (e.g., syphilis, chancroid, herpes genitalis)
- Lack of circumcision in males increases risk

💉 Blood Transfusion Transmission

- Greatly reduced by screening blood for anti-HIV antibodies.
- However, during the "window period", HIV may be present in blood before antibodies are detectable.
- To minimize this, blood banks also test for p24 antigen.

🌍 Epidemiological Overview

📊 In the United States (as of 2015–2016):

- ≈ 1.1 million people living with HIV
- ≈ 50,000 new infections/year
- ≈ 15% of infected individuals unaware of their status
- ≈ 630,000 deaths due to AIDS since 1981
- Major decline in transmission due to:
    - Better preventive measures
    - Effective antiretroviral therapy (ART)

🌐 Worldwide Statistics (2016):

- ≈ 37 million infected
- Two-thirds in sub-Saharan Africa
- Highest infection rates: Africa, Asia, Latin America
- AIDS = 4th leading cause of death globally
    - 1 Ischemic heart disease

- 2 Cerebrovascular disease
- 3 Acute lower respiratory disease
- 4 AIDS

Transmission Patterns

1980s (US & Europe):

- Predominantly:
  - Men having sex with men (MSM)
  - Intravenous drug users
  - Hemophiliacs receiving contaminated blood
- Heterosexual transmission was rare.

Present Day:

- Heterosexual transmission is now predominant in many regions, especially Africa.

Transmission in Healthcare Workers

- Very few cases despite regular exposure and needle-stick injuries.

- Infectious dose of HIV is high.
- Risk of infection after percutaneous exposure ≈ 0.3%.
- Transmission from healthcare worker → patient is exceedingly rare.

🧠 Pathogenesis & Immunity

🧩 Main Target Cells

HIV infects and destroys:

- Helper T cells ($CD4^+$ cells) → causes loss of cell-mediated immunity
    - Leads to opportunistic infections and certain cancers (e.g., Kaposi's sarcoma, lymphomas)

🧠 Note: HIV does not directly cause cancer — HIV genes are not found in tumor cells.

🎗️ Early Infection Sites

- Infection starts in dendritic (Langerhans') cells of the genital mucosa.

- Virus then infects local $CD4^+$ T cells → enters bloodstream (viremia) within 4–11 days.

Key Cellular Targets

- Th17 cells (subset of $CD4^+$ T cells) in mucosa are targeted early.
    - These produce IL-17, attracting neutrophils to infection sites.
    - Their loss → bacterial translocation and bloodstream infections (e.g., *E. coli* from gut flora).

CNS Involvement

- Infects monocytes & macrophages in brain

- Forms multinucleated giant cells (syncytia) → neuronal damage → neurologic symptoms

- gp41 mediates fusion of infected cells

- Infected cells also die due to:

- $CD8^+$ cytotoxic lymphocyte attack
- Apoptosis from syncytium formation

⚔️ Immune Evasion by HIV

- Tat and Nef proteins ↓ synthesis of MHC class I → evade $CD8^+$ cytotoxic killing.

🧪 Superantigen Hypothesis

- HIV may act as a superantigen, causing:
  - Nonspecific activation of helper T cells → massive cell death
- Supported by evidence from mouse mammary tumor virus (another retrovirus with superantigen-like properties).

🔽 Flowchart: Pathogenesis of HIV Infection

HIV entry through mucosal surface

↓

Infection of Langerhans' (dendritic) cells

Transmission to $CD4^+$ helper T cells

Replication and viremia (4–11 days post-infection)

Destruction of $CD4^+$ & Th17 cells

↓ Cell-mediated immunity

Opportunistic infections + Certain cancers

Late phase: CNS involvement, syncytia formation, and immune evasion

Persistence, Immunity & Clinical Stages of HIV

Persistent and Latent HIV Infection

HIV establishes both productive and latent infections within the host:

1 Persistent Noncytopathic Infection

- Occurs in T lymphocytes that continue to produce HIV without cell death.
- These persistently infected cells maintain ongoing viral production in the body.
- Lymphoid tissues (e.g. lymph nodes) are the main sites of active HIV replication.

2 True Latent Infection

- Found in resting $CD4^+$ memory T cells containing integrated but silent HIV DNA.

- No virus is produced until the cell is activated, after which replication resumes.

- This explains why HIV can remain dormant for months to years.

💡 Key Point:

HIV replication depends on host transcription factors that are present only in activated, not resting, $CD4^+$ T cells.

🔒 Lifelong Infection

- Once infected, a person remains HIV-positive for life.

- The integration of viral DNA into host DNA ensures lifelong persistence.

- Antiretroviral therapy (ART) can suppress viral replication but cannot eliminate latent reservoirs in $CD4^+$ memory cells.

🌟 Elite Controllers vs Long-Term Nonprogressors

Category	Description	Mechanism / Explanation

🧍 Elite Controllers	<1% of HIV-infected individuals who maintain undetectable viral loads and normal $CD4^+$ counts without ART	- Strong $CD8^+$ T-cell response eliminates infected cells - Presence of protective HLA alleles (e.g., HLA-B57, HLA-B27) - High p21 (CDK inhibitor) levels suppress HIV replication
🫁 Long-Term Non progressors (LTNPs)	HIV-infected individuals who live for many years with stable $CD4^+$ counts and no opportunistic infections, despite not receiving ART	- HIV strain has nef gene mutations → ↓ MHC I suppression (immune system recognizes infected cells) - High production of α-defensins → block CXCR4 receptors, preventing viral entry

⚔️ Immune System Effects

🧩 On T Cells

- $CD4^+$ cells are progressively destroyed.
- Cytotoxic $CD8^+$ T cells control early infection by killing infected cells.

- Failure of $CD8^+$ cells occurs later due to loss of $CD4^+$ helper support (↓ IL-2).

🧪 On B Cells

- Polyclonal activation → excessive immunoglobulin production

- Autoimmune diseases (e.g. thrombocytopenia) may develop

🧠 Host Immune Response

1 Cell-Mediated Immunity

- Main defense = $CD8^+$ cytotoxic lymphocytes (CTLs)

- CTLs control infection for years by targeting gp120 and other viral epitopes

- Escape mutants appear → new CTL clones arise

- Late-stage failure: when $CD4^+$ depletion causes CTL activity to collapse

2 Humoral Immunity

- Antibodies form against p24, gp120, and gp41, but:
    - They are weakly neutralizing
    - Do not prevent progression

🧬 Immune Evasion Strategies of HIV

1️⃣ Integration of viral DNA into host genome → persistence 🧩

2️⃣ Rapid mutation of *env* gene (gp120) → immune escape 🎭

3️⃣ Tat and Nef proteins ↓ MHC I synthesis → CTLs can't recognize infected cells 🦠

4️⃣ Destruction of $CD4^+$ T cells → overall immune collapse ⚡

🔽 Flowchart: Immune Pathogenesis of HIV

HIV infection of $CD4^+$ T cells

↓

Integration of viral DNA into host genome

Persistent & latent infections established

Continuous replication in lymphoid tissues

Destruction of $CD4^+$ T cells

↓ IL-2 and cytokine production

↓ $CD8^+$ cytotoxic activity

Emergence of escape mutants

↓

Progressive immune collapse → AIDS

 Clinical Stages of HIV Infection

The disease progresses through three main stages:

Stage	Description	Key Features
1 Acute (Primary) Infection	2–4 weeks post-infection	– Fever, sore throat, rash, lymphadenopathy 😷 – Rash: maculopapular, trunk/limbs, spares palms & soles – Leukopenia, normal CD4 count– High viremia → highly infectious – Self-limited (~2 weeks)
2 Latent Stage	Months to years	– Clinically silent but active replication in lymphoid tissues– Gradual fall in $CD4^+$ count – Constant viral set point (predicts progression speed)
3 Immuno	Final stage	– Severe $CD4^+$ depletion (<200 cells/μL)

deficiency Stage (AIDS)	- Opportunistic infections - Neoplasms (Kaposi's sarcoma, lymphoma) - CNS involvement

💧 Serologic and Viral Markers

Time After Infection	Event
10–14 days	Antibodies begin appearing
3–4 weeks	Most patients seroconvert
Before seroconversion	"Window period" → antibodies undetectable → possible false-negative tests
Early detection	PCR for viral RNA is best during window period
After initial infection	"Viral set point" established — higher set point = faster disease progression

📈 Viral Load and Prognosis

- Up to 10 billion new virions/day produced
- Viral RNA assay (PCR) measures plasma viral load
    - Detects free virions (not cell-associated)

- >10,000 copies/mL → higher risk of AIDS progression
- If ART fails to reduce viral load → therapy modification is needed

▼ Flowchart: Timeline of HIV Infection

Exposure to HIV

↓

Acute stage (2–4 weeks): fever, rash, lymphadenopathy

↓

Seroconversion (10–30 days) → antibodies appear

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Latent stage: asymptomatic, low-level viral replication

↓

Viral set point established

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Gradual $CD4^+$ decline

Immunodeficiency (AIDS) → opportunistic infections, malignancies, death

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 CD4-Positive T Cell Count and HIV Management

- CD4+ T cell count is a key indicator guiding HIV patient management.

- Used to determine:

    - 💊 Need for chemoprophylaxis against opportunistic infections
    - 💉 Need for anti-HIV therapy
    - 📊 Response to ongoing therapy

☑ Normal and Abnormal Ranges

- Normal lower limit: 500 cells/μL

  → Usually asymptomatic at this level

- <200 cells/μL:

  → Indicates AIDS (AIDS-defining condition)
  → Sharp increase in frequency & severity of opportunistic infections

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⏳ Middle and Late Stages of HIV Infection

1. Middle Stage (Latent Period)

- Duration: 7–11 years (in untreated patients)

- Asymptomatic, though virus continues replication in lymph nodes

- Virus remains active but sequestered, not truly latent

🦠 AIDS-Related Complex (ARC)

- Occurs during latent stage

- Symptoms:
    - Persistent fever 🌡️
    - Fatigue 😴
    - Weight loss ⚖️
    - Lymphadenopathy
- Often progresses to AIDS

♡ 2. Late Stage (AIDS)

- CD4 count <200/μL
- Marked increase in opportunistic infections and malignancies

☆ Characteristic Manifestations

- Pneumocystis jiroveci pneumonia
- Kaposi's sarcoma (HHV-8)

🦠 Common Opportunistic Infections in AIDS

Site	Disease/Symptom	Causative Organism

Lung	Pneumonia, Tuberculosis	*Pneumocystis jiroveci, CMV, Mycobacterium tuberculosis*
Mouth	Thrush, Hairy leukoplakia, Ulcers	*Candida albicans, EBV, HSV-1, Histoplasma capsulatum*
Esophagus	Thrush, Esophagitis	*C. albicans, CMV, HSV-1*
Intestine	Diarrhea	*Salmonella, Shigella, CMV, Cryptosporidium parvum, Giardia lamblia*
CNS	Meningitis, Brain abscess, PML	*Cryptococcus neoformans, Toxoplasma gondii, JC virus*
Eye	Retinitis	*Cytomegalovirus*
Skin	Kaposi's sarcoma, Zoster, Nodules	*HHV-8, VZV, C. neoformans*
Reticuloendothelial	Lymphadenopathy, Splenomegaly	*Mycobacterium avium complex, EBV*

Laboratory Diagnosis

1. HIV Combo Test 

- Detects both HIV antibodies + p24 antigen (early infection marker)

2. Confirmatory Tests

- Western blot (immunoblot) for confirmation of positive screening
- PCR / NAT detects viral RNA and confirms infection

3. Rapid Test – OraQuick 🦷

- Uses oral swab; ELISA-type home test
- Positive → Confirm by Western blot

4. Viral Load Testing 📉

- Quantifies HIV RNA via PCR
- Used for monitoring treatment response and disease progression

5. Other Important Tests

- CD4 count monitoring
- Drug resistance testing (genotypic & phenotypic)

💊 Treatment of HIV Infection

🎯 Goals of Therapy

1. Restore immune function → ↑ CD4 count

2. Reduce viral load → ↓ transmission risk
   💡 *Starting treatment early* after diagnosis yields the best outcomes.

💊 Highly Active Antiretroviral Therapy (HAART)

- Combination of 3–4 drugs for maximum efficacy

- Backbone: Emtricitabine + Tenofovir

- Add one of the following:

  - Efavirenz
  - Raltegravir
  - Rilpivirine
  - Ritonavir + (Atazanavir / Darunavir)
  - Elvitegravir + Cobicistat

Single-pill daily regimens improve compliance

👉 HAART prolongs life & suppresses virus but does not cure HIV.

⚠ Discontinuation of HAART

- Leads to:
    - Return of viremia
    - Drop in CD4 count

🧬 Resistance to Antiretroviral Drugs

- Cause: High mutation rate in HIV
- ~10% of new patients have resistant strains
- Testing:
    - Genotypic: Detects mutations in RT or PR genes
    - Phenotypic: Checks virus growth in presence of drug
- Tropism test: Determines if virus uses CCR5 → guides maraviroc use

🔥 Immune Reconstitution Inflammatory Syndrome (IRIS)

- Occurs after starting HAART in coinfected patients (e.g., HBV, HCV, TB, MAC, *Cryptococcus*, *Toxoplasma*)
- Mechanism:
  - Restoration of immune response → sudden inflammatory flare-up 😣
- 💡 *Prevention:* Treat coinfections before starting HAART

🛡️ Prevention

- 🚫 No vaccine available yet
- Prevent exposure:
  - Use condoms, avoid needle sharing, screen donated blood

- Postexposure prophylaxis (PEP):
    - Tenofovir + Emtricitabine (Truvada) + Raltegravir
    - Start ASAP, continue 28 days
- Preexposure prophylaxis (PrEP):
    - Truvada for high-risk individuals
- Reduce neonatal infections:
    - Treat HIV+ mothers and neonates
    - Avoid breastfeeding 🍼
    - Prefer C-section delivery
    - Circumcision lowers infection risk

💊 Prophylaxis Against Opportunistic Infections

Drug	Prevents
Trimethoprim-sulfamethoxazole	*Pneumocystis pneumonia, Toxoplasmosis*
Fluconazole	*Cryptococcal meningitis*
Clotrimazole (oral)	*Candidiasis (thrush)*

Ganciclovir	*CMV retinitis*
Azithromycin	*Mycobacterium avium complex (MAC)*