HIV(human immunodeficiency virus)

These viruses are enveloped positive-strand ribonucleic acid (RNA) viruses with a unique morphology and means of replication.

In 1970, Baltimore and Temin showed that the retroviruses encode an RNA-dependent deoxyribonucleic acid (DNA) polymerase (reverse transcriptase [RT]) and replicate through a DNA intermediate.

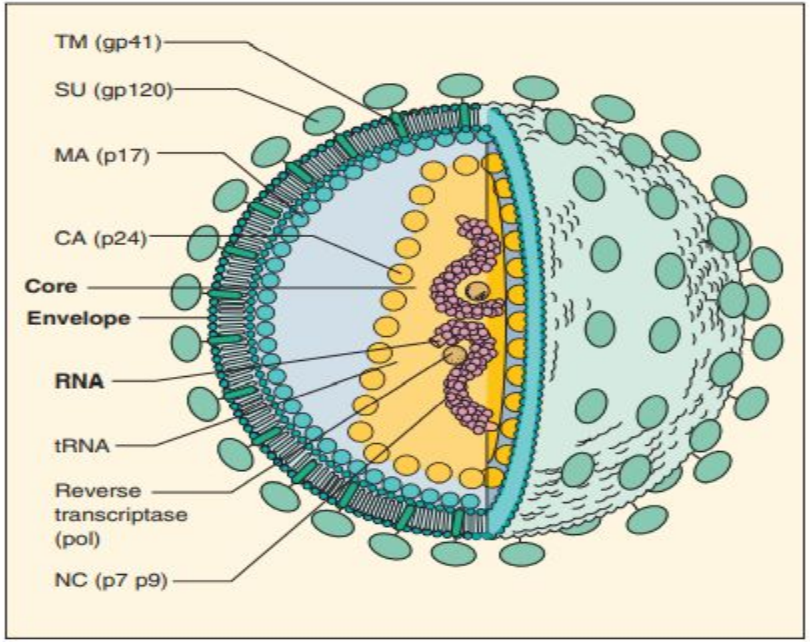
The DNA copy of the viral genome is then integrated into the host chromosome to become a cellular gene.

This discovery, which earned Baltimore, Temin, and Dulbecco the 1975 Nobel Prize, contradicted what had been the central dogma of molecular biology—that genetic information passed from DNA to RNA and then to protein.

There are four genotypes of HIV-1, designated

M (main), N, O, and P. Most HIV-1 is of the M subtype, and this is divided into 11 subtypes, or clades, designated A to K (for HIV-2, A to F). The designations are based on differences in the sequence of their env (7% to 12% difference) and gag genes and hence the antigenicity and immune recognition of the gp120 and capsid proteins of these viruses

Cross section of human immunodeficiency virus.



Box 54-1 Unique Characteristics of Retroviruses

Virus has an **enveloped** spherical virion that is 80 to 120 nm in diameter and encloses a capsid containing **two** copies of the **positive-strand RNA** genome (~9 kilobases for human immunodeficiency virus [HIV] and human T-cell lymphotropic virus).

RNA-dependent DNA polymerase **(reverse transcriptase),** two copies of tRNA, protease, and integrase enzymes are carried in the virion.

Virus receptor is the initial determinant of tissue tropism.

Replication proceeds through a DNA intermediate termed the *provirus.*

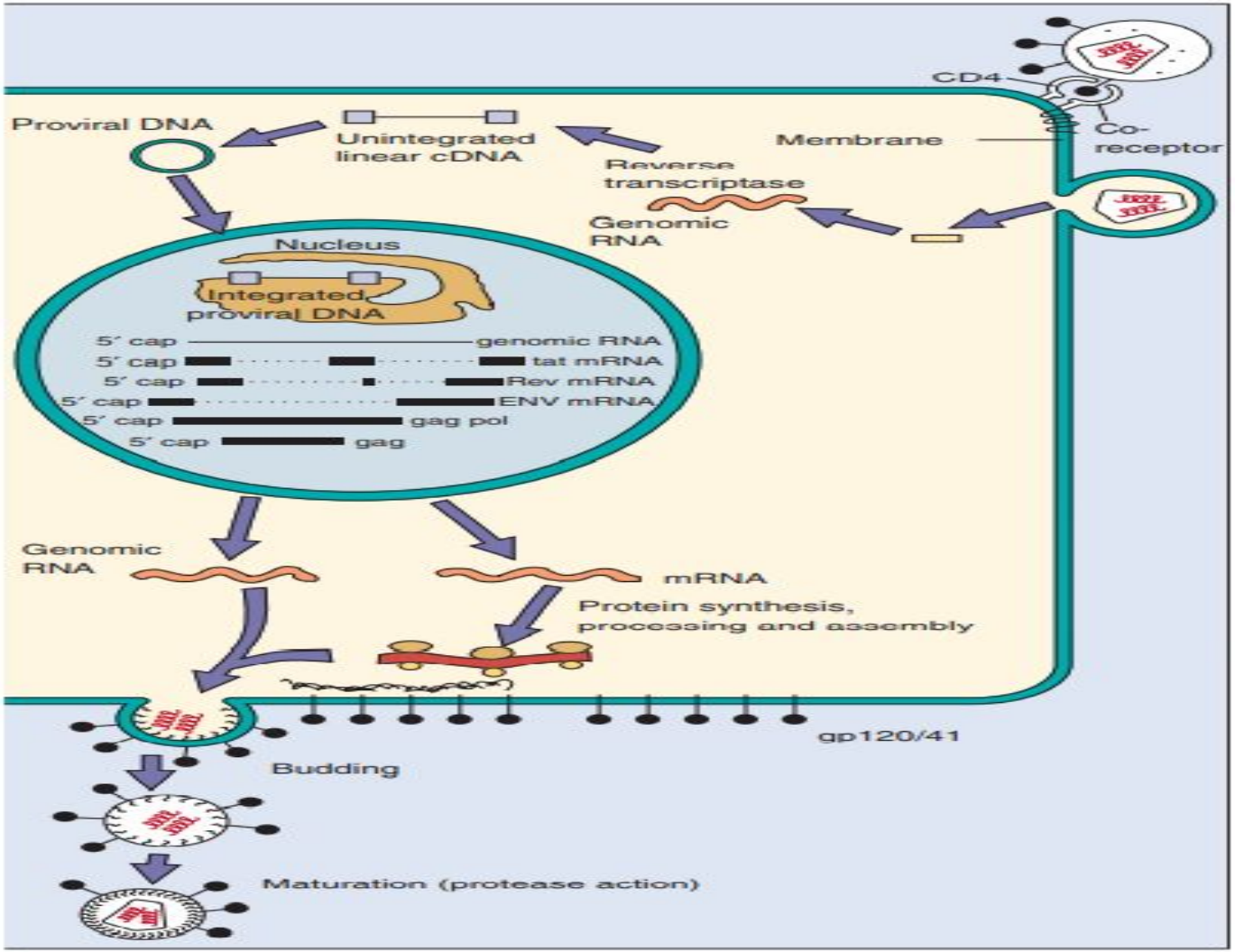
The provirus **integrates** randomly into the host chromosome and becomes a cellular gene.

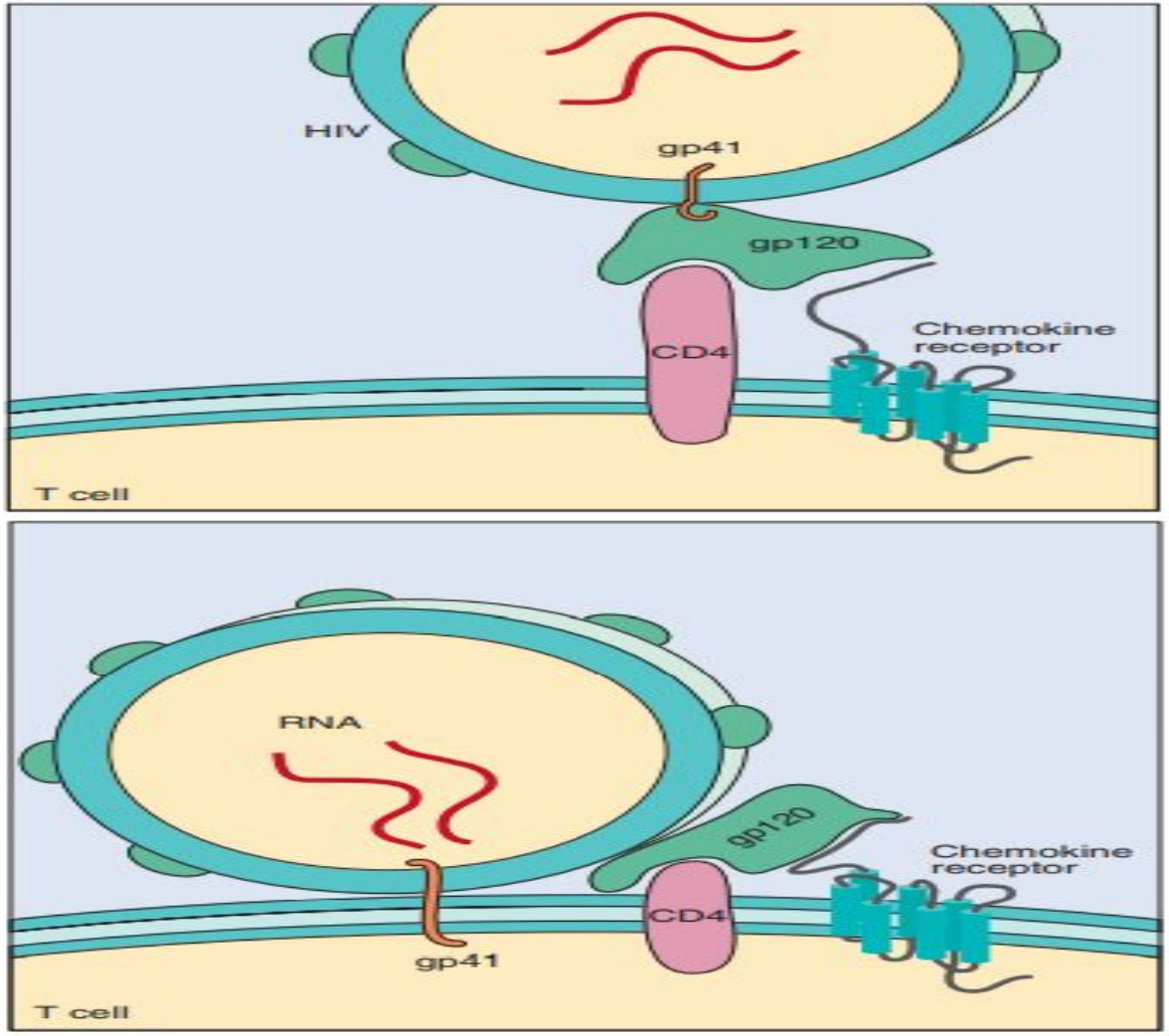
Transcription of the genome is regulated by the interaction of host transcription factors with promoter and enhancer elements in the long terminal repeat portion of the genome.

Simple retroviruses encode *gag, pol,* and *env* genes. **Complex viruses** also encode accessory genes (e.g., *tat, rev, nef, vif,* and *vpu* for HIV).

Virus assembles and buds from the plasma membrane.

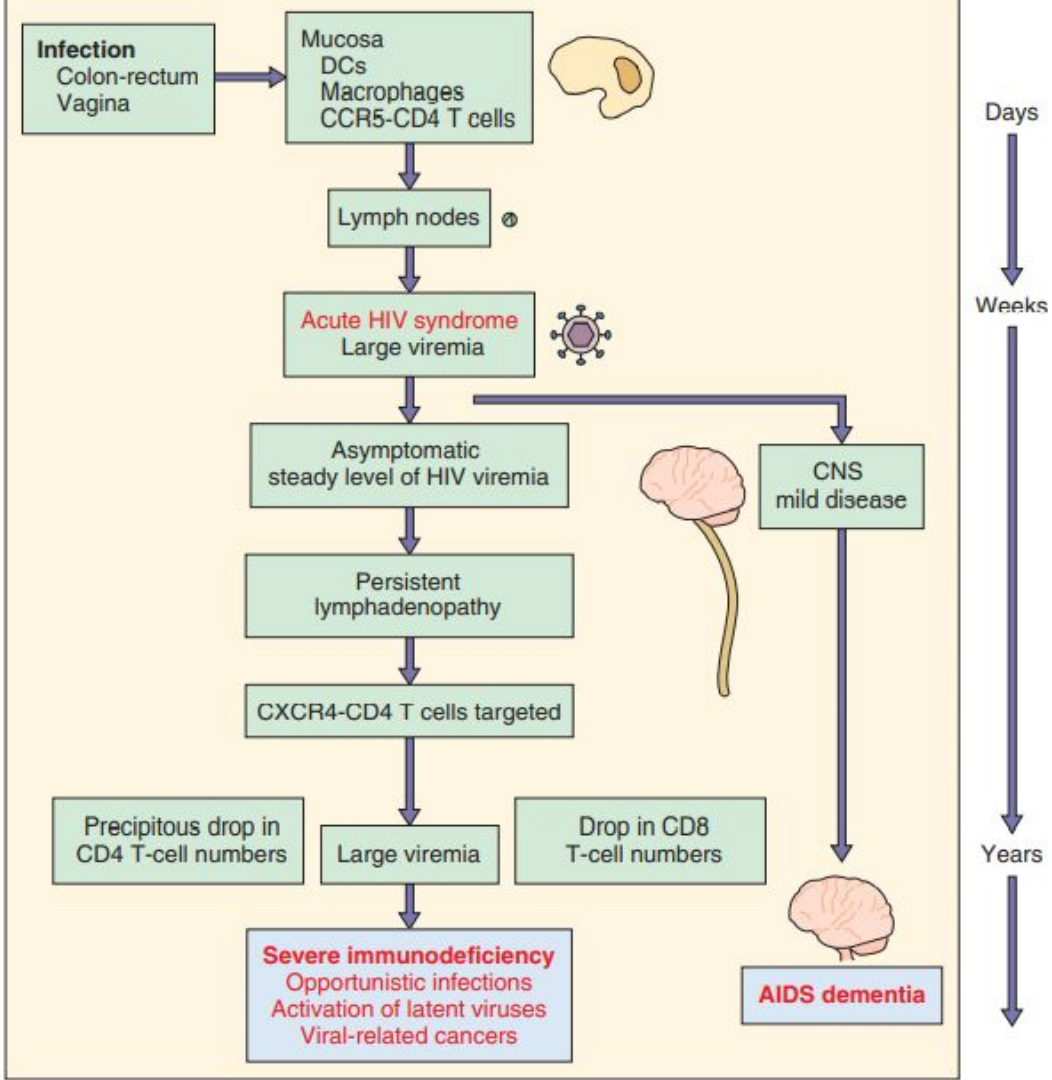
Final morphogenesis of HIV *requires* protease cleavage of Gag and Gag-Pol polypeptides after envelopment.


CD4
Co-
receptor
Membrane
Proviral DNA
Unintegrated
linear cDNA
Reverse
transcriptase
Genomic
RNA
Nucleus
Integrated
proviral DNA
5′ cap
genomic RNA
5′ cap
tat mRNA
5′ cap
Rev mRNA
5′ cap
ENV mRNA
5′ cap
gag pol
5′ cap
gag
Genomic
RNA
mRNA
Protein synthesis,
processing and assembly
gp120/41
Budding
Maturation (protease action)


HIV
gp41
gp120
CD4
Chemokine receptor
T cell
RNA
gp120
Chemokine receptor
CD4
gp41
T cell

Pathogenesis and Immunity

The major determinant in the pathogenesis and disease caused by HIV is the virus tropism for CD4-expressing T cells and myeloid cells . HIV induced immunosuppression (AIDS) results from a reduction in the number of CD4 T cells, which decimates the ability to activate and control innate and immune responses. During sexual transmission, HIV infects a mucosal surface, enters, and rapidly infects cells of the mucosa associated lymphoid tissue (MALT), including the intestine. The initial stages of infection are mediated by M-tropic viruses that bind to CD4 and the CCR5 chemokine receptors on dendritic and other monocyte-macrophage lineage cells, as well as memory, TH1, most intestine-associated T cells, and other CD4 T cells. Individuals who are deficient in the CCR5 receptor are also resistant to HIV infection, and CCR5 binding is a target for an antiviral drug


Infection
Colon-rectum
Vagina
Mucosa
DCs
Macrophages
CCR5-CD4 T cells
Lymph nodes
Acute HIV syndrome
Large viremia
Asymptomatic
steady level of HIV viremia
CNS
mild disease
Persistent
lymphadenopathy
CXCR4-CD4 T cells targeted
Precipitous drop in
CD4 T-cell numbers
Large viremia
Drop in CD8
T-cell numbers
Severe immunodeficiency
Opportunistic infections
Activation of latent viruses
Viral-related cancers
AIDS dementia
Days
Weeks
Years

Box 54-2 Disease Mechanisms of Human Immunodeficiency Virus

Human immunodeficiency virus primarily infects CD4 T cells and cells of the myeloid lineage (e.g., monocytes, macrophages, alveolar macrophages of the lung, dendritic cells, and microglial cells of the brain).

Virus causes lytic infection of activated permissive CD4 T cells and induces apoptosis-like death of nonpermissive CD4 T cells.

Virus causes persistent low-level productive and latent infection of myeloid lineage cells and memory T cells.

Virus causes syncytia formation, with cells expressing large amounts of CD4 antigen (T cells); subsequent lysis of the cells occurs.

Virus alters T-cell, dendritic cell, and macrophage cell function.

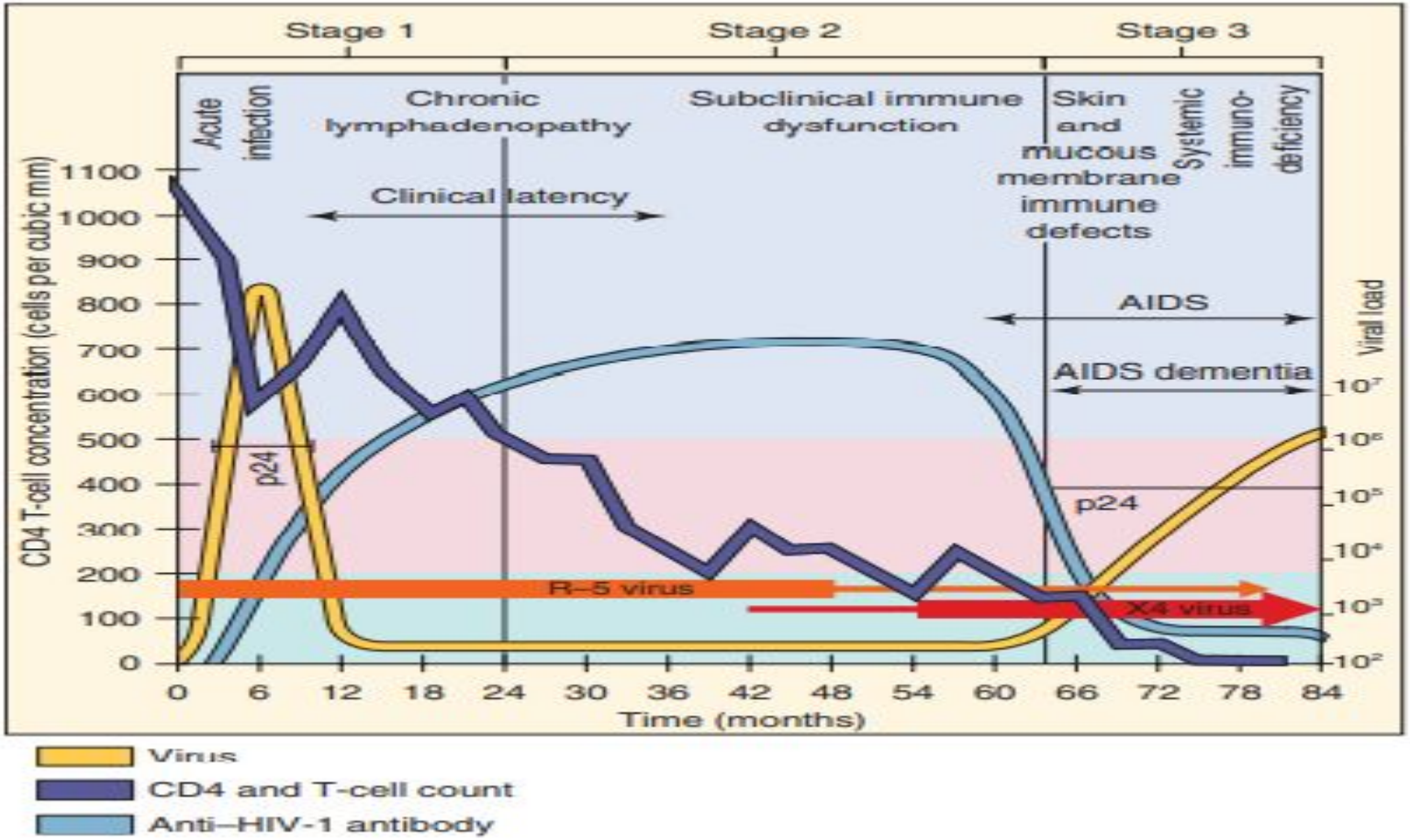
Virus reduces CD4 T-cell numbers and helper-cell activation of CD8 T-cell, macrophage, and other cell functions.

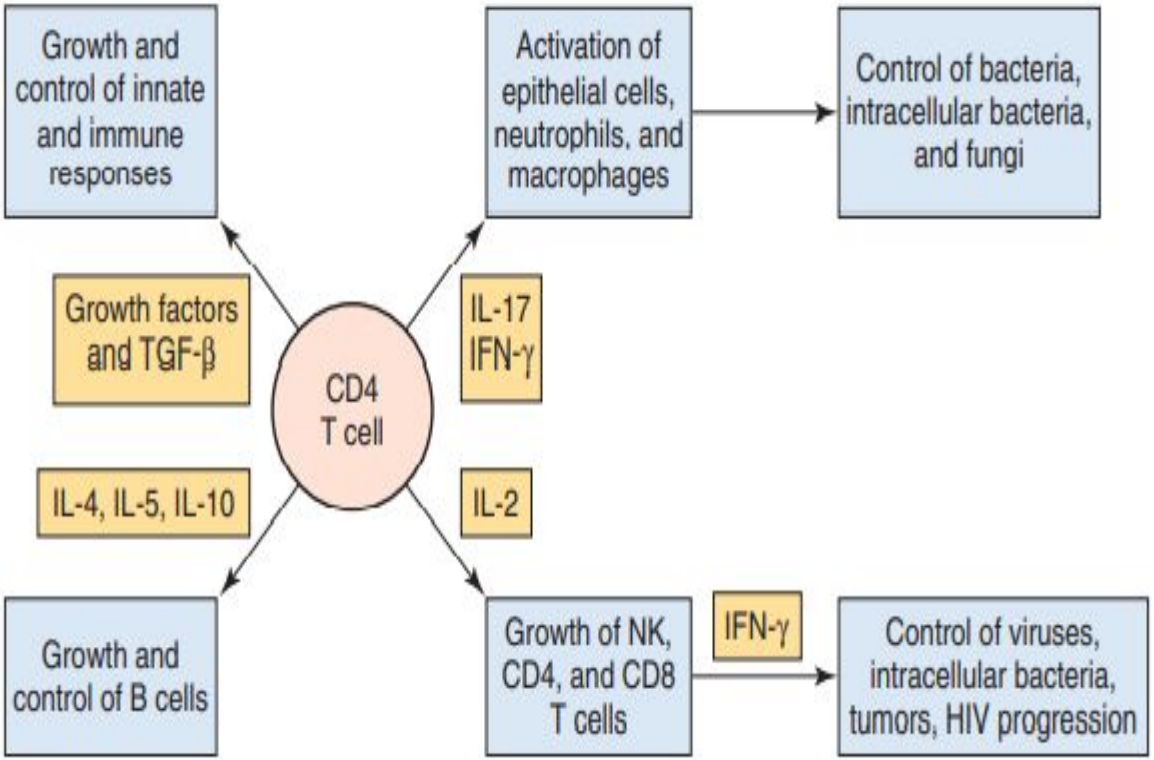
CD8 T-cell numbers and macrophage function decrease.

Infected microglial cells disrupt neuronal function.

Table 54-3 Means of Human Immunodeficiency Virus Escape from the Immune System

Characteristic	Function
Infection of dendritic cells, macrophages, and CD4 T helper cells	Loss of activators and controllers of the immune system
Antigenic drift (via mutation) of gp120	Evasion of antibody detection
Heavy glycosylation of gp120	Evasion of antibody detection
Direct cell-to-cell spread and syncytia formation	Evasion of antibody detection


Stage 1
Stage 2
Stage 3
Acute infection
Chronic lymphadenopathy
Subclinical immune dysfunction
Skin and mucous membrane immune defects
Systemic immuno-deficiency
Clinical latency
AIDS
AIDS dementia
p24
p24
R–5 virus
X4 virus
CD4 T-cell concentration (cells per cubic mm)
Viral load
1100
1000
900
800
700
600
500
400
300
200
100
0
10^7
10^6
10^5
10^4
10^3
10^2
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84
Time (months)
Virus
CD4 and T-cell count
Anti–HIV-1 antibody


Growth and control of innate and immune responses
Activation of epithelial cells, neutrophils, and macrophages
Control of bacteria, intracellular bacteria, and fungi
Growth factors and TGF-β
IL-17
IFN-γ
CD4 T cell
IL-4, IL-5, IL-10
IL-2
Growth and control of B cells
Growth of NK, CD4, and CD8 T cells
IFN-γ
Control of viruses, intracellular bacteria, tumors, HIV progression

Box 54-3 Epidemiology of Human Immunodeficiency Virus (HIV) Infections

Disease Viral Factors

Enveloped virus is easily inactivated and must be transmitted in body fluids.
Disease has a long prodromal period.
Virus can be shed before development of identifiable symptoms.

Transmission

Virus is present in blood, semen, and vaginal secretions.
See Table 54-4 for modes of transmission.

Who Is at Risk?

Intravenous drug abusers, sexually active people with many partners (MSM and heterosexual), prostitutes, newborns of HIV-positive mothers, sexual partners of infected individuals
Blood and organ transplant recipients and hemophiliacs treated before 1985 (before prescreening programs)

Geography/Season

There is an expanding epidemic worldwide.
There is no seasonal incidence.

Modes of Control

Antiviral drugs limit progression of disease.
Vaccines for prevention and treatment are in trials.
Safe, monogamous sex helps limit spread.
Sterile injection needles should be used.
Circumcision
Large-scale screening programs should be established for blood for transfusions, organs for transplants, and clotting factors used by hemophiliacs.

Table 54-4 Transmission of Human Immunodeficiency Virus Infection

Routes	Specific Transmission
Known Routes of Transmission	
Inoculation in blood	Transfusion of blood and blood products
	Needle sharing among intravenous drug abusers
	Needlestick, open wound, and mucous membrane exposure in health care workers
	Tattoo needles
Sexual transmission	Anal and vaginal intercourse
Perinatal transmission	Intrauterine transmission
	Peripartum transmission
	Breast milk
Routes Not Involved in Transmission	
Close personal contact	Household members
	Health care workers not exposed to blood

Table 54-5 Indicator Diseases of Acquired Immunodeficiency Syndrome*

Infection	Disease (Selected)
Opportunistic Infections	
Protozoal	Toxoplasmosis of the brain
	Cryptosporidiosis with diarrhea
	Isosporiasis with diarrhea
Fungal	Candidiasis of the esophagus, trachea, and lungs
	Pneumocystis jirovecii (previously called *Pneumocystis carinii*) pneumonia
	Cryptococcosis (extrapulmonary)
	Histoplasmosis (disseminated)
	Coccidioidomycosis (disseminated)
Viral	Cytomegalovirus disease
	Herpes simplex virus infection (persistent or disseminated)
	Progressive multifocal leukoencephalopathy (JC virus)
	Hairy leukoplakia caused by Epstein-Barr virus
Bacterial	*Mycobacterium avium-intracellulare* complex (disseminated)
	Any "atypical" mycobacterial disease
	Extrapulmonary tuberculosis
	Salmonella septicemia (recurrent)
	Pyogenic bacterial infections (multiple or recurrent)
Opportunistic Neoplasias	Kaposi sarcoma
	Primary lymphoma of the brain
	Hodgkin and non-Hodgkin lymphomas
	HPV-associated cancers
Others	HIV wasting syndrome
	HIV encephalopathy
	Lymphoid interstitial pneumonia

Modified from Belshe RB: *Textbook of human virology*, ed 2, St Louis, 1991, Mosby.

HIV, Human immunodeficiency virus; *HPV*, human papillomavirus.

*Manifestations of HIV infection—defining AIDS according to criteria of Centers for Disease Control and Prevention.

Table 54-6 Laboratory Analysis for Human Immunodeficiency Virus

Test	Purpose
Serology	
Enzyme-linked immunosorbent assay	Initial screening
Latex agglutination	Initial screening
Rapid oral antibody test	Initial screening
Western blot analysis (for antibody)	Confirmation test
Virion RNA RT-PCR	Detection of virus in blood
Real-time RT-PCR	Quantitation of virus in blood
Branched-chain DNA	Quantitation of virus in blood
p24 antigen	Early marker of infection
Isolation of virus	Test not readily available
CD4 T-cell counts, CD4:CD8 T-cell ratio	Indicators of HIV disease

DNA, Deoxyribonucleic acid; *HIV*, human immunodeficiency virus; *RNA*, ribonucleic acid; *RT-PCR*, reverse transcriptase polymerase chain reaction.

Box 54-5 Potential Antiviral Therapies for Human Immunodeficiency Virus Infection

Nucleoside Analog Reverse Transcriptase Inhibitors (NRTIs)
Azidothymidine (AZT) (Zidovudine) [Retrovir]
Dideoxyinosine (ddI) (Didanosine) [Videx]
d4T (Stavudine) [Zerit]
3TC (Lamivudine) [Epivir]
Tenofovir disoproxil fumarate (adenosine class) [Viread]
ABC (Abacavir) [Ziagen]
FTC (Emtricitabine) [Emtriva]

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)
Nevirapine [Viramune]
Delavirdine [Rescriptor]
Efavirenz [Sustiva]
Etravirene [Intelence]
Rilpivirine [Edurant]

Protease Inhibitors (PIs)
Tipranavir [Aptivus]
Darunavir [Prezista]
Ritonavir [Norvir]
Indinavir [Crixivan]
Nelfinavir [Viracept]
Fosamprenavir [Lexia]
Atazanavir [Reyataz]

Binding and Fusion Inhibitors
CCR5 inhibitor (maraviroc) [Selzentry]
T-20 (enfuvirtide) [Fuzeon]

Integrase Inhibitor
Raltegravir [Isentress]

Examples of Highly Active Antiretroviral Therapy (HAART)
Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) [Atripla]*
Abacavir/zidovudine/lamivudine [Trizivir]
Dolutegravir/abacavir/lamivudine [Triumeq]*
Emtricitabine, rilpivirine, and tenofovir disoproxil fumarate [Complera]*
Elvitegravir/cobicistat/tenofovir/emtricitabine [Stribild]*