Immunology and AIDS

- Human Immunodeficiency Virus type 1 (HIV-1)
- The etiologic agent of acquired immunodeficiency syndrome (AIDS)
- Probably originated in Sub-saharan Africa after crossing species barrier from Chimpanzees
- Three major groups for HIV-1
  - M = main
  - O = outlier
  - N = non-M and non-O
- Three independent crossings from chimps to humans

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Immunology and AIDS

- HIV-1
- Group M subtypes all originated form a common ancestor virus which is believed to have existed before 1940
  - A,B,C,D,F1,F2,G,H,I,J,K
- These organisms form a CLADE
  - Share common features and are derived from a common ancestor

- HIV-2
- is most closely related to a type of simian imunodeficiency virus (SIV) that occurs in sooty mangabey monkeys
- Probably crossed to humans from these primates
- Similar disease as HIV-1 but milder course and this isolate has only a limited spread in the population

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Immunology and AIDS

- HIV-1 infection and symptoms
- Initial infection
- Acute flu-like illness develops within several weeks of infection
- Usually clinically asymptomatic for an average of 10 years post infection
  - This stage can be as short as 2 years and long as 20 years
- Symptoms of AIDS then emerge
- Declining CD4+ T cells mark the development of AIDS
- Development of various infections and malignancies

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HIV viral structure

- Family Retroviridae
- Viruses that have and use reverse transcriptase
- Genus Lentiviridae
- A protein bullet shaped capsid
  - P24 gag protein
  - Two duplicate strands of RNA
  - Nucleocapsid proteins p7 and p9, reverse transcriptase enzyme, Rnase H, integrase enzyme, and protease enzyme

- surrounded by a spherical envelope of host derived membrane and membrane components
  - Envelope gylcoproteins gp41 and gp120

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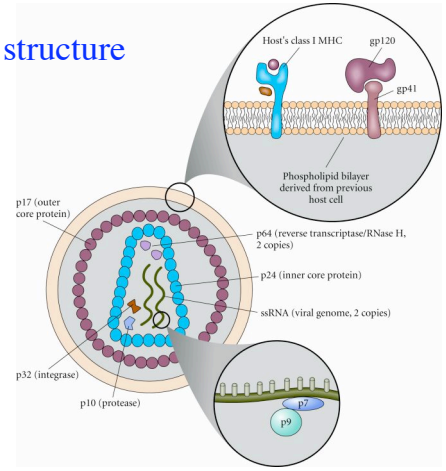
HIV viral structure



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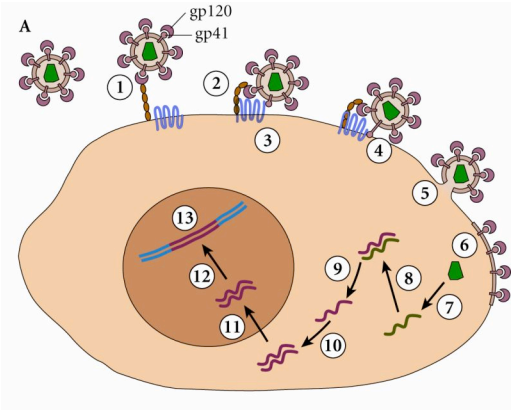
Life Cycle of HIV



- Infection by binding CD4 and gp120
- Host chemokine receptor CXCR4 or CCR5
- Virion host cell fusion
- Viral capsid entry into host cell
- Freeing of viral genome
- RNA to cDNA via RT
- viral DNA replication by host cell
- Integration of vral ds DNA into host genome

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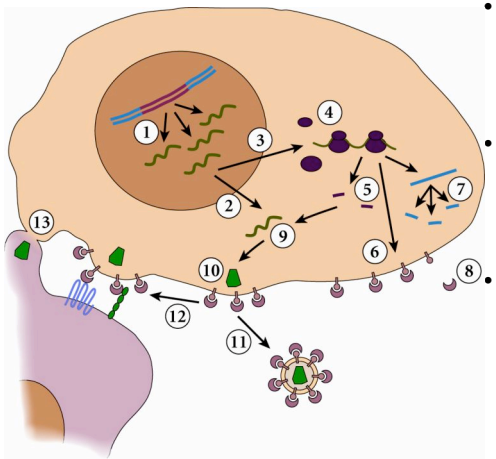
HIV Activation and Replication



- Transcription and translation of viral genes using host cell machinery
- Some packaged into new virions some transproted to cell surface
- New virions can emerge from cell or directly infect neighboring cell without forming a viral particle

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Animal models of HIV

- No really good animal model for disease
- HIV-1 only infects and causes AIDS in human cells
- HIV can cause infection in Chimps but not disease
- SIV can infect and cause disease in rhesus monkeys
- Not natural hosts and so develop an AIDS-like illness with similar pathogenesis (natural hosts are not harmed)
- Hybrid strains of SIV and HIV have been developed (SHIV) that cause disease and AIDS-like illness in monkeys
- Developing transgenic mice that express human CD4 and coreceptors for HIV infection

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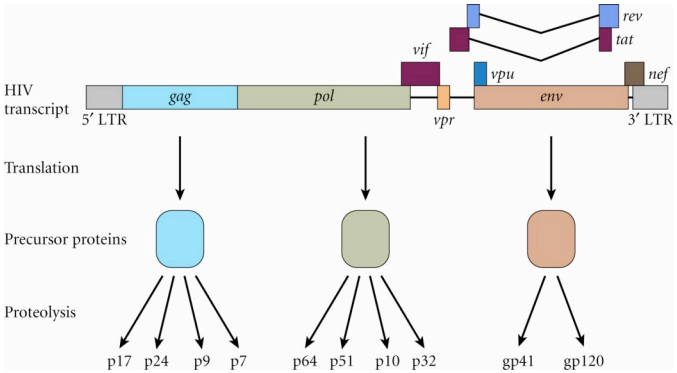
HIV-1 structural genes



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HIV Pathogenesis

- No longer thought to be a long period of viral latency
- The entire course of infection is the interplay of continuous dynamic viral replication and host responses
- Course of infection may be considered several stages based on the evolution of virologic and host parameters Including:
  - the concentration of virus in the blood,
  - the CD4+ T cell counts,
  - and antiviral immune responses.

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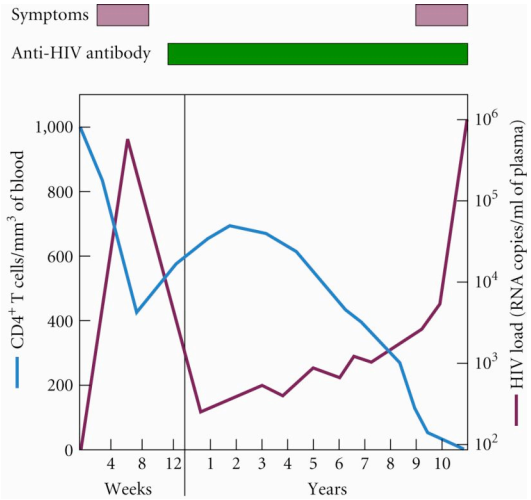

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Pathogenesis: Acute Phase

- Exposure to HIV-1
- Mucosal exposure leads to infection of DCs (CD4+),
- but no viral replication occurs in DCs
- DCs move to lymph nodes and expose T cells (CD4+)
- CD4+ T cells are infected and activated
- Vigorous HIV-1 replication in activated T cells
- Infection spreads systemically
- Explosive rate of infection and plasma viremia is due to lack of immune response
- Mononucleosis-like illness
- No antibodies to HIV-1 but HIV-1 DNA/RNA can be detected
- Illness symptoms are self limited and often go undiagnosed

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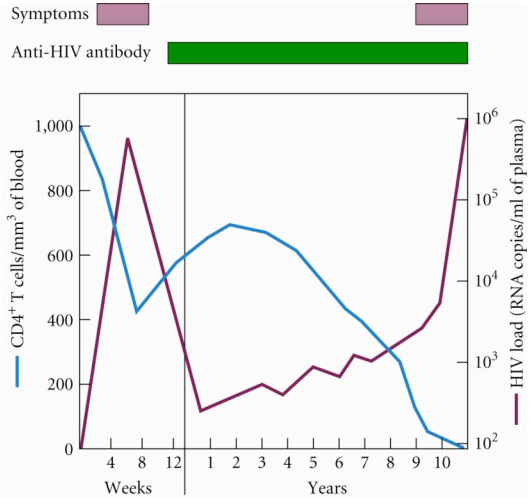

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Pathogenesis: Chronic Asymptomatic Infection

- Marked by ~stable levels of viremia and almost normal CD4+ T cell counts
- CD4+ T cell counts slowly decline but patient is relatively asymptomatic
- Essentially a dynamic equilibrium between virus and immune system
- PCR based detection shows that the majority of individuals have stable viremia
- Result of vigorous ongoing production and destruction of virus
- CD4+ T cells are produced and killed in large numbers
- Estimated $1X10^{10}$ viral particles are produced and cleared DAILY
  - 10,000,000,000 = 10 BILLION viral particles

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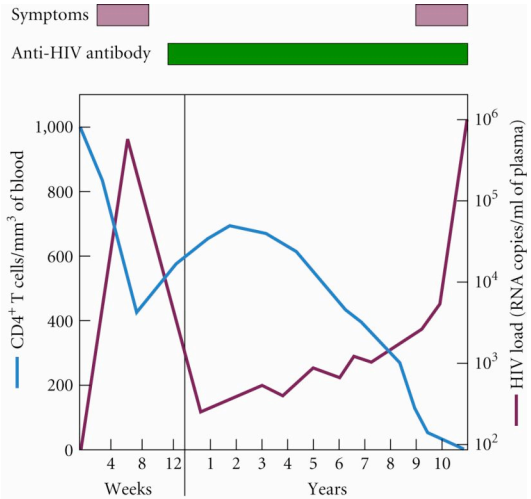

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Pathogenesis: Late Infection

- Rapid and progressive decline in CD4+ T cells
- Rapid and progressive increase in viral load (viremia)
- Accelerated phase usually begins after the CD4+ T cell count has dropped to ~ 500 cells per cubic milimeter (mm^3)
- Clinical symptoms often develop at this phase
- Fevers, sweats, enlarged lymph nodes, weight loss
- Risk of opportunistic infections increases
- At ~200 CD4+ T cells per mm^3 AIDS ensues
- The cause for the progressive failure of the immune system is unclear
- Loss of HIV-1 containment leads to loss of CD4+ T cells
- TH1 bias in early infection switches to TH2 bias in Late infection
- Cause or effect of Late phase?

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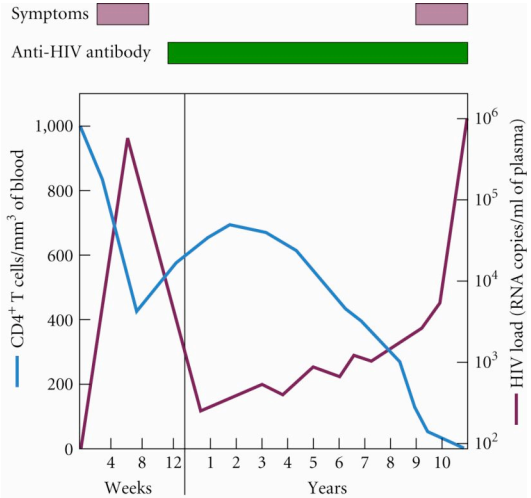

Immune Defects Due to HIV-1 Infection

- Almost all aspects of immunity are affected as the disease progresses
- Loss of CMI and increased susceptibility to intracellular pathogens
- Loss of Humoral immunity = no specific antibody responses
- Innate immune system is also damaged

Immune Defects Due to HIV-1 Infection
CD4+ T cell loss

- Both naive and memory cells are lost

Table 22.1 Mechanisms of leukopenia caused by chronic HIV-1 infection

Type of infection	Cellular effect	Molecular bases
Direct infection	Necrosis	
	Apoptosis	Aberrant signaling by gp120 Viral protein (Tat, Vpr?)
	Immune clearance	Cytotoxic T cells Antibody-mediated
Bystander cell loss	Syncytium formation	
	Free gp120 binding	Aberrant signaling Immune clearance (antibody)
	Superantigen	
Decreased production	Stem cell infection	
	Thymocyte gp120 binding	
	Loss of antigen-presenting cells	

Immune Defects Due to HIV-1 Infection
Antigen Presenting Cells (APCs)

- APCs = monocytes/macrophages and Dendritic cells (DCs) can be infected
- Numbers decrease during infection
- Loss of DCs probably contributes to loss of CMI
- Loss of Macrophage presentation probably contributes to loss of humoral immunity

Immune Defects Due to HIV-1 Infection
B cells

- B cell hyperreactivity
- polyclonal hypergammaglobulinemia
  - Too many antibodies of all specificities
- Terminal differentiation to plasma cells seems to occur without appropriate signals
  - Nonspecific polyclonal antibody production
- Consequences include autoimmunity, impaired switching, increased incidence of B cell lymphomas due to chromic activation

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Immune Defects Due to HIV-1 Infection
CD8+ T cells

- Loss of CD8+ cell functions (CTL function) and consequent loss of CMI
- Dependent on CD4+ helper T cells that are no longer around in significant numbers
- Loss of DCs also may contribute to nonresponsiveness of CD8+ T cells

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Immune Defects Due to HIV-1 Infection
Other Cell Types

- Pluripotent Stem cells can be infected with HIV-1 in vitro
- In vivo role is unclear
- Loss of stem cells could contribute to depletion of all immune cell types
- Natural killer cells have decreased cytolytic activity although nmumbers remain stable.
  - Loss of IFN-gamma stimulation?
- Neutrophils exhibit defective phagocytosis and chemotaxis

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Immune Responses to HIV-1 Infection

- CD4+ T cells that respond specifically to HIV-1 antigens
- CD8+ CTLs that respond specifically to HIV-1 antigens
  - Up to 14 different viral antigens in a single individual
    - Many more than other chronic viral infections
  - Some Multiply exposed but uninfected individuals have detectable CTL responses to HIV-1 but no circulating Antibodies
    - Suggests that CMI cleared infection before advent of humoral response
- Antiviral Cytokines produced by CD8+ T cells
  - See next figure
- Antiviral Antibodies have activity against replication in vitro are called neutralizing antibodies
  - In vivo affects on HIV infection are unknown

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Antiviral Cytokines Produced by CD8+ T Cells

Table 22.2 Secreted factors that inhibit HIV-1 infection

Factor	Example	Mechanism
Chemokines	RANTES, MIP-1α, MIP-1β, MCP-2	Competition with virus for binding to CCR5 viral coreceptor
	SDF-1α, SDF-1β	Competition with virus for binding to CXCR4 viral coreceptor
Other secreted factors	CAF	Inhibition of LTR-mediated viral transcription

Evasion of Immune Responses by HIV-1:

- Escape from Antiviral Cytokines?
  - Observed in vitro, but not known whether HIV-1 can escape effects in vivo
- Escape from Neutralizing Antibodies?
  - Gp120 CD4+ binding site is hidden in vivo
  - Gp120 is highly glycosylated - reducing immunogenicity
  - Virions hiding in folicular Dendritic Cells in lymph nodes
    - Site for latent reservoir of virus?
- Escape from CTLs
  - See next slide

Evasion of Immune Responses by HIV-1:

Table 22.3 Mechanisms by which HIV-1 evades host immunity

Mechanism		Arm of immunity affected
Prevention of T-cell help		CTLs and B cells
Antigenic drift		CTLs and B cells
Reduction of MHC class I expression		CTLs
Latent reservoir	CD4+ memory cells	All
Infection of immune-privileged sites	CNS	All

Pharmacologic Therapy for HIV-1 Infection

- Nucleoside RT inhibitors
  - First class of drugs , AZT, nucleoside analogs
  - Chain termination occurs when RT incorporates these
    - Prevent production of viral DNA
  - When used individually, resistance occurs rapidly
- Non-nucleoside RT inhibitors
  - Bind and inactivate RT enzyme
  - When used individually, resistance occurs rapidly
- Protease inhibitors
  - Bind and inactivate viral protease needed for processing of precursor proteins to functional proteins
  - Forms nonviable virions without viral protease
- Viral-host cell fusion inhibitors
  - Peptides that block viral entry into cells via gp41

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