

Secondary Immune Deficiencies.

Learning Objectives:

- The causes of acquired immune deficiency.
- A relative immune compromise occurring with normal aging.
- Molecular Biology of HIV and AIDS
- Cellular immune dysfunction due to AIDS.
- Immune response to HIV infection.
- Therapeutic and vaccine targets in HIV infection, and the draw backs.

Introduction.

- Acquired immune deficiencies may be caused by **infection** with **a virus**.
- Also, a relative immune compromise occurs with **normal aging**.
- Cancer, chronic disease, severe protein loss, liver disease- all cause a general diminution of the immune response.

- Some are due to decreases in **systemic immune globulins** (protein wasting diseases, malnutrition);
- Others are probably due to **systemic effects of cytokines** (some viral diseases, cancer);
- Still others are due to **unknown cause** (liver disease).

- Perhaps the most frequently overlooked is the role of the physician in producing immune compromise.
- Immunological suppressants such as **corticosteroids**, **chemotherapy**, **some potent antimicrobials**, and **transplant medications** can produce profound immune deficiencies that may lead to the death of the individual.

- The lecture will concentrate on a disease that produces profound immune deficiency through a relatively selective **depletion of CD4+ lymphocytes**.
- AIDS, first described in 1981 and, has been the subject of countless research publications and articles.

Human Immunodeficiency Virus.

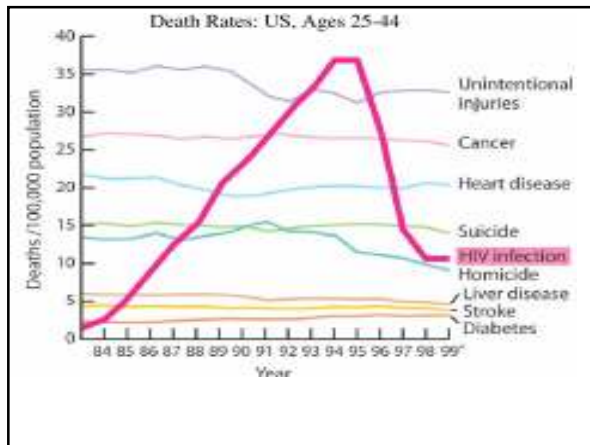
- The human immunodeficiency virus (HIV) is the **causative agent in the acquired immune deficiency syndrome** (AIDS).
- Need to be conversant with molecular biology of HIV as a virus.

**Acquired Immune Deficiency Syndrome:
(AIDS).**



1981: A new disease

- Demographic groups-- homosexuals, IV drug abusers, hemophiliacs
- Infections with opportunistic organisms
- Unusual cancers-- CNS lymphoma, Kaposi's sarcoma
- Decreased CD4⁺ T cells



HIV: Acute and Chronic Disease

- Acute infection-- flu-like illness with fever, weakness, lymphadenopathy
- Latency-- period of years during which infection is active but symptoms are few
- Chronic disease-- diminished CD4 T cell count contributes to immunodeficiency and secondary infection with opportunistic organisms

Opportunistic Infections

- Pneumocystis carinii pneumonia (PCP)
- HIV-associated wasting syndrome
- TB (tuberculosis)
- MAI (an atypical mycobacterium)
- HSV
- Bacterial pneumonias
- Toxoplasmosis
- CMV
- Other things-- dementia, Kaposi sarcoma

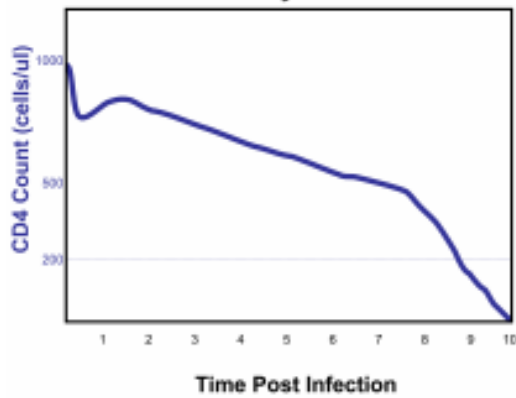
Diagnosis

- ELISA for anti-HIV antibodies
- Western blot using patient serum against viral proteins
- PCR for viral RNA in serum

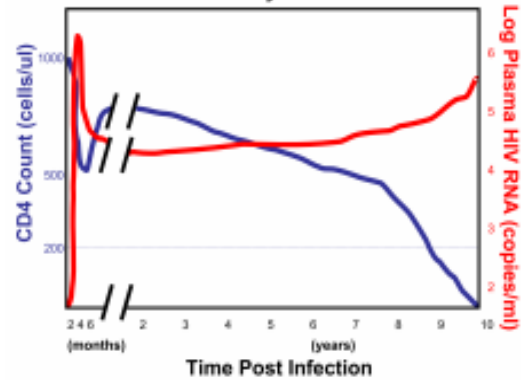
Modes of Transmission

- Blood and body fluids
- Sexual transmission: male:male >>> male:female
- IVDA
- During birth or nursing

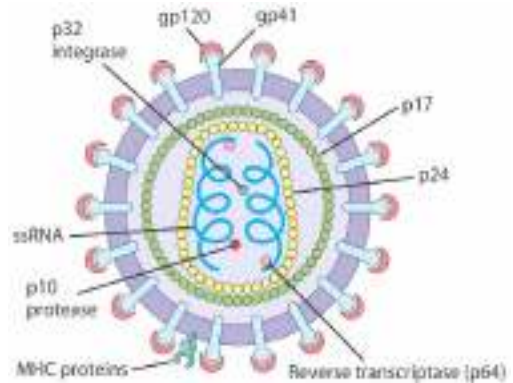
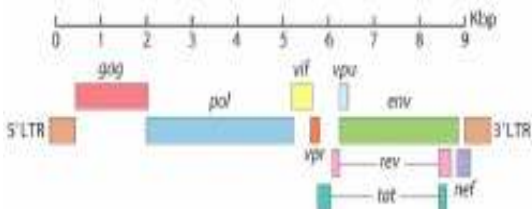
Natural History of HIV Infection



Natural History of HIV Infection



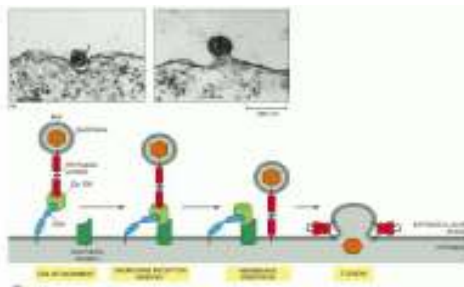
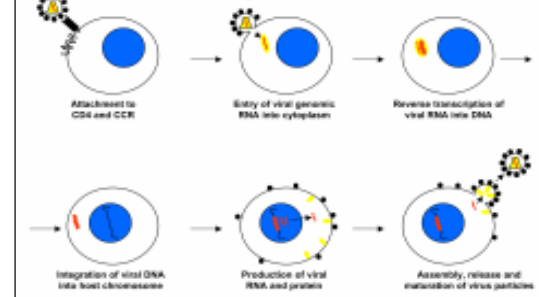
HIV Genome.



HIV Functional gene products.

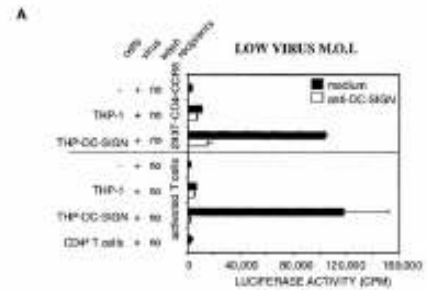
Gene	Protein product	Function of encoded proteins
gag	SAZto precursor	Nucleocapsid proteins: Forms outer cone protein layer Forms inner cone protein layer Is component of nucleoid core Binds directly to genomic DNA Envelopes glycoproteins
	p17	
	p24	
	p9	
pol	RTS-RTS precursor	Is transmembrane protein associated with gp120 and required for fusion Phosphatidylserine envelope and binds CD4
	gp120	
env	Prp2/3/4/5	Assembles Has reverse transcriptase and RNase activity Has reverse transcriptase activity Is lentivirus that shows gagpoxvirus to integrate Regulatory proteins: Strongly activates transcription of proviral DNA Allows export of unspliced and singly spliced mRNAs from nucleus
	p66	
	p51	
	p15	
	p12	
tat	p14	Auxiliary proteins: Downregulates host cell class I MHC and CD4 Is required for efficient viral assembly and budding Promotes extracellular release of viral particles, degrades CD4 on EB
	p19	
vif	p27	Promotes maturation and infectivity of viral particle Promotes nuclear localization of preintegration complex, inhibits cell division
	p33	
vpr	p18	
	p15	

Life Cycle of HIV-1



R5 and X4 strains of HIV differ in their co-receptor usage.

DC-SIGN and T cell infection



(Geijtenbeek et al. 2000)

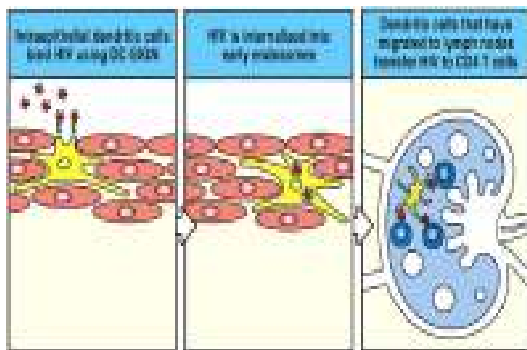
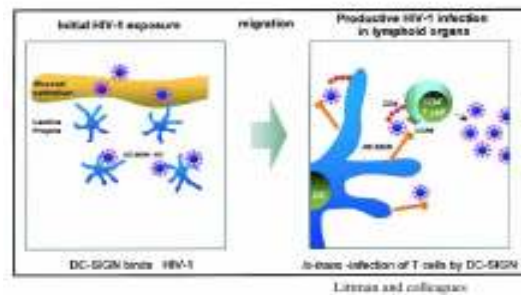


Figure 11-11 Immunology, An Introduction (© 2004)

DC-SIGN carries HIV to LN's to infect T cells



The immune response to HIV

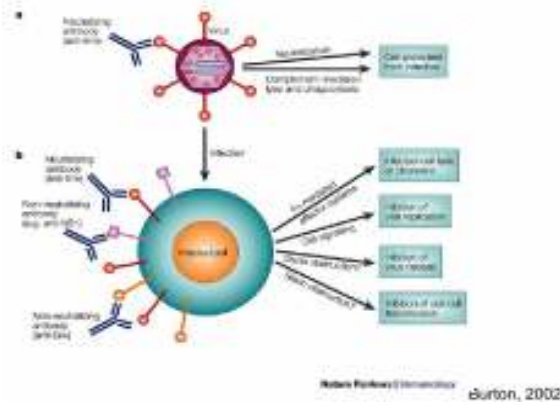
- Antibodies (some neutralize)
- Cytotoxic T Cells
- Complement
- NK Cells

The antibody response to HIV

In HIV infection, antibodies to all major structural proteins of virion (gag, pol, env) are made, but only antibodies to env protein have the potential to be neutralizing. In fact, only a subset of anti-env antibodies are neutralizing.



Antiviral activities of antibodies



Neutralizing Antibodies

- Definition of neutralization - loss of infectivity following binding of antibody to virus particle.
- One of few effector functions mediated by antibodies alone.
- Only effector mechanism that can prevent infection
- Target antigen must be in virus but does not have to be virally encoded
- Target antigen must be exposed on surface of virion, although exposure can be transient

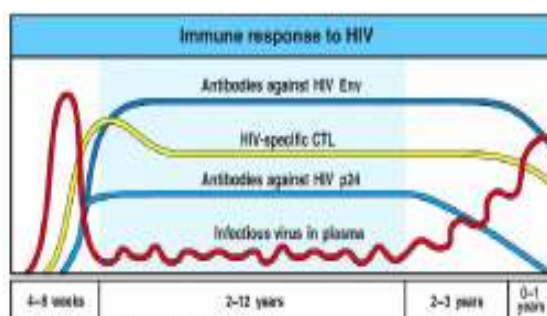


Figure 11.10 Immunology: An Introduction (© Garland Science 2015)

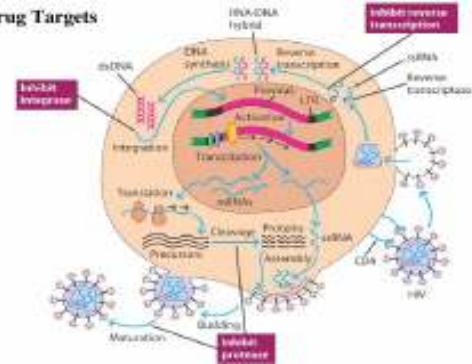
CD4+ T cell loss

- Destruction by HIV cytopathic effect
- Destruction by CD8+ cytotoxic T cells
- Dendritic cells carry HIV to lymph nodes
- Bystander effects
- Diminished production

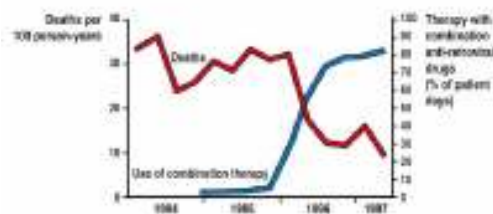
Immune Evasion by HIV

- Rapid mutation rate
- Nef protein suppresses class I MHC
- Switch from R5 to X4 strain co-receptor
- Depletion of T_H cells; ? Inhibition of T_C cells
- Latency

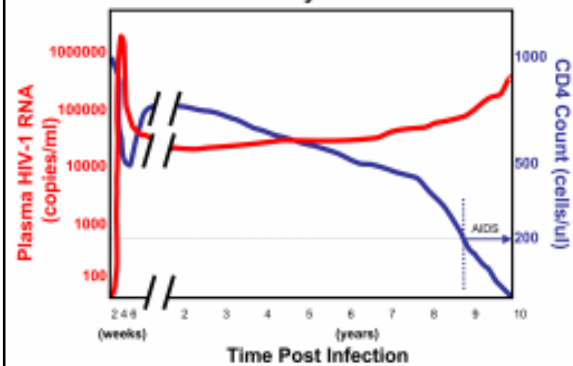
Drug Targets



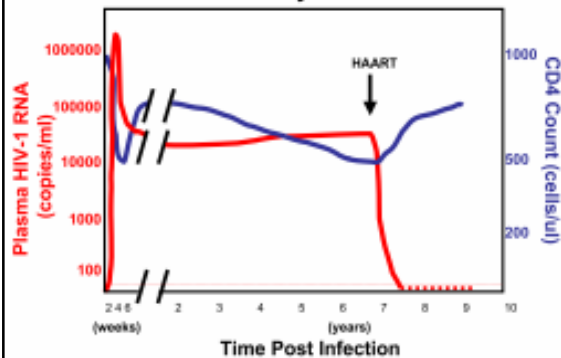
Major drop in mortality after introduction of HAART



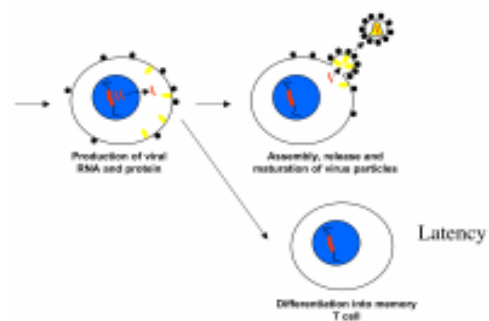
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Natural History of HIV Infection



Reservoir of latently infected cells



Vaccine Strategies

- Subunit vaccine-- recombinant protein plus adjuvant
- Attenuated virus vaccine-- like vaccinia for small pox
- Recombinant Virus vaccine
- DNA vaccine

Problems

- No ideal animal model
- No correlates of immune state
- Diversity of strains; mutation
- Ethics of live virus vaccine trials