

Immunodeficiency

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2005

Origins of Immunodeficiency

- **Primary or Congenital**
 - Inherited genetic defects in immune cell development or function, or inherited deficiency in a particular immune molecule
- **Secondary or acquired**
 - A loss of previously functional immunity due to infection, toxicity, radiation, splenectomy, aging, malnutrition, etc.

Infectious Consequences of Immunodeficiency

- Antibody deficiency, Phagocyte deficiencies, or Complement protein deficiencies are associated with recurrent infections with extracellular pyogenic bacteria (pneumonia, otitis media, skin infections)
- Deficiency in Cell-mediated immunity is associated with recurrent or chronic viral, fungal, or protozoal diseases.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	ADA deficiency	No T or B cells	General
	PNP deficiency	No T or B cells	General
	X-linked <i>scid</i> , γ_c chain deficiency	No T cells	General
	Autosomal <i>scid</i> DNA repair defect	No T or B cells	General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T and B cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott-Aldrich syndrome	X-linked; defective WASP gene	Defective anti-polysaccharide antibody and impaired T cell activation responses	Encapsulated extracellular bacteria
X-linked agammaglobulinemia	Loss of Btk tyrosine kinase	No B cells	Extracellular bacteria, viruses

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Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
X-linked hyper-IgM syndrome	Defective CD40 ligand	No isotype switching	Extracellular bacteria <i>Pneumocystis carinii</i> <i>Cryptosporidium parvum</i>
Common variable immunodeficiency	Unknown; MHC-linked	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially <i>Neisseria</i> spp.
Natural killer (NK) cell defect	Unknown	Loss of NK function	Herpes viruses
X-linked lymphoproliferative syndrome	SH2D1A mutant	Inability to control B cell growth	EBV-driven B cell tumors
Ataxia telangiectasia	Gene with PI 3-kinase homology	T cells reduced	Respiratory infections
Bloom's syndrome	Defective DNA helicase	T cells reduced Reduced antibody levels	Respiratory infections

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B cell Deficiencies

- **Congenital hypogammaglobulinemia**
 - Symptoms at 9 mo. to 2 yr of age
 - Treat with intravenous immunoglobulin (IVIG)
- **Hyper IgM: defective CD-40L expression**
- **Selective IgA deficiency**
 - Occurs in 1:600-1:800 people
 - Possible connection with increased sinopulmonary infections and allergies

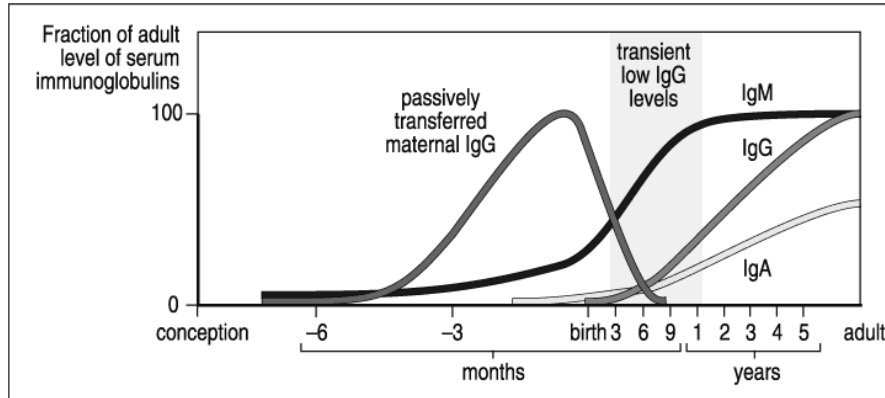


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T Cell Deficiencies

- **Congenital Thymic aplasia**
- **Chronic Mucocutaneous Candidiasis**

Severe Combined Immunodeficiency

- **X-linked SCID:**
 - Defect in IL-2 receptor
- **Swiss-Type SCID**
 - Adenosine deaminase deficiency
- **Bare Lymphocyte syndrome**
 - Absence of MHC Class II gene products

Phagocyte Deficiencies

- **Chronic Granulomatous Disease**
 - NADPH oxidase defect
- **Chediak -Higashi Syndrome**
 - Abnormal lysosome formation
- **Leukocyte Adhesion Deficiency**
 - Absence of leukocyte adhesion molecules

Complement Deficiencies

- **Single component deficiencies**
 - Example: C3 deficiency
- **Hereditary Angioedema**
 - C1 Inhibitor deficiency
- **C5,C6,C7,C8, or C9 deficiency**
 - Recurrent bacterial meningitis due defective membrane attack complex

Causes of Acquired Immunodeficiency

- **Cancer (immunoproliferative diseases)**
- **Cytotoxic drugs or radiation**
- **Malnutrition**
- **Splenectomy**
- **Immunosuppressive therapies**
- **Stress/emotions**
- **Aging (thymic atrophy)**
- **Infection**

Immunopathogenesis of HIV- Infection

- HIV infects and ultimately destroys CD4+ , CCR5+ or CXCR4+ T cells, monocytes, & dendritic cells.
- Primary HIV Infection: A vigorous immune response to HIV controls the primary infection. (clonal Cytotoxic T cells, suppressive chemokines, poorly neutralizing antibody)

Immunopathogenesis of HIV- Infection. (continued)

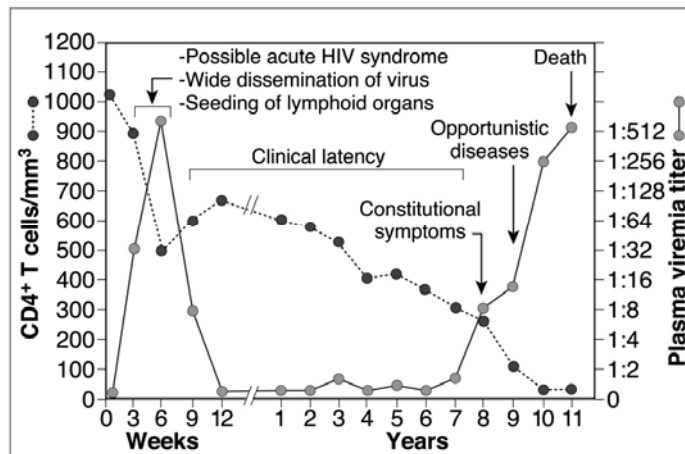
- Chronic Asymptomatic Phase: Viral trapping & replication in lymphoid tissues, **high rate turnover of virus and CD4 T cells**, **loss of CD4 functional help** to CTL and antibody responses, **destruction of lymph tissue**, **viral mutation** and escape from recognition, **exhaustion or viral inhibition of CD4 T cell renewal**.

Immunopathogenesis of HIV- Infection. (continued)

- Overt AIDS: CD4 count declines, viral load increases, opportunistic infections.

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Clinical course of HIV disease



From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 20-8a

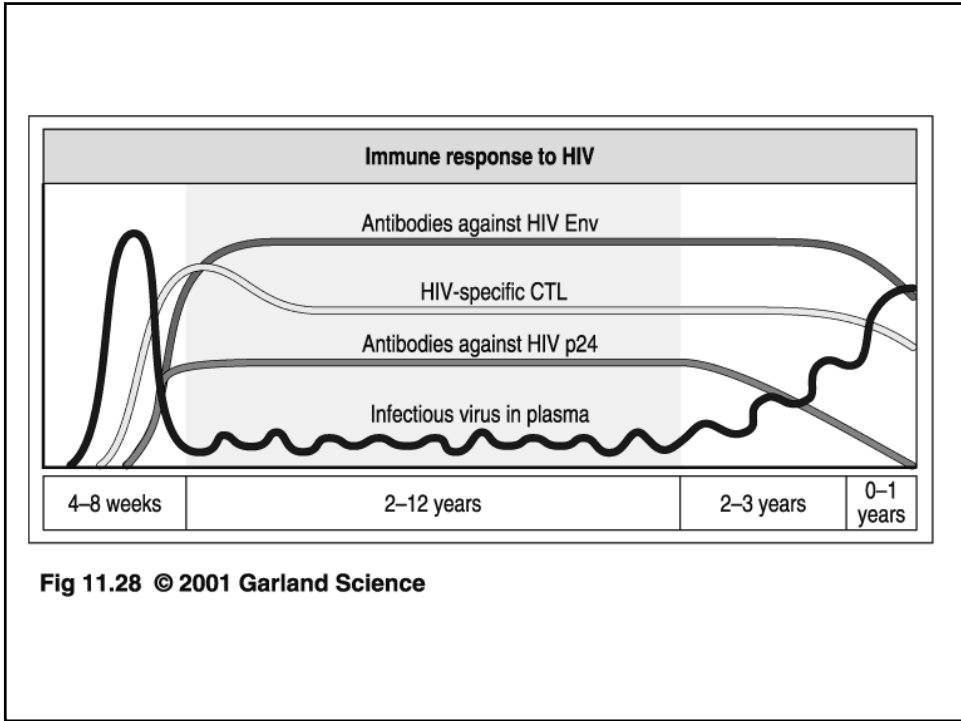
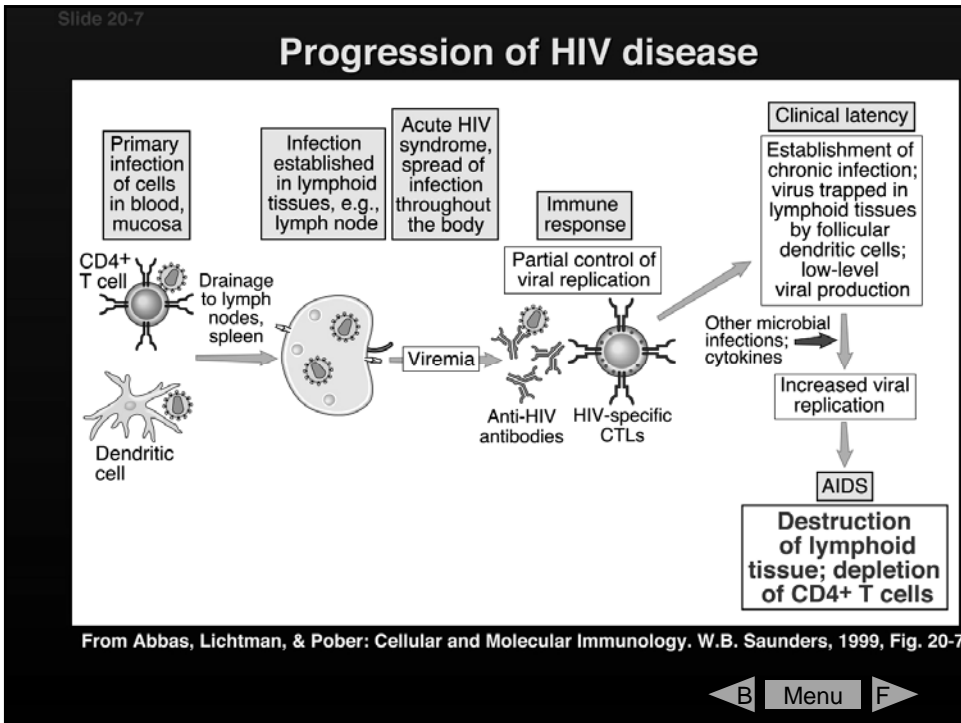


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Mechanisms of CD4+ T cell depletion- Dysfunction

- Accumulation of unintegrated viral DNA
- Loss of plasma membrane integrity due to viral budding
- Elimination of infected cells by HIV-specific immune effectors
- Syncytium formation
- Autoimmunity

Mechanisms of CD4+ T cell depletion- Dysfunction(continued)

- Superantigenic stimulation
- Apoptosis
- Infection of stem cells and interference with lymphopoiesis