Immunodeficiency

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Introduction

- Defects in the development or function of the immune system result in increased susceptibility to infections.
- Infections may be newly acquired or due to reactivation of latent pathogens such as cytomegalovirus, Epstein–Barr virus, and Mycobacterium tuberculosis.
- Disorders caused by defective immunity are collectively called immunodeficiency diseases.

- Some immunodeficiency diseases are associated with increased incidence of certain **cancers and autoimmune diseases**.
- **Primary (congenital) immunodeficiencies** result **from inherited mutations** affecting components of the immune system.
- Primary immunodeficiencies are usually caused by mutations in **one or two genes** affecting immune cell development or function.
- **Secondary (acquired) immunodeficiencies** result from infections, nutritional deficiencies, malignancies, or medical treatments.
- Secondary immunodeficiencies develop after birth **due to external or systemic factors**.
- Among acquired immunodeficiencies, special emphasis is placed **on AIDS caused by HIV** infection.

PRIMARY (CONGENITAL) IMMUNODEFICIENCIES

- Primary immunodeficiencies are diseases caused by defects **usually in one or two genes** that impair maturation or function of components of the immune system.
- It is estimated that as many as 1 in 500 individuals in the United States and Europe have congenital immune deficiencies of varying severity.
- Increased susceptibility to infections is the most common feature.
- Some cause severe, early-onset, life-threatening infections; others cause mild infections and may first be detected in adulthood.

Type of immunodeficiency	Histopathology and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Often absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections, enteric bacterial and viral infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens *in vitro*	Viral and other intracellular microbial infections (e.g., *Pneumocystis jiroveci*, other fungi, non-tuberculous mycobacteria) Some cancers (e.g., EBV-associated lymphomas, skin cancers)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable; pyogenic bacterial and viral infections

Fig. 12.1 Features of immunodeficiency diseases. Summary of the important diagnostic features and clinical manifestations of immunodeficiencies affecting different components of the immune system. Within each group, different diseases, and even different patients with the same disease, may show considerable variation. Reduced numbers of circulating B or T cells are often detected in some of these diseases. *DTH,* Delayed-type hypersensitivity; *EBV,* Epstein-Barr virus; *Ig,* immunoglobulin.

Genetics and Phenotypic Variability

- Mutations in over **450** different genes have been identified as causes of over **400** primary immunodeficiency disorders.
- Although X-linked recessive diseases were first defined genetically, most primary immunodeficiencies show **autosomal recessive** inheritance.
- Autosomal recessive alleles may be detected in consanguineous families, or may occur as **compound heterozygosity** when different mutations in the same gene are inherited from each parent.
- Some mutations arise **de novo** in the patient and are not present in either parent.
- Phenotypic variability is related to coinheritance of modifier genes, environmental factors, and epigenetic modifications, but often remains unexplained.

Overview of Innate Immunity Defects

- Abnormalities in two major components of innate immunity—**phagocytes and the complement system**—are important causes of immunodeficiency.
- These defects impair early defense mechanisms that normally limit microbial replication before adaptive immunity is fully activated.
- Defective microbial killing, defective leukocyte recruitment, or defective opsonization and complement activation may results.
- Recurrent bacterial and fungal infections are common presentations as these pathogens are normally controlled early by phagocytes and complement.

Disease	Functional Deficiencies	Genetic Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutations in genes encoding phagocyte oxidase complex; phox-91 (cytochrome b_{558} α subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion to endothelial cells and migration into tissues linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the β chain (CD18) of β2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling on endothelium and migration into tissues because of decreased or absent expression of leukocyte ligands for endothelial E- and P-selectins; recurrent bacterial and fungal infections	Mutations in gene encoding GDP-fucose transporter-1, required for transport of fucose into the Golgi and its incorporation into sialyl-Lewis X
Chediak-Higashi Syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, NK cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutations in gene encoding LYST, a protein involved in fusion of vesicles (including lysosomes)
Toll-like receptor signaling defects	Recurrent infections caused by defects in TLR signaling	Mutations in genes encoding TLR3 and MyD88 compromise NF-κB activation and type I interferon production in response to microbes

Chronic Granulomatous Disease

- Chronic granulomatous disease (CGD) is caused by mutations in genes encoding subunits **of phagocyte NADPH oxidase**, the enzyme complex that catalyzes production of microbicidal **reactive oxygen species in lysosomes**.
- The most common form is **X-linked CGD** due to mutations in a phagocyte oxidase subunit encoded by the **PHOX91 gene**.
- Neutrophils and macrophages ingest microbes but fail to destroy them, accumulating around foci of infections as granulomas.
- Catalase-producing organisms (e.g., *Staphylococcus, Aspergillus and Candida*) **degrade hydrogen peroxide**, eliminating a potential compensatory microbicidal mechanism

- Leukocyte adhesion deficiency is caused by mutations in genes encoding an essential **integrin** chain, **a Golgi transporter** required for expression of selectin ligands, or chemokine receptor–activated **signaling molecules** needed to activate integrins.
- Leukocytes fail to bind firmly to endothelium and are not recruited normally to sites of infection.

Complement deficiency

- **C3 deficiency** results **in severe infections** and may be fatal.
- Deficiencies **of C2 and C4** (classical pathway) occasionally result in increased **bacterial or viral infection** but more often in increased incidence of **systemic lupus erythematosus**, in part because of defective clearance of immune complexes.
- Deficiencies of complement regulatory proteins lead to various syndromes associated with **excessive complement activation**.

The Chédiak-Higashi syndrome

- The Chédiak-Higashi syndrome is an immunodeficiency disease in which **lysosomal trafficking and the transport of granules are defective** (LYST protein).
- Defective phagolysosome formation.
- Many immune cells are affected, including phagocytes, which normally kill ingested microbes in their lysosomes, and natural killer (NK) cells and cytotoxic T cells, which normally use proteins in specialized secretory lysosomes to kill other infected host cells.

TLRs, nuclear factor kB and other signaling protiens

- Mutations affecting Toll-like receptors (TLRs) or signaling pathways downstream of TLRs, including molecules required for activation of the nuclear factor kB (NFkB) transcription factor.
- Mutations affecting MyD88, an adaptor protein required for signaling by most TLRs, are associated with **severe bacterial** (most often pneumococcal) pneumonias.
- Mutations affecting TLR3 are associated with **recurrent herpesvirus encephalitis and severe influenza.**

Defects in Lymphocyte Maturation

- Many primary immunodeficiencies result from genetic abnormalities that block maturation of **B lymphocytes**, **T lymphocytes**, or both.
- Disorders affecting both arms of adaptive immunity are classified as **severe combined immunodeficiency (SCID)**.
- In many SCID syndromes, impaired humoral immunity is largely a consequence of loss of helper T cell function.
- Other disorders selectively affect B cell development (antibody deficiencies) or T cell development (cell-mediated immune deficiencies).

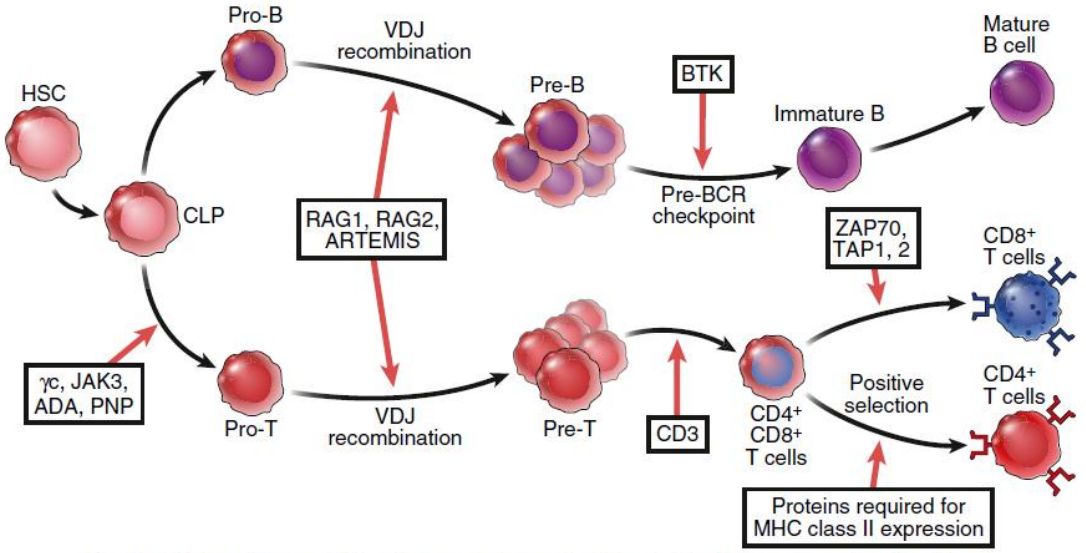


Fig. 12.3 Primary immunodeficiencies caused by genetic defects in lymphocyte maturation. Lymphocyte maturation pathways are described in Chapter 4. The proteins for which expression or functions are impaired by genetic mutations are listed in the boxes. The functions of the proteins are discussed in the text. *ADA,* Adenosine deaminase; *BCR,* B cell receptor; *CLP,* common lymphoid progenitor; *HSC,* hematopoietic stem cell; *PNP,* purine nucleoside phosphorylase; *RAG,* recombination-activating gene; *TCR,* T cell receptor.

Defects in T and B cell development:		
Disease	Functional deficiencies	Mechanism of defect
Severe Combined Immunodeficiency Disease (SCID)		
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to defective VDJ recombination	Markedly decreased T and B cells; reduced serum Ig	Mutations in *RAG* genes and other genes involved in VDJ recombination
Defective class II MHC expression: The bare lymphocyte syndrome	Impaired $CD4^+$ T cell development and activation; defective cell-mediated and humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
DiGeorge syndrome (22q11 deletion syndrome)	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia
Impaired B cell development		
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in Bruton tyrosine kinase (BTK)

Fig. 12.4 Features of primary immunodeficiencies caused by defects in lymphocyte maturation. The figure summarizes the principal features of the most common primary immunodeficiencies in which the genetic blocks are known. *ADA,* Adenosine deaminase; *Ig,* immunoglobulin; *IL-7R,* interleukin-7 receptor; *MHC,* major histocompatibility complex; *PNP,* purine nucleoside phosphorylase; *RAG,* recombination-activating gene.

Severe Combined Immunodeficiency

- Severe combined immunodeficiency encompasses disorders in which both **cellular and humoral immunity** are profoundly impaired.
- Most forms result from **defects** in **T cell development**, leading secondarily to **impaired B cell activation and antibody production**.
- Absence of functional T cells prevents effective responses against **viruses, fungi, and intracellular bacteria**.
- Without immune reconstitution, affected infants develop overwhelming infections early in life.

X-linked SCID and JAK3 Deficiency

- X-linked SCID accounts for about **half** of SCID cases and affects male children; >99% are caused by mutations in the **common γ (γc) chain** signaling subunit **of cytokine receptors**.
- The γc chain is shared by receptors for **IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21** (it is also called **IL-2Rγ** because it was first identified as part of the IL-2 receptor).
- When γc is not functional, immature lymphocytes—especially pro–T cells—cannot proliferate in response to **IL-7**, the **major growth factor** for these cells, leading to **reduced survival and maturation of lymphocyte precursors.**

- **T cell maturation is** profoundly impaired; B cell development may proceed, but **humoral immunity is defective** due to absence of T cell help.
- **NK cells** are deficient because γc is part of the **IL-15 receptor**, required for **NK cell proliferation and maturation**.
- An **autosomal recessive** form is caused by mutations **in JAK3,** a kinase **required for signaling by the γc chain**, resulting in the same abnormalities.

ADA and PNP Deficiency

- About half of autosomal recessive SCID cases are caused by mutations **in adenosine deaminase (ADA),** an enzyme involved in the breakdown of adenosine.
- ADA deficiency leads to **accumulation of toxic purine metabolites** in proliferating cells actively synthesizing DNA.
- **Developing lymphocytes** are particularly susceptible to injury, producing a block in T cell maturation more than in B cell maturation.
- A similar phenotype occurs in purine nucleoside phosphorylase **(PNP) deficiency**.

RAG and ARTEMIS Deficiencies

- Mutations in RAG1 or RAG2 genes impair the recombinase required for **immunoglobulin and T cell receptor gene recombination**.
- Without functional RAG proteins, B and T cells fail to develop because **antigen receptor genes cannot be assembled**.
- Mutations **in ARTEMIS**, an **endonuclease** involved in **V(D)J recombination**, also prevent B and T cell development.
- These defects demonstrate the requirement for antigen receptor gene recombination in lymphocyte maturation.

DiGeorge Syndrome (22q11 Deletion)

- DiGeorge syndrome is characterized in part by defective T cell maturation due to a deletion on chromosome 22 (**22q11 deletion** syndrome).
- The deletion i**nterferes with development of the thymus** (and parathyroid glands), producing impaired T cell maturation.
- The condition often improves with age, likely because **limited thymic tissue that develops can support some T cell maturation**.
- Newborn screening has increased identification of additional rare causes of SCID beyond these classic syndromes.

Selective B Cell Deficiencies:

- Selective B cell defects impair antibody-mediated immunity.
- Patients present with recurrent bacterial infections.
- T cell immunity is usually intact.
- The most common example is X-linked agammaglobulinemia.

X-linked Agammaglobulinemia (Bruton Agammaglobulinemia)

- A **block in B cell maturation that** is X-linked, initially called Bruton agammaglobulinemia.
- Pre–B cells in the bone marrow fail to survive, resulting in a **marked decrease or absence of mature B lymphocytes and serum immunoglobulins**.
- Caused by mutations in the gene encoding **Bruton tyrosine kinase (BTK)**, leading to defective production or function of this signaling enzyme.
- BTK is activated by the pre–B cell receptor and **delivers signals that promote survival, proliferation, and maturation of pre–B cells**; loss of BTK therefore **arrests** development at the pre–B stage.
- Female carriers are typically unaffected, but male offspring inheriting the mutant X chromosome develop disease.
- Autoimmunity (notably arthritis) occurs in some patients; one proposed mechanism is that defective BTK-dependent BCR signaling impairs B cell tolerance and allows accumulation of autoreactive B cells.

Defects in Lymphocyte Activation and Function

- Numerous immunodeficiency diseases are caused **by mutations affecting molecules involved in lymphocyte activation and function**.
- These defects may affect B cells, T cells, or both. The result is impaired adaptive immune responses.
- These defects **may impair antibody production** by disrupting B cell intrinsic pathways or T cell help.
- They may also impair **cell-mediated immunity** by interfering with antigen presentation, costimulation, or effector pathways.

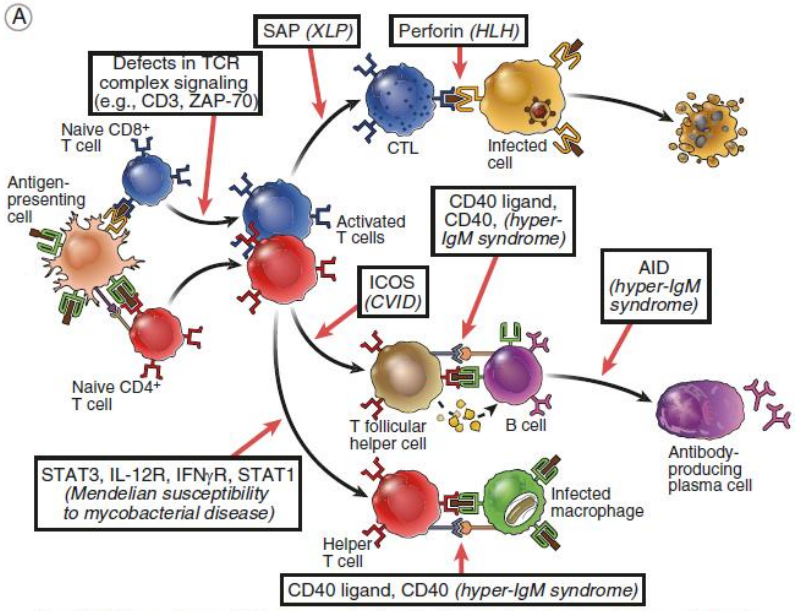


Fig. 12.5 Primary immunodeficiencies associated with defects in lymphocyte activation and effector functions. These immunodeficiencies may be caused by genetic defects in the expression of molecules listed in the boxes, required for antigen presentation to T cells, T or B lymphocyte antigen receptor signaling, helper T cell activation of B cells and macrophages, and differentiation of antibody-producing B cells. **A,** Examples showing the sites at which immune responses may be blocked. *AID,* Activation-induced deaminase; *CVID,* common variable immunodeficiency; *ICOS,* inducible costimulatory; *IFNγR,* IFN-γ receptor; *Ig,* immunoglobulin; *IL-12R,* IL-12 receptor; *MHC,* major histocompatibility complex; *SAP,* SLAM-associated protein; *ZAP-70,* ζ chain–associated protein of 70 kD.

Defects in B cell Responses:
X-linked Hyper-IgM Syndrome (CD40L Pathway Defect)

- Defective **B cell heavy-chain class (isotype) switching (**IgM is the major serum antibody) and deficient cell-mediated immunity against intracellular microbes.
- Most commonly X-linked and is caused by mutations in the **gene encoding CD40 ligand (CD40L)**, the helper T cell protein that binds CD40 on B cells, dendritic cells, and macrophages.
- Defective germinal center reactions in T cell–dependent B cell responses, causing **poor class switching and absence of affinity maturation**.
- Defective CD40L–CD40 signaling also impairs T cell–dependent activation of macrophages and dendritic cells, **reducing cell-mediated immunity**.
- Susceptibility to ***Pneumocystis jirovecii*** reflects inability of phagocytes to control this organism in the absence of T cell help.

B

Defects in T and B cell activation and function		
Disease	Functional deficiencies	Mechanism of defect
X-linked hyper-IgM syndrome	Defects in helper T cell-dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective Ig deficiency	Reduced or no production of selective Ig isotypes; susceptibility to infections or no clinical problem	Mutations in Ig genes or unknown mutations
Common variable immunodeficiency	Reduced immunoglobulins; susceptibility to bacterial infections	Mutations in receptors for B cell growth factors, costimulators
Hemophagocytic lymphohistiocytosis	Impaired CTL and NK cell killing function; uncontrolled compensatory macrophage activation	Mutations in perforin gene and other genes required for CTL and NK cell granule exocytosis
Mendelian susceptibility to mycobacterial disease	Decreased Th1-mediated macrophage activation; susceptibility to infection by atypical mycobacteria and other intracellular pathogens	Mutations in genes encoding IL-12, the receptors for IL-12 or interferon-γ, STAT1
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell-mediated immunity	Mutations or deletions in genes encoding CD3 proteins, ZAP-70
Mucocutaneous candidiasis, bacterial skin abcesses	Decreased Th17-mediated inflammatory responses	Mutations in genes encoding STAT3, IL-17, IL-17R
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation and CTL activation; defective NK cell and CTL function and antibody responses	Mutations in gene encoding SAP (involved in signaling in lymphocytes)

Fig. 12.5, cont'd **B,** Summary of the features of immunodeficiency disorders whose genetic basis is shown in part **A.** Note that abnormalities in class II MHC expression and TCR complex signaling can cause defective T cell maturation (see Fig. 12.2), as well as defective activation of the cells that do mature, as shown here. *CTL,* Cytotoxic T lymphocyte; *EBV,* Epstein-Barr virus; *NK,* natural killer.

Hyper-IgM Variants: CD40 and AID

- An autosomal recessive form with a similar combined immunodeficiency phenotype results from **mutations in CD40**.
- Another autosomal recessive form with **humoral abnormalities** but **no defect in cellular immunity** is caused by **mutations affecting activation-induced deaminase (AID).**
- AID is induced by CD40 signaling and is required for **immunoglobulin class switching** and **affinity maturation**.
- These variants distinguish defects in T–B collaboration from defects intrinsic to B cell DNA modification mechanisms.

Selective Ig Class Deficiencies

- Genetic deficiencies in production of selected immunoglobulin classes are relatively common.
- **IgA deficiency affects** as many as 1 in 700 people and is asymptomatic in most individuals.
- A minority develop recurrent sinus, lung, and intestinal infections, reflecting reduced mucosal antibody protection.
- In most cases, the precise defect is unknown; rarely, mutations in immunoglobulin heavy-chain constant region genes contribute.

Common Variable Immunodeficiency (CVID)

- CVID is a heterogeneous group of disorders characterized by **poor antibody responses to infections** and **reduced serum IgG, IgA, and sometimes IgM.**
- Underlying causes **include mutations in genes encoding signaling molecules** and **transcription factors involved in B cell activation.**
- Defects may also **involve receptors** important for **T cell–B cell** interactions required for effective antibody responses.
- Patients have recurrent **infections, autoimmune disease, and lymphomas.**

Defective Activation of T Lymphocyte: Bare Lymphocyte Syndrome (Class II MHC Expression Defect)

- This disease is caused by **failure to express class II MHC** molecules due to mutations in transcription factors that normally induce class II MHC expression.
- Because class II MHC molecules present peptides for recognition by CD4 T cells, defective class II **expression impairs CD4 T cell maturation and activation.**
- The disease is manifested by a **profound decrease in CD4 T cells** due to **defective maturation** in the thymus.
- **Poor activation of CD4 T cells in secondary lymphoid organs** contributes to severe combined immunodeficiency.

Hemophagocytic Lymphohistiocytosis (HLH)

- HLH syndromes are characterized by systemic, sometimes **life-threatening activation of immune cells, principally macrophages**, often triggered by infections.
- Many cases result from genetic defects **in cytotoxic CD8 T cells and NK** cells that prevent killing of virus-infected target cells.
- Examples include mutations in **perforin** and mutations in genes encoding proteins involved in **granule exocytosis**.
- Persistent viral infection drives excessive **IFN-γ** production by T cells and NK cells, causing **uncontrolled macrophage activation**.
- Activated macrophages may **ingest red blood cells in bone marrow**, producing the hemophagocytic phenotype.

Mendelian susceptibility to mycobacterial disease

- Mutations in the genes encoding components **of interleukin-12** (IL-12), **the IL-12 receptor**, the **interferon-g (IFN-g) receptor**, or associated signaling molecules.
- This result in **deficient cell-mediated immunity** because of defects **in Th1 development** or **Th1 cell-mediated macrophage activation.**
- Increased susceptibility to weakly virulent environmental Mycobacterium species (often **called atypical mycobacteria**) as well as other **intracellular pathogens**, including *Salmonella* and various other bacterial, fungal, and viral species.

Lymphocyte Abnormalities Associated with Other Diseases

- **Wiskott-Aldrich syndrome** is characterized by eczema, reduced blood platelets, and immunodeficiency.
- This **X-linked disease** is caused by a mutation in a gene that encodes a **regulator of the actin cytoskeleton** required for signal transduction, immune synapse formation, and cytoskeletal reorganization.
- Because of the absence of this protein, platelets and leukocytes do not develop normally, are small, and fail to migrate.

- **Ataxia-telangiectasia** is characterized by gait abnormalities (ataxia), vascular malformations (telangiectasia), and immunodeficiency.
- The disease is caused by mutations in **a gene that encodes a protein involved in DNA repair** (e.g., during recombination of antigen receptor gene segments), resulting in **defective lymphocyte maturation**.
- Disease caused by autoimmune regulator protein "**AIRE" mutations**, develop **autoantibodies against their own cytokines** and manifestations of immunodeficiency because of the resulting cytokine depletion.
- **Autoantibodies against type I IFN** are seen even in the absence of overt autoimmunity and have been associated with severe cases of **COVID-19**.

Therapy of Primary Immunodeficiencies

- **Hematopoietic stem cell transplantation** is the mainstay for SCID.
- **Intravenous immunoglobulin** provides passive immunity in B cell defects.
- Gene therapy has shown success in some forms of SCID (gc gene is introduced into their hematopoietic stem cells) and ADA deficiency (enzyme replacement as well).
- Infections are treated aggressively with antimicrobial agents.

Overview of Acquired (Secondary) Immunodeficiencies

- Secondary immunodeficiencies develop due to abnormalities that are not genetic but are acquired during life .
- The most serious acquired immunodeficiency worldwide is **HIV infection**, described in detail in this section.
- In developed countries, frequent causes **include cancers involving the bone marrow and immunosuppressive therapies**.
- These conditions reduce immune cell production, survival, or function, increasing susceptibility to infections.

Cause	Mechanism
Human immunodeficiency virus infection	Depletion of $CD4^+$ helper T cells
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Immunosuppression for graft rejection and inflammatory diseases	Depletion or functional impairment of lymphocytes
Involvement of bone marrow by cancers (metastases, leukemias)	Reduced site of leukocyte development
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Loss of spleen (surgically to treat trauma or by infarction)	Decreased phagocytosis of microbes

Fig. 12.6 Acquired (secondary) immunodeficiencies. The most common causes of acquired immunodeficiency diseases and how they lead to defects in immune responses.

Causes of Secondary Immunodeficiency

- **Cancers involving the bone marrow** (e.g., leukemias) impair production of leukocytes and disrupt normal immune function.
- **Chemotherapy and irradiation** damage proliferating cells, including bone marrow precursors and mature lymphocytes.
- **Immunosuppressive drugs** used to prevent graft rejection or treat inflammatory diseases blunt immune responses by design.
- Newer therapies such as **cytokine antagonists and leukocyte adhesion molecule blockers** can cause immunodeficiency as a complication.
- **Protein-calorie malnutrition** causes broad deficiencies of virtually all immune components and is a common cause worldwide in settings of poverty or famine.

Acquired Immunodeficiency Syndrome (AIDS)

- AIDS is caused by infection with human immunodeficiency virus HIV.
- It has resulted in millions of deaths worldwide.
- Effective therapies exist but are not universally accessible.
- The disease remains a major global health problem.

Structure and Classification of HIV

- HIV is a **retrovirus** that infects cells of the immune system, **mainly CD4 T lymphocytes**, causing progressive destruction of these cells.
- An infectious HIV particle contains **two RNA strands** within a protein core, surrounded by a lipid envelope derived from infected host cells but containing viral proteins.
- The viral RNA encodes structural proteins, enzymes required for replication, and regulatory proteins that control transcription and the viral life cycle.
- Most cases of AIDS are caused by **HIV-1**; a closely related virus, **HIV-2**, causes some cases.

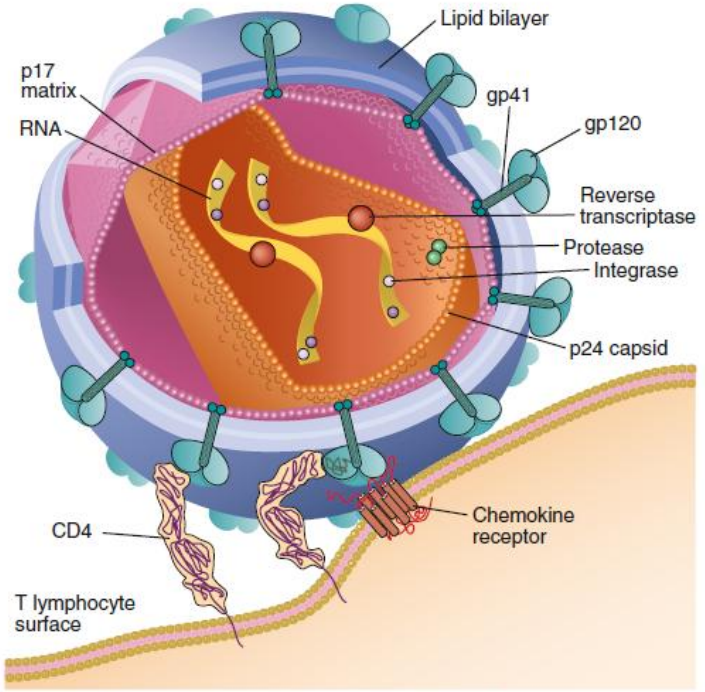


Fig. 12.7 Structure of the human immunodeficiency virus (HIV). An HIV-1 virion is shown next to a T cell surface. HIV-1 consists of two identical strands of RNA (the viral genome) and associated enzymes, including reverse transcriptase, integrase, and protease, packaged in a cone-shaped core composed of the p24 capsid protein with a surrounding p17 protein matrix, all surrounded by a phospholipid membrane envelope derived from the host cell. Virally encoded envelope proteins (gp41 and gp120) bind to CD4 and chemokine receptors on the host cell surface. *MHC*, Major histocompatibility complex. (Adapted from © 1996 Terese Winslow. Reproduced with permission.)

- **HIV Entry and Cellular Targets**
- HIV infects cells via its major envelope glycoprotein **gp120**, which binds to **CD4** and to particular chemokine receptors.
- The principal chemokine receptors used are **CCR5** and **CXCR4**, and receptor usage varies among viral strains.
- **CD4 T lymphocytes are the major target**; some strains can also infect macrophages.
- Macrophages and dendritic cells may also acquire virus by phagocytosis and can contribute to persistence.

HIV Life Cycle

- After gp120 binding, the viral membrane fuses with the host cell membrane, and viral RNA is released into the cytoplasm.
- **Reverse transcriptase** synthesizes a DNA copy of viral RNA, which becomes double-stranded DNA.
- Viral DNA integrates into the host genome via **integrase**, creating a **provirus** that may remain latent for months or years.
- When an **infected T cell is activated** by infection or cytokines**, proviral transcription increases**, producing viral RNAs.
- Viral proteins are synthesized as precursors and **processed into mature forms** by viral and cellular proteases; **new virions assemble and bud** from the cell membrane.

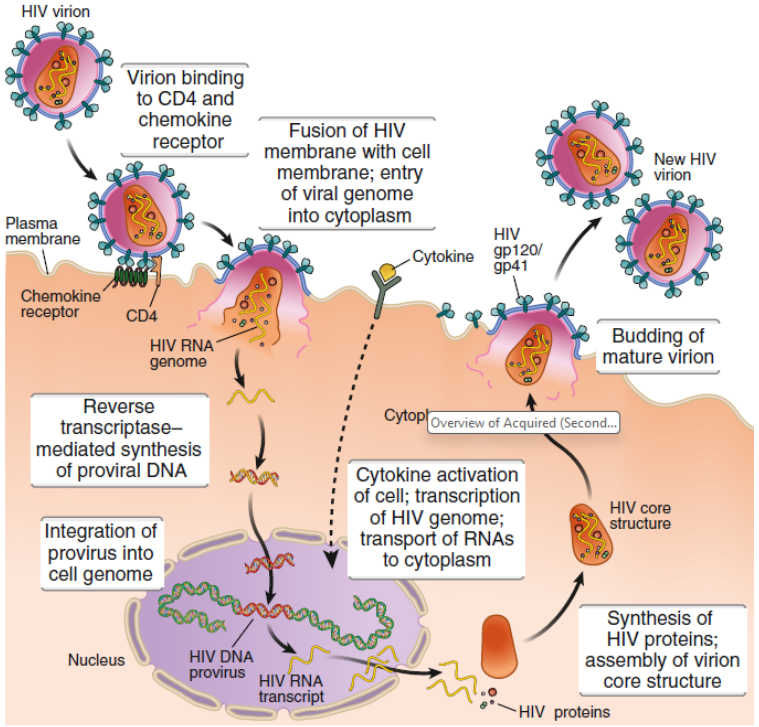


Fig. 12.8 Life cycle of HIV. The sequential steps in HIV reproduction are shown, from initial infection of a host cell to release of new virus particles (virions).

Pathogenesis of AIDS

- AIDS develops over many years **as latent HIV becomes activated** and progressively destroys cells of the immune system.
- **Activated CD4 T cells are the major source of infectious** viral particles **during chronic infection**.
- Follicular **helper T cells and macrophages** may serve as **reservoirs** in which virus can persist for months or years.
- The principal mechanism **of CD4 T cell depletion** is a **cytopathic effect of viral replication**, in which active viral gene expression and protein production disrupts cellular function and kills infected T cells.
- Loss of uninfected T cells also occurs and exceeds the number of infected cells.

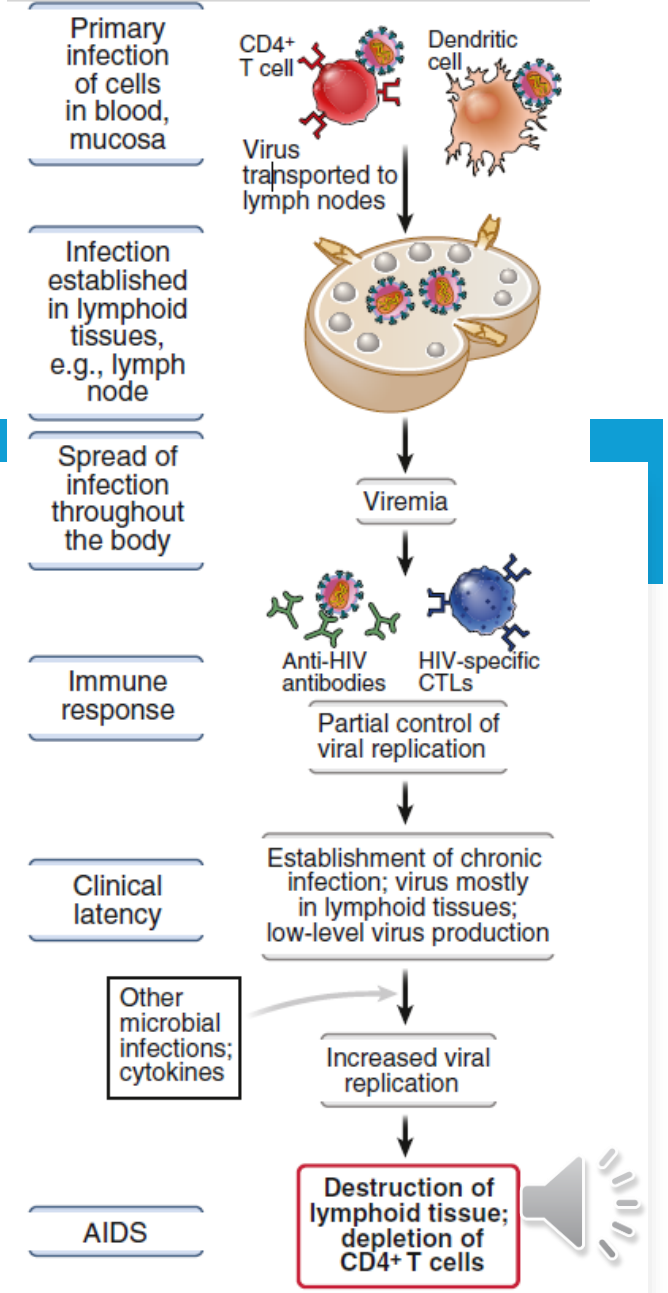


Fig. 12.9 Pathogenesis of disease caused by HIV. The development of HIV disease is associated with the spread of HIV from the initial site of infection to lymphoid tissues throughout the body. The immune response of the host temporarily controls acute infection but does not prevent establishment of

Transmission and Early Infection

- HIV is acquired by **sexual intercourse, sharing contaminated needles, transplacental transfe**r, or rarely **transfusion** of infected blood products.
- Early infection may include an **acute viremia detectable** in blood.
- The virus primarily infects **CD4 T cells in mucosal tissues** at entry sites, where substantial destruction of infected T cells can occur.
- Because many memory T cells reside in mucosa**, early local depletion can cause significant functional deficits** not immediately reflected by circulating blood counts.

Latency and Progressive Immune Decline

- **After acute infection**, the disease enters a period of **clinical latency** with few symptoms.
- Despite apparent latency, there is **progressive loss of CD4 T cells** in lymphoid tissues and destruction of lymphoid architecture.
- The blood CD4 count eventually declines; when it falls below **200 cells/mm^3** (normal **approximately 1500 cells/mm^3), patients become susceptible to opportunistic infections** and are diagnosed as having AIDS .
- CD4 T cell count decline remains the most reliable indicator of disease progression.

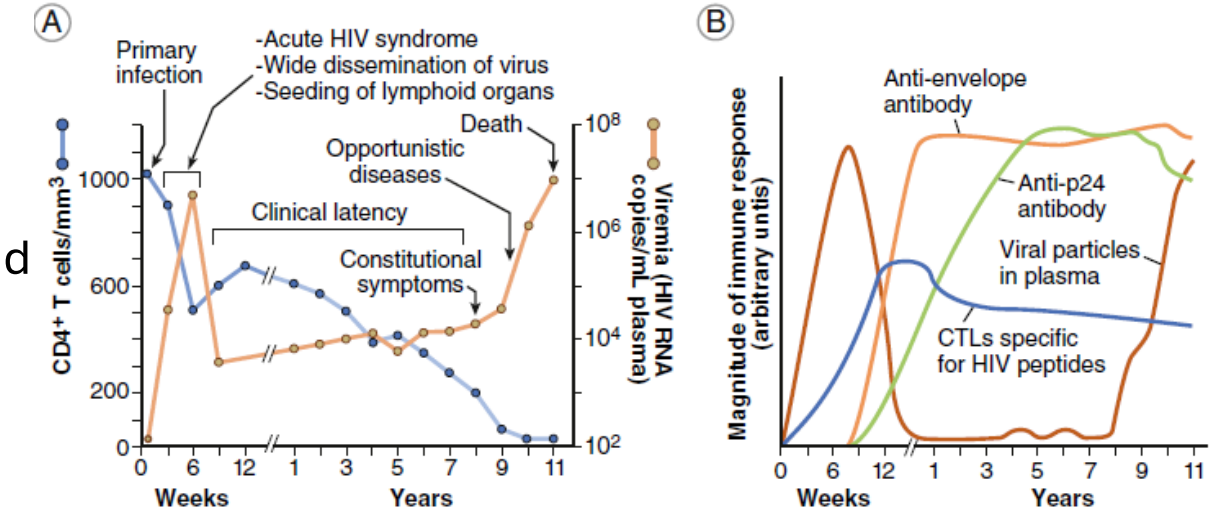


Fig. 12.10 Clinical course of *HIV* disease. **A,** Blood-borne virus (plasma viremia) is detected early after infection and may be accompanied by systemic symptoms typical of acute HIV syndrome. The virus spreads to lymphoid organs, but plasma viremia falls to very low levels (detectable only by sensitive reverse transcriptase–polymerase chain reaction assays) and stays this way for many years. $CD4^+$ T cell counts steadily decline during this clinical latency period because of active viral replication and T cell for of infection and other clinical components of acquired immunodeficiency syndrome. **B,** Magnitude and kinetics of immune responses, shown in arbitrary relative units. *CTLs,* Cytotoxic T lymphocytes. (Reproduced with permission from Pantaleo G, Graziosi C, Fauci AS: The immunopathogenesis of human immunodeficiency virus infection, *N Engl J Med* 328:327–335, 1993.)

Clinical AIDS: Opportunistic Infections and Immune Deficits

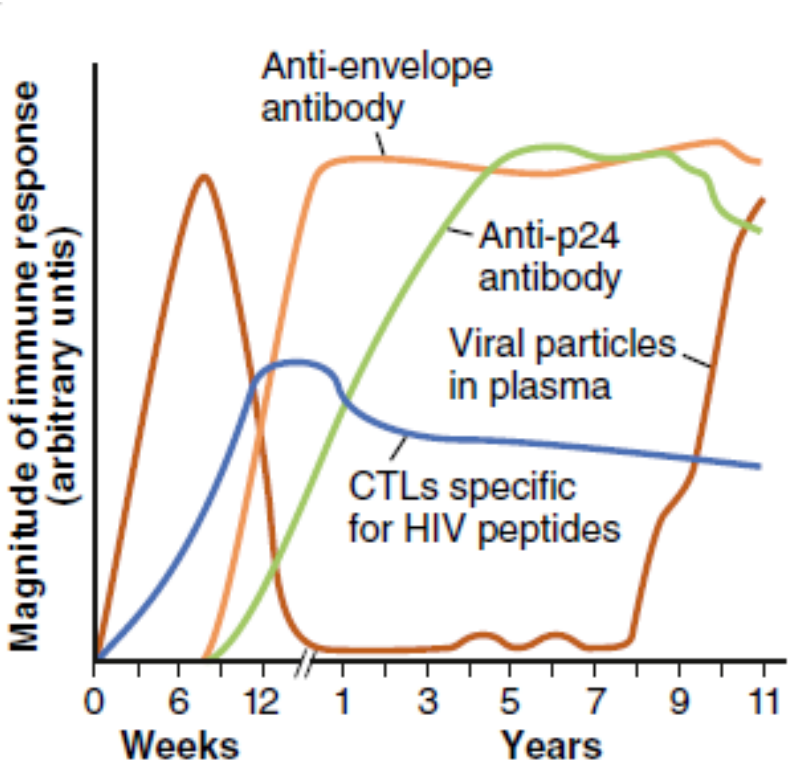
- Patients not treated with antiretroviral drugs develop **infections with intracellular microbes** normally controlled by T cell–mediated immunity.
- Common opportunistic pathogens include viruses, ***Pneumocystis jirovecii***, and **nontuberculous mycobacteria**, which do not cause disease in immunocompetent hosts.
- Latent viruses such as **cytomegalovirus** and **EBV** may be **reactivated because** of defective **cytotoxic T lymphocyte** responses.
- CTL defects occur even though HIV does not infect CD8 T cells, likely **because CD4 helper T cells are needed for full CTL responses**.
- Patients are also susceptible to **extracellular bacterial infections** due to impaired helper T cell–dependent antibody responses.

Malignancies and Other Manifestations

- AIDS patients are prone to **EBV-associated B cell lymphomas**.
- **Kaposi sarcoma** is caused by a herpesvirus.
- Wasting syndrome with significant loss of body mass, reflects altered metabolism and reduced intake.
- Neurocognitive disorders caused by infection of macrophages (microglial cells) in the brain or the effects of cytokines or shed viral particles.

Immune Response to HIV

- Infected patients mount antibody and CTL responses against HIV antigens, which help limit early acute HIV syndrome.
- These immune responses usually do not prevent progression to AIDS.
- Antibodies to envelope glycoproteins such as **gp120 may be ineffective** because the virus **rapidly mutates** antibody-targeted regions.
- CTLs may be ineffective because the virus **inhibits expression of class I MHC molecules** by infected cells.



Immune Responses May Promote Viral Spread

- **Antibody-coated viral particles** can bind Fc receptors on **macrophages and follicular dendritic cells**, increasing viral entry and creating additional reservoirs.
- Clearance of CTL-killed infected cells by macrophages may enable **dissemination if macrophages migrate to other tissues**.
- By infecting and interfering with immune cell function, **HIV prevents its own eradication.**
- These features contribute to persistence despite robust immune activation.

Elite Controllers and Genetic Resistance

- A small fraction of patients control HIV infection without therapy and are referred to as elite controllers or long-term non-progressors.
- Certain HLA alleles such as **HLA-B57** and **HLA-B27** are protective and are particularly **efficient at presenting certain HIV peptides to CD8 T cells.**
- Some of these presented peptides are **constrained** because the **virus cannot mutate them** without losing viability.
- Rare individuals homozygous for a **32-bp deletion in CCR5** lack functional CCR5 and are resistant to HIV infection.

Antiretroviral Therapy and Vaccine Development

- Combination antiretroviral therapy targets viral **reverse transcriptase, protease, and integrase** enzymes and is administered early in infection.
- **Inhibitors of viral entry and fusion** have also been developed, broadening therapeutic targets.
- ART has **markedly reduced opportunistic infections and cancers** in societies where it is widely available, and treated patients can live long life spans.
- HIV is not eradicated because **of viral mutation** leading to drug resistance and because **latent reservoirs** in lymphoid tissues may be inaccessible.
- A successful vaccine likely must induce broadly neutralizing antibodies, strong T cell responses, and mucosal immunity, but high viral mutability has limited success of vaccine trials.

- Abbasi, Abul K., Andrew H. Lichtman, and Shiv Pillai. *Basic Immunology: Functions and Disorders of the Immune System*. 7th ed. Elsevier, 2023, chapter 12.
- Abbas, Abul K., Andrew H. Lichtman, Shiv Pillai, and Sarah Henrickson. *Cellular and Molecular Immunology*, 11th ed. Elsevier, 2025, chapter 20.