IMMUNODEFICIENCY

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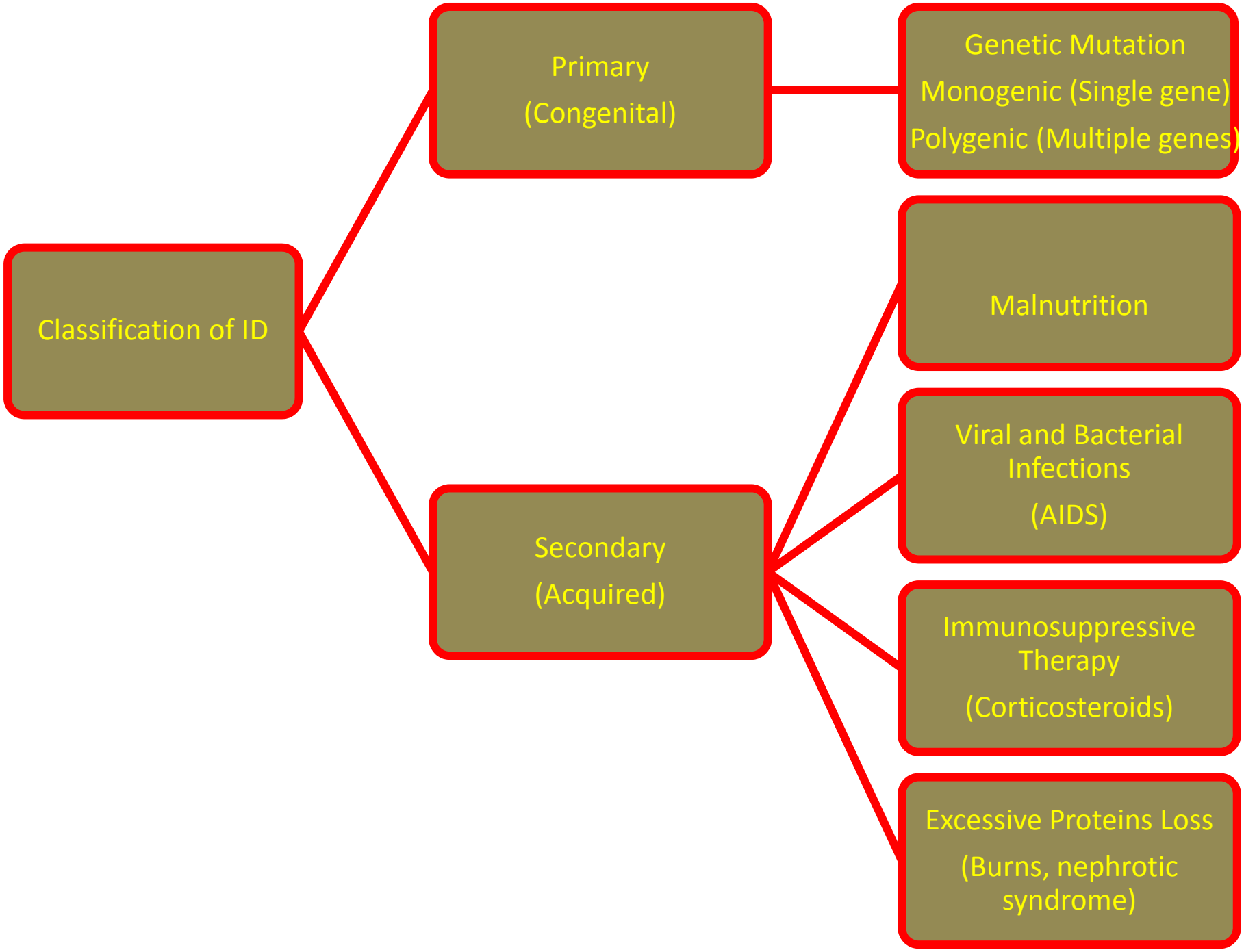
INTRODUCTION

- Integrity of the immune system is essential for defense against infectious organisms and their toxic products and therefore for the survival of all individuals.

- Defects in one or more components of the immune system can lead to serious and often fatal disorders, which are collectively called **immunodeficiency diseases.**
- These diseases are broadly classified into two groups. The **congenital, or primary, immunodeficiencies are genetic defects that** result in an increased susceptibility to infection that is frequently manifested early in infancy and childhood but is sometimes clinically detected later in life.
- **Acquired, or secondary, immunodeficiencies are not inherited diseases but** develop as a consequence of malnutrition, disseminated cancer, treatment with immunosuppressive drugs, or infection of cells of the immune system, most notably with the human immunodeficiency virus (HIV), the etiologic agent of acquired immunodeficiency syndrome (AIDS).


Classification of ID
Primary
(Congenital)
Genetic Mutation
Monogenic (Single gene)
Polygenic (Multiple genes)
Secondary
(Acquired)
Malnutrition
Viral and Bacterial Infections
(AIDS)
Immunosuppressive Therapy
(Corticosteroids)
Excessive Proteins Loss
(Burns, nephrotic syndrome)

PRIMARY IMMUNODEFICIENCY

Congenital (inherited)

- Primary immunodeficiencies are inherited defects of the immune system
- These defects may be in the specific or nonspecific immune mechanisms
- They are classified on the basis of the site of lesion in the developmental or differentiation pathway of the immune system

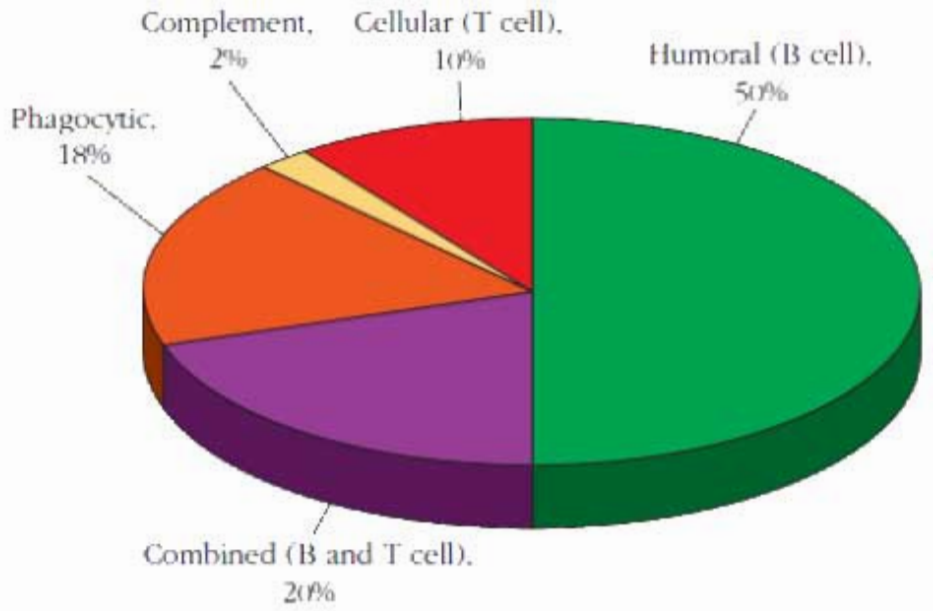
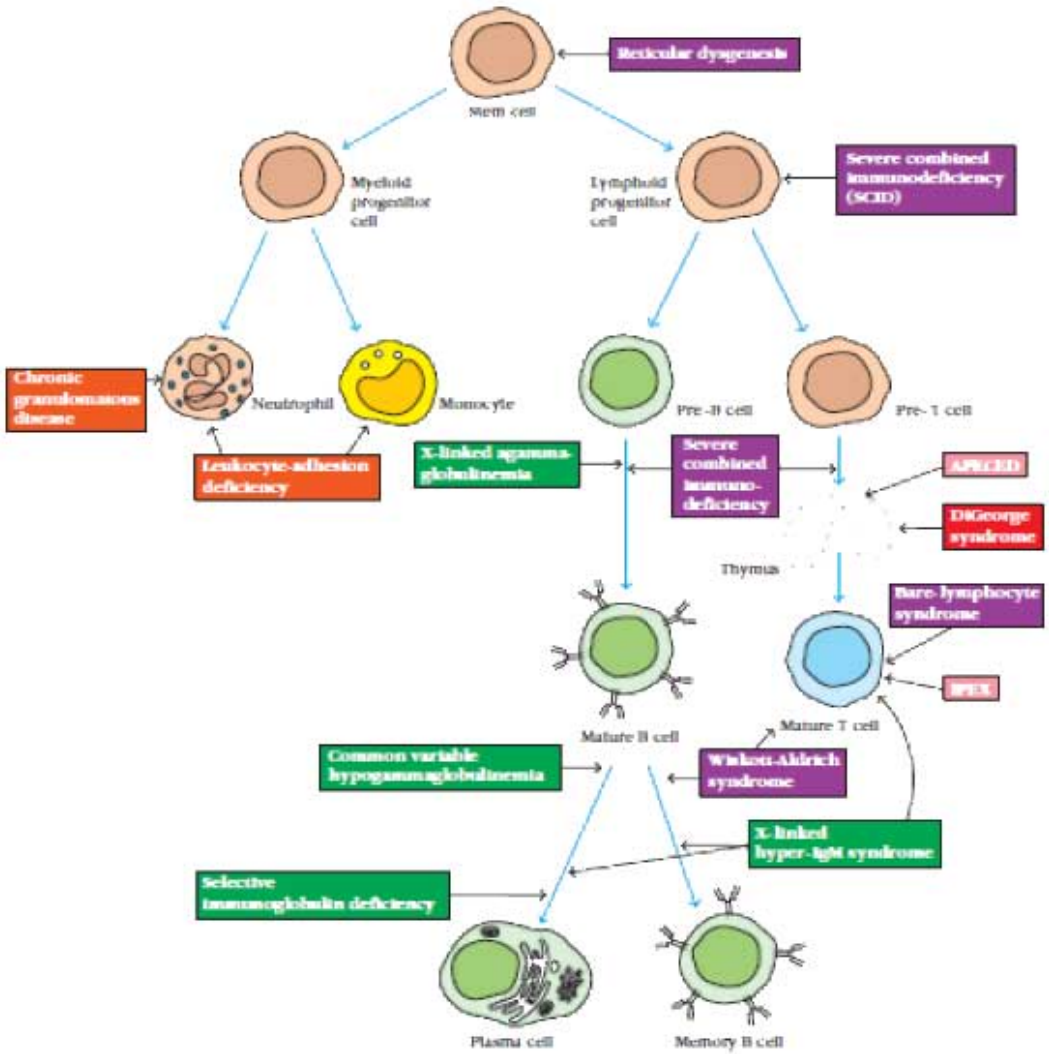


FIGURE 18-1 Distribution of primary immunodeficiencies by type. Primary immunodeficiency can involve either innate processes (phagocytosis, complement, or other defects) or the adaptive immune response (humoral, cellular, or both). Of these categories, adaptive immune disruptions are the most common, with antibody defects making up the largest portion of these. *[Song et al., 2011,* Clinical and Molecular Allergy ***9:10.*** *doi:10.1186/1476-7961-9-10]*

Primary Immunodeficiencies Result from Congenital Defects in Specific Cell Types



Orange = phagocytic deficiencies, green = humoral deficiencies, red = cell-mediated deficiencies, pink = regulatory cell deficiencies, and purple = combined immunodeficiencies, or defects that affect more than one cell lineage. APECED = autoimmune polyendocrinopathy and ectodermal dystrophy; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome.

TABLE 18-1 Some primary human immunodeficiency diseases and underlying genetic defects

Immunodeficiency disease	Specific defect	Impaired function	Inheritance mode*
Severe combined immunodeficiency (SCID)	*RAG1/RAG2* deficiency	No TCR or Ig gene rearrangement	AR
	ADA deficiency	Toxic metabolite in T and B cells	AR
	PNP deficiency		AR
	JAK-3 deficiency	Defective signals from IL-2, -4, -7, -9, -15, -21	AR
	IL-2Rγ deficiency		XL
	ZAP-70 deficiency	Defective signal from TCR	AR
Bare lymphocyte syndrome (BLS)	Defect in class II MHC gene promoter	No class II MHC molecules	AR
Wiskott-Aldrich syndrome (WAS)	Cytoskeletal protein (WASP)	Defective T-cells and platelets	XL
Mendelian susceptibility to mycobacterial diseases (MSMD)	IFN-γR IL-12/IL-12R STAT1	Impaired immunity to mycobacteria	AR or AD
DiGeorge syndrome	Thymic aplasia	T-cell development	AD
Gammaglobulinemias	X-linked agammaglobulinemia	Bruton's tyrosine kinase (Btk); no mature B cells	XL
	X-linked hyper-IgM syndrome	Defective CD40 ligand	XL
	Common variable immunodeficiency	Low IgG, IgA, variable IgM	Complex
	Selective IgA deficiency	Low or no IgA	Complex
Chronic granulomatous disease	$gp91^{phox}$	No oxidative burst for phagocytic killing	XL
	$p67^{phox}$, $p47^{phox}$, $p22^{phox}$		AR
Chediak-Higashi syndrome	Defective intracellular transport protein (LYST)	Inability to lyse bacteria	AR
Leukocyte adhesion defect	Defective integrin β2 (CD18)	Leukocyte extravasation	AR
Autoimmune polyendocrinopathy and ectodermal dystrophy (APECED)	AIRE defect	T-cell tolerance	AR
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	FoxP3 defect	Absence of T_{reg} cells	XL

* AR = autosomal recessive, AD = autosomal dominant, XL = X linked. "Complex" inheritance modes include conditions for which precise genetic data are not available and that may involve several interacting loci.

TABLE 18-2 Patterns of Infection and Illness associated with primary Immunodeficiency diseases

Disorder	Disease	
	OPPORTUNISTIC INFECTIONS	OTHER SYMPTOMS
Antibody	Sinopulmonary (pyogenic bacteria) Gastrointestinal (enterovirus, giardia)	Autoimmune disease (autoantibodies, inflammatory bowel disease)
Cell-mediated immunity	Pneumonia (pyogenic bacteria, *Pneumocystis carinii*, viruses) Gastrointestinal (viruses), mycoses of skin and mucous membranes (fungi)	
Complement	Sepsis and other blood-borne infections (streptococci, pneumococci, neisseria)	Autoimmune disease (systemic lupus erythematosus, glomerulonephritis)
Phagocytosis	Skin abscesses, reticuloendothelial infections (staphylococci, enteric bacteria, fungi, mycobacteria)	
Regulatory T cells	N/A	Autoimmune disease

Source: Adapted from H. M. Lederman, 2000, The clinical presentation of primary immunodeficiency diseases, Clinical Focus on Primary Immune Deficiencies. *Towson, MD: Immune Deficiency Foundation* **2**(1):1.

DiGeorge Syndrome

- Poorly developed or functioning thymus
- Associated with other developmental conditions
- Depression of T cell numbers
- Absence of T cell response
- Humoral response to T independent antigens only

Wiskott Aldrich Syndrome

- X linked disorder
- Affects platelet numbers/function
- Affects T cell function
- Cytoskeleton of lymphocytes affected
- Lower amounts of IgM
- Increased susceptibility to certain bacterial infections

LEUKOCYTE ADHESION DEFICIENCY:

- Leukocytes lack the complement receptor CR3 due to a defect in CD11 or CD18 peptides and consequently they cannot respond to C3b opsonin.

- Alternatively there may a defect in integrin molecules, LFA-1 or mac-1 arising from defective CD11a or CD11b peptides, respectively.

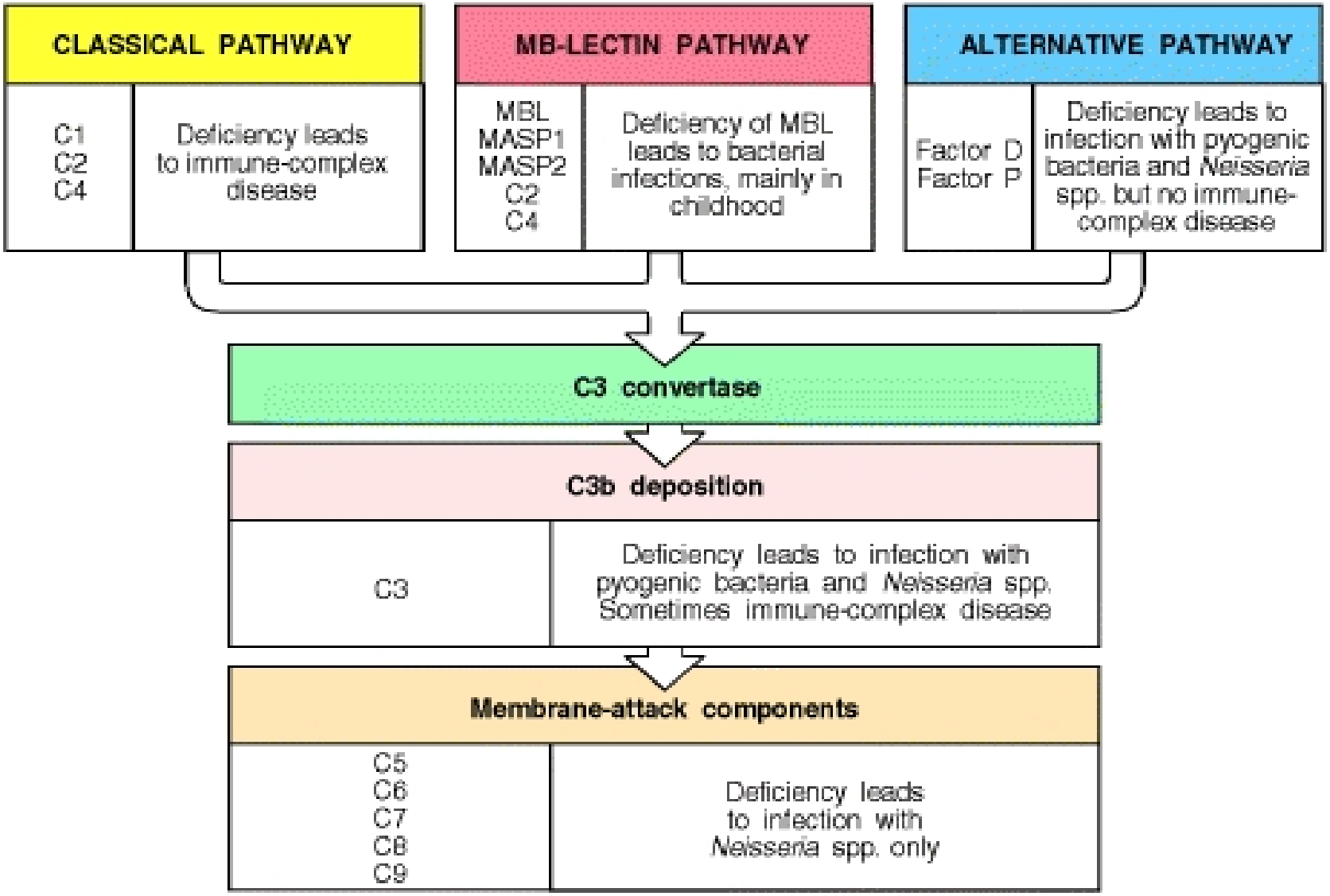
- These molecules are involved in diapedesis and hence defective neutrophils cannot respond effectively to chemotactic signals.

CHRONIC GRANULOMATOUS DISEASE (CGD):

- CGD is characterized by marked lymphadenopathy, hepato-splenomegaly and chronic draining lymph nodes.

- In majority of patients with CGD, the deficiency is due to a defect in NADPH oxidase that participate in phagocytic respiratory burst.

Deficiency of all complement components have been described C1-C9



SECONDARY IMMUNODEFICIENCY

Secondary immunodeficiencies, also known as acquired immunodeficiencies, can result from various immunosuppressive agents, for example, malnutrition, aging and particular medications (e.g., chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants, glucocorticoids).

For medications, the term immunosuppression generally refers to both beneficial and potential adverse effects of decreasing the function of the immune system, while the term immunodeficiency generally refers solely to the adverse effect of increased risk for infection. Many specific diseases directly or indirectly cause immunosuppression.

This includes many types of cancer, particularly those of the bone marrow and blood cells (leukemia, lymphoma, multiple myeloma), and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV). HIV directly infects a small number of T helper cells and also impairs other immune system responses indirectly.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

AIDS (acquired immune deficiency syndrome) was the great pandemic of the second half of the twentieth century. Fortunately the 2011 report issued by the Joint United Nations Programme on HIV I AIDS and the WHO indicates that the number of new HIV infections has decreased 2 1% since 1997, when the epidemic began to peak globally. Today 34 million people are infected and living with HIV/AIDS worldwide, up 17% since 2001.

First described in 1981, AIDS is the result of an infection by the human immunodeficiency virus (HIV), a positive- strand, enveloped RNA virus within the family Retroviridae. Molecular epidemiology data indicate that HIV-1 arose from the simian immunodeficiency virus (SIV) harbored by the chimpanzee (SIVcpz).

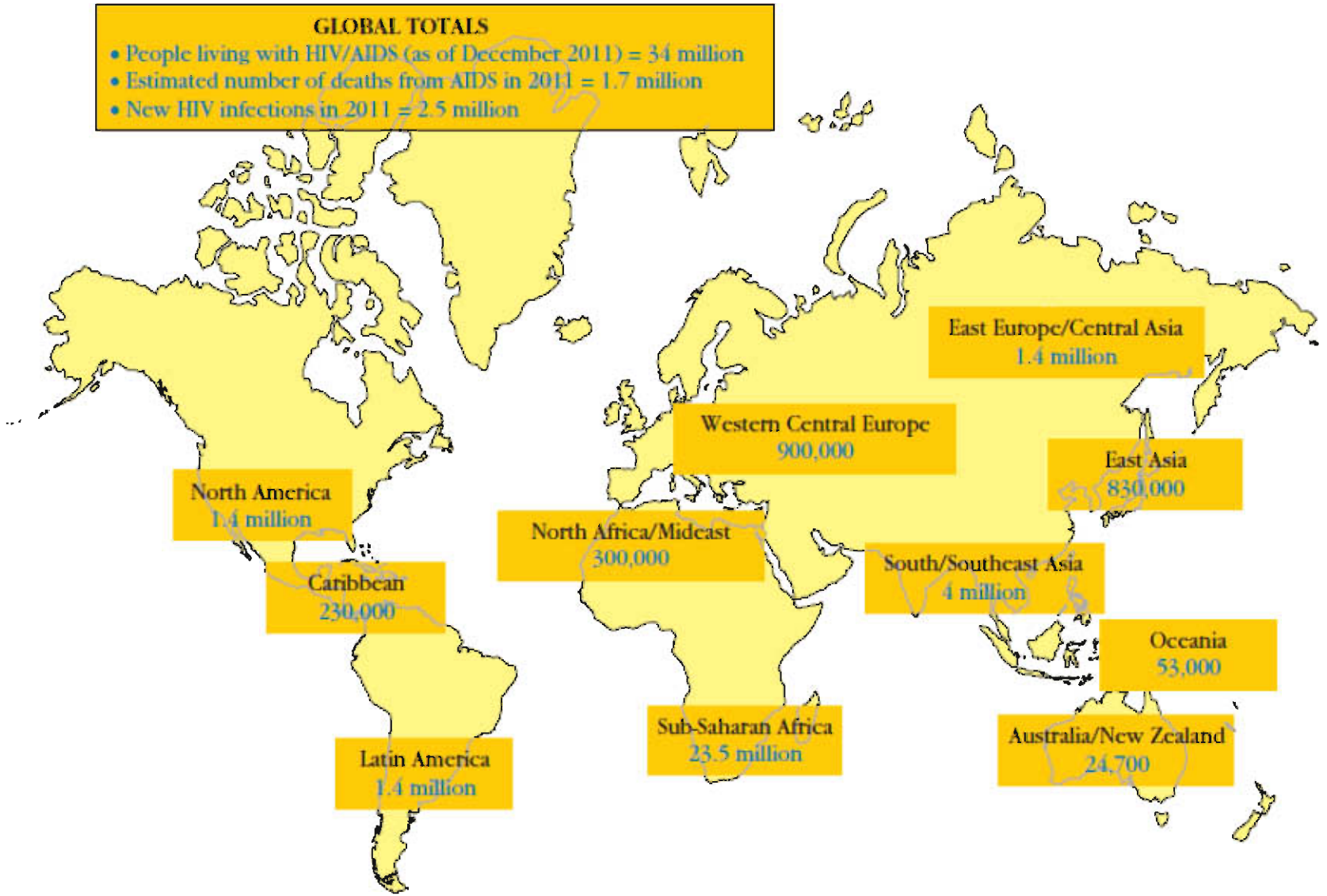


FIGURE 18-9 The global AIDS epidemic. As of 2011, approximately 34 million people worldwide were living with HIV; most of them were in sub-Saharan Africa and Southeast Asia. Although the rate of new infections is decreasing, 2.5 million people are estimated to have contracted HIV in 2011. *[UNAIDS Report on the Global AIDS Epidemic (2012), www.unaids.org/globalreport/global_report.htm.]*

HIV

The **human immunodeficiency viruses** (**HIV**) are two species of Lentivirus (a subgroup of retrovirus) that infect humans. Over time, they cause acquired immune deficiency syndrome (AIDS), a condition in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype. In most cases, HIV is a sexually transmitted infection and occurs by contact with or transfer of blood, pre-ejaculate, semen, and vaginal fluids.

HIV-1, was discovered and characterized in the laboratories of Luc Montagnier in Paris and Robert Gallo in Bethesda, Maryland.

About 2 years later, the infectious agent was found to be a **retrovirus of the lentivirus genus, which** display long incubation periods (*lente is Latin for "slow").* Retroviruses carry their genetic information in the form of RNA, and when the virus enters a cell this RNA is reversetranscribed (RNA to DNA, rather than the other way around) by a virally encoded enzyme, *reverse transcriptase* (RT).

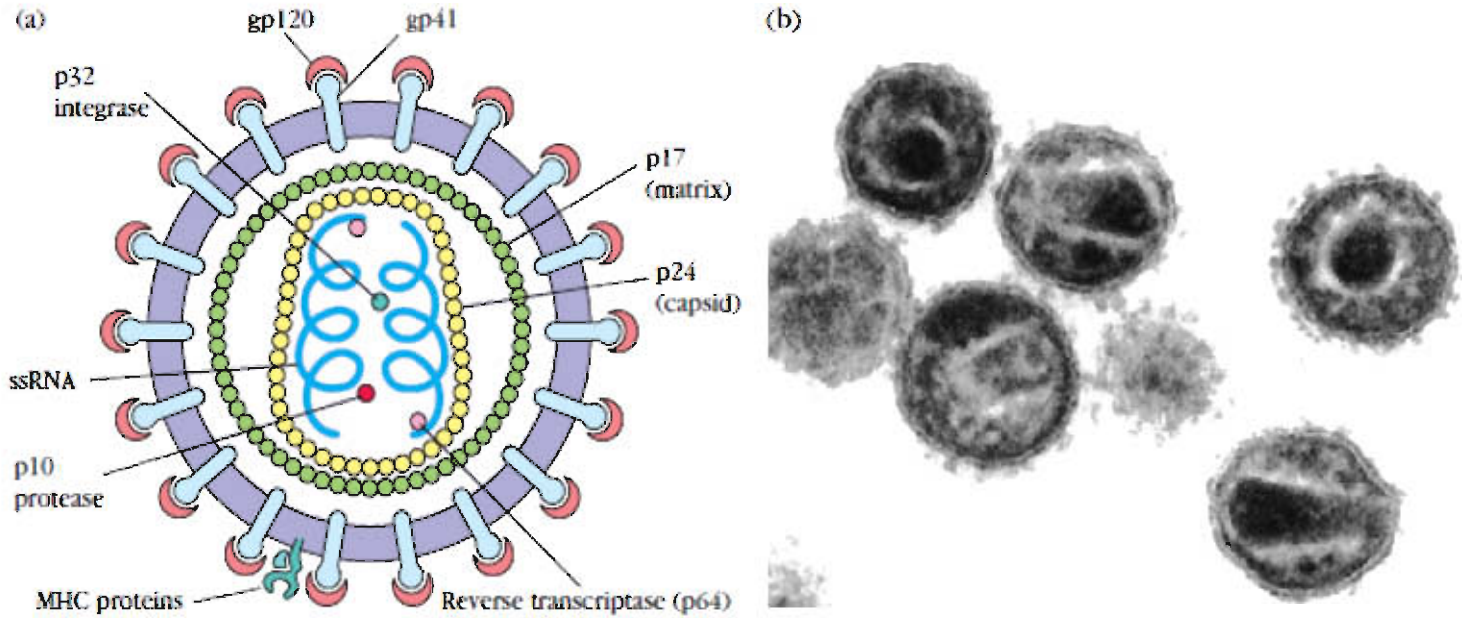
This copy of DNA, which is called a **provirus, is integrated** into the cell genome and is replicated along with the cell DNA. When the provirus is expressed to form new virions (viral particles), the cell lyses.

Alternatively, the provirus may remain latent in the cell until some regulatory signal starts the expression process. The discovery of a retrovirus as the cause of HIV was novel, since at the time only one other human retrovirus, *human T-cell lymphotropic virus I (HTLV-I),* had been identified.

Although comparisons of their genomic sequences revealed that HIV-1 is not a close relative of HTLV-I, similarities in overall characteristics led to use of the name HTLV-III for the AIDS virus in early reports.

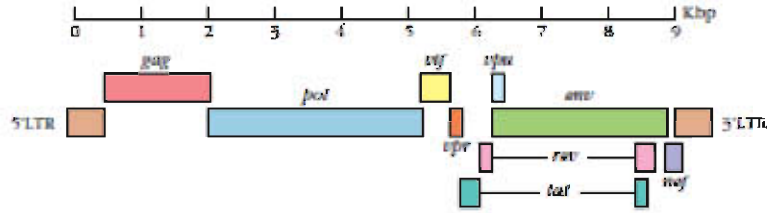
HIV-1 virions are approximately 110 nm in diameter, have a cylindrical core capsid, and their membrane envelopes are peppered with viral spike proteins. The core contains two copies of its RNA genome and several enzymes. Ten virus-specific proteins have been discovered. One of them, the gp120 envelope protein, facilitates attachment to a susceptible host cell (e.g., T-helper cell).

Structure of HIV



(a) Cross-sectional schematic diagram of HIV. Each virion carries 72 glycoprotein projections composed of gp120 and gp41: gp41 is a transmembrane molecule that crosses the lipid bilayer of the viral envelope, gp120 is associated with gp41, and together they interact with the target receptor (CD4) and coreceptor (CXCR4 or CCR5) on host cells. The viral envelope derives from the host cell and contains some host-cell membrane proteins, including class I and class II MHC molecules. Within the envelope is the viral matrix (p17) and the core, or nucleocapsid (p24). The HIV genome consists of two copies of single-stranded RNA (ssRNA), which are associated with two molecules of reverse transcriptase (p64) plus p10, a protease, and p32, an integrase. (b) Electron micrograph of HIV virions magnified 200,000 times. The glycoprotein projections are faintly visible as "knobs" extending from the periphery of each virion. *[Part a adapted from B. M. Peterlin and P. A. Luciw, 1988,* AIDS *2:S29; part b from a micrograph by Hans Geldenblom of the Robert Koch Institute (Berlin), in R. C. Gallo and L. Montagnier, 1988,* Scientific American *259(6):41.]*

(a)

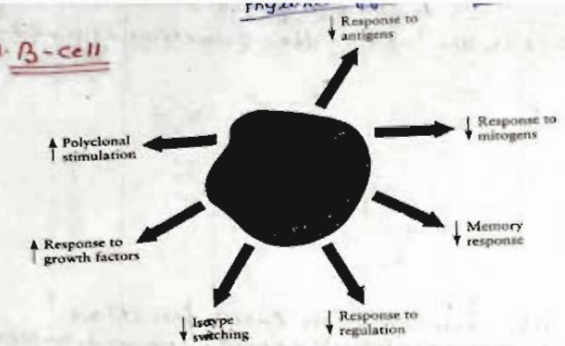


(b)

Gene	Protein product	Function of encoded proteins
gag	55-kDa precursor	*Nucleocapsid proteins*
	p17	Forms outer core-protein layer (matrix)
	p24	Forms inner core-protein layer (capsid)
	p9	Is component of nucleoid core
	p7	Binds directly to genomic RNA
env	160-kDa precursor	*Envelope glycoproteins*
	gp41	Is transmembrane protein associated with gp120 and required for fusion
	gp120	Protrudes from envelope and binds CD4
pol	Precursor	*Enzymes*
	p64	Has reverse transcriptase and RNase activity
	p51	Has reverse transcriptase activity
	p10	Is protease that cleaves *gag* precursor
	p32	Is integrase
		Regulatory proteins
tat	p14	Strongly activates transcription of proviral DNA
rev	p19	Allows export of unspliced and singly spliced mRNAs from nucleus
		Ancillary proteins
nef	p27	Down-regulates host-cell class I MHC and CD4
vpu	p16	Is required for efficient viral assembly and budding. Promotes extracellular release of viral particles, degrades CD4 in ER
vif	p23	Promotes maturation and infectivity of viral particle
vpr	p15	Promotes nuclear localization of preintegration complex, inhibits cell division

FIGURE 18-12 Genetic organization of HIV-1 (a) and functions of encoded proteins (b). The three major genes—*gag*, *pol*, and *env*—encode polypeptide precursors that are cleaved to yield the nucleocapsid core proteins, enzymes required for replication, and to envelop core proteins. Of the remaining six genes, three (*tat*, *rev*, and *nef*) encode regulatory proteins that play a major role in controlling expression, two (*vif* and *vpu*) encode proteins required for virion maturation, and one (*vpr*) encodes a weak transcriptional activator. The 5′ long terminal repeat (LTR) contains sequences to which various regulatory proteins bind. The organization of the HIV-2 and SIV genomes is very similar except that the *vpu* gene is replaced by *vpx* in both of them.

1. B-cell

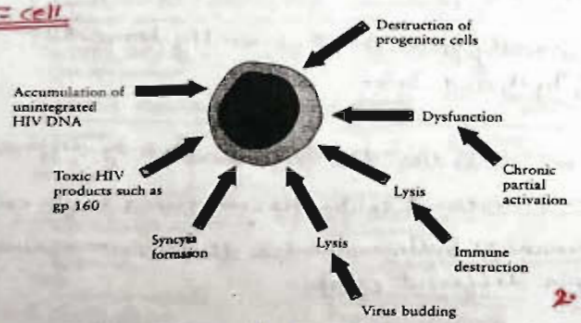


1. **Figure 27–9** The various effects of HIV on B-cell functions.

Major Dysfunction

B-cells → Abnormal proliferation
→ Poor antigen Response
→ Production of autoantibodies
⇓ leads to
Development of autoimmunity

2. T-cell



2. **Figure 27–10** The various ways in which HIV may impair CD4 T-cell function.

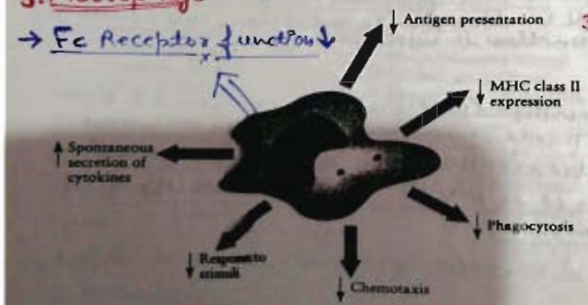
$CD8^+$ T-cells
→ Total number increases and then decreases.
→ Loss of anti-HIV activity

$CD4^+$ T-cells
→ Total numbers decreases
→ Expression of IL-2 decreases
→ Expression of IFN-γ decreases

SYNCYTIUM → The fusion of many cells into one large cytoplasmic mass containing multiple nuclei. This is the result of viral action.

3. Macrophage

→ Fc Receptor function ↓



3. **Figure 27–11** The effects of HIV-1 infection on macrophage function.

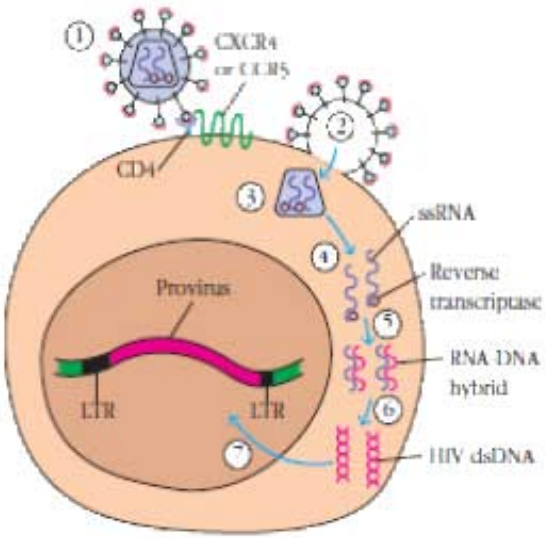
4. *NK-Cell Abnormalities*

Activity of natural killer (NK) cells is suppressed in AIDS patients, although NK-cell numbers are normal. These NK cells have reduced cytotoxic ability. This may be restored to normal by exposure of the NK cells to IL-2 or to concanavalin A. This suggests that NK cells are normally activated by T-cell–derived IL-2 and in its absence show defective function.

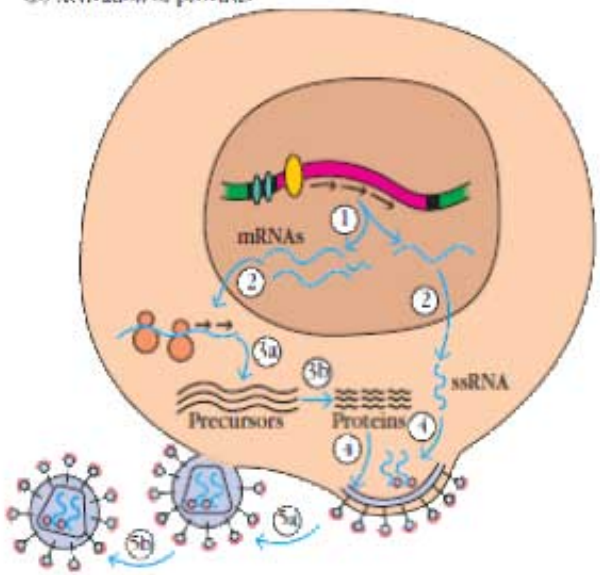
NK → Cytotoxicity function decreases.
→ NK cell cytotoxicity depends on IL-2.

HIV Infection of Target Cells and Activation of Provirus

(a) Infection of target cell



(b) Activation of provirus



(1) HIV gp120 binds to CD4 on target cell.

(2) HIV gp41 binds to a chemokine receptor (CXCR4 or CCR5) and fuses with the target cell membrane.

(3) Nucleocapsid containing viral genome and enzymes enters cells.

(4) Viral genome and enzymes are released following removal of core proteins.

(5) Viral reverse transcriptase catalyzes reverse transcription of ssRNA, forming RNA-DNA hybrids.

(6) Original RNA template is partially degraded by ribonuclease H, followed by synthesis of second DNA strand to yield HIV dsDNA.

(7) The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the viral integrase enzyme.

(1) Transcription factors stimulate transcription of proviral DNA into genomic ssRNA and, after processing, several mRNAs.

(2) Viral RNA is exported to cytoplasm.

(3a) Host-cell ribosomes catalyze synthesis of viral precursor proteins.

(3b) Viral protease cleaves precursors into viral proteins.

(4) HIV ssRNA and proteins assemble beneath the host-cell membrane, into which gp41 and gp120 are inserted.

(5a) The membrane buds out, forming the viral envelope.

(5b) Released viral particles complete maturation, incorporated precursor proteins are cleaved by viral protease present in viral particles.

(a) Following entry of HIV into cells and formation of dsDNA, integration of the viral DNA into the host cell genome creates the provirus. (b) The provirus remains latent until events in the infected cell trigger its activation, leading to formation and release of viral particles.

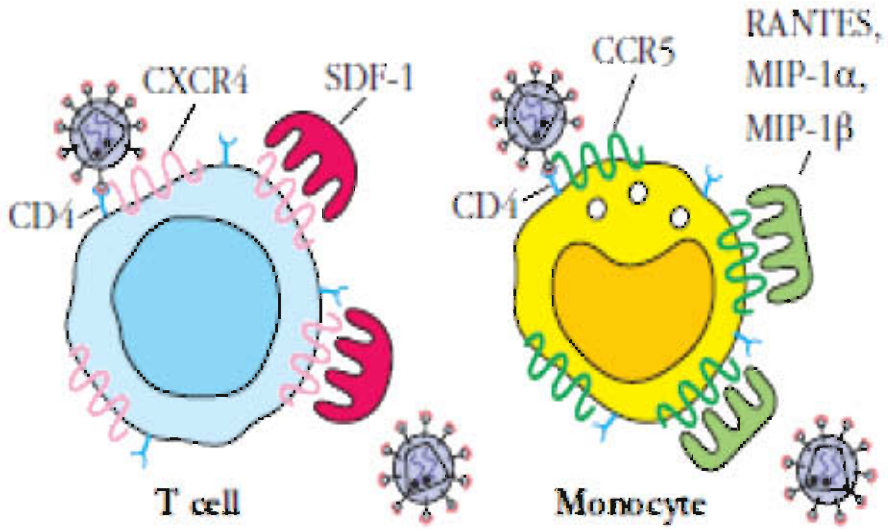


FIGURE 18-15 CXCR4 and CCR5 serve as coreceptors for HIV infection. Although CD4 binds to the envelope glycoprotein of HIV-1, a second coreceptor is necessary for entry and infection. T-cell–tropic strains of HIV-1 use the coreceptor CXCR4, whereas the macrophage-tropic strains use CCR5. Both are receptors for chemokines, and their normal ligands (SDF-1, RANTES, and MIP) can block HIV infection of the cell.

TABLE 18-3 Stage definition for HIV infection among adults and adolescents

Stage*	$CD4^+$ T-cell count		$CD4^+$ T-cell percentage		Clinical evidence
1	≥ 500/μL	or	> 29%	and	No AIDS-defining condition
2	200–499/μL	or	14–28%	and	No AIDS-defining condition
3 (AIDS)	< 200/μL	or	< 14%	or	Presence of AIDS-defining condition

AIDS-DEFINING CONDITIONS:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (> 1 month duration) or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1 month duration)
- Kaposi's sarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome attributed to HIV

* All require laboratory confirmation of HIV infection

TABLE 18-4 Immunologic abnormalities associated with HIV infection

Stage of infection	Typical abnormalities observed
	LYMPH NODE STRUCTURE
Early	Infection and destruction of dendritic cells; some structural disruption, especially to gastrointestinal tract-associated lymphoid tissues
Late	Extensive damage and tissue necrosis; loss of follicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells
	T HELPER (T_H) CELLS
Early	Depletion of $CD4^+$ T cells, especially in the gut (T_H17 main targets); loss of in vitro proliferative response to specific antigen
Late	Further decrease in T_H-cell numbers and corresponding helper activities; no response to T-cell mitogens or alloantigens
	ANTIBODY PRODUCTION
Early	Enhanced nonspecific IgG and IgA production but reduced IgM synthesis
Late	No proliferation of B cells specific for HIV 1; no detectable anti-HIV antibodies in some patients; increased numbers of B cells with low CD21 expression and enhanced Ig secretion
	CYTOKINE PRODUCTION
Early	Increased levels of some cytokines
Late	Shift in cytokine production from T_H1 subset to T_H2 subset
	DELAYED-TYPE HYPERSENSITIVITY
Early	Highly significant reduction in proliferative capacity of T_H1 cells and reduction in skin-test reactivity
Late	Elimination of DTH response; complete absence of skin-test reactivity
	T CYTOTOXIC (T_C) CELLS
Early	Normal reactivity
Late	Reduction but not elimination of CTL activity due to impaired ability to generate CTLs from T_C cells

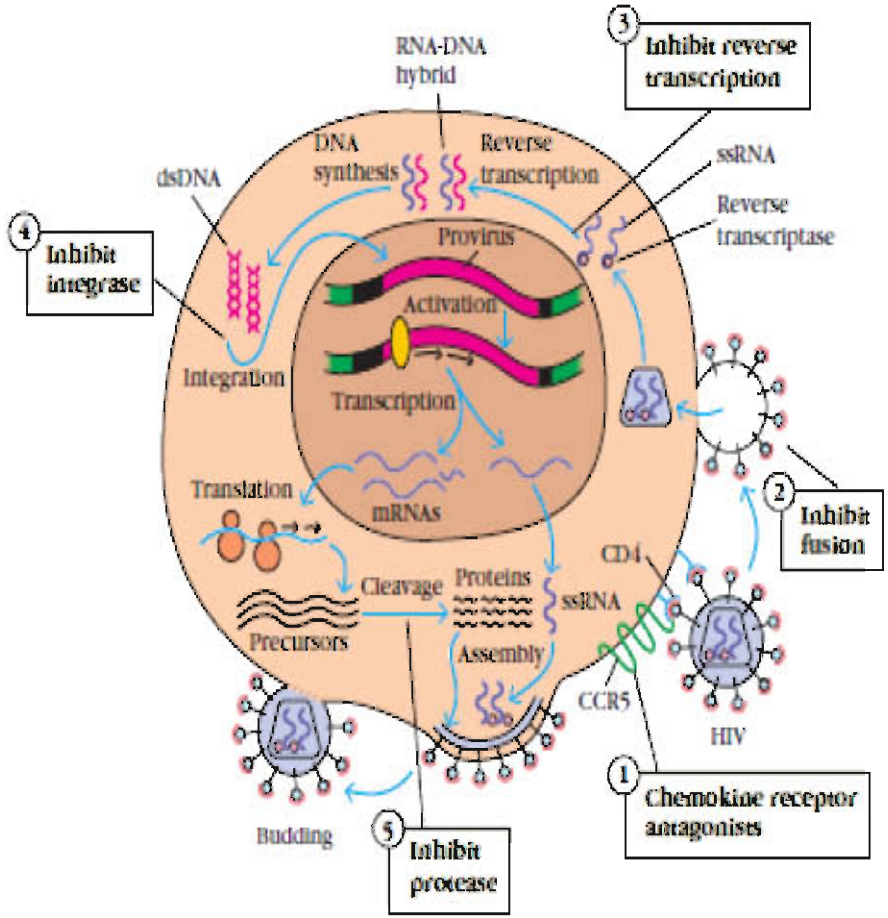


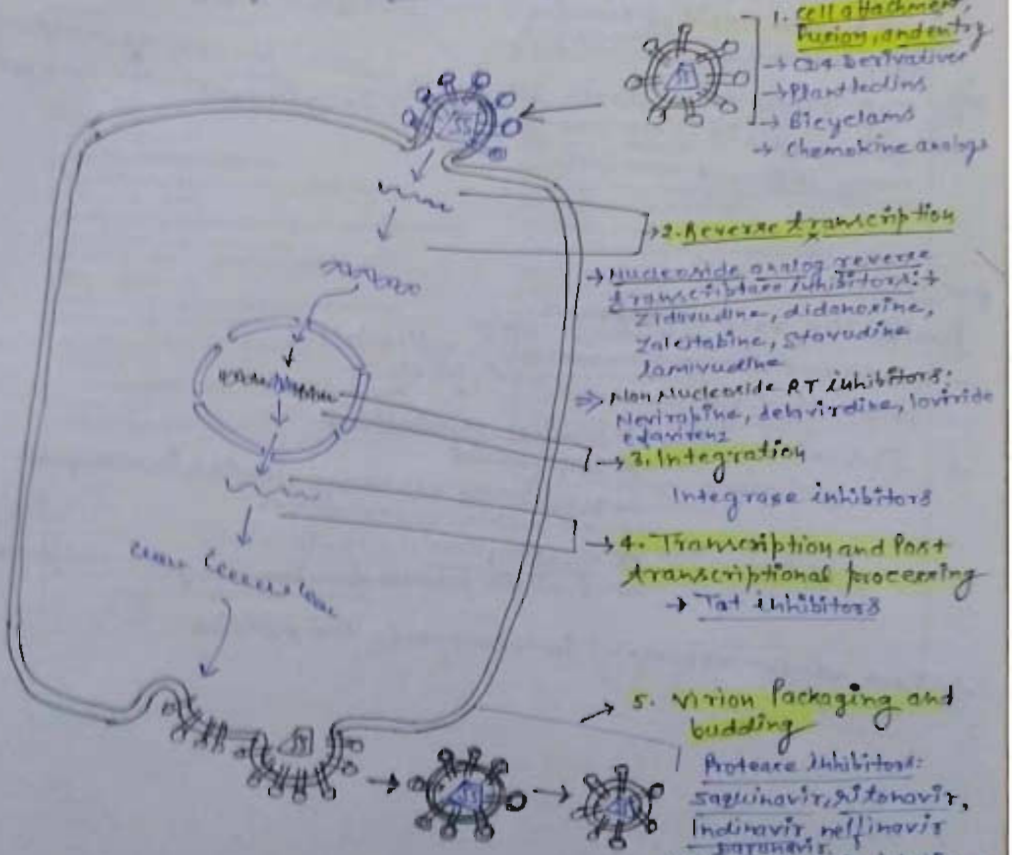
FIGURE 18-18 Stages in the viral replication cycle that provide targets for therapeutic antiretroviral drugs. The first licensed drugs with anti-HIV activity interfered with reverse transcription of viral RNA to cDNA (3), followed by drugs which blocked the viral protease that cleaves precursor proteins into the peptides needed to assemble new virions (5). In the past decade, newer drugs have come on the market that interfere with other steps in the viral life cycle, such as HIV coreceptor attachment (1) or fusion to the cell membrane (2), as well as the viral integrase necessary for insertion of proviral DNA into the host cell chromosome (4).

Prevention and control of Viral Diseases

- The antiretro agents inhibit retrovirus replication.
- Treatment of HIV infection with antiretroviral drugs that targets specific steps in the viral life cycle, especially in combination, can lower the viral load and provide relief from some symptoms of infection. However, no cures for HIV are available.

Daily use

- Important steps in the Replication of HIV:
- There are five step for antiviral compounds in the life cycle of HIV are highlighted as potential targets for antiviral compounds



IMPORTANT POINT

• **Primary immunodeficiency diseases** result from intrinsic defects in immune system cells, complement components, and phagocytic cells.

• **Defects in B cell function** result in recurrent pyogenic infections. Defective antibody responses are due to failure of B cell function, as occurs in X-linked agammaglobulinemia, or failure of proper T cell signals to B cells, as occurs in hyper-IgM (HIgM) syndrome, common variable immunodeficiency (CVID), and transient hypogammaglobulinemia of infancy.

• **Poor T cell function** results in susceptibility to opportunistic infections. Defective cell-mediated immunity is due to failure of T cell function, seen for example in severe combined immunodeficiency (SCID), MHC class II deficiency, ataxia telangiectasia (AT), the Wiskott–Aldrich syndrome (WAS), and the DiGeorge anomaly.

• **Hereditary complement component defects** are found in a number of clinical syndromes, the most common of which is that of the C1 inhibitor, which results in hereditary angiedema (HAE). Hereditary complement deficiencies of the terminal complement components (C5, C6, C7, and C8) and the alternative pathway proteins (factor H, factor I, and properdin) lead to extraordinary susceptibility to infections with the two *Neisseria species*, *N. gonorrheae and N. meningitidis.*

• **Genetic defects of phagocytes** can result in overwhelming infection. Defects in the oxygen reduction pathway of phagocytes, such that the phagocytes cannot assemble NADPH oxidase and produce the hydrogen peroxide and oxygen radicals that kill bacteria, are the basis of chronic granulomatous disease (CGD). The resulting persistence of bacterial products in phagocytes leads to abscesses or granulomas, depending on the pathogen.

• **Leukocyte adhesion deficiency (LAD)** is associated with a persistent leukocytosis because phagocytic cells with defective integrin molecules cannot migrate through the vascular endothelium from the blood stream into the tissues.

IMPORTANT POINTS
(AIDS and Secondary Immundeficiency)

• Some drugs selectively alter immune function.
Immunomodulatory drugs can severely depress immune functions. Steroids affect cell traffic, induce leukocytopenia, and inhibit cytokine synthesis. Cyclophosphamide, azathioprine, and mycophenolate mofetil act directly on DNA or its synthesis.

• Nutrient deficiencies are generally associated with impaired immune responses. Malnutrition increases the risk of infant mortality from infection through reduction in cell-mediated immunity, reduced CD4 helper cells, reduced T cell help, and a reduction of secretory IgA. Trace elements, iron, selenium, copper, and zinc are important in immunity. Lack of these elements can lead to diminished neutrophil killing of bacteria and fungi, susceptibility to viral infections, and diminished antibody responses. Vitamins A, B6, C, E, and folic acid are important in overall resistance to infection.

• **Antioxidant activity.** Carotenoids are antioxidants like vitamin C and E and can enhance NK cell activity, stimulate the production of cytokines and increase the activity of phagocytic cells. Diet and nutrition are powerful innovative tools to reduce illness and death caused by infection.

• **The most significant global cause of immunodeficiency is HIV infection.** AIDS is caused by HIV, which is a double stranded RNA retrovirus that infects CD4 T cells. Severe CD4 depletion results from a variety of mechanisms, with drastic functional impairment of cell-mediated immunity and death from opportunistic infections.

• **Combination therapy for AIDS with inhibitors of reverse** transcriptase, protease, and viral entry are reasonably successful, but associated with long-term toxicities in almost 50% of persons. An effective vaccine remains an elusive goal.

Note: A state in which the ability of the immune system to fight infectious disease is compromised or entirely absent. A person who has an immunodeficiency is said to be **immuno-compromised.**

THANKS