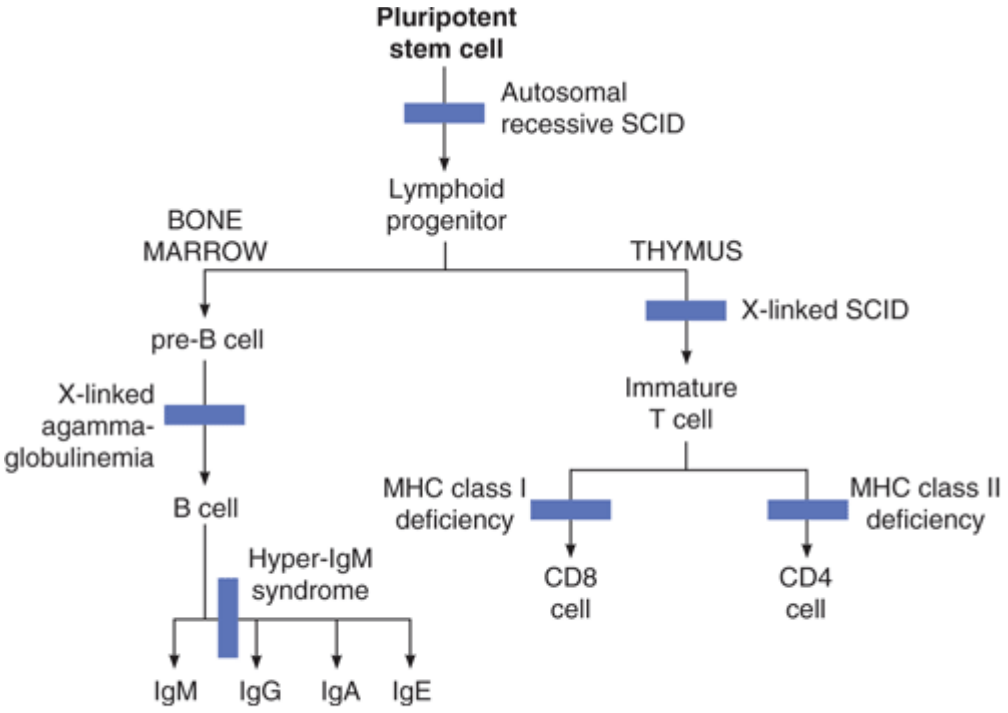
IMMUNODEFICIENCY DISEASES

Kenneth Alonso, MD, FACP

Immunodeficiency diseases

- Leukocyte adhesion deficiency involves neutrophils and macrophages.
- The lymphoid progenitor cell (or the pre-B and pre-T cell) is involved in severe combined immunodeficiency.
- X-linked agammaglobulinemia involves the pre-B cell, while the other immunoglobulin deficiencies involve mature B cells.
- DiGeorge's syndrome involves thymocytes.
- Wiskott-Aldrich involves the mature B-cell and mature T-cell.
- The bare lymphocyte syndrome involves the mature T-cell.

Block in B and T cell development



(Modified from Rosen FS, Cooper MD, Wedgwood RJP: The primary immunodeficiencies. *N Engl J Med* 1995;333:431.)

Fig. 3-12 Accessed 07/01/2010

Inheritance patterns

- **Autosomal recessive**
- Chediak-Hagashi
- Leukocyte adhesion deficiency
- Adenosine deaminase deficiency
- Ataxia-telangiectasia
- Bare lymphocyte syndrome
- Defect in signal transduction
- Defect in recombinase activity

Inheritance patterns

- **X-linked**
- Chronic granulomatous disease
- Agammagloublinemia
- Hyper IgM syndrome
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Properdin deficiency

- **Autosomal dominant**
- Hereditary angioedema
- DiGeorge’s syndrome

Chronic granulomatous disease

- Mutation in one of 4 genes for NADPH Oxidase; failure to generate reactive Oxygen species.
- X-linked.
- Severe and recurrent infections with catalase positive organisms and fungi.
- Staphylococcus, Klebsiella, Serratia, Candida, Pseudomonas and Aspergillus.
- Unresolved infections lead to granuloma formation.
- Nitrotetrazolium blue test diagnostic.
- Treat with antibiotics, interferon-γ. Bone marrow transplant may be curative.

Chediak-Hagashi

- Phagocytosed material is not delivered to the lysosomes because of a fusion defect. Affects the synthesis and maintenance of storage granules in many cell types including neutrophils, melanocytes, monocytes, and NK cells.
- Autosomal recessive.
- Recurrent bacterial Infections. Partial albinism.
- A routine blood smear reveals giant granules in neutrophils and monocytes. Neutropenia.
- No NK activity (increased incidence of lymphomas).
- Maintained with gamma globulins. Bone marrow transplant is curative.

Leukocyte adhesion deficiency

- Autosomal recessive.
- Mutation in CD18 (LADI) or
- Mutation in ligands for E/P selectins which share a common β-chain with CD18 (LADII).
- Loss of cell adhesion molecules CR2, CR4 and LFA-1
- No diapedesis. Impaired opsonization.
- Patients suffer with recurrent pyogenic infections, impaired wound healing and severe gum inflammation despite leukocytosis.
- Treatment with antibiotics and Interferon-γ. Bone marrow transplant is curative.

Other phagocytic disorders

- **Glucose-6-phosphate dehydrogenase deficiency.**
- Manifests similar to Chronic Granulatous Disease. Hemolytic anemia as well.
- G6PD is required to generate much of NADPH from which NADPH oxidase draws electrons for reactive oxygen species.
- **Myeloperoxidase deficiency.**
- Myleoperoxidase is found in neutrophil granules and catalyzes the conversion of H_20_2 and chloride ions to the potent oxidizer, hypochlorous acid.
- May go undiagnosed if no severe infections.

Defects in early complement components

- C2 deficiency is the most common complement deficiency. Primarily presents in young children (upper airway and ear infections). Streptococcus pneumoniae common agent.
- As C3 is common to all pathways, deficiencies in complement proteins C1, C2, and C4, lead to the accumulation of immune complexes in the blood and lymph and may deposit in the tissues causing inflammation and tissue damage.
- Factor H deficiency leads to uncontrolled activation of the alternative pathway with depletion of C3. May present as atypical Hemolytic-Uremic syndrome or age-related macular degeneration.

Defects in early complement components

- Mannose binding lectin deficiency is found in up to 30% of individuals. Important in infancy until child's own antibody production fully functional. Susceptible to Herpes simplex virus-2, influenza A, Staphylococcus aureus, and Pseudomonas aeruginosa infections.
- Fc receptor deficient leukocyte activation leads to recurrent pyogenic infections.
- Treatment varies depending on severity, immunosuppression and supportive care are common.
- Other mutations in glycophosphatidyl inositol linkages affect decay accelerating factor (DAE) and CD59, leading to hemolysis.

Defects in early complement components

- Properdin deficiency as well as C5-C9 (Membrane Attack Complex) deficiency are associated with increased susceptibility and severity of infections with Neisseria species.
- MAC deficiencies present later in life.
- Patients are treated with 3rd and 4th generation cephalosporins for infection. Meningococcemia may be seen.

Defects in early complement components

- **Hereditary angioedema (HAE)**
- Autosomal dominant. C1inh deficiency.
- Leads to uncontrolled activation of the classic complement pathway.
- Overproduction of C2 as a result of the loss of protease inhibitor leads to increased kallikrein activity with resulting edema.
- Presents in puberty.

Defects in early complement components

- HAE usually noticeable after trauma.
- Airway obstruction may be fatal.
- Acute abdominal pain as a presenting sign in these patients is not a surgical emergency.
- Acute attack treated with commercial C1inh or fresh frozen plasma.
- Androgens suppress the symptoms of HAE.

B-cell deficiencies

- Usually characterized by recurrent bacterial infections with normal immunity to viruses, fungi, and parasites.
- Most common infections include Staphylococcus and Streptococcus spp/ because antibody is critical for the opsonization and clearance of these organisms.
- X linked agammaglobulinemia
- X linked hyper IgM
- Common variable hypogammaglobulinemia
- Hyopgammaglobulinemia of infancy
- Selective IgA deficiency (1 in 600 patients)

X-linked agammaglobulinemia

- btk mutation (Bruton's tyrosine kinase). Important in the development of pre-B cells to mature B cells.
- Rudimentary germinal centers. No circulating B cells. Immunoglobulin levels depressed.
- Patients have difficulty with encapsulated bacteria such as H.influenzae, S.pneumoniae, S.pyogenes and S.aureus and increased severity of enteroviral infections.
- Usually appears around 6 months of age. Presents with sinus or pulmonary infections. Giardia infections may be difficult to eradicate (little secretory IgA).
- Treated with intravenous gamma globulin monthly and antibiotics as needed. T cell function intact.

Hyper-IgM syndrome

- X-linked.
- Mutation in CD40 Ligand (CD 154) on T cells.
- CD40 Ligand is necessary for T cell contact with B cell to permit class switching to antibodies other than IgM.
- No germinal centers are formed.
- Increased levels of IgM and decreased levels of other immunoglobulins noted.
- Patients usually have recurrent bacterial and opportunistic infections and severe diarrhea.
- Treated with intravenous gamma globulin and antibiotics.

Common variable immunodeficiency

- Heterogeneous disease.
- There is a disorder that occurs in 2nd-3rd decade that is associated with inadequate T cell to B cell signaling. Thus, B cells do not differentiate into plasma cells.
- Germinal centers are hyperplastic. B cells can be found in the peripheral blood.
- Immunoglobulin levels are low, however (at times only IgG is affected). Immunoglobulin levels decrease with age.

Common variable immunodeficiency

- 20% of patients will have autoimmune disorders.
- 30% of patients have serious infections with Herpes simplex virus. May present with sinus or pulmonary infection, diarrhea. Meningoencephalitis may result.
- Treated with intravenous gamma globulin and antibiotics.

Transient hypo-gammaglobulinermia of infancy

- Delayed onset of normal IgG synthesis.
- Usually presents in the 5^{th} to 6^{th} month of life.
- Usually resolves by 2-6 years of age.
- Patients usually have recurrent respiratory infections.
- Treatment with intravenous gamma globulin and antibiotics as needed.

Selective IgA deficiency

- Most common of the Immunodeficiency Diseases.
- Genetic component not known.
- 40 types have antibodies to IgA. In the others the IgA+ B cells do not differentiate into plasma cells. IgG2-4 deficit as well.
- May be asymptomatic. However, may present with an increased incidence of respiratory and gastrointestinal tract infections.
- Intestinal malabsorption, allergies, and autoimmune disorders are also seen.
- May see severe transfusion reaction.
- Treated with antibiotics as need. Intravenous immunoglobulins are not used.

T-cell deficiencies

- Because T cells orchestrate the immune response, T cell deficiencies can affect both the humoral and cell mediated responses.
- Generally severe.
- Patients usually have increased incidence of Infections with fungal and viral pathogens.
- DiGeorge’s.
- Thymus aplasia.

DiGeorge's syndrome

- Autosomal dominant (del 22q11).
- Failure of formation of 3rd and 4th pharyngeal pouches between weeks 10-12 of gestation (development of aortic arch). Thymus absent.
- Associated cardiovascular anomalies; abnormal facial features.
- Depleted paracortical areas and periarteriolar sheaths.

DiGeorge's syndrome

- Few T cells. Poor cell mediated immunity.
- Normal numbers of plasma cells.
- Recurrent infections with intracelluar pathogens, Candida (chronic mucocutaneous candidiasis), and viruses.
- Treated with fetal thymic transplants and bone marrow transplants.

MHC I deficiency

- Failure of TAP-1 molecules to transport peptides to endoplasmic reticulum.
- MHC I expression blocked. No T cell development.
- Delayed type hypersensitivity intact.
- Normal levels of immunoglobulins.
- Recurrent infections with intracellular pathogens.
- Bone marrow transplant may be curative.

Combined immunodeficiency diseases

- Usually comprises defects in both the humoral and cell mediated arms of the immune system.
- Patients are susceptible to any type of pathogen, even those with low virulence.
- Severe combined immunodeficiency disease.
- Wiskott-Aldrich Syndrome.
- Ataxia-Telangiectasia.

Severe combined immunodeficiency

- X-linked.
- Mutations in the IL-2R γ- chain (shared by IL 4, 7, 9, 15). Acts through Jak3 kinase.
- No response to mitogens.
- Few circulating large lymphocytes.
- Impaired sexual and lymphoid tissue development (IL-7 defect).
- Bone marrow transplant may be curative.

Severe combined immunodeficiency

- Morbiliform rash at birth as a result of transplacental transfer of maternal T cells (a graft versus host reaction).
- Chronic diarrhea. Mucocutaneous lesions. Opportunistic infections.

Adenosine deaminase deficiency

- Autosomal recessive.
- Increases deoxyadenosine and this is converted back to dATP. Synthesis of dCTP, dUTP, dGTP is blocked. 2'-deoxyadenosine also inhibits S-adenosyl homocysteine hydrolase which decreases methylation reactions vital to normal cell function. T and B cell function is impaired.
- No response to mitogens.
- Chronic diarrhea. Mucocutaneous lesions. Opportunistic infections.
- Few circulating large lymphocytes.
- Bone marrow transplant may be curative.

Defect in signal transduction

- Autosomal recessive.
- Mutation in Jak3 gene impairs signal transduction through the common cytokine receptor γ chain.
- No response to mitogens.
- Impaired sexual and lymphoid tissue development.
- Chronic diarrhea. Mucocutaneous lesions. Opportunistic infections.
- Few circulating large lymphocytes.
- Bone marrow transplant may be curative.
- Method of inheritance distinguishes this from severe combined immunodeficiency disease.

Mutation in recombinase activity genes

- Autosomal recessive.
- Affects somatic gene rearrangement. Blocks T and B cell development. No response to mitogens.
- Chronic diarrhea. Mucocutaneous lesions. Opportunistic infections.
- Few circulating large lymphocytes.
- Bone marrow transplant may be curative.

Wiskott-Aldrich syndrome

- Complex X-linked disorder (Xp11.23).
- Mutation in leukosialin (CD43) which is responsible for actin filament assembly and cytoskeletal rearrangement; necessary for T cell signaling.
- Thymus normal.
- IgM levels depressed. IgG normal. IgA and IgE increased.
- Thrombocytopenia, eczema, immunodeficiency. No antibody to polysaccharide antigens.
- Severity increases with age. Usually results in fatal infections or B cell lymphoid malignancy.
- Treated with immunoglobulins and corticosteroids. Bone marrow transplant curative.

Ataxia-telangiectasia

- Autosomal recessive (11q22.3).
- Mutation in a DNA repair kinase.
- Choreoathetosis. Ataxia presents as child learns to walk.
- Oculomotor apraxia.
- Oculo-cutaneous telangiectasia. May see broken capillaries.
- IgA and occasionally IgE deficient.
- Cell mediated immunity defects are variable.
- Greater risk of malignancy.
- No specific therapy.

Bare lymphocyte syndrome

- Autosomal recessive.
- MHC II expression blocked. Few CD4+ cells.
- T cells present and respond to non-specific mitogens.
- No graft versus host disease.
- Diminished levels of immunoglobulins.
- Recurrent infections with intracellular pathogens. May present with mucocutaneous candidiasis.
- Bone marrow transplant may be curative.

Acquired immunodeficiency syndrome

- The human immunodeficiency retrovirus (HIV) is thought to be the cause of a syndrome characterized by profound immunosuppression and opportunistic infections and secondary neoplasms.
- Transmitted in semen, blood and blood products, and in passage from infected mothers to their newborns either in utero, in the birth canal, or in colostrum. (Female-female transmission is very slight. Female-male transmission is 1 in 100,000.)
- Direct inoculation of blood vessels breached by trauma or entry into dendritic cells (rich in CCR5) or CD4 cells within the mucosa.

Acquired immunodeficiency syndrome

- CD4 molecule is high affinity receptor for HIV. HIV gp120 envelope glycoprotein binds and leads to conformational change that exposes a recognition site for a chemokine coreceptor. CCR5 (M tropic strains) and CXCR 4 (T tropic strains) are the receptors utilized.
- Following such binding, the HIV gp41 transmembrane glycoprotein noncovalently attached to gp120 undergoes a conformational change that results in the insertion of a fusion peptide at the tip of gp41 into the cell membrane of the target cell, permitting virus entry.

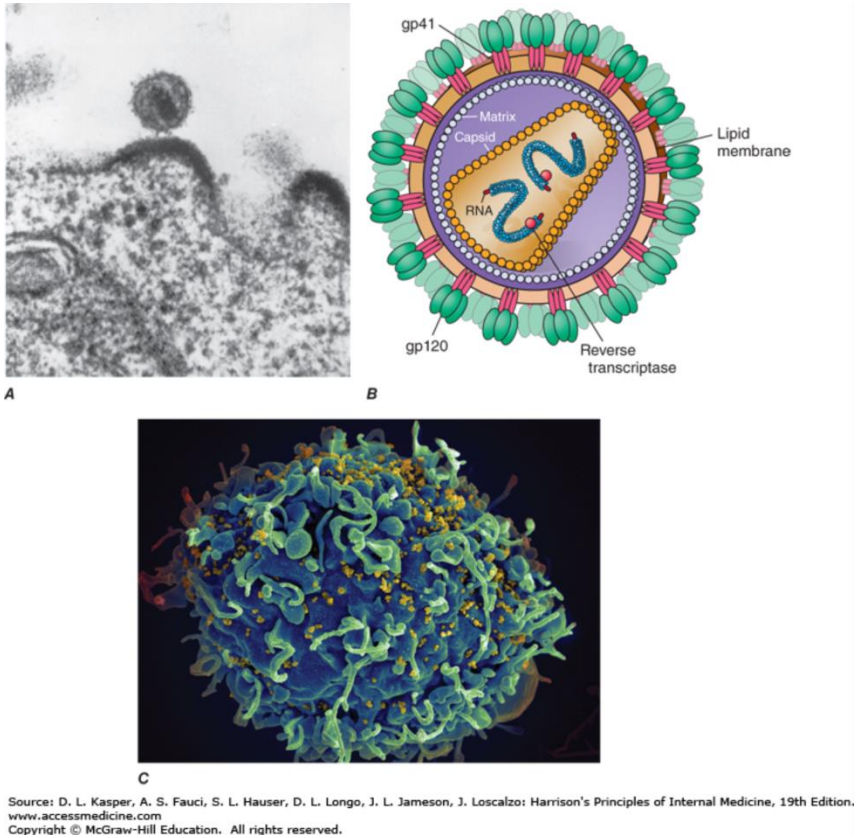
Acquired immunodeficiency syndrome

- M tropic viruses are more efficient in transmission. In addition to high density of CCR5 and lack of expression of CXCR4 on dendritic cells, binding triggers cell to produce chemotactic factors for other T-cells.
- Lymphoid organs are reservoir of infected cells.
- Productive infection of T cells and viral replication in infected cells is the major mechanism by which HIV causes lysis of CD4 cells. Killing of virus infected cells as well as apoptosis of chronically activated uninfected cells are other mechanisms of cell loss.

HIV

- HIV-1 common type associated with AIDS in the US, Europe, Central Africa
- HIV-2 common type associated with AIDS in West Africa and Asia
- Capsid is icosahedral.
- Retrovirus genomic RNA contains gag, pol, env genes. Gag and pol gene products cleaved by protease to yield mature proteins.
- The viral core contains the capsid proteins, two copies of single stranded genomic RNA, and, as well, protease, reverse transcriptase, and integrase.

HIV morphology



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A. Electron micrograph of HIV. Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. B. Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). (Copyright by George V. Kelvin.) (Adapted from RC Gallo: Sci Am 256:46, 1987.) C. Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 8000× magnification. (Courtesy of Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases; with permission.)

HIV

- p24 is the capsid protein, and binds cyclophilin A.
- p7 is the nucleocapsid protein that binds RNA.
- p6 interacts with vpr, participates in terminal steps of virion budding.
- p17 is a matrix protein that surrounds the viral core and underlies the viral envelope and stabilizes it; helps target Gag proteins to lipid rafts, promoting virus assembly at cell surface.
- 50 copies of reverse transcriptase (reverse transcriptase is error prone; associated with high HIV mutation rate)

HIV

- Gp 160 is the envelope protein that is cleaved in the endoplasmic reticulum. It yields, gp120, the surface protein that binds to CD4 on the host cell and then to one of the two chemokine receptors (CCR5 or CXCR4); and, gp41, the transmembrane protein that permits fusion
- Gene specific to HIV include nef, rev, tat, vpr, vpu, and vif.
- The nef gene produces negative factor that down-regulates MHC I expression on infected T_H cells, enhancing virion infectivity.

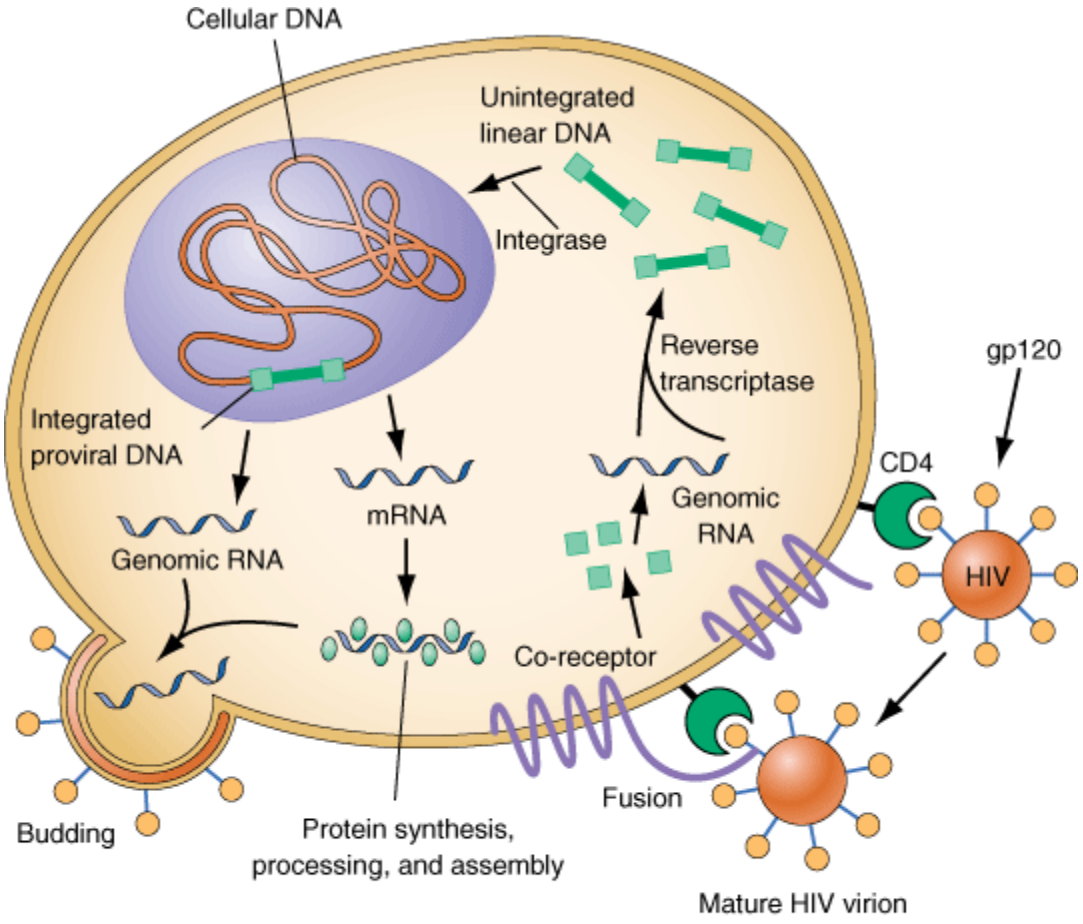
HIV

- The rev gene promotes nuclear export of incompletely spliced RNA into cytoplasm.
- The tat gene upregulates Pol-II mediated elongation of integrated viral DNA.
- The long terminal repeat is required for initiation of transcription. It contains control regions that bind transcription factors (e.g., NF-κB) as well as the RNA trans-acting response element (TAR) that binds tat.
- The presence of NF-κB binding sites in the genome promotes proviral transcription in the face of any environmental antigen exposure that activates T cells and macrophages.

HIV

- The vpr gene increases viral replication as well as facilitates infection of mucosal dendritic cells (macrophages). Interacts with p6.
- The vpu gene promotes CD4 degradation and increases virion release.
- The vif gene produces an infectivity factor that overcomes the inhibitory effect of host factor (APOBEC3G) in unactivated T cells by binding to this cytidine deaminase and promoting its degradation by protease.

HIV replication cycle



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

(Adapted from Fauci AS: Host factors and the pathogenesis of HIV-induced disease. Nature 384:529, 1996

Fig. 182-3 Accessed 07/01/2010

HIV replication cycle

- gp120 binding to CD4 occurs first. Requires binding to other chemokine receptors to enter cell (CCR5, CXCR4)
- Conformational change leads to exposure of chemokine binding site and chemokine binding.
- Conformational change in gp41 exposes fusion peptide in hydrophobic region at gp41 tip. Fusion peptide penetrates cell membrane
- Fusion of HIV membrane with host cell membrane leads to entry of viral genome into cytoplasm
- Dendritic cells bind HIV with ganglioside Selgic-1 and present virus to T cell in that fashion.

HIV replication cycle

- Reverse transcriptase mediated synthesis of double stranded complementary (proviral) DNA. Remains in linear form in quiescent cell.
- In dividing cells, the cDNA circularizes, enters the nucleus, and integration of provirus into host cell genome occurs.
- HIV RNA transcripts leave nucleus for cytoplasm where virion assembled. Membrane budding and release of mature virion follows.

HIV tropism

- M-tropic R5 virus found in 90% of acutely infected individuals early in the course of infection
- Attracted to CCR5 co-receptors; macrophages allow entry (early in infection).
- T-tropic X4 virus
- Attracted to CXCR4 co-receptors; T-cells allow entry (late in infection). Infects even thymus T-cell precursors. Correlates to a more rapid progression to AIDS.
- Form syncytia in cell culture.

HIV tropism

- HIV persistence noted more frequently in those populations without HLA DRB1*1302 (Gambia).
- HIV progression associated with HLA B35, HLA A1, HLA B8, HLA DR3 antigens (and absence of HLA B27) not reproduced consistently.

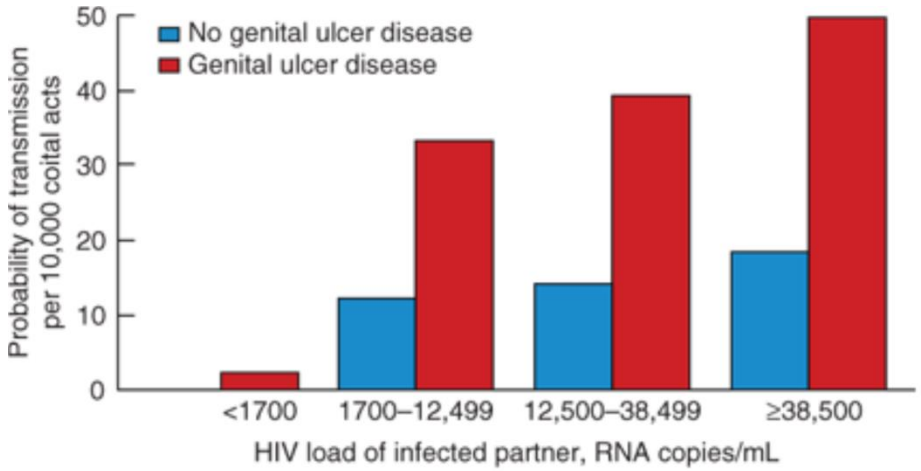
HIV

- Very rapid decrease in GALT CD4 lymphocytes.
- Slow progressive decrease in circulating CD4 lymphocytes (chronic activation of uninfected cells leads to apoptosis)
- Diminished antigen induced T-cell proliferation as well as a decrease in T_{H1} response (as opposed to T_{H2}) noted.
- Memory cell subset of T_H cells lost early in disease.

HIV

- 70% of patients experience a “mononucleosis syndrome” of fever, rash, sore throat, lymphadenopathy, and a flu-like syndrome with athralgia, headache, and diarrhea. Typically occurs 3-6 weeks after infection and resolves in 2-4 weeks. EBV VCA and CMV antibody negative as clues.
- Virus present in semen, blood, body fluids. Markedly lower concentrations of virus present in cervical secretions; perhaps viral transmission occurs from infected female-to-male if other STD present and a very high viral load is present.

Probability of HIV transmission



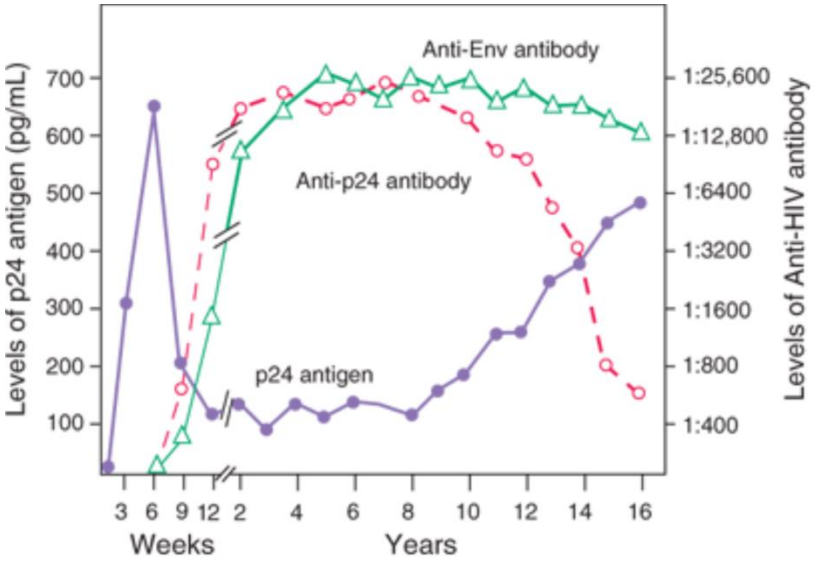
Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. (From RH Gray et al: Lancet 357:1149, 2001.)

Accessed 02/03/2016

HIV assays

- The serologic tests for HIV infection are based upon detection of IgG against HIV-1 antigens in serum. These antigens include p24, gp 120 and gp 41.
- Antibodies to gp41 and p24 antigens are the first detectable serologic markers following HIV infection.
- Criteria for positive serology include reactivity to gp120/160 plus either gp 41 or p 24. (Western blot)
- Screen initially with a combination assay for HIV 1 and HIV 2 as well as p24 antigen. If negative, it is unlikely HIV infection is present. If positive or indeterminate, test with separate assays for HIV 1 and HIV 2. If the separate assays are negative or indeterminate, then test for HIV nucleic acid. This may detect early infection.

Development of antibody response



Relationship between antigenemia and the development of antibodies to HIV. Levels of plasma HIV parallel those of p24 antigen. Antibodies to HIV proteins are generally seen 6–12 weeks following infection and 3–6 weeks after the development of plasma viremia. Late in the course of illness, antibody levels to p24 decline, generally in association with a rising titer of p24 antigen.

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Percentage of patients progressing to AIDS within 3 years

	HIV RNA <500 copies/ml	HIV RNA >3000-10,000 copies/ml	HIV RNA >10,000-30,000 copies/ml	HIV RNA >30,000 copies/ml
CD4 >750 cells/uL	0	3.2	9.5	32.6
CD4 <750 cells/uL	3.7	8.2	40.1	47.9

When to initiate HAART therapy

- Always test for drug resistance as 20-25% drug naïve patients possess resistant strains.
- Therapy that achieves a plasma viral load of < 50 copies/mL has been shown to provide a durable response to the therapy employed.
- At any cell count.
- Highly active antiretroviral therapy involves administration of two nucleoside reverse transcriptase inhibitors with either a protease inhibitor or an integrase strand transfer inhibitor or a non-nucleoside reverse transcriptase inhibitor.

Integrase strand transfer inhibitor based therapy

- Integrase inhibitor increases circulating 2-LTR circles of viral DNA even in those patients where virus is otherwise undetected.
- Demonstrate the absence of HLA B*5701 if dolutegravir/abacavir/lamivudine is to be employed; abacavir use associated with hypersensitivity reaction.
- Demonstrate the presence of normal renal function if elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine is to be employed;
- Demonstrate the presence of a creatinine clearance >30ml/min if elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine is to be employed.

Protease inhibitor based therapy

- Protease inhibitors are potent inhibitors of viral replication.
- Darunavir/ritonavir plus tenofovir disoproxil fumarate/emtricitabine is the preferred regimen.
- Lipodystrophy is a problem with protease inhibitor use.

Non-nucleoside reverse transcription based therapy

- Non-nucleoside reverse transcription based therapy is preferred in those in whom adherence to the other regimens is unlikely.
- Must use before drug resistance develops. HIV-2 infection is resistant to this therapy.
- Efavirenz/tenofovir disoproxil fumarate/emtricitabine is the preferred initial choice. It is a fixed dose combination taken once daily.
- Neurotoxicity is a problem with efavirenz.

HIV therapy

- Efavirenz is the non-nucleoside reverse transcriptase inhibitor employed except during first trimester of pregnancy or in women who are trying to conceive or who are sexually active with men and not using effective and consistent contraception. Its use is associated with a significant risk of neural tube defects in the fetus.
- Oral contraceptive use may interfere with antiretroviral drug functioning.
- IV zidovidine is administered to the mother at labor if RNA copies >400/ml.

HIV therapy

- Emtricitabine has few adverse effects, selects for the M184V resistance mutation which confers high-level resistance, and improves susceptibility to tenofovir. Both are effective against Hepatitis B.
- Zidovudine/lamivudine remains as the preferred option in pregnant women. This dual-nucleoside reverse transcriptase inhibitor regimen has the most safety and efficacy data for both mother and newborn.
- Triple NRTI regimens are biologically inferior.
- Dolutegravir is approved for use in children 12 years or older

HIV therapy in children

- Dual-nucleoside reverse transcriptase inhibitor combinations are preferred:
- For neonates/infants aged ≥42 weeks postmenstrual and ≥14 days postnatal and children <3 years: lopinavir/ritonavir;
- For infants <3 months: zidovudine plus (lamivudine or emtricitabine);
- For children aged ≥3 months: abacavir plus (lamivudine or emtricitabine) or zidovudine plus (lamivudine or emtricitabine);

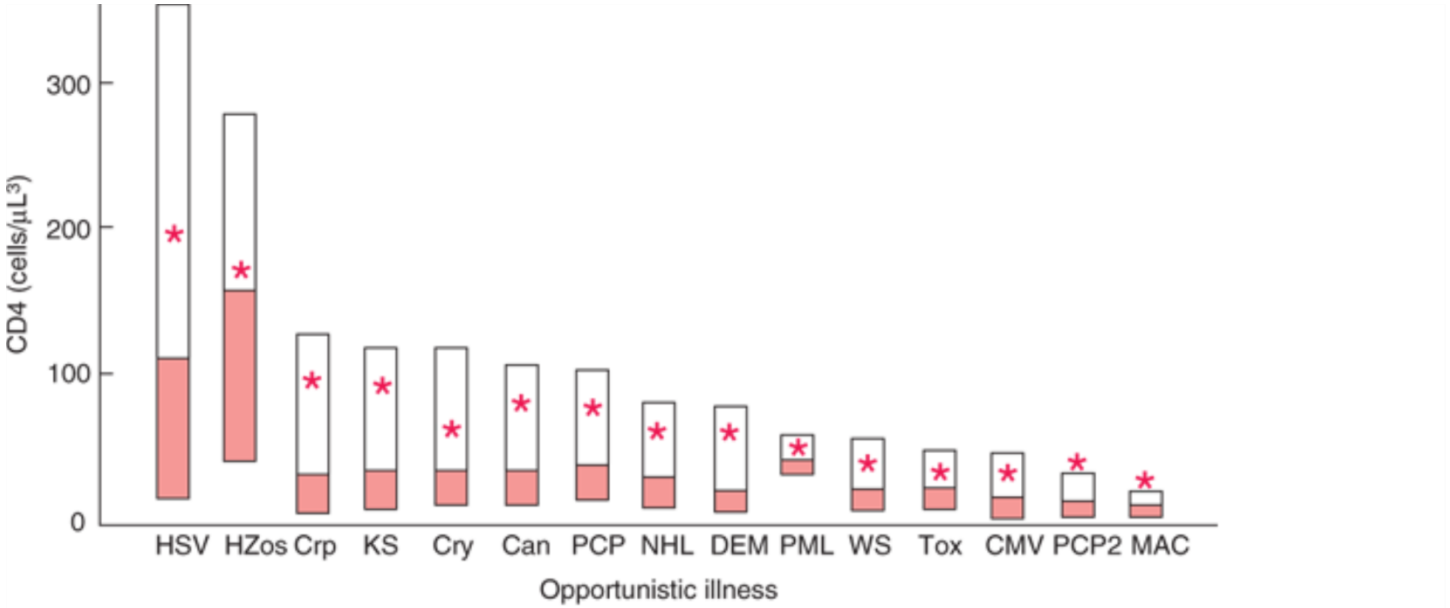
HIV therapy in children

- For children aged 3 years to <6 years: efavirenz or lopinavir/ritonavir;
- For children aged ≥6 years: atazanavir/ritonavir or efavirenz or lopinavir/ritonavir
- For children aged ≥12 years: abacavir plus lamivudine or plus emtricitabine.
- For adolescents at Tanner Stage 4 or 5: abacavir plus lamivudine or plus emtricitabine or tenofovir disoproxil fumarate plus lamivudine or plus emtricitabine.

Exposure prophylaxis

- Pre-exposure prophylaxis with tenofovir disoproxil fumarate.
- Post-exposure prophylaxis with a 28 day course of HAART therapy.
- This is not 100% effective in blocking HIV infection.

CD4 counts and development of opportunistic infections



Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease. Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary Pneumocystis jiroveci pneumonia; PCP2, secondary P. jiroveci pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, Toxoplasma gondii encephalitis; WS, wasting syndrome. (From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.)

Accessed 02/03/2016

Opportunistic infections

- Isoniazid and vitamin B6 for 12 months if PPD>5mm.
- Treatment of drug-susceptible tuberculosis should include a standard regimen that consists of isoniazid AND rifabutin AND pyrazinamide AND ethambutol given for 2 months, followed by isoniazid AND rifabutin for 4 to 7 months
- Trimethoprim-sulfisoxazole or dapsone (PCP prophylaxis) if CD4<200 or thrush is present. Add pyrimethamine and folic acid if the CD4<100 and Toxoplasma serologic tests are positive.
- Clarithromycin or azithromycin if CD4<75 (Mycobacterium Avium Complex prophylaxis).

Prophylaxis of opportunistic infections

- Patients with CD4 counts below 200 cells/μL, a CD4 lymphocyte percentage below 14%, or weight loss or oral candidiasis should be offered primary prophylaxis for Pneumocystis jiroveci pneumonia. Patients with a history of Pneumocystis jiroveci pneumonia should receive secondary prophylaxis until they have had a durable virologic response to HAART for at least 3–6 months and maintain a CD4 count of > 250 cells/μL.

Prophylaxis of opportunistic infections

- Patients whose CD4 counts fall to below 75–100 cells/μL should be given prophylaxis against M avium complex infection. Prophylaxis against M avium complex infection may be discontinued in patients whose CD4 counts rise above 100 cells/μL in response to HAART and whose plasma viral load has been optimally suppressed to < 50–75 copies/mL.
- Toxoplasmosis prophylaxis is desirable in patients with a positive IgG toxoplasma serology and CD4 counts below 100 cells/μL.

Prophylaxis of opportunistic infections

- Oral ganciclovir (1000 mg orally three times daily with food) is approved for CMV prophylaxis among HIV-infected persons with advanced disease (eg, CD4 counts below 50 cells/μL). Causes neutropenia. Incidence diminishing following introduction of HAART therapy.
- Decreased incidence of cryptococcal disease with prophylaxis using fluconazole, 200 mg orally daily

Pediatric HIV therapy

- Transplacental spread, infection in the birth canal, infection through breast milk most common causes of transmission to child. Chorioamnionitis increases risk of transmission.
- Antiretroviral therapy is initiated in infants <12 months of age regardless of clinical status, CD4 count, or viral load.
- The 1-year risk of AIDS or death is substantially higher in younger than older children at any given level of CD4 count, particularly for infants age <12 months.
- Always test first for drug resistance.

HIV treatment results

- HAART treatment of HIV infection is very expensive. When does one initiate treatment?
- Early treatment of HIV infection with HAART is associated with increased life expectancy regardless of viral load if the patient is <30 years old and CD4 count is >200 cells/mm^3.
- Life expectancy ranges from 14.5 years if viral load >300,000 copies/ml
- (and rises) to 18.2 years if viral load <10,000 copies/ml and CD4 >500 cells/mm^3.

HIV treatment results

- Early treatment of HIV infection with HAART in patients OVER 40 YEARS OF AGE is associated with a life expectancy of 11.4 years if CD4 counts are >200cells/mm^3 AND viral loads are >300,000 copies/ml, rising to 12.9 years if CD4 counts are >500cells/mm^3 AND viral loads are <10,000 copies/ml.
- Little improvement in the life expectancy of 9.2 years of those patients OLDER THAN 50 YEARS is seen with early treatment with HAART.
- 70% of infants <12 months of age progress.

PRIMARY PROPHYLAXIS AGAINST OI'S IN HIV INFECTED PATIENTS

I. Strongly recommended as **Standard of Care**:

Pneumocystis jiroveci (carinii)	$CD_4 < 200$ **or oral pharyngeal candidiasis**	TMP-SMZ	1 DS po q.d or 1 DS po t.i.w
		Allergy to above	Dapsone 50 mg po QD
Mycobacterium tuberculosis	Reaction > 5mm	Isoniazid	300 mg po + pyridoxine 50 mg q.d X **9 mo**
Toxoplasma gondii	$CD_4 < 100$ **& IgG +**	TMP-SMZ	1 DS po q.d
		Allergy to above	Pyrimethamine 50 mg po Q Week Leucovorin 25 mg po Q Week
Mycobacterium avium complex	$CD_4 < 50$	Biaxin Zithromax	500 mg po b.i.d. 1200 mg po q.w.
Varicella zoster	Sig. Exposure	Vericella zoster immune globulin	

II. Generally recommended:

Streptococcus pneumoniae	**$CD_4 \geq 200$**	Pneumococcal Vaccine	
Hepatitis B	All Susceptible	Hepatitis B Vaccine; 3 doses	
Influenza	All	Inactivated vaccine / Oseltamivir,Rimantadine,amantadine	
Hepatitis A	**All Susceptible with Chronic Hep C**	**Hep A Vaccine**	**2 doses**

III. Not routinely indicated

Bacteria	Neutropenia	Granulocyte-colony-stimulating-factor
Cryptococcus neoformans	$CD_4 < 50$	Fluconazole
Histoplasma capsulatum	$CD_4 < 100$	Itraconazole
Cytomegalovirus	$CD_4 < 50$ CMV Ab +	Oral gancyclovir

Guidelines fot Preventing Opportunistic Infections Among HIV-Infected Persons --- 2002
Recommendations of the US Public Health Service and the Infectious Disease Society of America
MMWR, June 14, 2002

Related neoplasias

- Kaposi's sarcoma (with Herpes Simplex 8 virus). Infects endothelial cells and B-cell. Proliferation of small vascular channels that may arise from primitive mesenchye. Factor VIII can be demonstrated in endothelial cells. Incidence diminished with HAART therapy.
- B-cell lymphoma (with Epstein-Barr virus). Primary CNS lymphoma, lymphomas at extranodal sites. EBV Latent membrane protein-1 behaves as consitutively activated CD40 receptor; EBNA-2 behaves as consitutively activated Notch receptor; viral IL-10 blocks T-cell activation.
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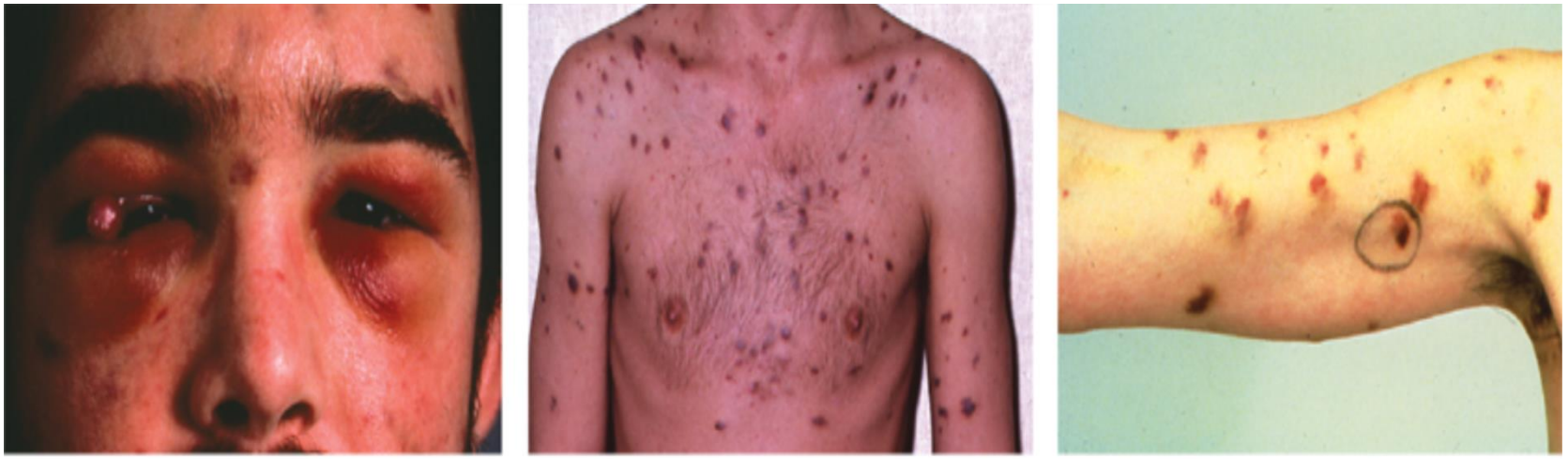
Related neoplasias

- Cervical and anal cancer (Human papilloma virus 16 and 18). E6 protein degrades p53 and stimulates expression of telomerase. E7 protein binds to Rb protein, promoting progression through the cell cycle.

Kaposi’s sarcoma



Kaposi’s sarcoma in three patients with AIDS demonstrating (A) periorbital edema and bruising; (B) classic truncal distribution of lesions; and (C) upper extremity lesions.

Accessed 02/03/2016