Immune-deficiency diseases

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Immune deficiency general signs

- Predisposing the patient more to infection by normal pathogens that usually do not cause disease in a healthy with a healthy immune system and this is called opportunistic infection.
- Predisposing to cancers
- Predispose to autoimmune diseases

Types of ID

- Congenital or primary *Immunodeficiency (PID):* These disorders are caused by a genetic abnormality, which is in some cases X-linked, mostly boys are affected. Mild to sever, can be discovered at birth or later at any time.
  - Although most PIDs are diagnosed in childhood, ~40% are not diagnosed until adolescence or early adulthood
- Acquired or secondary: 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

Types of PID

- B cell (antibody) deficiencies
- T cell deficiencies
- Defective innate
  - In number;as neutropenia (less than 500cells/µl), no symptoms to severe.
  - In function (failure of producing oxygen radicals) by phagocytes; as chronic granulomatous disease,
  - Chédiak-Higashi syndrome
  - The leukocyte adhesion deficiencies
  - Complement deficiencies

Classification

T cell disorders	B cell defects
-Severe combined immunodeficiency -Wiskott aldrich syndrome(Xp11) -Ataxia telengectiasia(11q) -Digeorge anomaly	-XL agammaglobulinemia -Common variable immunodeficiency -Selective IgA deficiency -AR agammaglobulinemia -Hyper-IgM syndromes- XL
Phagocyte disorders	**Complement disorders**
-Chronic granulomatous disease -Leukocyte adhesion defect -Chediac higashi syndrome -Myeloperoxidase deficiency -Cyclic neutropenia (elastase defect)	-C1q deficiency -Factor I deficiency -Factor H deficiency -Factor D deficiency -Properdin deficiency

Chédiak-Higashi syndrome

- This disease is caused by mutations in the gene which regulates intracellular trafficking of lysosomes.

result in

  - defective phagosome-lysosome fusion in neutrophils and macrophages (causing increased infection),

  - defective melanosome formation in melanocytes (causing albinism),

  - and lysosomal abnormalities in cells of the nervous system (causing nerve defects)

  - and platelets defect (leading to bleeding disorders).

- ***The leukocyte adhesion deficiencies***
- ***are a group of autosomal recessive disorders caused by defects in leukocyte and endothelial adhesion molecules***.
- These diseases are characterized by a failure of leukocyte, particularly neutrophil, recruitment to sites of infection, resulting in severe periodontitis (gum infection) and other recurrent infections starting early in life, and the inability to make pus.
- Different types of leukocyte adhesion deficiencies are caused by mutations in different genes.

Determining defects in cellular immunity

Often present with:

- **Opportunistic infections [*Pneumocystis carinii*), *Cryptococcus, Candida spp.*]**
- **Disseminated viral infections (CMV, EBV, VZV)**
- **Failure to thrive, chronic diarrhea, persistent thrush**

Clinical evaluations:

- **Complete blood count (CBC) with differential, lymphocyte subsets**
- **Vaccine titers (eg., tetanus, diphtheria)**
- **Ig levels (IgA, IgE, IgM, IgG)**
- **T cell proliferation assays,**

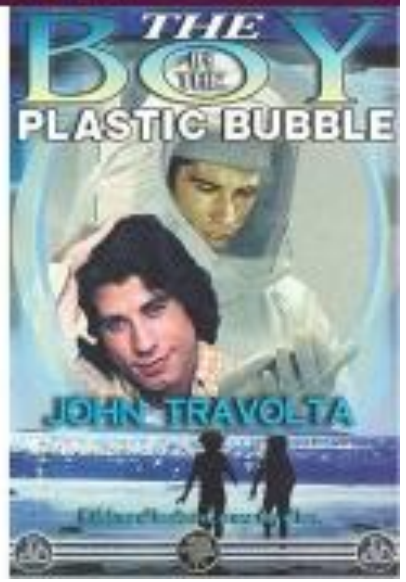
Skin testing (eg., Candida protein)

Abnormal in lymphocytes

- Abnormalities in B lymphocyte development and function result in deficient antibody production and increased susceptibility to infection by extracellular microbes (low Ig levels).
- Abnormalities in T lymphocyte maturation and function lead to deficient cell-mediated immunity and humoral immunity (B cell activation) so is the main cause of SCID
- an increased incidence of viral infection and opportunistic infections
  - Primary T cell immunodeficiency are diagnosed by reduced numbers of peripheral blood T cells; and deficient delayed-type hypersensitivity (DTH) reactions to common antigen (- skin test to candida).

SCIDs:
Severe Combined Immunodeficiencies

- Typically the most severe types of immunodeficiencies.
- Lethal within 6-12 months if not treated.



SCID is often called "bubble boy disease"
SCID became widely known during the 1970's and 80's, when the world learned of David Vetter, a boy with X-linked SCID, who lived for 12 years in a plastic, germ-free bubble

Severe combined immunodeficiencies (SCID)

- Disorders that affects both humoral and cell-mediated immunity because of T cell Deficiencies with or without B cells and NK cells
- Severe opportunistic infections, death during the first year of life unless given antibody and a bone marrow transplant
- Causes and types

1. **Lymphocyte precursor cell death due to purine metabolism defect.** ADA (adenosine deaminase) or PNP (purine neucleoside phosphorylase) deficiency results in an accumulation of toxic precursors, which affects developing T NK and B cells
2. A- Defective signaling through the common γ-chain-dependent cytokine receptorsIL-2, IL-4, IL-7, IL-9, and IL-15 (most common) called x-linked SCID

   B- Patients with mutations in the gene encoding the IL-7Rα chain are autosomal recessive inheritance.
3. Defective V(D)J recombination; mutation in RAG1 or RAG2 genes, impair T and B cells
4. Defective pre-TCR/TCR signaling, pure T cell deficiency
5. Reticular dysgenesis (most severe)

SCIDs:
Severe Combined Immunodeficiencies

Disorders that affect T cells, and sometimes B cells and/or NK cells
No effect on myeloid or erythroid cells

Lymphocyte phenotype			
T	**B**	**NK**	**Type of SCID**
−	+	−	X-linked IL–2Rγ–chain deficiency JAK-3 deficiency CD45 deficiency
−	+	+	IL-7R α-chain deficiency CD3 δ-chain deficiency
−	−	−	Adenosine deaminase (ADA) deficiency
−	−	+	*RAG1* or *RAG2* deficiency Artemis deficiency

Reticular dysgenesis (form of SCID) (Aleukocytosis,)

- Fist described in 1959
- Less than 2% of SCID
- The most severe SCID
- Total lack of lymphocytes and granulocytes in blood and bone marrow
- Lack of innate and adaptive humoral and cellular immunity
- Fatal sepsis within days after birth
- Myeloid differentiation is blocked at the promyelocytic stage
- Erythro- and megakaryocytic maturation is normal
- Mutation in adenylate kinase 2 (AK2), enzyme of mitochondrial energy. Leads to loss of energy required for Differentiation and proliferation of hematopoietic stem cells.
- First example of PIDs that is causally linked to energy metabolism (mitochondoriopathy)

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- T cell immune-deficiency
  - Digeorge syndrome (DGS) is hereditary disease associated with defective development of thymus due to deletion of a small piece in chromosome 22. The classical presentation for DGS is CATCH-22
  - SCID

  Cardiac abnormality (especially tetralogy of Fallot)
  Abnormal facies
  Thymic aplasia
  Cleft palate
  Hypocalcemia/**H**ypoparathyroidism

  T cells absent and decreased memory B cells
- clinical presentation is very broad –

- no heart defects vs severe congenital heart defects
- normal immune system vs complete absence of T cells

T cells defects,

Defective expression of MHC :

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General

Figure 11-8 part 1 of 3 Immunobiology, 6/e. (© Garland Science 2005)

-Bare lymphocyte syndrome 1&2•
-MHC class I antigen deficiency (•
No or decreased CD8+ T cells•
Mutations in *TAP1, 2*•
TAP proteins function to transport peptide antigens from the • cytoplasm to Golgi to join MHC class I molecules
-MHC class II antigen deficiency •
No or decreased CD4+ T cells•
Defective humoral immunity although normal numbers of b cells•

Defect T cell signaling

- Wiskott-Aldrich syndrome, an X-linked disease characterized by eczema, thrombocytopenia (reduced blood platelets), and susceptibility to bacterial infection.
- In the initial stages of the disease, lymphocyte numbers are normal,
- With increasing age, the patients show reduced numbers of lymphocytes and more severe immunodeficiency.

T cell deficiency

- Ataxia-telangiectasia is an autosomal recessive disorder characterized by abnormal gait (ataxia), vascular dilatation (telangiectases) on the whites of the eyes and on sun-exposed areas of skin, neurologic deficits, increased incidence of tumors, and immunodeficiency and radiation sensitivity.
- The immunologic defects are of variable severity and may affect both B and T cells. The most common is humoral immune defects.
- Gene mutation of ATM (ataxia-telangiectasia mutated) which plays in class-switch recombination.

Defect in B Cell Maturation

1. X-Linked Agammaglobulinemia, also called Bruton's agammaglobulinemia, is characterized by the absence of gamma globulin in the blood. The defect is in a failure of B cells to mature beyond the pre-B cell stage in the bone marrow

   The infectious complications of X-linked agammaglobulinemia are greatly reduced by periodic (e.g., weekly or monthly) injections of pooled gamma globulin preparations (IVIG)

2. Common Variable Immune Deficiency is a disorder characterized by low levels of serum immunoglobulins (antibodies) and an increased susceptibility to infections. It is a relatively common form of immunodeficiency, hence, the word “common.” The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from patient to patient, hence, the word “variable.”

3. Patients with Hyper IgM (HIM) syndrome have an inability to switch production of antibodies of the IgM type to antibodies of the IgG, IgA, or IgE type. The affected protein is called "CD40 ligand". it is inherited as an X-linked recessive trait and usually found only in boys.

4. Selective IgA Deficiency is the complete absence of the IgA class . Many of these individuals appear healthy or with severe significant illnesses.

5. IGG subclasses deficiency. Patients who lack, or have very low levels of, one or two IgG subclasses, but whose other immunoglobulin levels are normal, are said to have a selective IgG subclass deficiency.

Treatment of PID

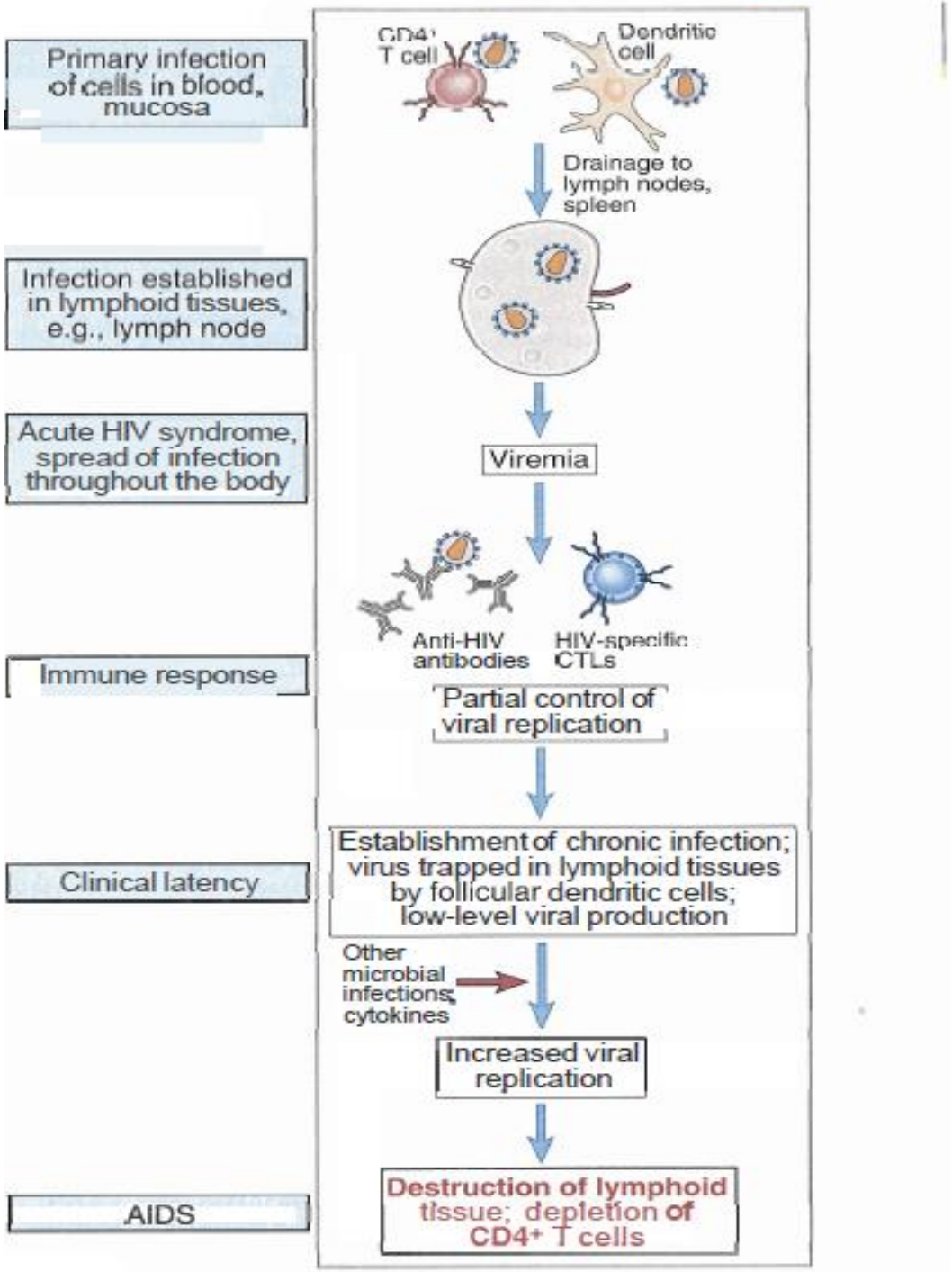
- Managing infections treatment and prevention
- Immunoglobulin transfusion.
- Interferon-gamma therapy. It's used to treat chronic granulomatous disease
- Growth factors for immune cells
- Bone marrow transplantation in SCID

Secondary immune- deficiency

AIDS (acquired Immune Deficiency Syndrome)

- HIV is a retrovirus that primarily infects CD4+ T cells , macrophages and dendritic cells. It destroys CD4+ T cells
- Once the number of $CD4^+$ T cells per microliter of blood drops below 200, cellular immunity is lost and AIDS start. HIV infection usually progresses over time from
  - Acute HIV infection: flue symptoms+ spread of virus
  - clinical latent HIV infection: immune system act (start antibodies and CD8 action) + trapping of virus by dendritic cells in lymph node, more CD4 destruction
  - and later to AIDS, CD4 suppression

In the absence of therapy, the median time of progression from HIV infection to AIDS is nine to ten years, and the median survival time after developing AIDS is only 9.2 months.


Primary infection of cells in blood, mucosa
CD4+ T cell
Dendritic cell
Drainage to lymph nodes, spleen
Infection established in lymphoid tissues, e.g., lymph node
Acute HIV syndrome, spread of infection throughout the body
Viremia
Anti-HIV antibodies
HIV-specific CTLs
Immune response
Partial control of viral replication
Clinical latency
Establishment of chronic infection; virus trapped in lymphoid tissues by follicular dendritic cells; low-level viral production
Other microbial infections, cytokines
Increased viral replication
AIDS
Destruction of lymphoid tissue; depletion of CD4+ T cells

Phase of disease	Clinical feature
Acute HIV disease	Fever, headaches, sore throat with pharyngitis, generalized lymphadenopathy, rashes
Clinical latency period	Declining *blood* $CD4^+$ T cell amount
AIDS	**Opportunistic infections** Protozoa *(Pneumocystis carinii, Cryptosporidium)* Bacteria *(Toxoplasma, Mycobacterium avium, Nocardia, Salmonella)* Fungi *(Candida, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum)* Viruses (cytomegalovirus, herpes simplex, varicella-zoster) **Tumors** Lymphomas (including EBV-associated B cell lymphomas) Kaposi's sarcoma Cervical carcinoma **Encephalopathy** **Wasting syndrome**

Steps of HIV infection of CD4 T cells

- First, a portion or domain of the HIV surface glycoprotein gp120 binds to its primary receptor, a CD4 molecule on the host T cell.
- Then the gp120 interact with a host cell chemokine receptor. The chemokine receptor functions as the viral co-receptor.
- This interaction brings another conformational change that exposes a buried portion of another glycoprotein gp41 called fusion protein that enables the viral envelope to fuse with the host T cell membrane.
- Fusion of virus and T cell membrane lead to destruction of CD4 T cells.

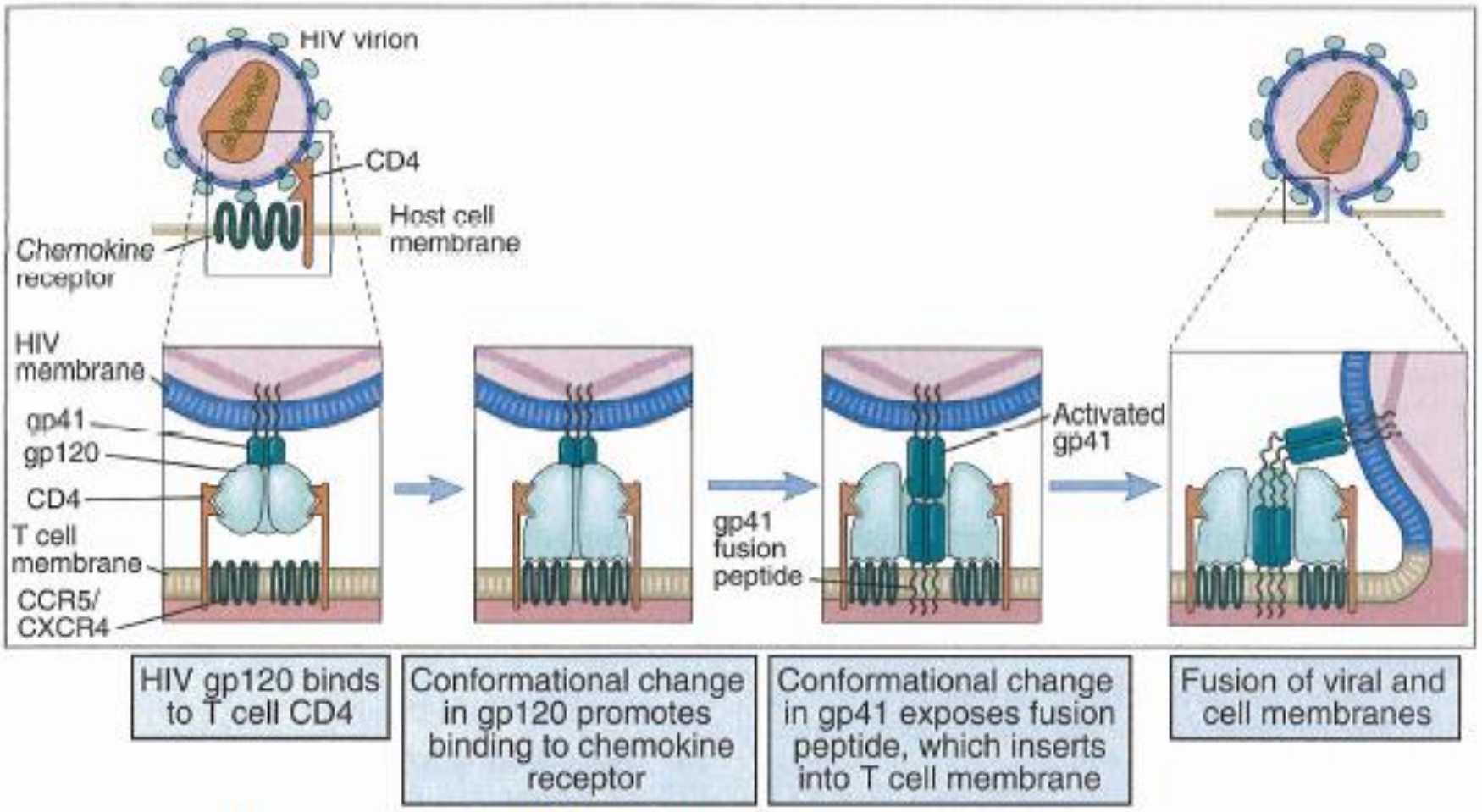


Figure 20-6 Mechanism of HIV entry into a cell

Mechanisms of immune evasion

- Very high mutation rate
- Down regulation of MHC 1
- Killing CD4

Transmission

- Sexual transmission
- Blood products
- Mother to fetus

HIV test

- HIV tests are usually performed are
  - Serologic tests which detect anti-HIV antibody (IgG and IgM) positive after 1-3 months of infection
  - ELISA; look for the HIV p24 antigen in patient fluids
  - Detection of the virus gene using polymerase chain reaction (PCR) during the window period is possible, and evidence suggests that an infection may often be detected earlier . The window period (the time between initial infection and the development of detectable antibodies against the infection). It occurs before 1-3 months after infection.

treatment

- Standard goals of highly active antiretroviral therapy (HAART) include improvement in the patient's quality of life, reduction in complications, and reduction of HIV viremia below the limit of detection, but it does not cure the patient of HIV nor does it prevent recurrence of high HIV levels. Moreover, it would take more than the lifetime of an individual to be cleared of HIV infection using HAART.
- Even with anti-retroviral treatment, over the long term HIV-infected patients may experience the disease complications as neurocognitive disorders, cancers, nephropathy, and cardiovascular disease.
- Typical regimens consist of two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI) all work to inhibit virus from making new DNA for replication.