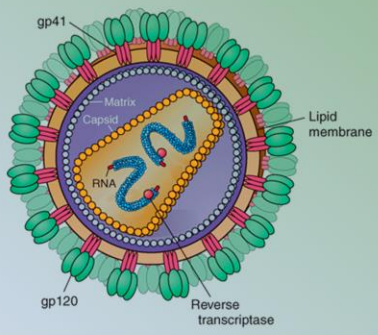
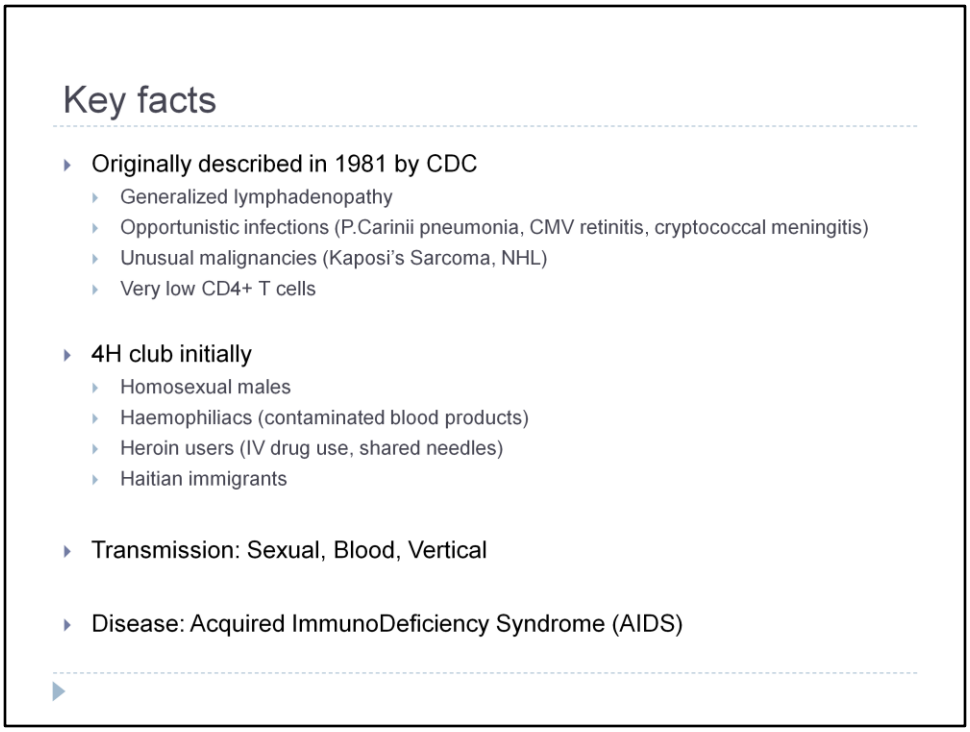


HIV & AIDS

Dr. Mazin Al-Salihi

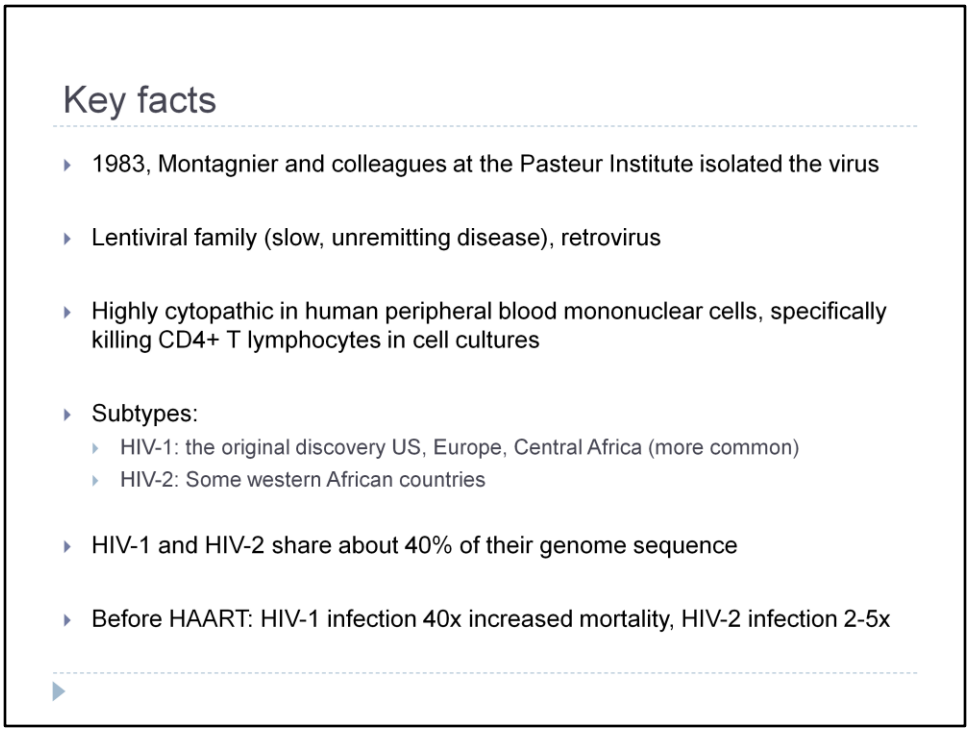


Two attributes make AIDS unique among infectious diseases: it is uniformly fatal, and most of its devastating symptoms are not due to the causative agent

Male to Male sex is the highest risk group in developed countries. Male to female is higher than female to male (anatomy). Injured skin
(e.g. STD lesions) increase risk.

Contaminated blood products have mostly been eradicated as a cause of transmission. Don't forget to mention health care worker to/from transmission. If exposed combined antiretroviral has shown efficacy.

Vertical transmission may occur transplacentally, perinatally during the birth process, or postnatally through breast milk with varying percentages depending on the location of the study and if anti-viral therapy is given.

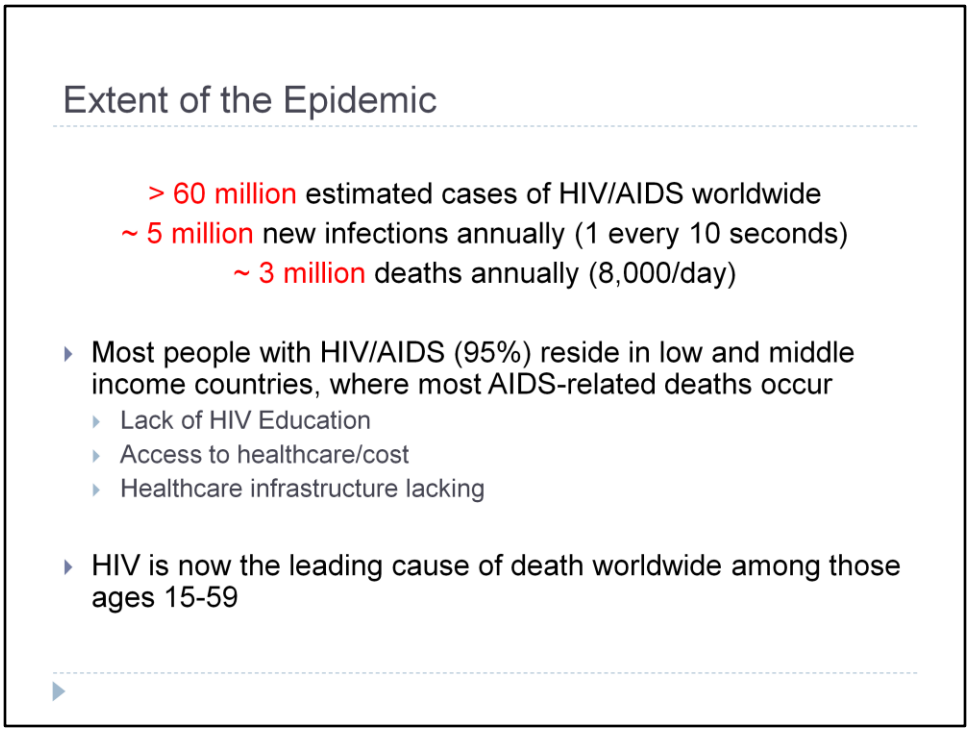


1984-1985, virus identified as the causative agent and ELISA test produced which showed the extent of the epidemic

HIV is remarkably similar to the simian immunodeficiency virus SIV

Because of the close contact between humans and monkeys, which are hunted for food or kept as pets in West Africa, it is currently thought that HIV represents a zoonotic transmission of SIV from monkeys to humans

HAART = highly active antiretroviral therapy



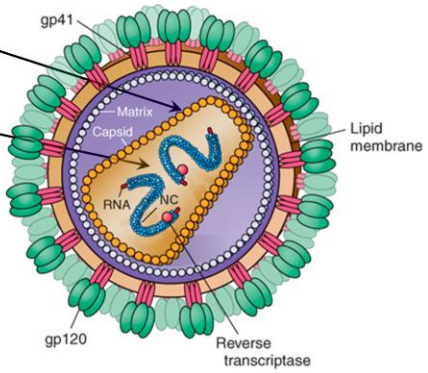
In 2009, just 5 years ago the estimates were about 33 million!

We are in the midst of a Global epidemic (actually multiple local epidemics), and we may still be early in the epidemic to really see how many are infected (long term disease)

Molecular Biology

Structure

- Cone shaped cylindrical core
- 2 identical ssRNA genome, +ve sense, extensive genetic heterogeneity
- Highly variable envelope protein gp160 (even in samples isolated from the same individual)
- Highly conserved gp41 induces a non-neutralizing antibody response (detect infection)

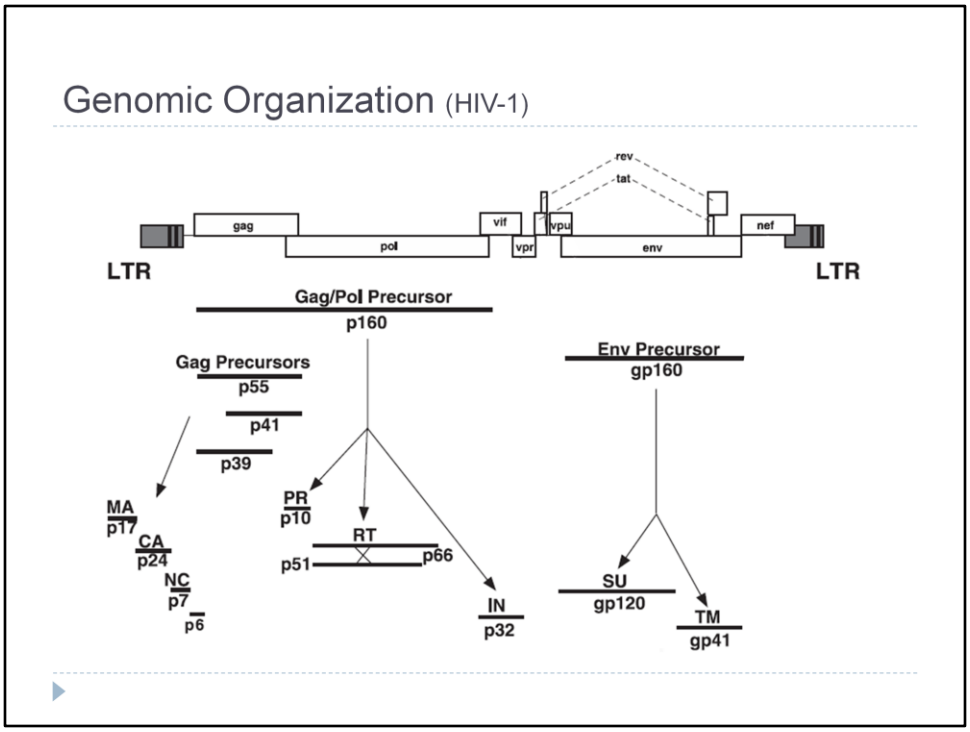


Nucleocapsid binds & protects RNA from digestion

gp160 is processed into gp120 and gp41 (glycoprotein)

The virion buds from the surface of the infected cell and incorporates a variety of host proteins, including major histocompatibility complex
class I and II antigens, into its lipid bilayer

Although of positive polarity, HIV genome is not infectious



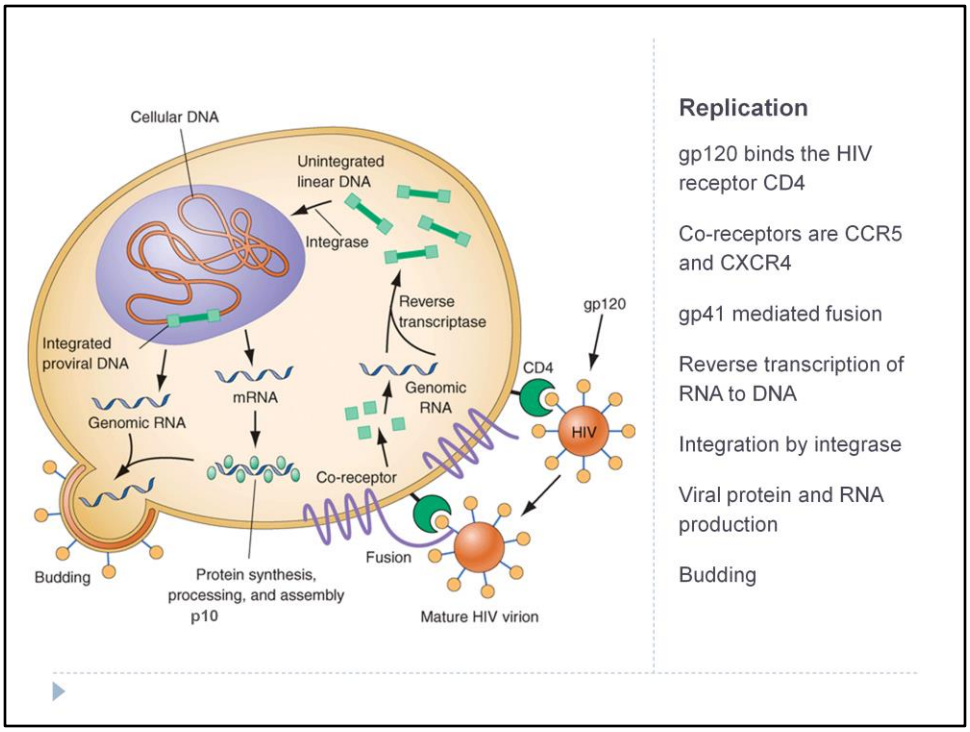
Typically retroviruses are organised into gag/pol/env but HIV was found to have multiple open reading frames in addition to the usual

MA=Matrix - CA=Capsid - NC=Nucleocapsid - P6 is important for budding of viral particles from the infected cells (late domains)

PR=Protease - RT=reverse transcriptase+Rnase H - IN=integrase

SU=Surface - TM=transmembrane

LTR=Long terminal repeats, in part, are used to integrate viral genetic material into the host cell

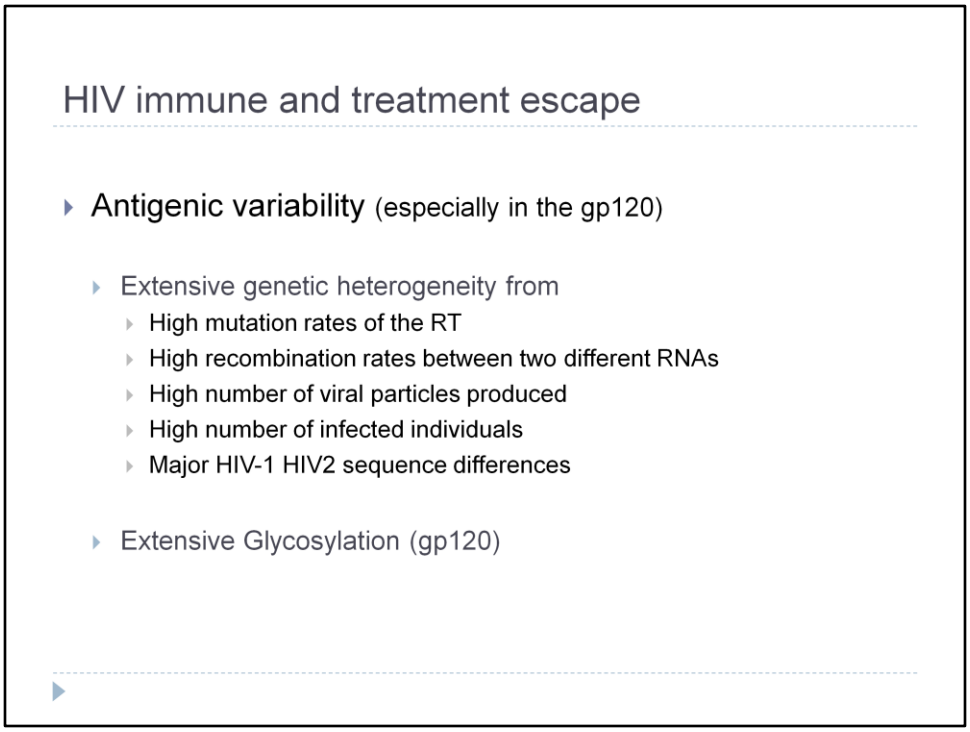


HIV directly infects and kills cells that are critical for effective immune responses

The CD4 molecule is found predominantly on T helper cells. It is also expressed on the surface of monocytes/macrophages and dendritic/Langerhans cells

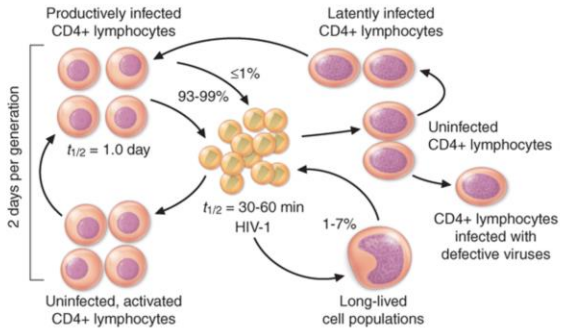
CCR5 and CXCR4 belong to the family of seven-transmembrane-domain G protein–coupled cellular receptors (chemokine receptors)

Reverse transcriptase, Integrase, and p10 Protease are major targets of anti-HIV treatments



Iterations of antibody production & viral adaptation. While some of the antibodies produced may be able to neutralize the virus (if they can see the protein from all the glycosylation) this induces evolution of the virus.

HIV immune and treatment escape

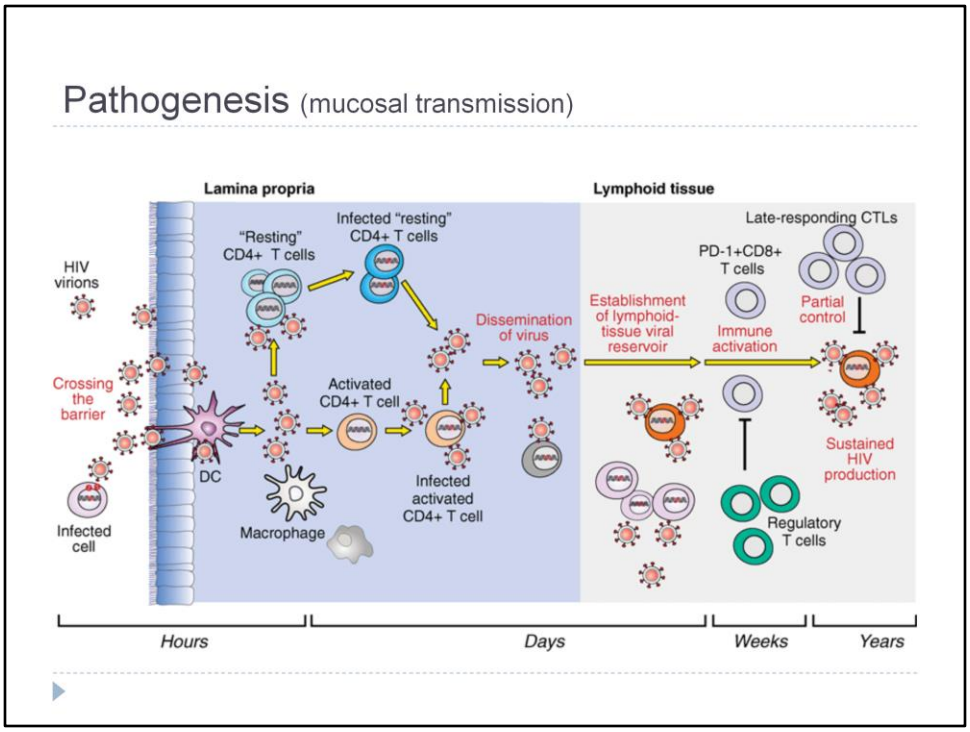


- Infected cell half life
  - Activated cells (viral production within minutes, death 1-2d)
  - Resting cells (virus production after immune stimulation, $t_{1/2}$ 5-6mo.)
  - Infection with defective virus ($t_{1/2}$ 3-6mo.)

Activated cells are the major source of virus production

The time required to complete a single HIV life-cycle is approximately 2 days.

These long lived quiescent cell populations also provide a challenge to anti-viral therapy. Especially the latently (viral latency) infected resting cells with integrated but transcriptionally silent virus that could reactivate to produce virons. These cells escape both immune and treatment destruction. This occurs whether or not persons are started on treatment in the initial symptomatic stage of infection.



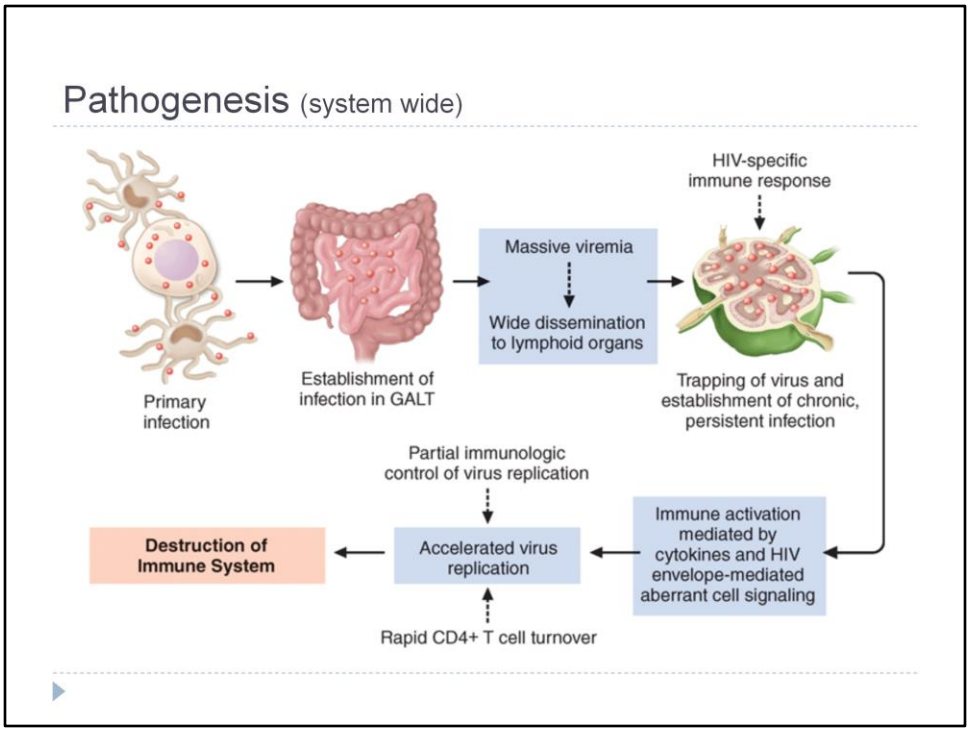
Access via dentritic cells or through compromised mucosa

Activated T cells produce more virus but are less abundant initially than resting T cells

A number of mechanisms responsible for cellular depletion and/or immune dysfunction of CD4+ T cells have been demonstrated in vitro; these include direct infection and destruction of these cells by HIV, as well as indirect effects such as immune clearance of infected cells, immune exhaustion due to aberrant cellular activation, and activation-induced cell death

CD8 T cells recognize viral infected cells through the MHCI proteins. Depletion of these cells in animal models show a dramatic increase in viremia. However these cells are not able to keep up with the amounts of virus produced & CD8 T cell exhaustion sets in. During prolonged immune activation this exhaustion is associated with expression of the programmed death (PD) 1 molecule. Additionally these cells cannot see latently infected cells so some virus persists.

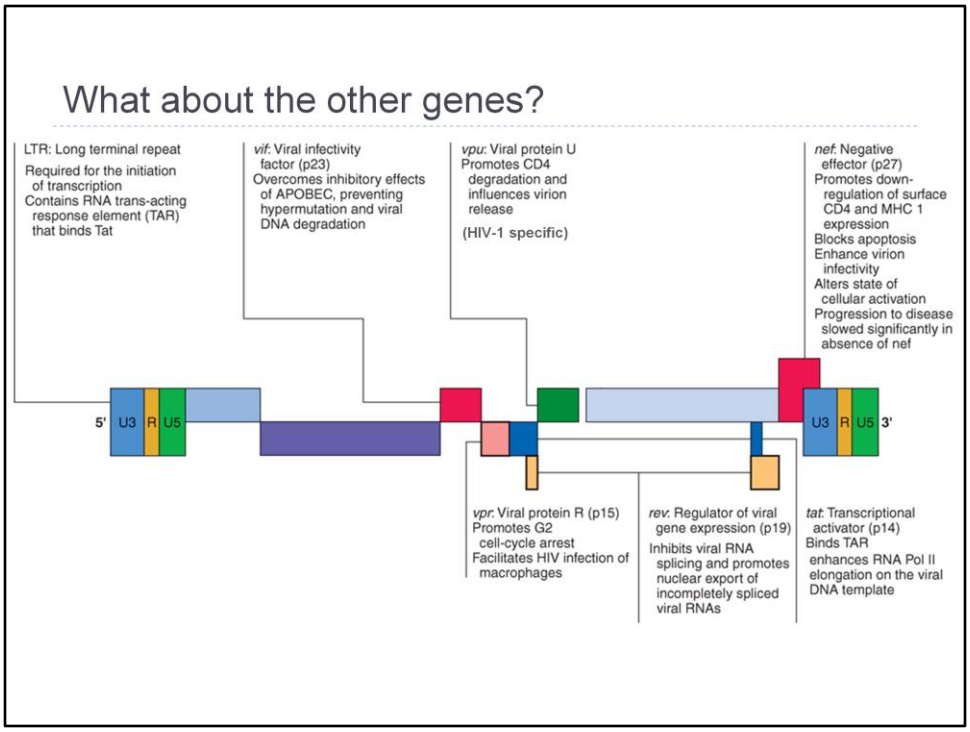
HIV preferentially infects and depletes HIV-specific CD4 T cells. This may partially explain the low frequency of HIV-specific CD4 T cells and their inability to adequately coordinate humoral and CD8 T-cell responses to HIV.



An important lymphoid organ, the gut-associated lymphoid tissue (GALT), is a major target of HIV infection and the location where large numbers of CD4+ T cells (usually memory cells) are infected and depleted, both by direct viral effects and by activation-associated apoptosis.

The loss of CD4 T cells from the gut during acute infection has two effects upon the immune system:

1. It depletes a major portion of the immune reserve in the form of memory CD4 T cells
2. It allows microbial translocation, which establishes a state of chronic immune activation that further promotes systemic HIV infection and replication.



Tat & rev are essential while rest are accessory proteins

Tat is required for better RNA transcriptional activity, without it no viral progeny. Same for Rev, without it no viral progeny.

Rev: Typically mRNA is processed in the nucleus to remove any intronic sequences before export to the cytoplasm to prevent non-functional proteins from being translated. However, HIV as we have seen produces several intronic containing proteins to be processed post translation. Rev binds and allows nuclear export of these sequences despite the usual cellular machinery requirements

APOBEC is a cytidine deaminase that results in G to A mutations in the viral geome. VIF prevents APOBEC from being incorporated into the virion particle normally to prevent this hypermutation. It does this by inducing it's destruction by the ubiquitin proteasomal pathway.

Another mechanism contributing to the evasion by HIV of immune system control is the downregulation of HLA class I molecules on the surface of HIV-infected cells by the Nef protein of HIV, resulting in the lack of ability of the CD8+ CTL to recognize and kill the infected target cell

The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2

lacks the vpu gene and has a vpx gene not contained in HIV-1 (vpx and vpr in HIV-2 share the function of vpr here)

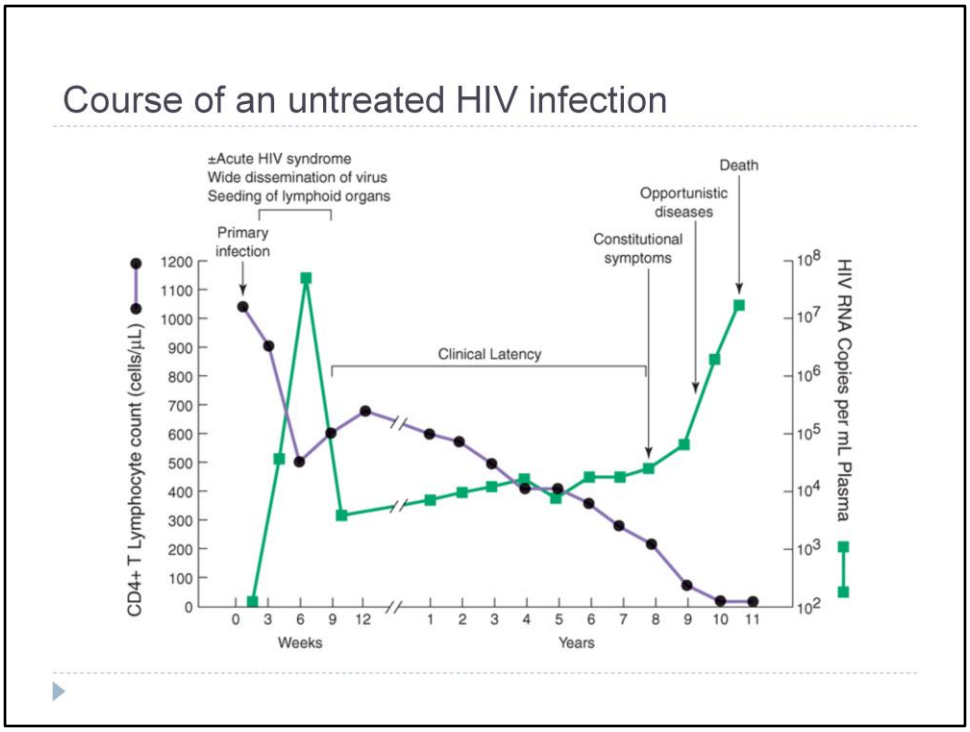
Clinical Syndrome

Acquired ImmunoDeficiency Syndrome

- The course of HIV disease can be divided into 3 stages:
  - primary (or acute) infection
  - chronic (asymptomatic) infection
  - advanced disease (AIDS)

AIDS is a constellation of clinical illnesses, primarily opportunistic infections & malignancies

Advancing immunodeficiency caused by the progressive loss of CD4+ T lymphocytes is the underlying mechanism



Acute mononucleosis-like symptoms. Best indicator of future disease progression is viral load after acute symptoms abate, but viral load at any time point is an important determinant of disease state.

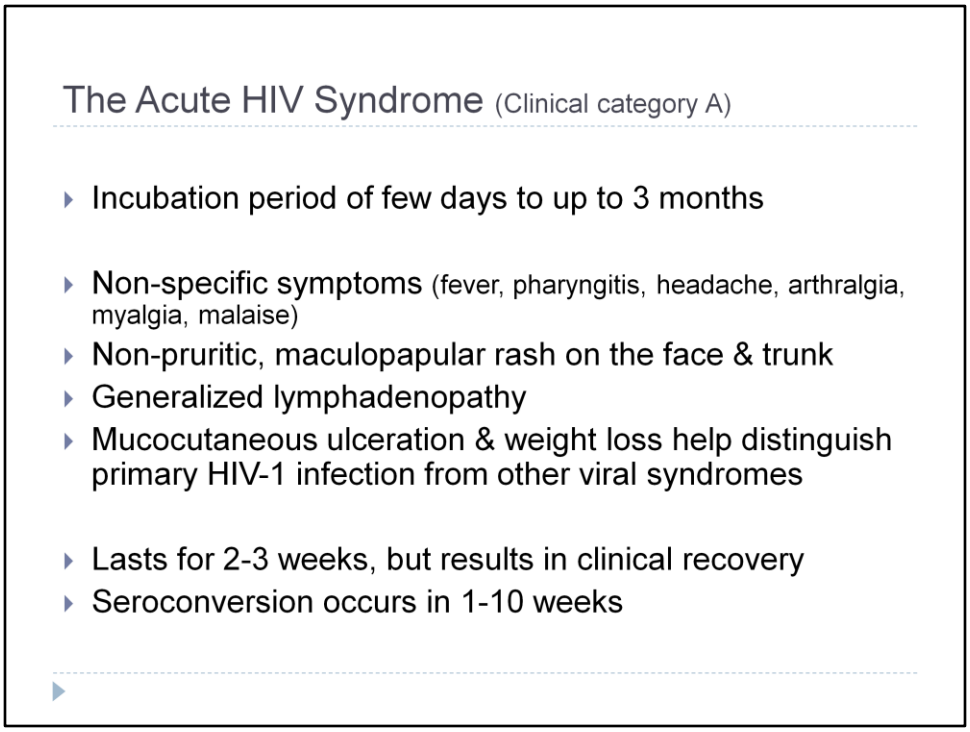
Clinical latency not to be confused with viral latency (here there is continuing viral replication and clearance) till replication outpaces the immune system

When the CD4+ T cell count falls below a critical level (<200/µL) the patient becomes highly susceptible to opportunistic disease. A diagnosis of AIDS is made in anyone with HIV infection and a CD4+ T cell count <200/µL and in anyone with HIV infection who develops one of the HIV-associated diseases considered to be indicative of a severe defect in cell-mediated immunity.

Clinical latency can be as short as 6 months while other persons have been known to be infected >25 years maintaining normal CD4 cell levels despite never having been treated with anti-HIV medications. Over 95% of HIV infected individuals progress to AIDS within 15 years of infection.

The duration of each stage is highly variable and can be altered by antiretroviral therapy.

Prognosis & monitoring of ART patient response: Viral Load



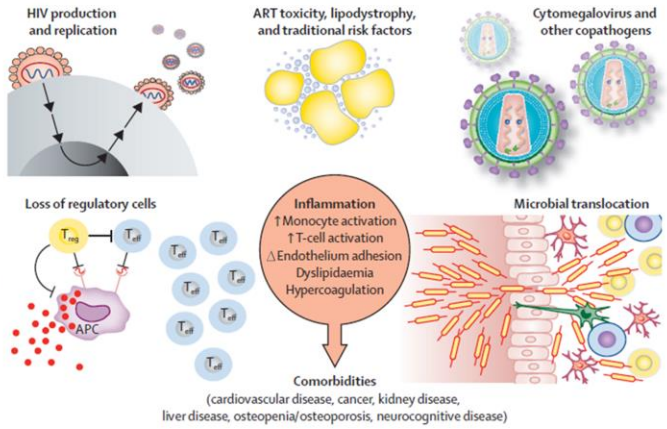
Aseptic meningoencephalitis is the most common neurologic manifestation of primary HIV-1 infection

Persistence of symptoms beyond 8 to 12 weeks, along with a severely depressed CD4+ T-lymphocyte count and high plasma HIV-1 RNA levels may predict more rapid progression of disease

Laboratory characteristics of primary HIV-1 infection include lymphopenia and a decrease in the absolute CD4+ T-lymphocyte count, usually accompanied by an increase in circulating activated CD8+ T cells

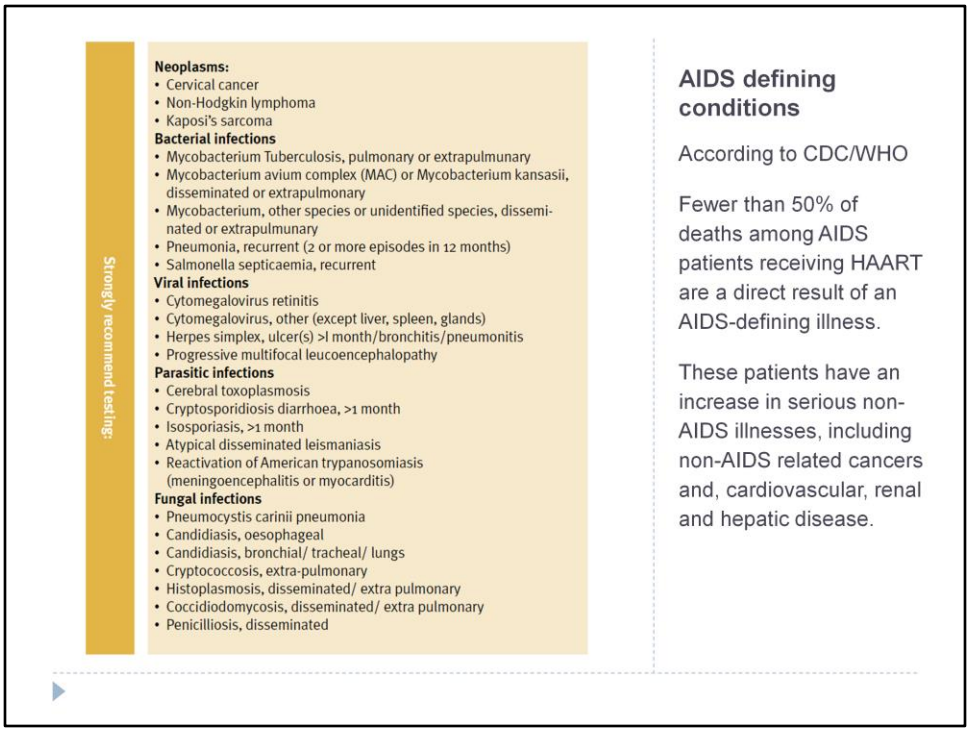
Symptomatic HIV Infection (Clinical categories B&C)

- Organ systems manifestations of an underlying cellular deficiency
  - Skin
  - Mucous Membranes
  - GI tract
  - Endocrine
  - Kidneys
  - Heart & lung
  - Hematologic
  - Ocular
  - CNS

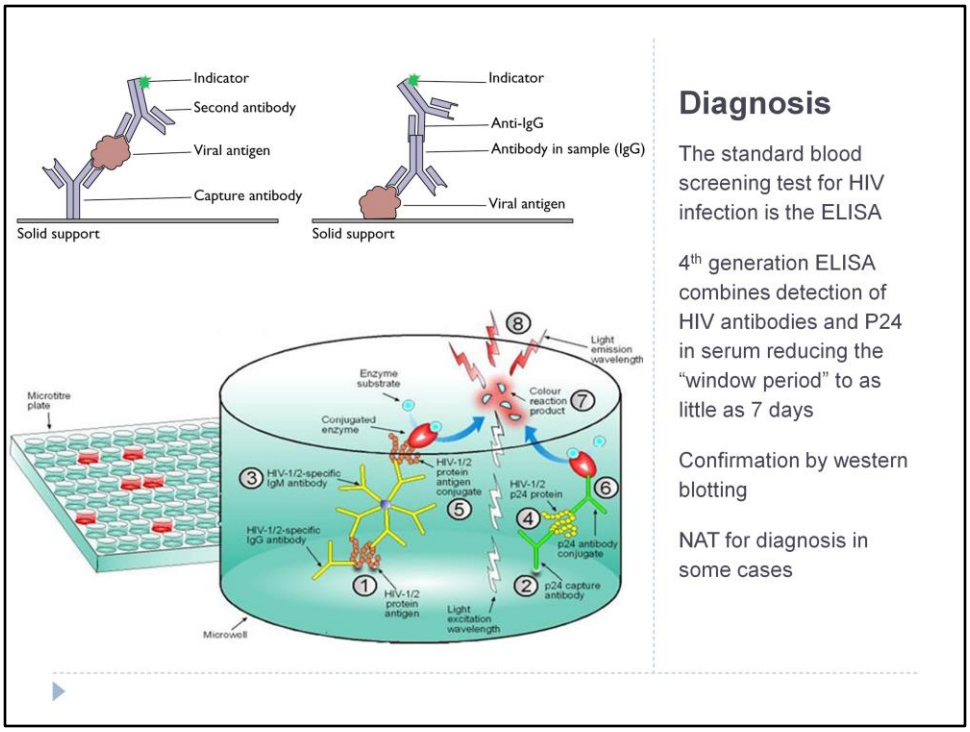


Markers of Progression to AIDS

- Increased viral load
- P24 antigenemia
- Decline of anti P24 antibodies
- CD4+ T cell count below 200 cells/ul



A growing number of end-organ complications not traditionally considered “AIDS-defining” events have been recognized to occur more frequently in HIV-1–infected patients. These include an increased risk of cardiovascular disease, non-AIDS defining malignancies, HIV-associated neurologic dysfunction (HAND), and HIV-associated nephropathy (HIVAN), and may also include loss of bone mineral density (BMD) and other changes typically associated with increasing age, suggesting that HIV-1 infection may accelerate the aging process.



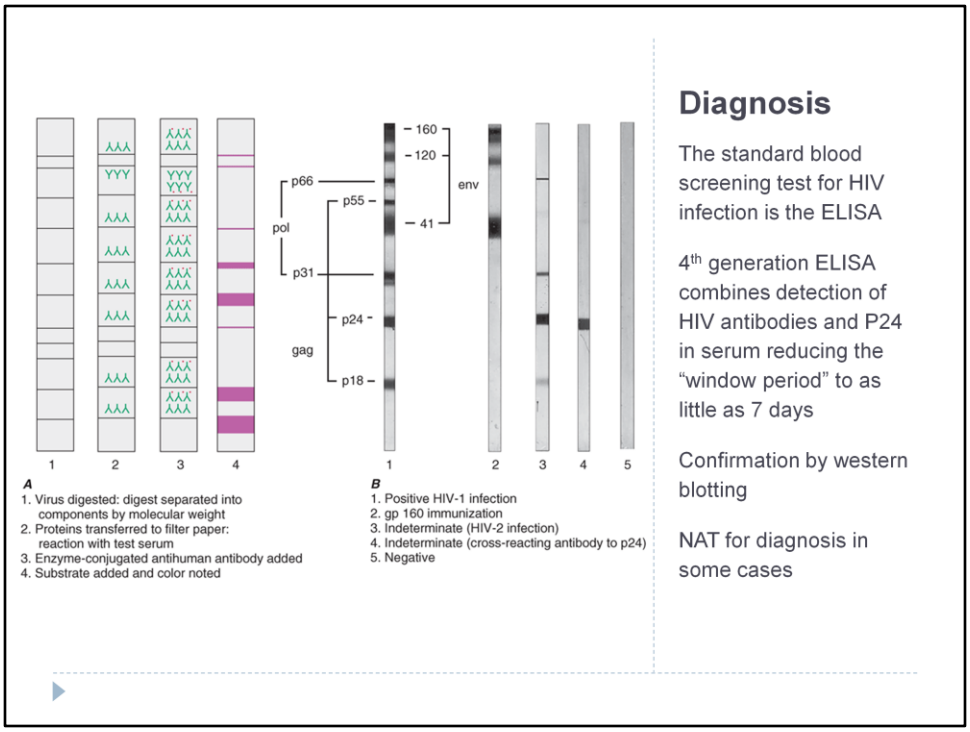
ELISA = enzyme-linked immunosorbent assay

Tests are divided into screening and confirmatory assays

Screening assays should be as sensitive as possible whereas confirmatory assays should be as specific as possible

Virus is readily detectable in peripheral blood and lymph nodes throughout the course of infection

NAT: Nucleic acid testing for diagnosis of HIV infection looking for HIV pro-DNA, and RNA. However, there are very few circumstances when
this is justified e.g. diagnosis of HIV infection in babies born to HIV-infected mothers (babies have maternal antibodies but not necessarily virus)

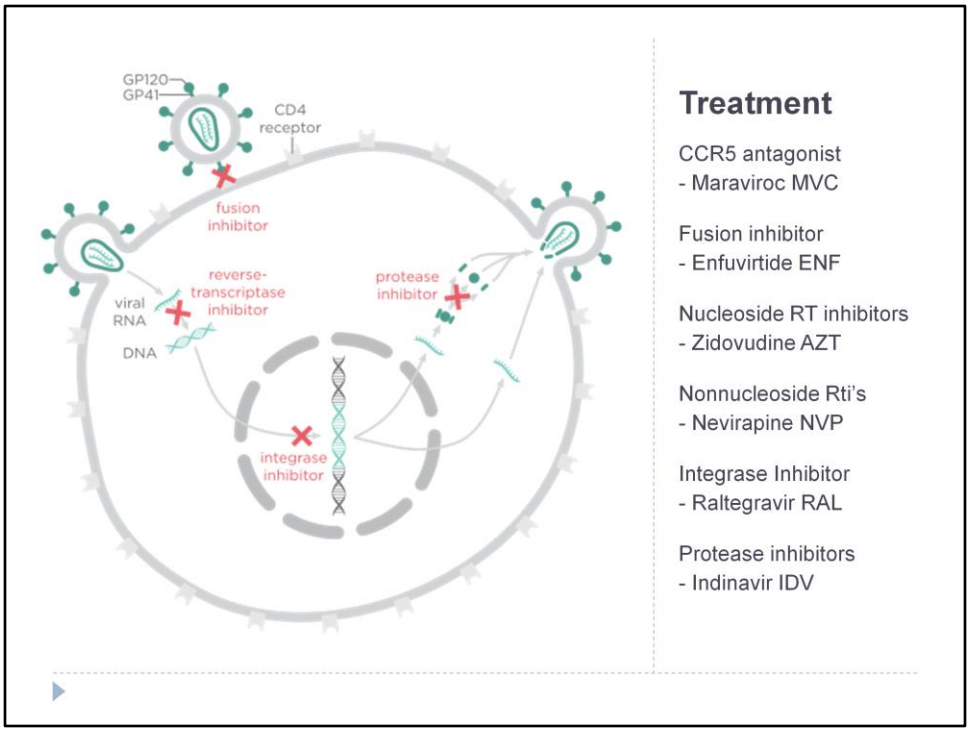


Lower sensitivity than ELISA but higher specificity

There are different criteria for the interpretation of HIV Western blot results e.g. CDC, WHO, American Red Cross.

The most important antibodies are those against the envelope glycoproteins gp120, gp160, and gp41

p24 antibody is usually present but may be absent in the later stages of HIV infection



The drugs mentioned are only examples (i.e. NON-exhaustive list). More than 30 approved drugs are now available.

Commonly used in combination.

The advent of potent combination antiretroviral therapy has had a profound influence on the course of HIV-1 infection in the developed world, where AIDS-related mortality has decreased by more than 80% since the introduction of combination therapy in the mid-1990s.

Remember that Most people with HIV/AIDS (95%) reside in low and middle income countries, and these are the countries least equipped to respond.

Image modified from "HIV-drug-classes" by Thomas Splettstoesser (www.scistyle.com)

Education

Lifestyle changes

Prophylactic treatment (vertical transmission, exposed health care workers)

Blood product screening

Vaccines