HIV-1/AIDS

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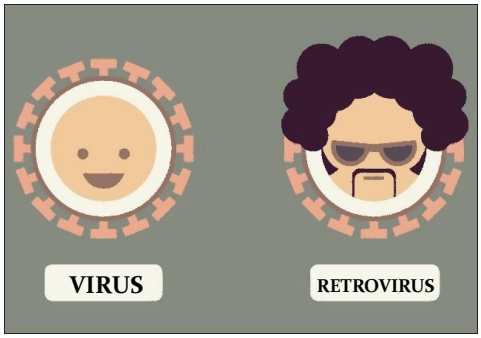
Retroviruses

- **Retroviruses** contain an RNA genome and an RNA-directed DNA polymerase (**reverse transcriptase; RT**).

- RNA tumor viruses in this family mainly cause tumors of the reticuloendothelial and hematopoietic systems (leukemias, lymphomas) or of connective tissue (sarcomas).



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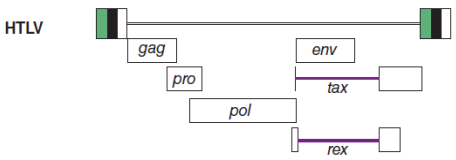
Retrovirus Structure

- The retrovirus genome is **diploid** consisting of single-stranded, positive-sense RNA, each 7–11 kb in size.
- The **reverse transcriptase** *contained in virus particles* is essential for viral replication.



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Retrovirus Features

Important Properties of Retroviruses

Virion: Spherical, 80–110 nm in diameter, helical nucleoprotein within icosahedral capsid
Composition: RNA (2%), protein (about 60%), lipid (about 35%), carbohydrate (about 3%)
Genome: Single-stranded RNA, linear, positive-sense, 7–11 kb, diploid; may be defective; may carry oncogene
Proteins: Reverse transcriptase enzyme contained inside virions
Envelope: Present
Replication: Reverse transcriptase makes DNA copy from genomic RNA; DNA (provirus) integrates into cellular chromosome; provirus is template for viral RNA
Maturation: Virions bud from plasma membrane
Outstanding characteristics: Infections do not kill cells May transduce cellular oncogenes, may activate expression of cell genes Proviruses remain permanently associated with cells and are frequently not expressed Many members are tumor viruses

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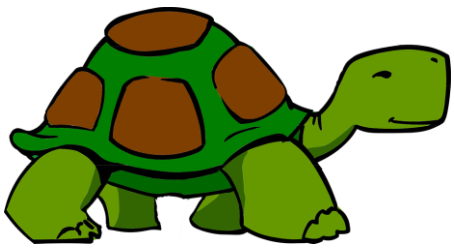
Classification

- The *Retroviridae* family is divided into seven genera.
- The clinically relevant genera are:
  - ❖**Deltaretrovirus** (human T-lymphotropic viruses).
  - ❖**Lentivirus** (agents able to cause chronic infections with slowly progressive neurologic impairment, including the human immunodeficiency virus).



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Host and origin

- Retroviruses have been isolated from virtually all vertebrate species.
- Natural infections across species barriers may occur.
- Exogenous retroviruses are spread horizontally and behave as typical infectious agents.
- Endogenous viruses are usually not pathogenic for their host animals. They do not produce any disease and cannot transform cells in culture.

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Human T-cell lymphotropic viruses types 1 & 2

- Human T-cell lymphotropic viruses types 1 & 2 (HTLV-1 & HTLV-2) are genetically and biologically similar. However, their worldwide distribution is different.
- HTLV-1 is present throughout the world, with clusters of high endemicity (Southwestern part of Japan, sub-Saharan Africa and South America).
- HTLV-2 has a more restricted distribution, more prevalent among some native Americans and some Central African tribes, but is relatively common among intravenous drug users and their sex partners in Europe, North America.

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Epidemiology & Transmission

- HTLV transmission occurs via one of three routes.

❖First, in highly endemic regions, **vertical transmission** is the most common mode of transmission. This is accomplished via infected lymphocytes either transplacentally or in breast milk.

❖Second, infection can be transmitted **sexually** by infected lymphocytes contained in semen.

❖Third, any **blood products** containing intact cells are also a potential source of infection.

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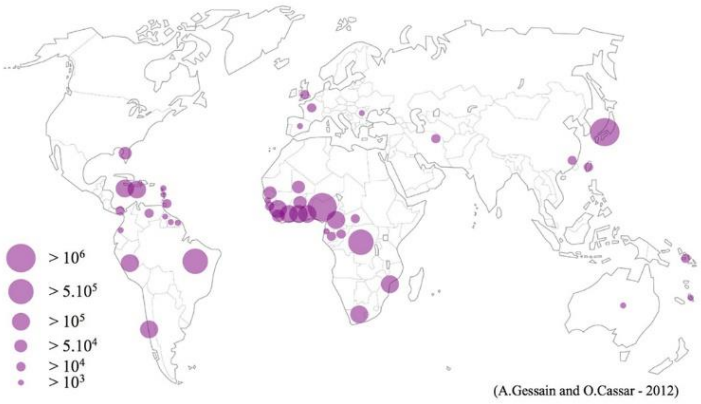
Epidemiology & Transmission

It is estimated that 10 million to 20 million people live with HTLV-1 worldwide



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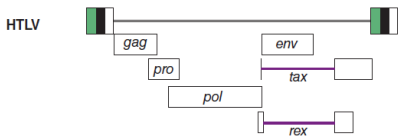
Pathogenesis & Clinical Features

- HTLV is considered an **oncovirus**.
- The viral *Tax* is the critical viral oncoprotein.



- HTLV infection both stimulates mitosis and immortalizes T lymphocytes.
- Following infection, the virus becomes integrated in the host cell as a **provirus**.
- In the course of continued multiplication over a period of many years, the infected T cells accumulate many ***chromosomal aberrations***, leading to appearance of malignant phenotypes.

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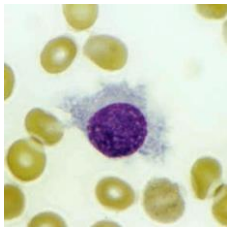
Pathogenesis & Clinical Features

- Most individuals remain asymptomatic during their entire lives, whereas a small fraction of carriers develop HTLV-1–associated diseases:
- Adult T cell leukemia.
- Cutaneous T-cell lymphoma.
- Hairy cell leukemia (HTLV-2).



- HTLV-associated myelopathy/tropical spastic paraparesis (characterized by progressive spasticity and weakness of the extremities, urinary and fecal incontinence, hyperreflexia, and some peripheral sensory loss).

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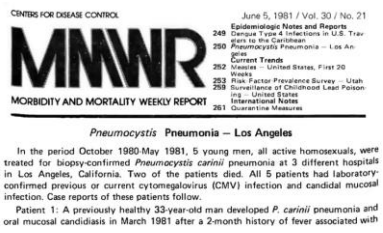
Diagnosis and Treatment

- HTLV-1 infection can be diagnosed by the presence of antibody to HTLV-1 (usually by ELISA).
- ATL is treated with aggressive chemotherapy.
- Attempts to treat HAM have been unsuccessful.
- For prevention, screening of blood units can be done, experimental vaccines are tested.

Background on AIDS

1908	HIV-1 tMRCA	1981	Reporting of AIDS
1930	Group M tMRCA	1982	AIDS term coined
1955	Subtype B tMRCA	1983	HIV-1 isolated
1966	Spread to Haiti	1990	AZT approved
1969	Spread to US	1996	Hit early hit hard


CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

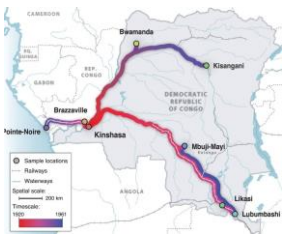
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with



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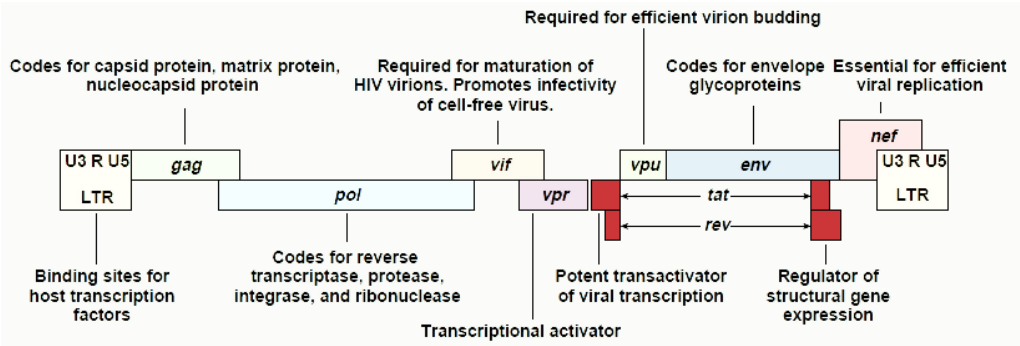
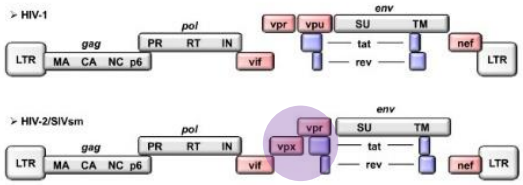
HIV Genome





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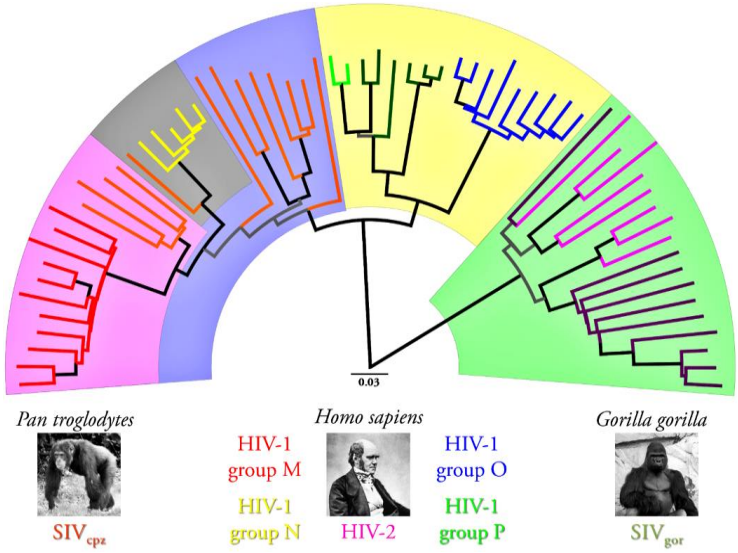
Classification



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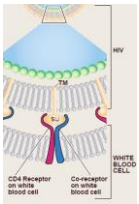
HIV, Important Features

- *Natural Host:* Human.
- *Tropism:* CD4+ T cells, MΦ and DCs
- *Cellular receptors:* CD4 + (CCR5 and/or CXCR4)
- *Geography:* Worldwide (HIV-1 group M)

  West Africa (HIV-2)



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Epidemiologic characteristics of HIV-1/AIDS

- According to UNAIDS, and by the end of 2015, about 37 million people were living with HIV/AIDS (PLWHA), of which about 2 million individuals acquired the infection in 2015.

- The unequal distribution of HIV/AIDS around the world is notable mostly in **Sub-Saharan Africa**, with more than two-thirds of PLWHA.

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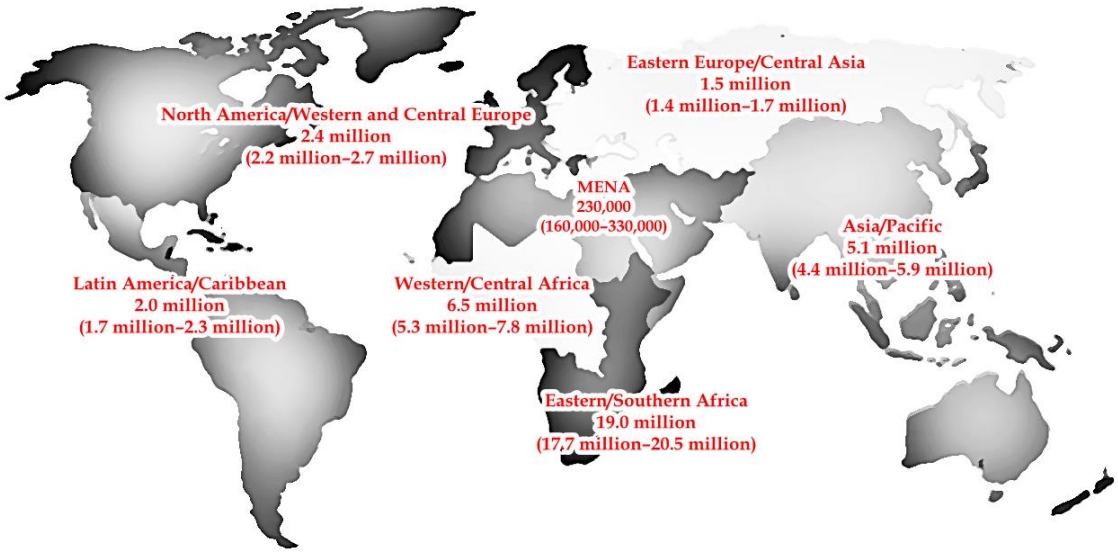
Epidemiologic characteristics of HIV-1/AIDS



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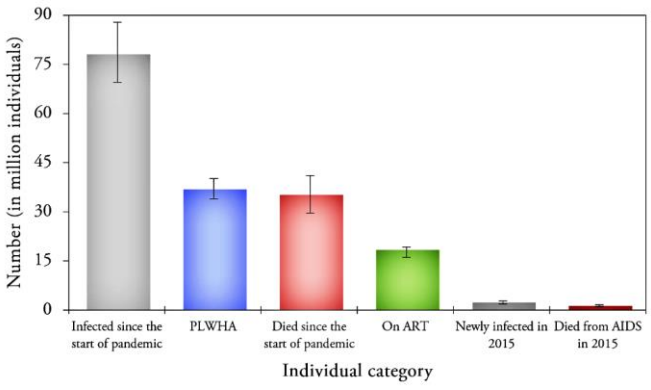
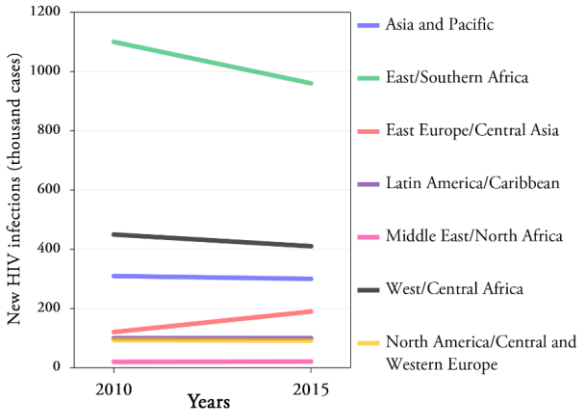
Epidemiologic characteristics of HIV-1/AIDS





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HIV-1 Transmission

- HIV-1 is a **blood-borne virus** (i.e. it can be transmitted through *transfusion*, *needlestick injury* and *IDU*) and the infection can be considered an **STI** (occurring through homosexual and heterosexual practices via vaginal, penile and anal mucosa).
- **Vertical transmission** can occur in utero, perinatally and through breast milk of infected mothers.
- Nowadays, the most common mode of transmission globally is **HET** contact but different regions differ in the most common route (e.g. **MSM** in US and Western Europe, **IDU** in Former Soviet Union countries and **HET** in sub-Saharan Africa).

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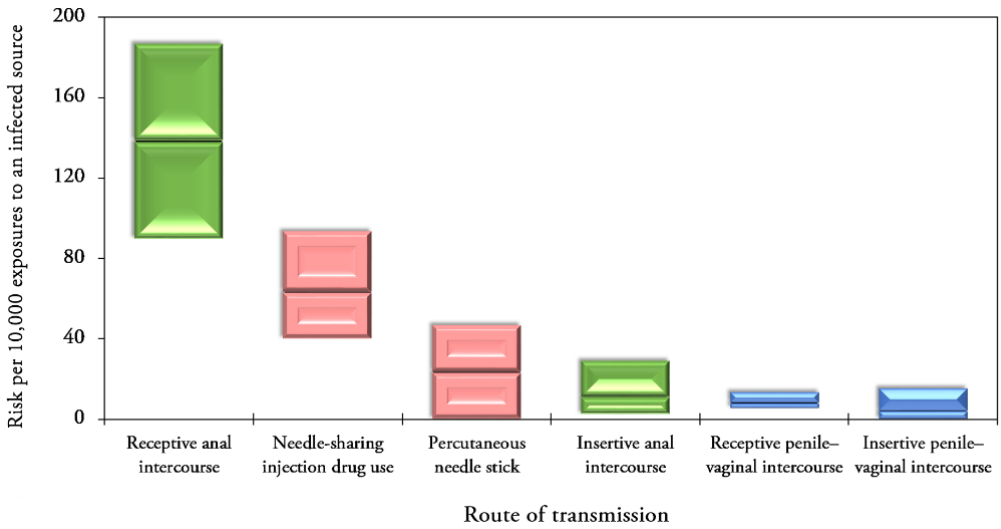
HIV-1 Transmission



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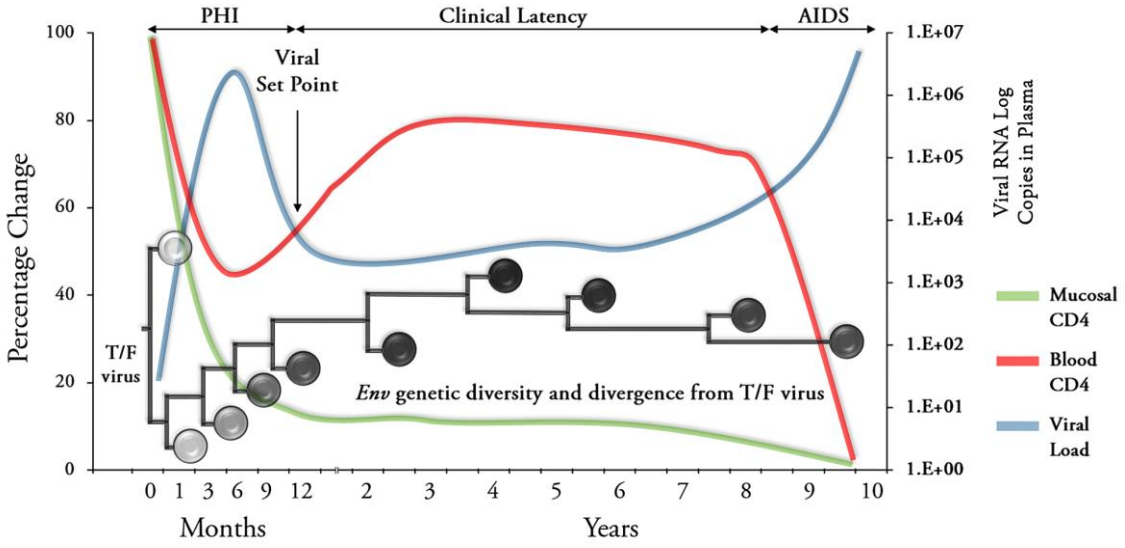
HIV-1 Pathogenesis



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HIV-1 Pathogenesis

- The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of **CD4+ T cells**.
- After HIV-1 inoculation, the virus infects its target cells, mostly macrophages through binding of **gp120** (part of ENV) to **CD4** and chemokine receptors **CCR5** or **CXCR4**.
- The virus starts to establish the infection for about 10 days locally before **systemic** spread.
- Subsequent virus spread into the lymphoid tissues including the gut-associated lymphoid tissue (**GALT**), ends-up in the establishment of infection chronically.

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HIV-1 Pathogenesis

- Viremia follows, which remains at high levels for about 8–12 weeks, coinciding with **mononucleosis-like features** in a majority of infected individuals.
- **The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT**.
- The adaptive immune response takes over at this stage to control viral replication manifested in the decline of viral load to a nadir "**viral set-point**", which fluctuates at low level throughout the clinical latency.
- **HIV-1 set-point** is considered an important **prognostic marker for assessment of disease progression**.

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Clinical features

❖**Primary infection (first few months):** Nonspecific and resemble those of infectious mononucleosis.

❖**Clinical latency (3-20 years, average 8-10 years):** The majority of HIV-1 infected individuals remain **asymptomatic** during the clinical latency period, nevertheless, *generalized lymphadenopathy* might persist from the primary infection period.

❖**AIDS:** The diagnosis of AIDS is made at **CD_4 T cell count of less than 200/µL** or **the presence of an AIDS defining condition** (MAC, PCP, extrapulmonary TB, **PML**, **KS**, toxoplasmosis, cryptococcosis, esophageal candidiasis, lymphomas, etc.).

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Diagnosis, management and prevention

- Screening for HIV-1 infection relies on **enzyme immune assays** with fourth-generation assays combining the detection of Abs (IgM and IgG) to HIV-1 (groups M, O, and N) and HIV-2 together with detection of p24.

- This is followed if positive by a confirmatory test, mostly **western blot** or detection of HIV-1 RNA.

- The biggest challenge in diagnosis is the presence of an interval between infection and detection (**window period**) and refinements of different diagnostic tests aimed to shrink this period particularly in testing of blood/blood products.

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Diagnosis, management and prevention

- For management of the HIV-1 infected individuals, ***CD_4 T cell count*** and ***plasma viral load*** measurements are indispensable for evaluation of disease progression and response to ART.

- The cornerstone of HIV-1 management is the so-called **HAART**.

- Despite the incurable nature of HIV-1 infection so far (with the exception of the Berlin patient) the treatment with combinations of antiretroviral drugs aims to suppress viral replication to a degree that permits the recovery of immune system responses in order to prolong the infected-individuals' survival.

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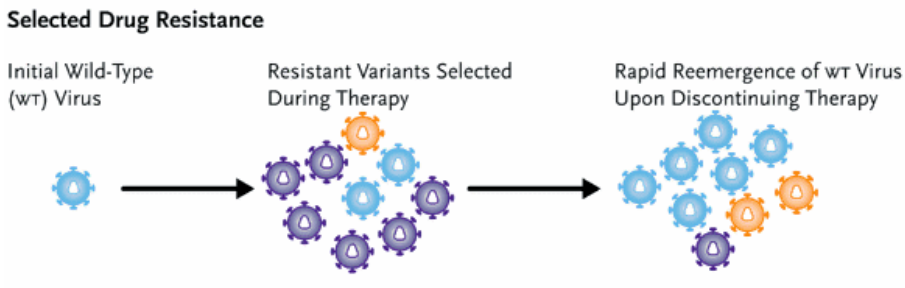
Diagnosis, management and prevention

- The latency of HIV-1 infection is evident upon treatment interruption which will lead to resurgence of viral replication.
- ARV drugs are classified currently based on its mechanism of action into six classes:

NRTI	NNRTI	PI	Integrase Inhibitor	Fusion Inhibitor	CCR5 antagonist
Zidovudine	Nevirapine	Saquinavir	Raltegravir	Enfuvirtide	Maraviroc
Didanosine	Delavirdine	Ritonavir	Dolutegravir		
Stavudine	Efavirenz	Indinavir	Elvitegravir		
Lamivudine	Etravirine	Nelfinavir			
Abacavir	Rilpivirine	Atazanavir			
Tenofovir		Tipranavir			
Emtricitabine		Darunavir			

Diagnosis, management and prevention

- Several biologic properties of HIV-1 make the emergence of drug resistance an inevitable outcome in the individuals receiving suboptimal ART (high rate of mutation, possibility of recombination).



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Diagnosis, management and prevention

In the absence of an effective vaccine towards HIV-1 infection, the preventive efforts rely on the following measures: (1) **HIV-1 testing** particularly among most-at-risk groups. (2) Consideration of (**PrEP**) and (**PEP**) among individuals at risk along with *early initiation of ART among HIV-1 infected individuals*. (3) Counselling and education of most-at-risk groups regarding the behavioural practices that are associated with higher probability of transmission (e.g. needle-sharing, unprotected sex, etc.), along with implementing protective measures (needle exchange program [**NEP**], STI screening and condom use).

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