Human Immunodeficiency Virus

- Virion
- Genome
- Genes and proteins
- Viruses and hosts
- Diseases
- Distinctive characteristics

Viruses and hosts

- Lentivirus from Latin *lentis* (slow), for slow progression of disease
  - Human immunodeficiency virus types 1 and 2 (HIV-1, HIV-2)
  - Simian immunodeficiency virus
  - Equine, bovine, feline immunodeficiency viruses

Table 29.1 Lentiviruses

Virus	Host
Human immunodeficiency virus type 1	Humans
Human immunodeficiency virus type 2	Humans
Simian immunodeficiency virus	Apes and old world monkeys
Feline immunodeficiency virus	Cats
Equine infectious anemia virus	Horses
Caprine arthritis-encephalitis virus	Goats
Visna-maedi virus	Sheep

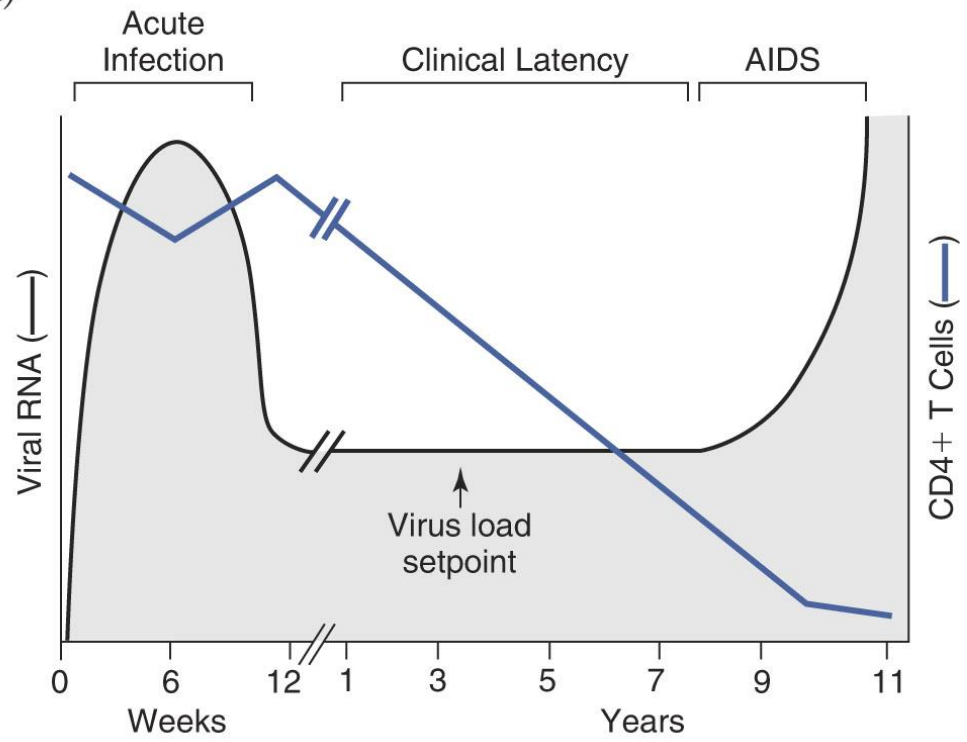
Diseases

- Acquired immune deficiency syndrome (AIDS) was first described in 1981
- A major global pandemic today (more than 33 million people infected)
- HIV replicates in and kills lymphocytes and macrophages
- Infection results in depletion of CD4+ T cells, rendering the host immune-incompetent
- As a result, opportunistic infections by other pathogens are often fatal
- HIV is transmitted through sexual contact and blood exchange

Diseases

- HIV-1 infection leads to a progressive loss of cellular immunity and increased susceptibility to opportunistic infections
  - Three phases of disease: (1) acute disease, (2) clinically latent phase, and (3) AIDS

(a)



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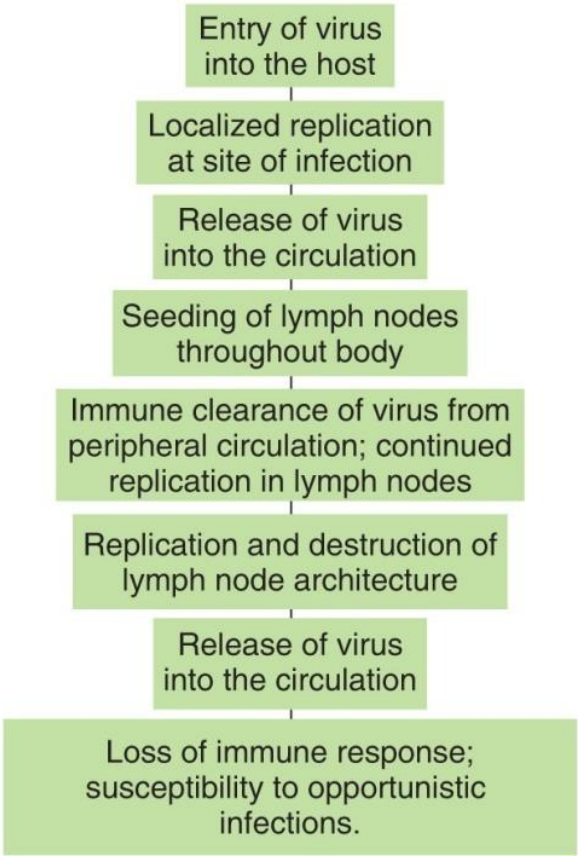
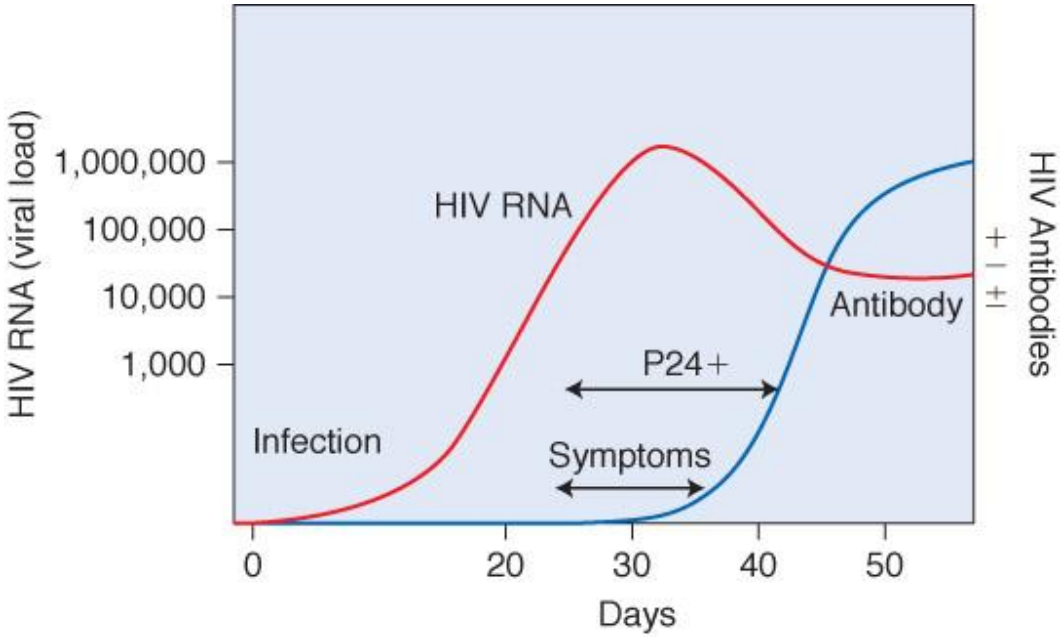


Diseases

(1) Acute disease

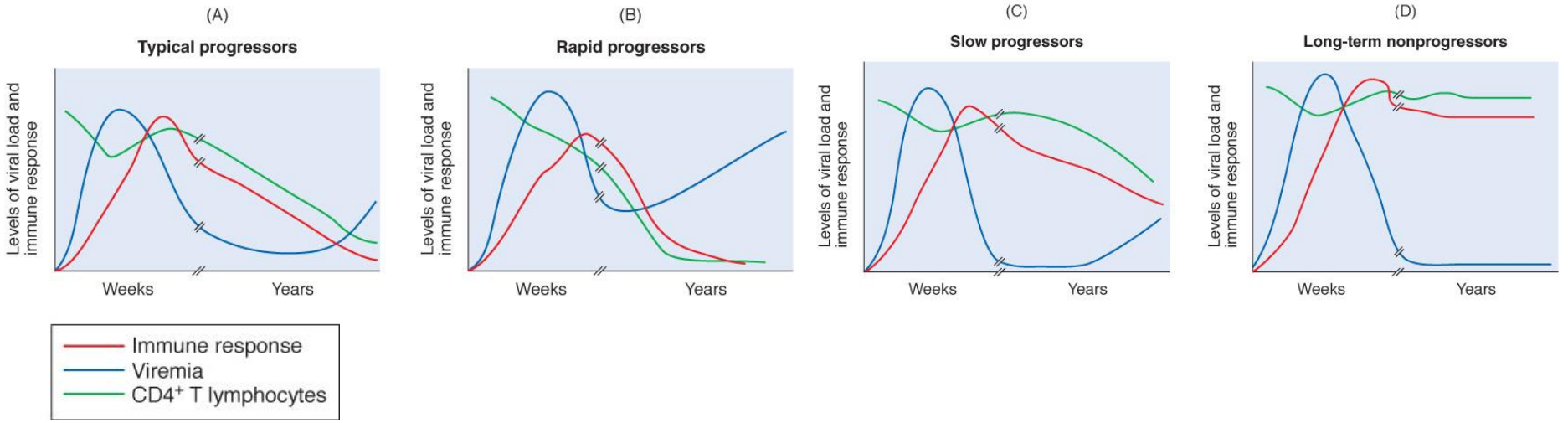
- Mononucleosis or influenza-like syndrome occurs in the first 2 to 6 weeks.
  - Fever, fatigue, rash, muscle pain, sore throat, swelling of lymph nodes
- Frequent symptoms experienced more than 50% of infected individuals
- Virus titers drop as cytotoxic T lymphocytes and antibodies respond (the more **epitopes** recognized the better the prognosis)



Diseases

(2) Clinical latency

- Virus replication persists in lymph nodes resulting in gradual depletion in CD4+ T cells
- Neither signs nor symptoms of the disease present
- Several courses of clinically latent phase in absence of treatment:
  - Typical progressors: (Most) develop late stage symptoms in 8 to 10 years
  - Rapid progressors: (10-15%) develop late stage symptoms in 2 to 3 years
  - Slow progressors: (5-15%) develop late stage symptoms in over 15 years
  - Long-term nonprogressors: (1%) show no decline in CD4+ T cell levels



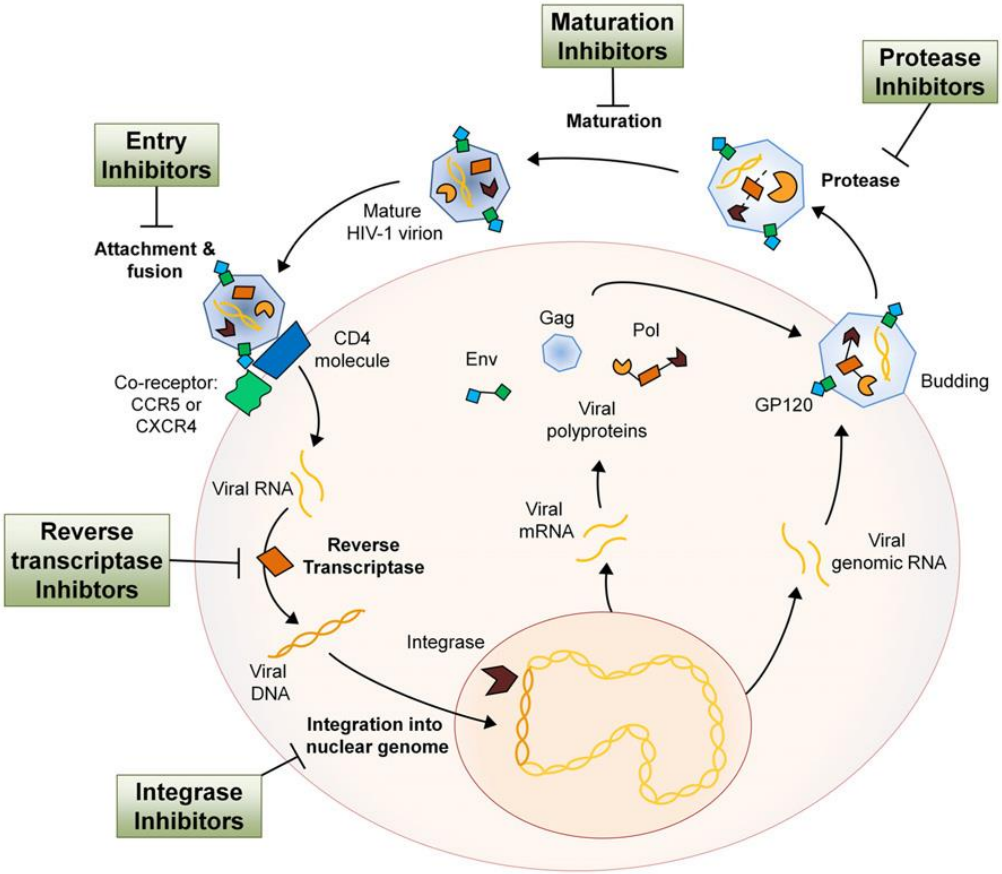
Diseases

(3) AIDS

- As T-lymphocyte counts decrease below 50 cells/μl, the number of opportunistic infections increases
  - High levels of virus in blood
  - Chronic fever, night sweats, diarrhea, and many opportunistic infections
  - AIDS patients also suffer from malignancies such as nonHodgkin's lymphoma
  - Wasting syndrome also common (a loss of more than 10% of body weight due to fever or diarrhea for more than 30 days).
  - Neurological and neuromuscular syndromes
- Without anti-retroviral therapy, the patient will die within 2 to 3 years

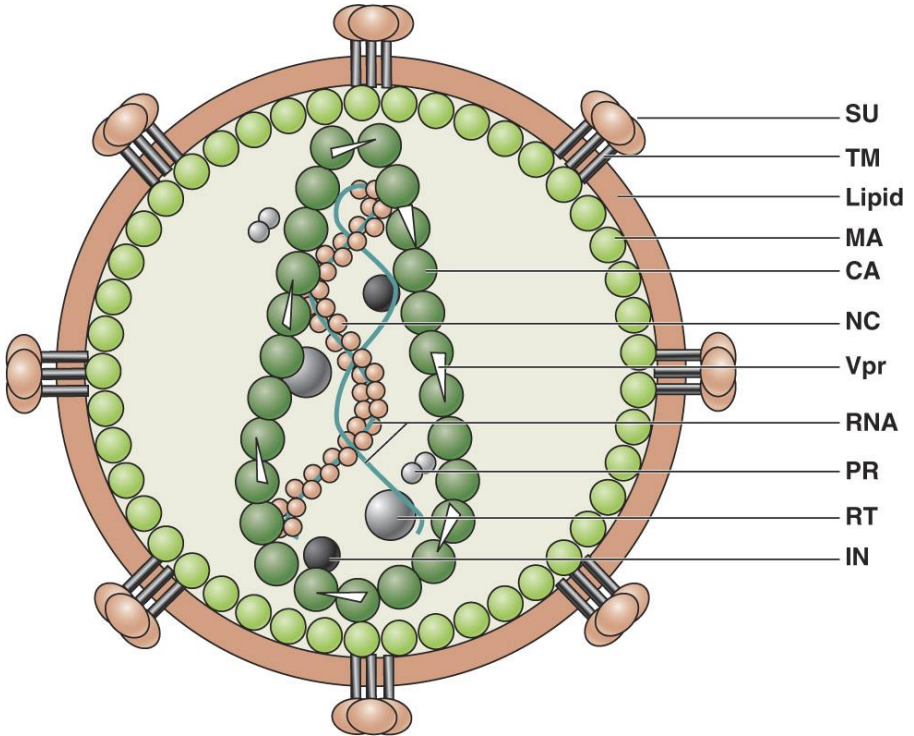
Diseases

- Antiviral drugs can control HIV-1 infection and prevent disease progression, but an effective vaccine has yet to be developed
  - Treatment involves a combination of drugs targeted at the reverse transcriptase and protease; Highly active antiretroviral therapy (HAART)



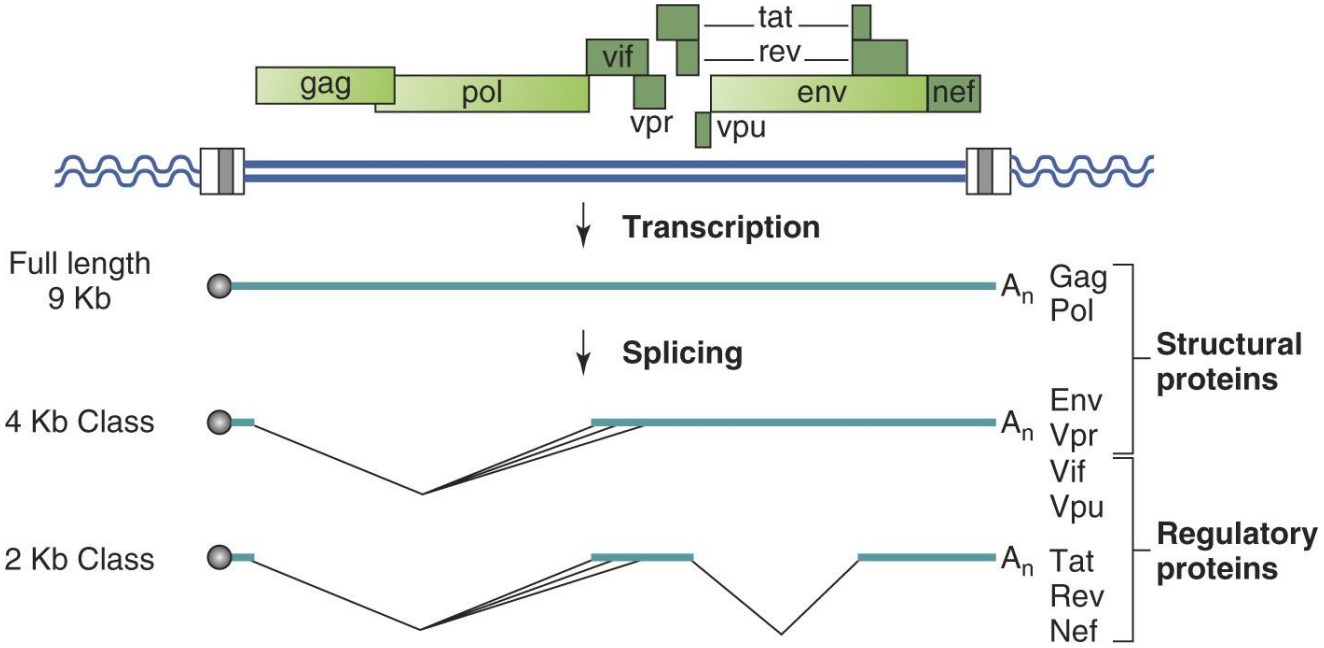
Virion

- HIV-1 is a complex retrovirus
- Spherical enveloped particle; Diameter 100 nm
- Conical capsid with probably icosahedral symmetry
- Two identical genome RNAs in each virion
- Cellular $tRNA^{lys3}$ molecules packaged in virions used as primers for reverse transcription



Genome, genes and proteins

- Linear single-stranded RNA, positive sense, 9.3 kb
- 4 capsid proteins: matrix (MA), capsid (CA), nucleocapsid (NC), p6
- 3 enzymes: protease (PR), reverse transcriptase (RT), integrase (IN)
- 2 envelope proteins: surface (SU) and transmembrane (TM)
- 6 regulatory proteins: Vif, Vpu, Vpr, Tat, Rev, Nef



Genes and proteins

Table 29.2 HIV-1 structural proteins

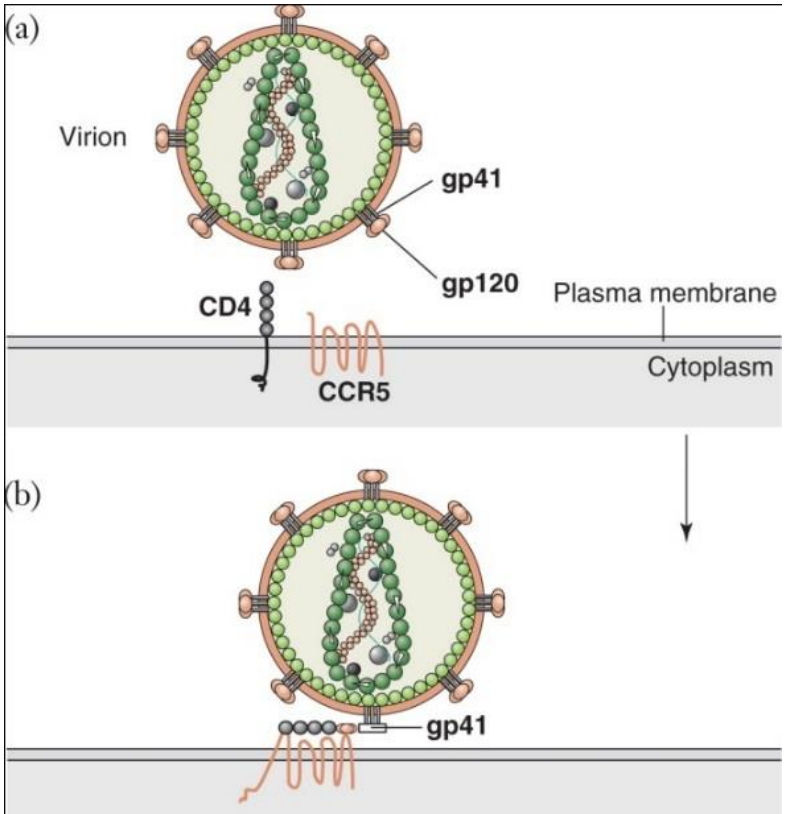
Name	Abbreviation	Alternative name (M. Wt. in KDa)
Matrix	MA	p17
Capsid	CA	p24
Nucleo**c**apsid	NC	p7
Protease	PR	p14
Reverse **t**ranscriptase	RT	p66/51
Integrase	IN	p32
Surface protein	SU	gp120
Trans**m**embrane protein	TM	gp41
Virion **p**rotein **R**	Vpr	p15

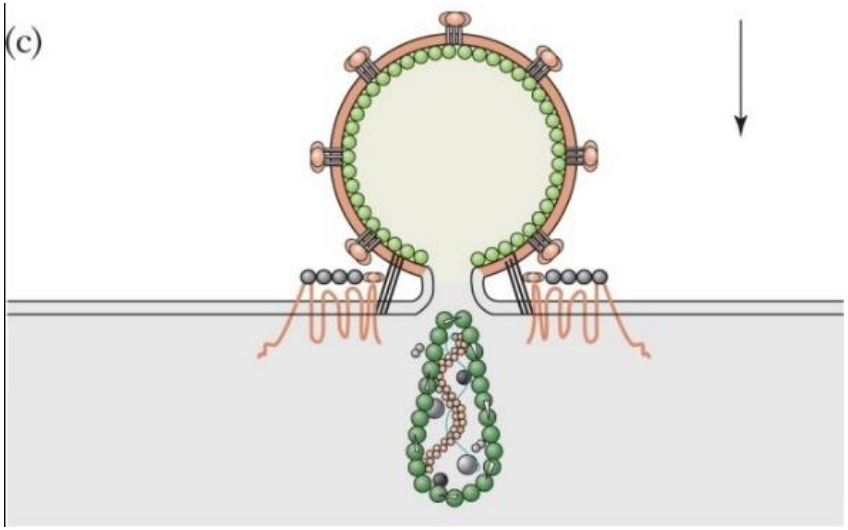
Table 29.3 HIV-1 nonstructural proteins

Name	Abbreviation	Alternative name (M. Wt. in KDa)
Viral **i**nfectivity **f**actor	Vif	p23
Virion **p**rotein **u**nique to HIV-1	Vpu	p16
Trans**a**ctivator of transcription	Tat	p15
Regulator of **e**xpression of **v**irion proteins	Rev	p19
Negative **e**ffector	Nef	p27

Entry

- HIV-1 targets cells of the immune system by recognizing CD4 antigens and chemokine receptors
  - CD4 is found on both macrophages and T lymphocytes
  - A co-receptor of either CCR5 or CXCR4 is also required

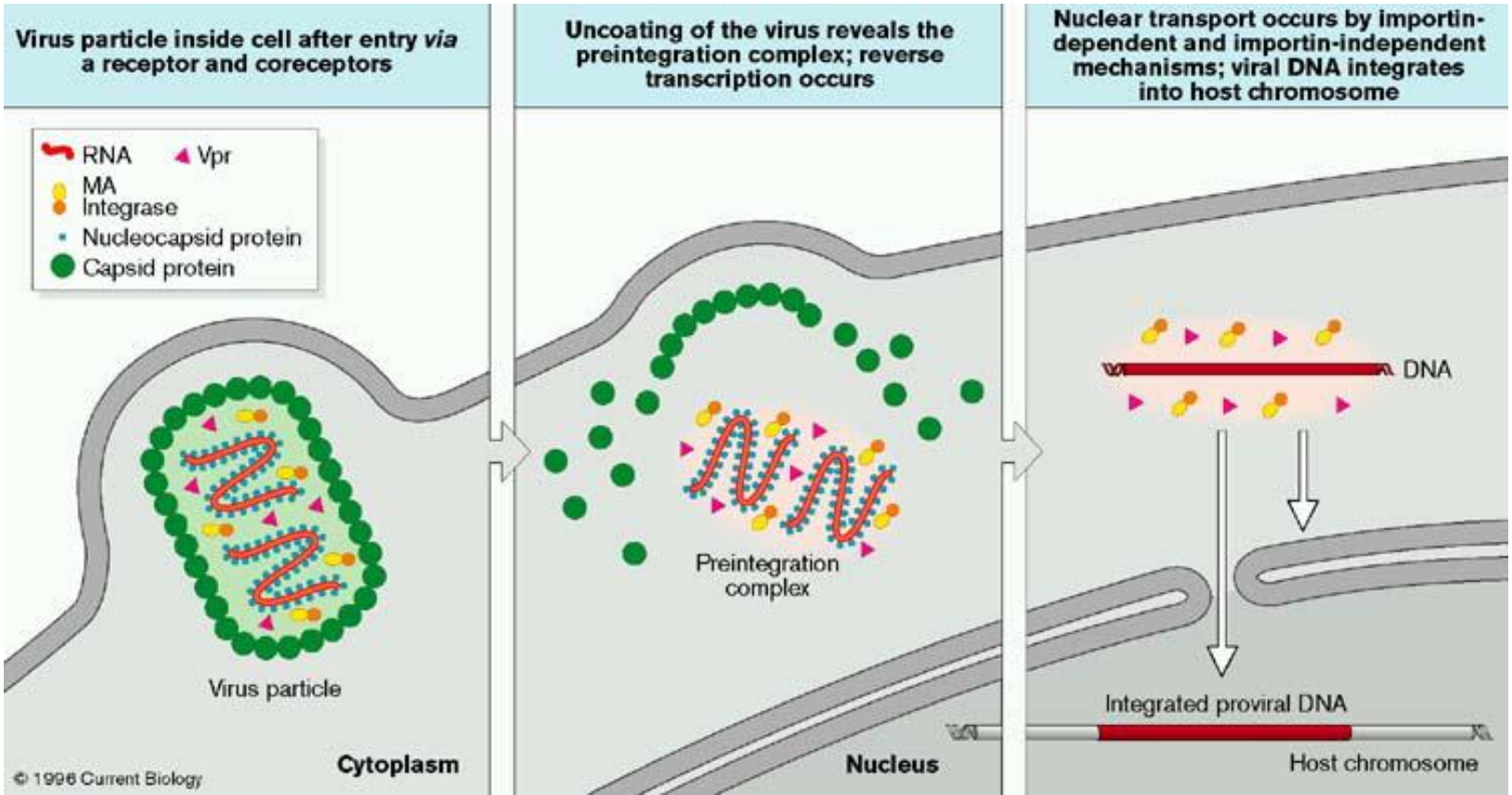




Model of HIV-1 entry

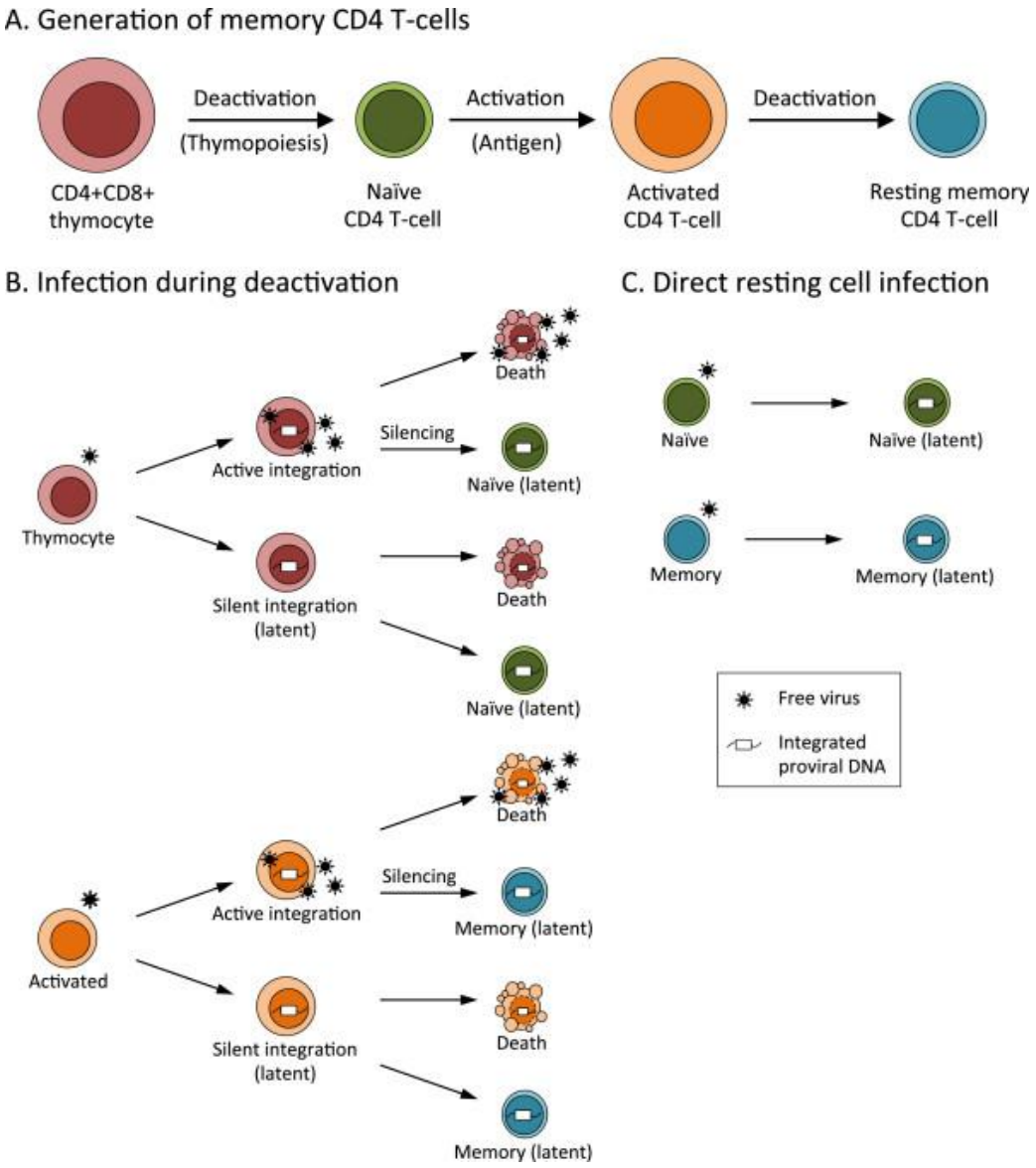
Entry

- Unlike other retroviruses, HIV-1 directs transport of proviral DNA into the cell nucleus
  - Allows for productive infection in non-dividing cells
  - MA, Vpr and IN direct transport into nucleus



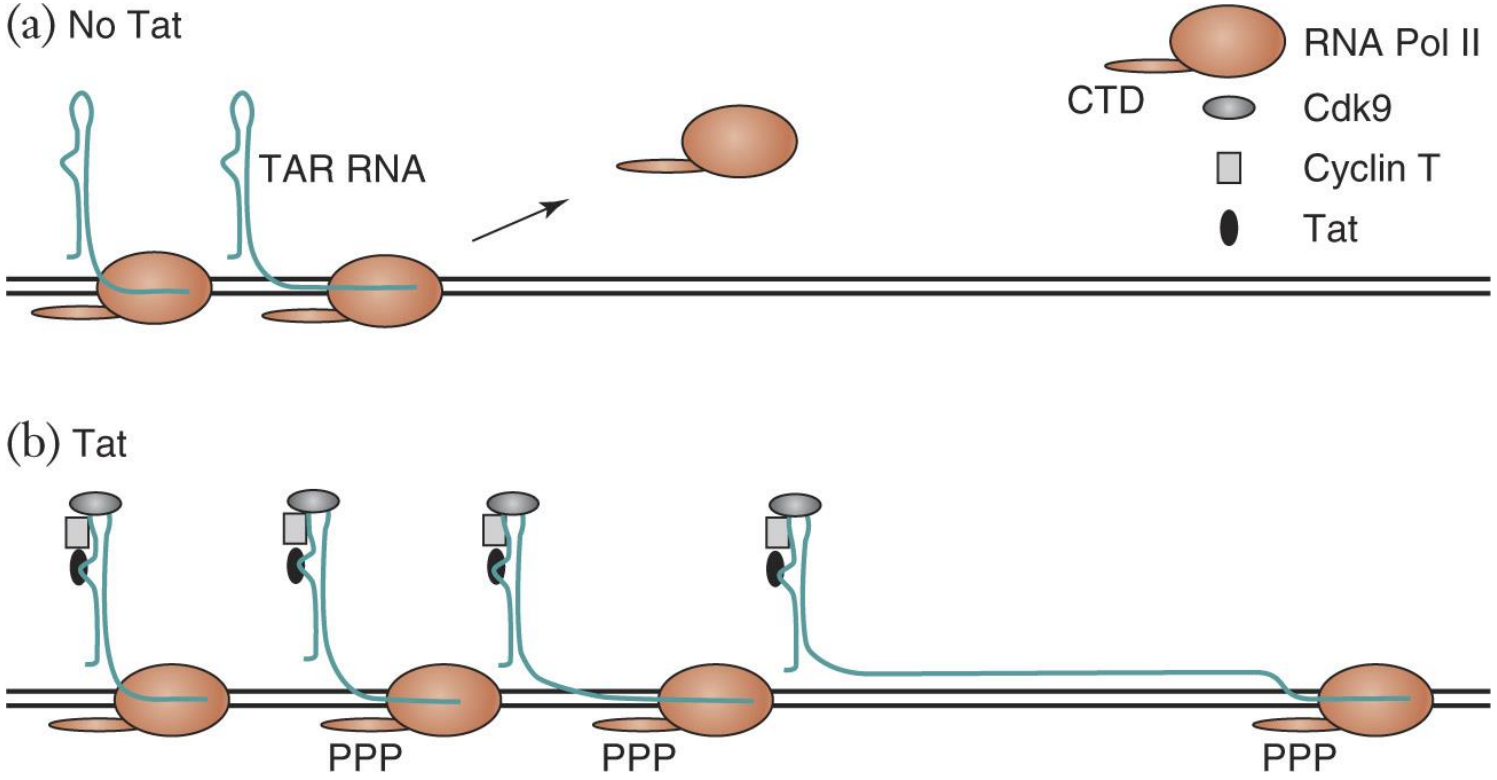
Latent infection

- Latent infection complicates the elimination of HIV-1
  - Integration of proviral DNA is followed by either **latent** or active infection
  - Latency is regulated by transcriptional control elements, where binding sites for **NFκB** and NFAT exist



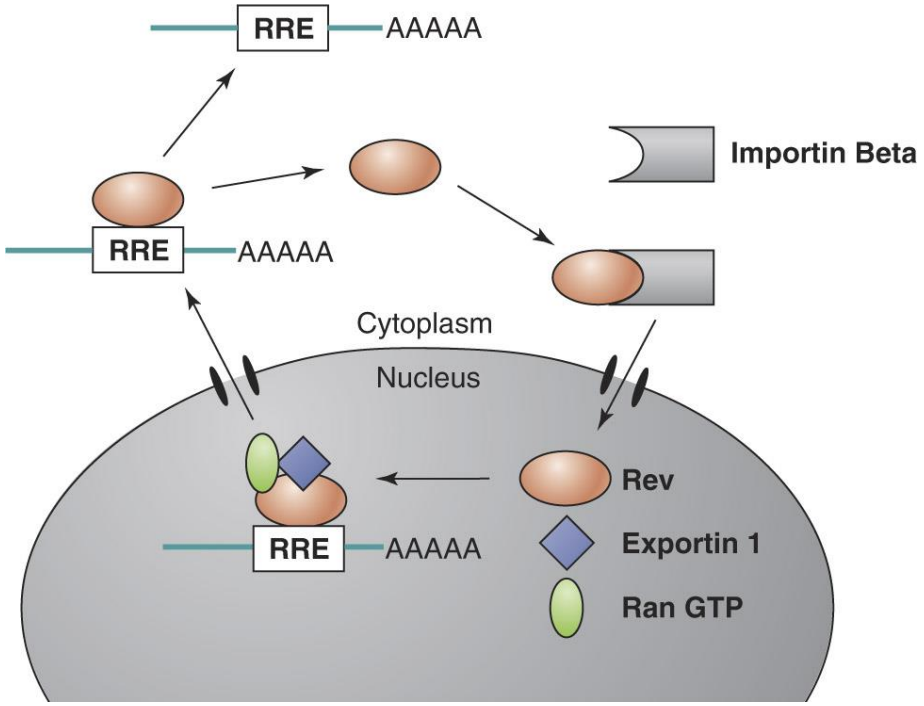
Genes and proteins

- The Tat (transactivator of transcription) protein increases HIV-1 transcription by stimulating elongation by RNA polymerase II



Genes and proteins

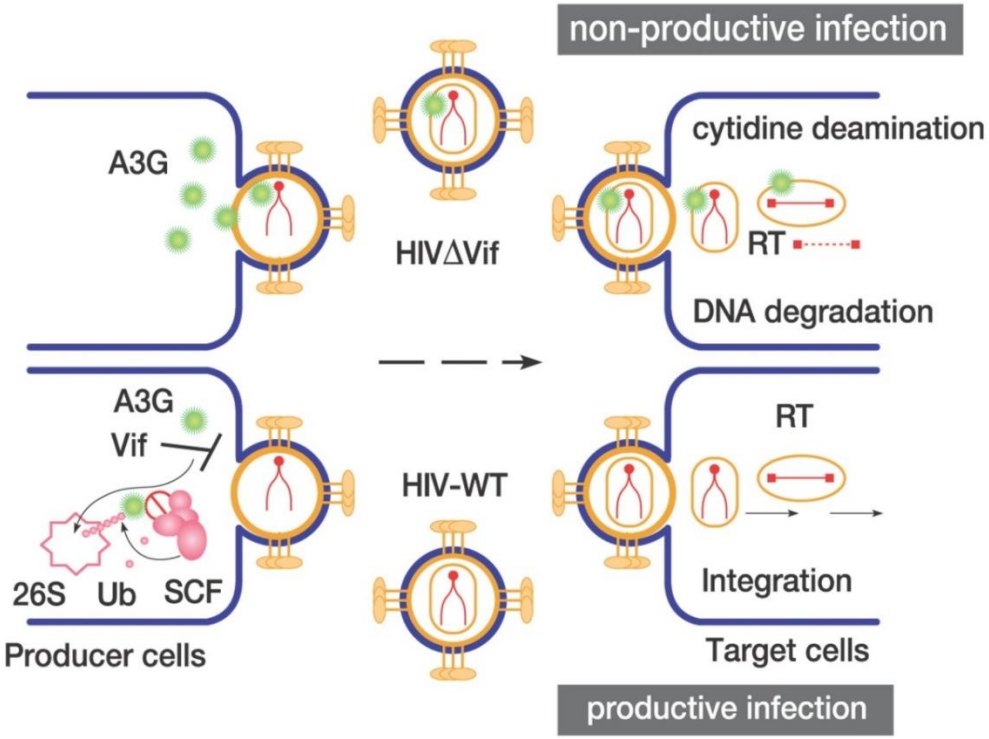
- The Rev (regulator of expression of virion proteins) protein mediates cytoplasmic transport of viral mRNAs that code for HIV-1 structural proteins
  - Requires two classes of sequences of RNA: *cis*-acting repressive sequences (CRS) and *Rev response element (RRE)*



Mechanism of Rev function

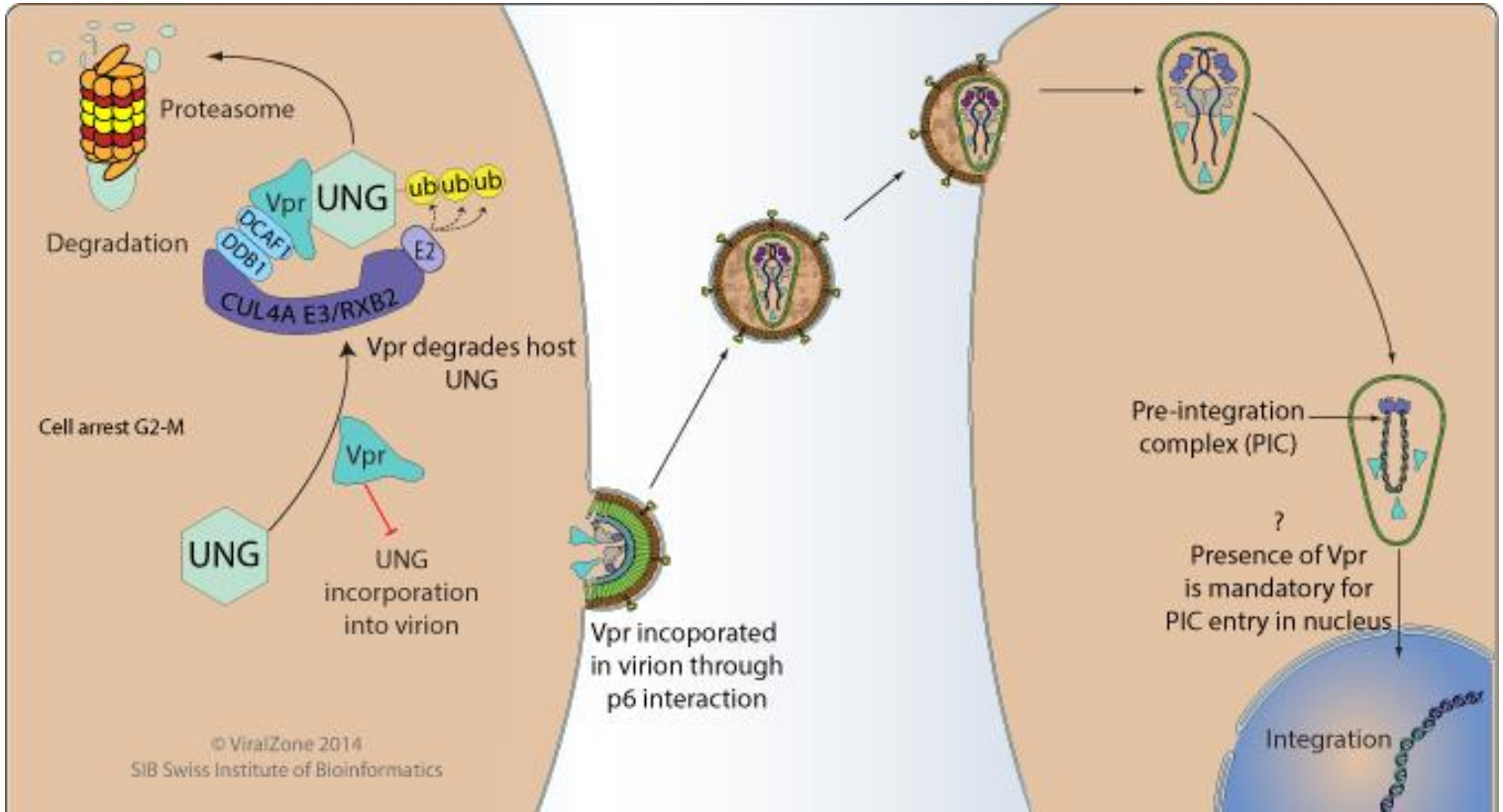
Genes and proteins

- The Vif (virus infectivity factor) protein increases virion infectivity by counteracting a cellular deoxycytidine deaminase, APOBEC3G
  - APOBEC3G is incorporated into virions and could deaminate deoxycytidine residues in viral DNA
  - Vif induces **ubiquitination** and degradation of APOBEC3G by **proteosomes**



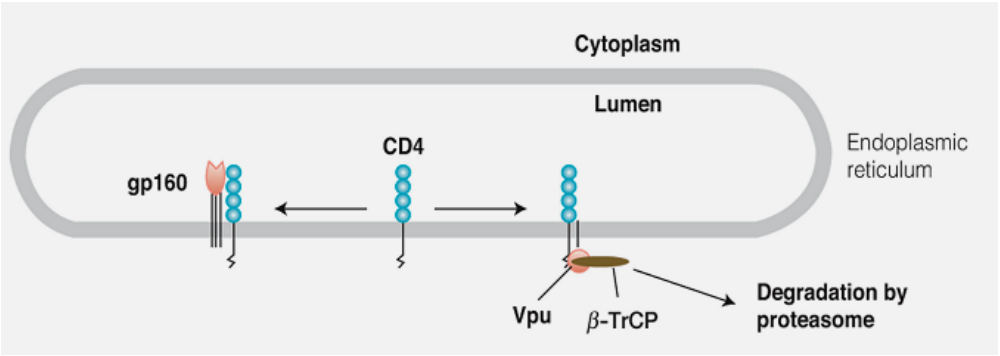
Genes and proteins

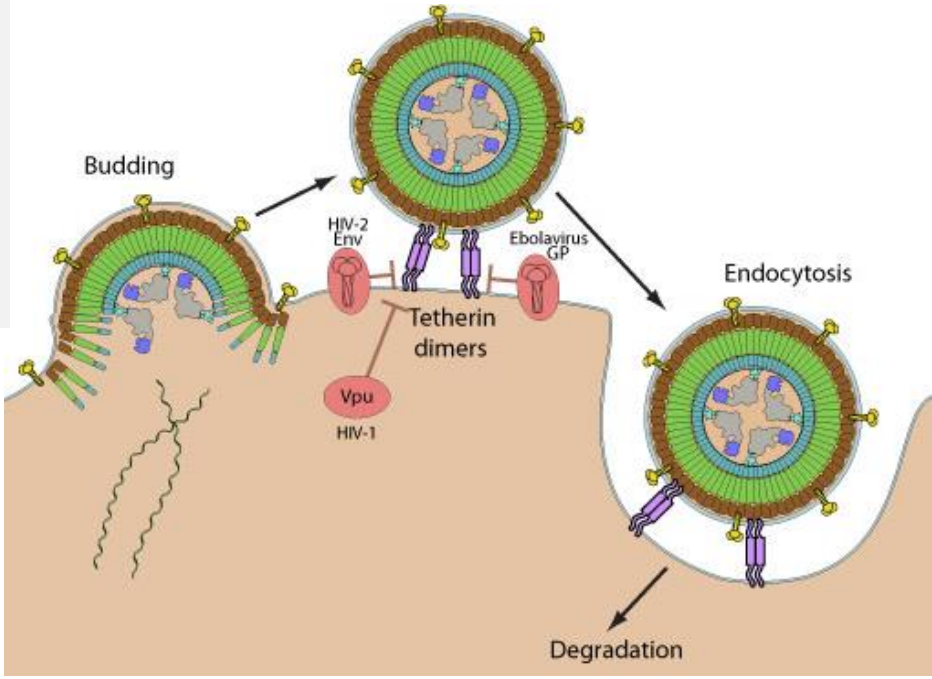
- The Vpr (virion protein R) protein enhances HIV-1 replication at multiple levels
  - Helps to transport preintegration complex into nucleus
  - Arrests cells in the G2 stage of cell cycle
  - Facilitates packaging enzymes into virion



Genes and proteins

- The Vpu (**v**irion **p**rotein **u**nique to HIV-1) protein enhances release of progeny virions from infected cells
  - Degrades CD4; CD4 in the cytoplasm can bind to and retain viral gp160
  - Enhances virus release from plasma membrane by antagonizing the tethering effect of tetherin





Genes and proteins

- The Nef (**N**egative **ef**fector) protein is an important mediator of pathogenesis
  - Localized to inner surface of plasma membrane via a myristate
  - Decreases surface expression of CD4 and MHC-1
  - Enhances virus infectivity
  - Modifies cell signaling