

HIV: A 60 Year Retrospective

IMPORTANT DATES IN THE FIRST DECADE OF THE AIDS EPIDEMIC.*

DATE	REPORTED EVENT	COMMENT†
June 5, 1981	5 Cases of <i>Pneumocystis carinii</i> pneumonia in homosexual men ¹	Initial report
July 3, 1981	26 Additional cases of new immunodeficiency syndrome ²	Cases in New York and California
June 18, 1982	Cluster in southern California ⁴	First report that “infectious agents [may be] sexually transmitted” ³
July 9, 1982	Initial cases in 34 Haitians ⁵	Mode of transmission unclear
July 16, 1982	Initial cases in 3 persons with hemophilia ⁶	Possibility of tainted blood supply
September 24, 1982	Term “acquired immune deficiency syndrome” (AIDS) used for first time ⁷	Term coined at July 1982 meeting, replacing “gay-related immune deficiency” (GRID)
October 1982	5 Cases in women reported, including 1 with only heterosexual exposure ⁸	First possibly heterosexually transmitted case
November 5, 1982	Precautions published for clinical and laboratory staff ⁹	“Patterns resemble the distribution and modes of spread of hepatitis B”
December 10, 1982	Initial transfusion-related case, in an infant ¹⁰	Further evidence of tainted blood supply
December 17, 1982	Initial vertically transmitted cases reported in 4 infants ¹¹	Reported as “Possible that these infants had AIDS”
January 7, 1983	Report of heterosexual transmission to 2 female partners of injection-drug users ¹²	“Supports infectious agent hypothesis”
January 7, 1983	Initial cases in 16 prisoners ¹³	Given known risk groups, occurrence in prisoners “might have been anticipated”
March 4, 1983	CDC releases prevention recommendations ¹⁴	Groups at risk advised not to donate blood
March 19, 1983	Initial cases in 5 persons from Central Africa ¹⁵	“Black Africans may be another group predisposed to AIDS”
May 20, 1983	Isolation of a virus from a patient with AIDS ¹⁶	Retrovirus belongs to HTLV group, but is “clearly distinct from each previous isolate”
July 15, 1983	Report of 4 possibly occupational cases among health care workers ¹⁷	Occupational transmission suspected but not proven
September 22, 1983	Infection-control guidelines published for care of patients with AIDS ¹⁸	“Measures consistent with those suggested for prevention of hepatitis B should be followed”
January 13, 1984	AIDS tabulated as “notifiable disease” for first time ¹⁹	25 Cases reported in first week
May 4, 1984	Frequent detection of HTLV-III in patients at risk ²⁰	“HTLV-III may be the primary cause of AIDS”
March 1985	FDA approves commercial test to detect HIV	Tremendous impact on patients at risk and blood supply
1986	CDC provides working definition of AIDS ²¹	Updated in 1993 ²²
1986	AIDS Clinical Trials Group established by NIH	Now largest clinical trials group in the United States
March 1987	FDA approves AZT (zidovudine)	First drug active against HIV

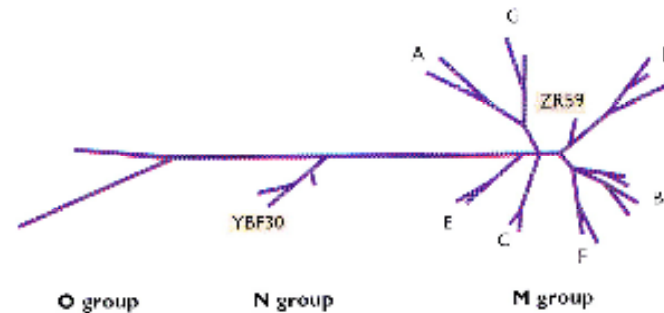
*CDC denotes Centers for Disease Control, FDA Food and Drug Administration, HIV human immunodeficiency virus, HTLV human T-cell lymphotropic virus, and NIH National Institutes of Health.

†Each quoted statement is from the reference cited under the corresponding Reported Event.

IMPORTANT DATES IN THE SECOND DECADE OF THE AIDS EPIDEMIC.*

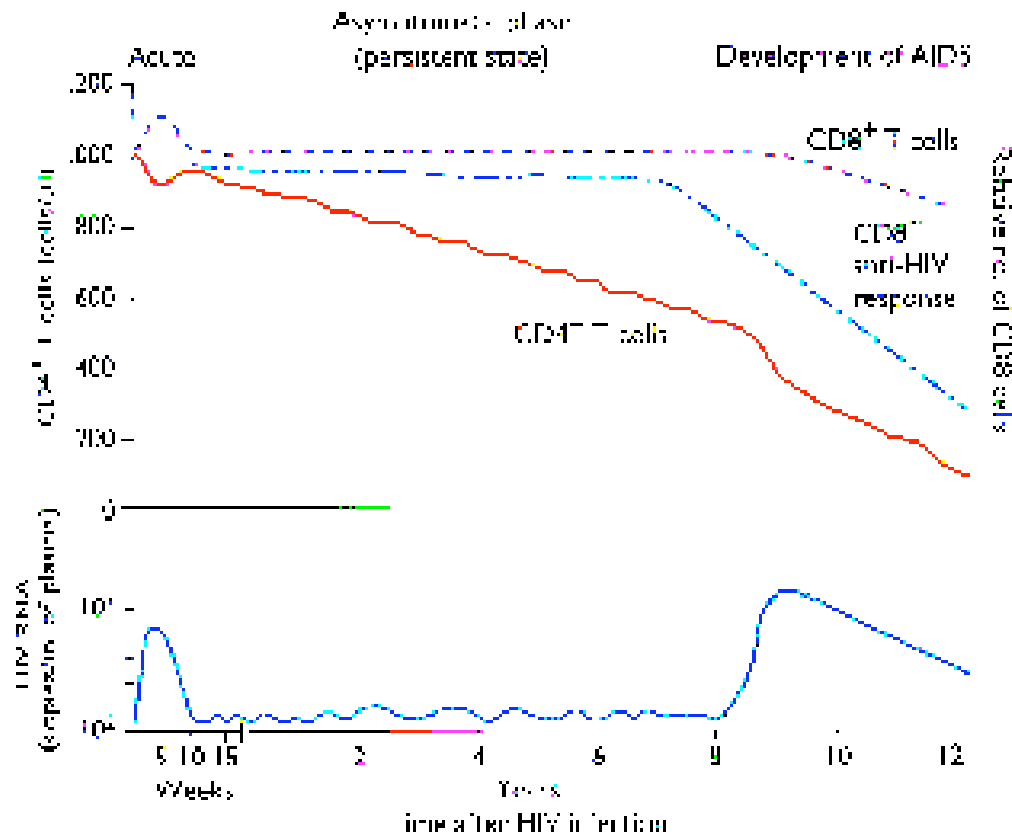
DATE	REPORTED EVENT	COMMENT
1991	Approval of didanosine and zalcitabine	Second and third approved drugs; combination therapy used increasingly
1993	AIDS becomes leading cause of death of Americans 25–44 years old ⁵³	AIDS surpasses unintentional injuries as cause of death in this group
January 12, 1995	Dynamics of HIV replication redefined ⁵⁴	“Primary [therapeutic] strategy ought to be to target virally mediated destruction”
May 4, 1995	Identification of viral cause of Kaposi’s sarcoma ⁵⁵	Human herpesvirus 8 isolated
July 15, 1995	First Public Health Service guidelines to prevent opportunistic infections ⁵⁴	Two subsequent revisions
August 1995	First protease inhibitor, saquinavir, approved ⁵⁶	Within 18 months, 3 additional protease inhibitors approved
1996	U.S. AIDS death rate decreases ⁵⁷	“For the first time, deaths among persons with AIDS have decreased substantially”
May 24, 1996	Prognostic power of viral-load determination established ⁵⁸	Important laboratory determination for routine management
1997	President Bill Clinton seeks AIDS vaccine in 10 years	HIV Vaccine Trials Network established
May 7, 1998	First published report of lipodystrophy syndrome ⁵⁹	Lipodystrophy, hyperlipidemia, diabetes, and other metabolic abnormalities described with increasing frequency in patients with AIDS
June 1998	Efavirenz approved ⁶⁰	“Protease-sparing” regimens introduced
January 10, 2000	UN Security Council discusses AIDS ⁶¹	“AIDS threatens our security”
December 2000	WHO estimates 36.1 million have HIV–AIDS, with an additional 21.8 million already dead ²	5.3 million new infections in 2000; 14,500 new infections per day
March 2001	U.S. pharmaceutical companies substantially reduce prices and may allow generic drugs for Africa ^{62,63}	Cost will be 1–10% of U.S. price

*UN denotes United Nations, and WHO World Health Organization.



1959 Serum from Bantu Male @ Kinchasa DRC => ZR59
 Suggests single trans-species jump in 1940-1950 and radiation after WWII
 YBF30 is a sequence outlier isolated from a patient in Cameroon

Disease Progression



Pathological conditions associated with HIV-1 infection¹

Acute phase

Morbillivirus-like syndrome: fever, malaise, pharyngitis, lymphadenopathy, headache, arthralgias, diarrhea, maculopapular rash, meningoenephalitis

Asymptomatic phase

Often none, but patients may present sporadically with one or more of the following symptoms: fatigue, mild weight loss, generalized lymphadenopathy, thrush, oral hairy leukoplakia, shingles

Symptomatic phase and AIDS

200–500 CD4⁺ T cells per ml; generalized lymphadenopathy, oral lesions (thrush, hairy leukoplakia, aphthous ulcers, salivary gland cysts/cytopia, molluscum contagiosum, basal cell carcinoma of the skin, Kaposi's sarcoma, squamous carcinoma of larynx, *Agmatococcus* adenitis)

Less than 200 CD4⁺ T cells per ml

Bacterial infections: *Pneumocystis carinii*, *Toxoplasma gondii*, *Isospora belli*, cryptosporidiosis, microsporidiosis

Bacterial infections: *Mycobacterium avium* (including *M. avium* *pallidum*)

Fungal infections: *Candida albicans*, *Cryptococcus neoformans*, *Coccidioides immitis*

Viral infections and malignancies: human cytomegalovirus, recurrent bouts of oral or genital HSV, lymphoma (mosty EBV), some HIV Br, Kaposi's sarcoma (HHV-8), anogenital carcinoma (HPV)

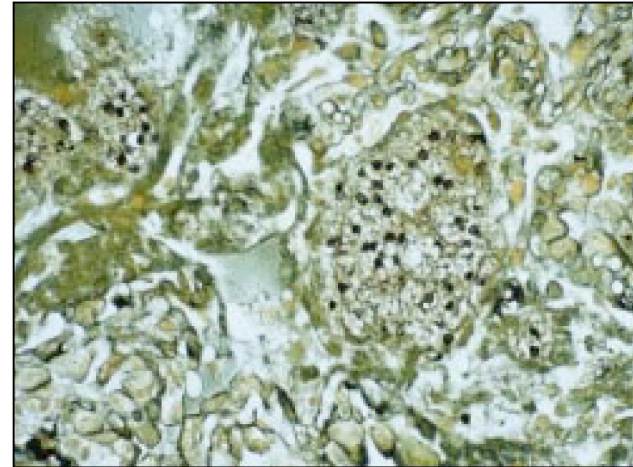
Neurological symptoms: aseptic meningitis; myelopathies, such as vacuolar myelopathy; pure sensory ataxia; parietal/occipital parietal neuropathies, such as acute demyelinating polyneuropathy; mononeuropathy multiplex; bilateral symmetric polyneuropathy; myopathy; AIDS dementia complex (ADC)

¹ Adapted from Trossel et al. & Lane and R. G. Desrosiers, p. 684-685, W. M. Gulik et al. (eds.), *The Kaposi Sarcoma (KCS) Exotic Harbors Laboratory for Hematology*, N.Y., 1992, with permission. F50: Epstein-Barr virus (EBV), *Leishman-Donovan* virus (LDV), human herpesvirus 8 (HHV-8), human papillomavirus

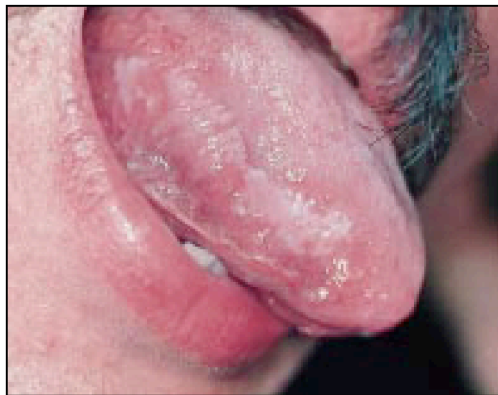
Clinical Picture



Varicella zoster



Pneumocystis carinii

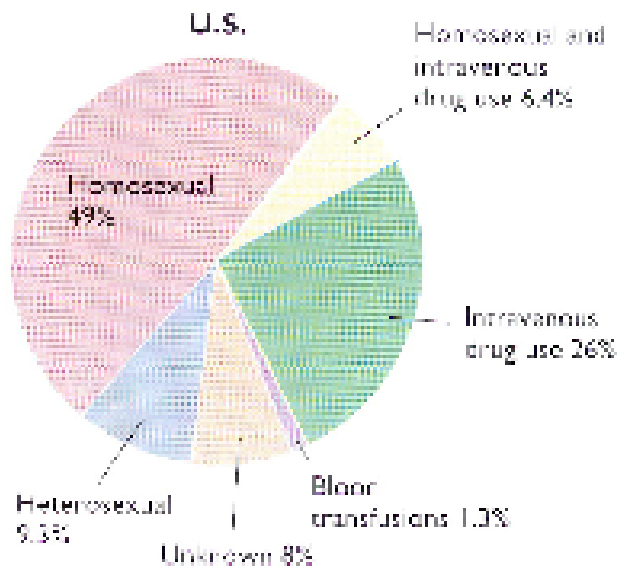
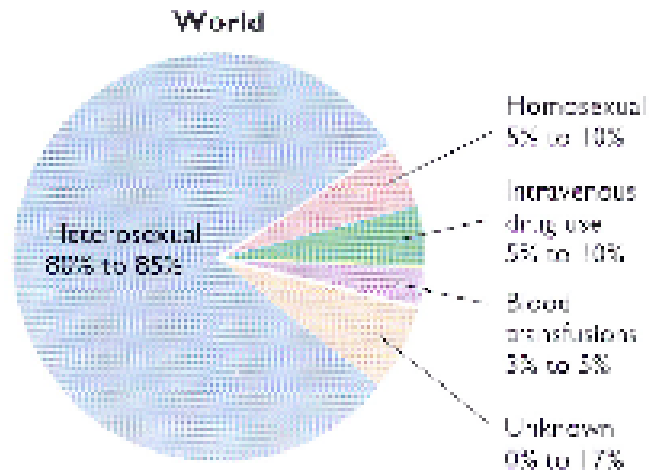


Hairy leukoplakia



Oral candida

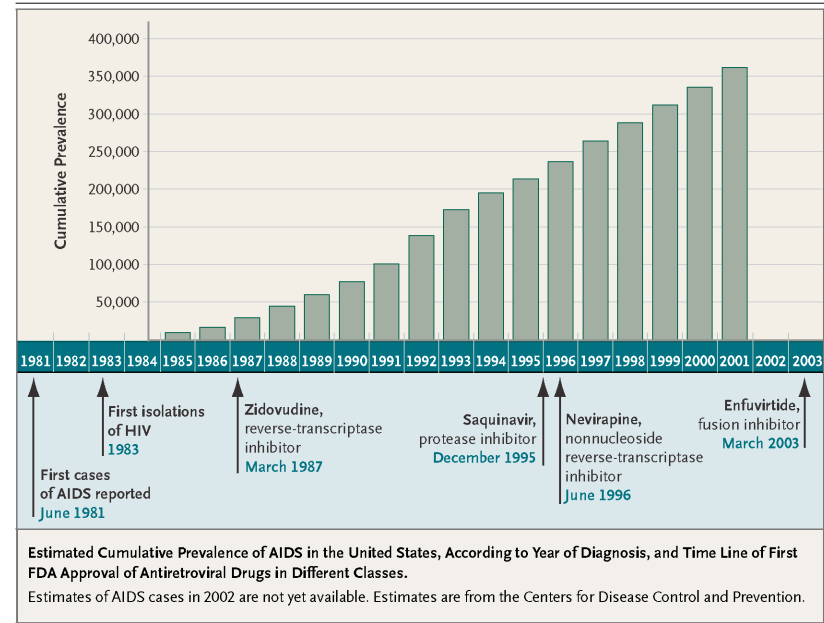
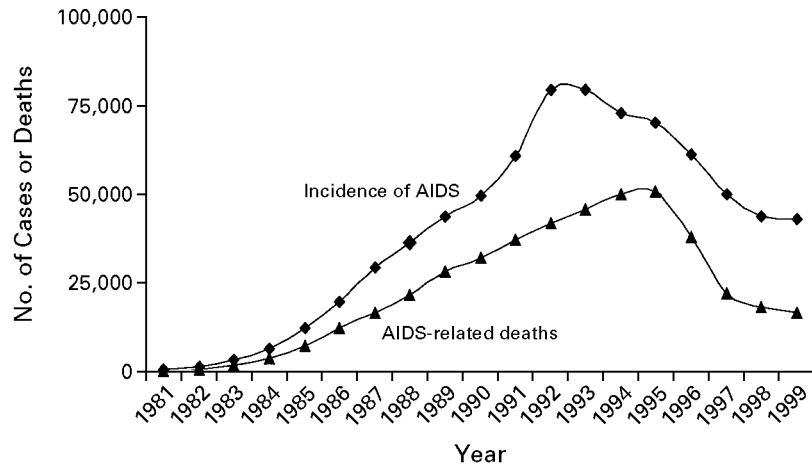
Modes of Horizontal Transmission



Also Vertical Transmission!

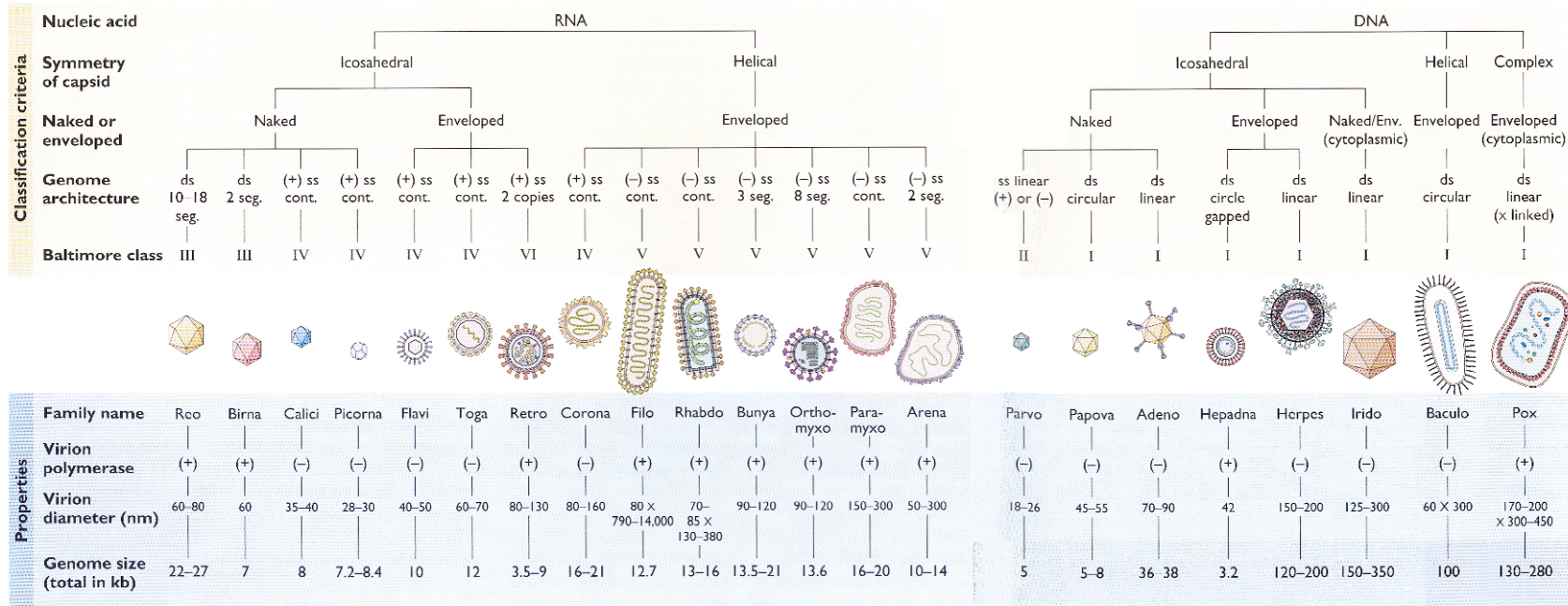
(11-60% depending on severity of maternal infection and \pm breastfeeding)

Incidence and Prevalence



- 36.1 million worldwide are infected
- Another 21.8 million have died
- 13.2 million children currently are “AIDS Orphans”
- 14,000 new infections daily (5.3 million in 2000)
- 70% of cases in sub-Saharan Africa where seroprevalence can exceed 25%
- Caribbean, Southeast Asia and Eastern Europe are other trouble areas

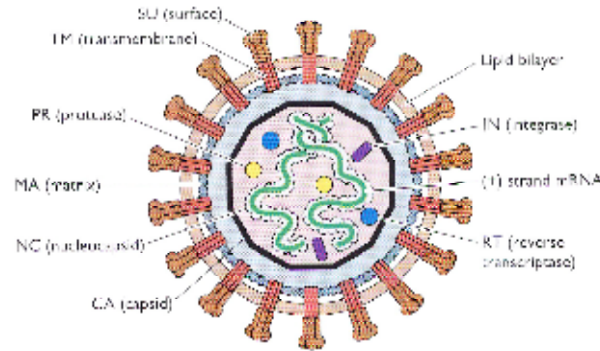
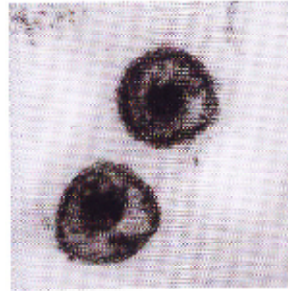
Virus Taxonomy



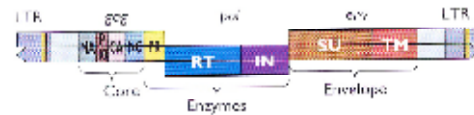
HIV belongs to the lentivirus subclass of retroviruses

- 2 copies of the +RNA strand; goes through a dsDNA intermediate
- icosahedral capsid
- enveloped
- 80-130 nm virion

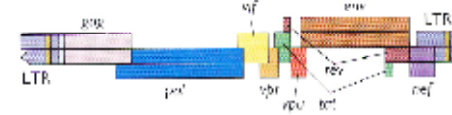
Anatomy of a Retrovirus



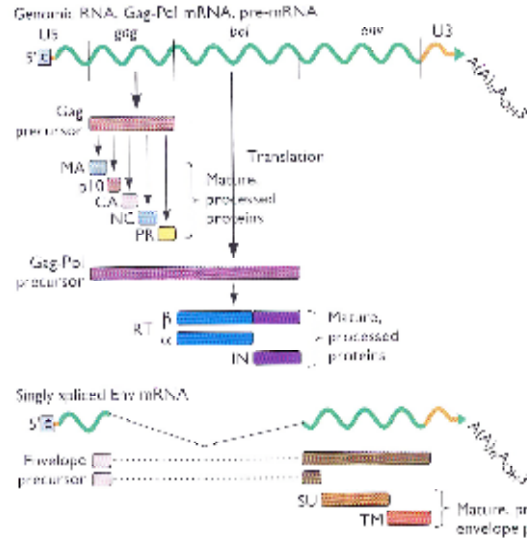
Simple retrovirus (ALV)



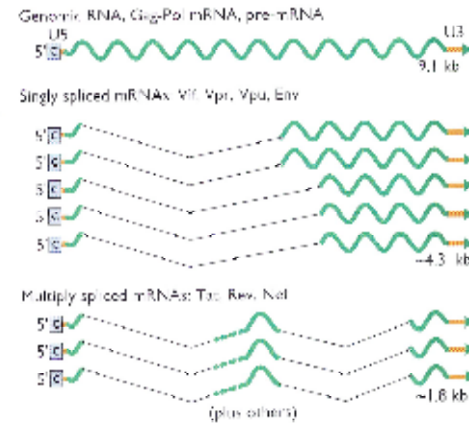
Complex retrovirus (HIV-1)



Genome expression

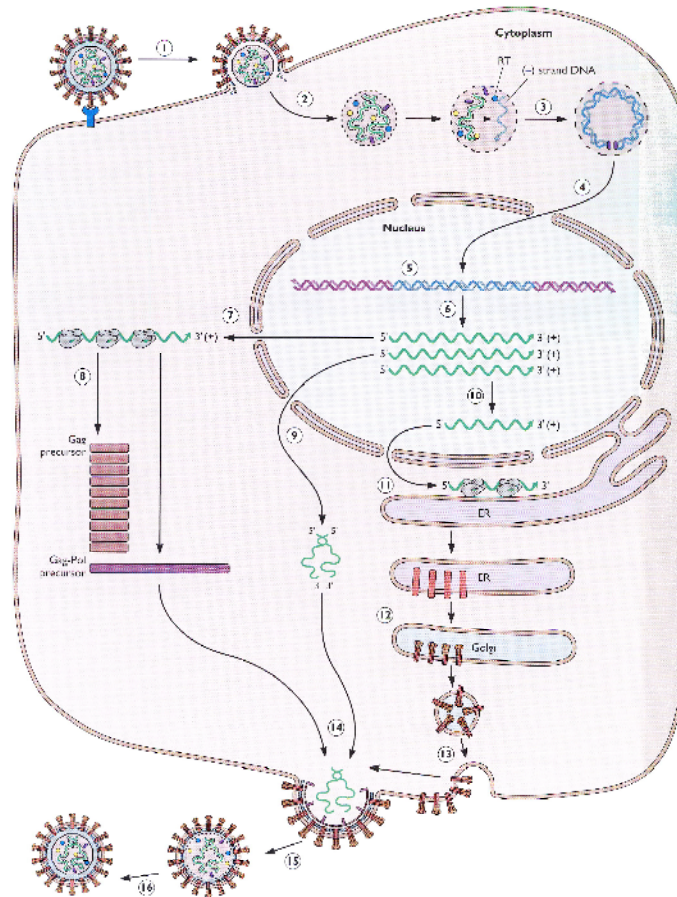


Genome expression



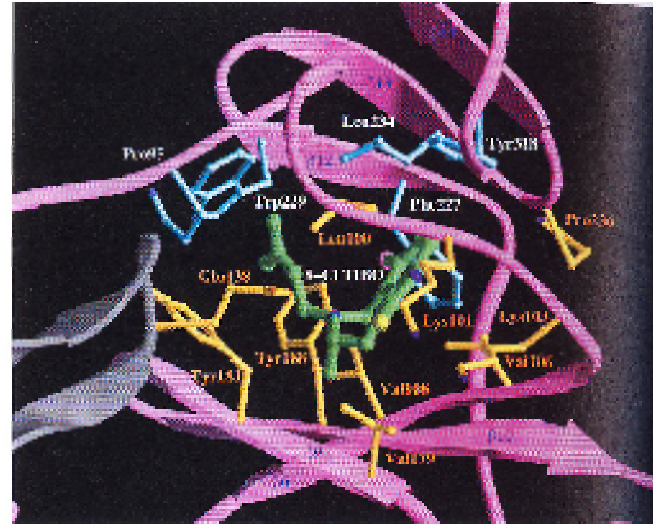
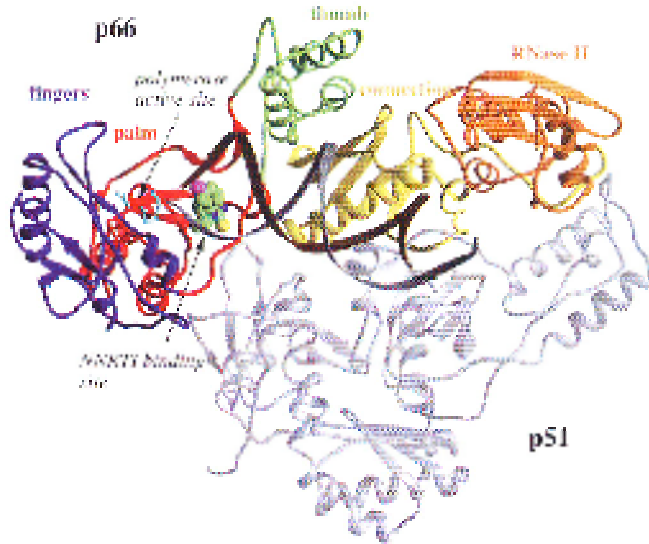
-NEF Attenuation

Viral Replication Cycle

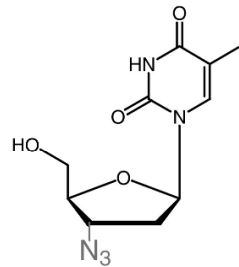


- 10^9 copies/day in fulminant AIDS
- Every single-base mutation of the genome occurs at least once per day per patient

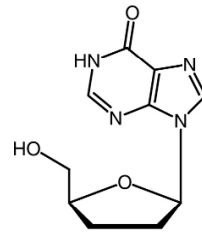
RT Inhibitors



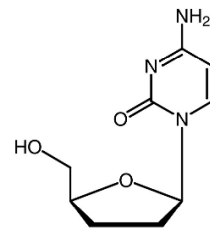
Nucleoside:



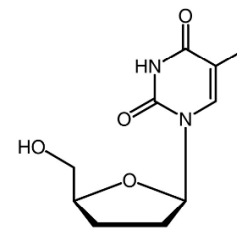
Zidovudine (AZT)



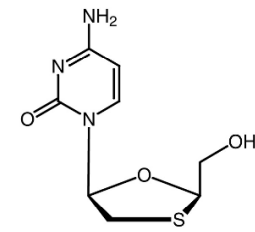
Didanosine (ddI)



Zalcitabine (ddC)

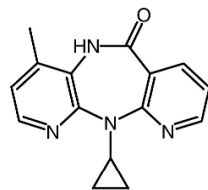


Stavudine (d4T)

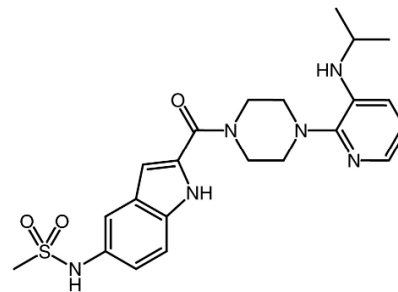


Lamivudine (3TC)

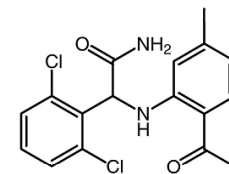
Non-Nucleoside:



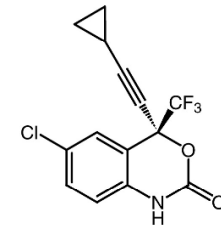
Nevirapine



Delavirdine

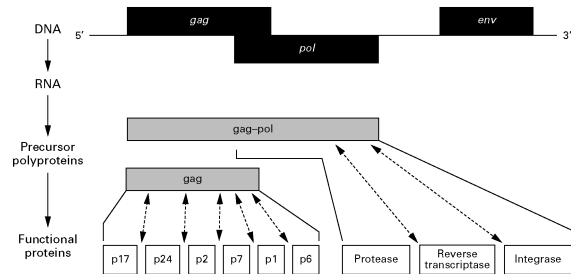
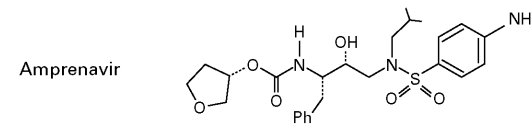
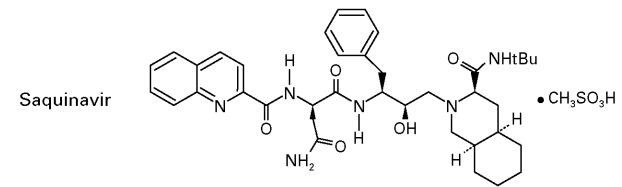
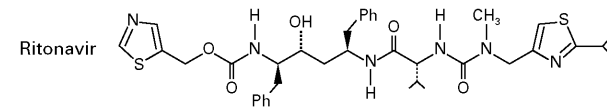
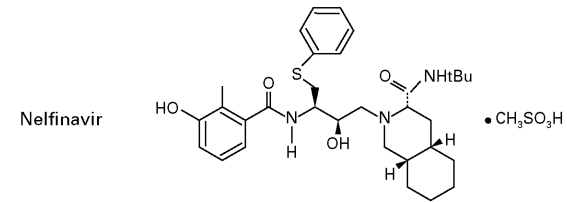
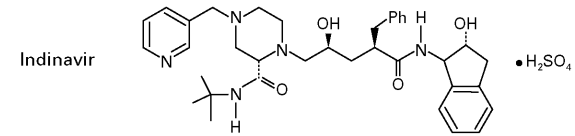
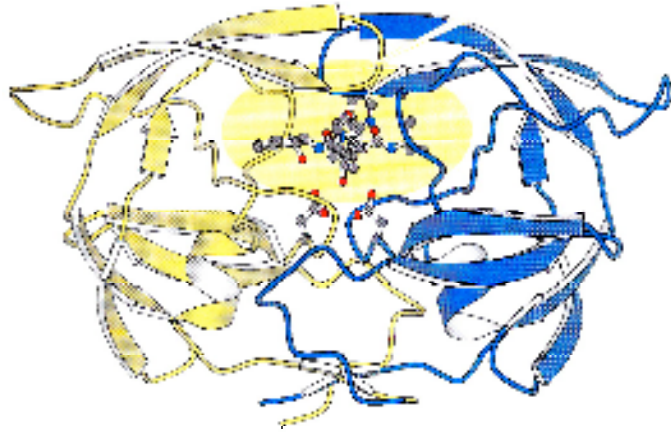


Loviride

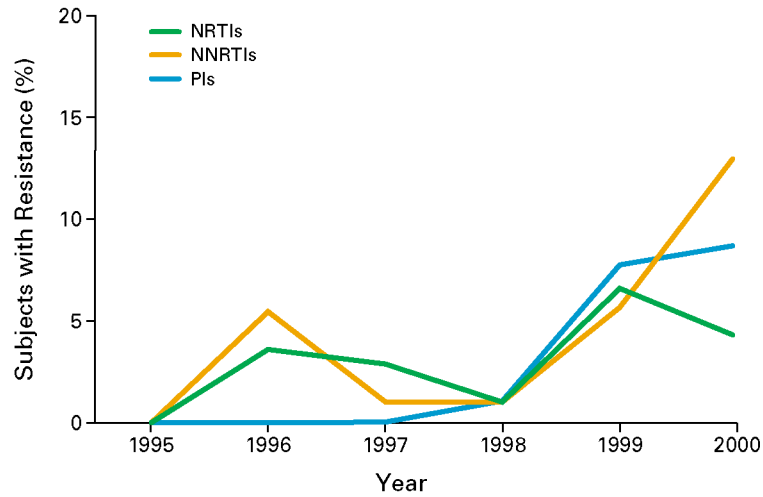


Efavirenz

Protease Inhibitors



Retroviral Drug Resistance in New Patients



No. Evaluated 11 55 101 97 90 23

TEMPORAL CHANGES IN THE PREVALENCE OF DRUG RESISTANCE AT BASE LINE.*

VARIABLE	SUBJECTS IDENTIFIED WITH DRUG-RESISTANT VIRUS		
	1995–1998	1999–2000	P VALUE†
	no./no. of samples analyzed (%)		
High-level drug resistance (phenotype assay)‡			
Any antiretroviral drug	9/264 (3.4)	14/113 (12.4)	0.002
NRTIs	6/264 (2.3)	7/113 (6.2)	0.07
NNRTIs	5/264 (1.9)	8/113 (7.1)	0.03
PIs	1/264 (0.4)	9/113 (8.0)	<0.001
Multidrug resistance	3/264 (1.1)	7/113 (6.2)	0.01
Major drug-resistance mutations (genotype assay)			
Any antiretroviral drug	17/213 (8.0)	20/88 (22.7)	<0.001
NRTIs	15/176 (8.5)	13/82 (15.9)	0.09
NNRTIs	3/176 (1.7)	6/82 (7.3)	0.03
PIs	2/213 (0.9)	8/88 (9.1)	0.001
Multidrug resistance§	8/213 (3.8)	9/88 (10.2)	0.05

*Both resistance assays were performed at ViroLogic. NRTI denotes nucleoside reverse-transcriptase inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.

†P values are two-sided and were determined by Fisher's exact test.

‡Data are numbers (and percentages) of samples containing virus with a 50 percent inhibitory concentration (IC_{50}) that was more than 10 times that of a reference virus.

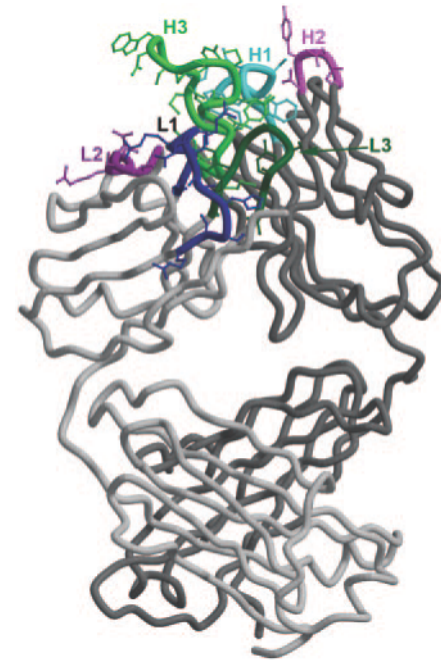
§These results did not change when T215D, T215N, T215S, T215C, and T215E mutations were excluded from the analysis (i.e., all subjects with a revertant mutation detected at position 215 had at least one additional major drug-resistance mutation).

HIV Vaccine

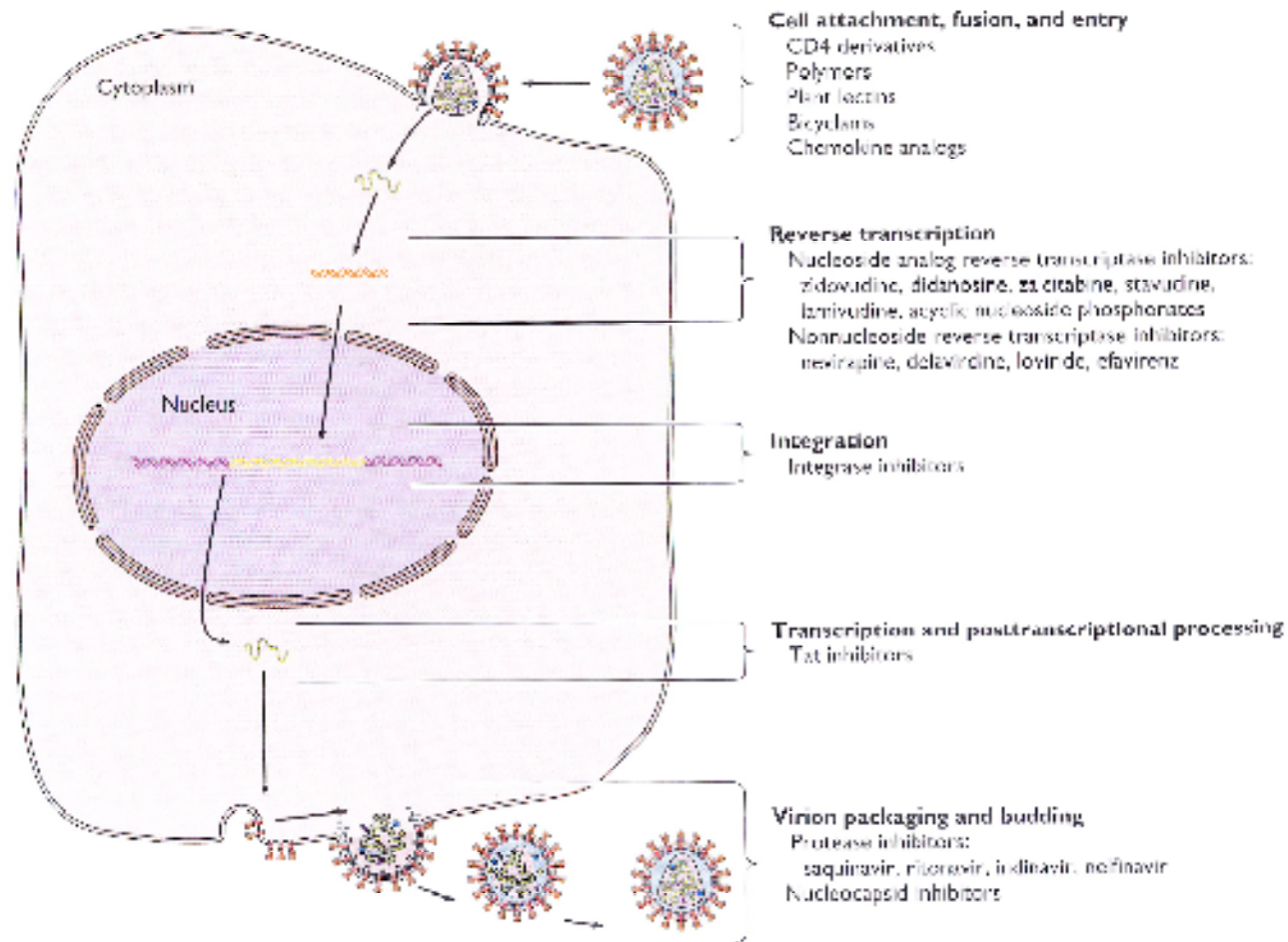
- >50 preparations have entered clinical trials (HIV Vaccine Trials Network)
- 1997 Clinton's HIV vaccine challenge: 10 years
- NIH currently spends >500 million/year on trying to find an HIV vaccine
- NOTHING! (punctuated equilibrium)
- Do aspects of the immune response facilitate HIV pathogenesis?

Broadly Neutralizing Antibodies

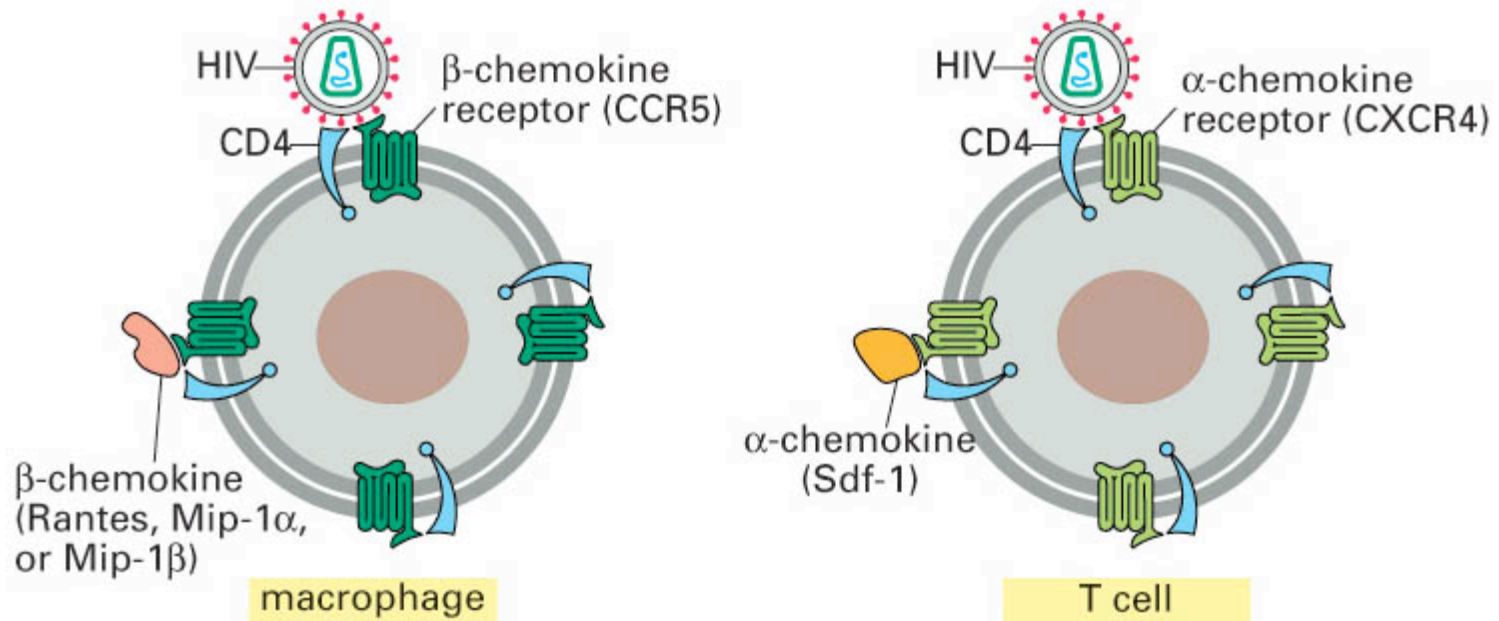
- mAb b12: convex recombining site
- 447-52D: V3 GPGR motif and main-chain (MHC)
- mAb 2G12: domain-swap binds oligomannose
- 2F5, 4E10: TM epitopes



Where Else to Attack?

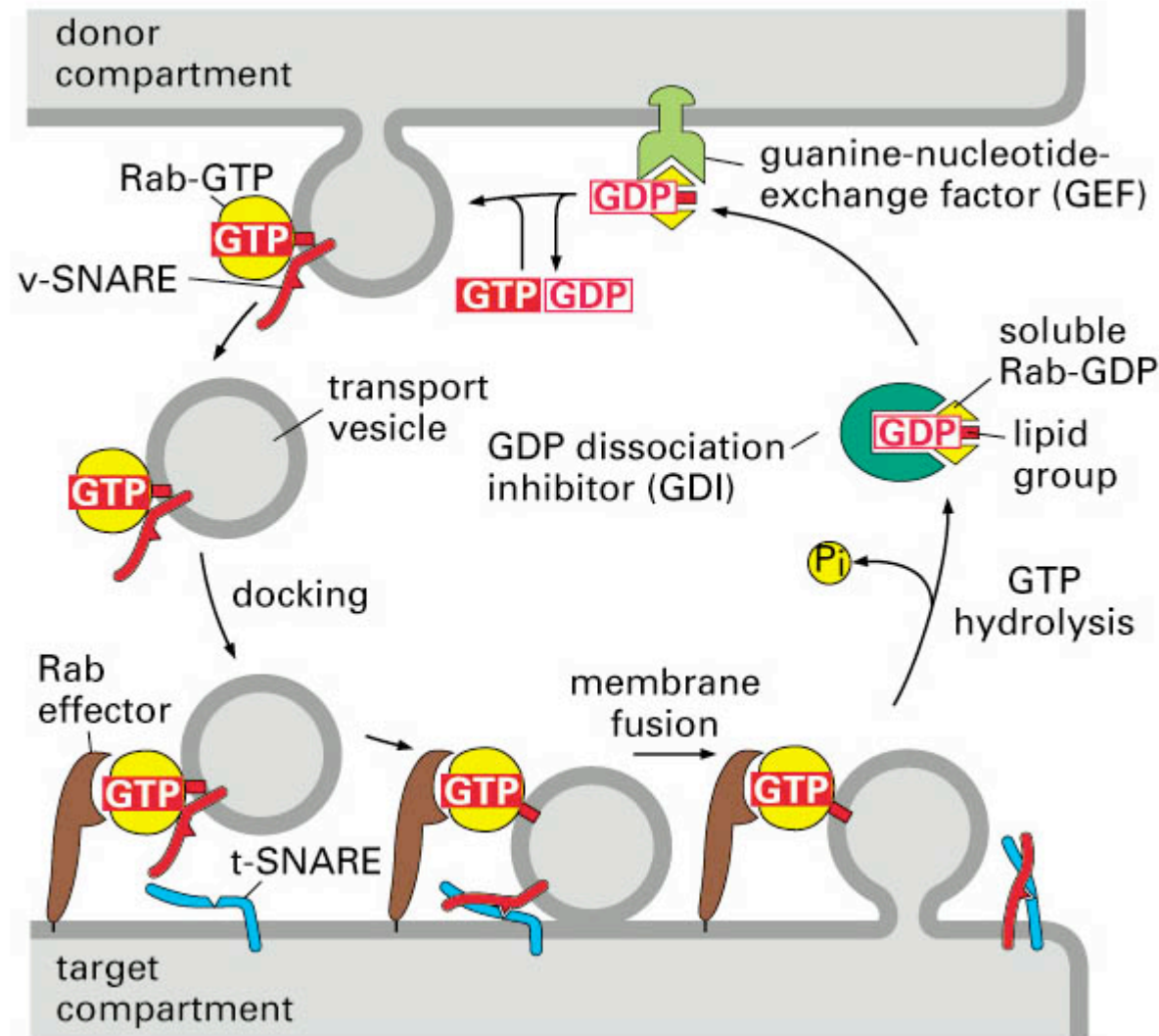


HIV Association with Targets

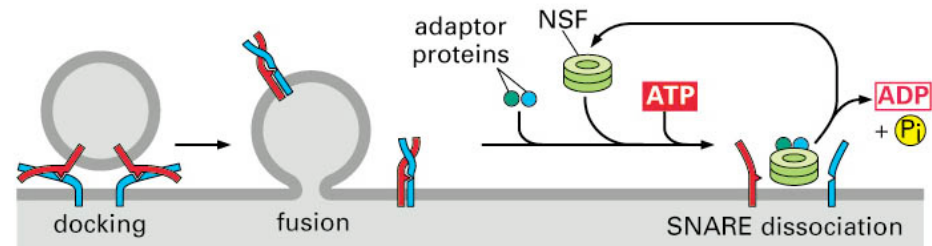
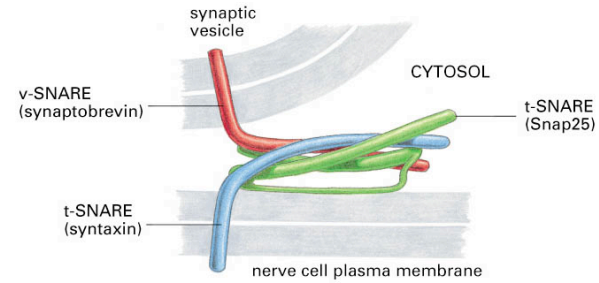
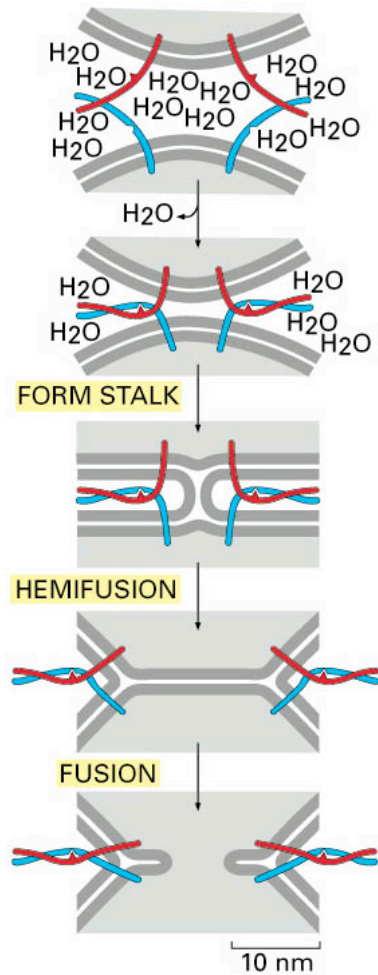


- CCR5 Homozygous Mutants are HIV resistant and otherwise healthy
- RANTES promoter overexpression mutants are HIV resistant

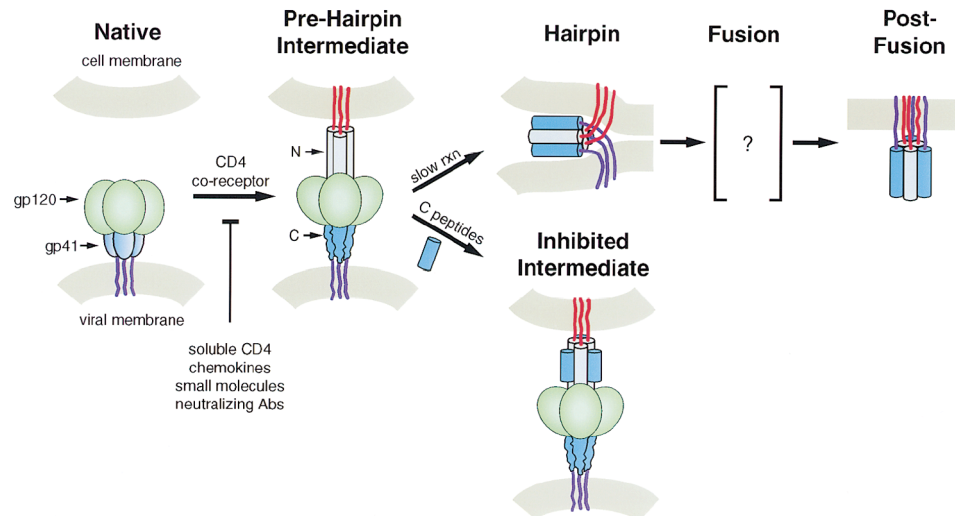
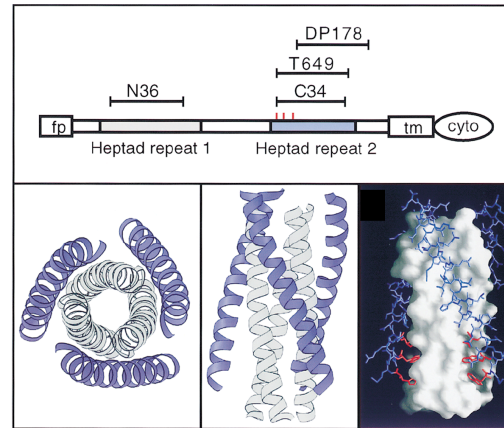
SNARE proteins Mediate Membrane Fusion Inside Cells



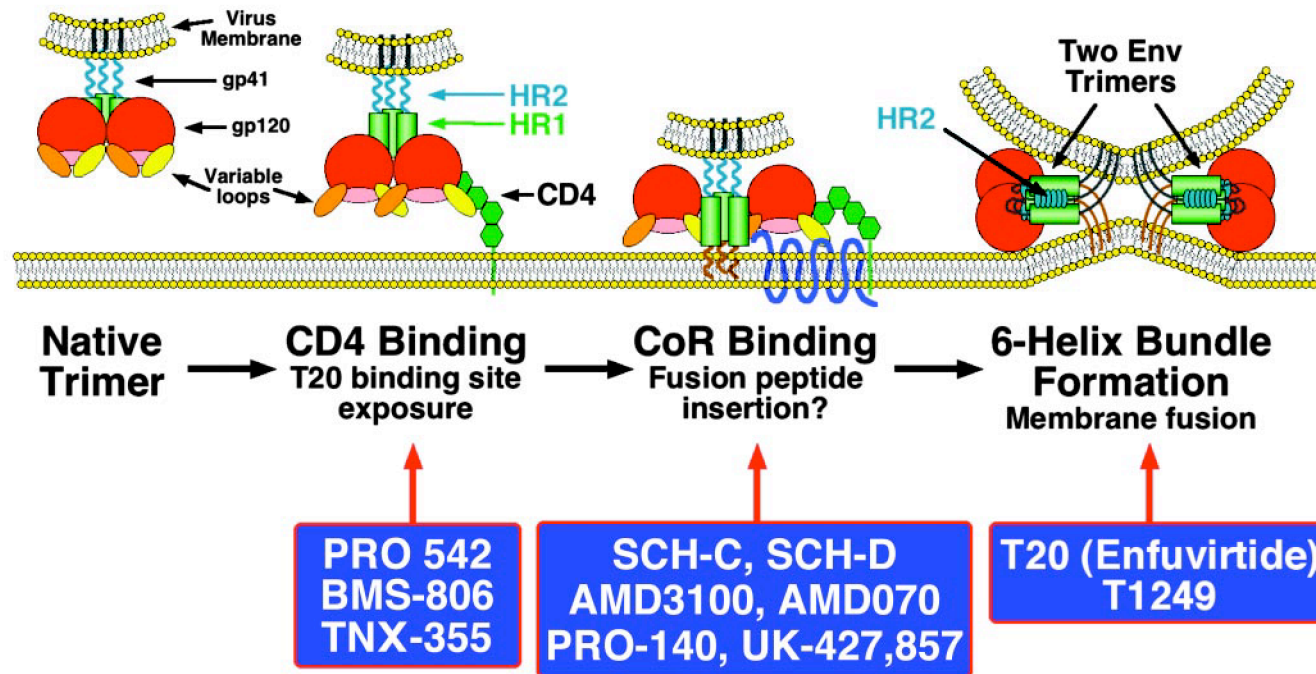
Energy from Helix Coiling Drives Fusion



The Model for Viral Fusion



Preventing HIV Entry



- PRO542 (Progenics): gp120 tetramer to IgG Fc that blocks CD4-gp120 interaction
- BMS-806 (Bristol-Myers Squibb): small molecule that targets the CD4 binding site on gp120
- TNX-355 (Tanox): an anti-CD4 antibody
- SCH-C, SCH-D (Schering-Plough) and UK-427,857 (Pfizer:) block CCR5
- AMD3100, AMD070 (AnorMED): block CXCR4

Other Ideas

- TRIM5a: a species restriction factor that is an E3! (*J. Vir.* **79**(14): 8870-8877 2005)
- Target HIV immunomodulators (Vpr, Vpu, etc.)
- Block inflammatory response

The Future of the Arms Race?

1. Lalezari, J.P. *et al.* Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* **348**, 2175-2185 (2003).
2. Lau, A. *et al.* Suppression of HIV-1 infection by a small molecule inhibitor of the ATM kinase. *Nature Cell Biology* **7(5)**, 493-500 (2005).