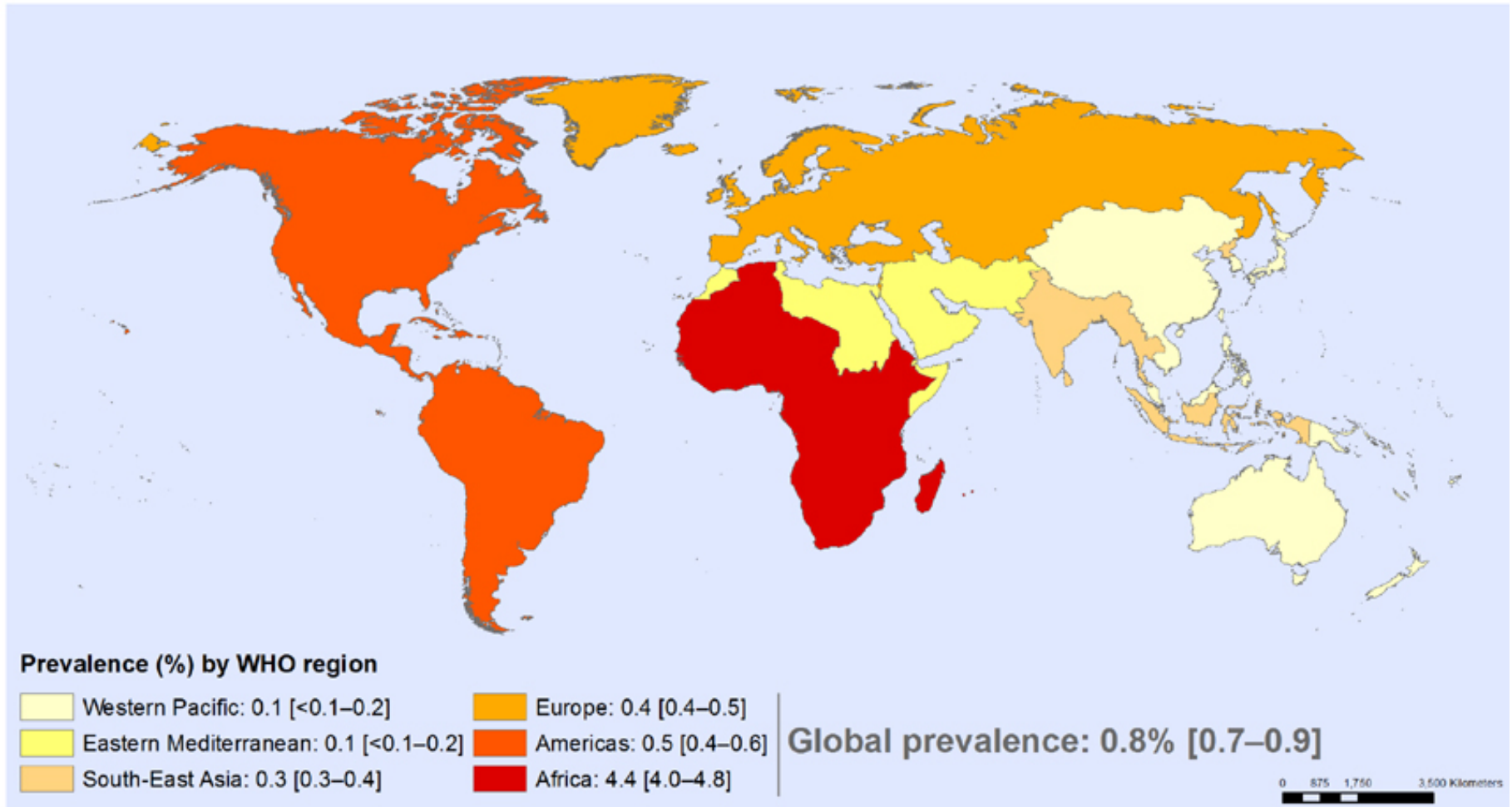


Adult HIV prevalence (15–49 years), 2015 By WHO region



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

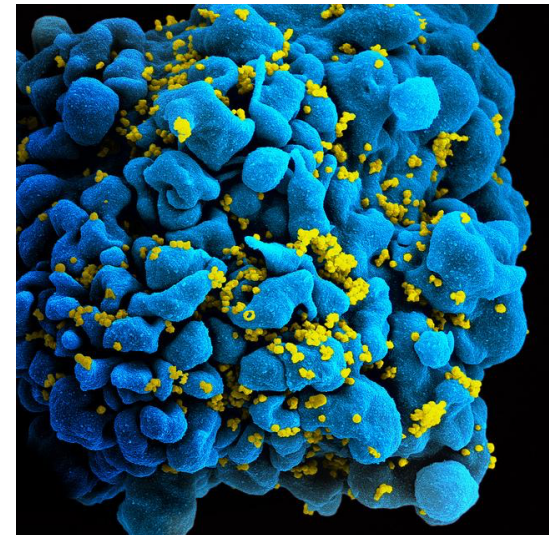
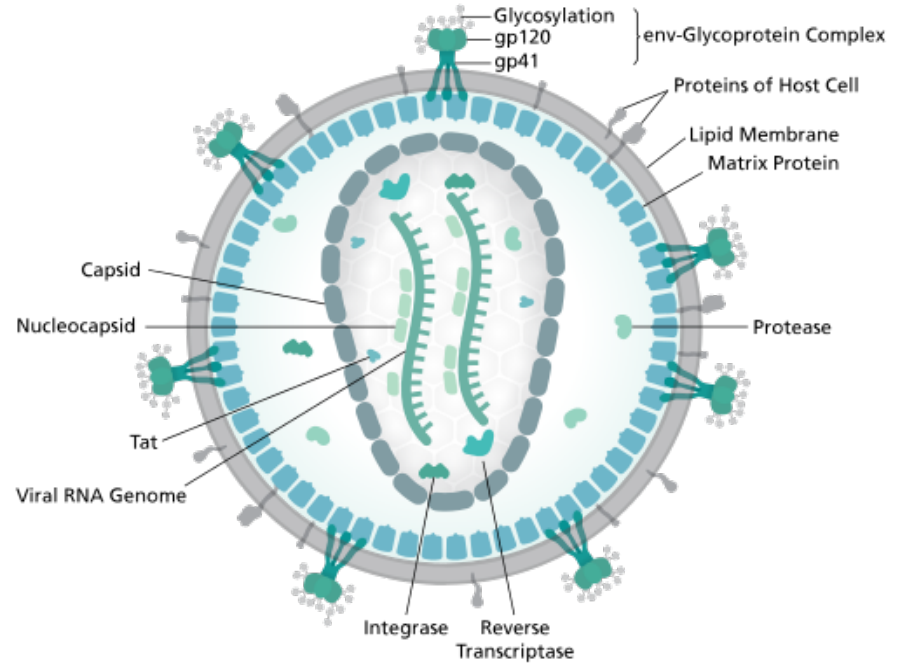
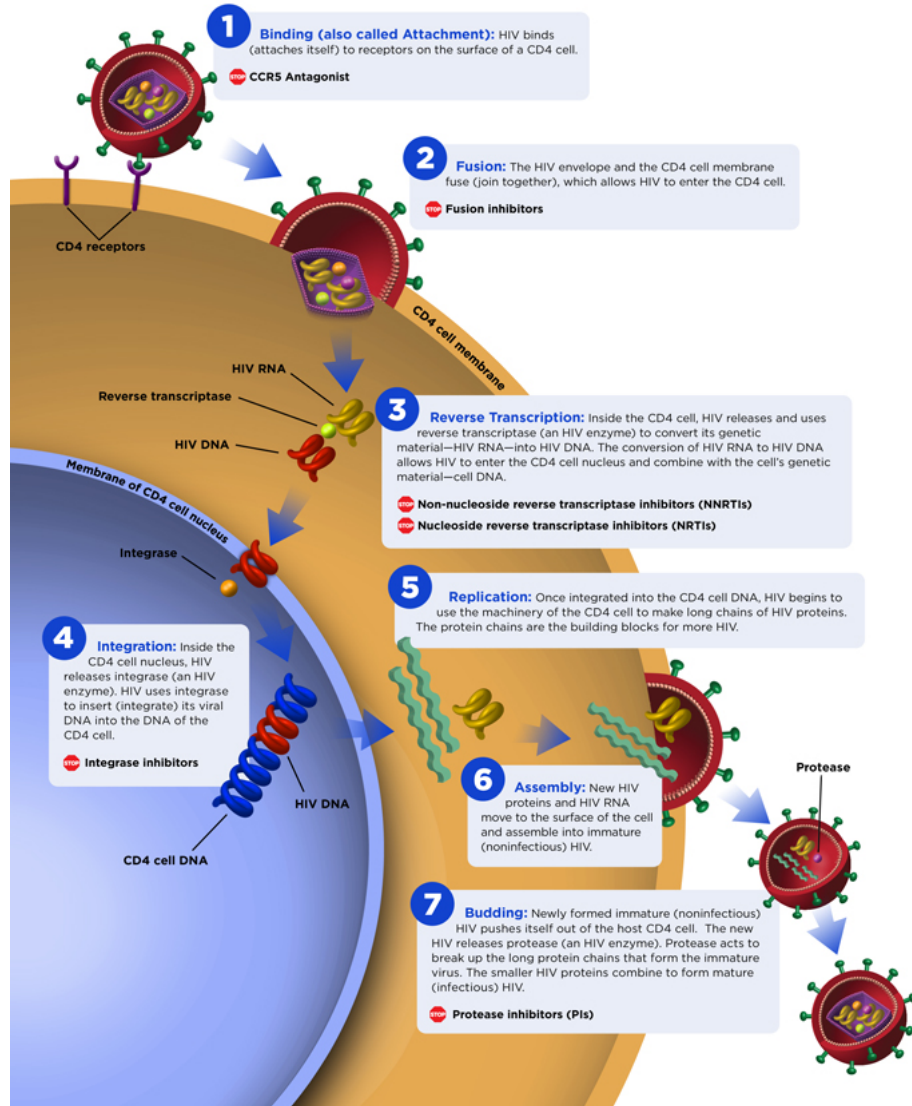
Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization



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The HIV Life Cycle

HIV medicines in six drug classes stop HIV at different stages in the HIV life cycle.



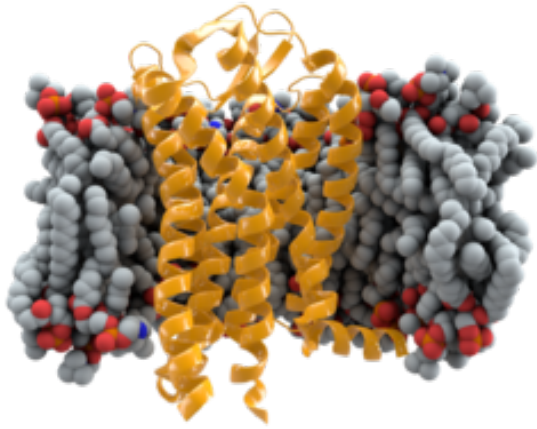
FDA Approval of HIV Medicines

'80- '84	1981 First AIDS cases reported in United States			
'85- '89	1987 Zidovudine (NRTI)			
'90- '94	1991 Didanosine (NRTI)	1992 Zalcitabine (NRTI)	1994 Stavudine (NRTI)	
'95- '99	1995 Lamivudine (NRTI) Saquinavir (PI)	1996 Indinavir (PI) Nevirapine (NNRTI) Ritonavir (PI)	1997 Combivir (FDC) Delavirdine (NNRTI) Nelfinavir (PI)	1998 Abacavir (NRTI) Efavirenz (NNRTI)
'00- '04	2000 Didanosine EC (NRTI) Kaletra (FDC) Trizivir (FDC)	2001 Tenofovir DF (NRTI)	2003 Atazanavir (PI) Emtricitabine (NRTI) Enfuvirtide (FI) Fosamprenavir (PI)	2004 Epzicom (FDC) Truvada (FDC)
'05- '09	2005 Tipranavir (PI)	2006 Atripla (FDC) Darunavir (PI)	2007 Maraviroc (EI) Raltegravir (INSTI)	2008 Etravirine (NNRTI)
'10- '14	2011 Complera (FDC) Nevirapine XR (NNRTI) Rilpivirine (NNRTI)	2012 Stribild (FDC)	2013 Dolutegravir (INSTI)	2014 Cobicistat (PE) Elvitegravir (INSTI) Triumeq (FDC)
'15- '16	2015 Evotaz (FDC) Genvoya (FDC) Prezcobix (FDC)	2016 Descovy (FDC) Odefsey (FDC)		

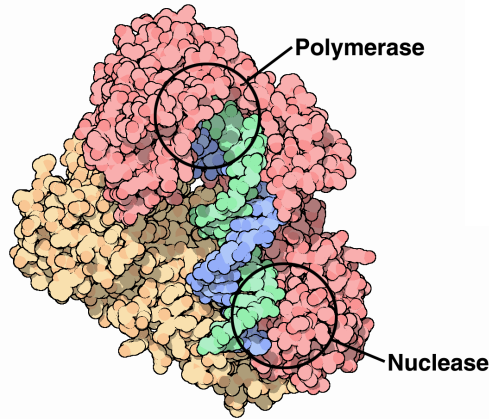
Drug Class Abbreviations:

EI: Entry Inhibitor; **FDC:** Fixed-Dose Combination; **FI:** Fusion Inhibitor; **INSTI:** Integrase Inhibitor; **NNRTI:** Non-Nucleoside Reverse Transcriptase Inhibitor; **NRTI:** Nucleoside Reverse Transcriptase Inhibitor; **PE:** Pharmacokinetic Enhancer; **PI:** Protease Inhibitor

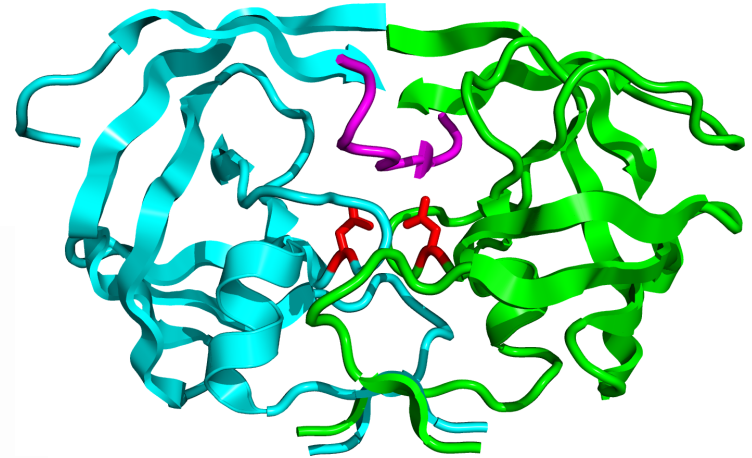
Note: Drugs in gray are no longer recommended for use in the United States by the HHS HIV/AIDS medical practice guidelines.



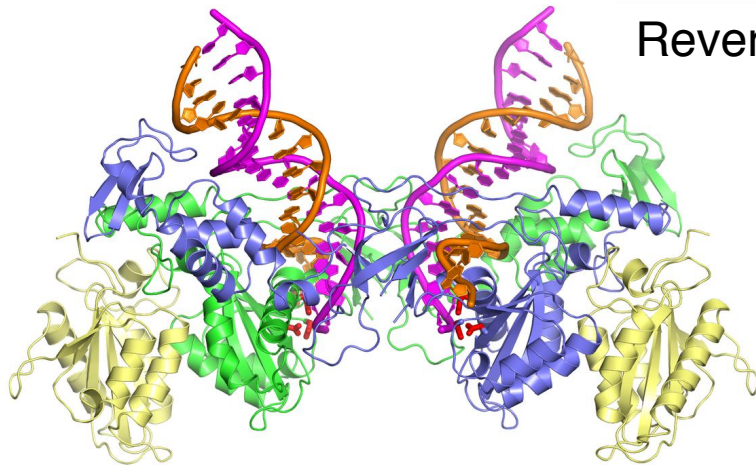
CCR5



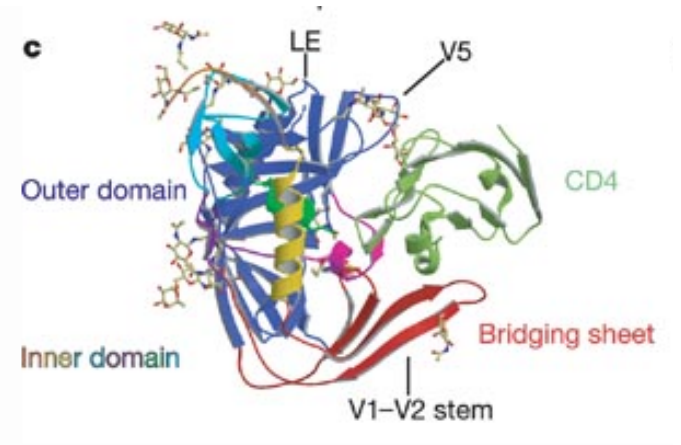
Reverse Transcriptase



Protease



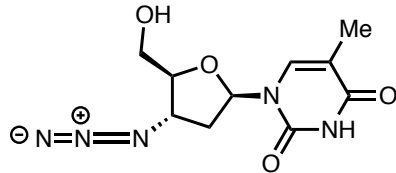
Integrase



gp120 Fusion

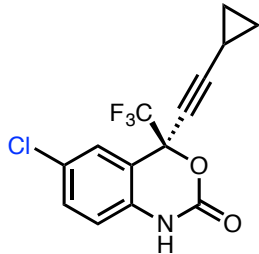
Reverse Transcriptase Inhibitors

• Nucleoside (NRTIs)

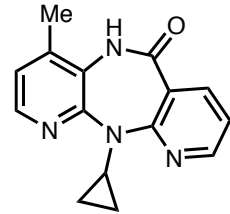


Zidovudine (AZT)

• Non-Nucleoside (NNRTIs)

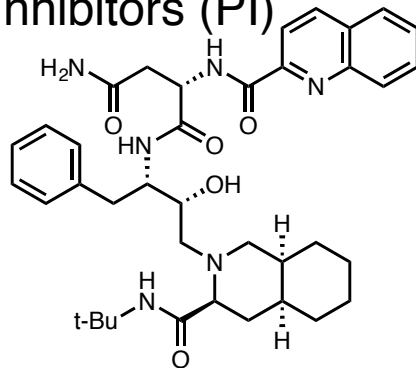


Efavirenz (EFV)



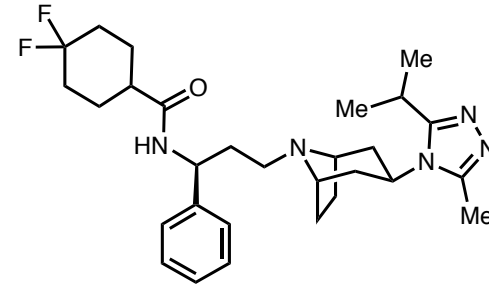
Nevirapine (NVP)

Protease Inhibitors (PI)



Saquinavir (SQV)

CCR5 Antagonists (Entry Inhibitors)



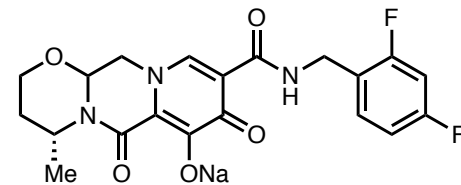
Maraviroc (MVC)

Fusion Inhibitors

Ac-Tyr-Thr-Ser-Leu-Ile-His-Ser-Gln-Asn-Gln-Gln-Glu-Lys-Asn-Glu-Gln-Glu-Leu-Leu-Glu-Leu-Asp-Lys-Trp-Ala-Ser-Leu-Trp-Asn-Trp-Phe-NH₂

Enfuvirtide (T-20)

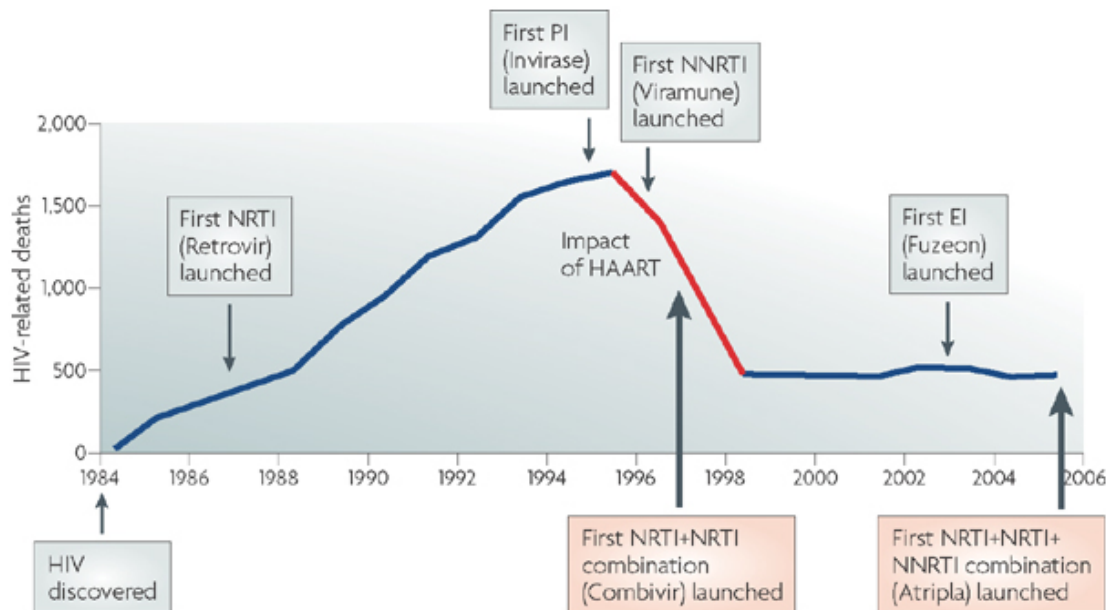
Integrase Strand Transfer Inhibitors (INSTIs)



Dolutegravir (DTG)

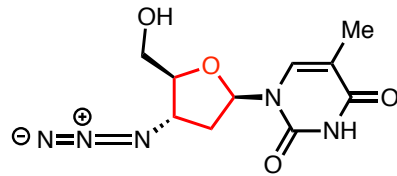
- ✧ Lifecycle is as short as 1.5 days
- ✧ Virus lacks proofreading enzymes
- ✧ High mutation rate leads to high resistance rate
- ✧ First fixed-dose combination approved in 1997. 14 FDA approvals to date

- ✧ Combinations contain up to 4 API molecules.
- ✧ 1997-2004 GSK leader in approvals. 2004-Present Gilead leader in approvals.
- ✧ Until 2006 all FDCs contained single drug class (ex: only NRTIs)

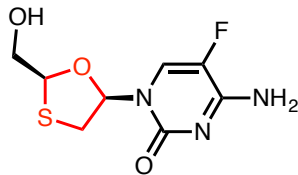


❖ Oldest drug class (first approval 1987)

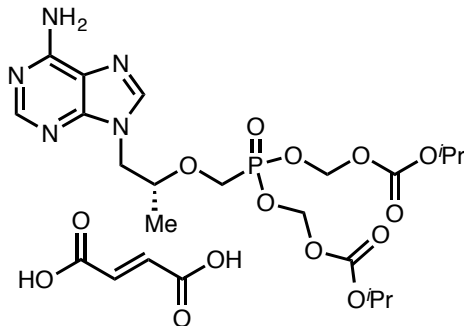
❖ 7 single drug approvals to date



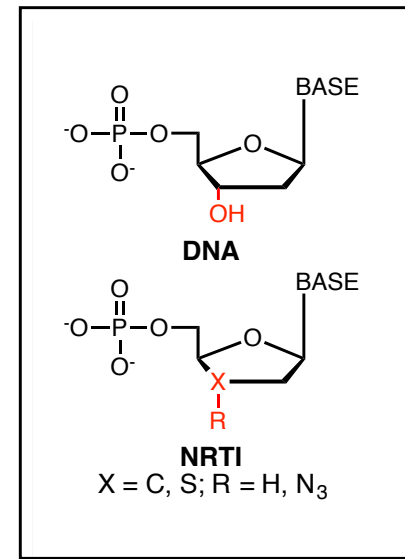
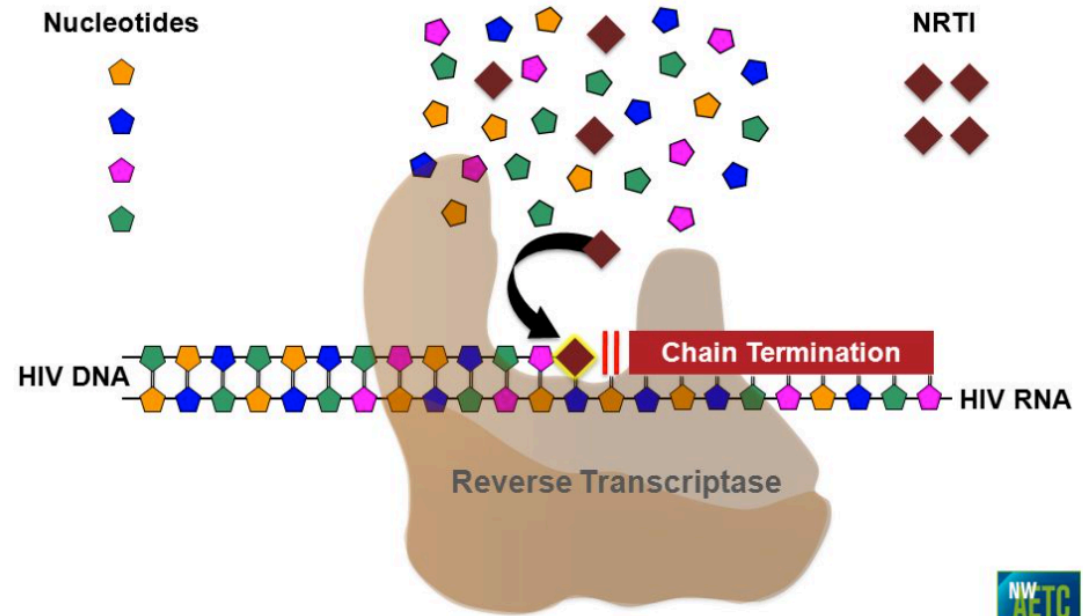
Zidovudine (AZT)



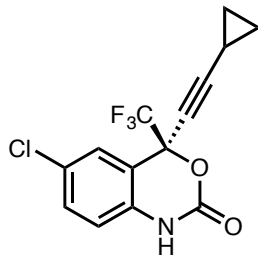
Emtricitabine (FTC)



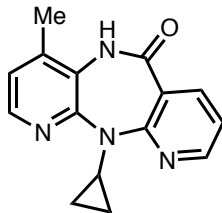
Tenofovir Diisopropoxyl Fumarate (TDF)



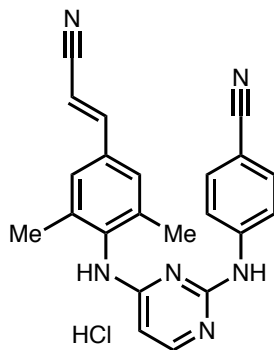
- ✧ 4 single drug approvals to date
- ✧ NNRTIs binds secondary site in the reverse transcriptase



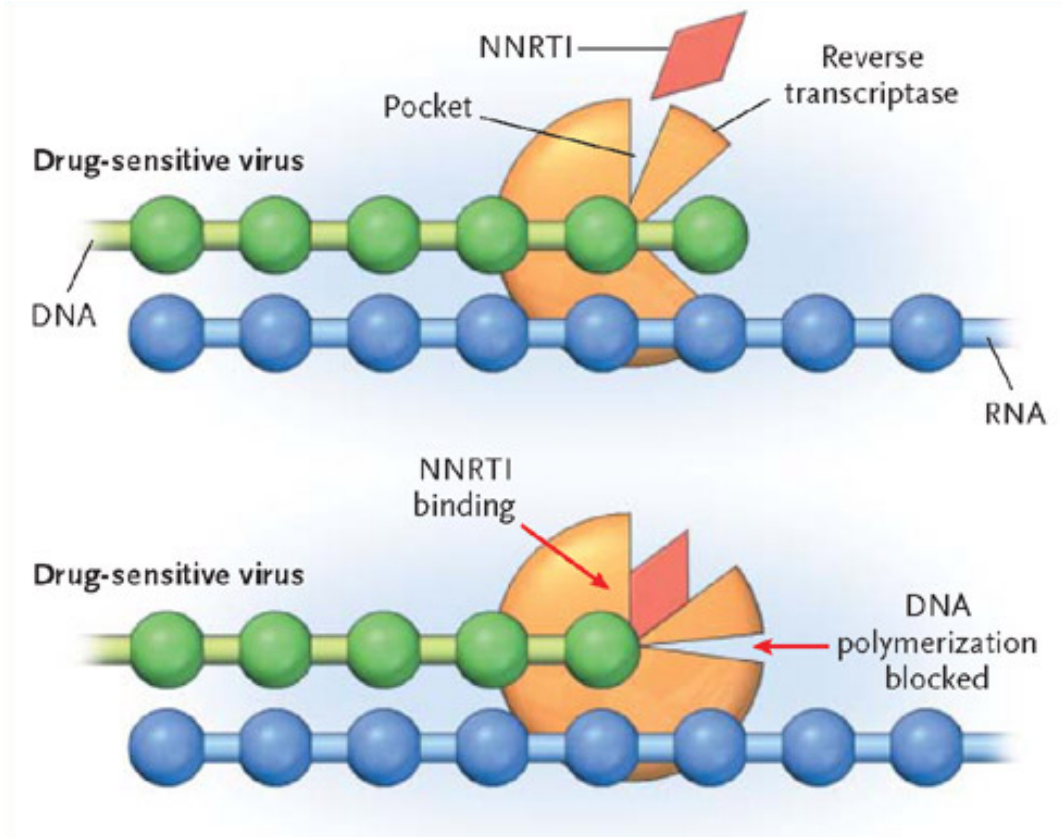
Efavirenz (EFV)

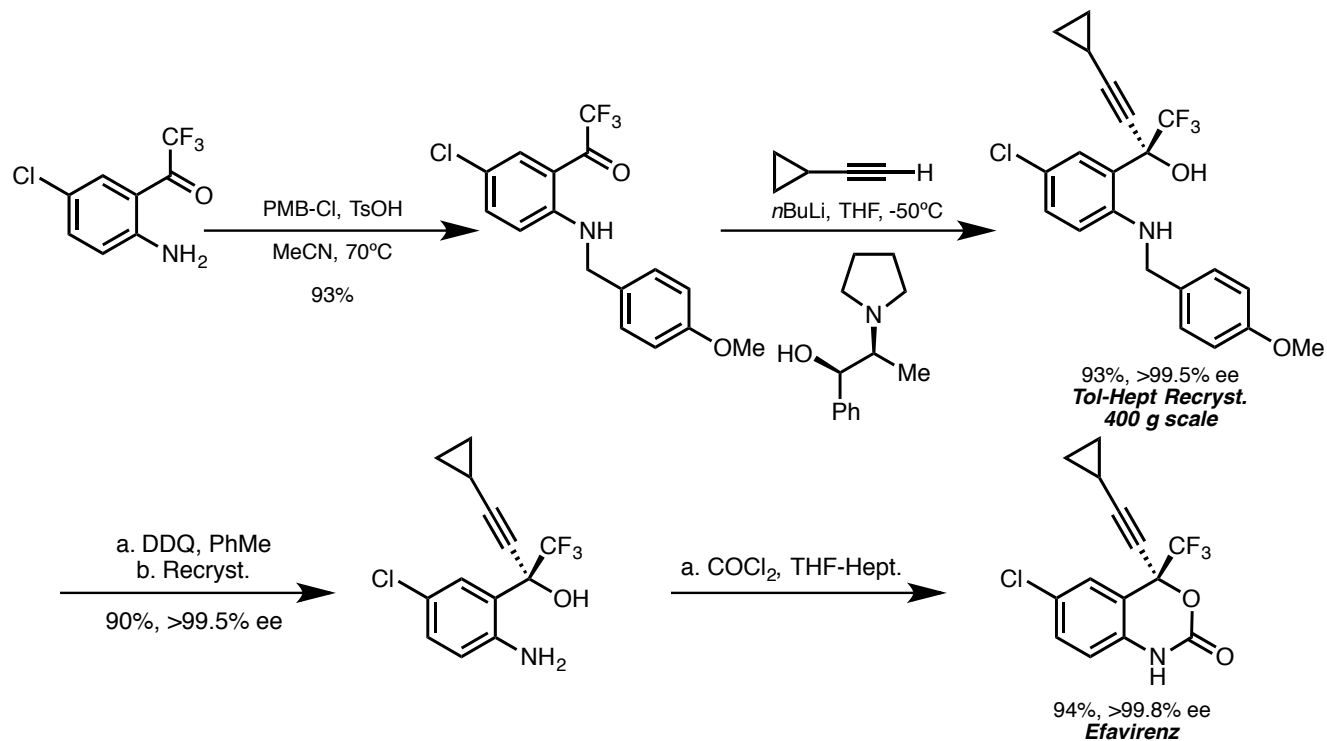


Nevirapine (NVP)



Rilpivirine (RPV)





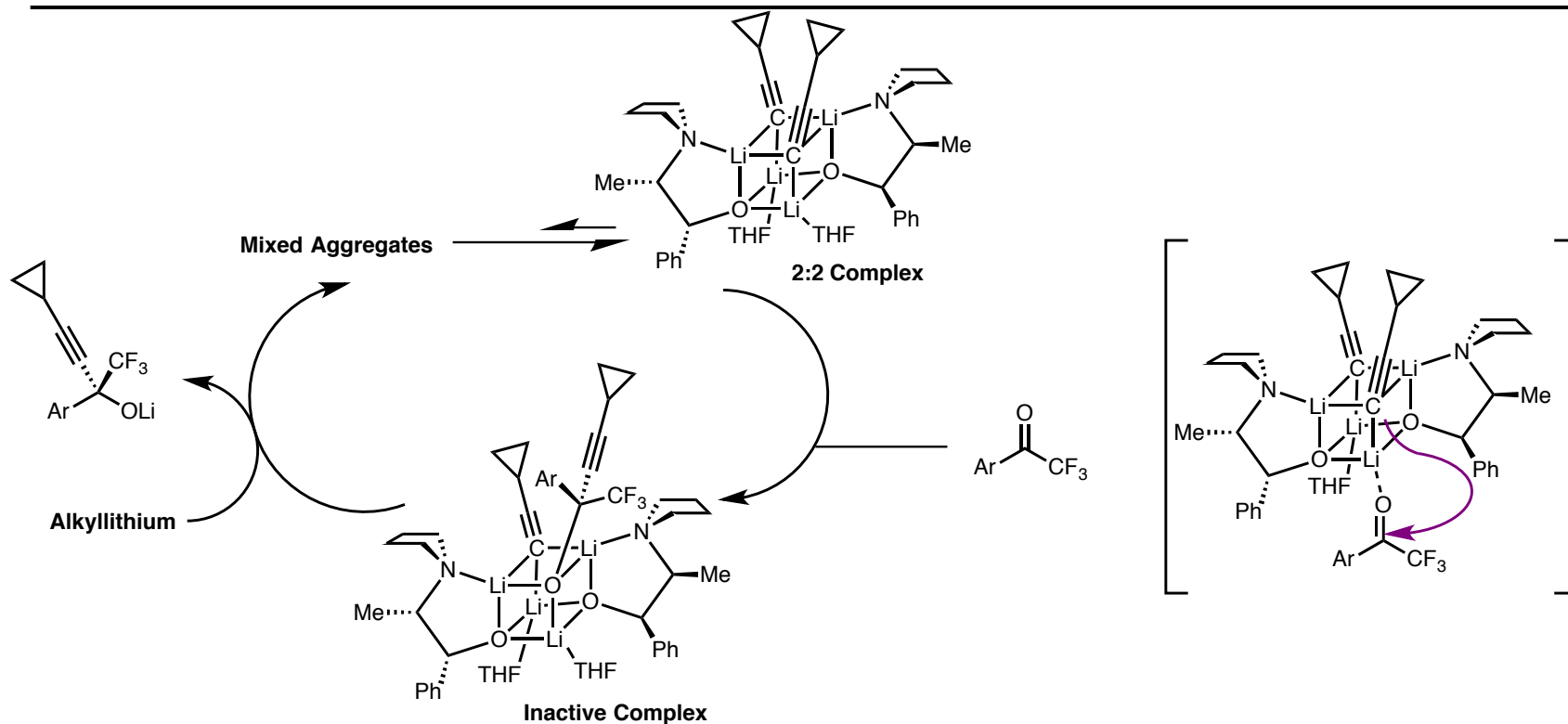
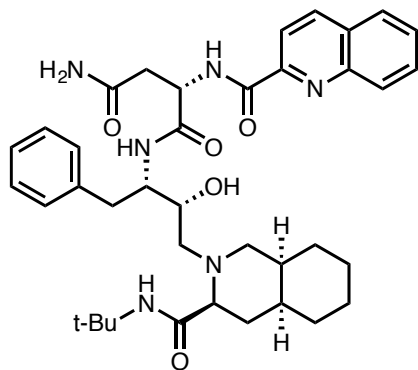


Table 1. Asymmetric Addition of Lithium Cyclopropylacetylide **3a** to Ketones **2a/2b** in the Presence of Chiral Ligand **4b**

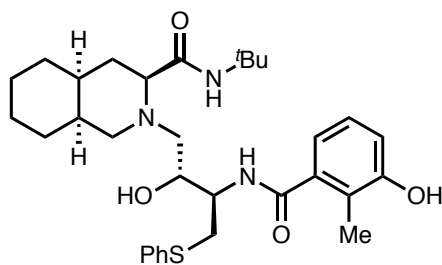
entry	ketone (equiv in each cycle)	CPA (3b) (equiv)	<i>n</i> -hexyllithium (5) (equiv)	ligand 4b (equiv)	conversion ^a %, first cycle (overall)	% (<i>S</i>)-isomer ^b first cycle (overall)
1	2a (1)	2.15	4.4	2.3	>98	>98
2	2b (1)	2.15	4.4	2.3	>98	94
3	2a (1)	1.07	2.15	1.15	50	>98
4	2a (1 + 0.5)	2.2	4.8 + 1	2.6	92.7 (87)	99.4 (97.4)
5	2a (1 + 0.4)	2.3	4.4 + 1	2.1	97 (91)	(97.8)
6	2a (1 + 0.3)	2.36	4.44 + 1.07	2.3	>99 (100)	99 (99.03)
7	2a (1 + 1)	2.1 + 1.05	4.4 + 1.05	2.3	>99 (73)	99 (96.9)
8	2a (1 + 1)	2.1 + 1.05	4.4 + 1.5	2.3	98 (91)	97.9 (96)
9	2a (1 + 1)	3.33 ^c	4.33 + 2	2.3	>99 (99.0)	98.1 ^d
10	2a (1 + 1 + 1)	2.2 + 1 + 1	4.8 + 2 + 2	2.65	>96	94 ^e
11	2a (1 + 1 + 1 + 1)	2.2 + 1 + 1 + 1	4.8 + 2 + 2 + 2	2.65	>95	90.8

✧ Largest class of single drug inhibitors

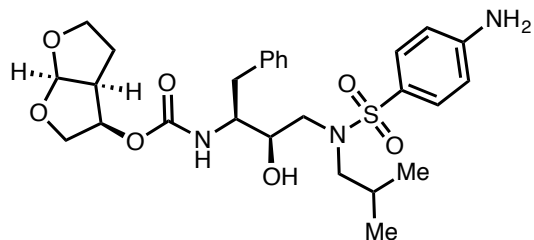
✧ 8 single drug approvals to date



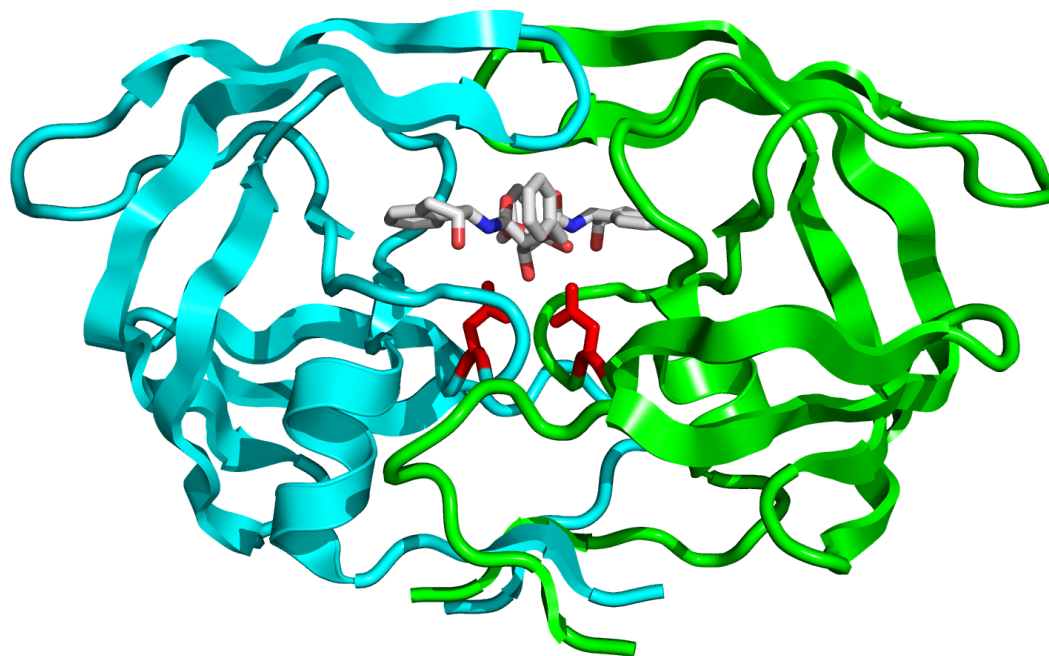
Saquinavir (SQV)



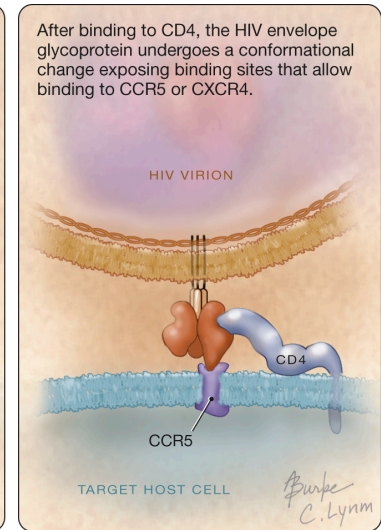
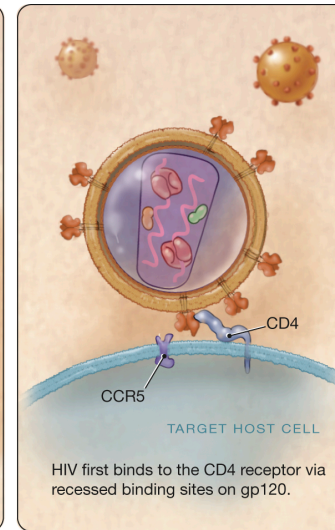
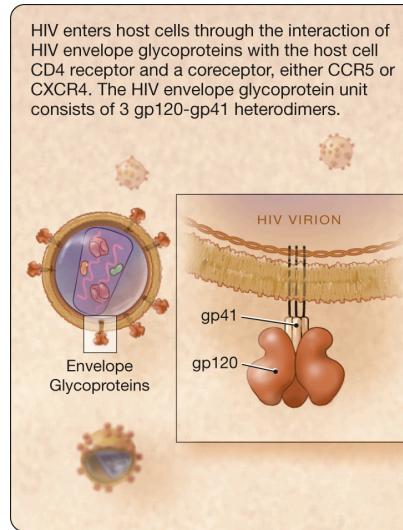
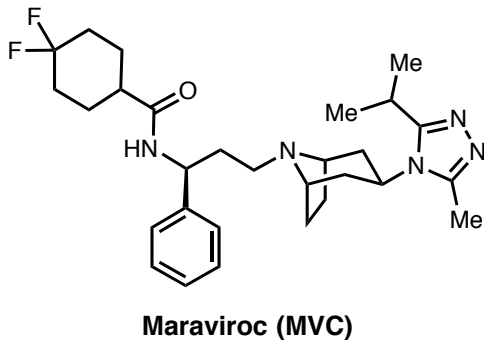
Nelfinavir (NFV)



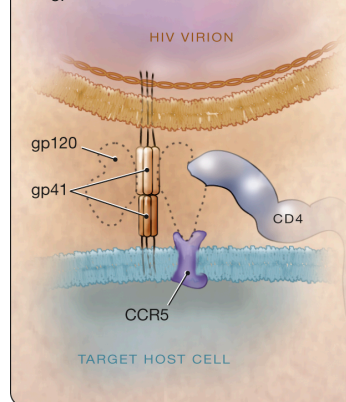
Darunavir (DRV)



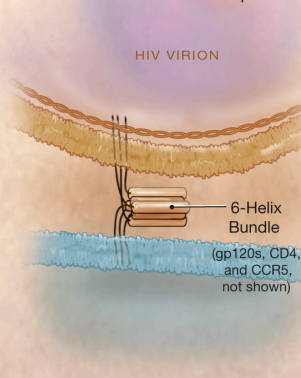
- ✧ Only one single drug approved.
- ✧ FDA approval 2007.
- ✧ Only treatment which targets host cells rather than HIV enzymes.



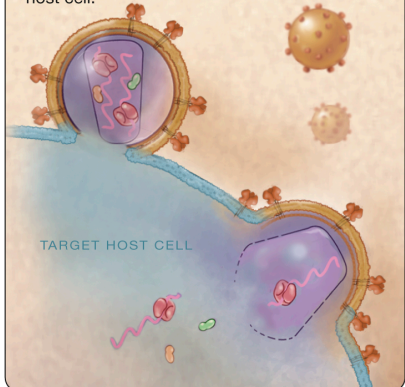
Once bound to both CD4 and the coreceptor, the HIV envelope glycoprotein undergoes a second conformational change that allows insertion of the hydrophobic fusion domain of gp41 into the membrane of the host cell.

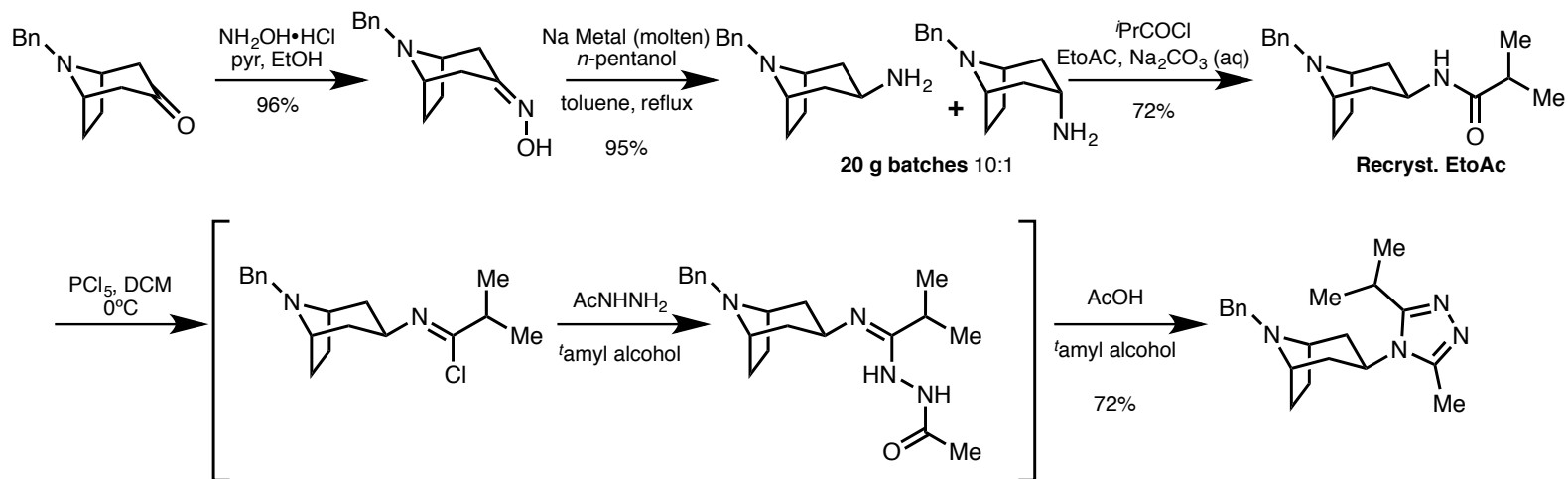


Each of the 3 gp41 molecules folds upon itself forming a 6-helix bundle, which brings the viral membrane and host cell membrane in close proximity.

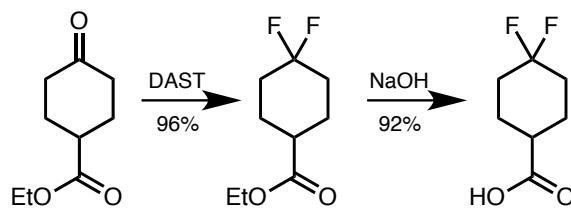


As a result of several such interactions between the HIV envelope and host cell CD4 receptors and CCR5 or CXCR4 coreceptors, the viral membrane and host cell membrane fuse, and contents of the virion enter the host cell.

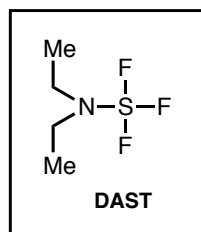


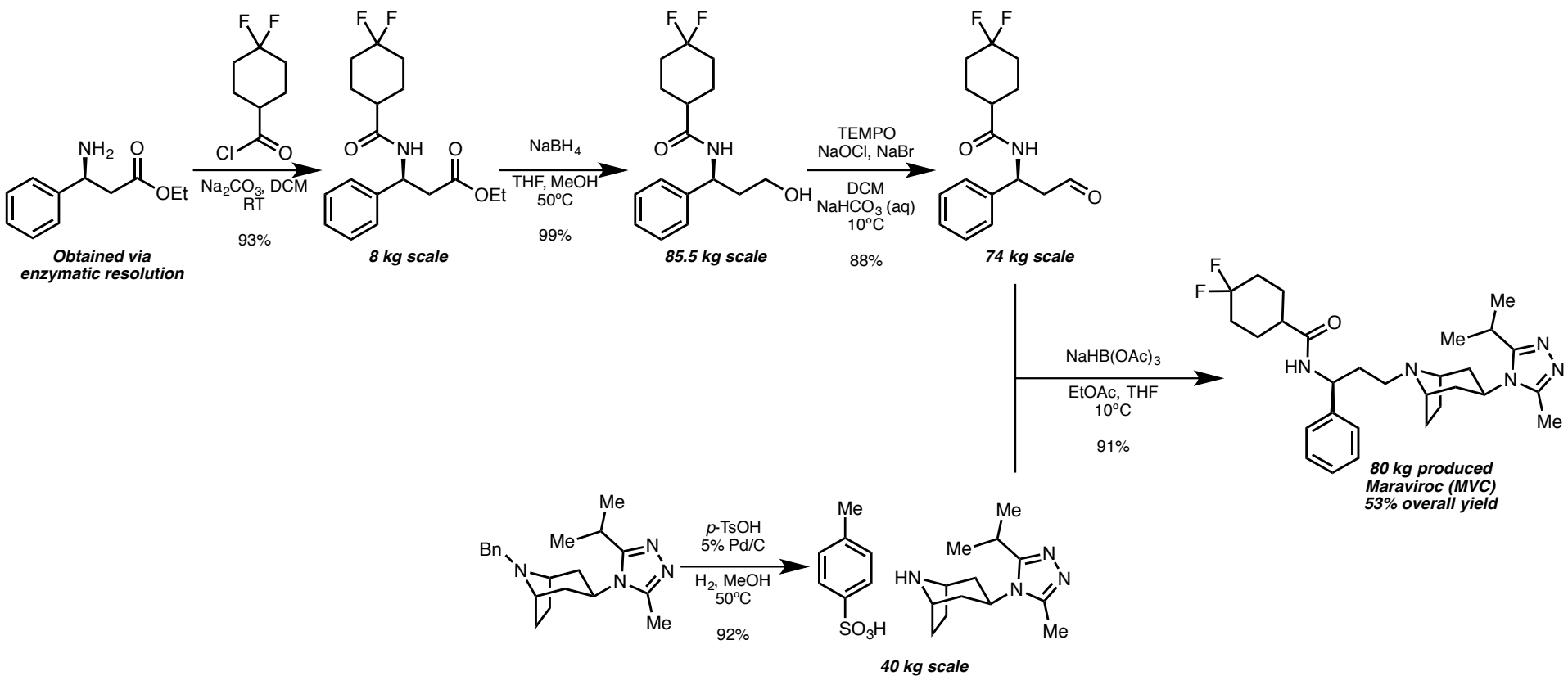


Produced by contractor

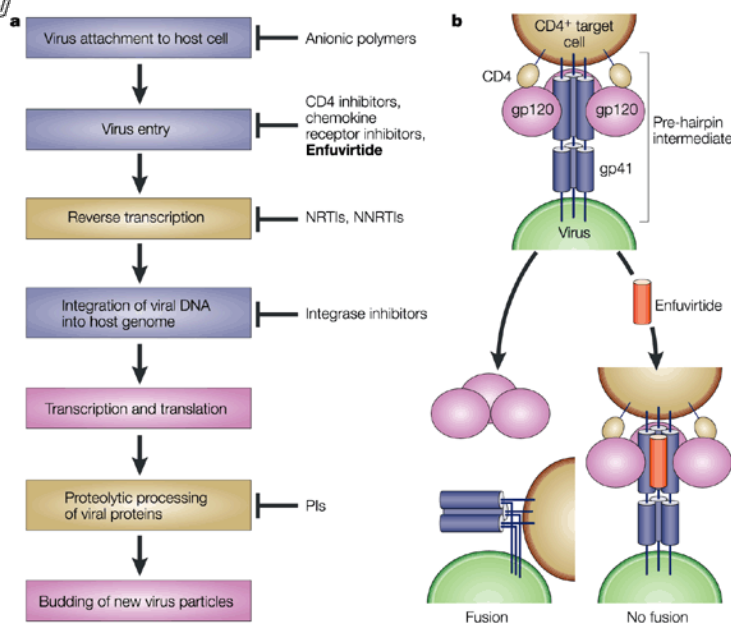
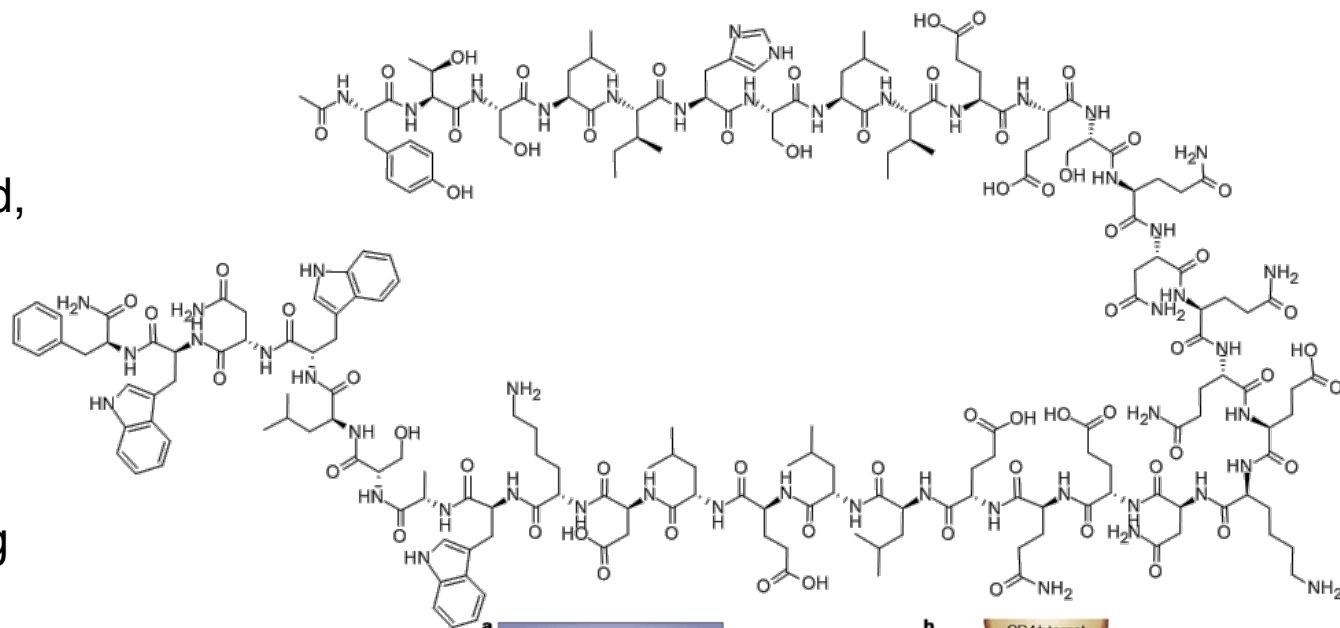


dangerously exothermic;
produces vinyl fluoride biproduct



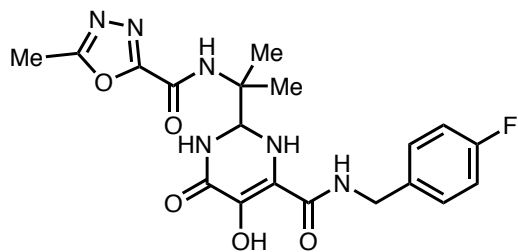


- Single drug approved, Enfuvirtide.
- FDA approval 2003.
- Expensive and only subcutaneous dosing options available.
- Used as salvage therapy in combination with other treatments for multidrug resistant strains of HIV.

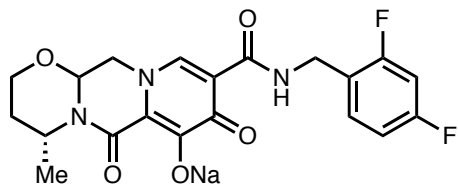


✧ Newest class of single drug treatment. First approval 2007.

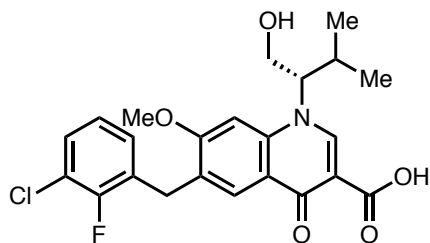
✧ 3 FDA approvals to date.



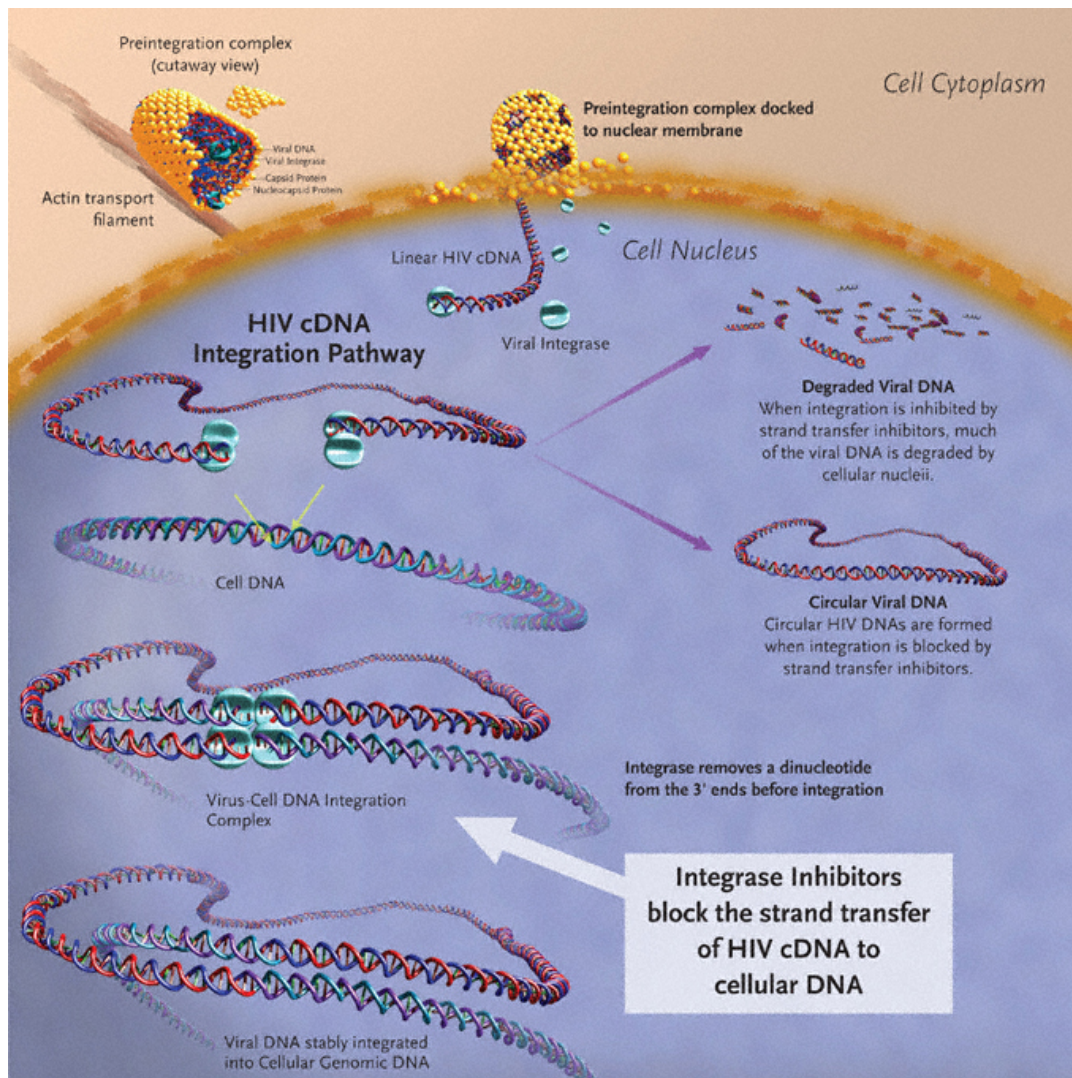
Raltegravir (RAL)

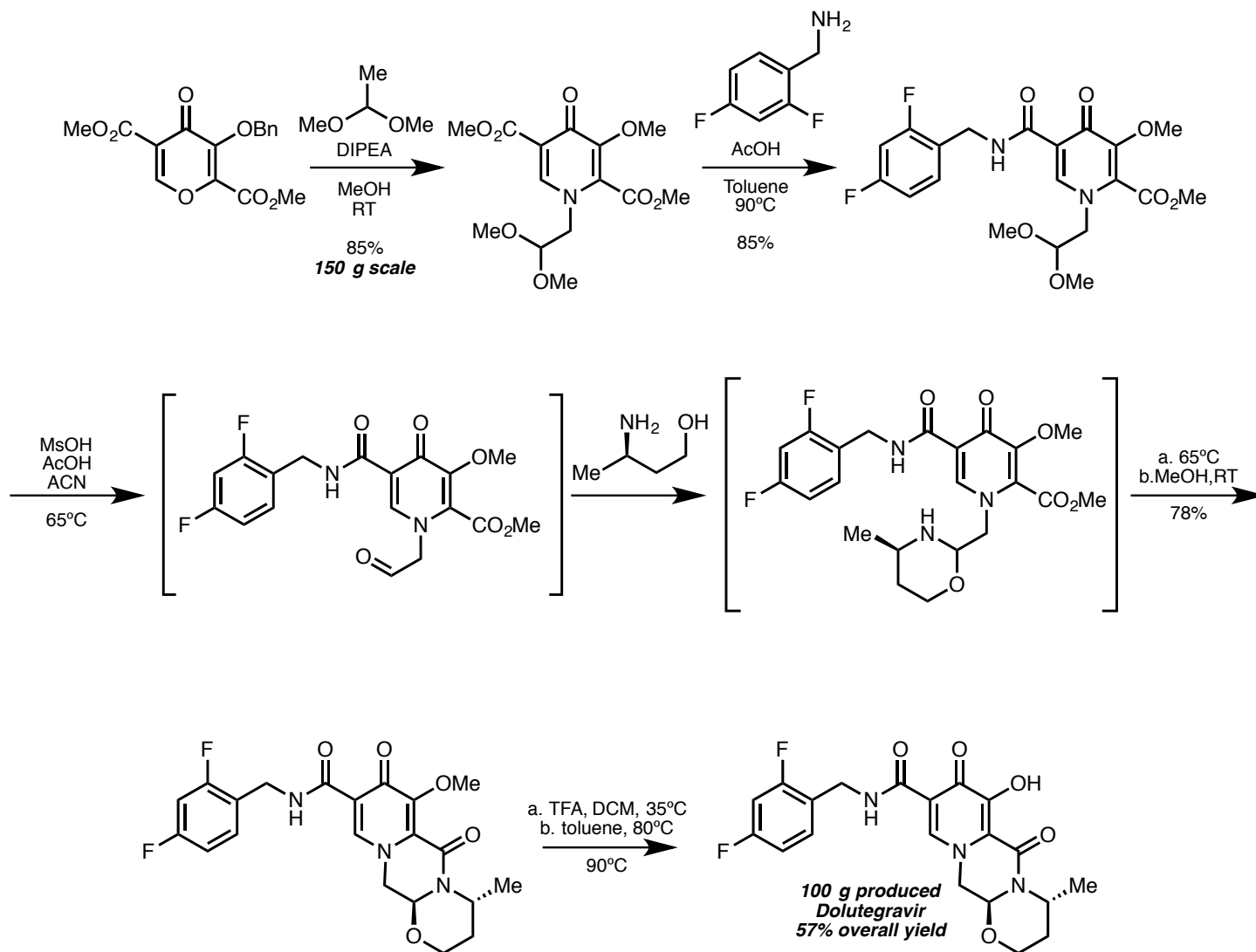


Dolutegravir (DTG)

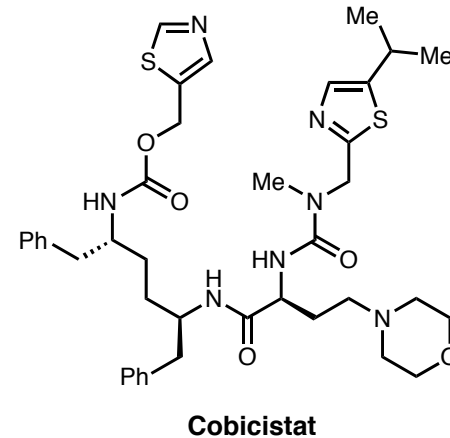


Elvitegravir (EVG)

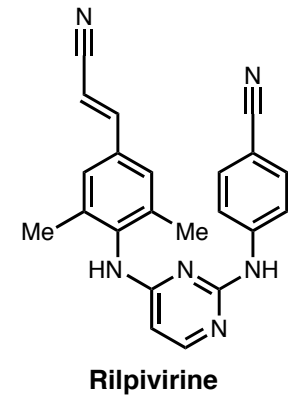
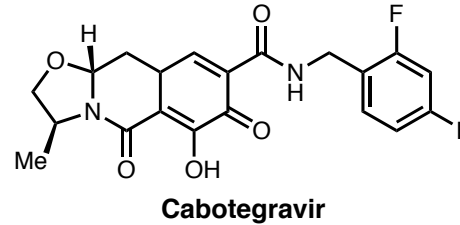




- ✧ Approved 2014. Developed by Gilead.
- ✧ Inhibits liver enzyme CYP3A, which is responsible for the metabolism of several HIV treatments.
- ✧ Taken in combination with HAART to minimize loss of drug efficacy.



✧ 4 or 8 week dosing trials for cabotegravir/rilpivirine in Phase II trials.



✧ BMS has 2 single drug treatments in clinical trials with new mechanisms of action.

- ✧ Attachment inhibitors
- ✧ Maturation inhibitors

✧ Monoclonal Antibodies entering Phase II trials for HIV treatment.

