Human Immunodeficiency Virus

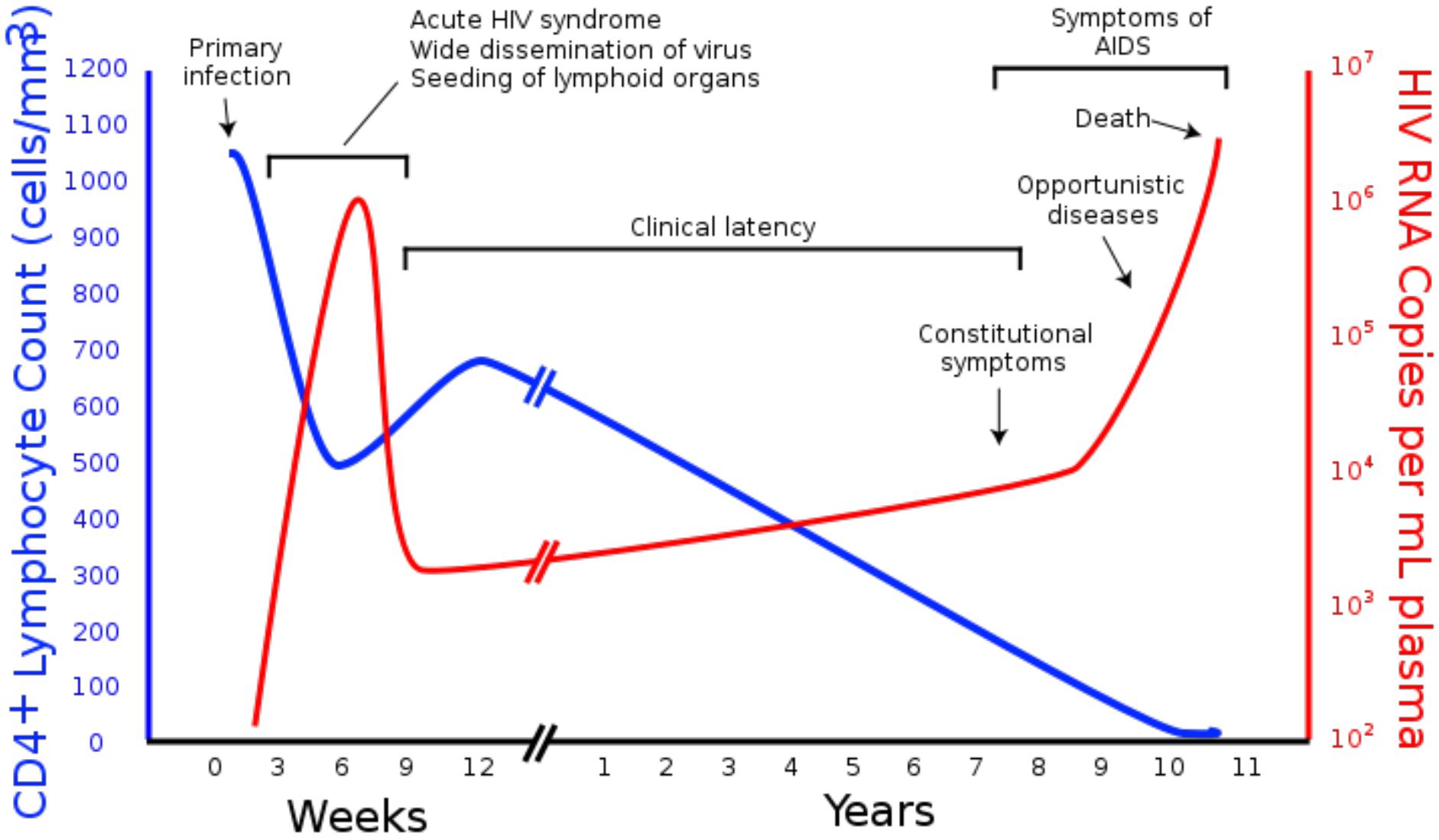
And targets for its treatment

By: Matt Doherty

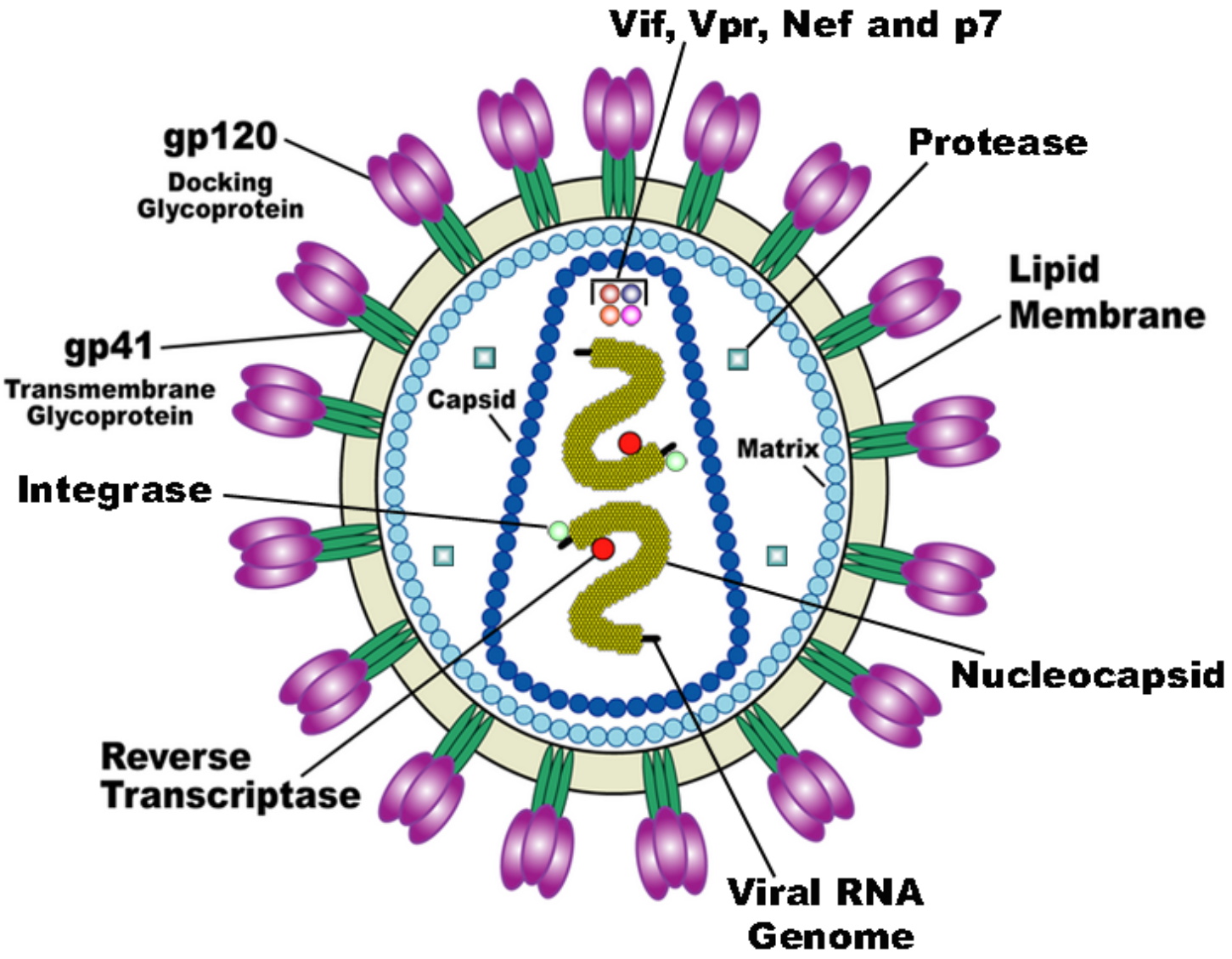
HIV Background

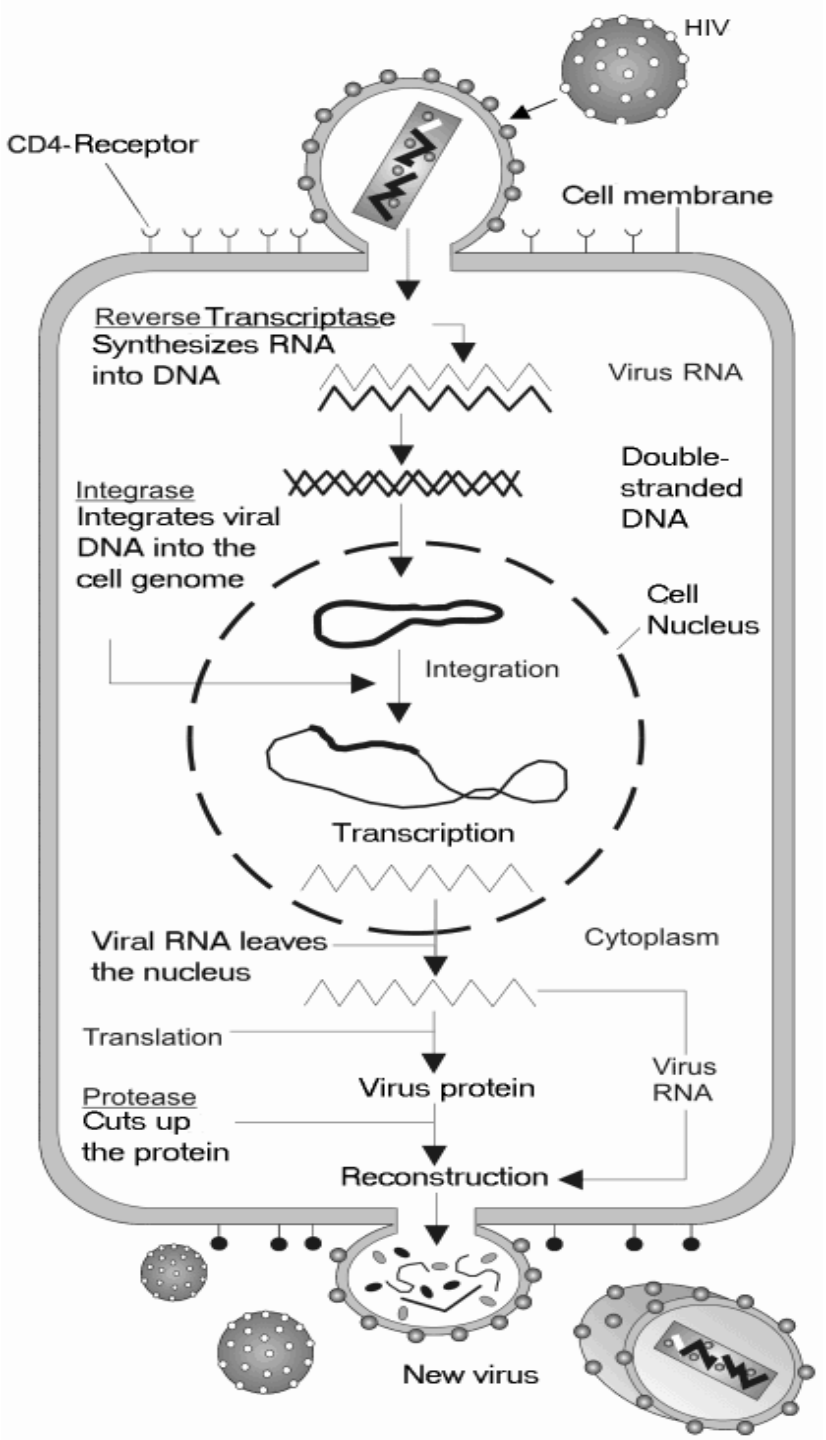
- Lentivirus, member of retroviruses
- Genome is single stranded RNA that converts to double stranded DNA by reverse transcription
- Responsible for Acquired Immunodeficiency Syndrome (AIDS)

Progression of Illness



Structure


Vif, Vpr, Nef and p7
gp120
Docking
Glycoprotein
Protease
Lipid
Membrane
gp41
Transmembrane
Glycoprotein
Capsid
Matrix
Integrase
Nucleocapsid
Reverse
Transcriptase
Viral RNA
Genome

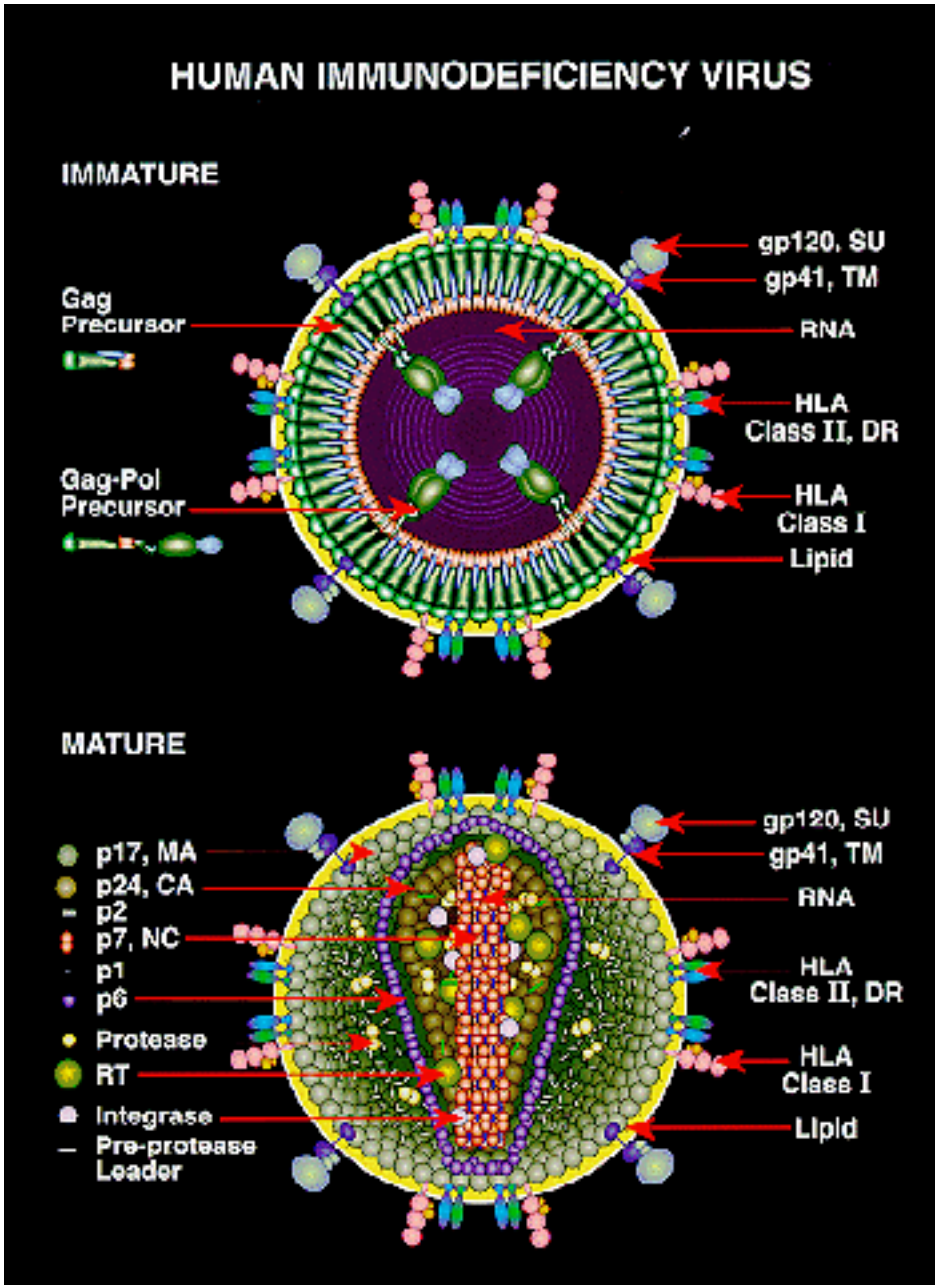


Replication Cycle

- Attaches to the target cell by binding to the CD4 receptor
- leads to membrane fusion and virus entry
- reverse transcription turns viral RNA into proviral DNA
- Provirus integrates into host cells and begins making new virus RNA/proteins/ genome

- Viral genomic mRNA is transported to the membrane where it is packaged with other viral proteins and is released

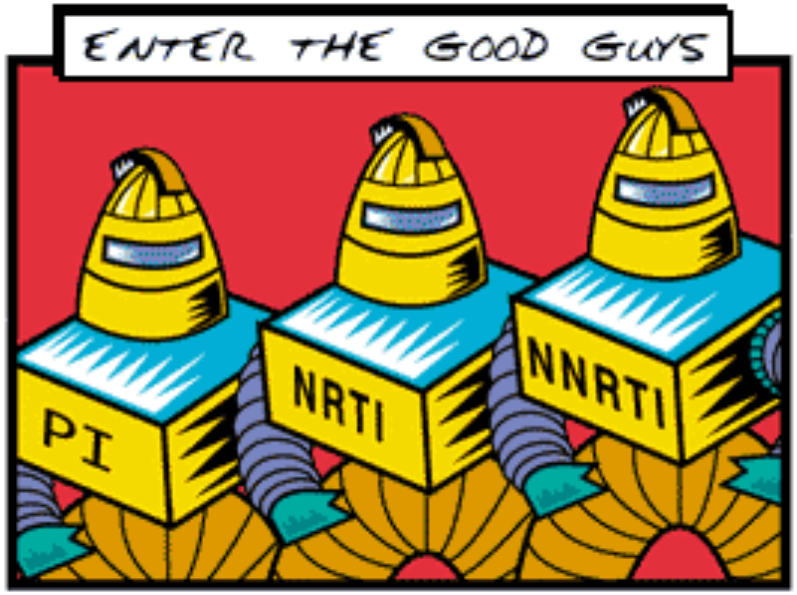
- Protease/Maturase converts virus into infectious form.



Treating HIV

- Prevention/vaccination still the best option, but no vaccine yet…
- Drugs used to treat HIV target key steps in the replication cycle
- Primary treatment is Highly Active Antiretroviral Therapy (HAART)
  - Uses 3+ drugs from 2+ antiretroviral drug classes

Antriretrovirals Classes

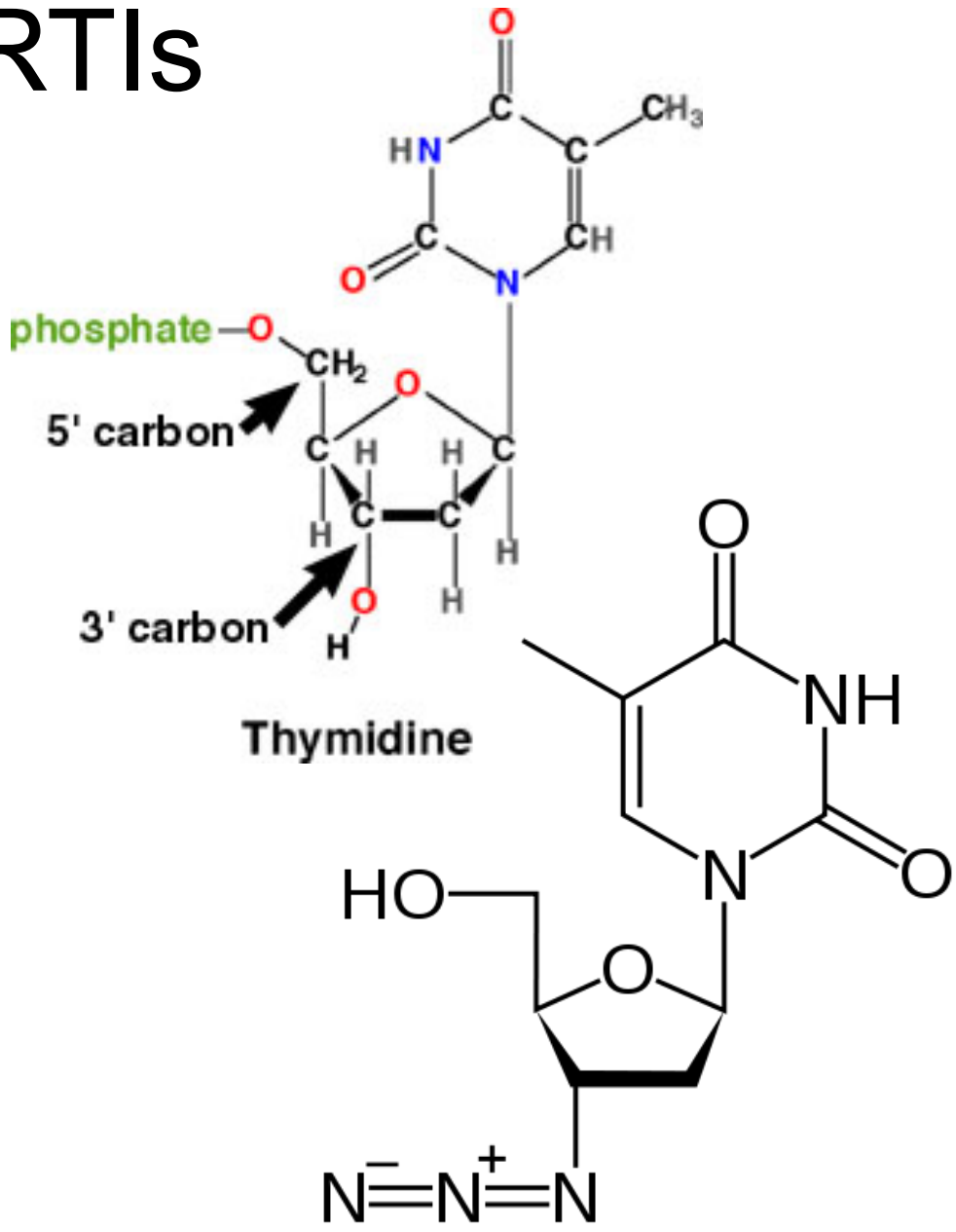


- Nucleos(t)ide Reverse Transcriptase Inhibitors (N(t)RTIs)
- Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease/Maturation Inhibitors
- Integrase Inhibitors
- Entry Inhibitors

NRTIs

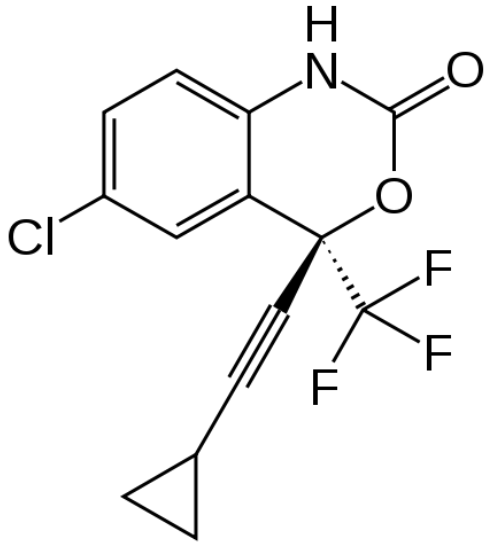
- Competitive inhibitors that act as chain terminators

- Target the functions of the RT enzyme:
  - Recognition and binding
  - Formation of a phosphodiester bond
  - Cause chain termination by altering the 3' hydroxyl group.
  - No 3' hydroxyl = no elongation



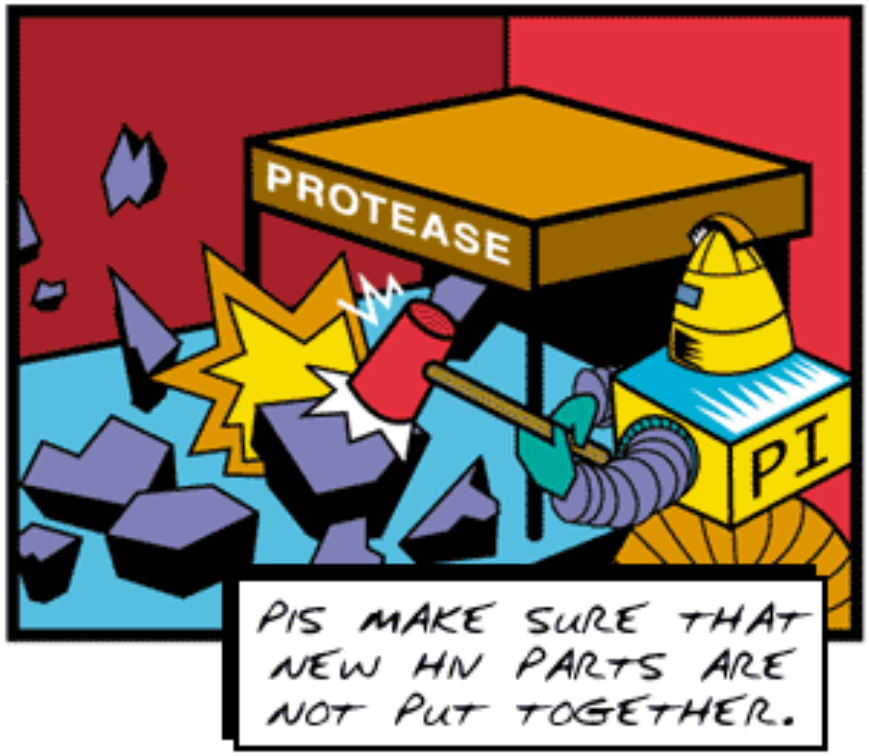
NNRTIs

- Allosteric noncompetitive inhibitors that bind noncovalently away from the active site
- Stop RT activity by somehow altering the active site
- Example: Efavirenz



Protease and Integrase Inhibitors

Protease Inhibitors



Ex:
Ritonavir

- Integrase Inhibitors
  - Prevent integration of provirus into host genome
- Example: Raltegravir

Entry Inhibitors

- Block any of the stages in entry
  - Attachment
  - Co-receptor binding
    - Ex: Maraviroc
  - Membrane fusion
    - Ex: Enfuvirtide

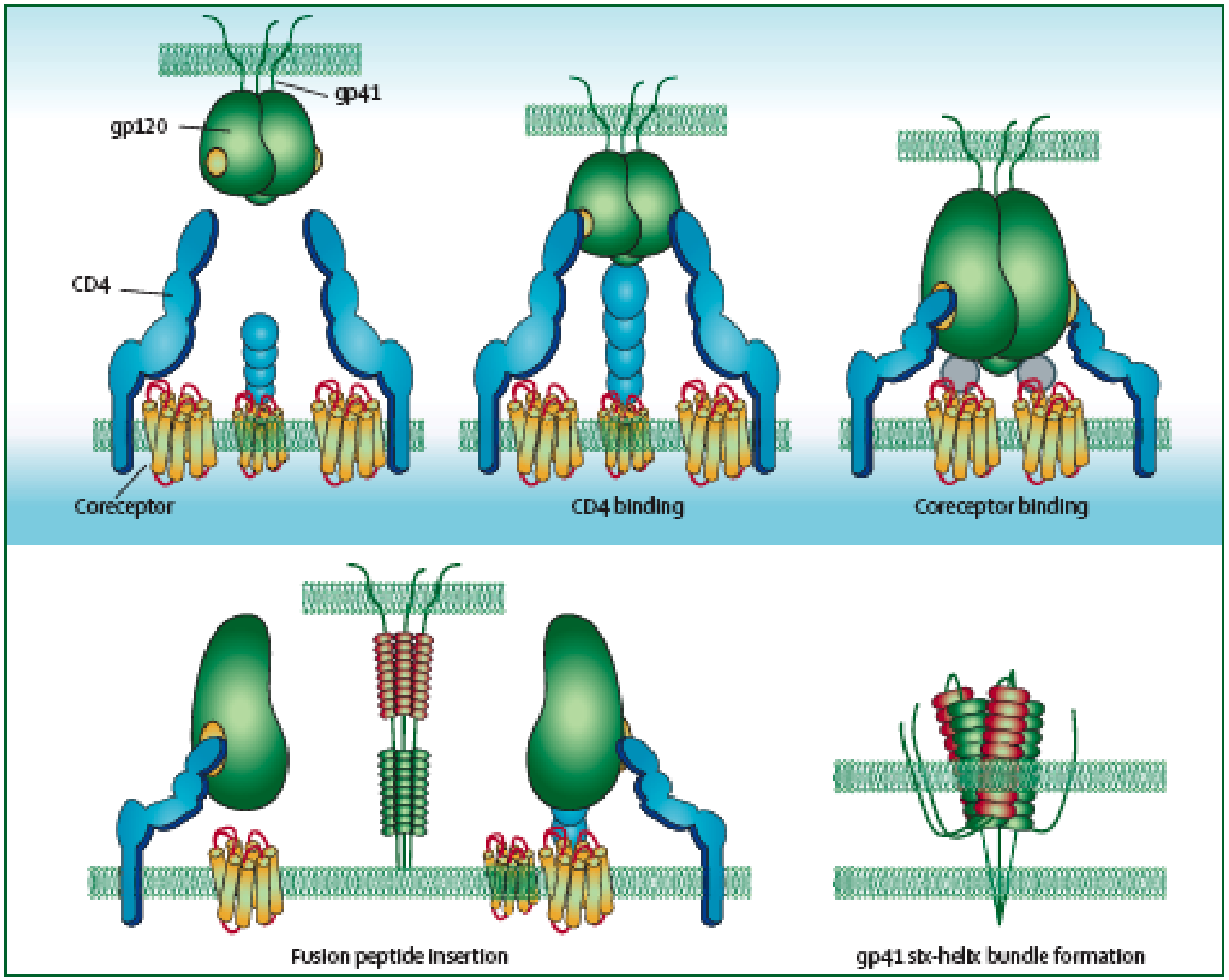
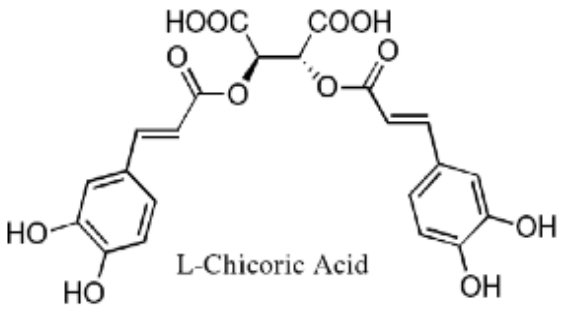


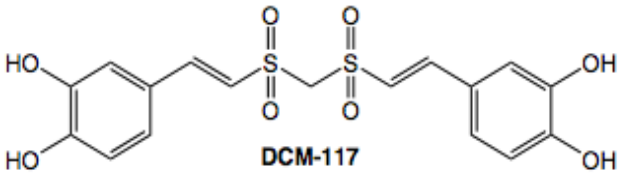
Figure 1: Mechanism of HIV entry

On CD4 binding (binding site for CD4 is shown in yellow), gp120 undergoes conformational changes. CD4-induced epitopes can then bind to chemokine receptors. Thereafter, gp41 is released into a fusogenic conformation and its N-terminal (green) and C-terminal (red) helices form a hairpin structure, leading to the approximation of viral and cellular membranes, which results in membrane fusion.

My Research on HIV

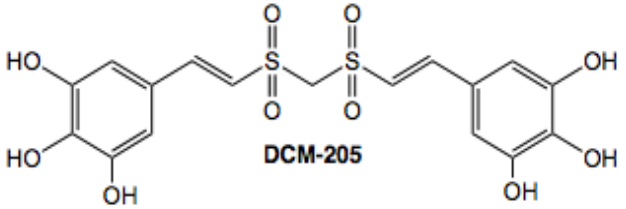
- New potential integrase inhibitor developed on campus assayed for anti-HIV activity by time of addition assay
  - Cells infected and treated with drug at different times
- One drug* shown to act early, ie. under 2 hours post infection





HIV-IN 3' Processing IC_{50}: 4 ± 1 μM
HIV-IN Strand Transfer IC_{50}: 5 ± 1 μM
HIV Antiviral EC_{50}: 2.4 ± 0.3 μM
TOA studies consistent with RT/IN inhibition

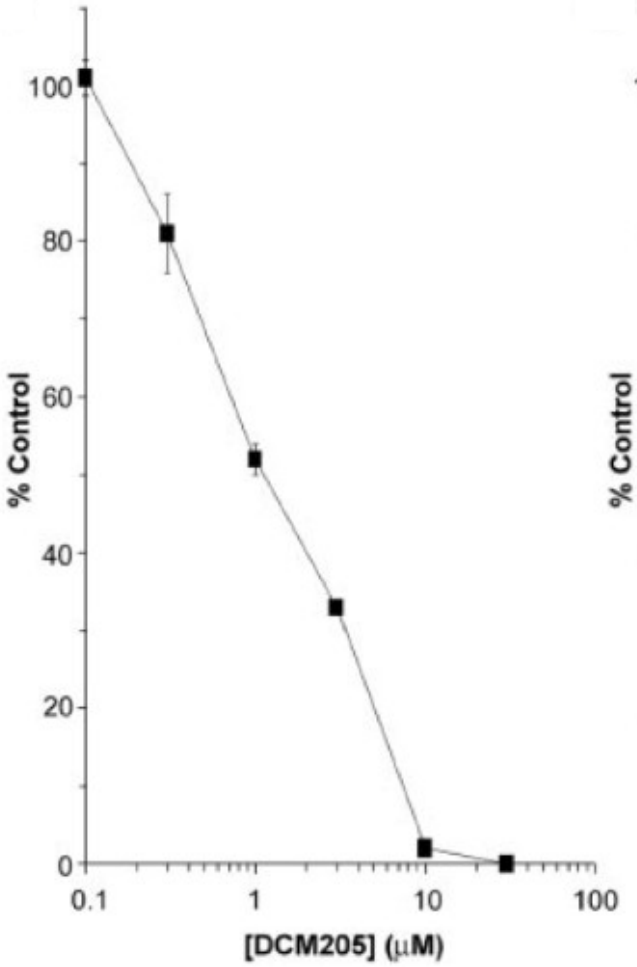
*

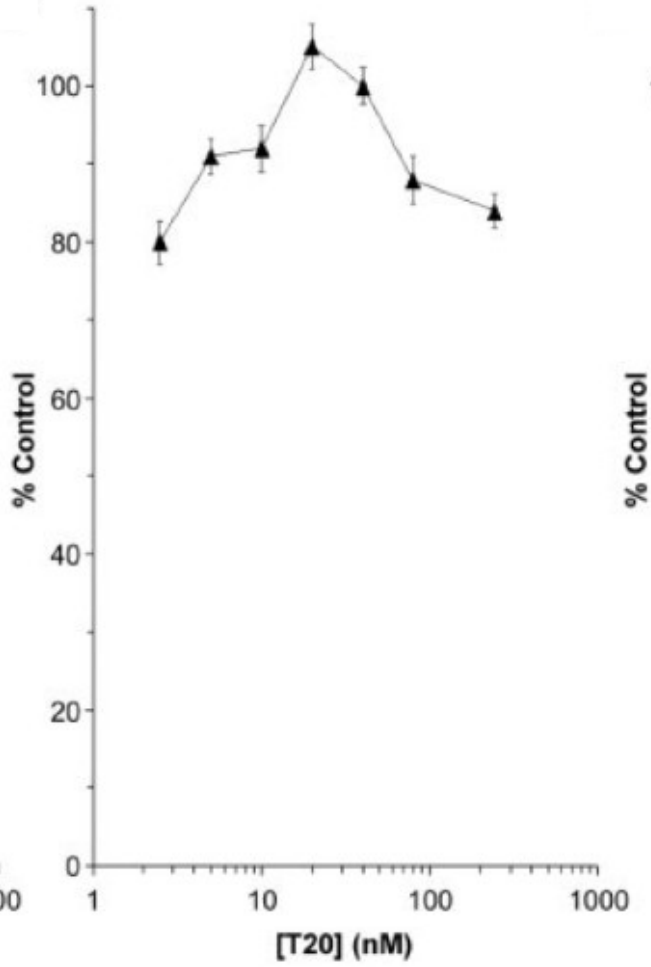


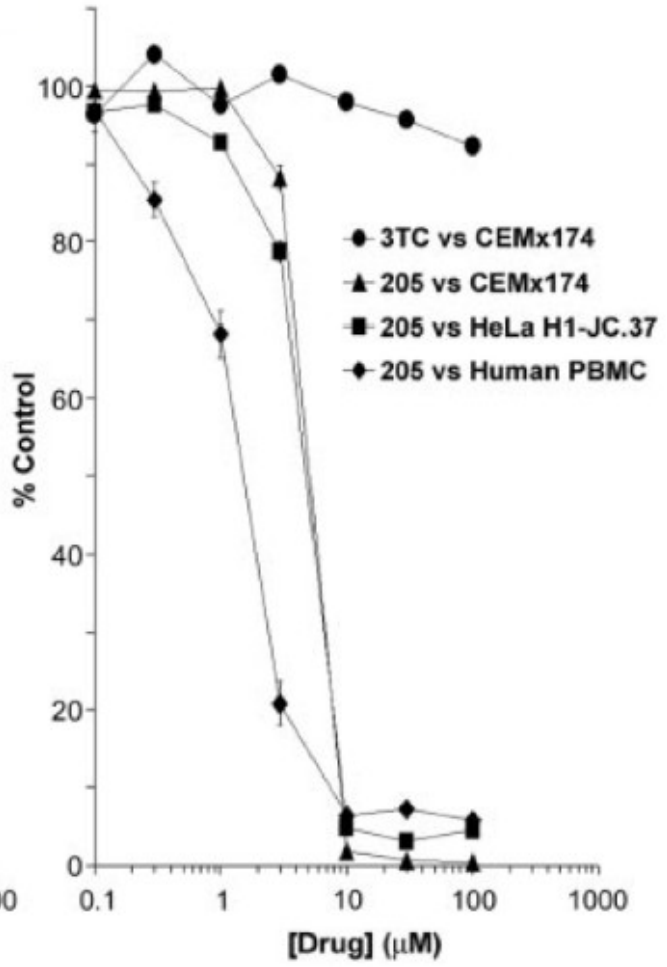
HIV-IN 3' Processing IC_{50}: 1.8 ± 0.3 μM
HIV-IN Strand Transfer IC_{50}: 0.9 ± 0.1 μM
HIV Antiviral EC_{50}: 0.3 ± 0.03 μM
TOA studies consistent with entry inhibition

Figure 1. L-Chicoric acid and potent disulfone inhibitors of HIV-IN in pilot stu

Direct Inactivation





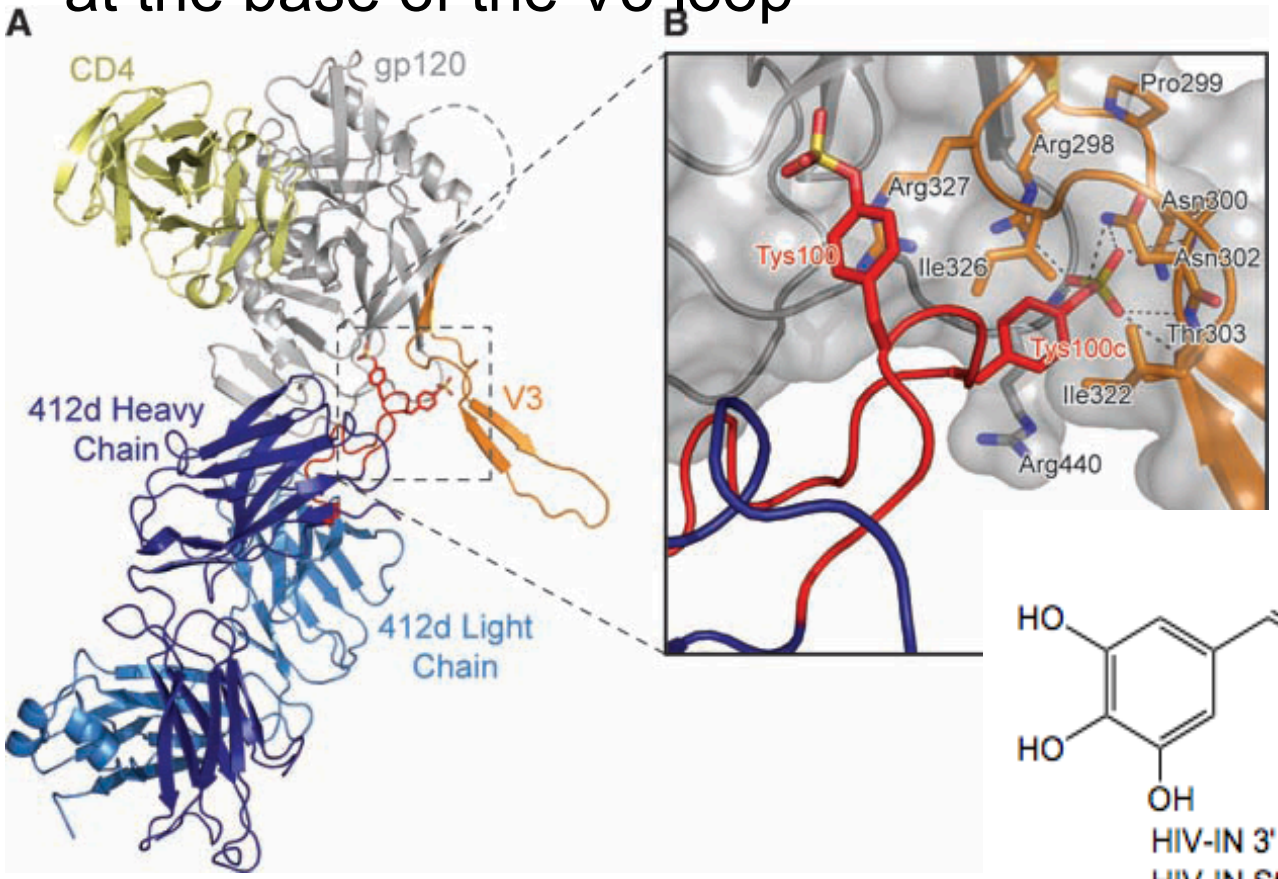


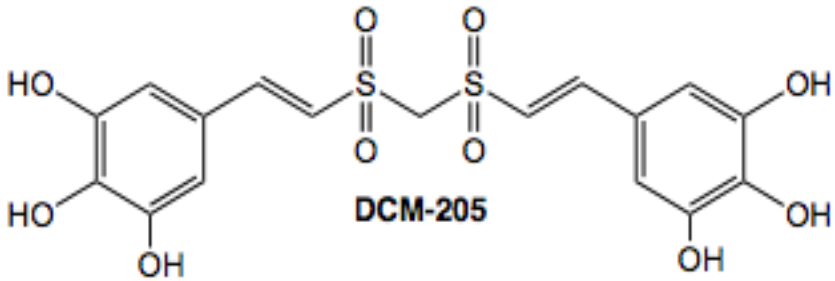
Wide Range of Activity

Virus type	Strain	Clade	Co-receptor Usage	Mean EC_{50} (nM) ± SEM
Lab-adapted HIV-1	Ba-L	B	R5	850 ± 90
	HXBc2	B	X4	530 ± 60
	NL4-3	B	X4	330 ± 20
	89.6	B	X4R5	410 ± 40
Primary Strain HIV-1	92RW016	A	R5	700 ± 100
	SF162	B	R5	400 ± 100
	92HT593	B	X4R5	340 ± 20
	92TH014	B	R5	190 ± 20
	97ZA009	C	R5	2300 + 400
	98TZ013	C	R5	190 ± 30
	93TH078	E	R5	500 ± 20
SIV	mac239	–	R5	1200 ± 200

Proof of Concept?

Prior resistance studies indicated that DCM205 might bind at the base of the V3 loop





DCM-205

HIV-IN 3' Processing IC_{50}: 1.8 ± 0.3 μM
HIV-IN Strand Transfer IC_{50}: 0.9 ± 0.1 μM
HIV Antiviral EC_{50}: 0.3 ± 0.03 μM
TOA studies consistent with entry inhibition

What Happened Next?

- Funding ran out

- Hoped to develop as a microbicide
  - Some already in development

Questions?