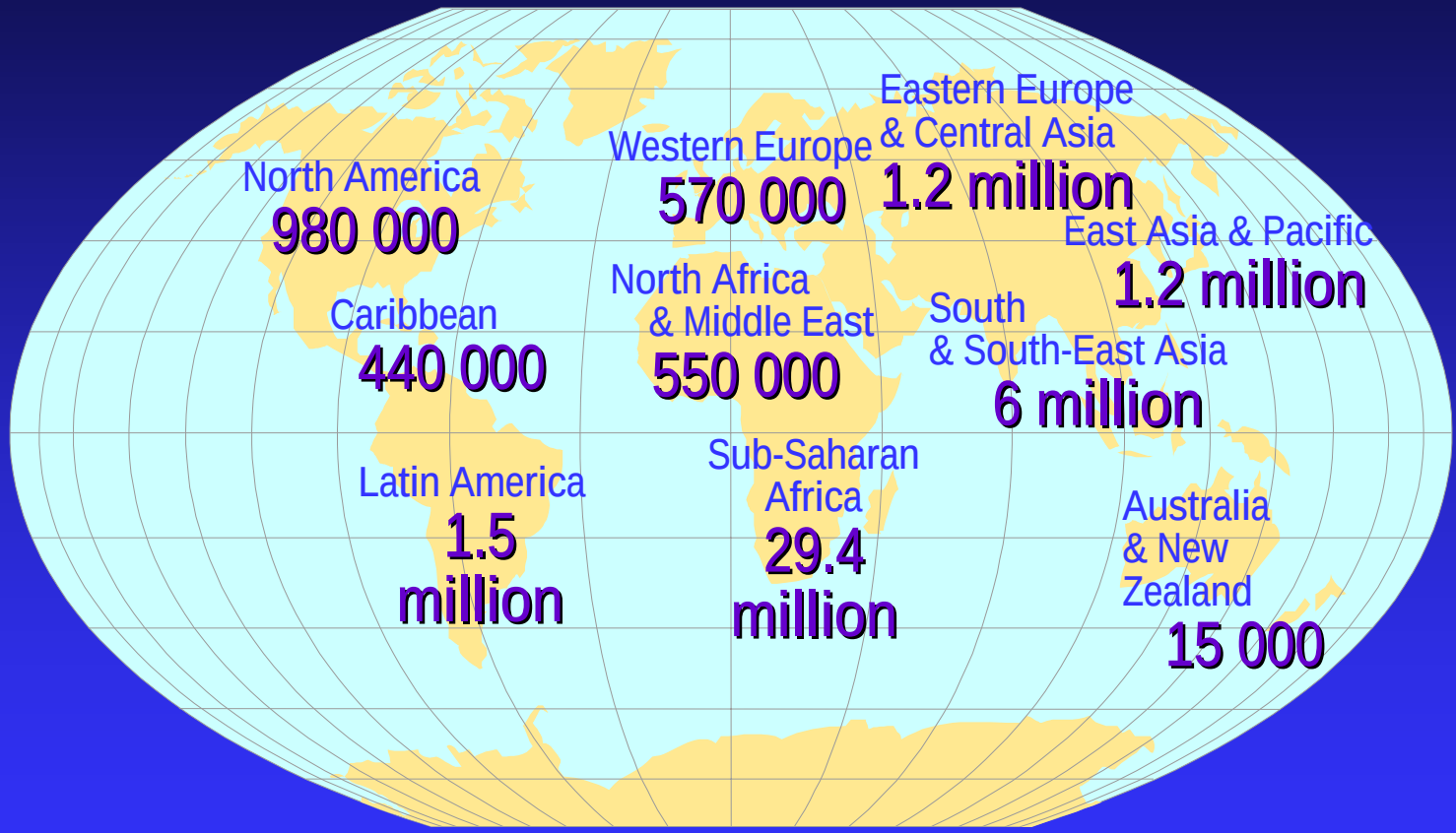
HIV and HIV chemotherapy

Adapté des exposés

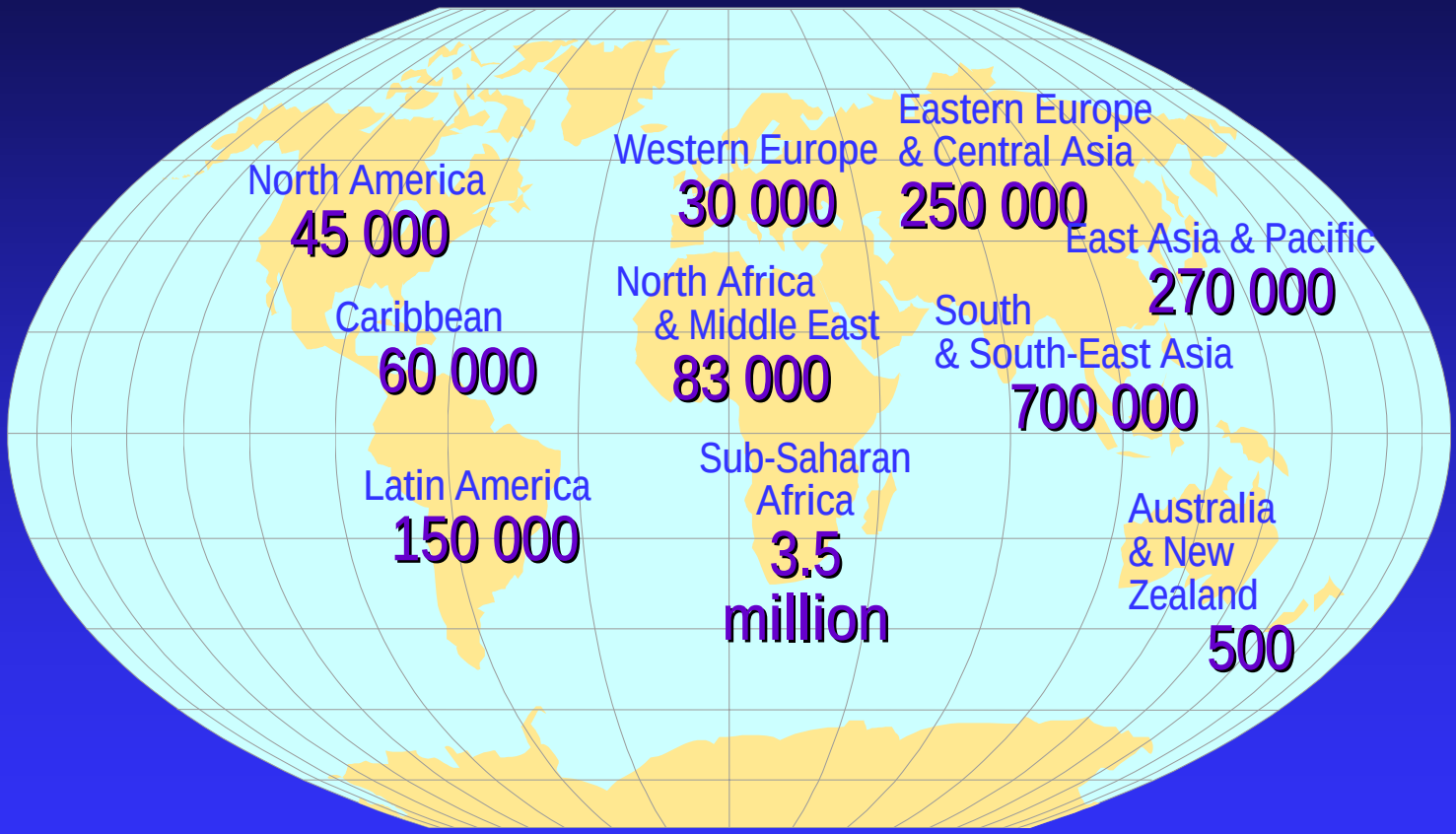
- **de la Chaire Franqui 2003**
  "*Antiviral drugs and Discoveries in Medicine*"
  Prof. E. De Clercq, KU-Leuven
  http://www.md.ucl.ac.be/chaire-francqui/
- **du Dr J. Nachega, Johns Hopkins University donné à l'Ecole de Pharmacie en 2003**

Adults and children estimated to be living with HIV/AIDS as of end 2002



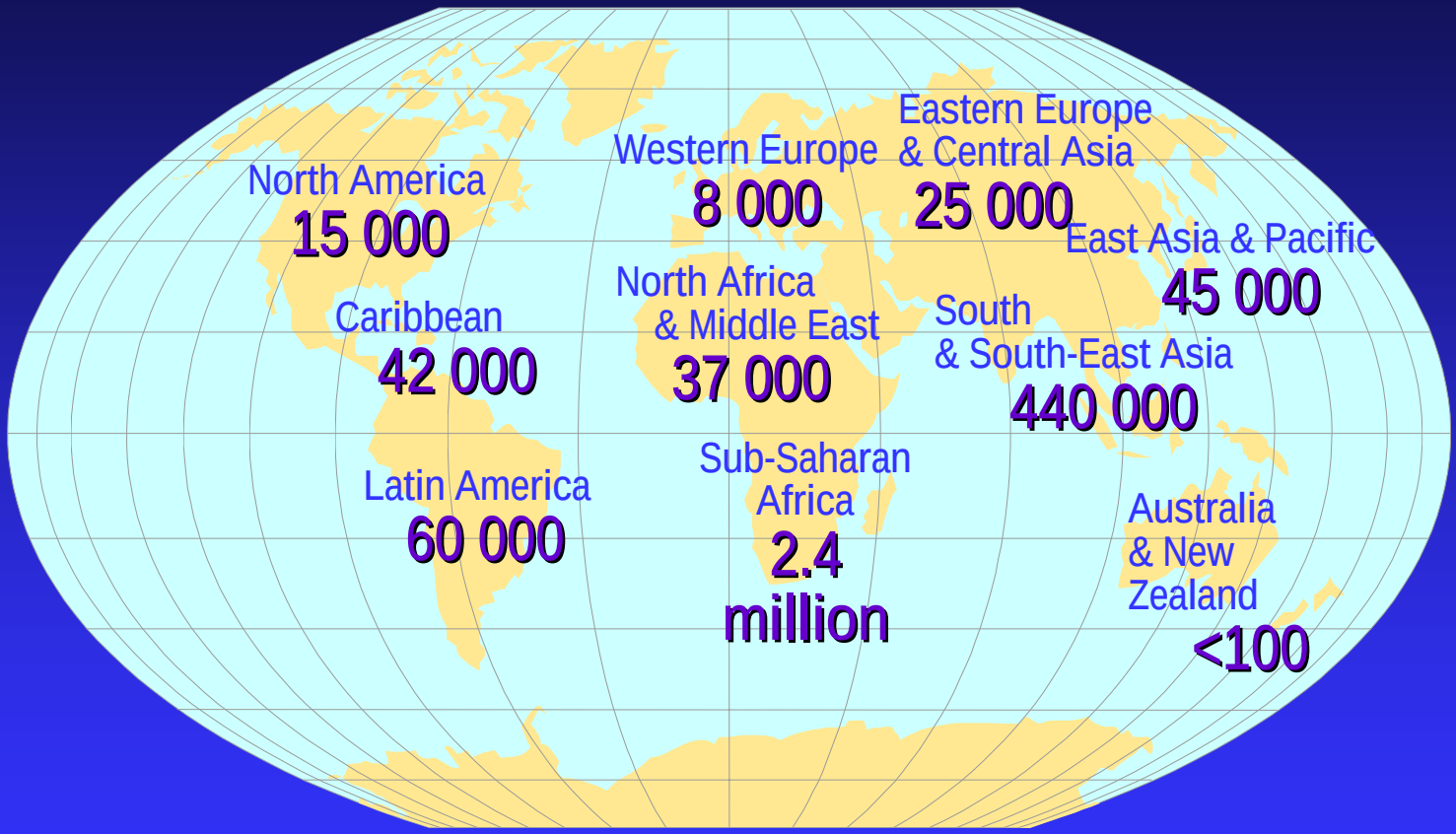
42 million

Estimated number of adults and children newly infected with HIV during 2002



5 million

Estimated adults and child deaths due to HIV/AIDS during 2002



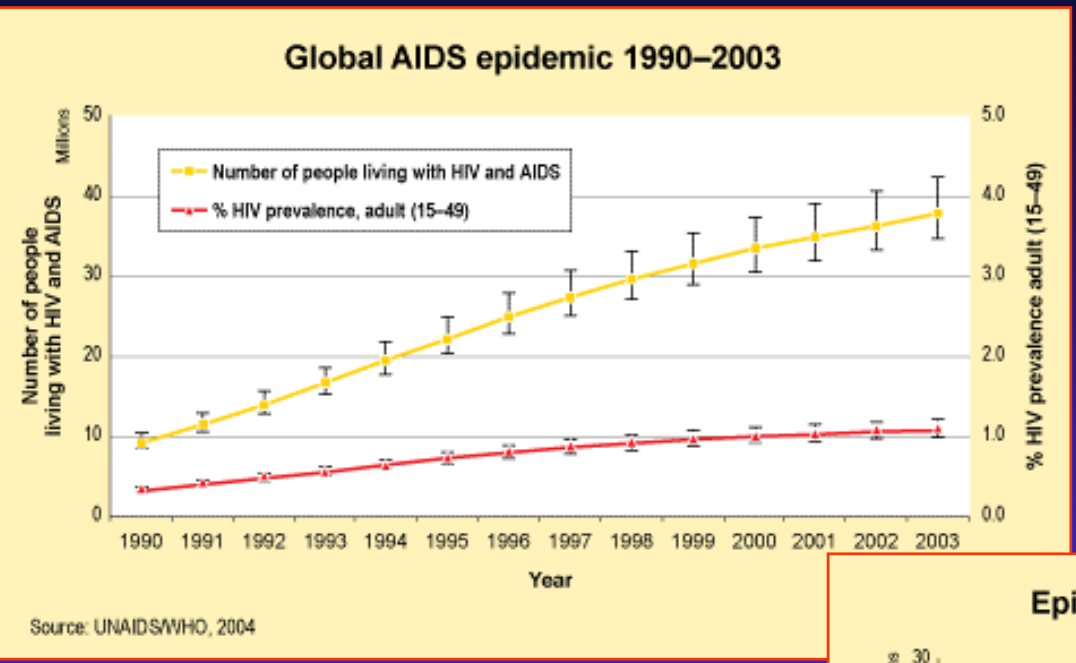
3.1 million

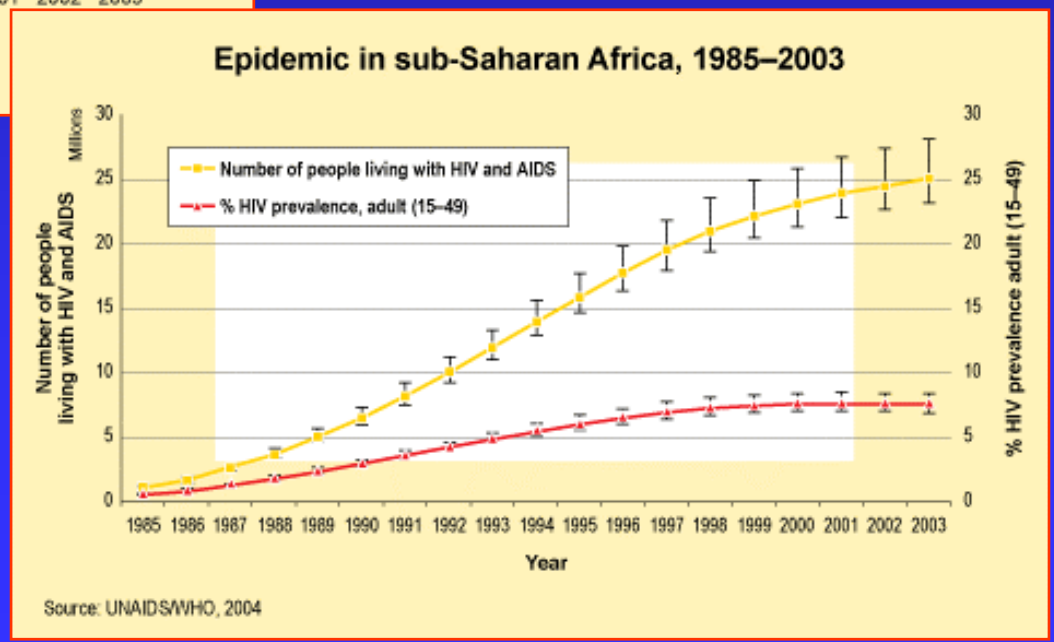
Progress update on the global response to the AIDS epidemic, 2004

- **AIDS epidemic continues to expand; vulnerable populations at greatest risk**
- **Sub-Saharan Africa is most heavily affected**
- diverse epidemics are under way in Eastern Europe and Central Asia. Injecting drug use is the main driving force behind epidemics across the region.
- In many high-income countries, sex between men plays an important role in the epidemic.
- Drug injecting accounted for more than 10% of all reported HIV infections in Western Europe

Source: UNAIDS

Progress update on the global response to the AIDS epidemic, 2004



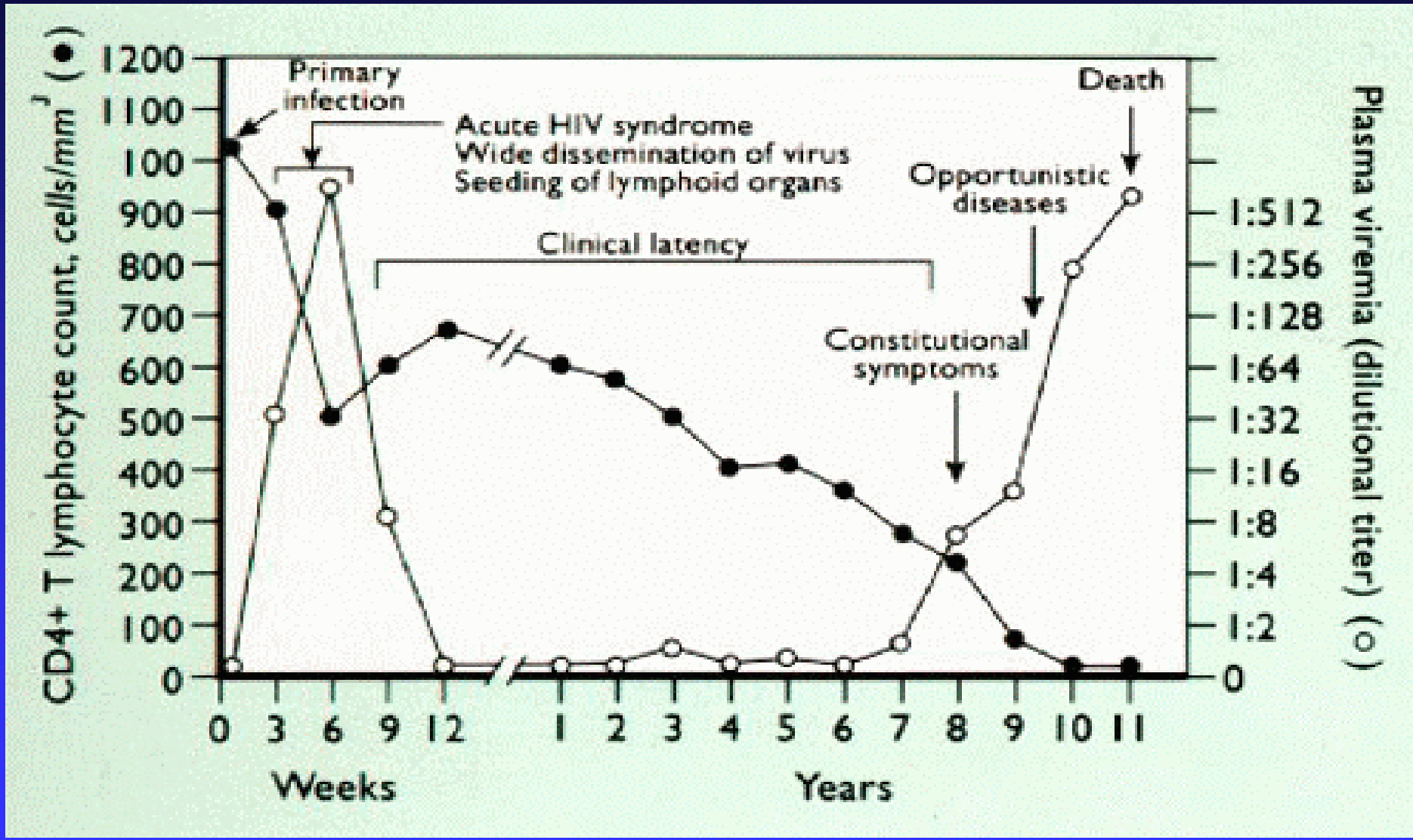


Leading causes of death in Africa, 2001

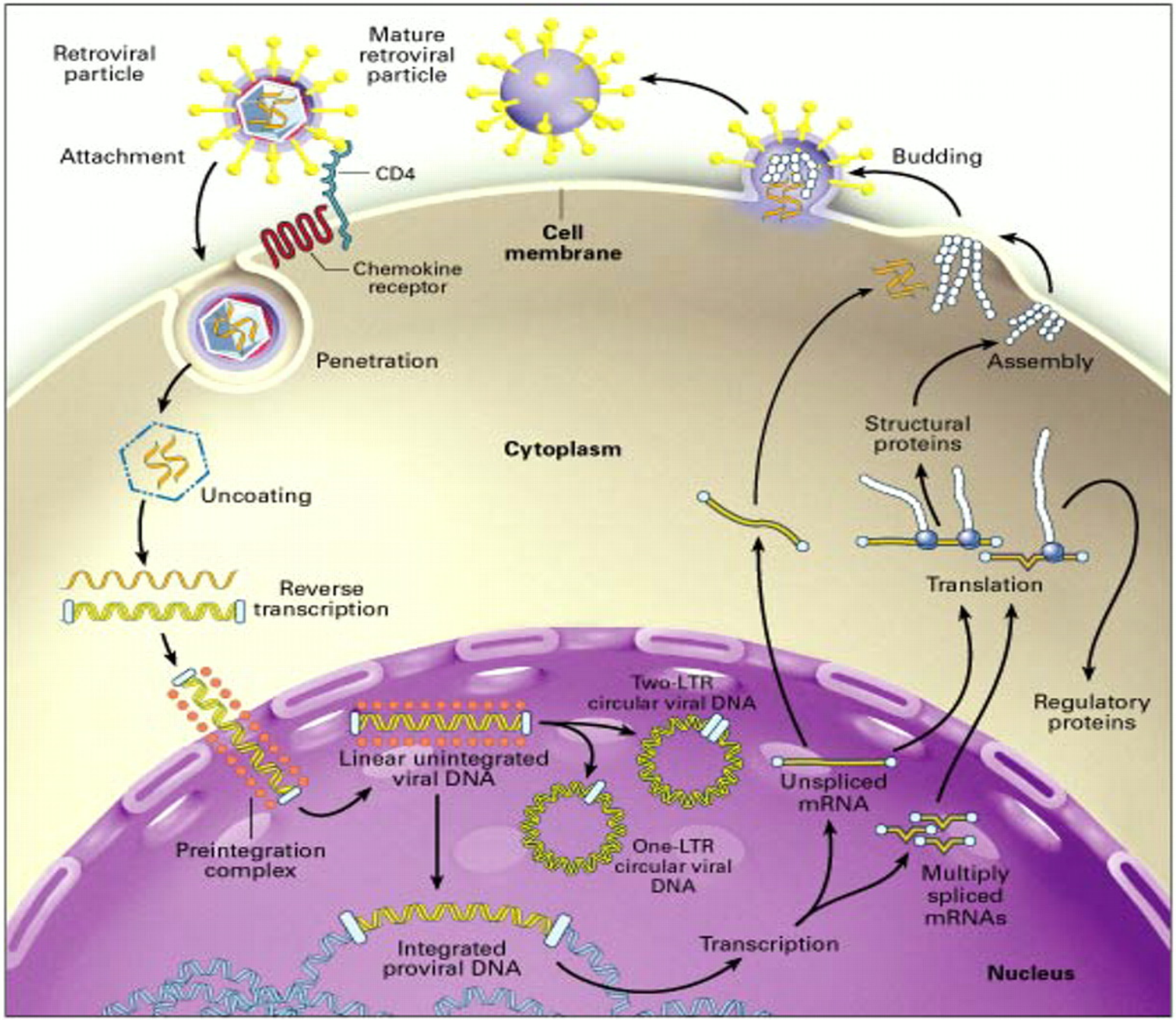
Rank		% of total
1	HIV/AIDS	20.6
2	Acute lower respiratory infections	10.3
3	Malaria	9.1
4	Diarrhoeal diseases	7.3
5	Perinatal conditions	5.9
6	Measles	4.9
7	Tuberculosis	3.4
8	Cerebrovascular disease	3.2
9	Ischaemic heart disease	3.0
10	Maternal conditions	2.4

Source: ***The World Health Report 2000, WHO***

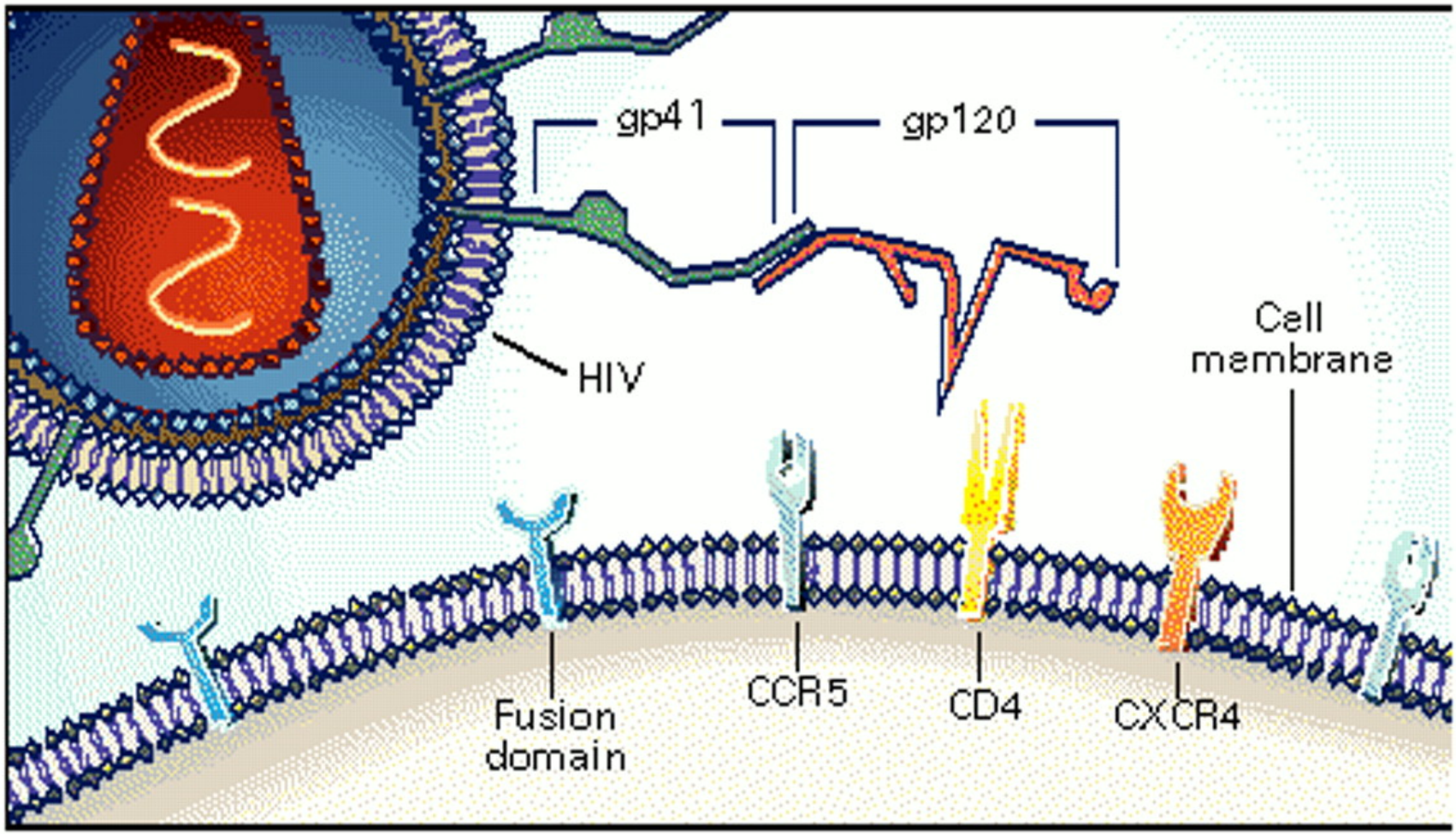
Natural History of HIV disease



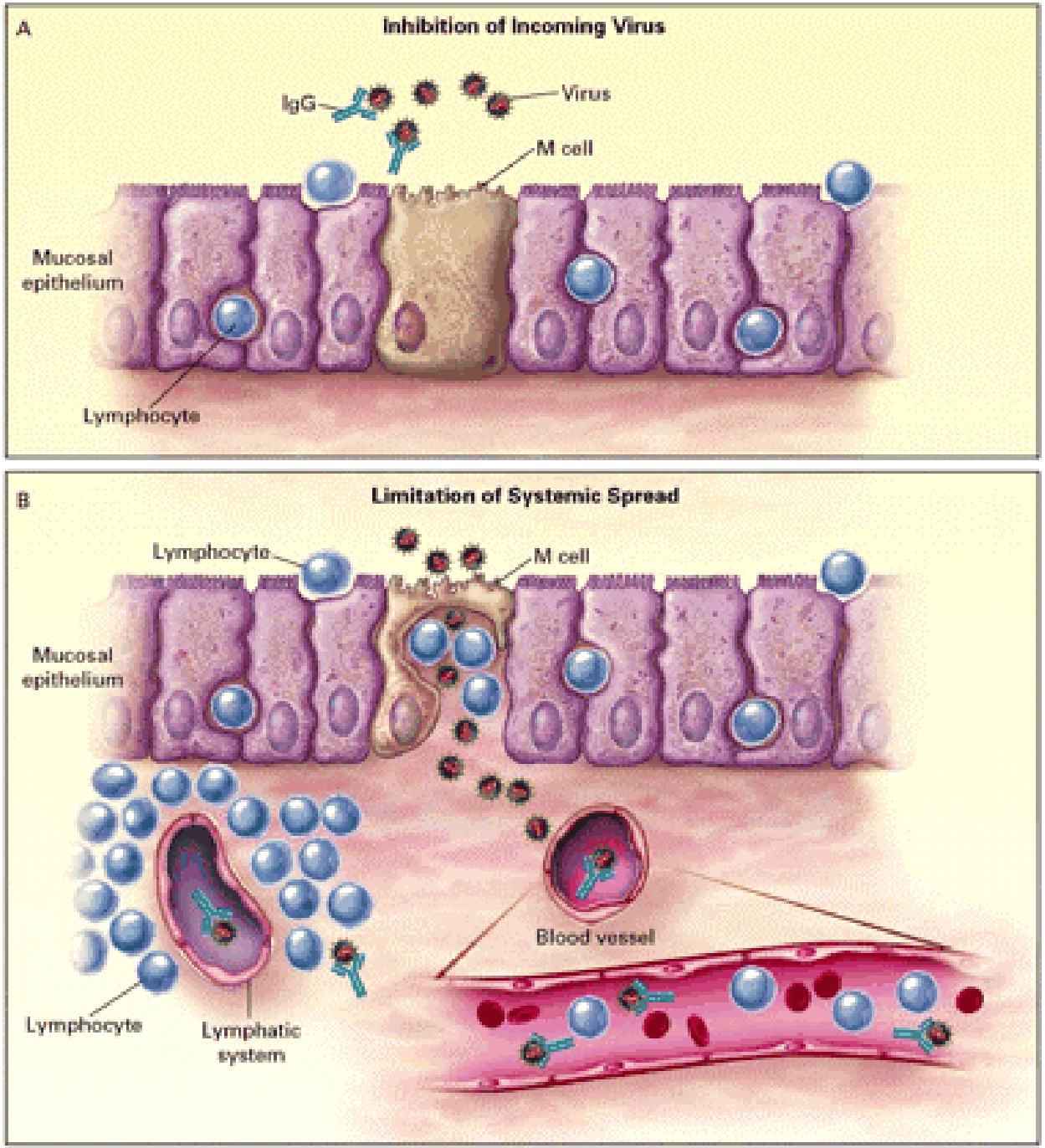
HIV-1 Life Cycle



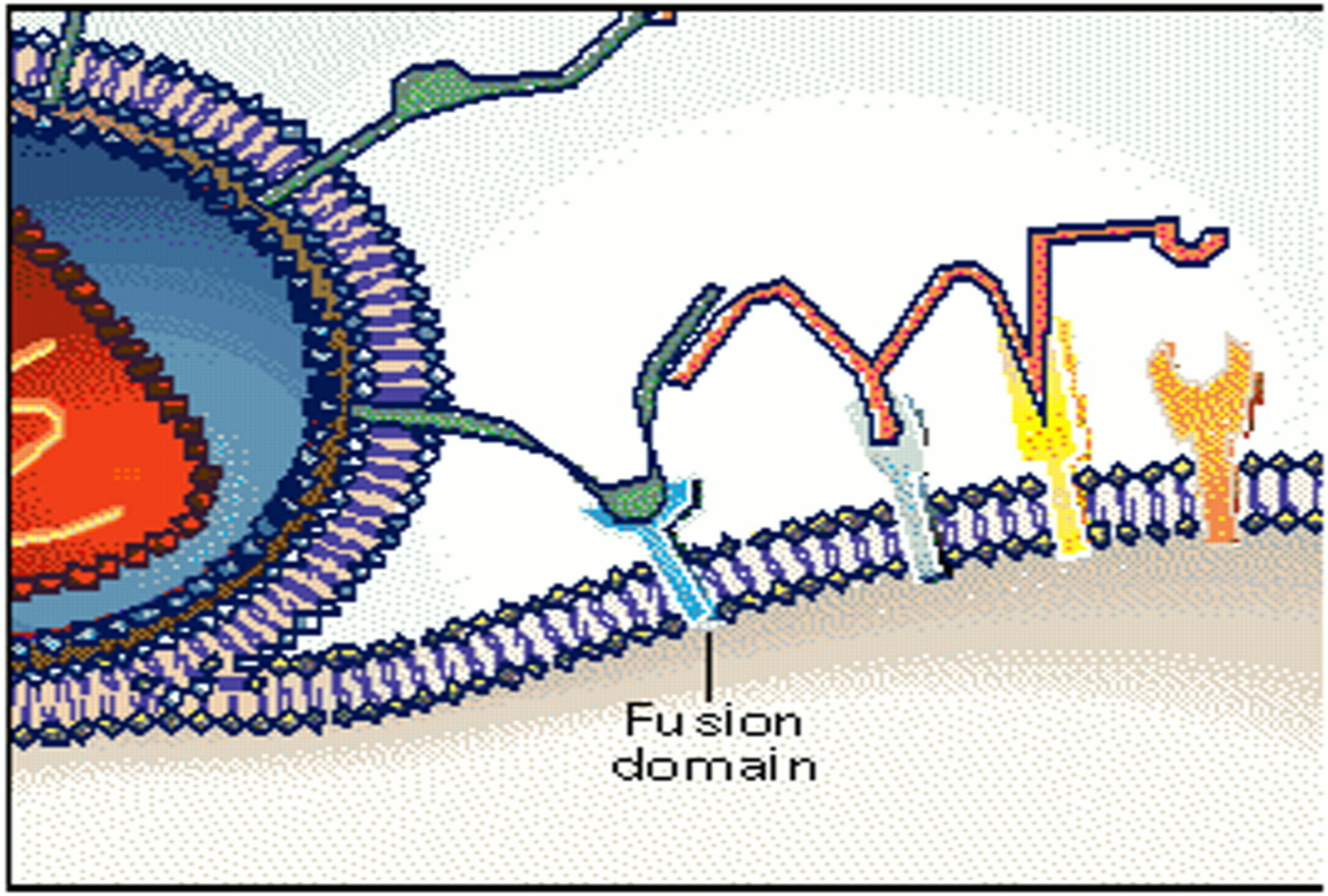
HIV Receptors



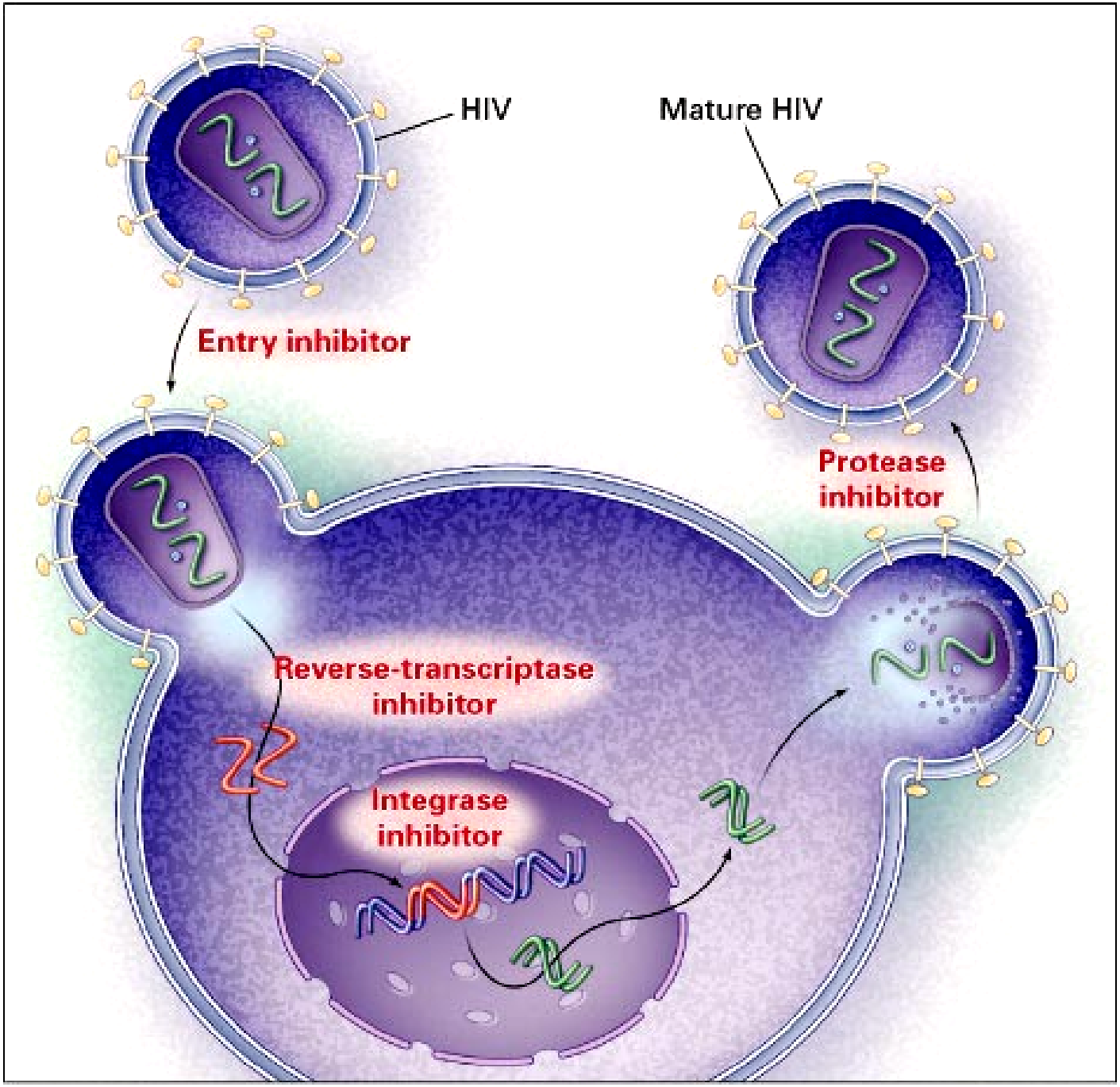
Mucosal Entry HIV



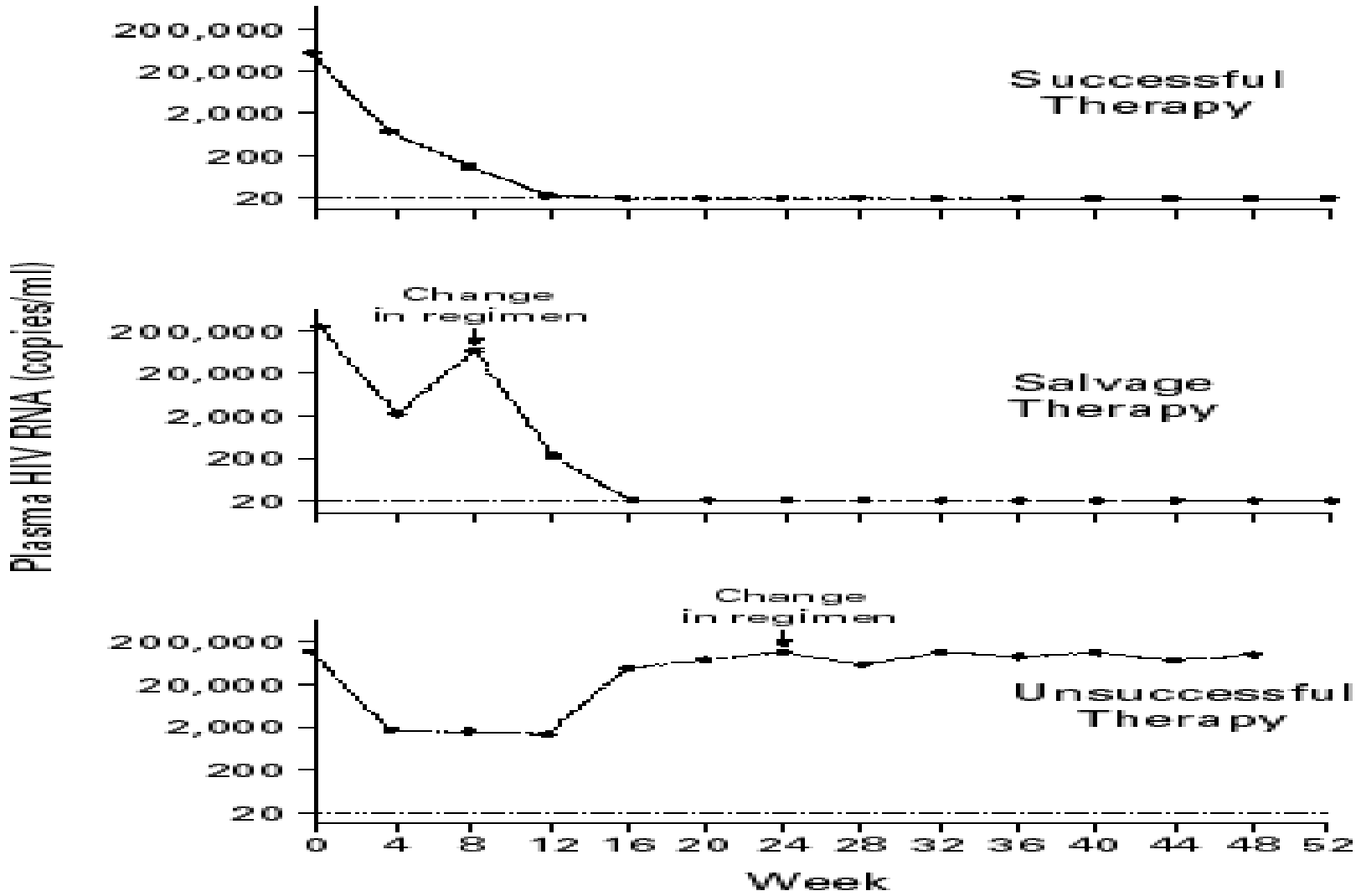
HIV Binding



HIV Drug Targets



HIV Therapeutic Possibilities



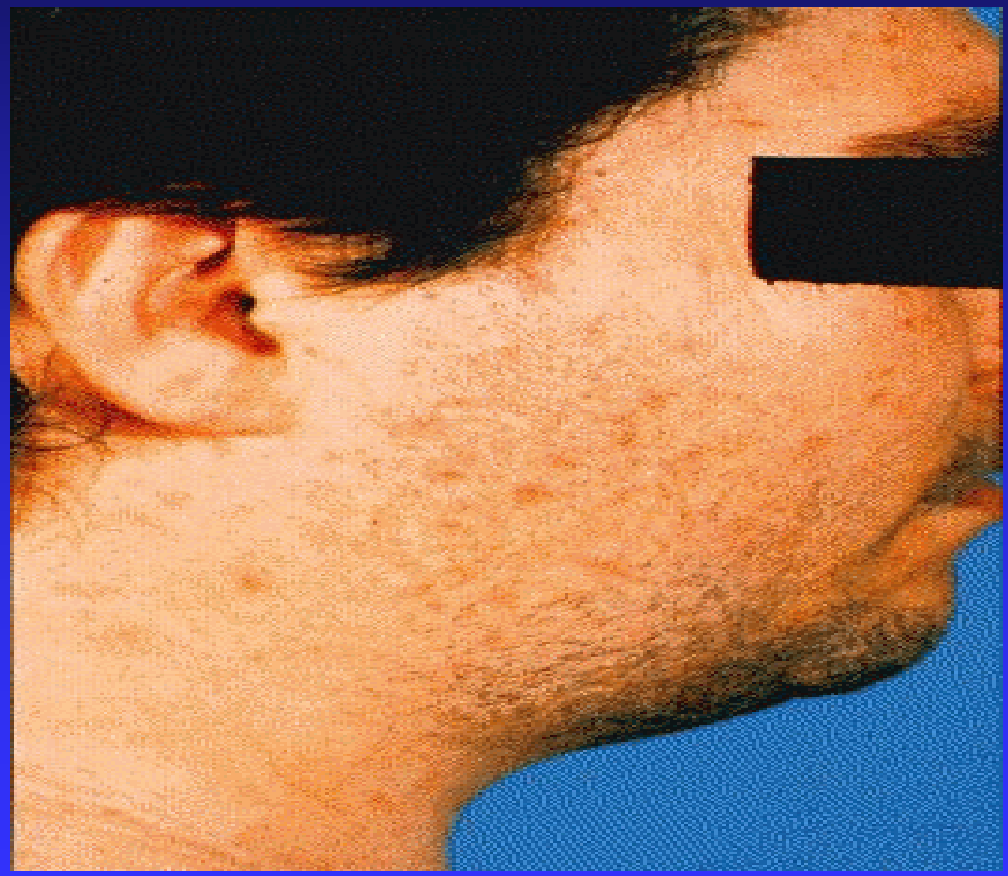
AIDS definition - CDC

- CD4 < 200 / mm3 or
- AIDS-defining illness
  - Candidiasis
  - Cervical cancer
  - Coccidiodomycosis
  - Cryptococcosis
  - Cryptosporidiosis
  - CMV
  - HSV > 1 month
  - Histoplasmosis
  - HIV-related dementia
  - HIV wasting
  - Isoporosis
  - Kaposi's sarcoma
  - Burkitts Lymphoma
  - NH Lymphoma
  - MAI - disseminated
  - MTb
  - Nocardia
  - PCP
  - Bacterial PNA (>2 in 12 mos)
  - PML
  - *Salmonella* septicemia
  - Strongyloidosis
  - Toxoplasmosis

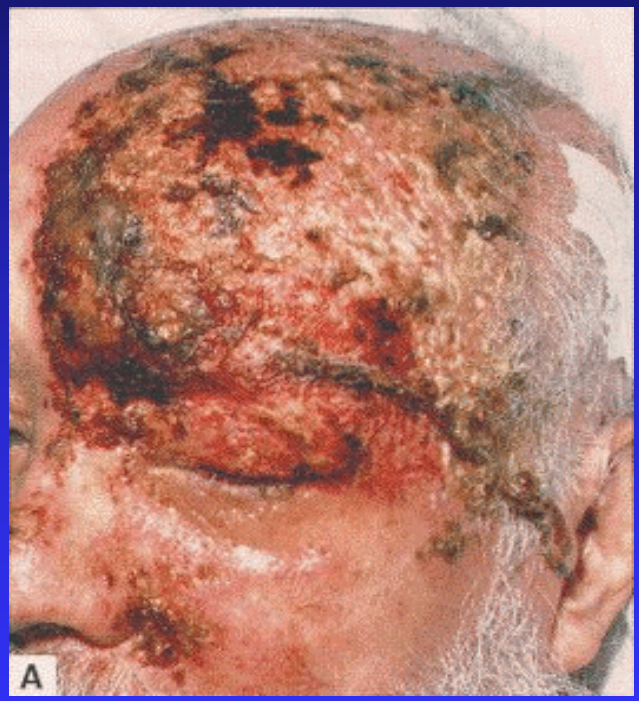
WHO Staging System

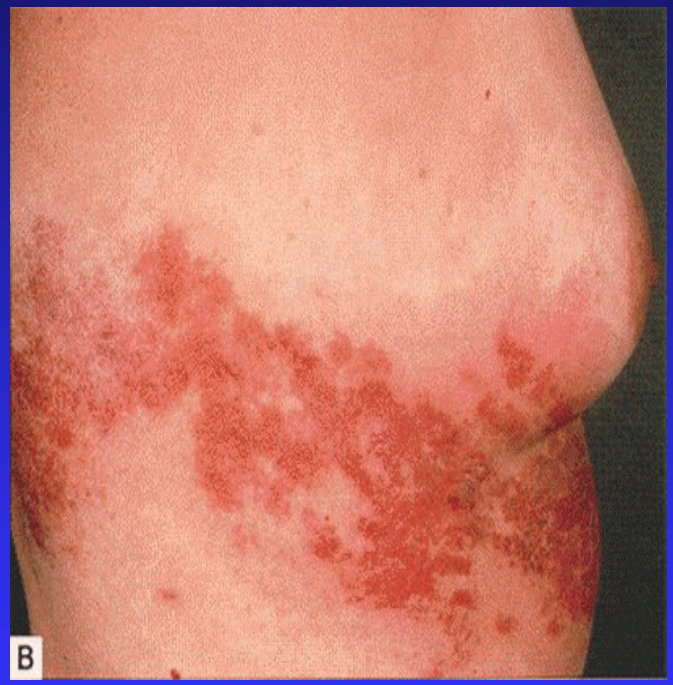
- **Clinical Stage I**
  - Aysmptomatic
  - Persistent Generalized Lymphadenopathy
  - Performance scale - 1
- **Clinical Stage II**
  - Weight loss < 10% body wt
  - Minor skin manifestations
  - HSV
  - recurrent URI
  - Performance scale- 2
- **Clinical Stage III**
  - Weight loss > 10% body wt
  - Chronic diarrhea
  - Fever
  - Thrush, OHL, Pulmonary TB
  - Severe bacterial infections
  - Performance scale - 3
- **Clinical Stage IV**
  - AIDS by CDC definition
  - HIV wasting syndrome
  - Disseminated mycosis
  - HIV encephalopathy
  - Performance scale - 4

Primary HIV Infection

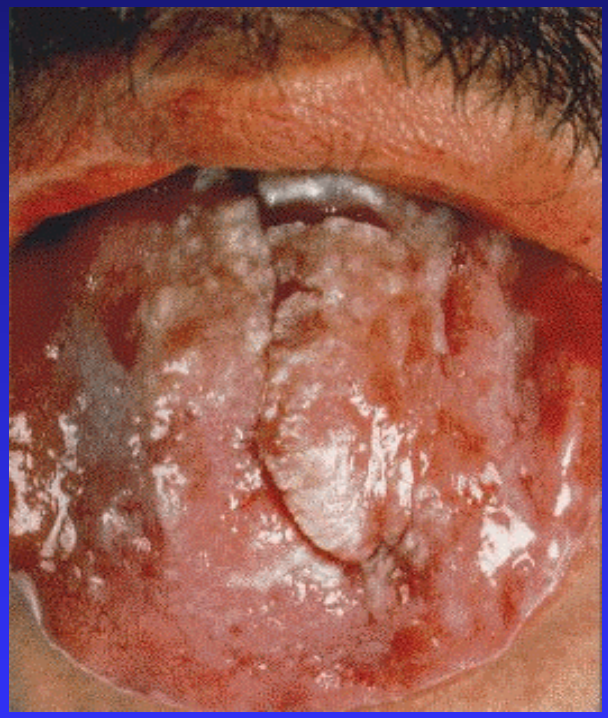


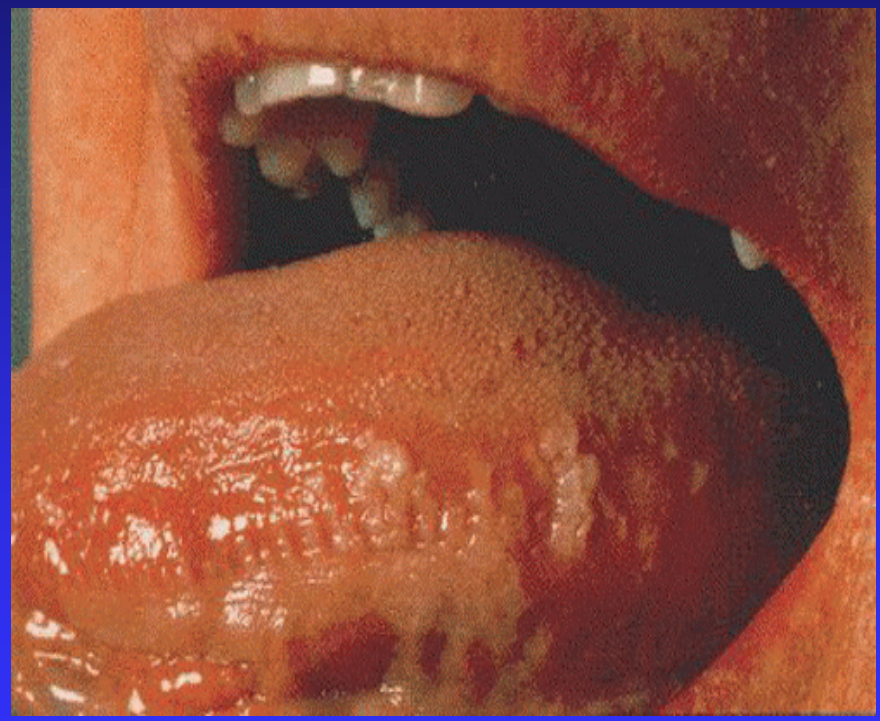
Varicella-Zoster Infection



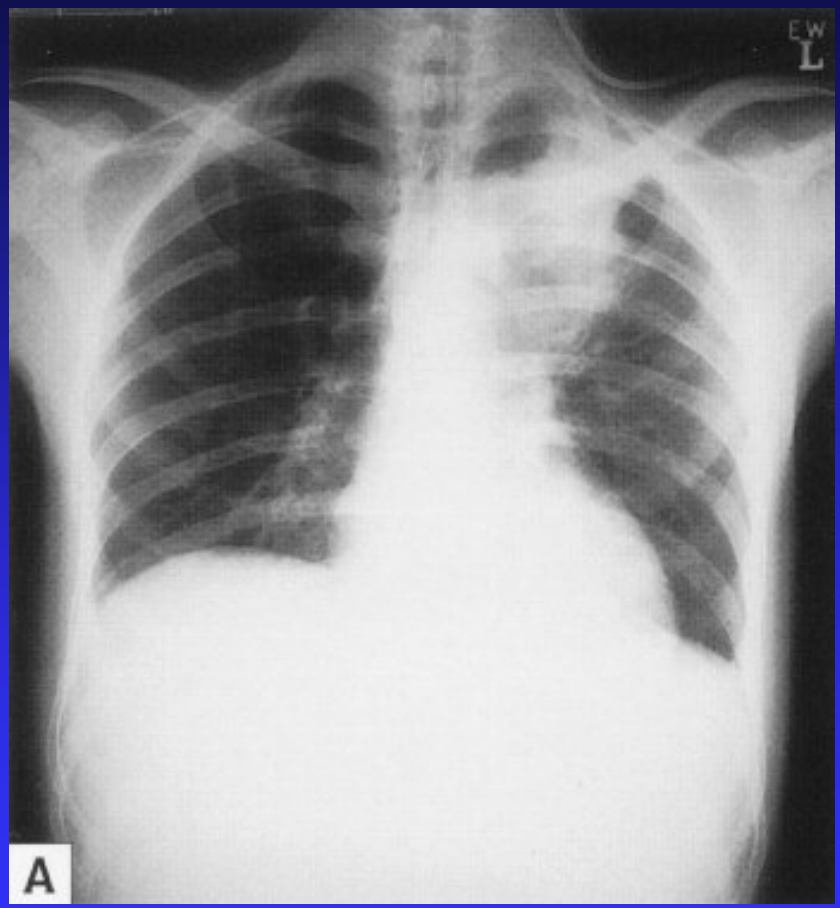


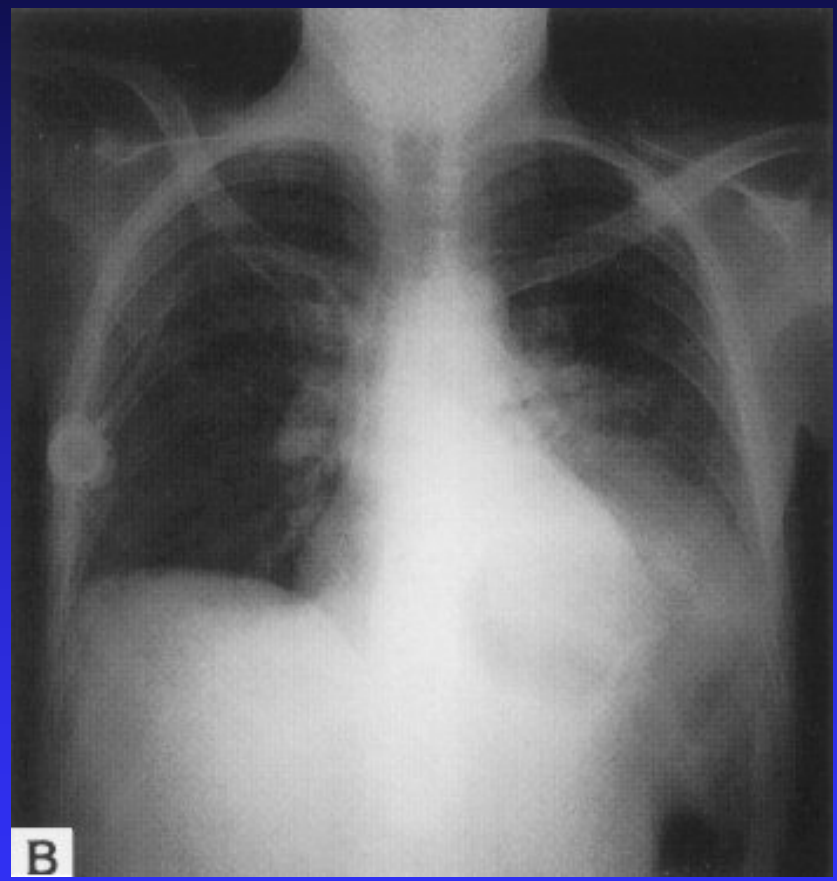
Oral Candidiasis(Thrush) vs. Oral Hairy Leukoplakia (OHL)



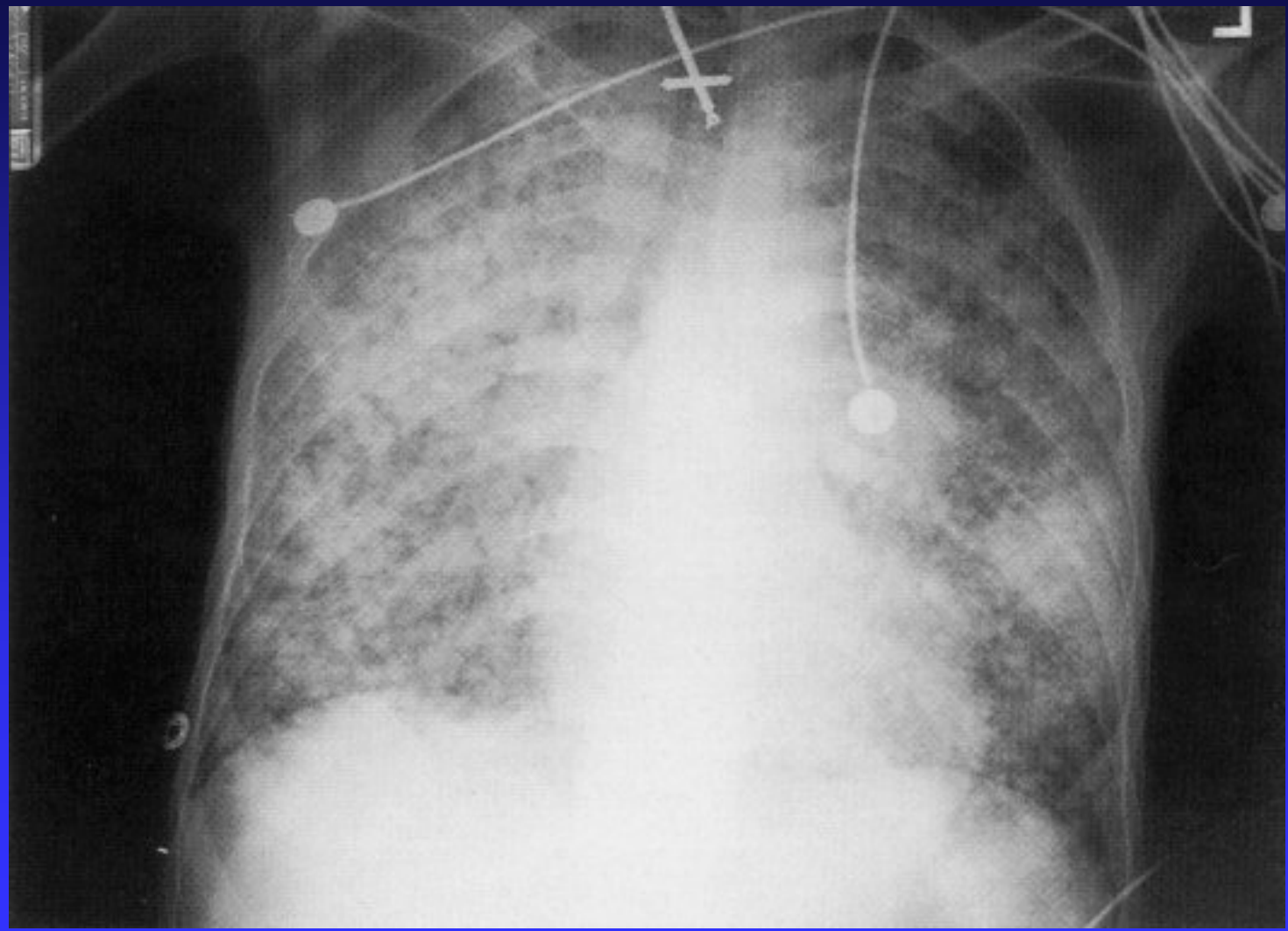


AIDS related Tuberculosis

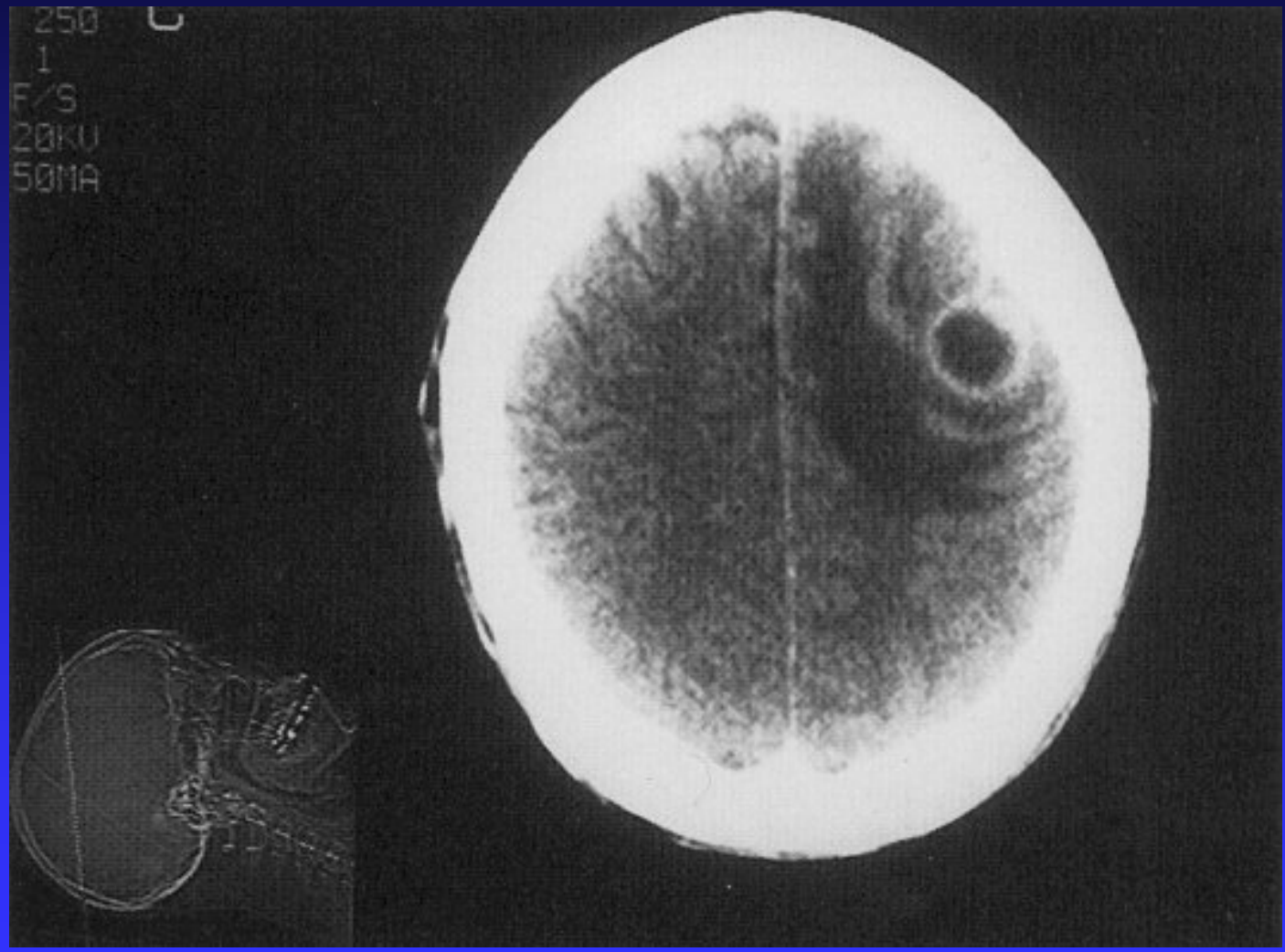




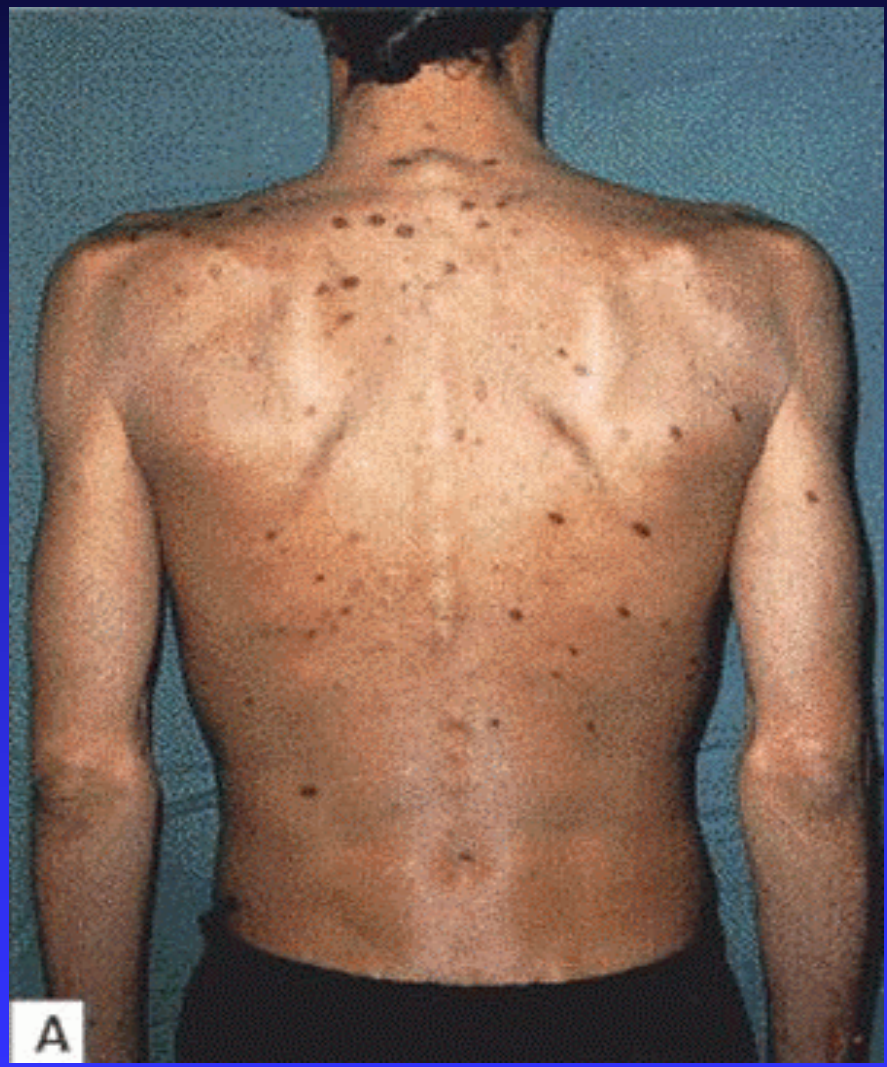
Pneumocystis Carinii Pneumonia



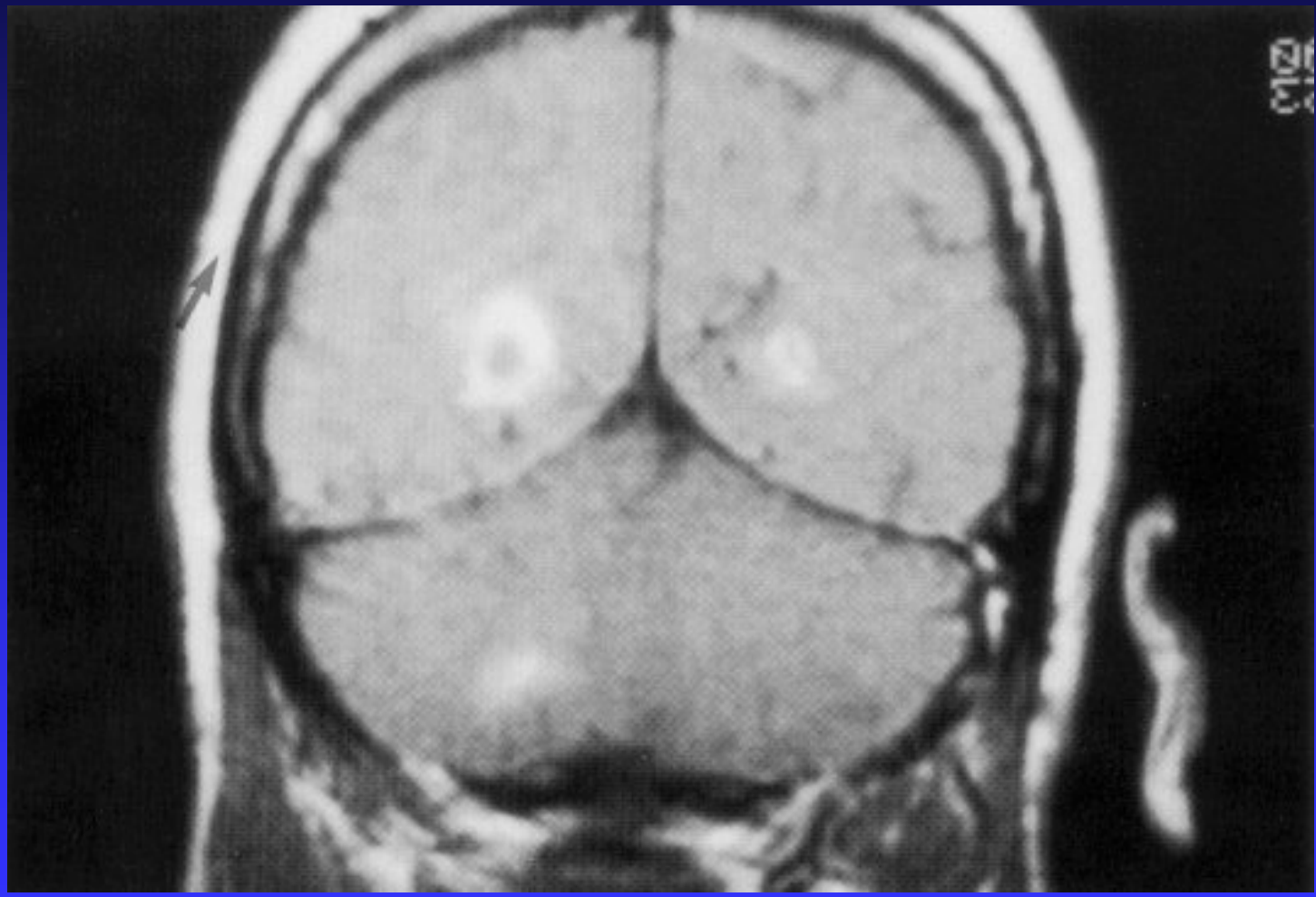
Cerebral Toxoplasmosis:CAT-SCAN



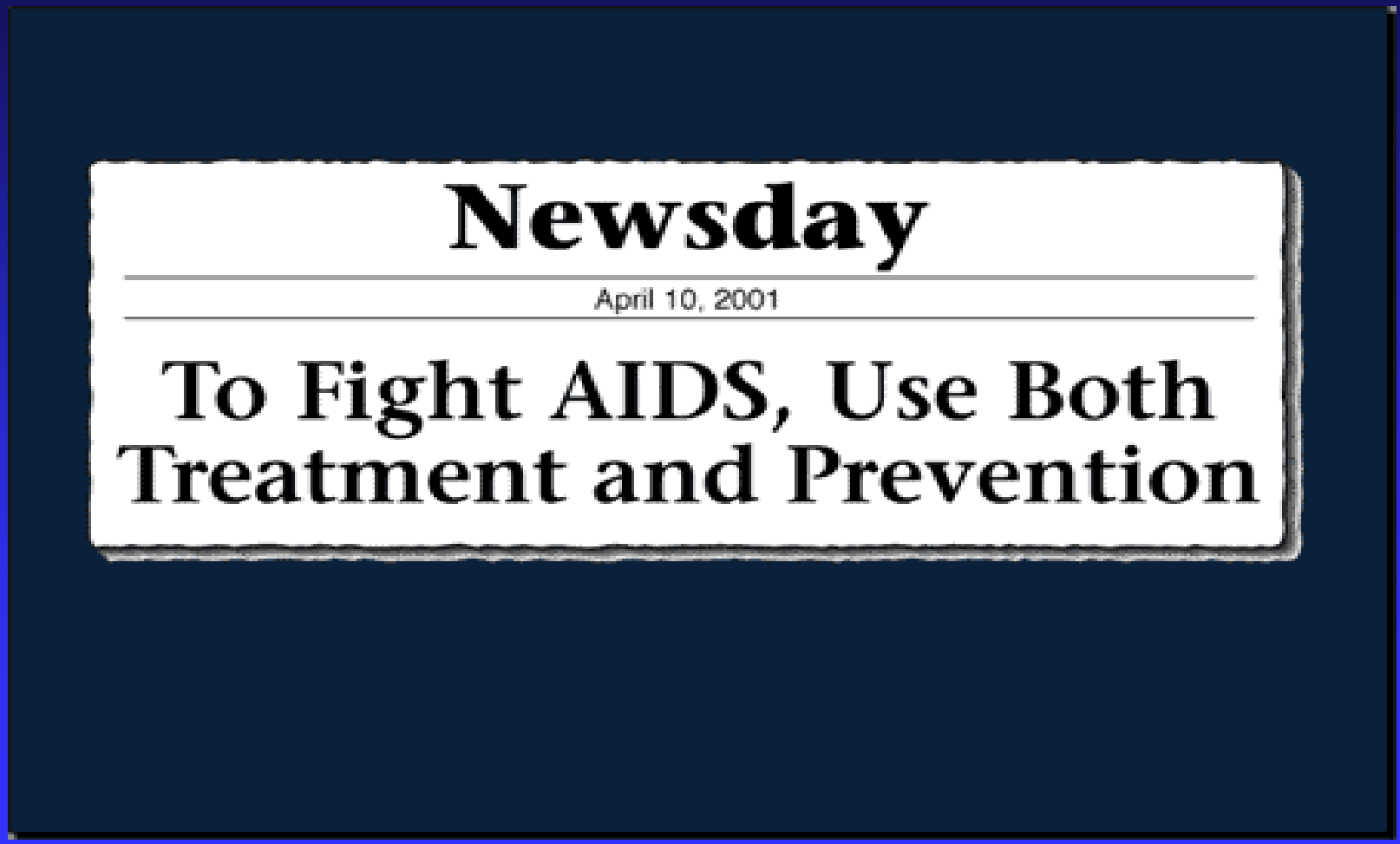
Kaposi Sarcoma



Cerebral Toxoplasmosis: MRI



Prevention vs. Rx

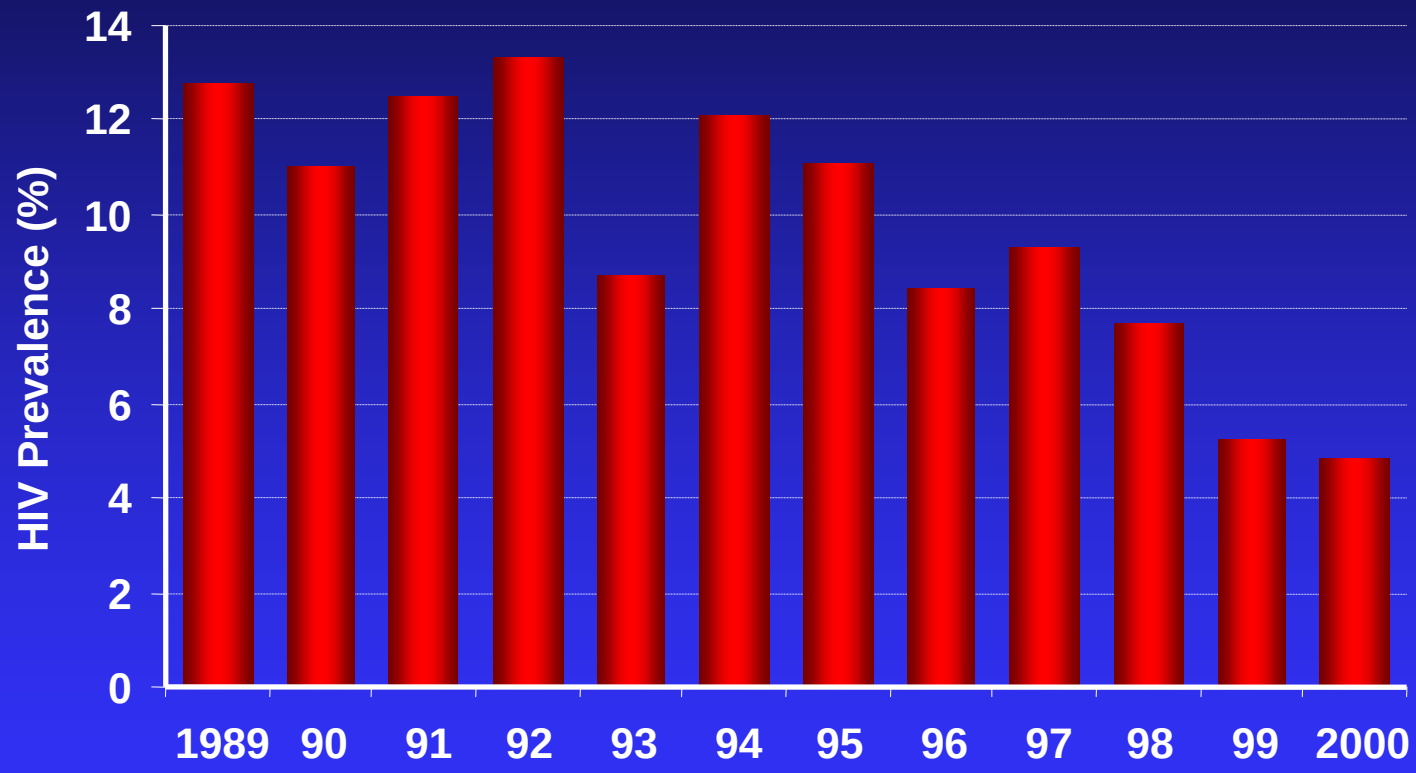


Newsday

April 10, 2001

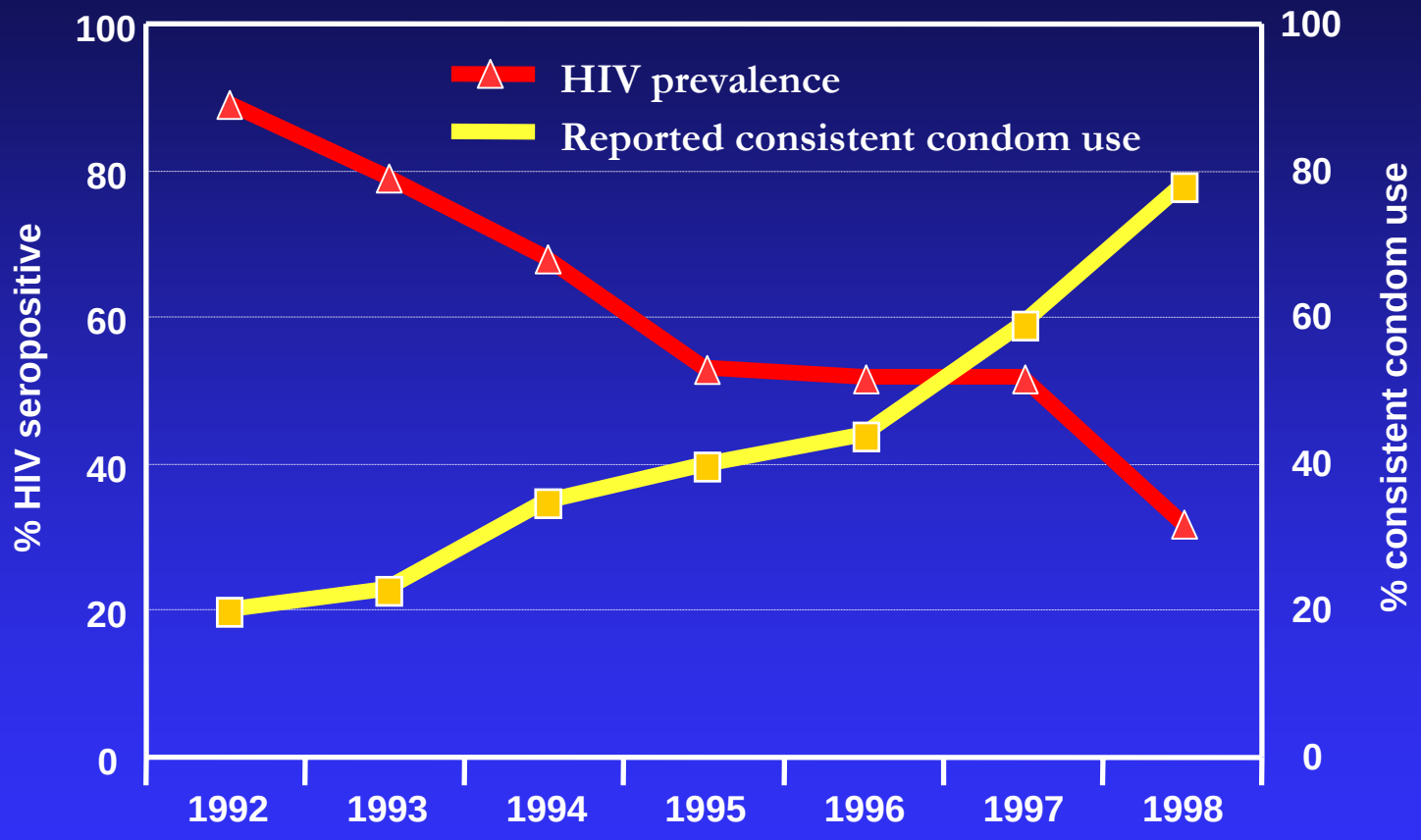
To Fight AIDS, Use Both Treatment and Prevention

Prevalence among pregnant women, outside major urban areas, Uganda



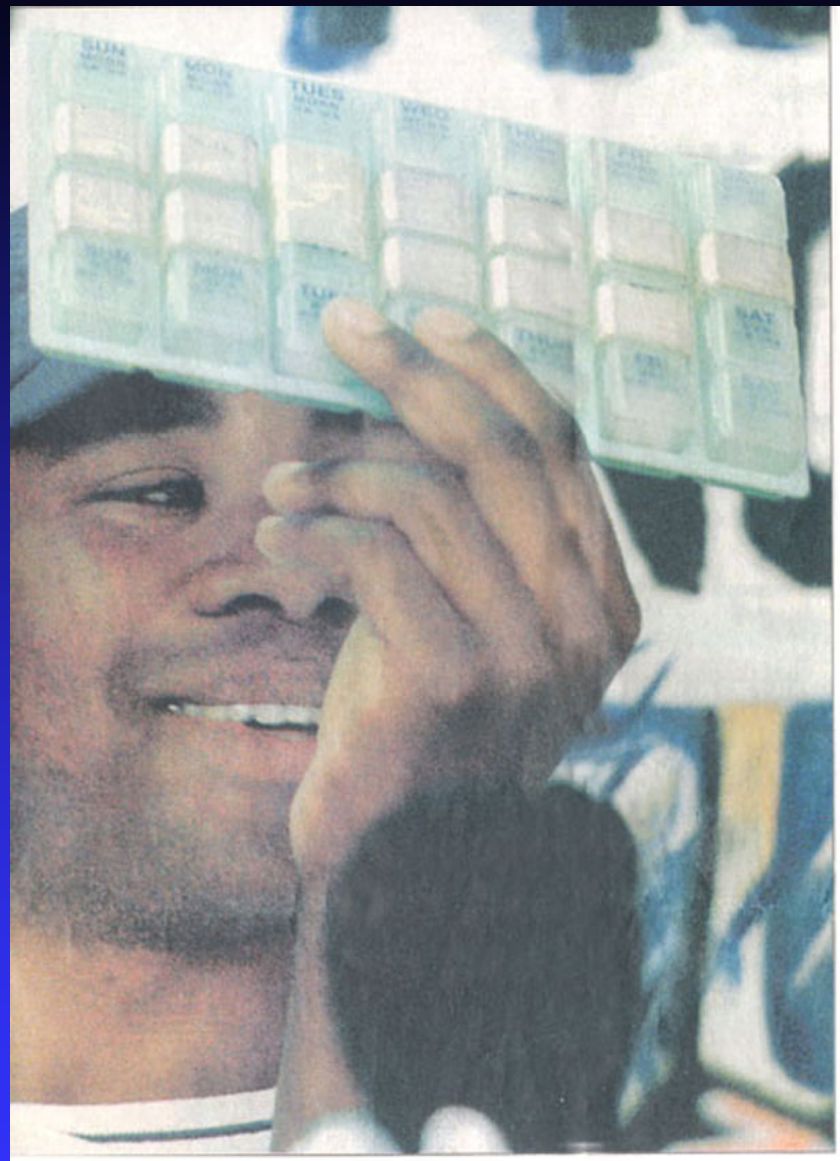
Source: Uganda National AIDS Programme

HIV prevalence and reported consistent condom use among female sex workers, Abidjan, Côte d'Ivoire, 1992-1998



Source: Ghys PD et al. (2002) *AIDS*

Patent Rights vs. Patient Rights



'Aids drugs made me well again'

LYNNE ALTENROXEL and JO-ANNE SMETHERHAM

DOCTORS gave Matthew Damane just a few years to live after he was diagnosed with HIV, the virus that causes Aids, in 1997.

At that time, life-saving Aids medicines, widely available in the West, were too expensive for poor people in countries like South Africa.

The brand-name medicines, which cost R1 400 a month, even with discounts offered by drug companies, are still too expensive.

But Damane, 25, from Khayelitsha, has had access to less expensive generic versions, imported from Brazil, and he credits the drugs with restoring his health.

"I am now well," he told a packed news conference in Johannesburg yesterday as he held up a plastic pill box. It has one pill compartment for each day of the week, helping him take his Aids medicines on schedule.

Damane, a nervous smile showing under his blue base-

activist groups announced it had imported the medicines from Brazil in violation of drug-company patent rights but with the full blessing of the Medicines Control Council (MCC).

Citing preliminary results from a pilot project in Khayelitsha, the activists said the Aids drugs had reduced the presence of the virus in people's bloodstreams to undetectable levels after less than one year of treatment. They said patients were getting off their deathbeds and returning to productive work and family lives.

"We literally resuscitated people," said Eric Goemaere, who heads the Aids clinic run by Médecins Sans Frontiéres (MSF) in Khayelitsha.

The preliminary results of the Khayelitsha pilot study – which has reported findings for 85 patients taking the Aids medicines – are the first evidence from a township clinic in South Africa that the Aids drugs can be taken on a long-term basis and can have the same dramatic effect in improving health as they have had in industrialised countries.

ment Action Campaign (TAC), Oxfam and Cosatu – pointed to the findings yesterday to urge the government to set up pilot projects to provide the drugs to symptomatic Aids patients in each province. They also referred to the results to support their argument that the government should follow Brazil's lead and make its own low-cost generic versions of the drugs.

"It is difficult but it is feasible in developing-country conditions," said Mark Heywood, TAC secretary.

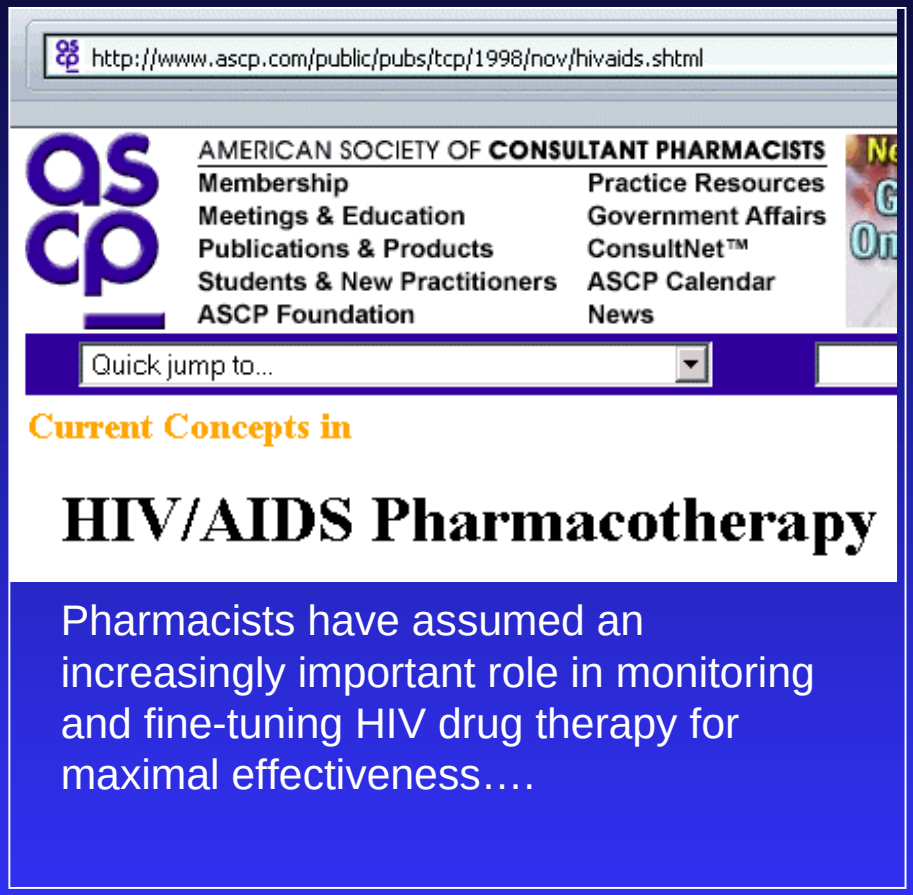
The government did not comment on the activists' calls. It said the MCC would check whether the Brazil import was legal.

The drug companies that own the patent rights to the drugs do not have plans to sue the activists. Peter Moore, medical director at GlaxoSmithKline, said the company would wait for the MCC to act.

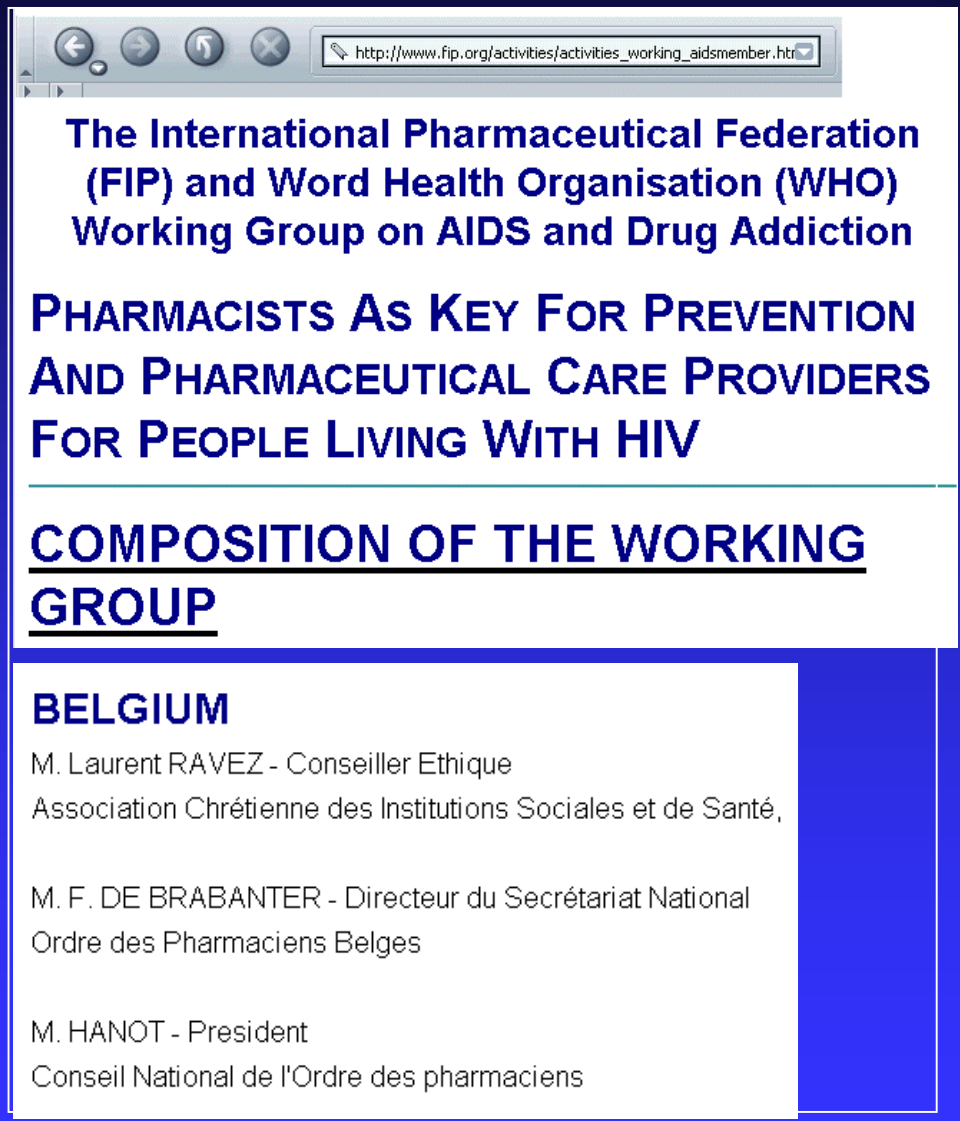
Boehringer-Ingelheim spokesman Kevin McKenna said he was not surprised at the developments.

"I don't think we're falling off our chairs at the moment,"

SIDA et pharmaciens …



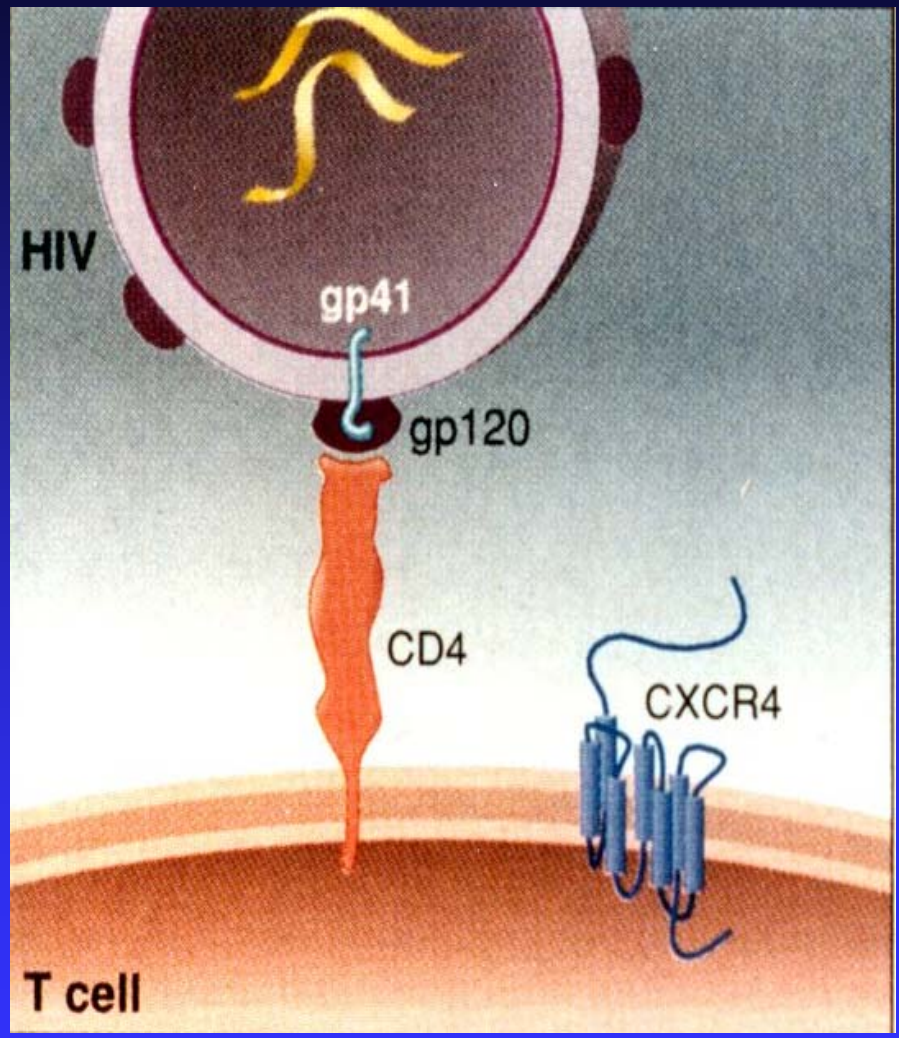
Pharmacists have assumed an increasingly important role in monitoring and fine-tuning HIV drug therapy for maximal effectiveness….



HIV REPLICATIVE CYCLE

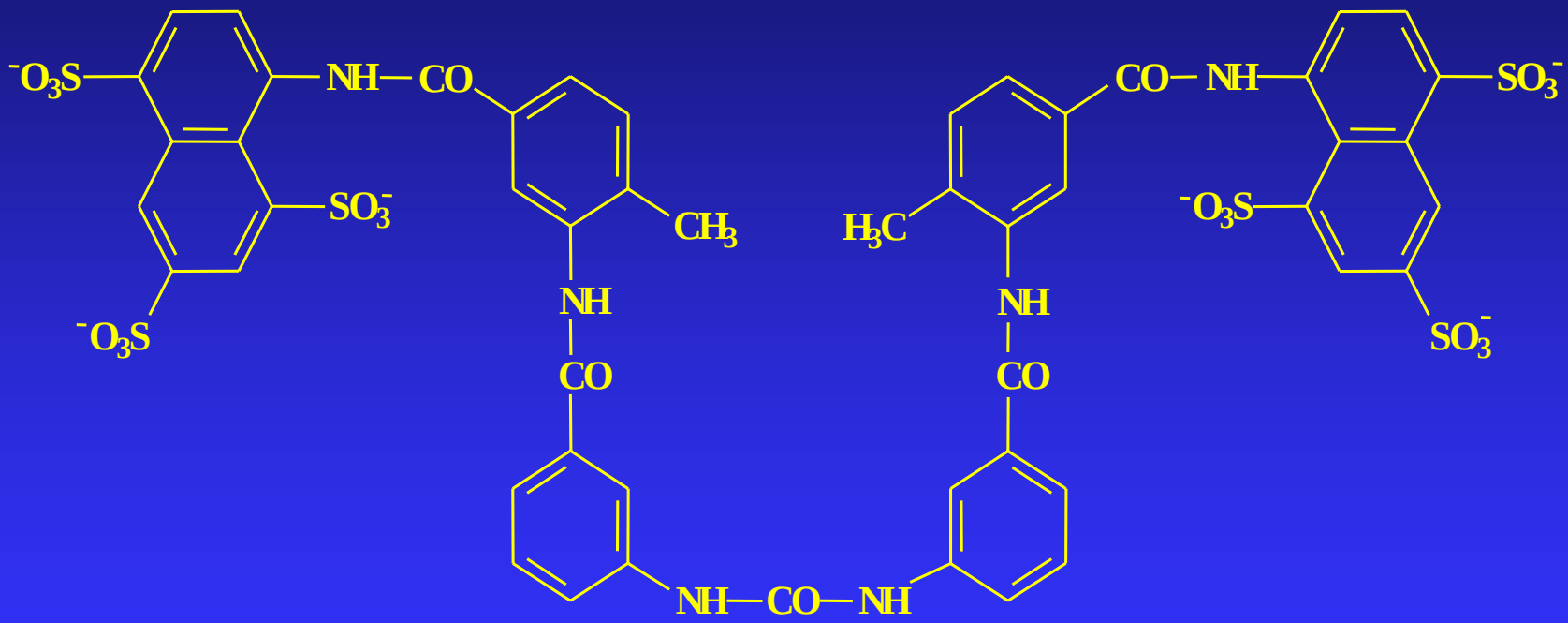
1. **Virus adsorption**
2. **Virus-cell fusion**
3. **Virus uncoating**
4. **Reverse transcription**
5. **Proviral DNA integration**
6. **Proviral DNA replication**
7. **Proviral DNA transcription to viral mRNA**
8. **Viral mRNA translation to viral precursor proteins**
9. **Maturation (proteolysis/myristoylation/glycosylation)**
10. **Budding (Assembly/Release)**

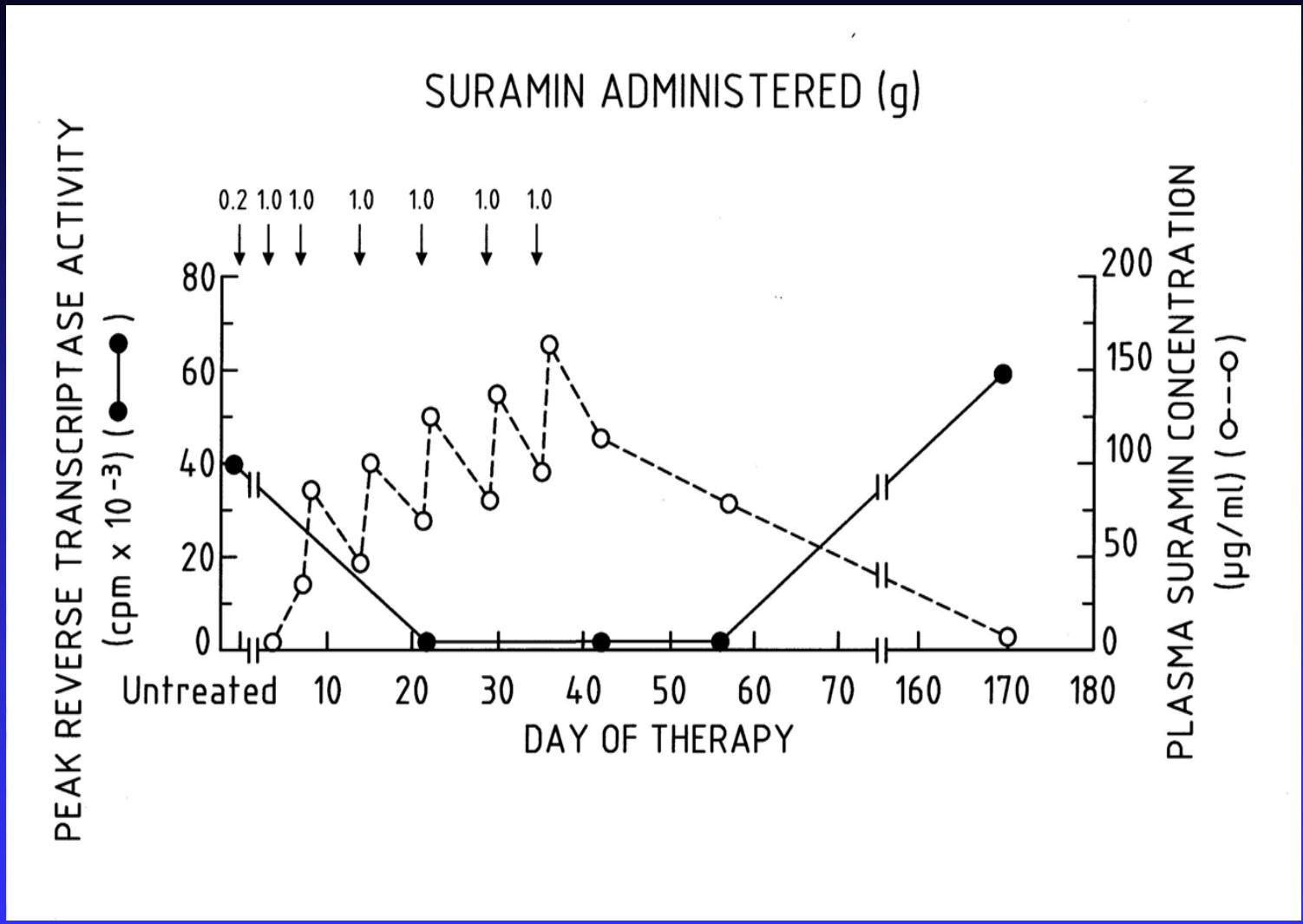
VIRUS ADSORPTION



J. Cohen, Science 274, 502 (1996)

Suramin




SURAMIN ADMINISTERED (g)
0.2 1.0 1.0 1.0 1.0 1.0 1.0
PEAK REVERSE TRANSCRIPTASE ACTIVITY
(cpm x 10⁻³) (●—●)
PLASMA SURAMIN CONCENTRATION
(µg/ml) (○--○)
80
60
40
20
0
200
150
100
50
0
Untreated 10 20 30 40 50 60 70 160 170 180
DAY OF THERAPY

HIV REPLICATIVE CYCLE

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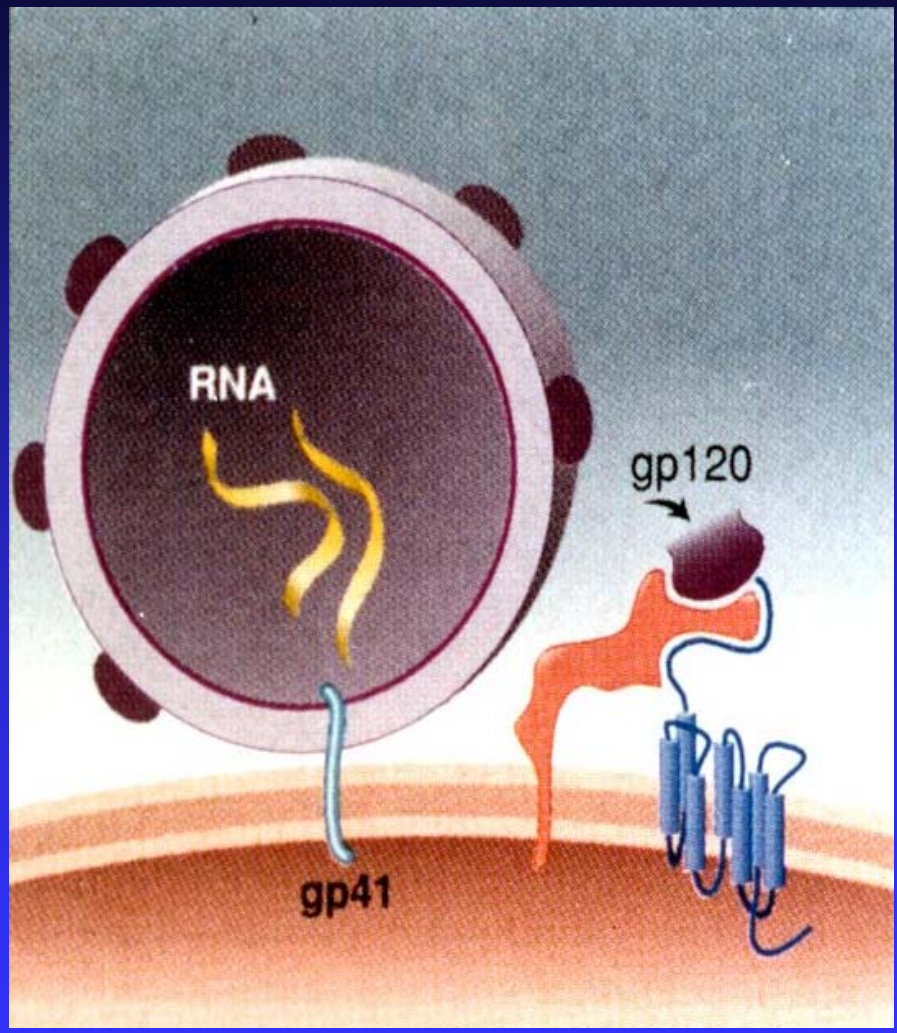
VIRUS-CELL FUSION

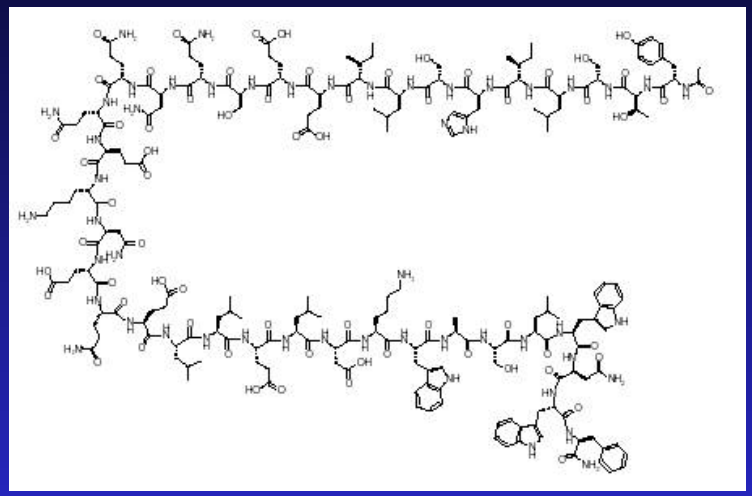


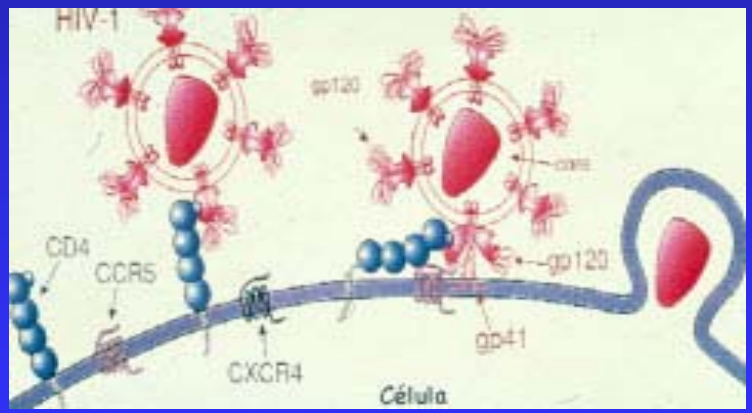
J. Cohen, Science 274, 502 (1996)

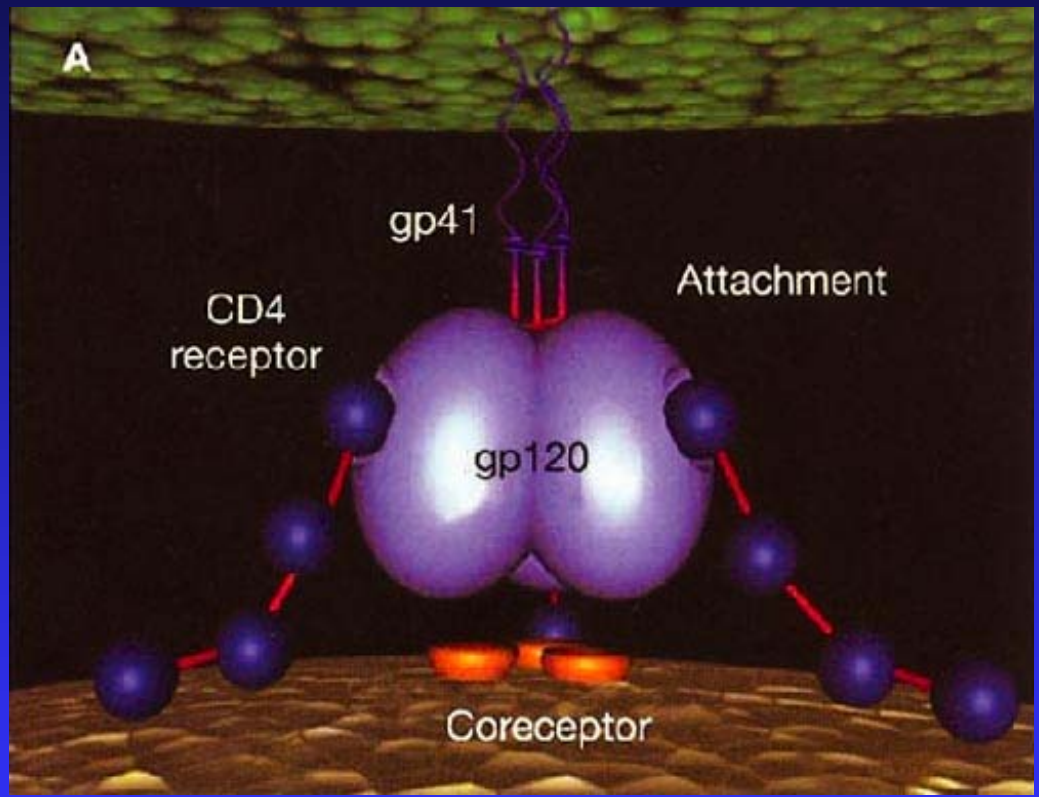
TAK-779

SCH-C
(SCH-351125)

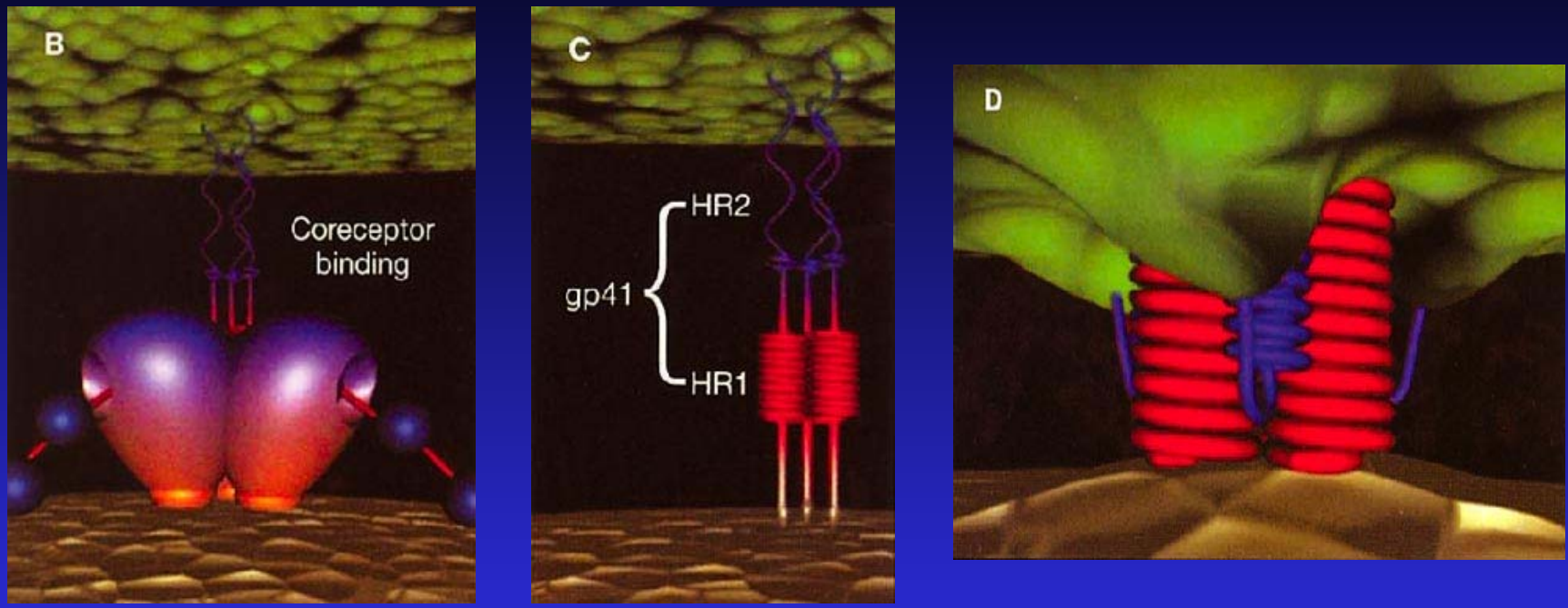
Inhibiteur de fusion: l'enfuvirtide







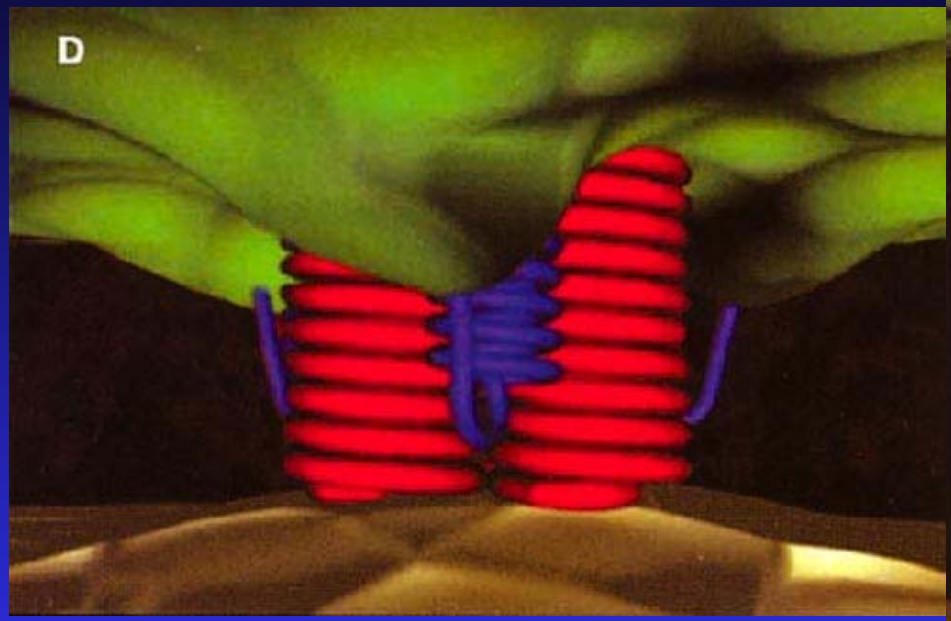
Inhibiteur de fusion: l'enfuvirtide

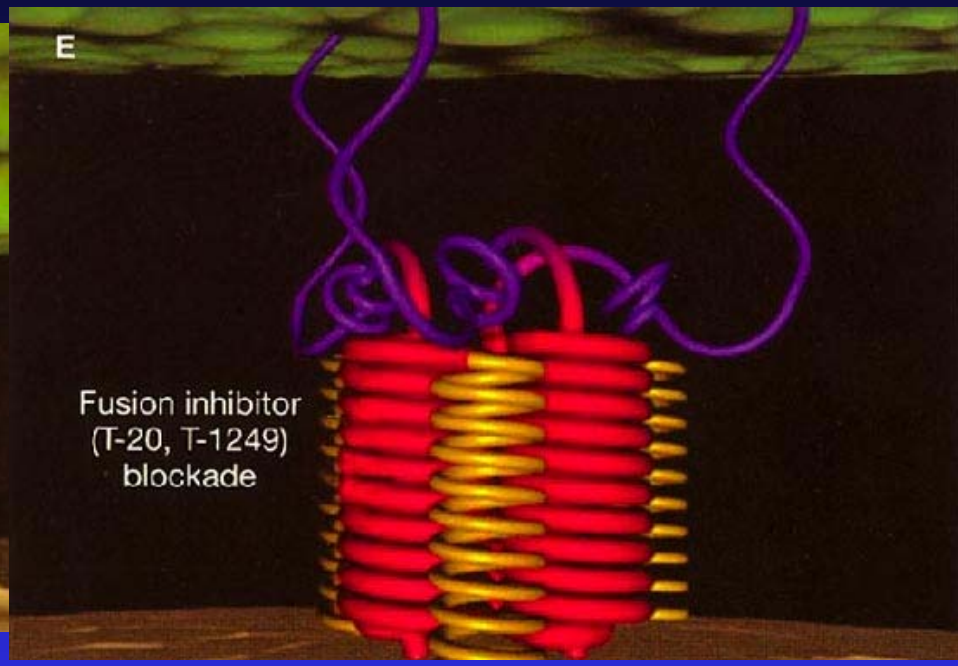


The extracellular domain of gp41 contains a fusion peptide (FP) and 2 helical regions (HRs), HR1 and HR2. The FP region is made up of hydrophobic, glycine-rich residues essential for initiation of penetration into target cell membranes [1, 3, 4]. When fusion occurs, FP inserts into the target cell membrane, and HR1 and HR2 alter their conformation to form a 6-helix structure. The process results in the formation of a fusion pore through which the HIV capsid passes into the CD4+ cell.

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106

Inhibiteur de fusion: l'enfuvirtide





ENF is a synthetic peptide corresponding to the 36-aa sequence of the HR2 domain in gp41. ENF binds to the HR1 domain in the gp41 subunit of the viral envelope protein, which prevents the formation of the 6-helix structure and interferes with the conformational changes required for membrane fusion. ENF, in effect, binds to a structural intermediate of the fusion process, which impedes the transition of gp41 into a fusion-active state

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106

Clinical uses of entifurvide

- must be used in combination with other antiretrovirals
- lack a bioavailable oral formulation (repeated subcutaneous injections are necessary)
- Therefore, use is restricted to patients with advanced disease who have few remaining antiretroviral treatment options (deep-salvage therapy)

Cervia & Smith, Clinical Infectious Diseases 2003;37:1102-1106

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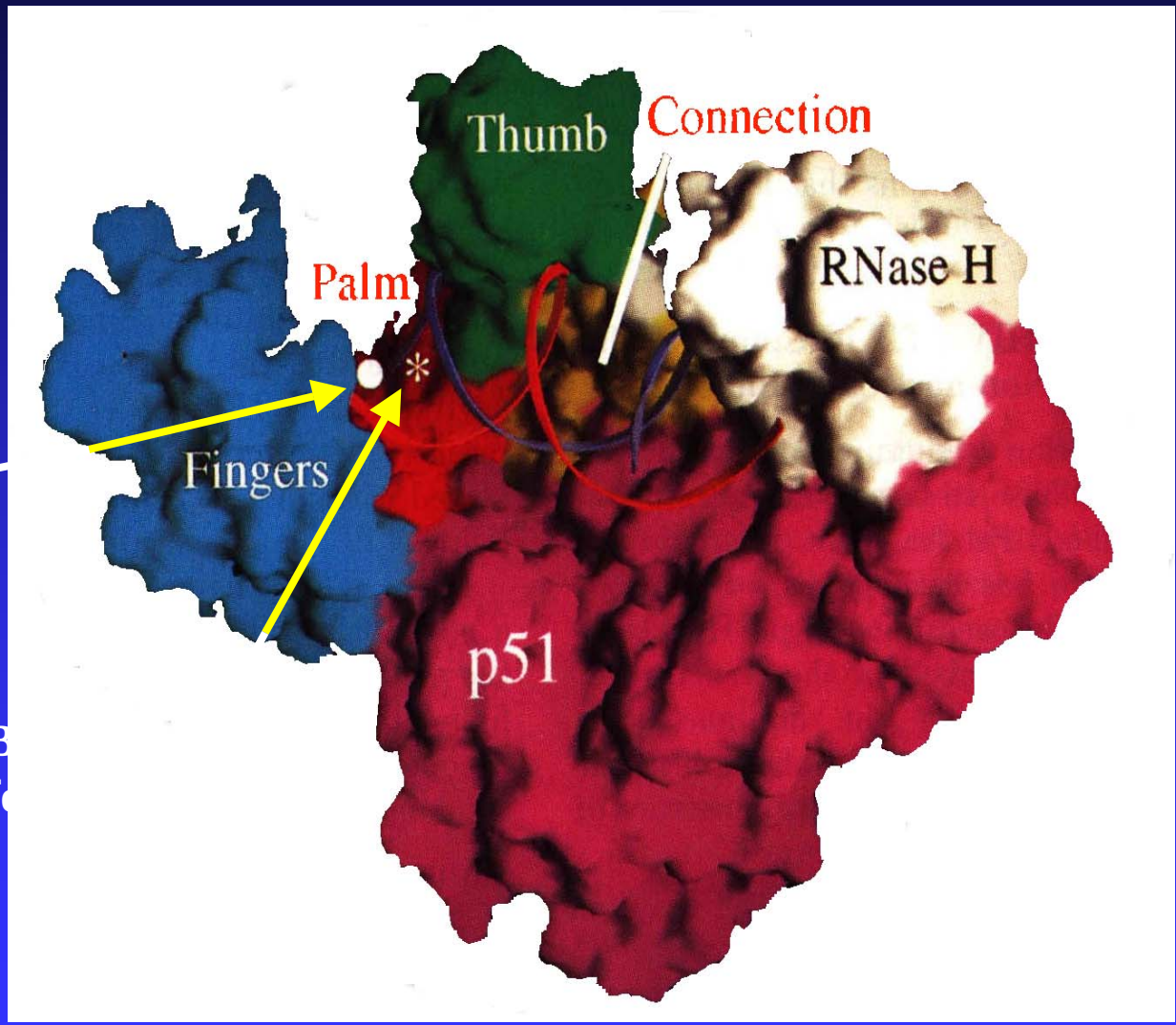
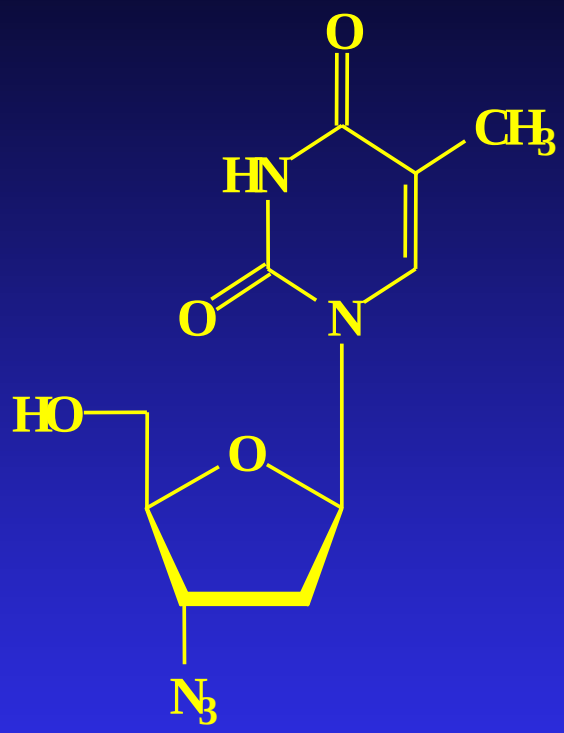
HIV Reverse Transcriptase

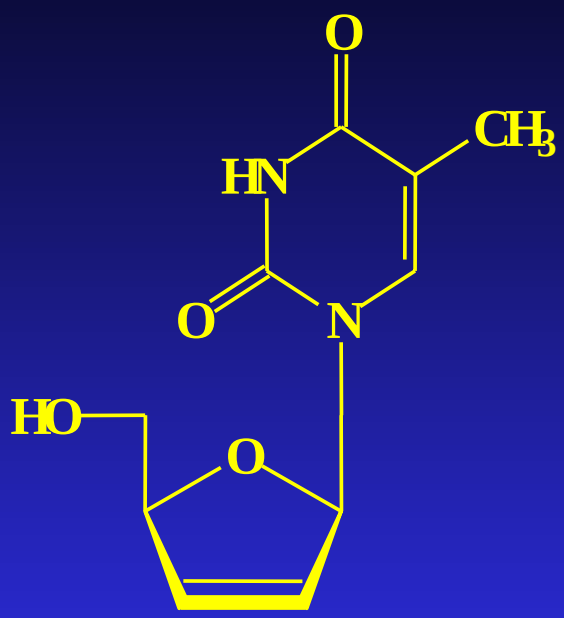


Binding site for NRTIs and NtRTIs

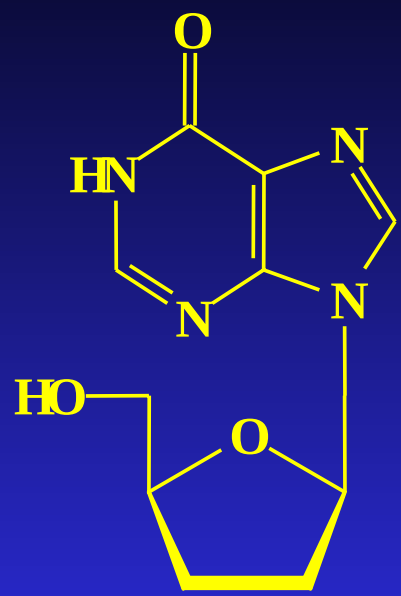


Zidovudine

3’-Azido-2’,3’-dideoxythymidine
AZT

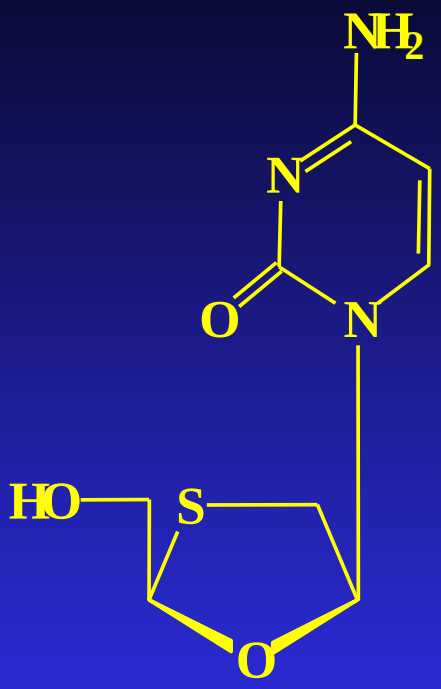


2’,3’-Didehydro-
2’,3’-dideoxythymidine
D4T



Didanosine

2’,3’-Dideoxyinosine
DDI

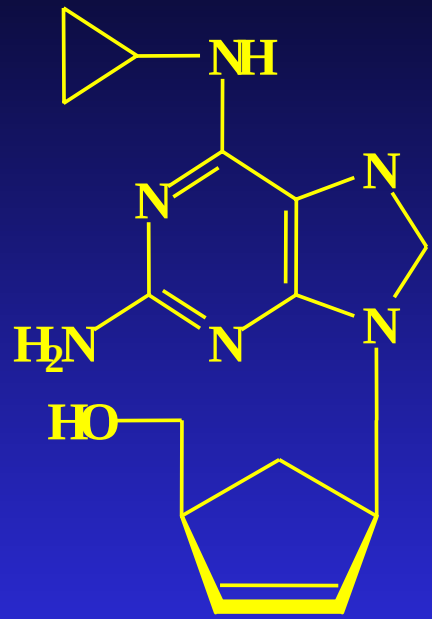


Lamivudine

2’,3’-Dideoxy-3’-thiacytidine
3TC

Zalcitabine

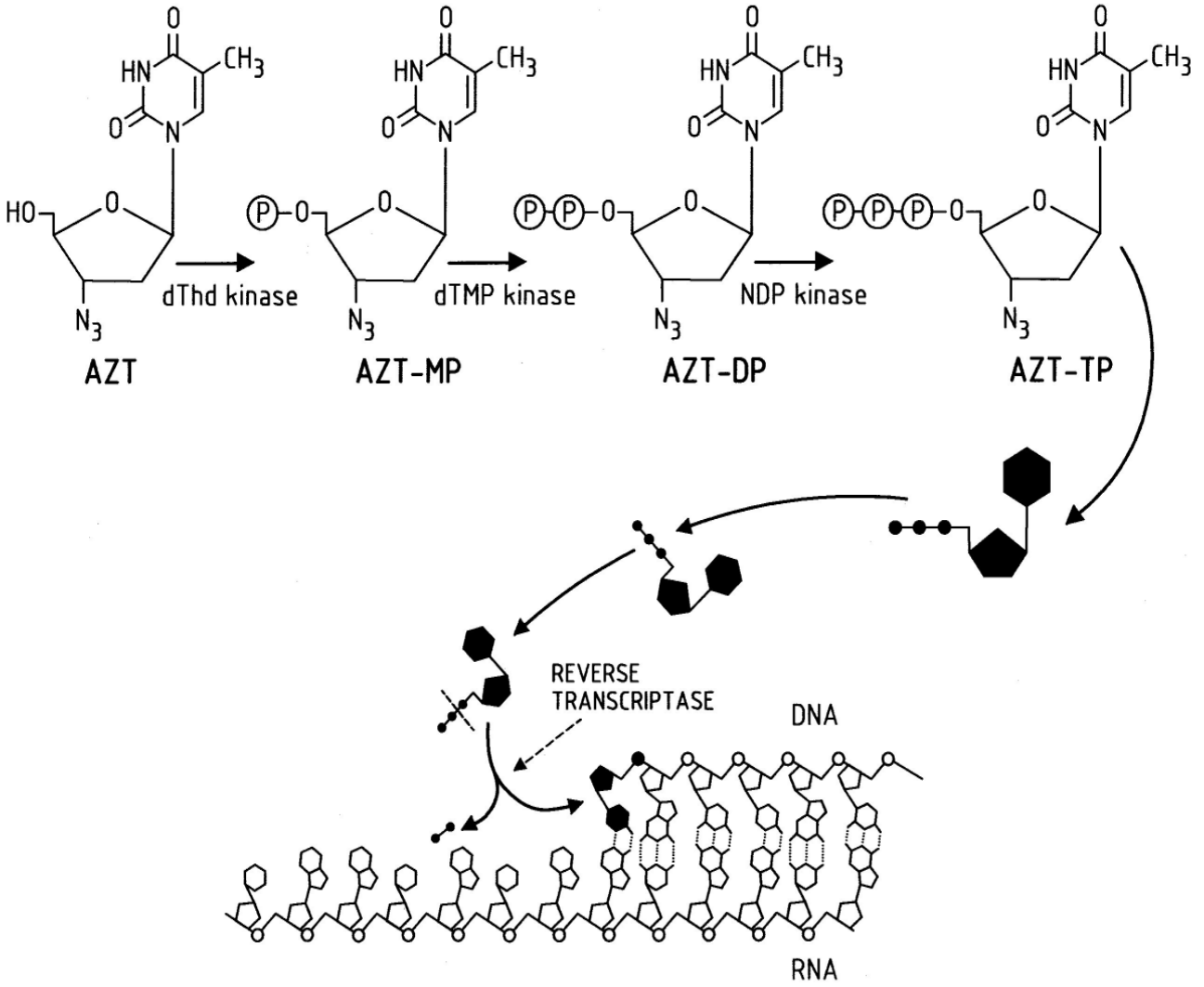
2’,3’-Dideoxycytidine
DDC

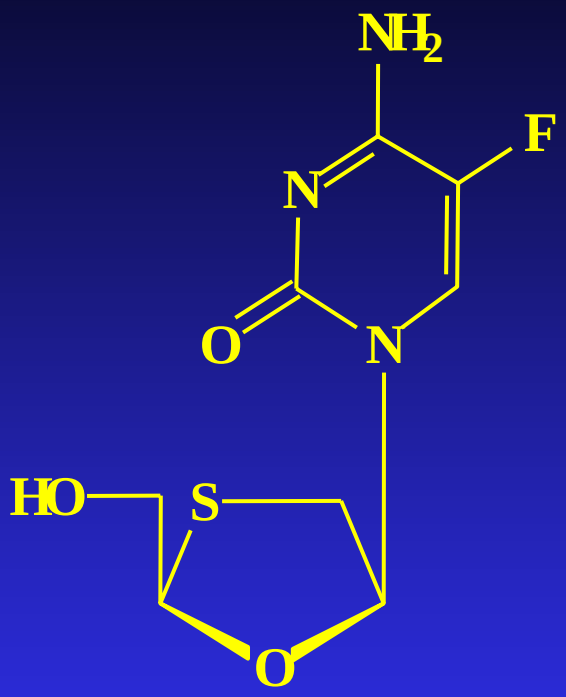


Abacavir

1592U89

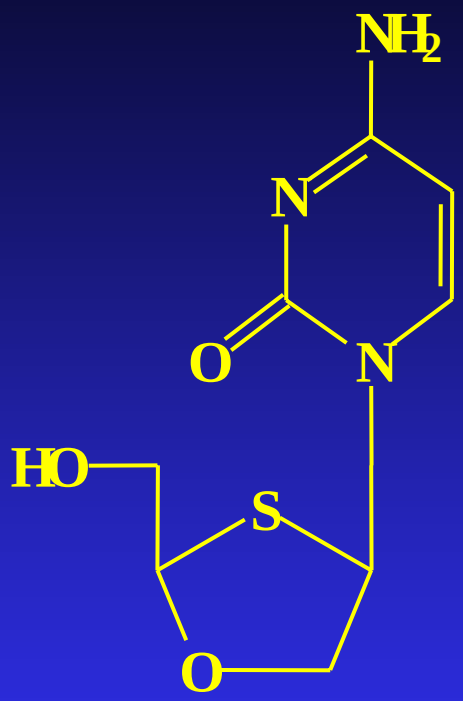
Mechanism of action of 2',3'-dideoxynucleoside analogues, as exemplified for AZT



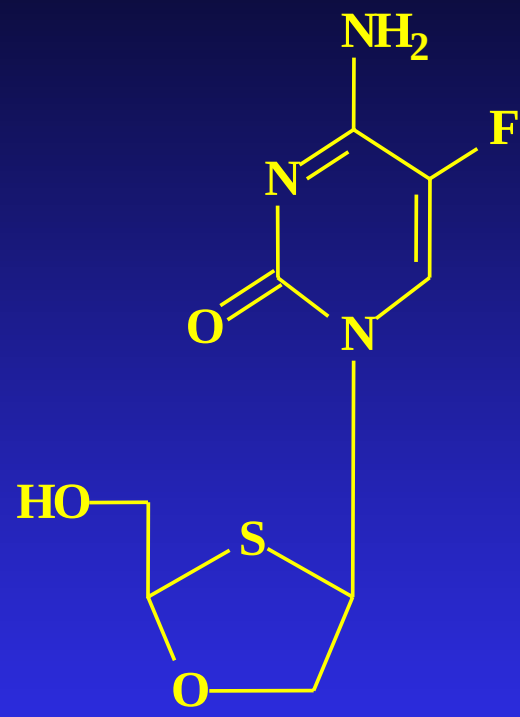


Emtricitabine

2’,3’-dideoxy-3’-thia-5-fluorocytidine (-)FTC



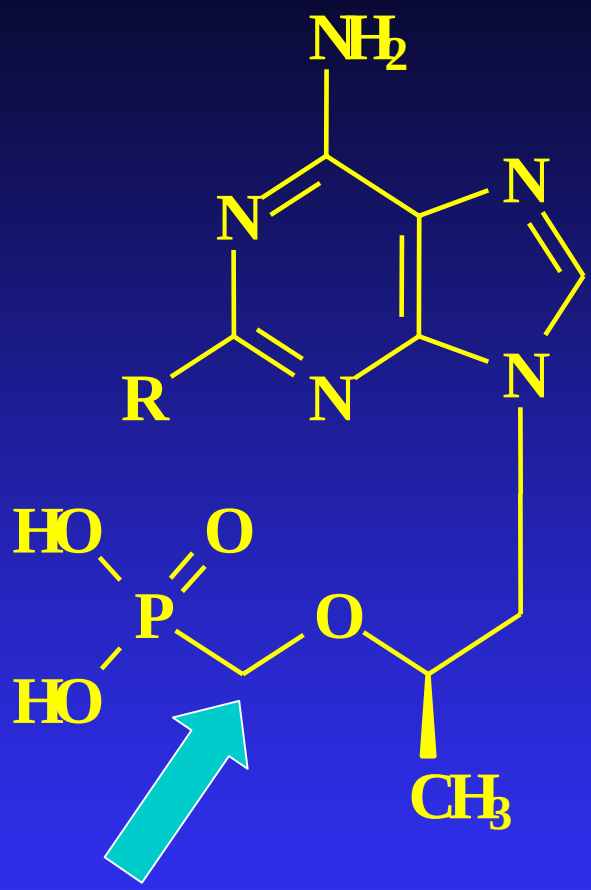
(±)2’-deoxy-3’-oxa-4’-thiacytidine (dOTC)



FdOTC

R = H : PMEA

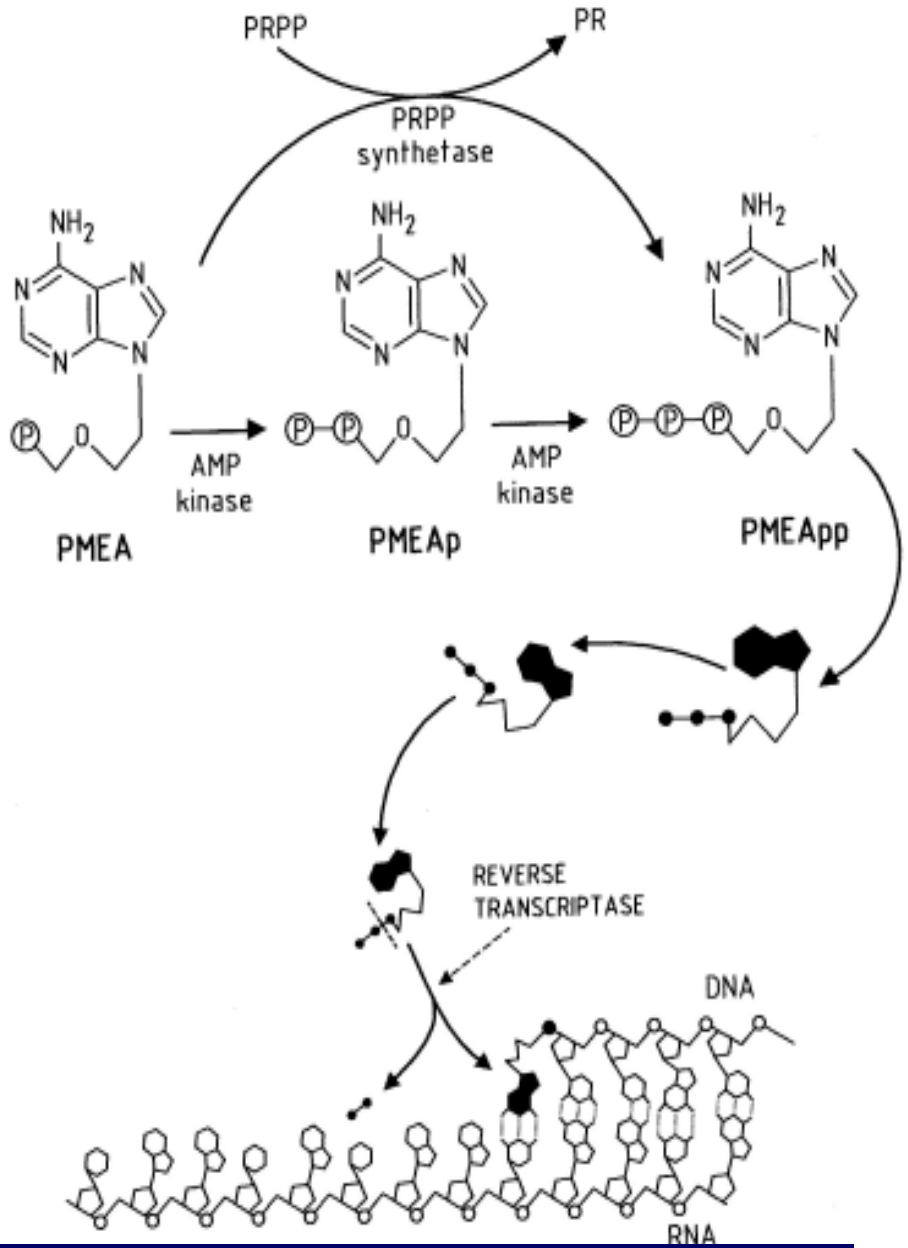
adefovir



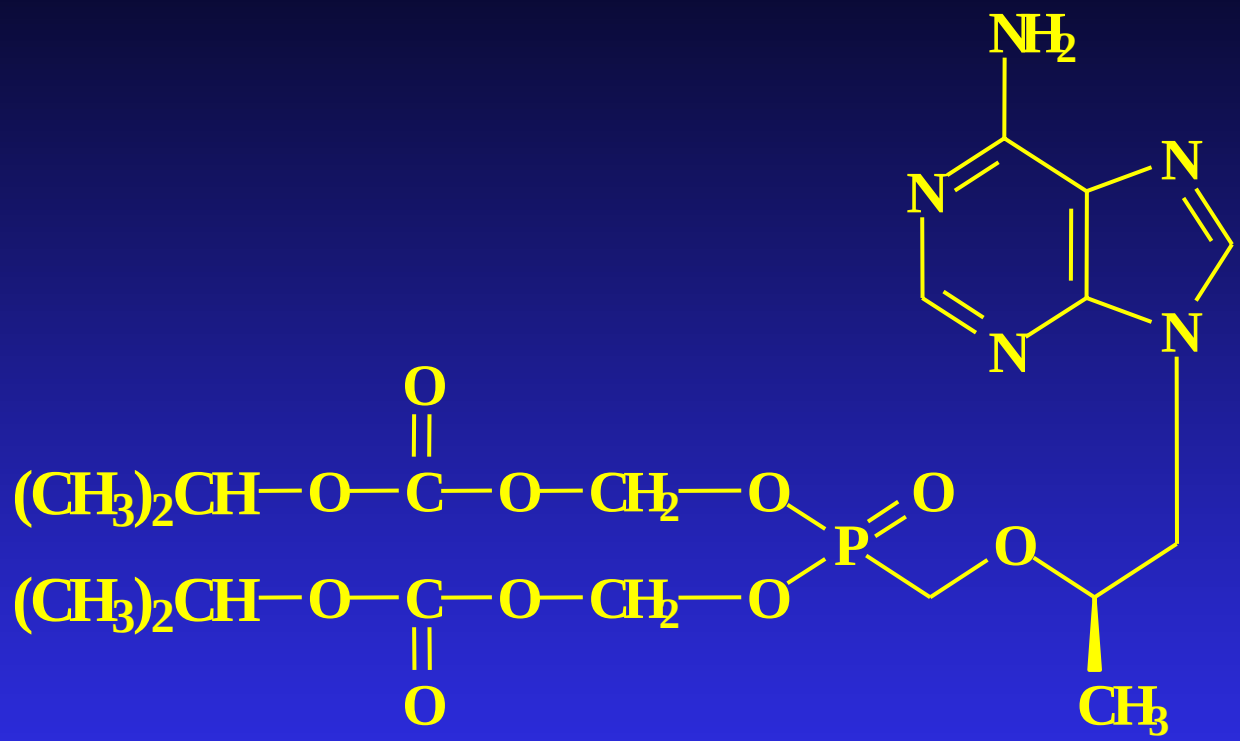
R = H : (*R*)-PMPA

tenofovir

Mechanism of action of adefovir (PMEA)



Similar mechanism of action applicable to tenofovir (PMPA)

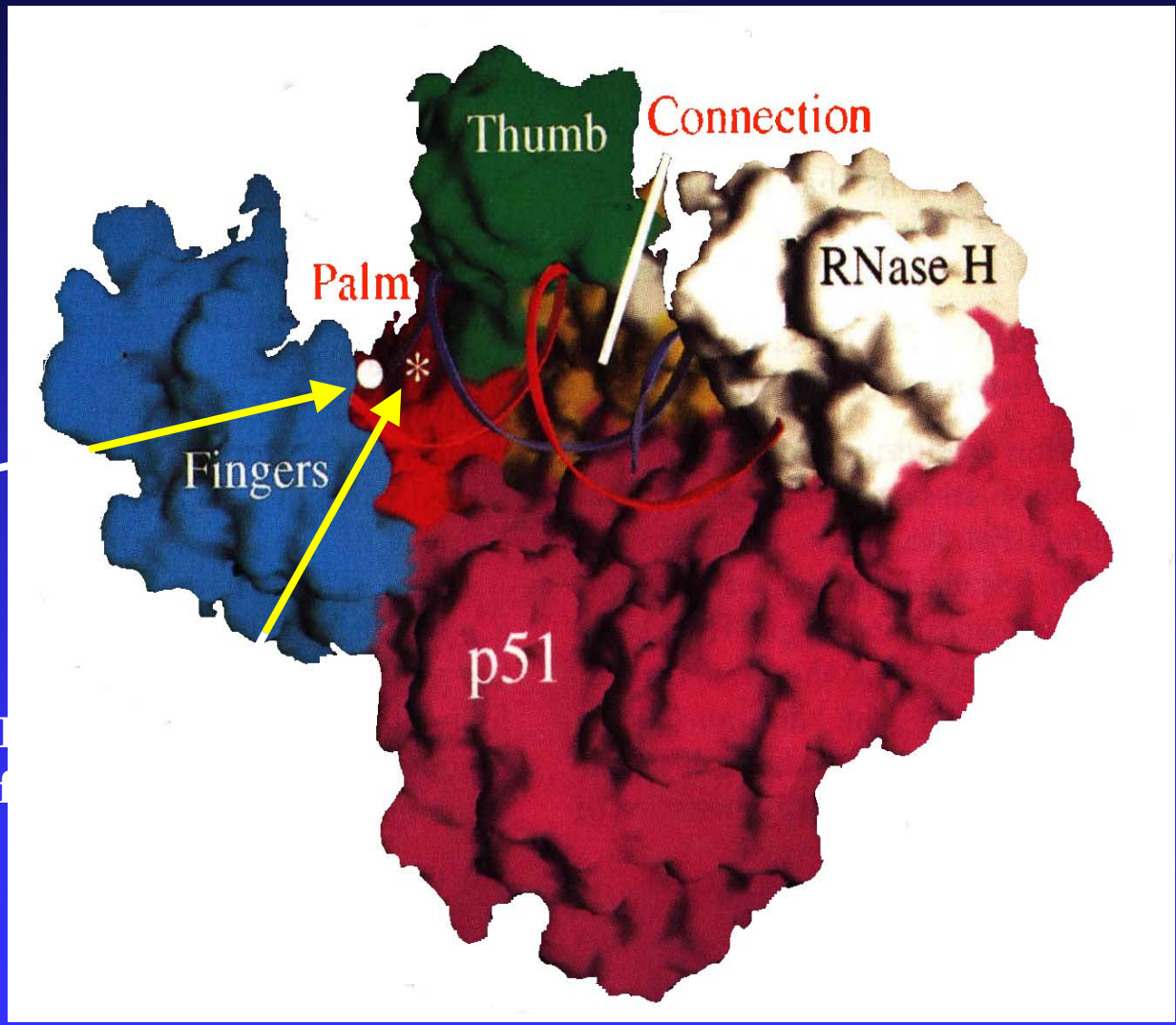


fumarate

bis(POC)-PMPA
Tenofovir disoproxil
Viread®

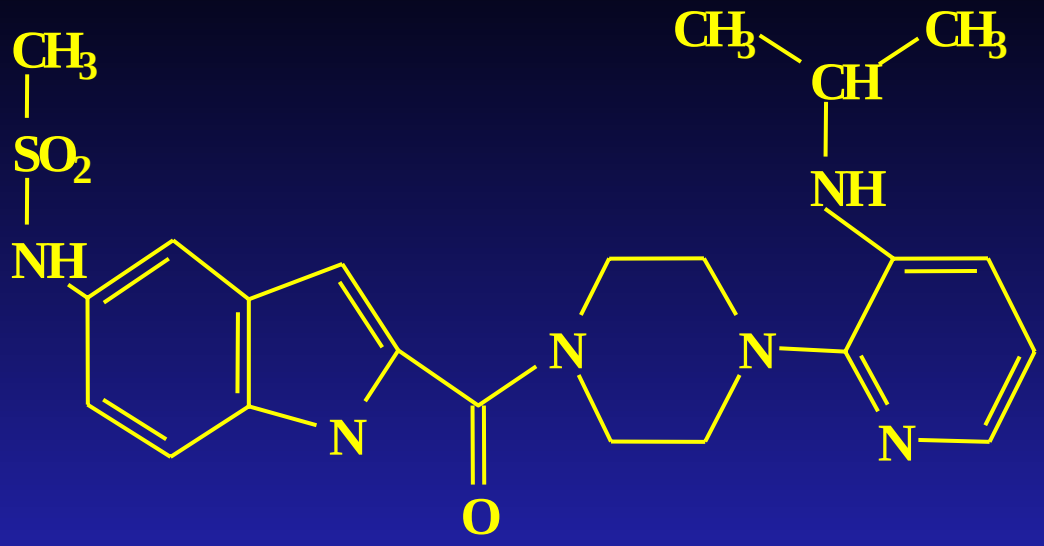
HIV Reverse Transcriptase

Binding site for NRTIs and NtRTIs

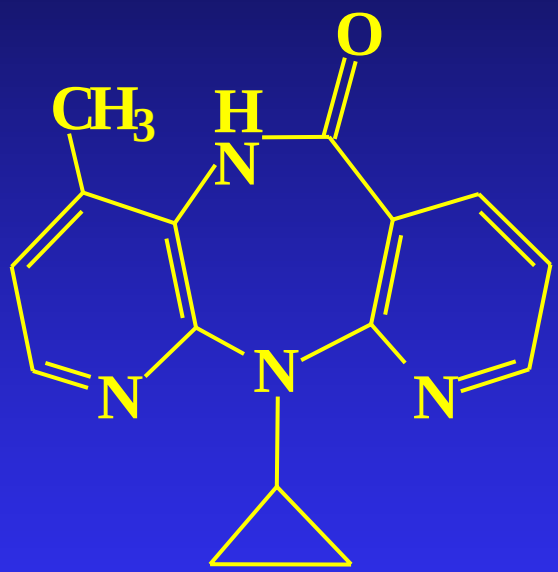


U-90152S

Delavirdine



• CH_3SO_3H



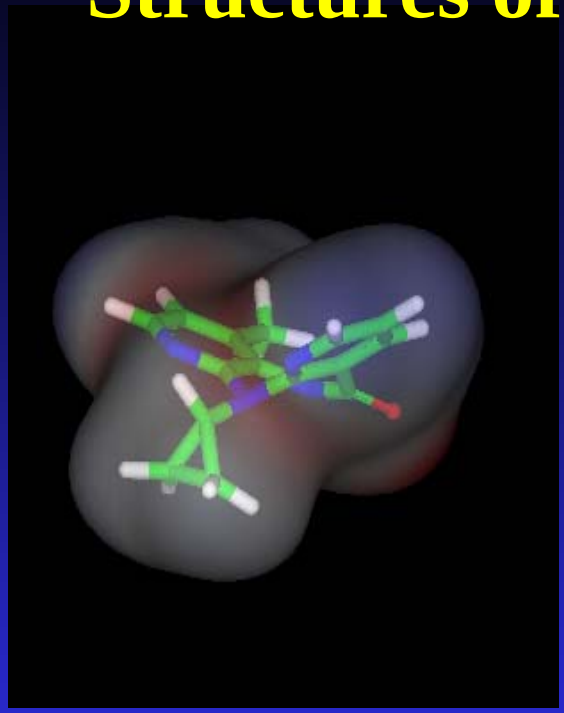
Nevirapine

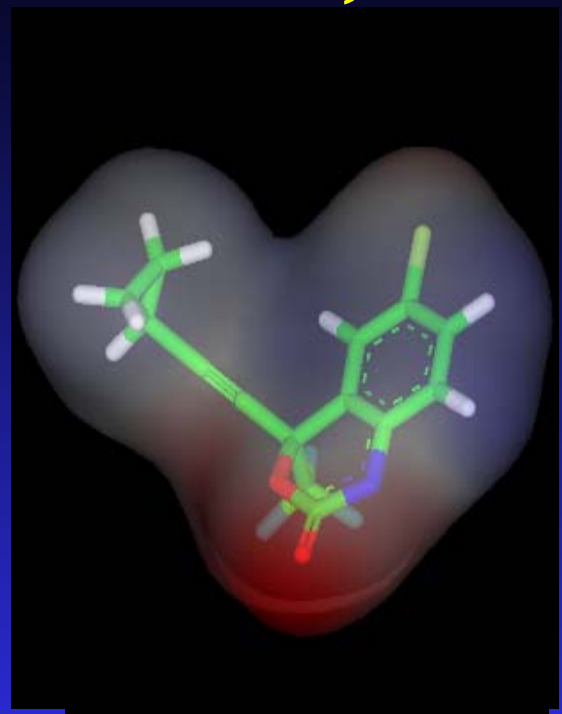
BI-RG-587

Benzoxazinone

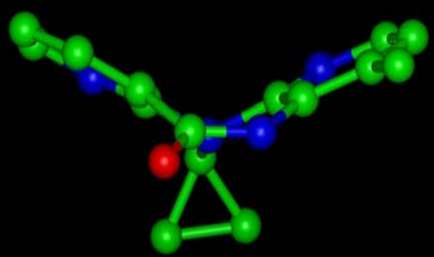
Efavirenz

Structures of classical NNRTI's, ...

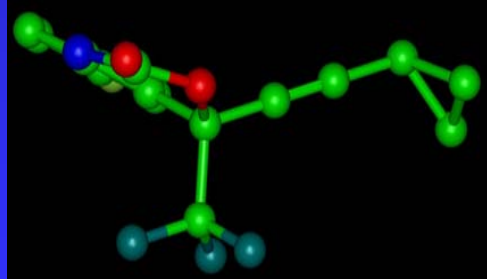




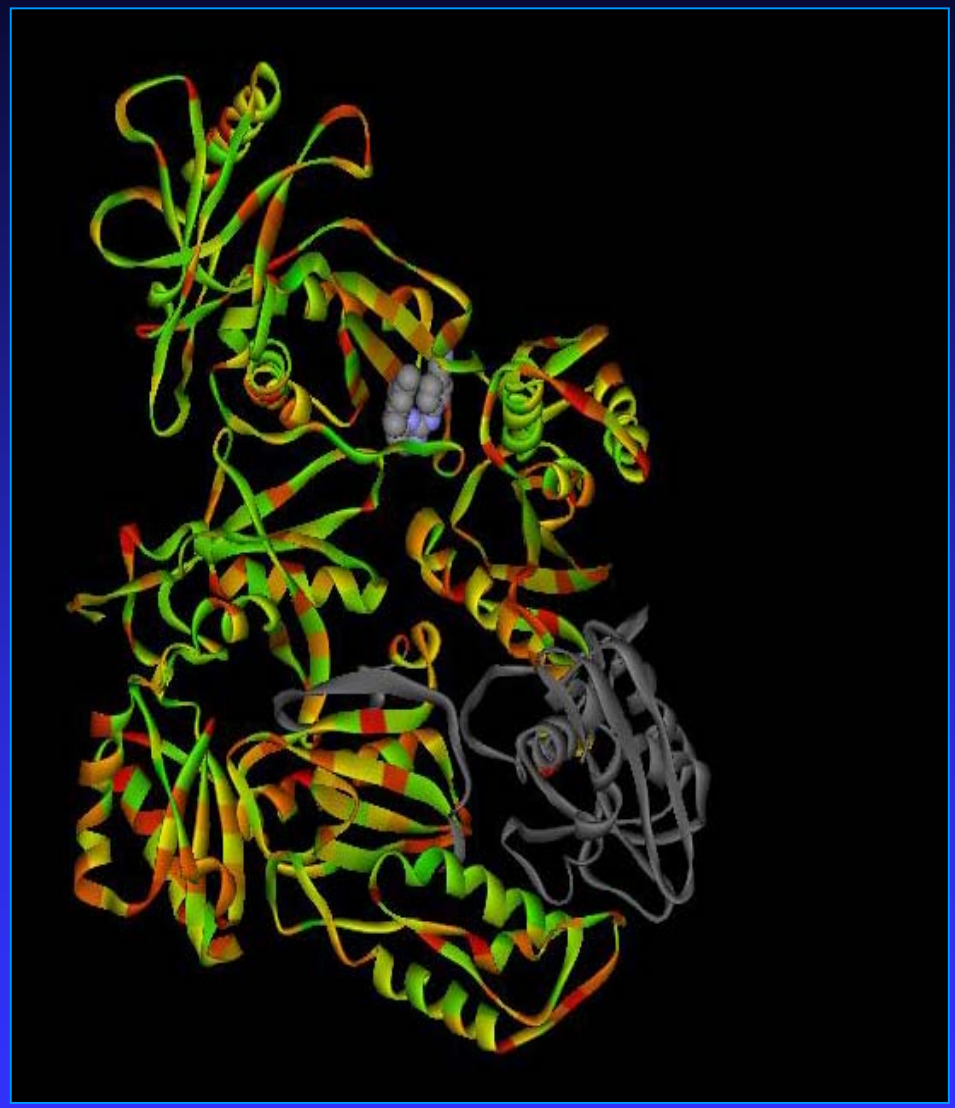
nevirapine

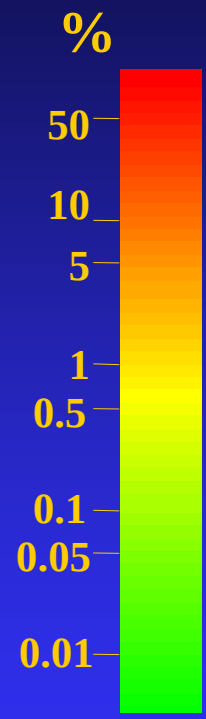


efavirenz



HIV RT genetic variability after drug pressure (N = 30,000)





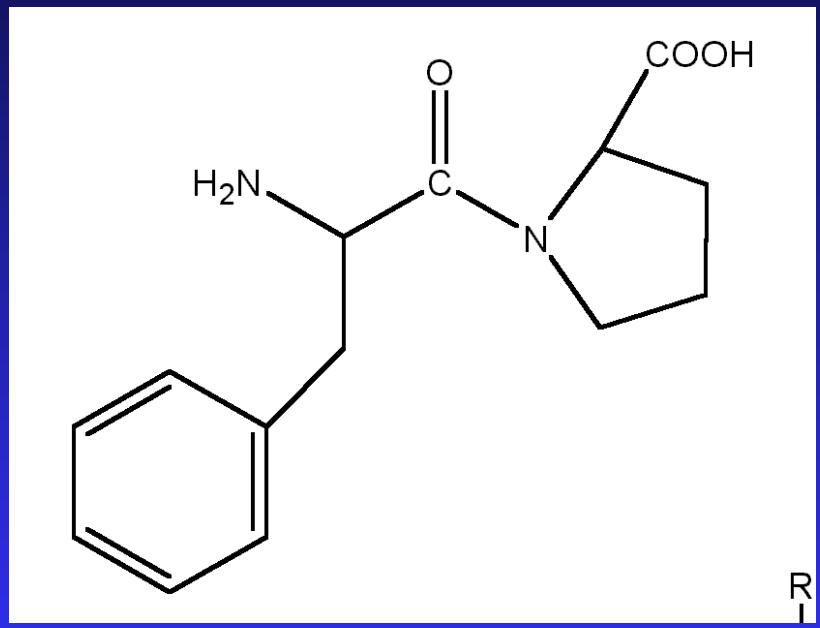
HIV REPLICATIVE CYCLE

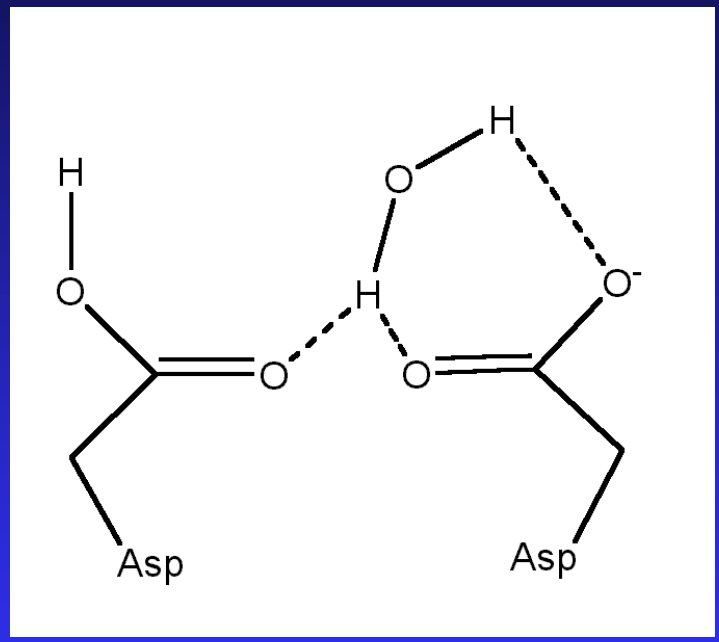
- Virus adsorption
- Virus-cell fusion
- Virus uncoating
- Reverse transcription
- Proviral DNA integration
- Proviral DNA replication
- Proviral DNA transcription to viral mRNA
- Viral mRNA translation to viral precursor proteins
- **Maturation (proteolysis/myristoylation/glycosylation)**
- Budding (Assembly/Release)

Processing of peptide synthetized by the HIV genome

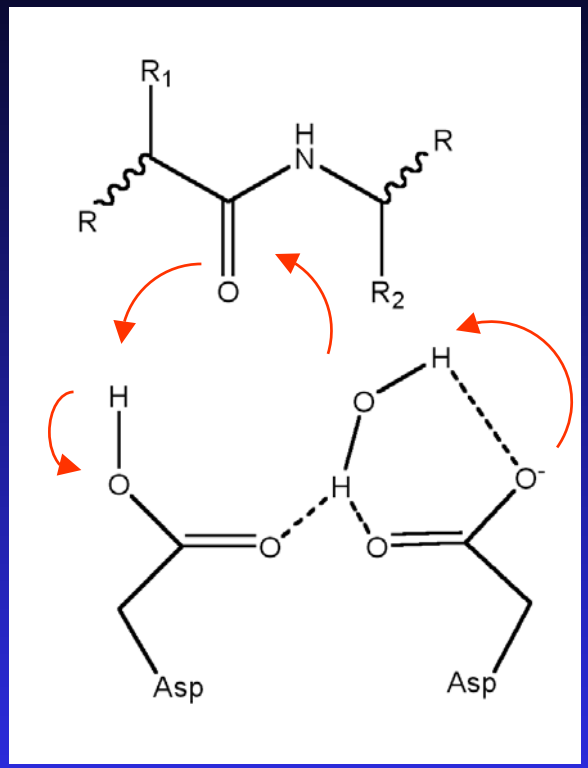
- Retrovirally encoded proteases are responsible for the maturation of immature viral particles yielding mature, infectious virus.
- This is done by self-activation of the protease (PR) from a larger viral gag-PR-(pol) protein (zymogen) precursor and subsequent processing of the viral reverse transcriptase (RT) and integrase (IN), and the gag protein precursor into mature gag proteins.
- Blocking this proteolytic process results in production of immature, non-infective virions.
- **All retroviral proteases are aspartic-type proteases and act on a Phe-Pro scissile bond of the gag/pol gene polyprotein product.**

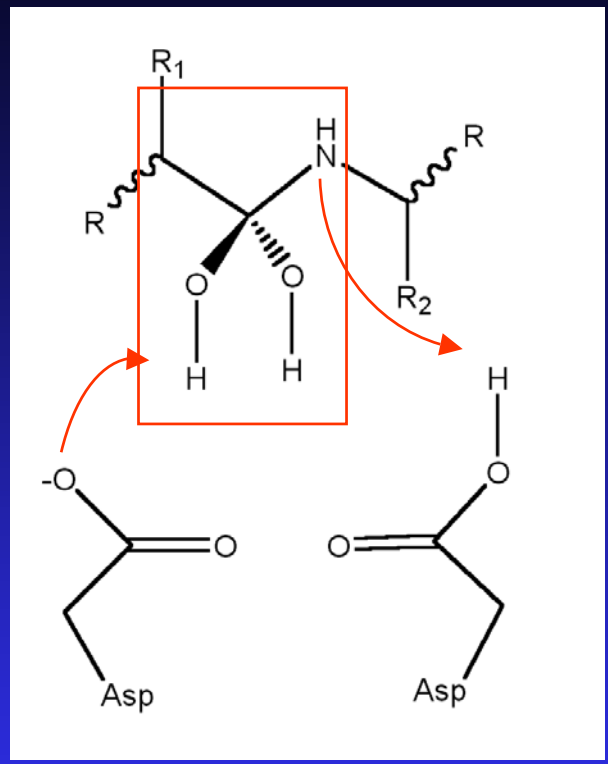
Lien Phe-Pro et aspartate protease ...

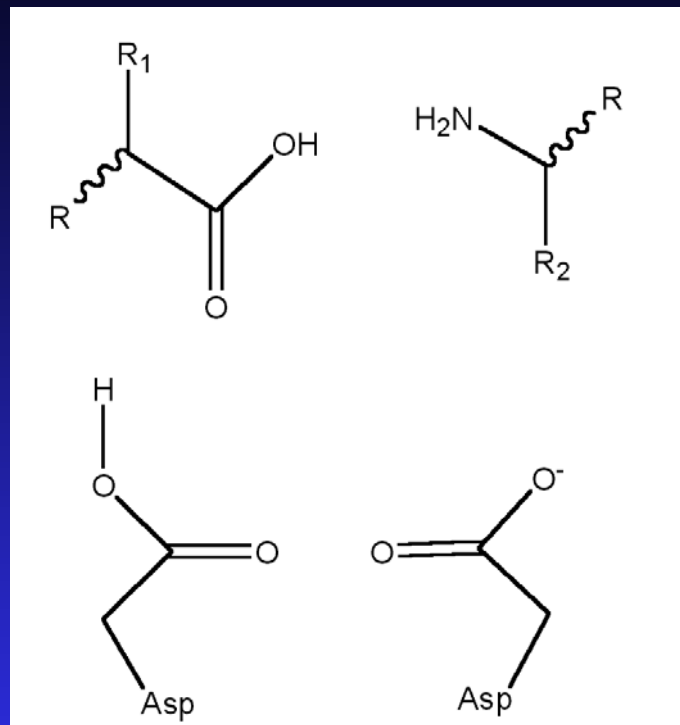




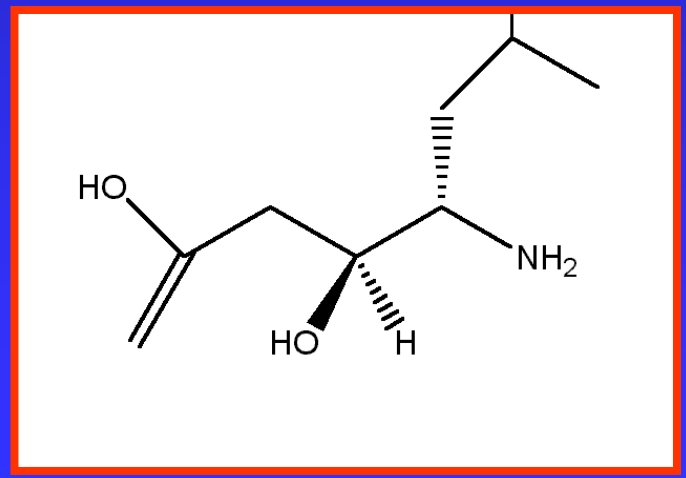
Mechanism of aspartate protease and typical inhibitor (pepstatin)

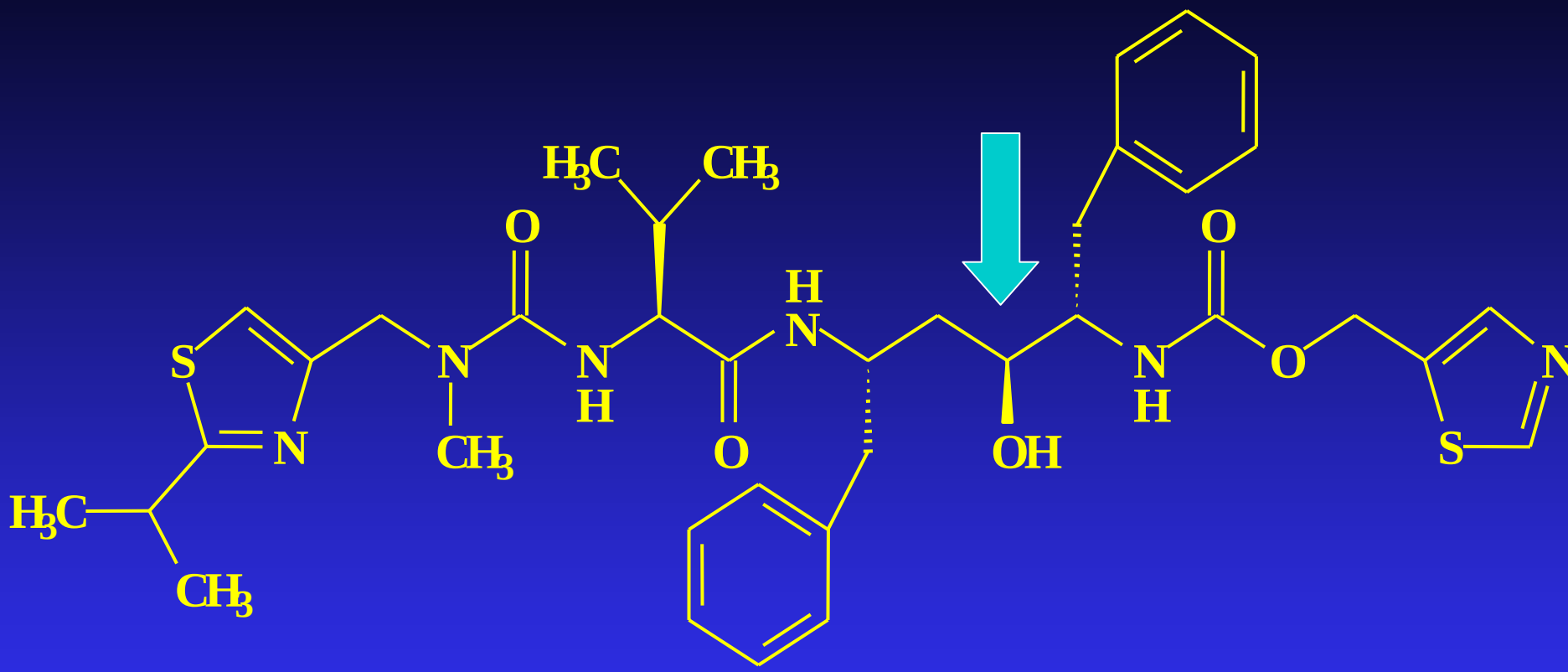




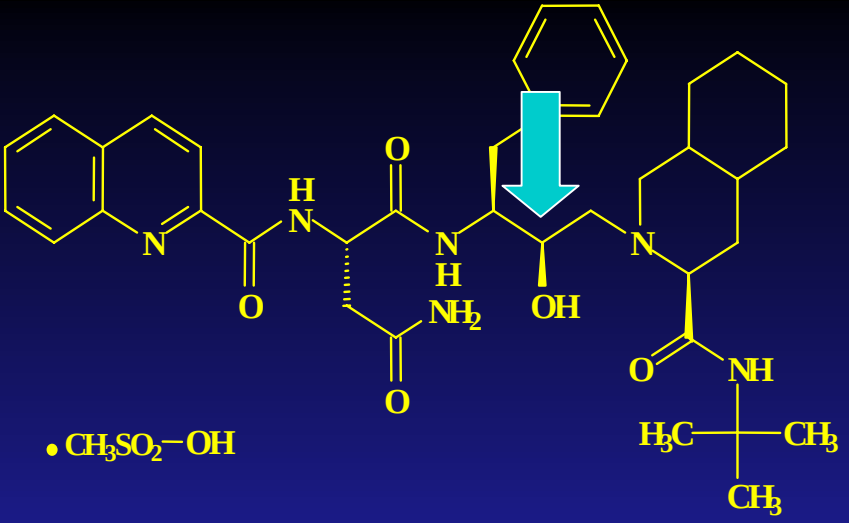


Pepstatine...

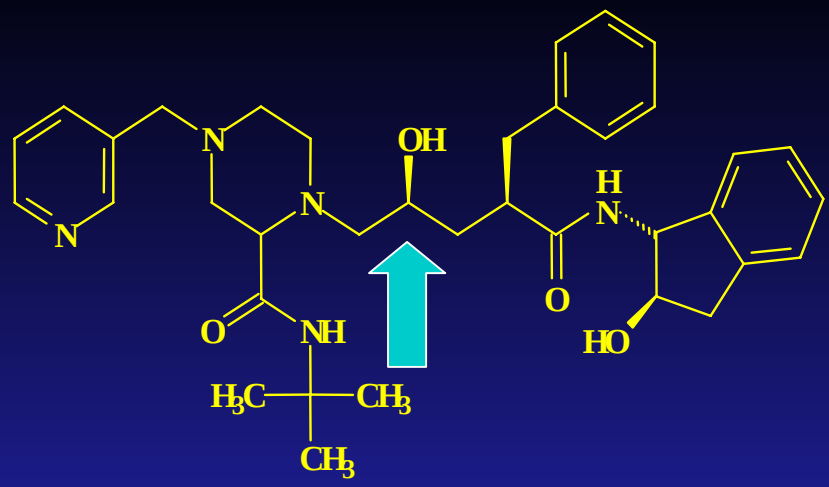




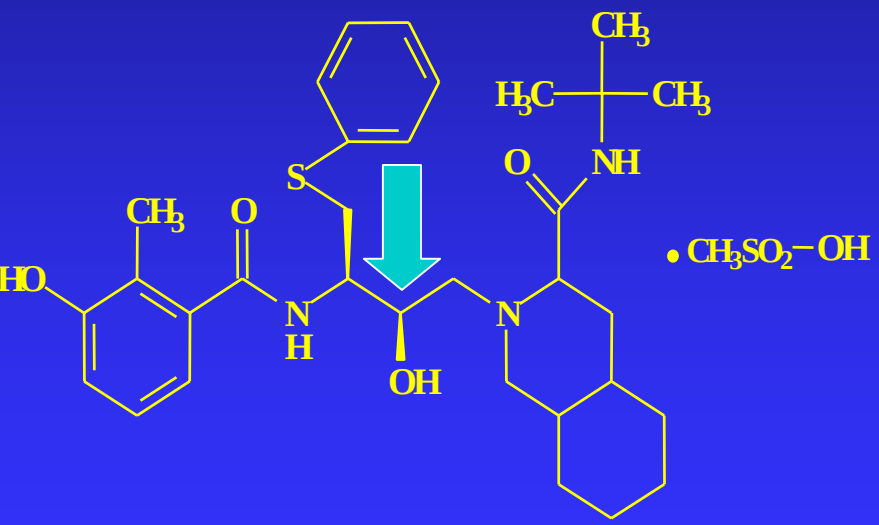
Ritonavir



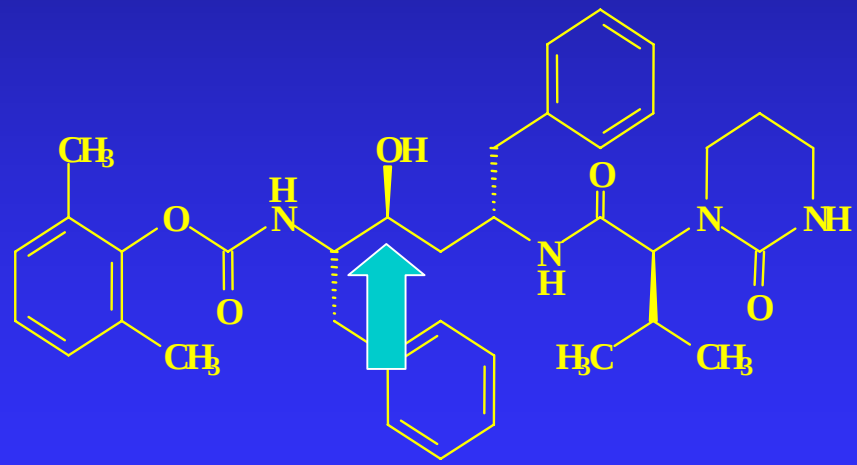
Saquinavir



Indinavir

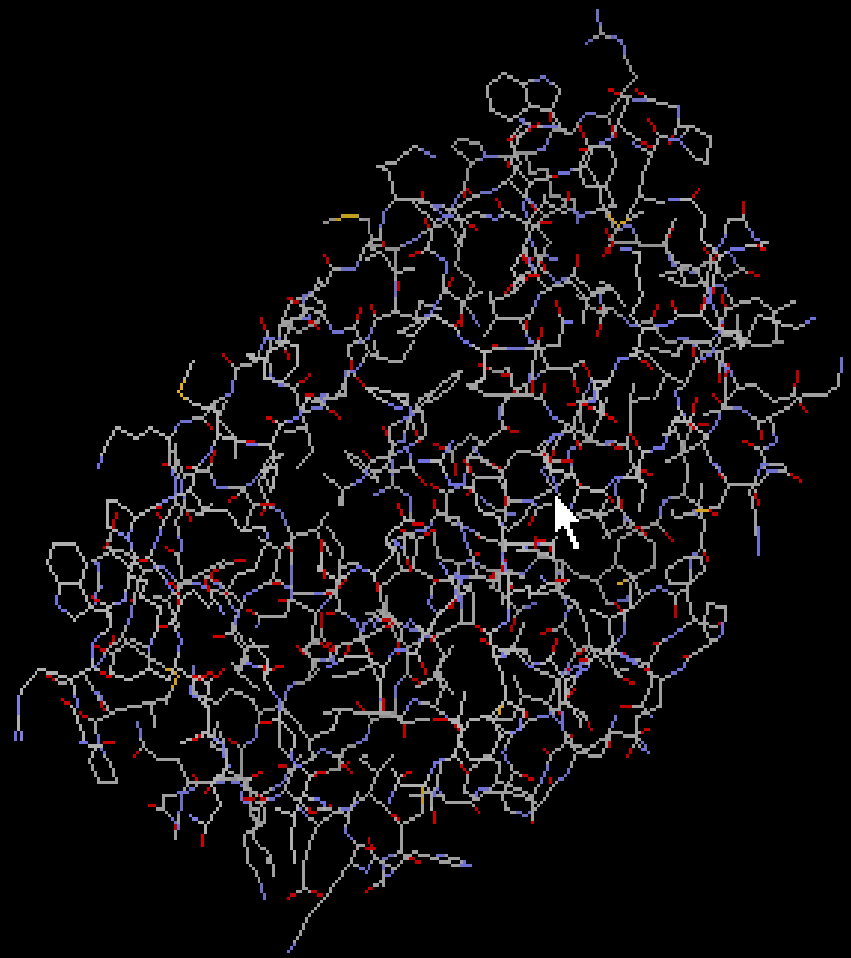


Nelfinavir

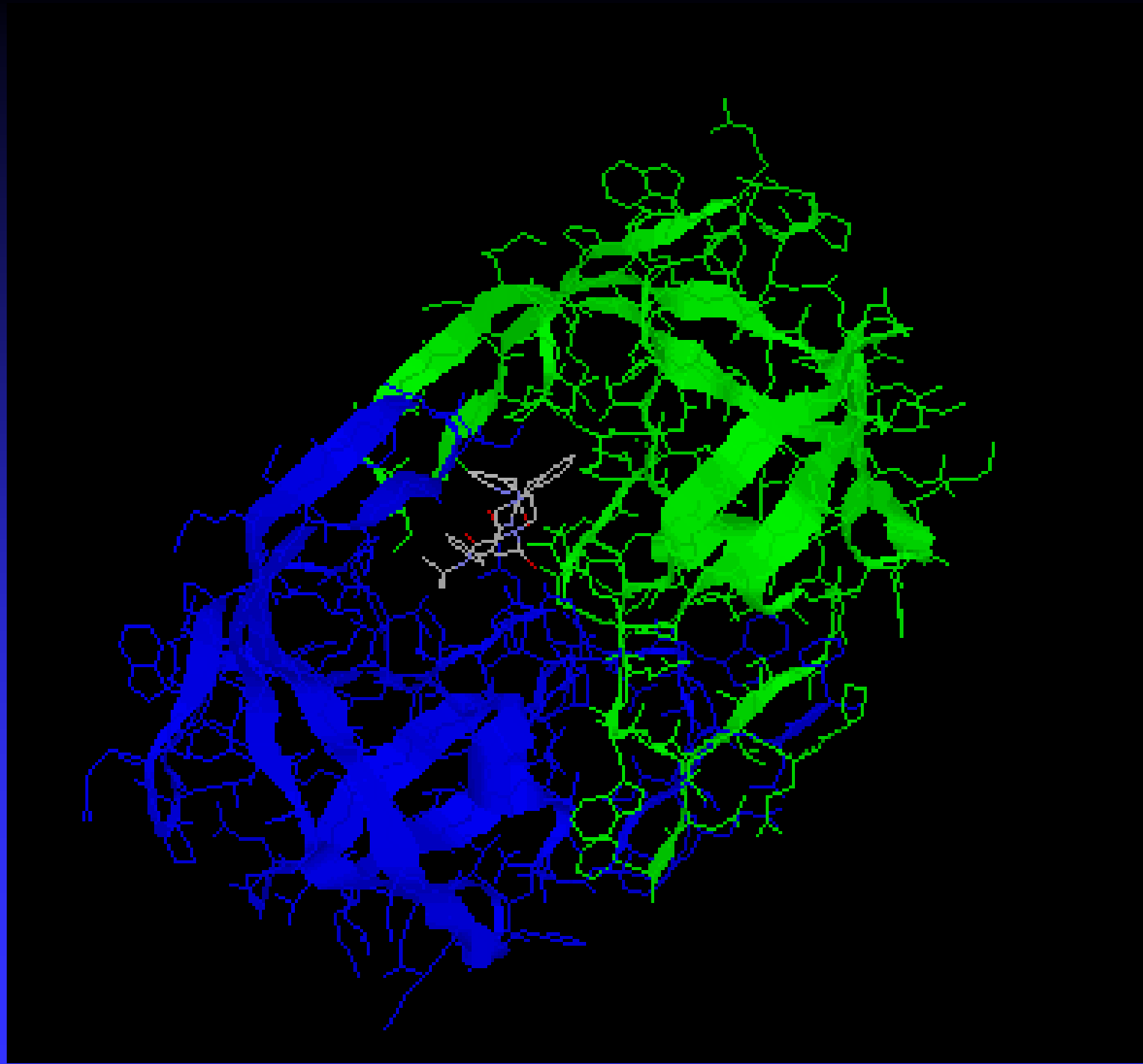


Lopinavir

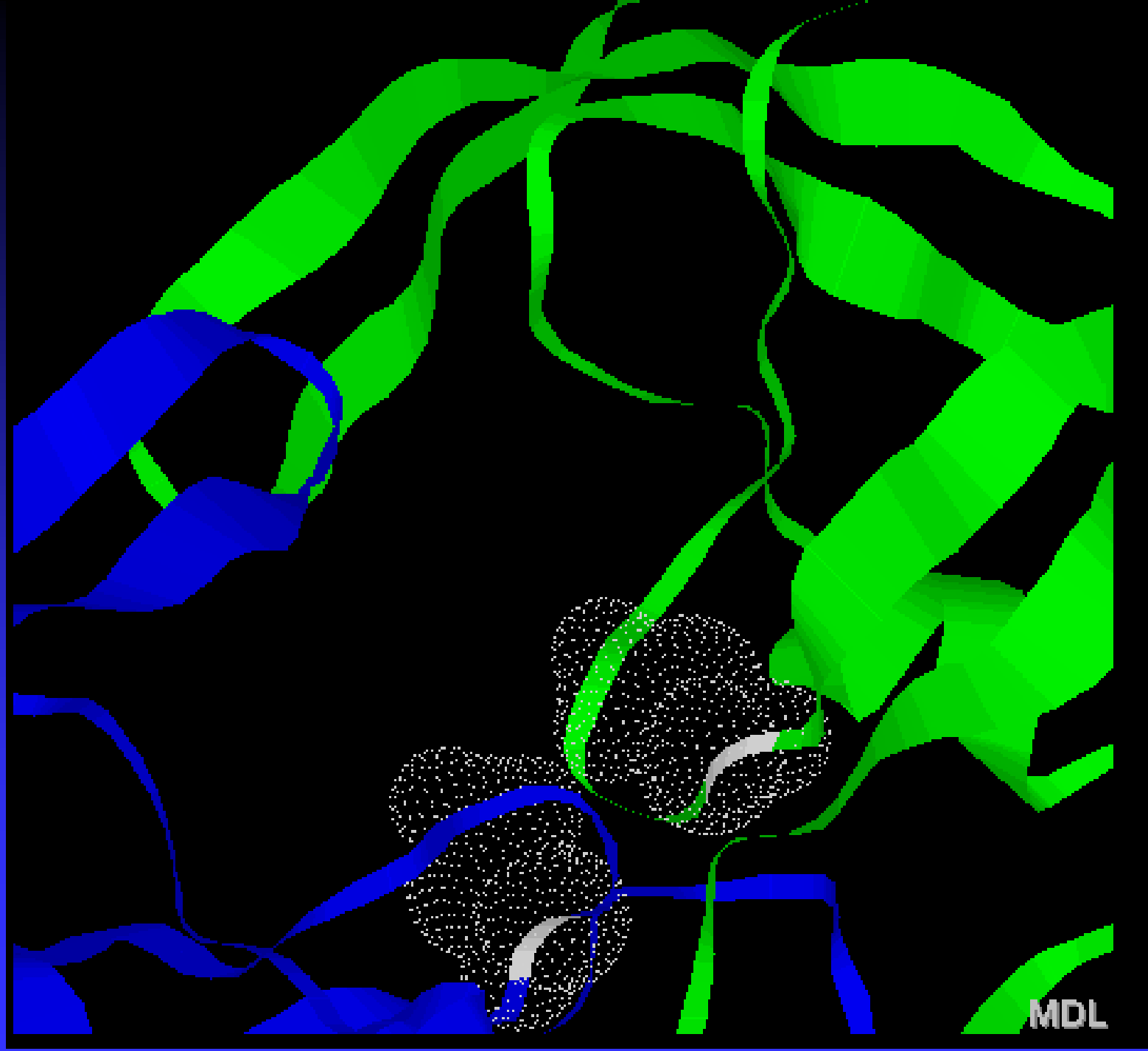
HIV protease



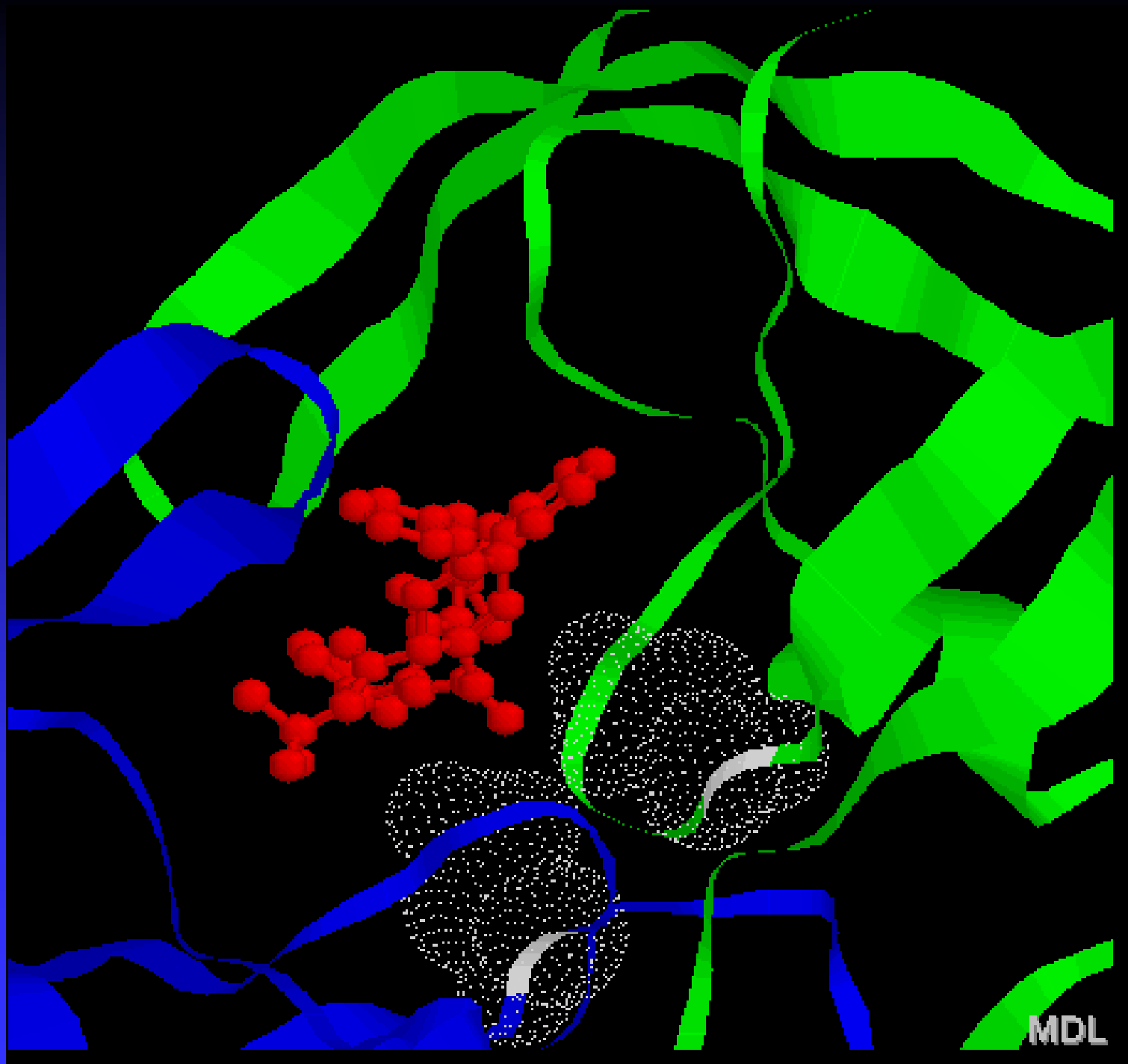
HIV protease



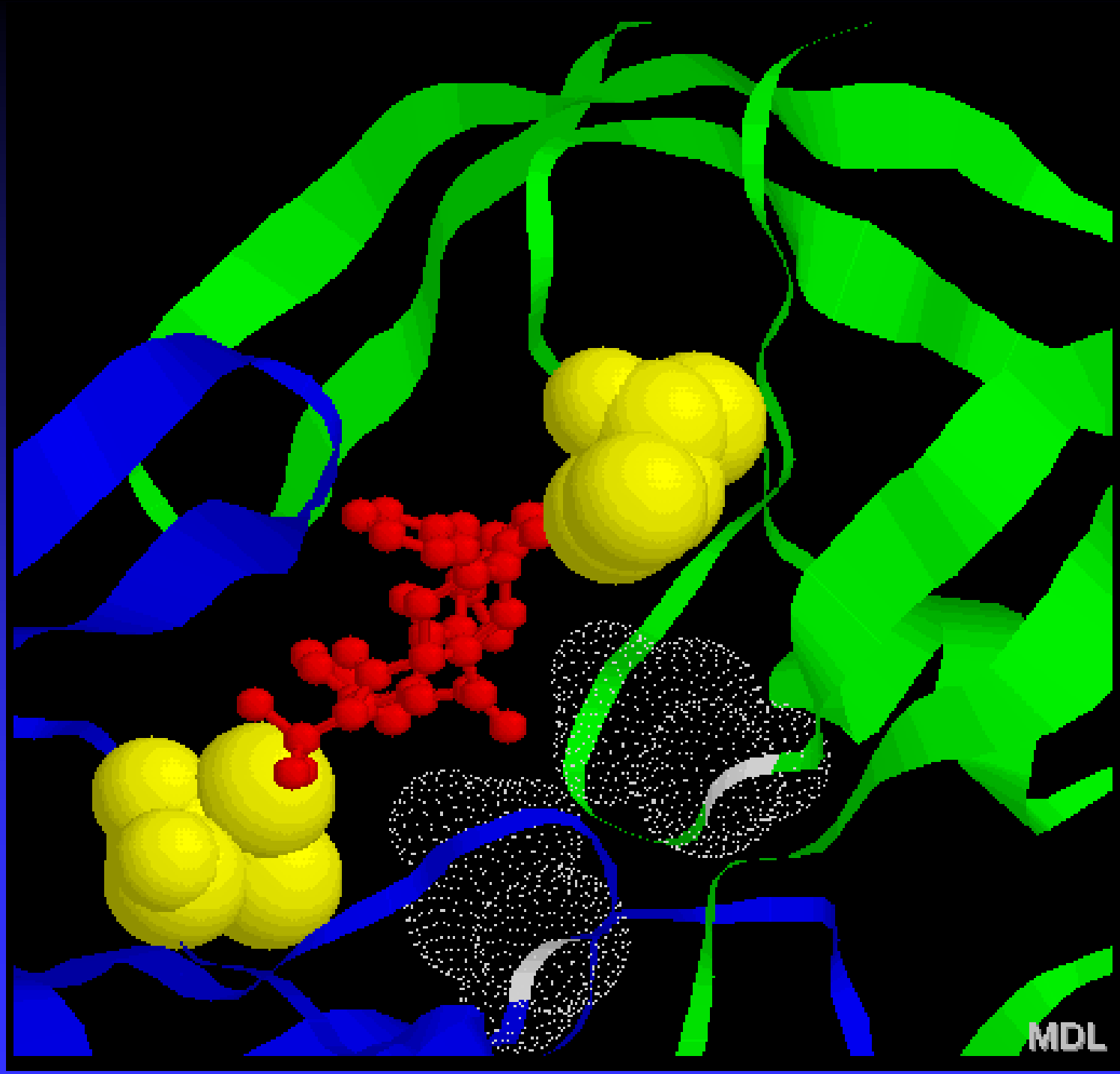
HIV protease



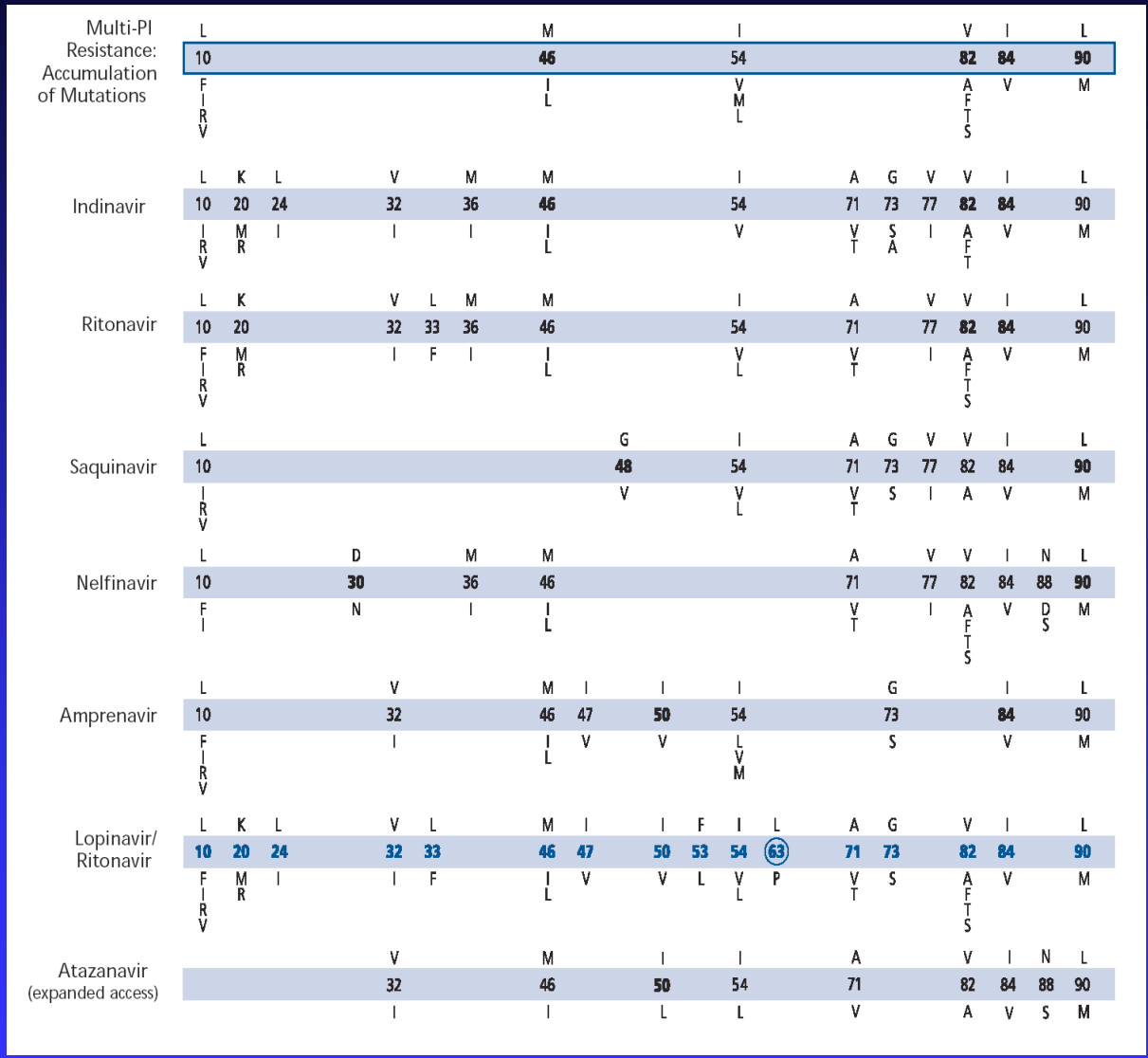
HIV protease



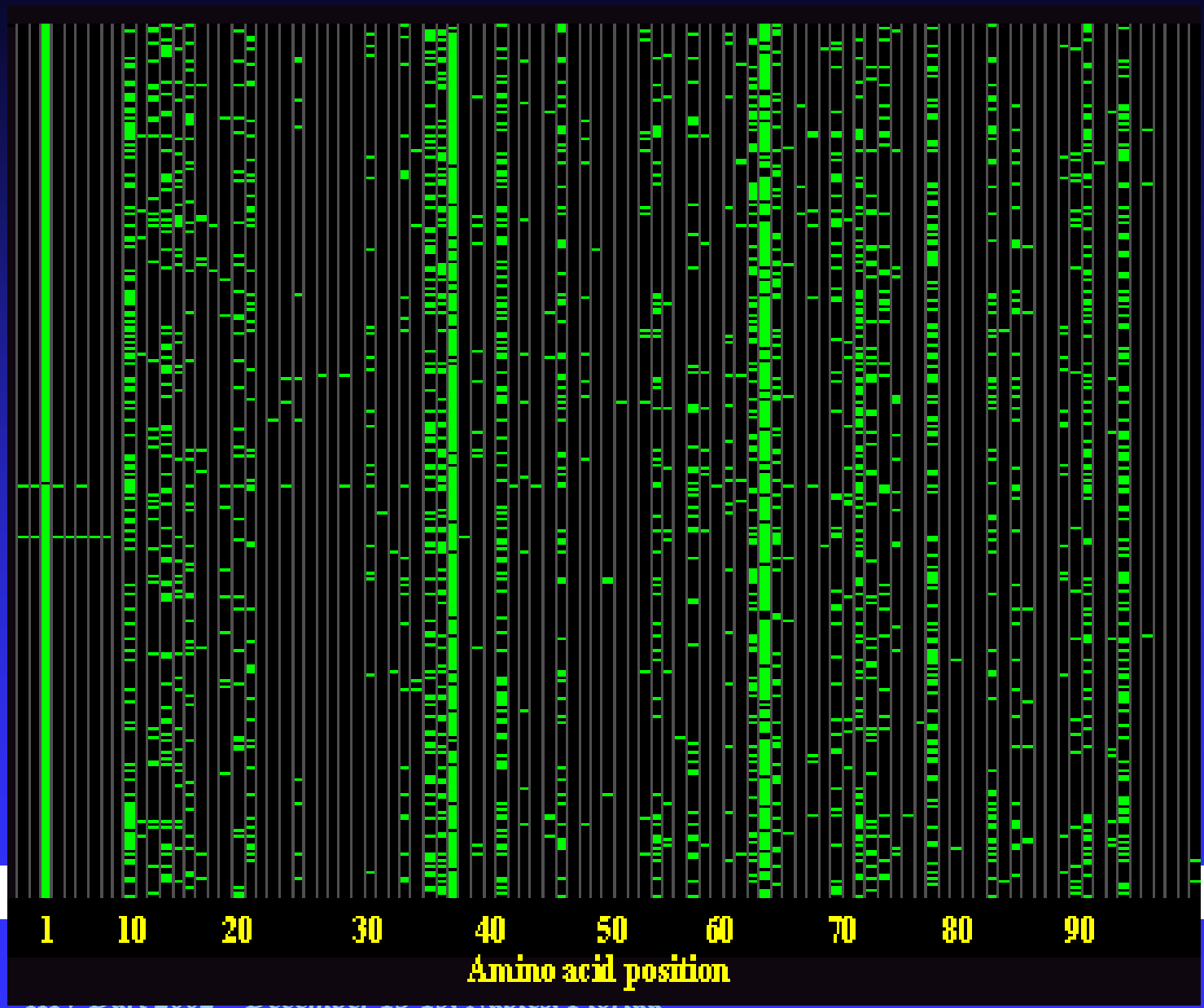
HIV protease



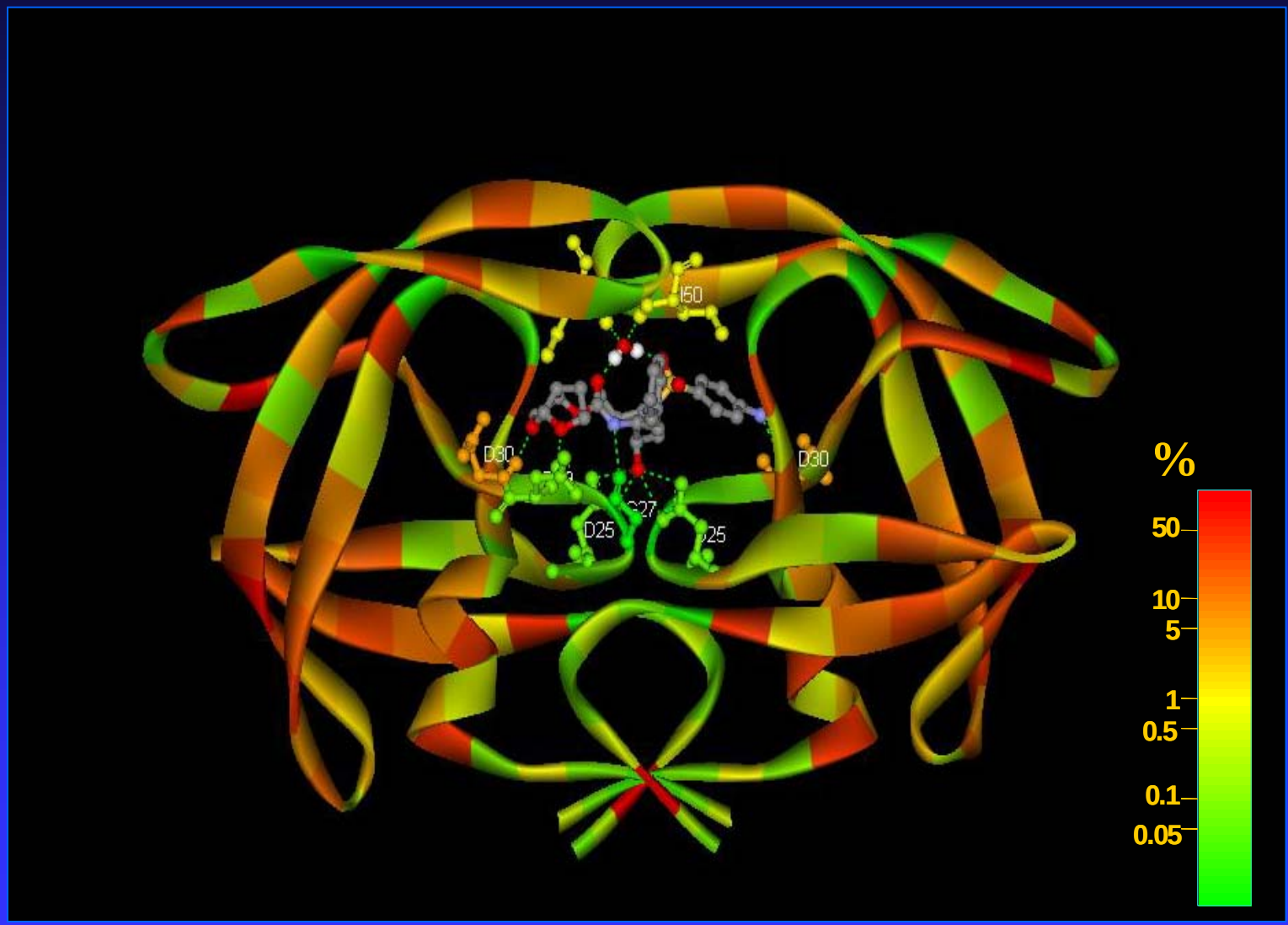
MUTATIONS IN THE HIV PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS (PIs)



HIV protease gene diversity matrix

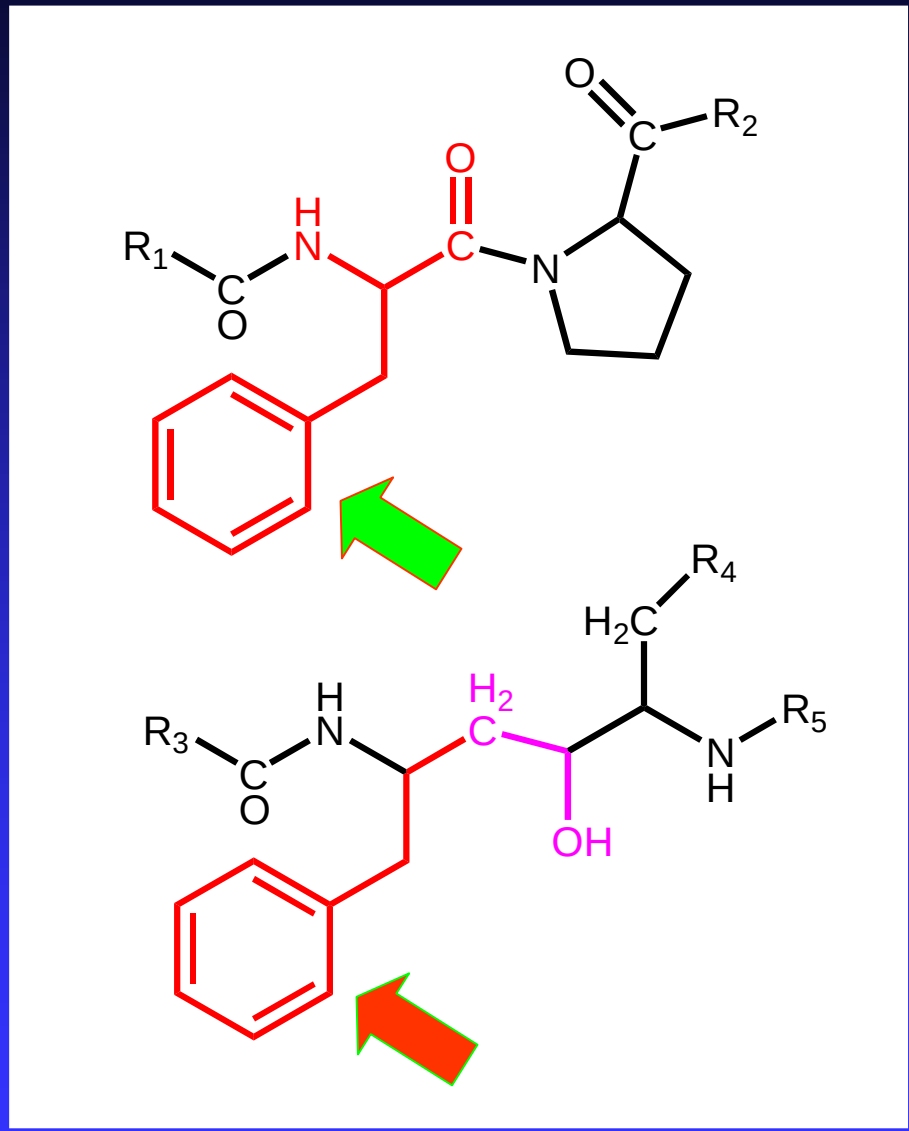


HIV protease genetic variability after PI drug pressure (N = 30,000)



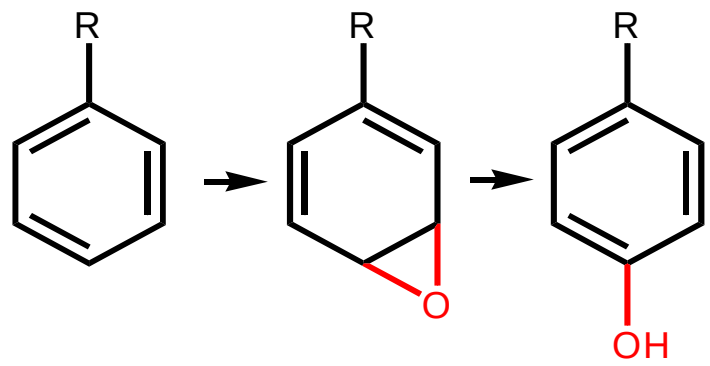
Interférences médicamenteuses et inhibiteurs de protéase …

- Cette protéase doit scinder un lien Phe-Pro
- Les inhibiteurs miment donc tous une Phe…

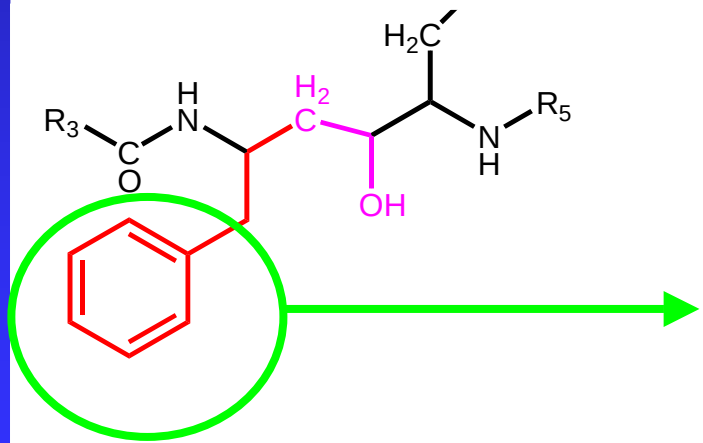


Métabolisme des substances à noyau aromatique…

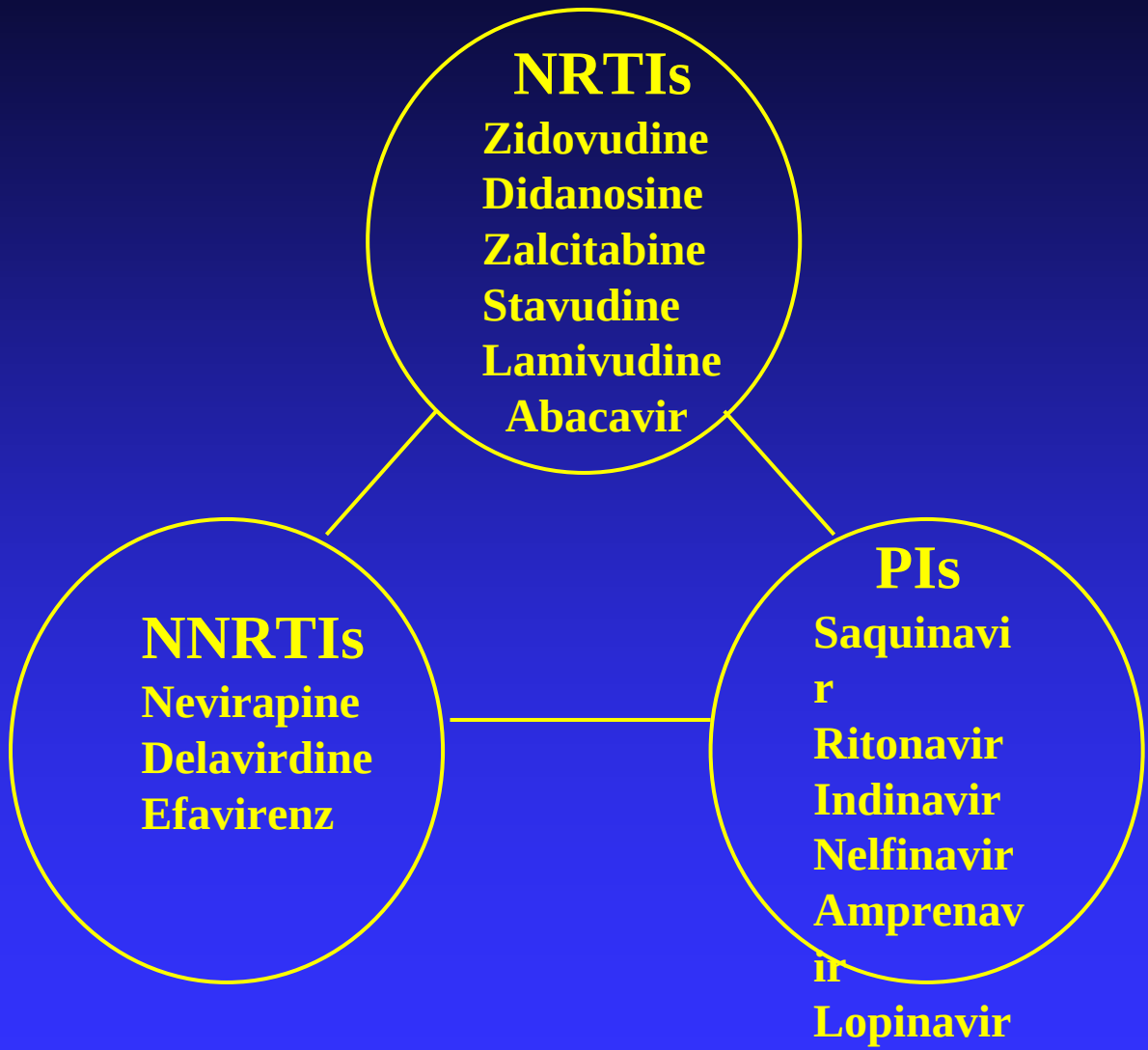
- La plupart des médicaments (et autres substances) à noyau aromatique sont métabolisées en dérivés hydroxylés, ce qui est essentiel pour leur élimination

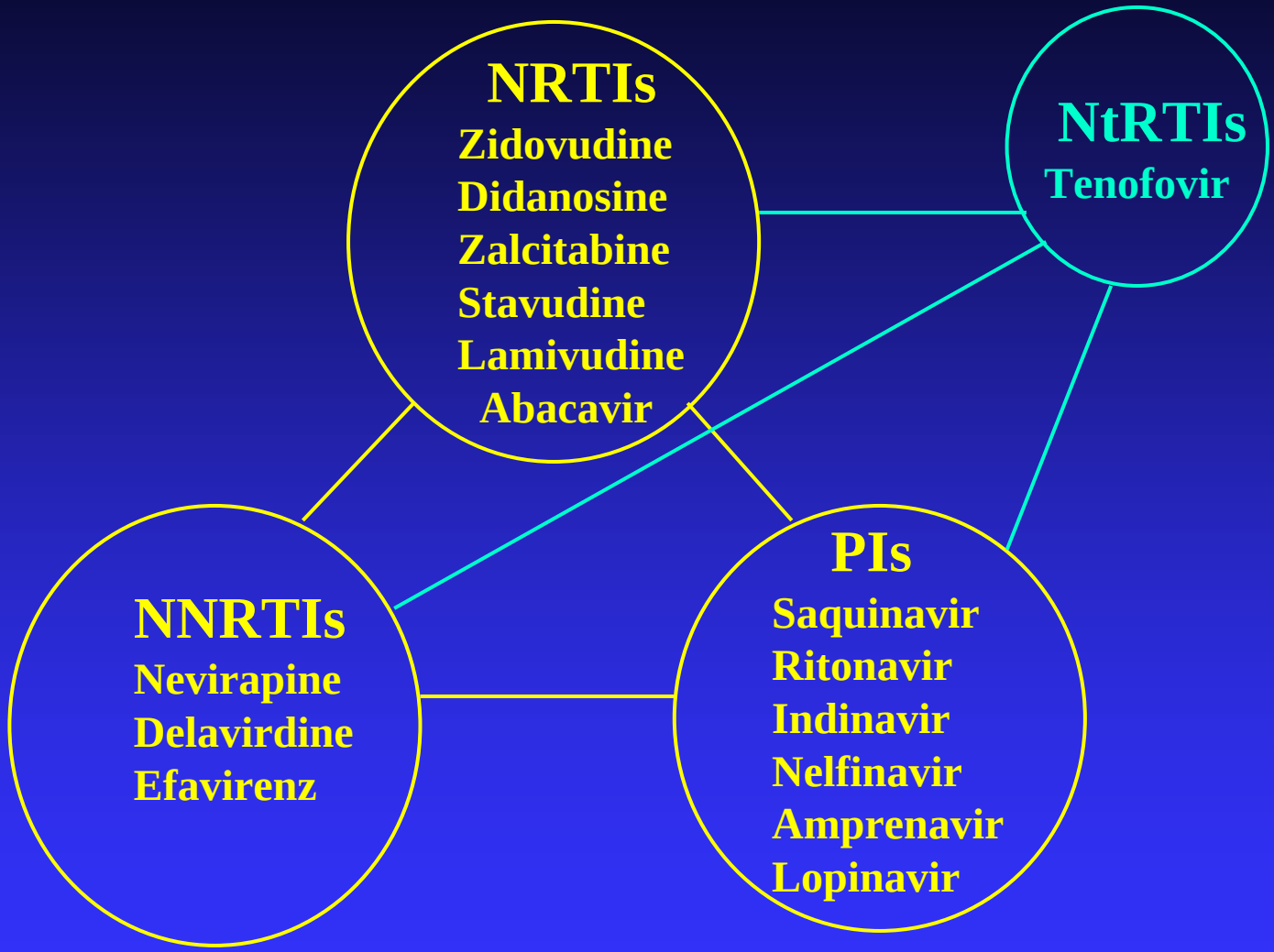


- phénytoïne (antépileptique)
- phénobarvital (sédatif)
- propranolol (antihypertenseur)
- phénylbutazone (antiinflammatoire)
- éthinyloestradiol (hormone)
- dicoumarol (anticoagulant)
- …..



- Par leur noyau aromatique (essentiel pour l'activité !!), les inhibiteurs de protéase entrent en **compétition** avec ces médicaments (et bien d'autres)
- il vont **ralentir leur élimination**, et, dès lors
- créer un risque d'**intoxication par excès** …


NRTIs
Zidovudine
Didanosine
Zalcitabine
Stavudine
Lamivudine
Abacavir
NNRTIs
Nevirapine
Delavirdine
Efavirenz
PIs
Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprenavir
Lopinavir


NRTIs
Zidovudine
Didanosine
Zalcitabine
Stavudine
Lamivudine
Abacavir
NtRTIs
Tenofovir
NNRTIs
Nevirapine
Delavirdine
Efavirenz
PIs
Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprenavir
Lopinavir

Anti-retroviral Therapy (ART): When to initiate treatment - CDC Guidelines

Clinical Category	CD4 count	HIV RNA VL	Recommendation
Symptomatic/AIDS	Any value	Any value	Treat
Asymptomatic AIDS	<200 /mm3	Any value	Treat
Aymptomatic	200-350 /mm3	Any value	Offer treatment; controversial
Aymptomatic	> 350 /mm3	>55,000	Some would initiate or follow CD4/VL closely
Aysmptomatic	>350 /mm3	<55,000	Many defer and observe as 3 yr risk AIDS <15%
Acute HIV infection	Any value	Any value	Offer treatment

Anti-retroviral Therapy (ART): When to initiate treatment - WHO guidelines

- WHO stage IV (AIDS-defining diagnosis), regardless of CD4 count
- CD4 available: WHO stage I,II,III and CD4 <200 cells/mm3
- CD4 not available: WHO stage II,III (symptomatic HIV) plus absolute lymphocyte count <1200/mmm3

Anti-retroviral Therapy (ART): Goals of Treatment

- Decrease viral load (0.5-0.75 log10) within 4 weeks or
- Decrease in viral load 1 log 10 in 8 weeks
- Undetectable VL (<50 or <20 copies) at 4-6 months
- Restoration or preservation of immune function
- Reduction of HIV related morbidity and mortality

Anti-Retrovirals

Nucleoside Reverse Transcriptase Inhibitors (NsRTIs)

Drug	CDC Group	Dose	Side Effects
Abacavir (ABC)	Group A	300 mg bid	Hypersensitivity rxn, fever, rash, lactic acid
Zidovudine (AZT, ZDV)	Group B	200 mg tid 300 mg bid	BM supp, anemia, GI, LA, HA,insomnia
Stavudine (d4T)	Group B	40 mg bid 30 mg bid	Pancreatitis, LA w/ steatohep, neuropathy
Lamivudine (3TC)	Group B	150 mg bid	LA w/ steatohepatitis
Didanosine (ddI)	Group B	200 mg bid, 400 mg qd 125 mg bid, 250 mg qd	Pancreatitis, neuropathy, GI, LA w/ steatohepatitis
Zalcitabine (ddC)	Group B	0.75 mg qd	Neuropathy, stomatitis, LA

Anti-Retrovirals
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Drug	Brand	Dose	Side Effects
AZT + 3TC	Combivir	1 tab bid	Same as AZT, 3TC
AZT + 3TC + ABC	Trizivir	1 tab bid	Same as AZT, 3TC, ABC
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)			
Tenofovir (TDF)	Group A	300 mg qd	No renal toxicity; limited expanded access

Anti-Retrovirals

Non-nucleotide Reverse Transcriptase Inhibitors (NNRTIs)

Drug	Brand	Dose	Side Effects
Efavirenz (EFV)	Sustiva	600 mg qhs	Rash, CNS, hepatitis, induce, inhibits P450
Nevirapine (NVP)	Viramune	200 mg bid	Rash, elevated LFTs, hepatitis, induce P450
Delavirdine (DLV)	Rescriptor	400 mg tid	Rash, elevated LFTs, HA, inhibits P450

Anti-Retrovirals
Protease Inhibitors (PIs)

Drug	Brand	Dose	Side Effects
Saquinavir (SQV)	Inivirase	400 mg bid w/ ritonavir	GI intolerance, N/D/HA
Saquinavir (SQV)	Fortovase	1200 mg tid	Elevated LFTs, fat redistn, DM
Ritonavir (RTV)	Norvir	600 mg q12	GI, N/V/D, hepatitis, pancreatitis, incr lipids, DM, fat redistn, neuro
Nelfinavir (NFV)	Viracept	1250 mg bid 750 mg tid	D/N, DM, Fat redistn, Lipids abnl
Indinavir (IDV)	Crixivan	800 mg q8h	Nephrolithiasis, GI intol, N, HA, incr LFTs, DM, fat redistn
Lopinavir + Ritonavir	Kaletra	400 mg lop+ 100 mg rit bid	GI, N/V/D, DM, fat redistn, elevated LFTs
Amprenavir (APV)	Agenerase	1200 mg bid	GI, N/V/D, rash, DM, fat redistn, LFTs, Lipid

Anti-Retrovirals: Strongly Recommended Regimens

- ***Group A***
  - Efavirenz
  - Indinavir
  - Nelfinavir
  - Ritonavir + Indinavir
  - Ritonavir + Lopinavir
  - Ritonavir + Saquinavir
- ***Group B***
  - Didanosine + Lamuvidine
  - Stavudine + Didanosine
  - Stavudine + Lamuvidine
  - Zidovudine + Didanosine
  - Zidovudine + Lamivudine

Anti-Retrovirals
CDC Recommended Regimens

- Combine one from Group A and one from Group B
- No mono or dual therapies
- Class sparing regimens:
  - 2 NRTIs + NNRTI
  - 3 NRTIs
  - 2 NRTIs + 1 or 2 PIs
- If previous treatment, consider resistance testing prior to initiating treatment

Anti-retroviral Therapy: WHO Guidelines for Resource Limited Settings

NsRTIs	NtRTIs	NNRTIs	PIs
Zidovudine (ZDV, AZT)	Tenofovir (TDF)	Nevirapine (NVP)	Saquinavir (SQV)
Didanosine (ddI)		Efavirenz (EFV)	Ritonivir (RTV)
Stavudine (d4T)			Indinavir (IDV)
Lamivudine (3TC)			Nelfinavir (NFV)
Abacavir (ABC)			Lopinavir/ritonavir (LPV/r)

Anti-retroviral Therapy (ART): First Line agents in resource limited settings

- 2 nucleoside analogs + NNRT or PI
- Examples starting regimen:
  - Abacavir regimen: AZT/3TC/ABC
    - trizavir - one pill bid
  - NNRTI regimen: AZT/3TC/EFZ or AZT/3TC/ NVP (NVP in pregnancy)
  - PI regimen: AZT/3TC + one of IDV/RTV, SQV/RTV, or NFV

Prevention of Mother-to-Child Transmission: Resource Limited Settings

- Short course ARV regimens for prevention of MTCT can be associated with ARV resistance
  - Most often seen with Nevirapine and 3TC
- Suggested Regimens:
  - AZT or AZT/3TC - continued through delivery
  - Nevirapine - one dose to mother & child
- PIs do not cross placenta
- d4T/ddI *not* recommended during pregnancy due to side effects (lactic acidosis/steatohepatitis)

Antiretroviral Therapy
Adherence Support

- One-on-one support
  - Counselling
  - Treatment assistant (self-selected)
  - Home visits
- Peer support
  - Support groups composed of people on ART
- Adherence materials
  - Pill box (with customized packing instructions)
  - Daily schedule
  - Self-monitoring form

Antiretroviral Therapy
Adherence Support

Opportunistic Infections & Complications by CD4 Count

CD4 Count	Infectious	Non-Infectious
> 500/mm3	Acute HIV Candidal vaginitis	PGL GBS Myopathy Aseptic meningitis
200-500/ mm3	Pneumococcal PNA Pulm Tb Zoster Thrush Crytosporidiosis KS OHL	CIN Cervical Cancer B-cell Lymphoma Anemia Mononeuronal multiplex ITP Hodkin's Lymphoma LIP

Opportunistic Infections & Complications by CD4 Count

CD4 Count	Infectious	Non-Infectious
< 200/mm3	*P. carinii* pneumonis Disseminated mycoses Miliary /extrapulm Tb PML	Wasting Peripheral neuropathy HIV dementia Cardiomyopathy Vacuolar myelopathy Polyradiculopathy NH Lymphoma
< 100/mm3	Disseminated HSV Toxoplasmosis Crytococcosis Cryptosporidiosis Microsporidiosis Candidal esophagitis	
< 50/mm3	Disseminated CMV Disseminated MAI	CNS lymphoma

Primary Prophylaxis of Opportunistic Infections

Pathogen	Indication	First agent	Alternative
Pneum. Cyst. C.	CD4<200	Cotrimox.1 DSqd or 1 SS qd	Dapsone 100 qd Dapsone 50 + pyrimethamine + leuco Atovaquone 1500/day
MTb	PPD > 5 mm Exposure	INH 300 + B6 x 9 m	Rifampin 600 qd x 4 m
MTb (INH resistant)	PPD > 5 mm	Rifampin 600 qd Rifabutin 300 qd	Pyrazinamide + rifampin or rifabutin
Toxo	IgG Ab + & CD4<100	Cotrimox.1 DSqd	Bactrim 1 SS qd, Dapsone+ pyrimethamine+ leuvovorin
MAI	CD4<50	Azithromycin 1200 qw Clarithromycin 500 bid	Rifabutin, azithro + rifabutin
Zoster	Exposure	VZIG –5 vials within 96 hours	-

Primary & Secondary Prophylaxis of Opportunistic Infections

Pathogen	Indication	First agent	Alternative
Strep PNA	CD4<200	Pneumovax	
HBV	HbsAb neg	HBV vaccine x 3	
Influenza	Oct-dec	Flu vaccine	Anti-virals
HAV	HAV negative + risk	HAV vaccine x 2	
Crypto		Fluconazole 200 qd	Itraconazole 200 bid
Histo		Intraconazole 200 qd	
Coccidio		Fluconazole 400 qd	Itraconazole 200 bid
CMV		Consult expert	

OI Prophylaxis in Resource Limited Settings

- *Pneumocystis Carinii* Pneumonia & Toxoplasma
  - Cotrimoxazole 1 DS or 1 SS qd
- Recurrent Bacterial PNA and Infections
  - Cotrimoxazole 1 DS or 1 SS qd
- Mycoses (ie Cryptococcus) when CD4<100
  - Fluconazole 200 mg qd
- Esophageal Candidiasis
  - Fluconazole 200 mg qd
- *Mycobacterium* Tb
  - PPD, Chest X-ray
  - INH 300 mg po qd + B6 x 9 months or short regimens

Web Resources

- WHO - Expanded Access to HIV/AIDS treatment
  - http://www.who.int/hiv/topics/arv/scaling_exe_fr.pdf
  - http://www.who.int/hiv/topics/arv/en/
  - http://www.who.int/hiv/en/
- STI treatment
  - http://www.who.int/docstore/hiv/STIManagemntguidelines/who_hiv_aids_2001.01/
- JHU Medical Management of HIV
  - http://www.hopkins-aids.edu/
  - http://www.hopkins-aids.edu/publications/abbrevgd/abbrevgd.pdf
- CDC/USPHS Guidelines
  - http://www.hivatis.com

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