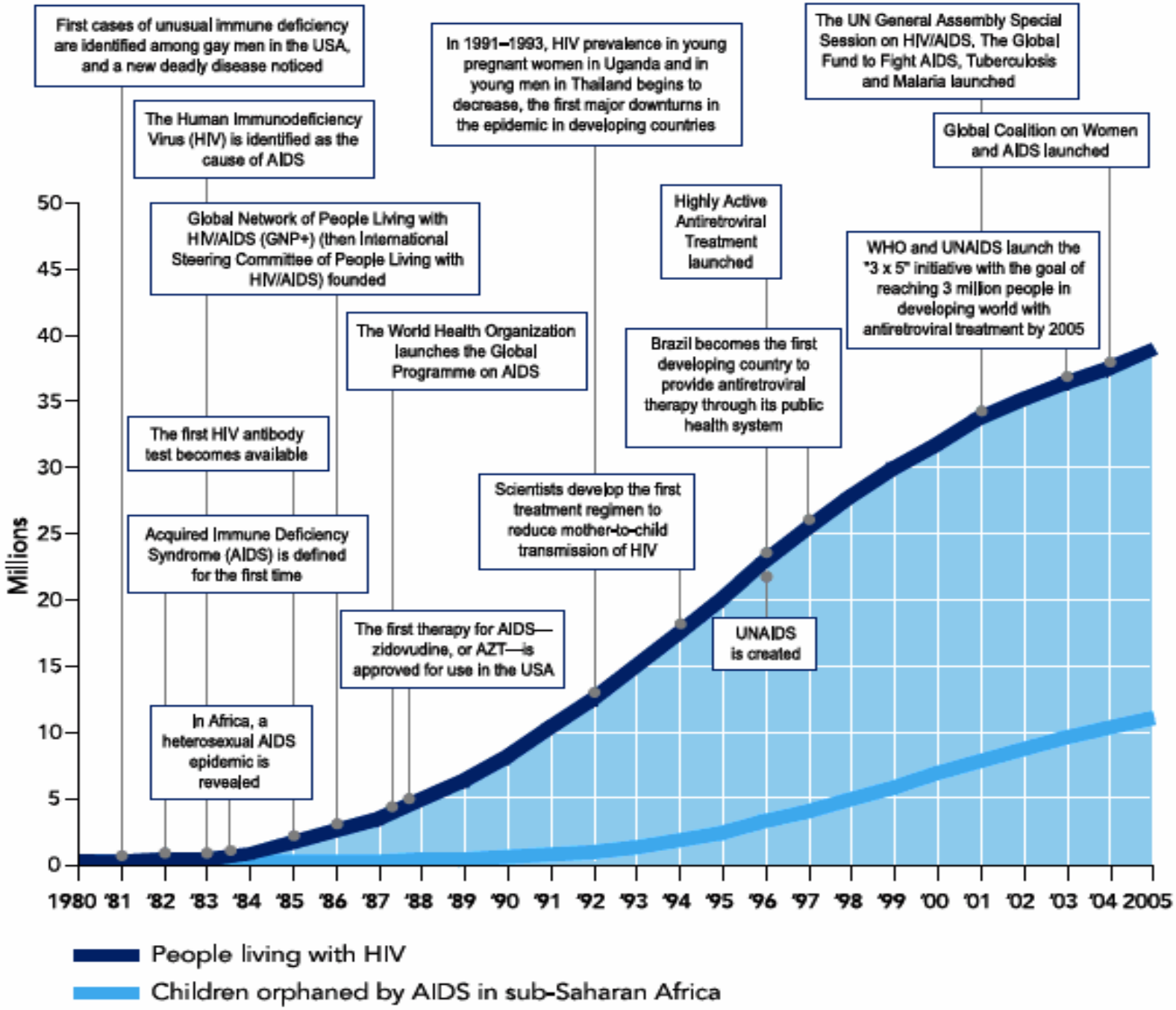
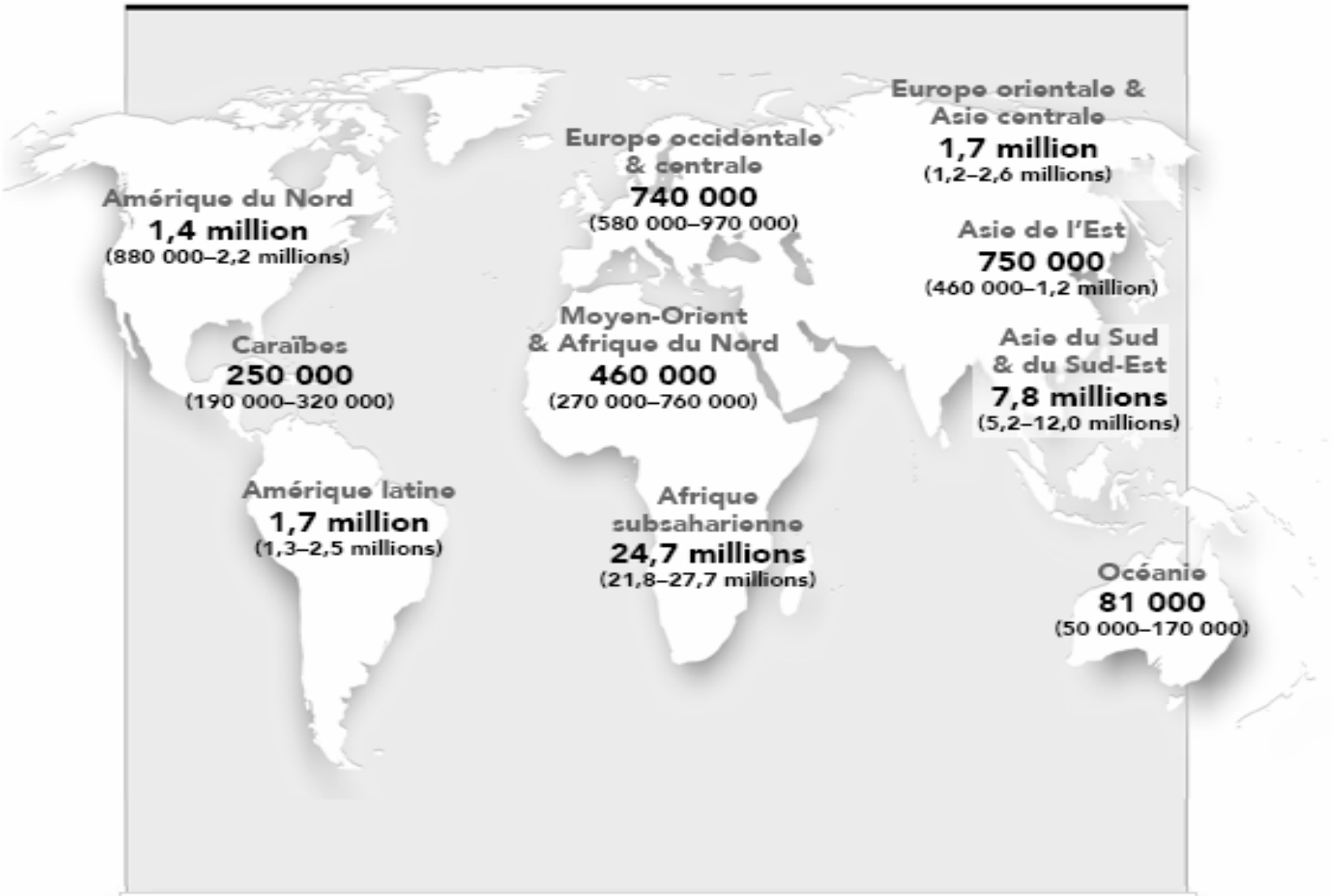
HIV and HIV chemotherapy

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/
et du cours du Dr J. Nachega
(Johns Hopkins University) donné à l'Ecole de Pharmacie de l'UCL en 2004

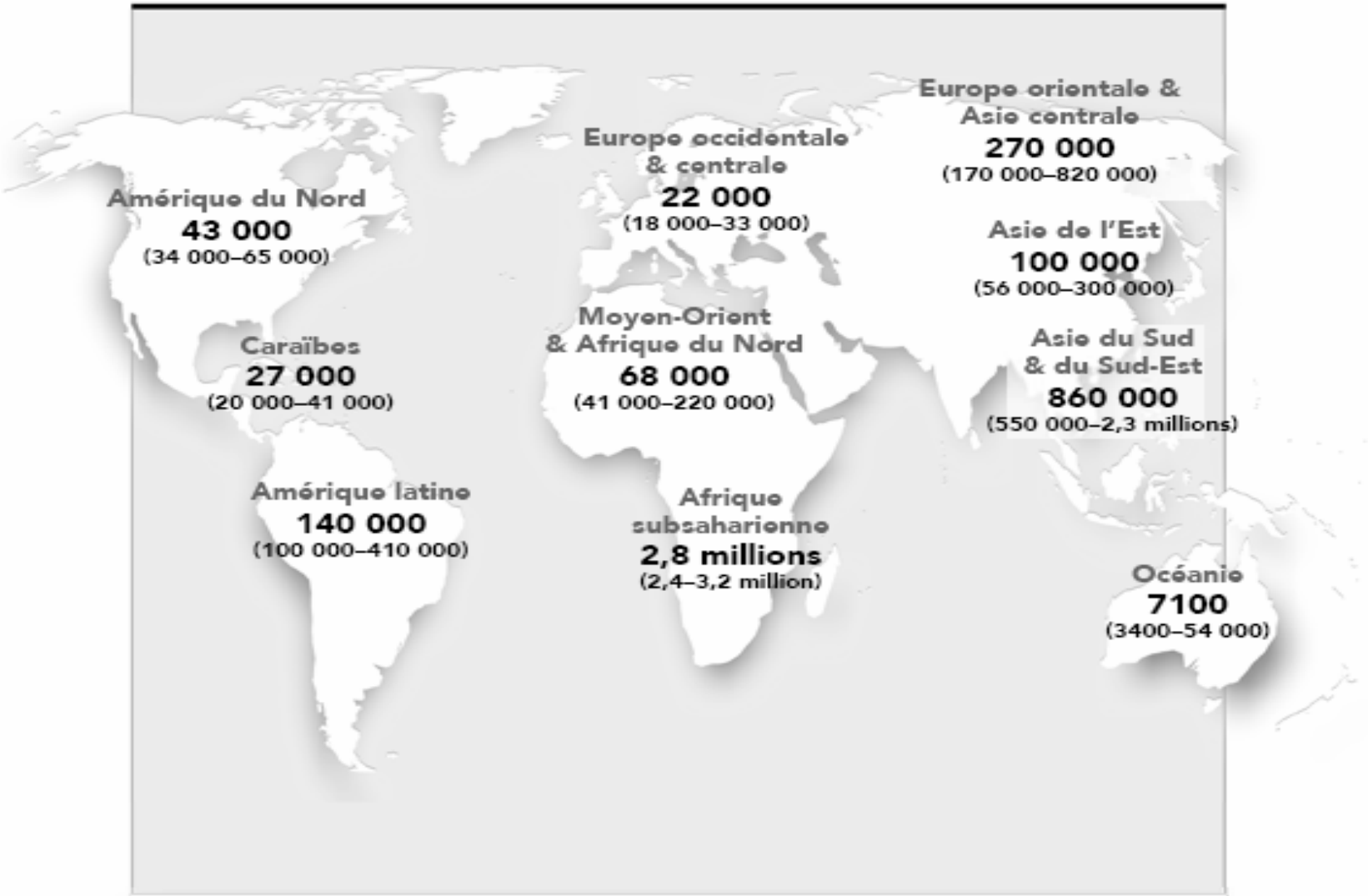

First cases of unusual immune deficiency are identified among gay men in the USA, and a new deadly disease noticed
The Human Immunodeficiency Virus (HIV) is identified as the cause of AIDS
Global Network of People Living with HIV/AIDS (GNP+) (then International Steering Committee of People Living with HIV/AIDS) founded
The first HIV antibody test becomes available
Acquired Immune Deficiency Syndrome (AIDS) is defined for the first time
In Africa, a heterosexual AIDS epidemic is revealed
The World Health Organization launches the Global Programme on AIDS
The first therapy for AIDS—zidovudine, or AZT—is approved for use in the USA
In 1991–1993, HIV prevalence in young pregnant women in Uganda and in young men in Thailand begins to decrease, the first major downturns in the epidemic in developing countries
Scientists develop the first treatment regimen to reduce mother-to-child transmission of HIV
Highly Active Antiretroviral Treatment launched
Brazil becomes the first developing country to provide antiretroviral therapy through its public health system
UNAIDS is created
The UN General Assembly Special Session on HIV/AIDS, The Global Fund to Fight AIDS, Tuberculosis and Malaria launched
Global Coalition on Women and AIDS launched
WHO and UNAIDS launch the "3 x 5" initiative with the goal of reaching 3 million people in developing world with antiretroviral treatment by 2005
Millions
0
5
10
15
20
25
30
35
40
45
50
1980 '81 '82 '83 '84 '85 '86 '87 '88 '89 '90 '91 '92 '93 '94 '95 '96 '97 '98 '99 '00 '01 '02 '03 '04 2005
People living with HIV
Children orphaned by AIDS in sub-Saharan Africa

ADULTES ET ENFANTS VIVANT AVEC LE VIH
ESTIMATIONS EN 2006



Total: 39,5 (34,1–47,1) millions

Nombre estimatif d'adultes et d'enfants nouvellement infectés par le VIH en 2006



Total: 4,3 (3,6–6,6) millions

BELGIUM

I. DEMOGRAPHIC, SOCIAL AND ECONOMIC INDICATORS

Estimated Population	10 419 000
Population Growth Rate	0.2%
Life expectancy at birth	
Women 81 Men	75
Human Development Index	9
Human Poverty Index	
Rank	13[1]
Value	12.4[2]
Percentage of people with less than US$ 2 a day	–
Per Capita Gross National Income, ppp, Intl dollar rate	31 360
Per Capita Government Expenditure on Health at Intl dollar rate	1902

II. HIV AND AIDS ESTIMATES

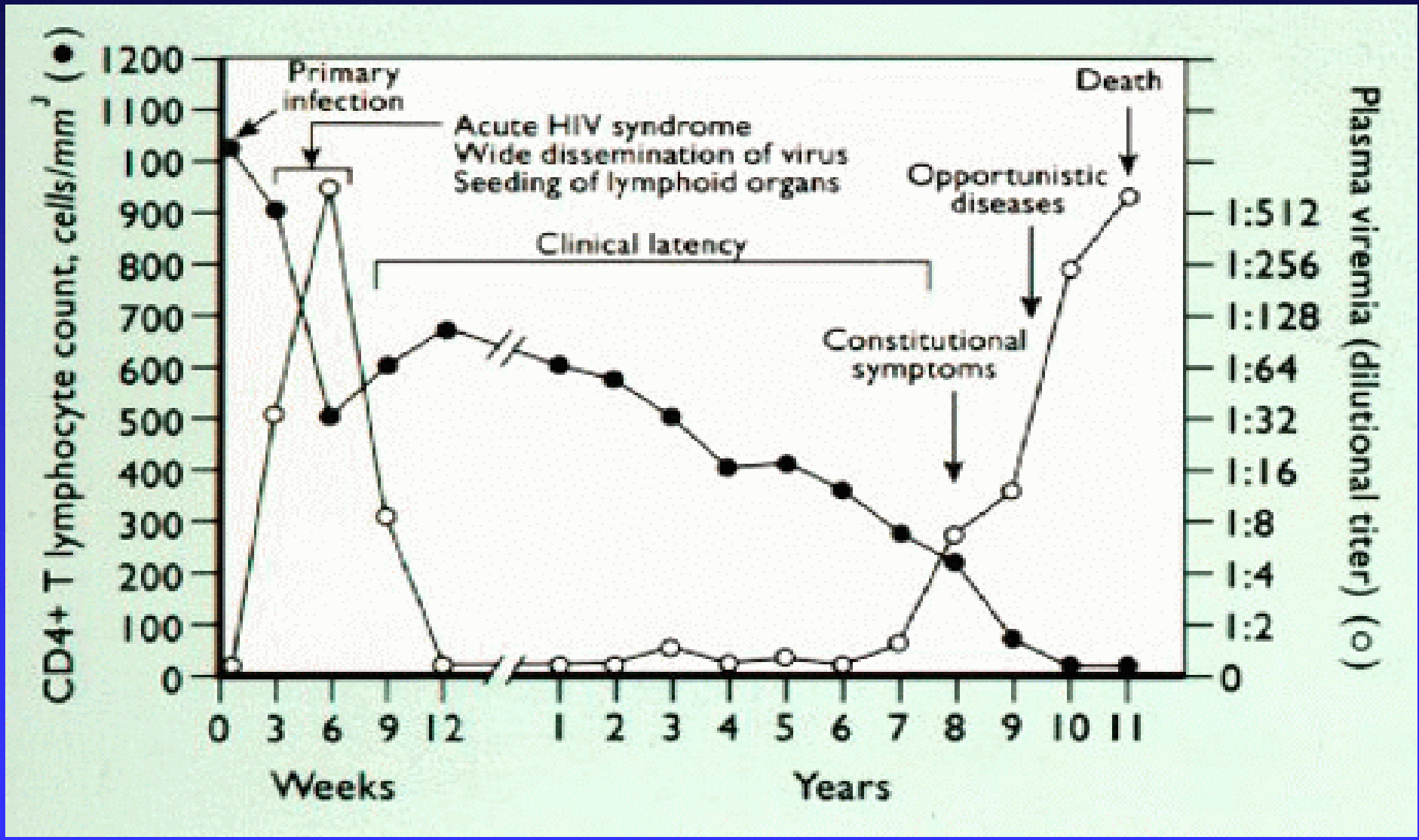
Number of people living with HIV	14 000 [8100 – 22 000]
Adults aged 15 to 49 HIV prevalence rate	0.3 [0.2 – 0.5%]
Adults aged 15 and over living with HIV	14 000 [8100 – 22 000]
Women aged 15 and over living with HIV	5400 [2800 – 9500]
Deaths due to AIDS	<100 [<200]

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



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

* Centers for Disease Control and Prevention, Atlanta, GA – http://www.cdc.gov

WHO Staging System

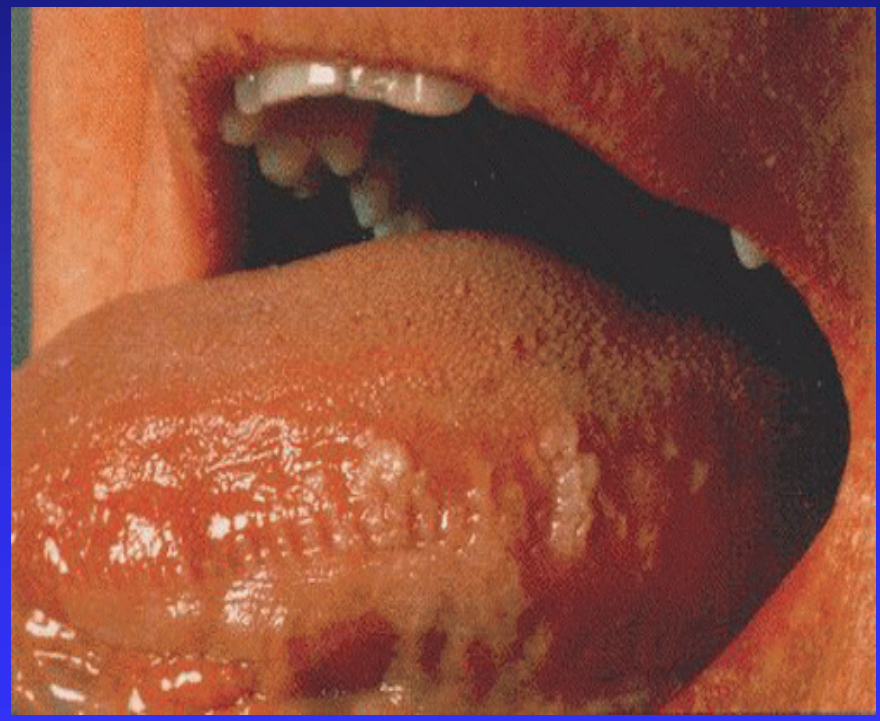
- **Clinical Stage I**
  - Aysmptomatic
  - Persistent Generalized Lymphadenopathy
  - Performance scale - 1
- **Clinical Stage II**
  - Weight loss < 10% body wt
  - Minor skin manifestations
  - HSV
  - recurrent URI
  - Performance scale- 2
- **Clinical Stage III**
  - Weight loss > 10% body wt
  - 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

Organisation mondiale de la Santé

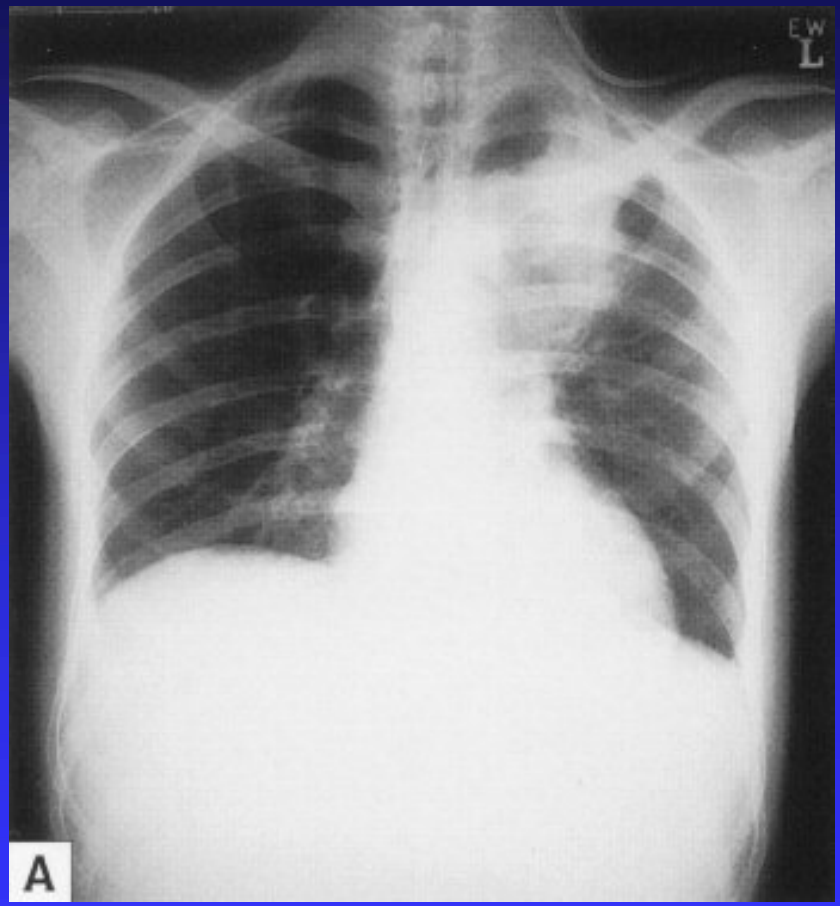
http://www.who.int/

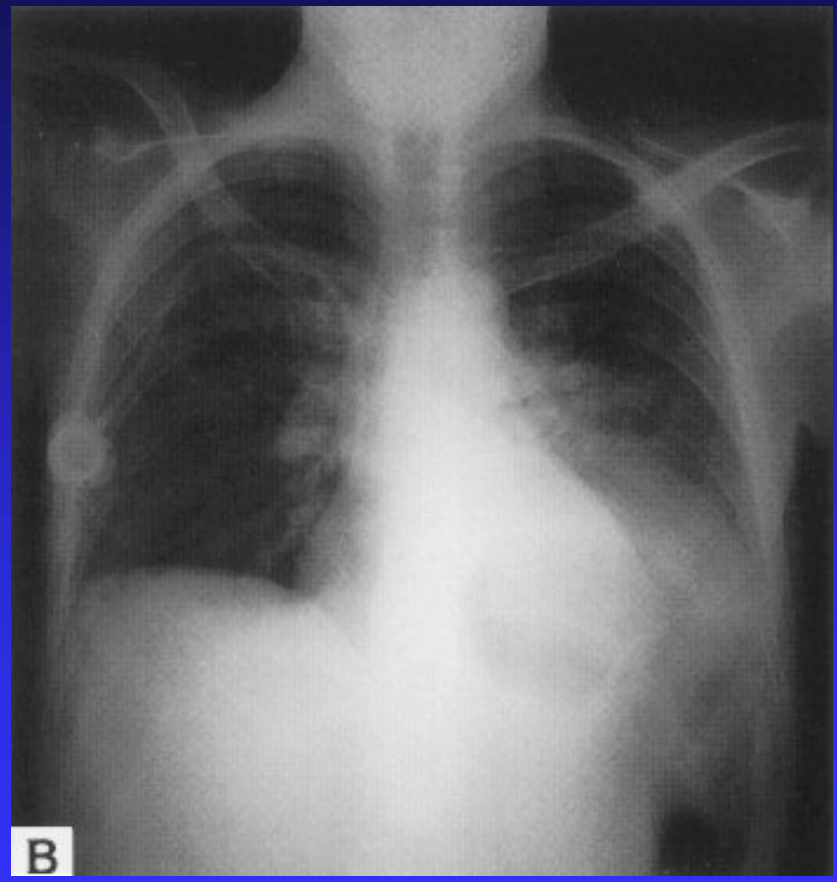
AIDS-related *Varicella-Zoster* Infection

AIDS-related Oral Candidiasis(Thrush) vs. Oral Hairy Leukoplakia (OHL)

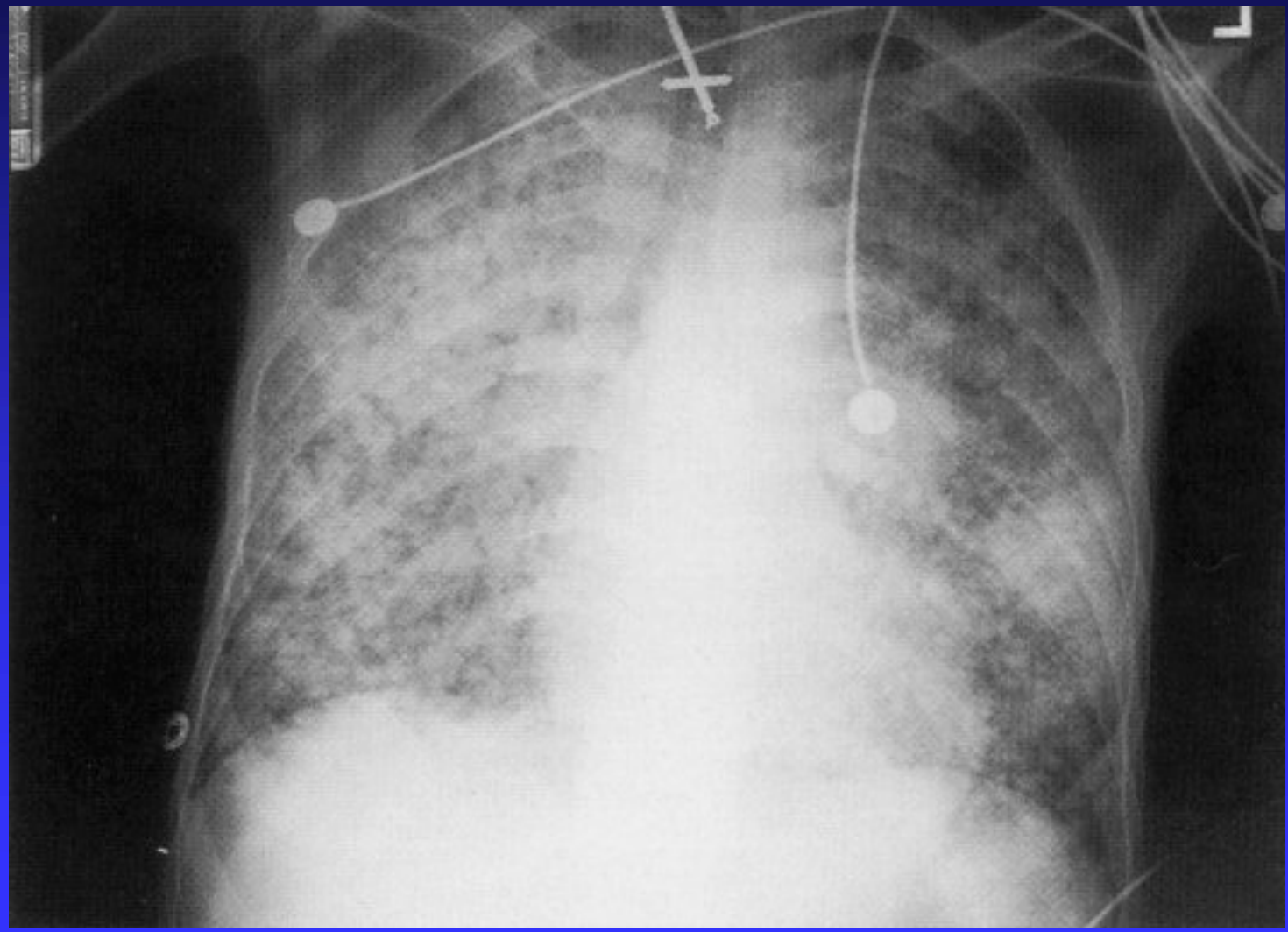


AIDS related Tuberculosis

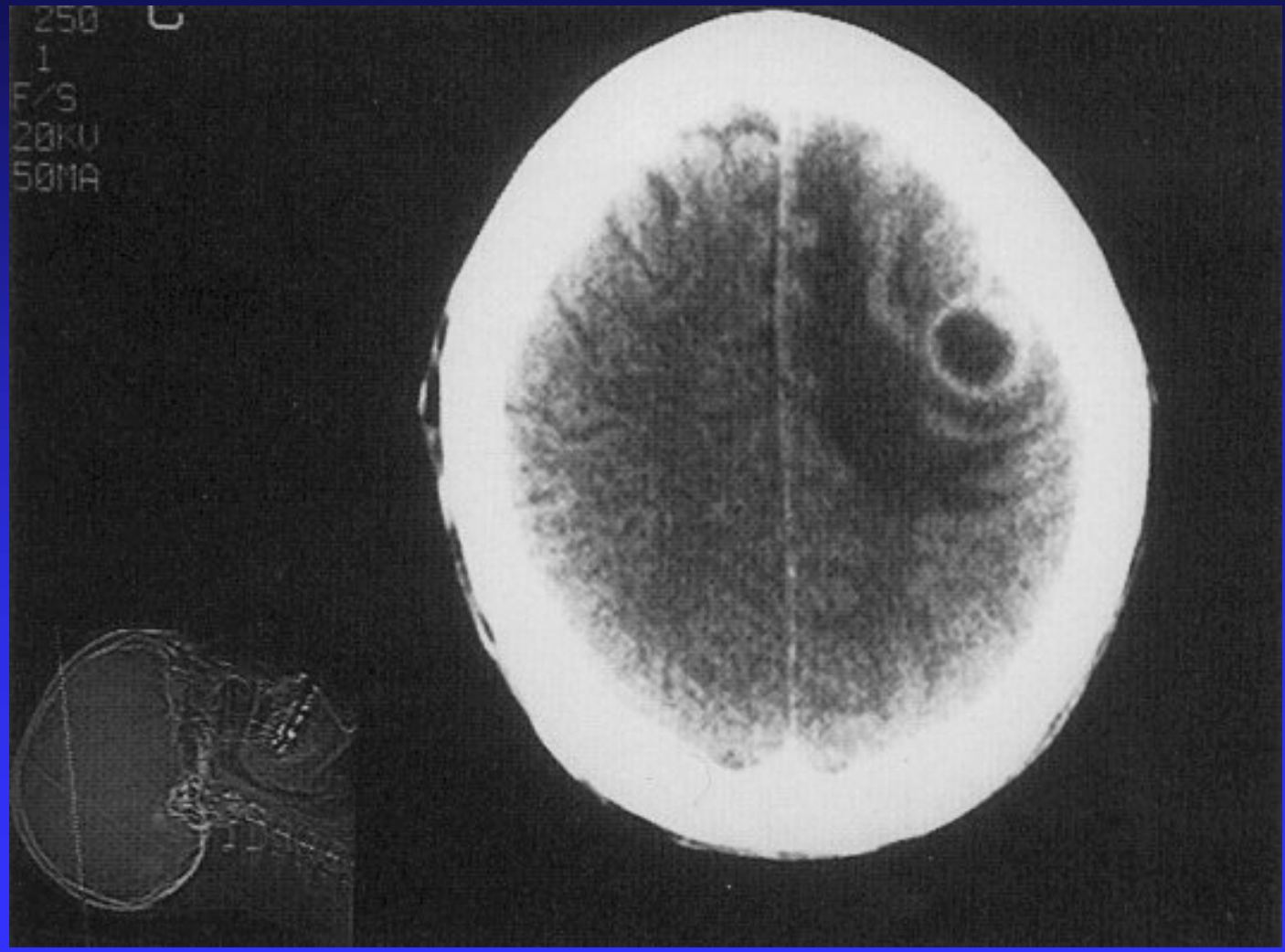




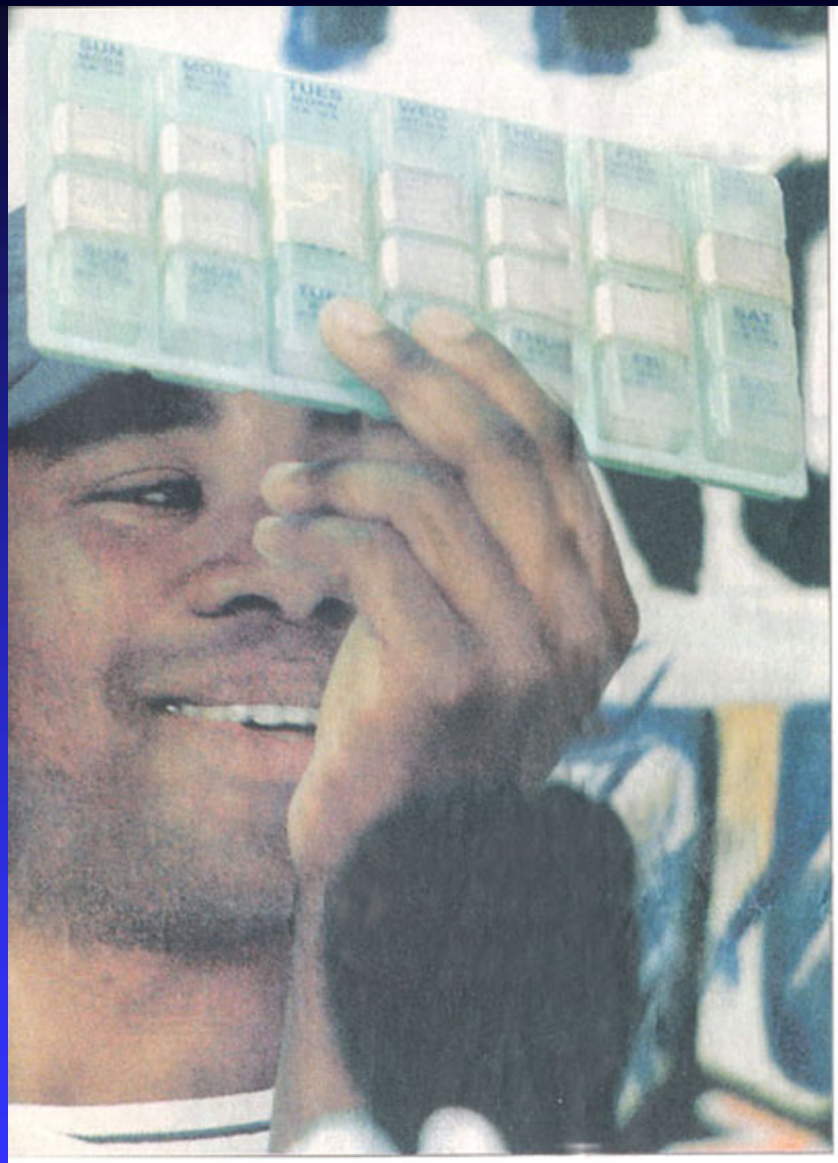
AIDS-related *Pneumocystis carinii* Pneumonia



AIDS-related cerebral Toxoplasmosis:CAT-SCAN



AIDS-related Kaposi Sarcoma



'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.

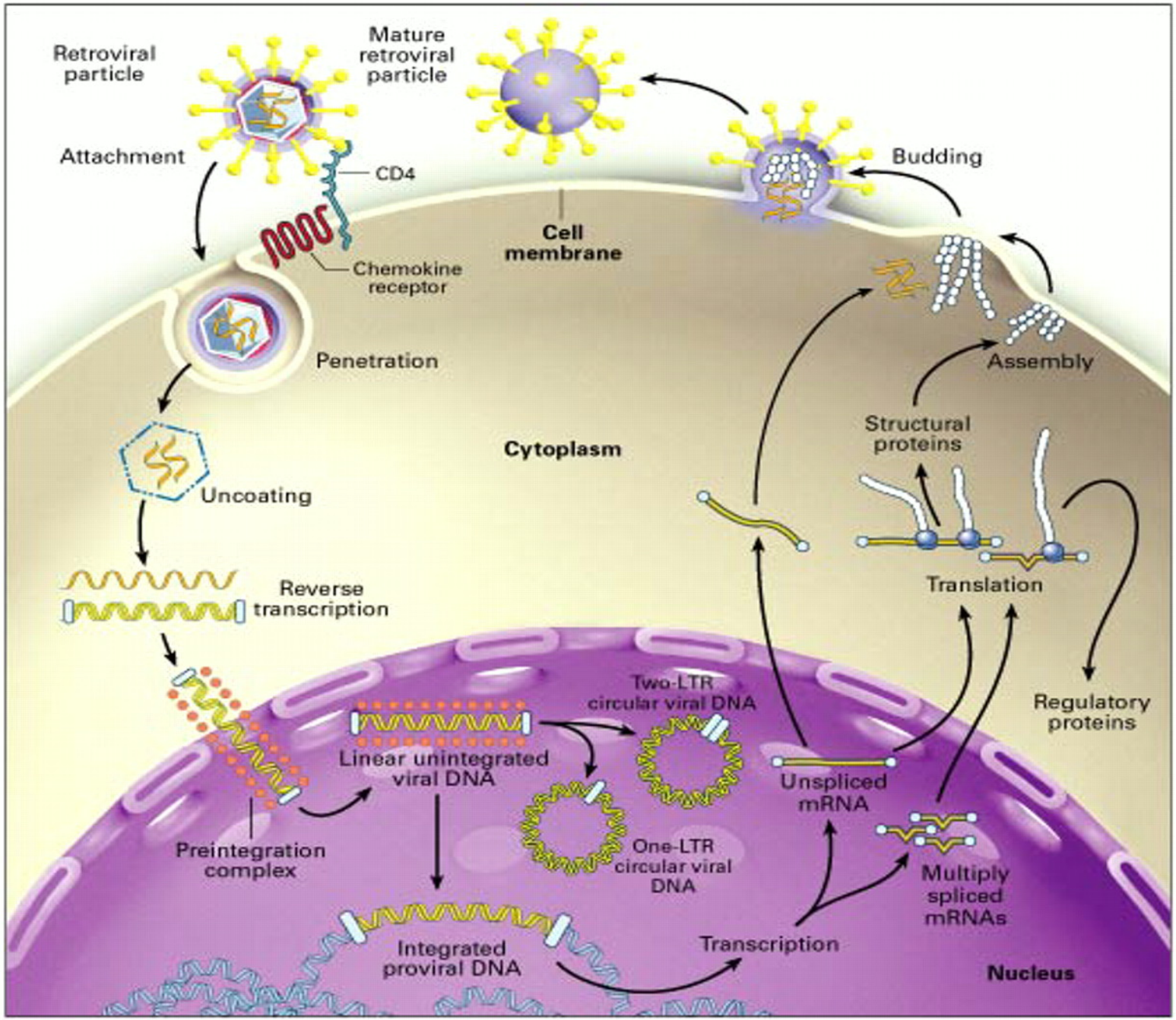
The government did not comment on the activists' calls. It said the MCC would check whether the Brazil import was legal.

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,"

HIV-1 Life Cycle

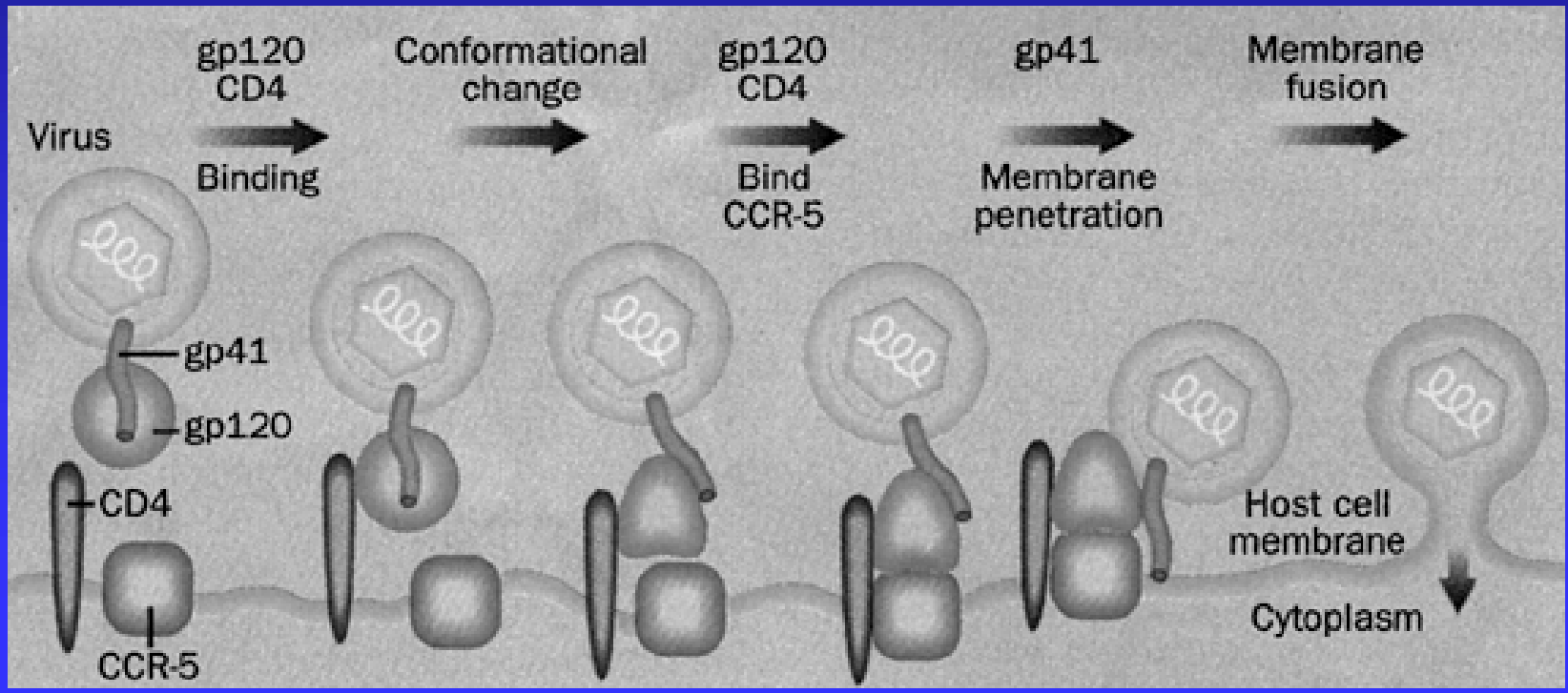


HIV REPLICATIVE CYCLE

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)**

The CCR5 story ...

Doranz, Benjamin J.; Rucker, Joseph; Yi, Yanjie; Smyth, Robert J.; Samson, Michel; Peiper, Stephen C.; Parmentier, Marc; Collman, Ronald G.; Doms, Robert W. **A dual-tropic primary HIV-1 isolate that uses fusin and the β-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors.** Cell (Cambridge, Mass.) (1996), 85(7), 1149-1158.



The CCR5 story ...

Nature 1996 Aug 22;382(6593):722-5

Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene.

Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, Saragosti S, Lapoumeroulie C, Cognaux J, Forceille C, Muyldermans G, Verhofstede C, Burtonboy G, Georges M, Imai T, Rana S, Yi Y, Smyth RJ, Collman RG, Doms RW, Vassart G, Parmentier M

IRIBHN and Services de Génétique Médicale, Virologie and immunodéficiences, Université Libre de Bruxelles, Belgium.

… White blood cells from an individual homozygous for the null allele were found to be highly resistant to infection by M-tropic HIV-1 viruses, confirming that CCR-5 is the major co-receptor for primary HIV-1 strains.

A number of CCR5 antagonists are currently in clinical trials…

HIV REPLICATIVE CYCLE

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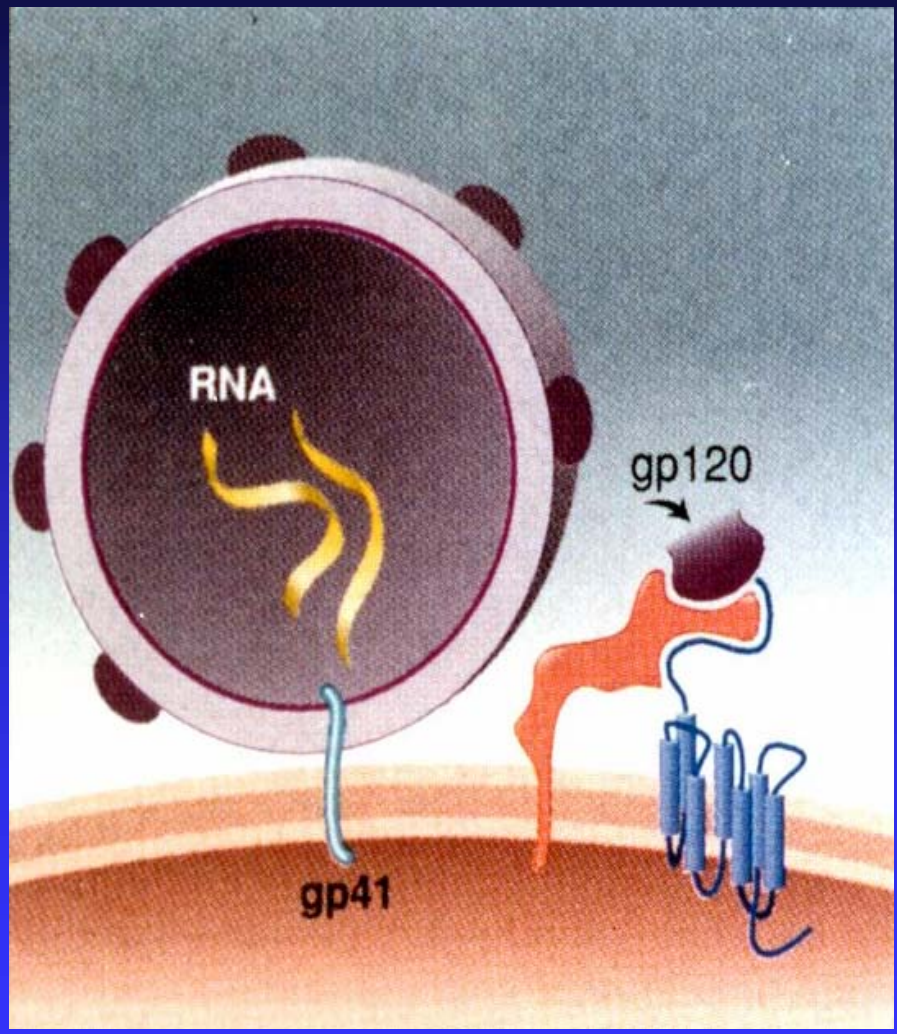
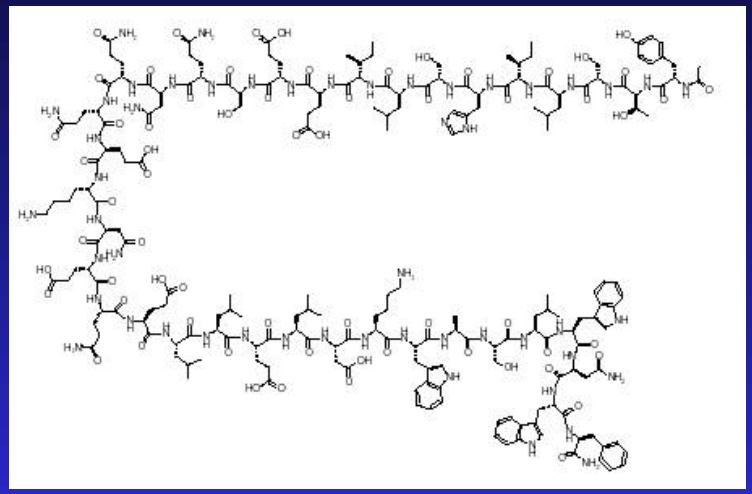
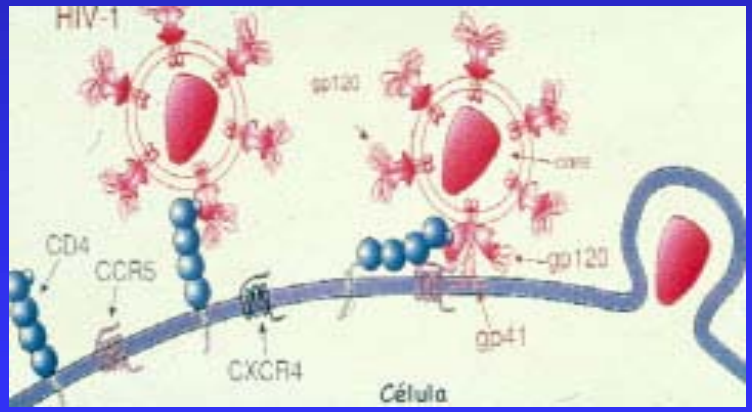
VIRUS-CELL FUSION

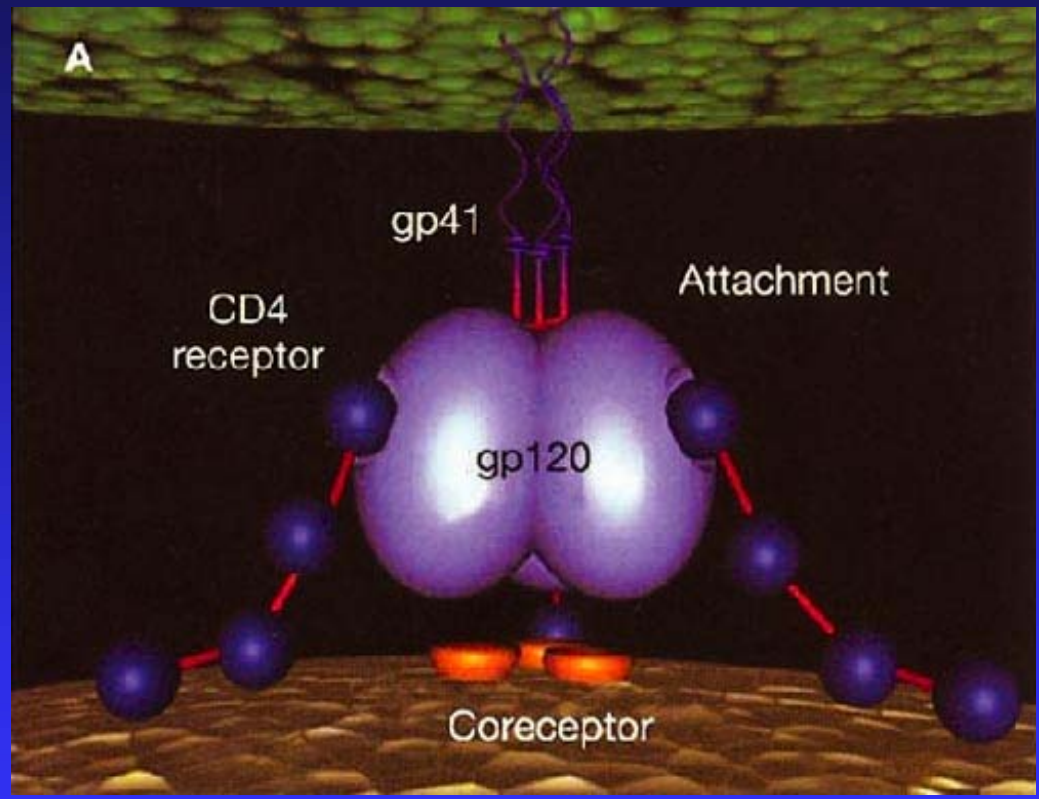


J. Cohen, Science 274, 502 (1996)

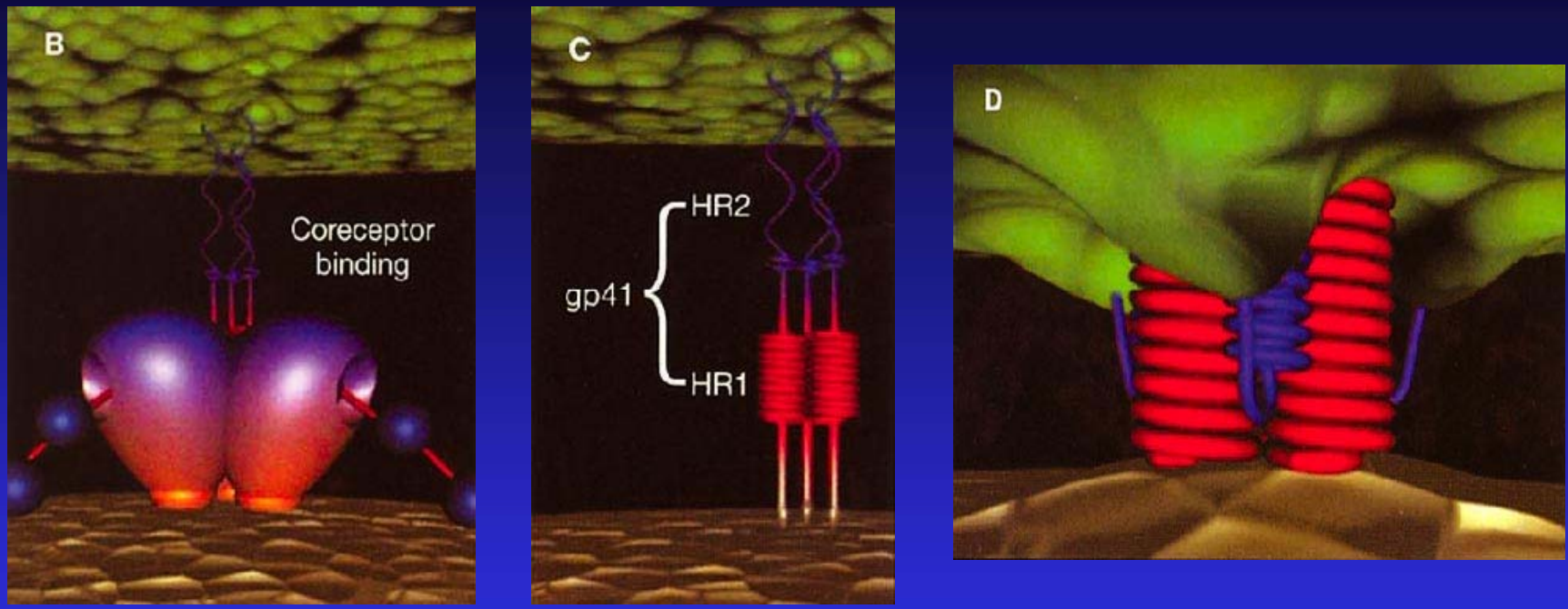
Inhibiteur de fusion: l'enfuvirtide







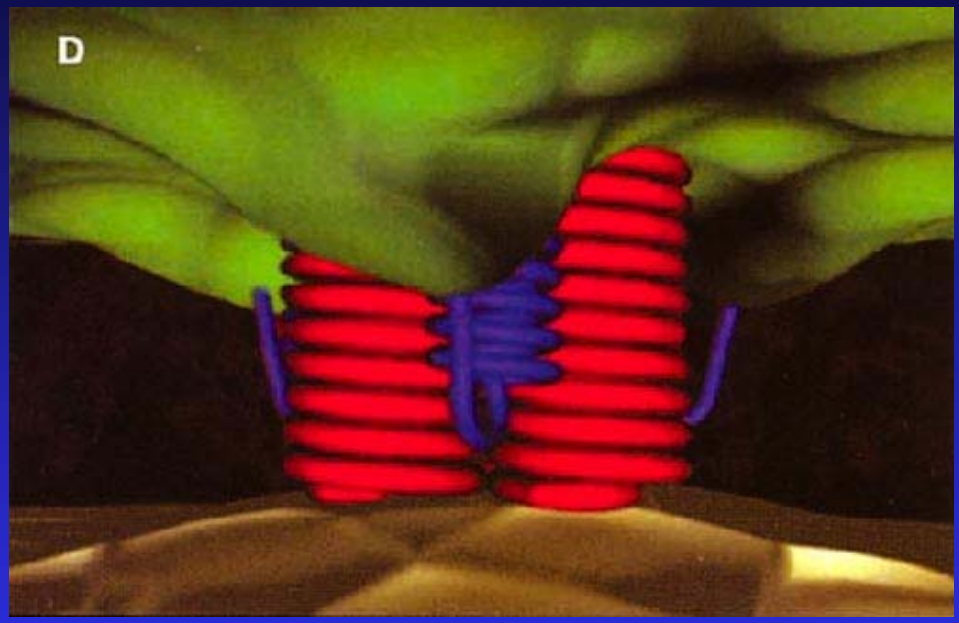
Inhibiteur de fusion: l'enfuvirtide

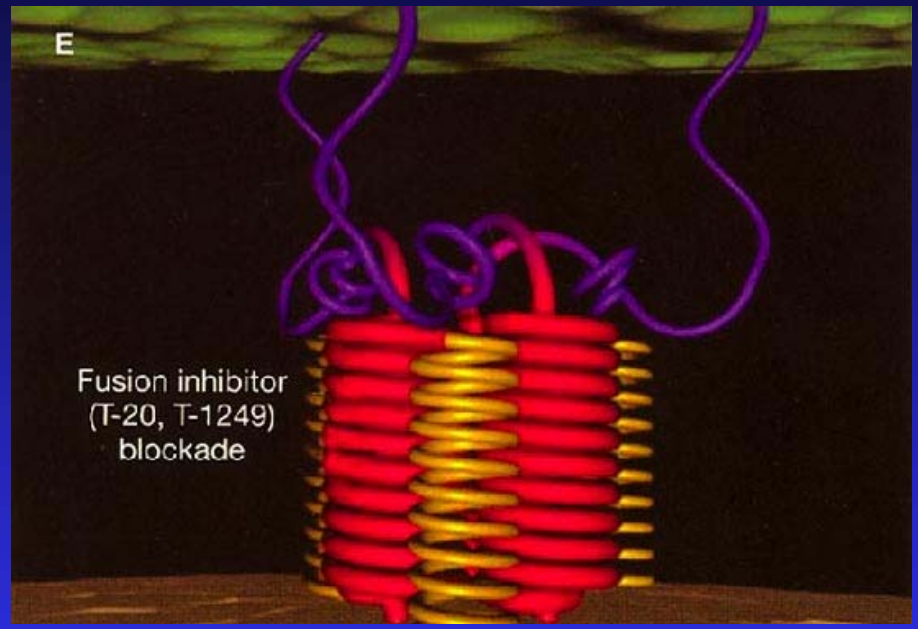


The extracellular domain of gp41 contains a fusion peptide (FP) and 2 helical regions (HRs), HR1 and HR2. The FP region is made up of hydrophobic, glycine-rich residues essential for initiation of penetration into target cell membranes [1, 3, 4]. When fusion occurs, FP inserts into the target cell membrane, 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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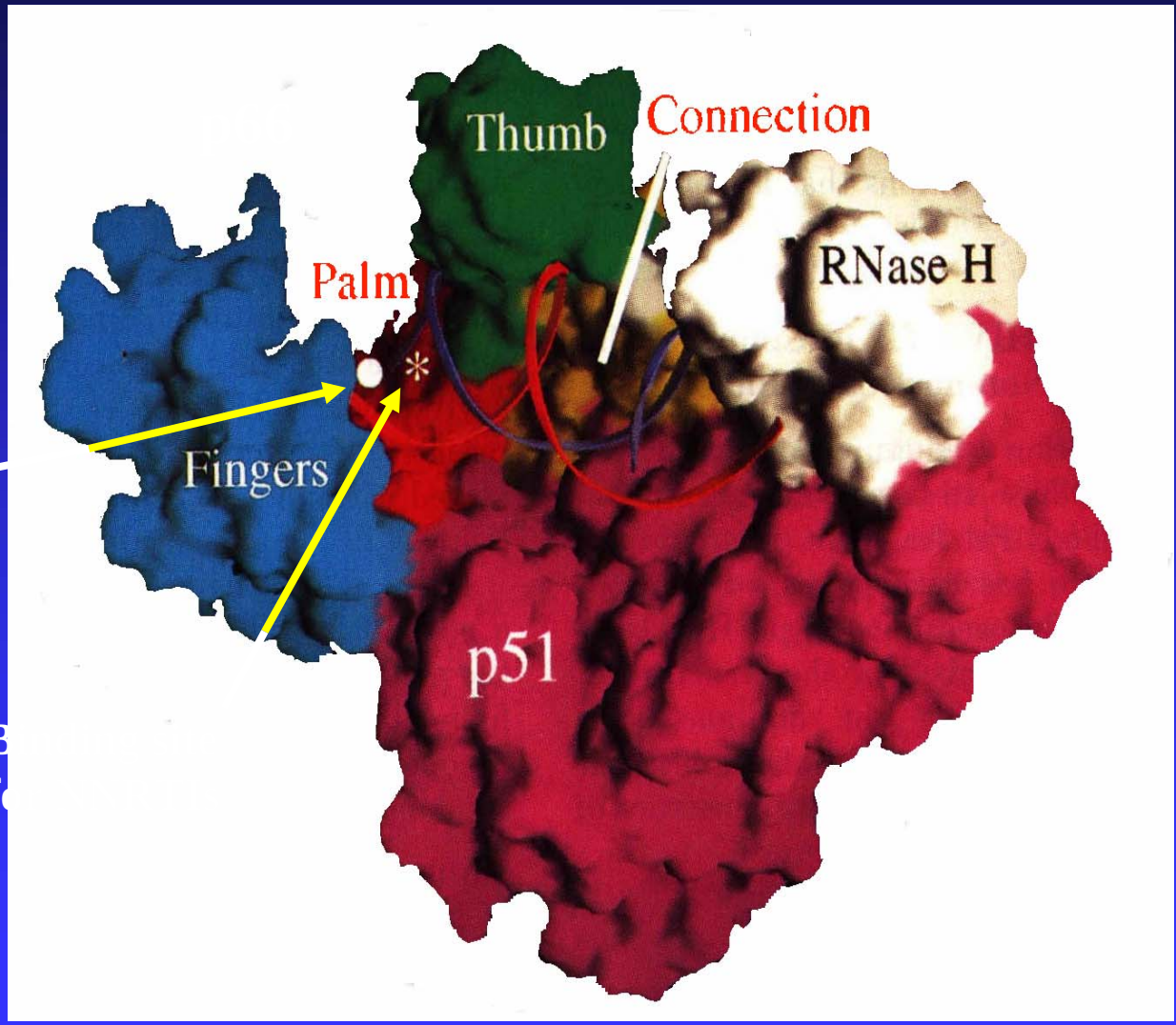
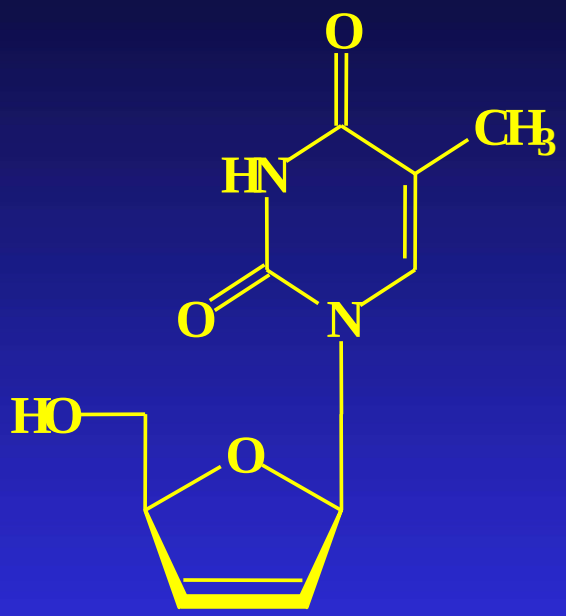
HIV Reverse Transcriptase



Binding site for NRTIs and NtRTIs

Zidovudine

3’-Azido-2’,3’-dideoxythymidine
AZT



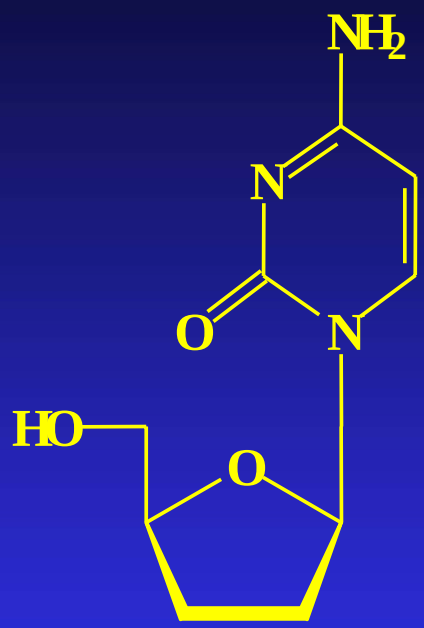
2’,3’-Didehydro-
2’,3’-dideoxythymidine
D4T

Didanosine

2’,3’-Dideoxyinosine
DDI

Lamivudine

2’,3’-Dideoxy-3’-thiacytidine
3TC



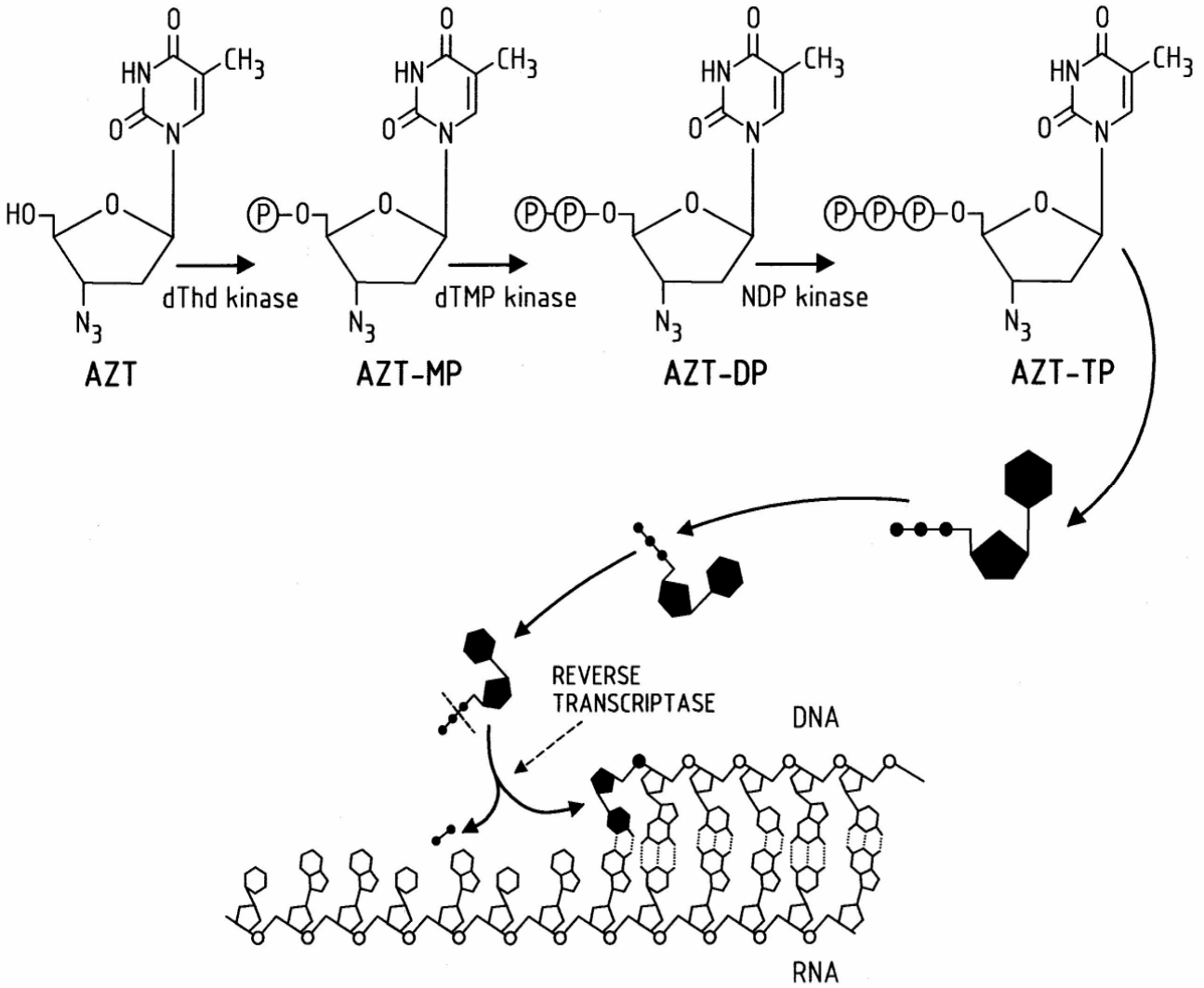
Zalcitabine

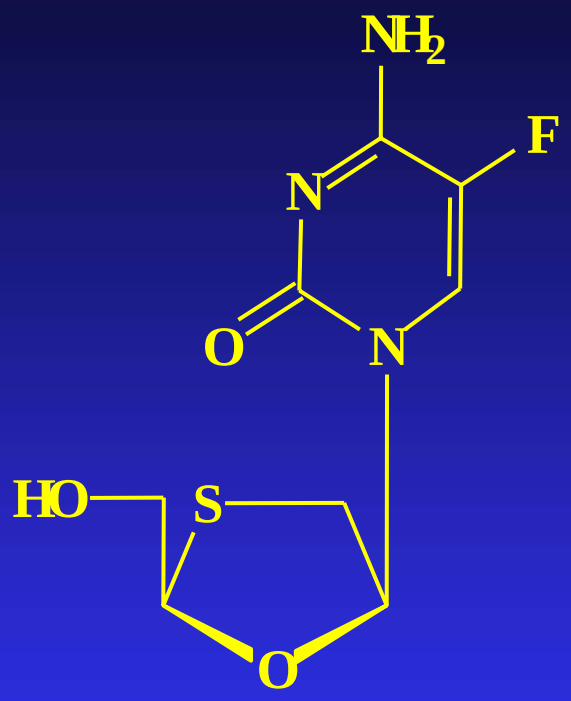
2’,3’-Dideoxycytidine
DDC

Abacavir

1592U89

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

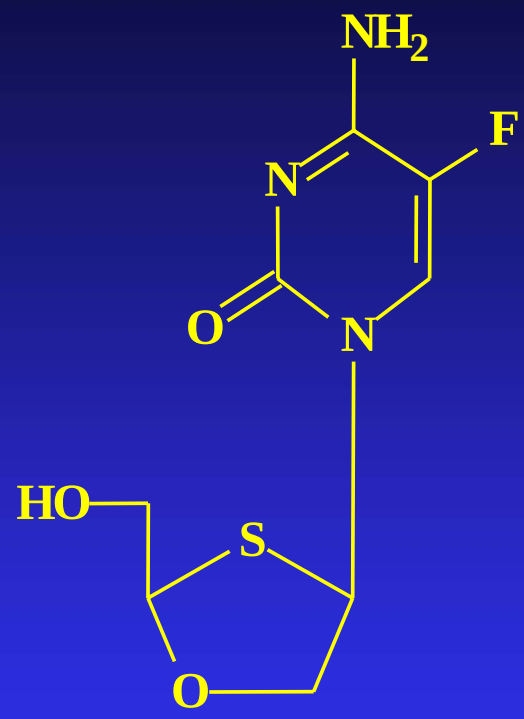




Emtricitabine

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

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



FdOTC

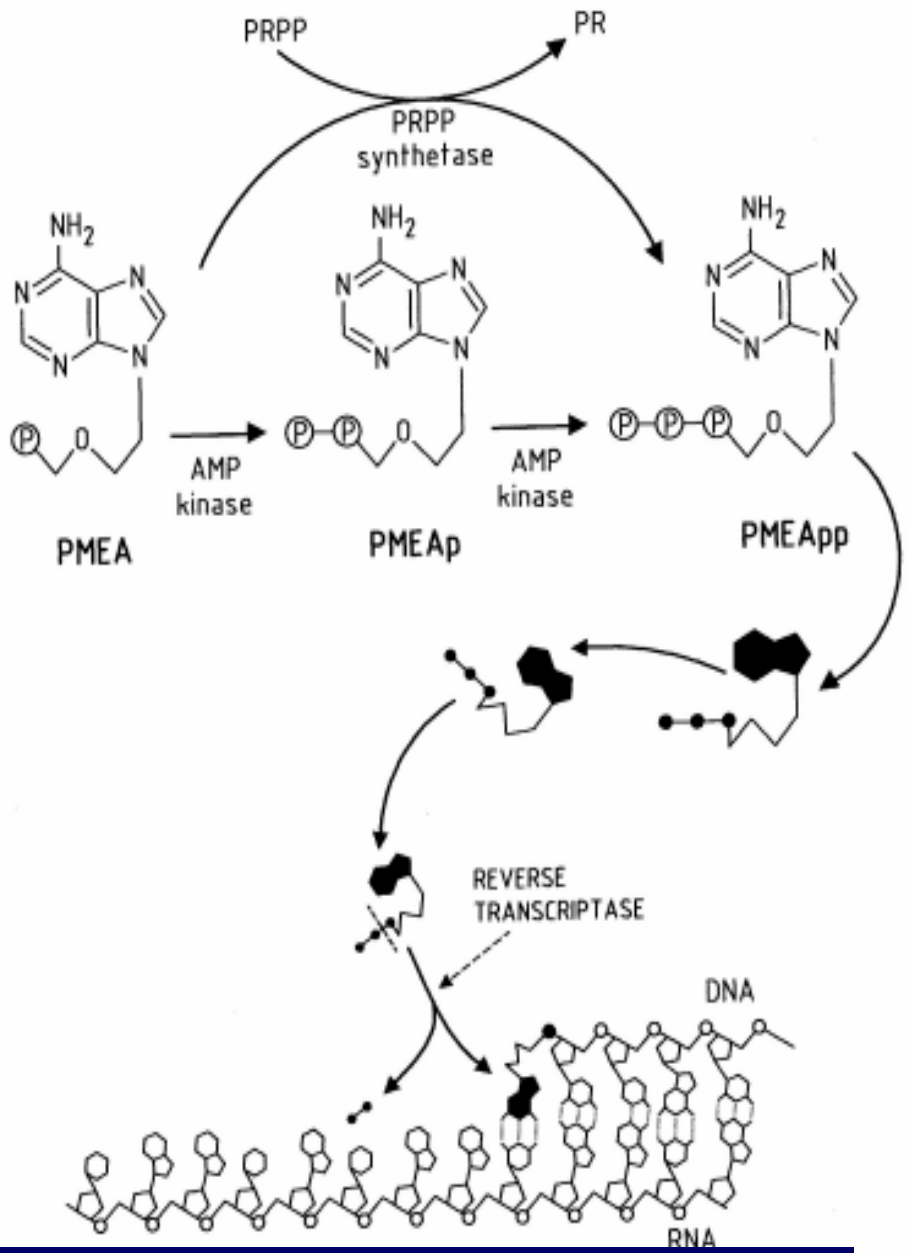
R = H : PMEA

adefovir

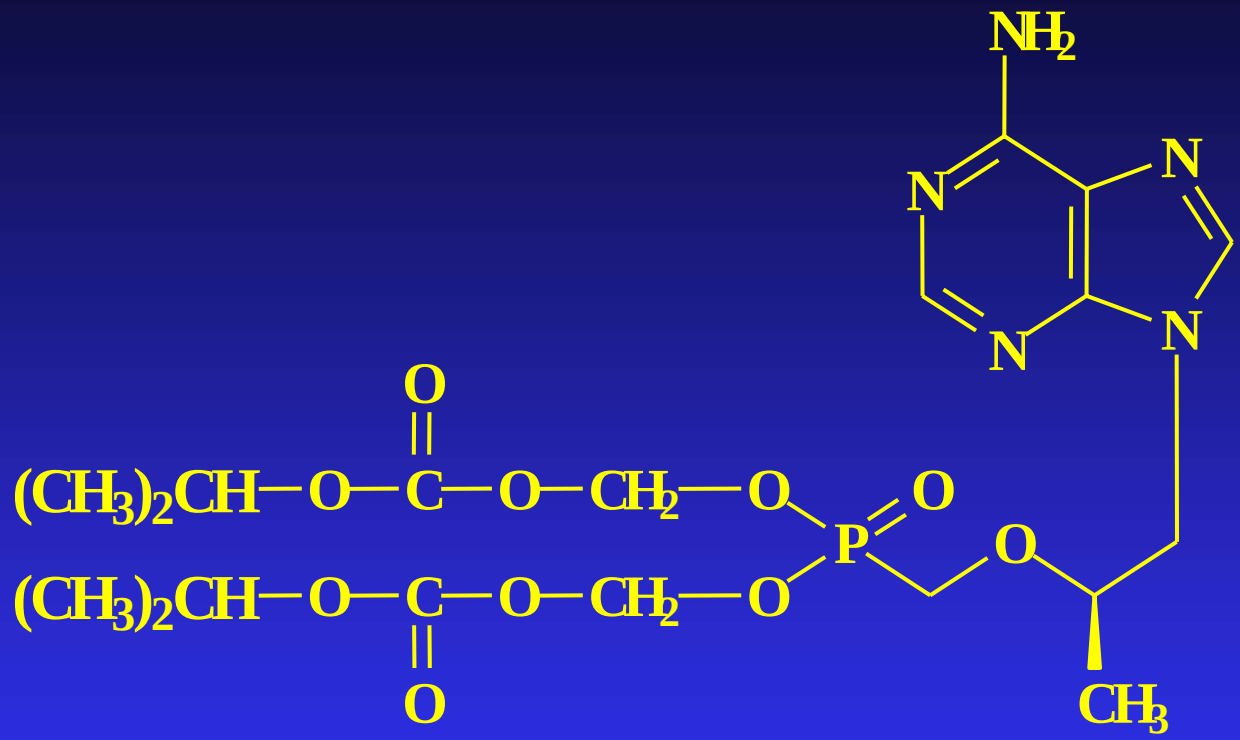
R = H : (R)-PMPA

tenofovir

Mechanism of action of adefovir (PMEA)



Similar mechanism of action applicable to tenofovir (PMPA)

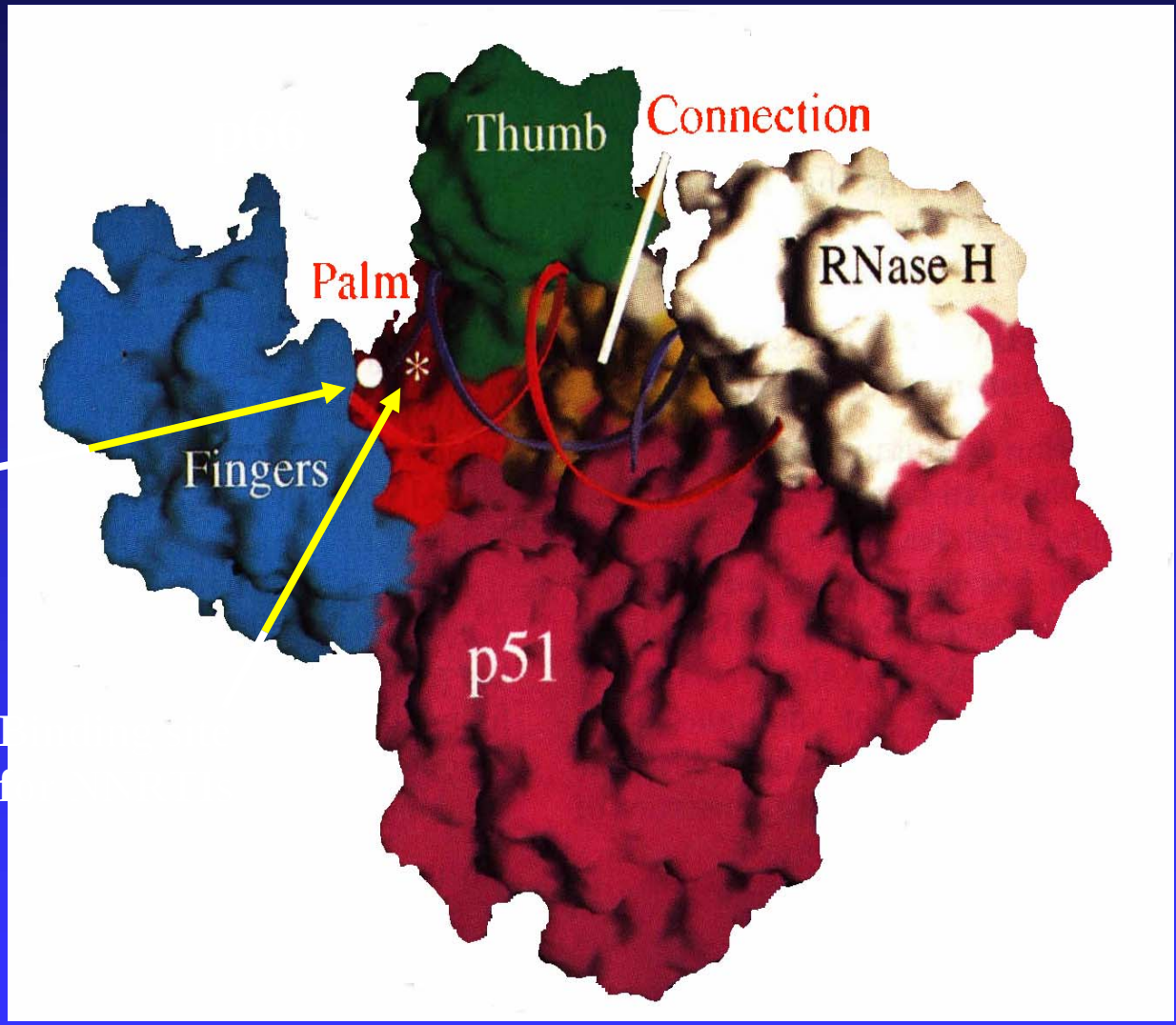


fumarate

bis(POC)-PMPA
Tenofovir disoproxil
Viread®

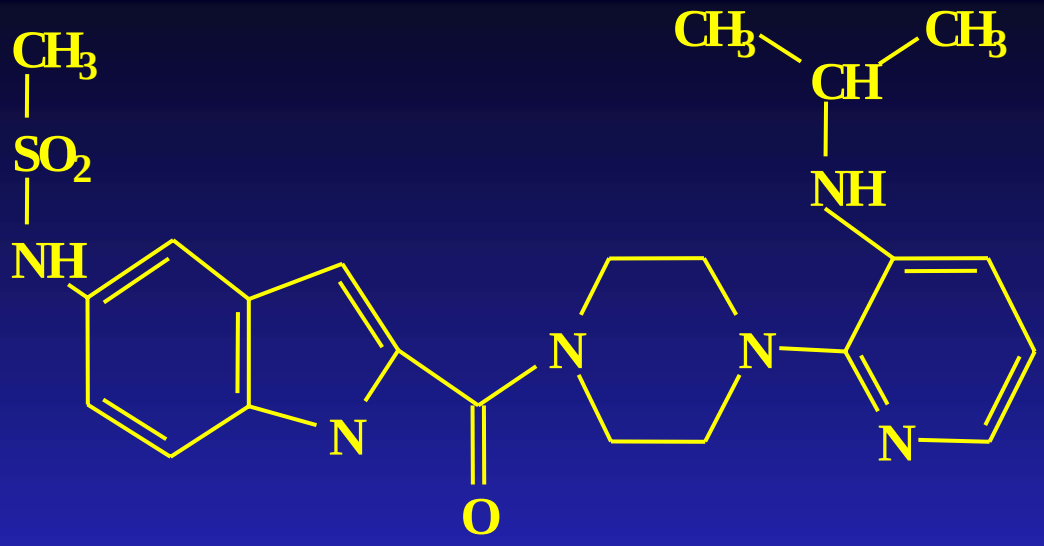
HIV Reverse Transcriptase

Binding site for NRTIs and NtRTIs

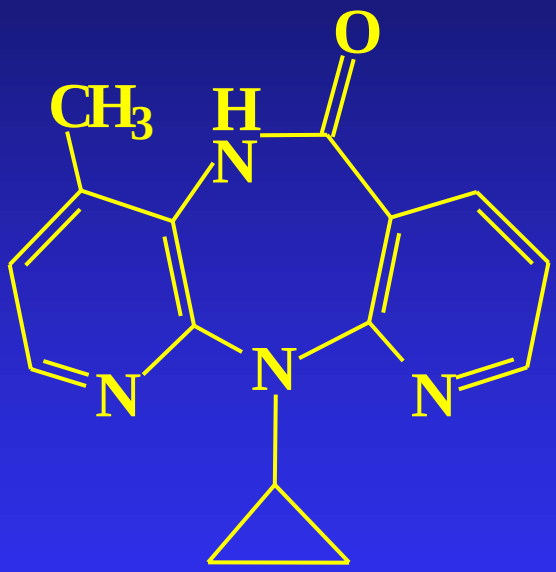


U-90152S

Delavirdine



• CH_3SO_3H



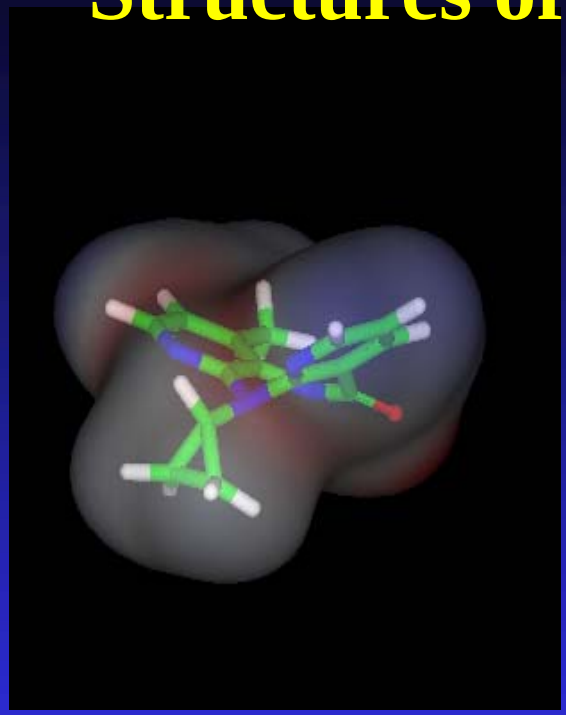
Nevirapine

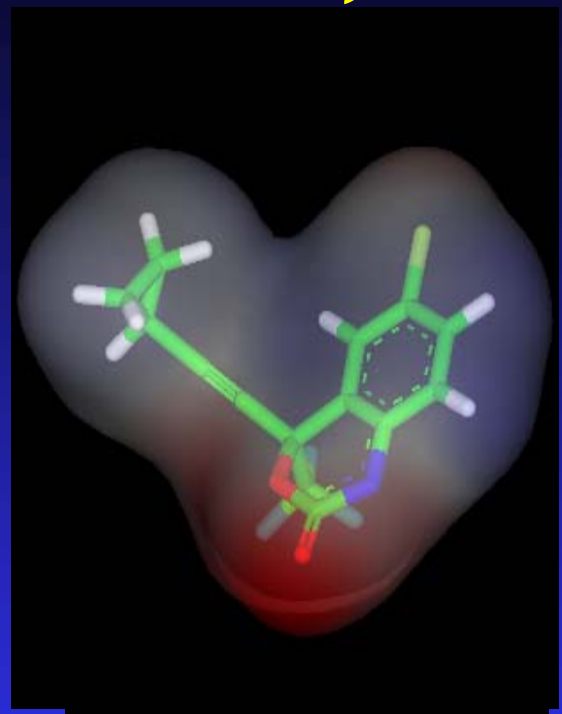
BI-RG-587

Benzoxazinone

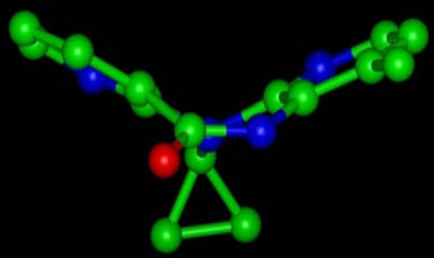
Efavirenz

Structures of classical NNRTI's, ...

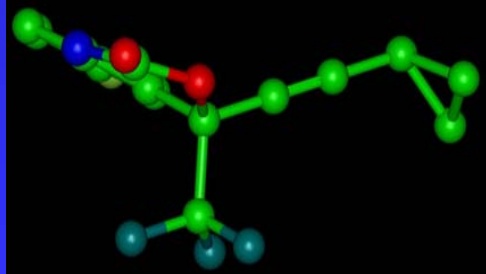




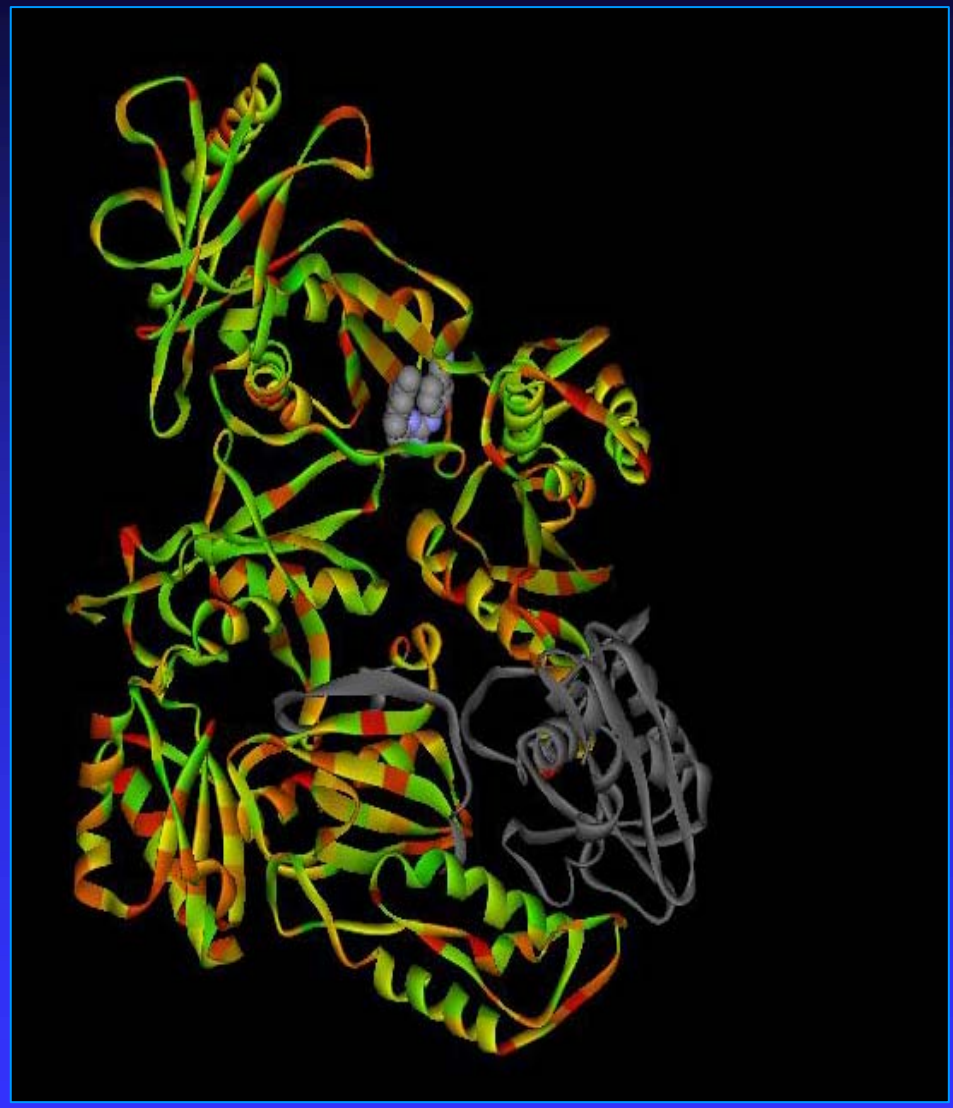
nevirapine

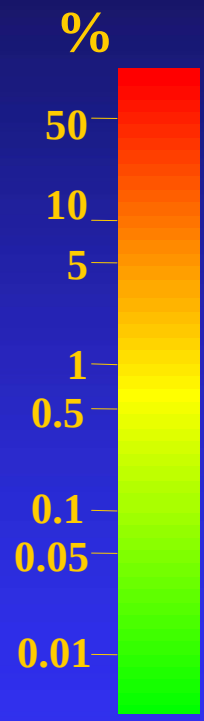


efavirenz



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





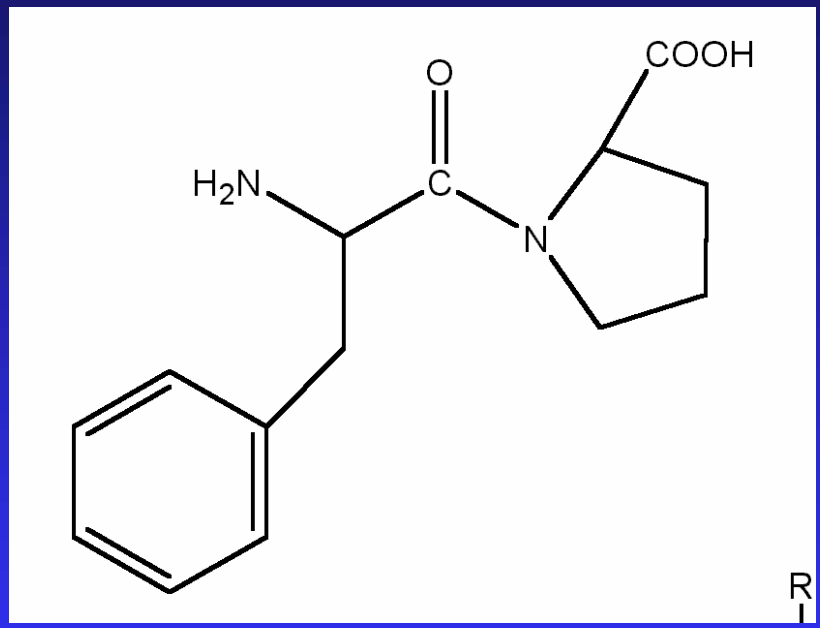
HIV REPLICATIVE CYCLE

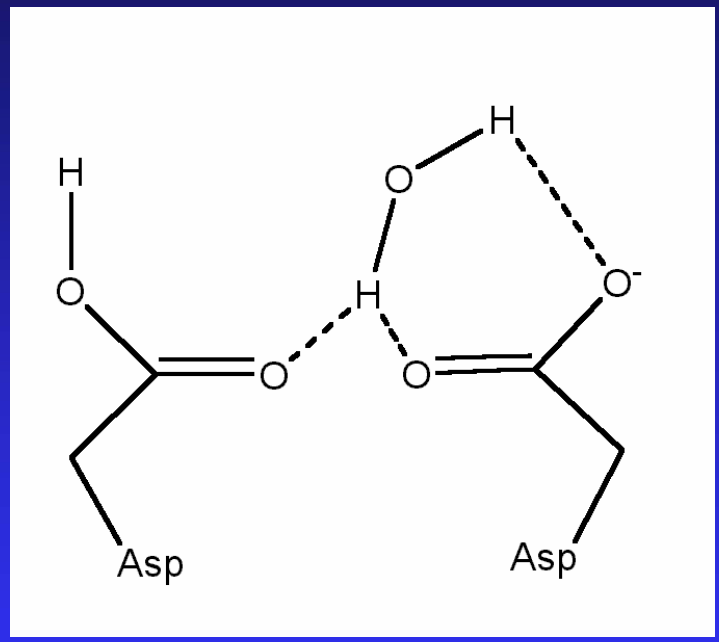
- Virus adsorption
- Virus-cell fusion
- Virus uncoating
- Reverse transcription
- Proviral DNA integration
- Proviral DNA replication
- Proviral DNA transcription to viral mRNA
- Viral mRNA translation to viral precursor proteins
- **Maturation (proteolysis/myristoylation/glycosylation)**
- Budding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

Processing of peptide synthetized by the HIV genome

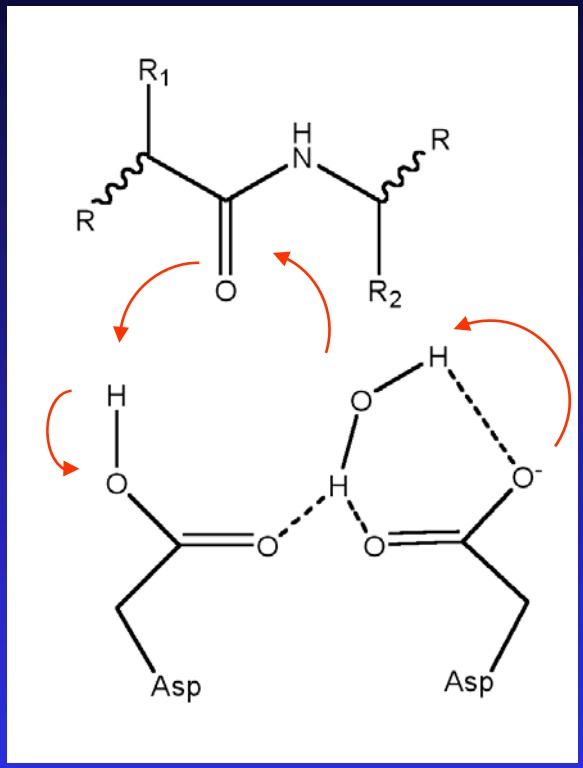
- Retrovirally encoded proteases are responsible for the maturation of immature viral particles yielding mature, infectious virus.
- This is done by self-activation of the protease (PR) from a larger viral gag-PR-(pol) protein (zymogen) precursor and subsequent processing of the viral reverse transcriptase (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.**

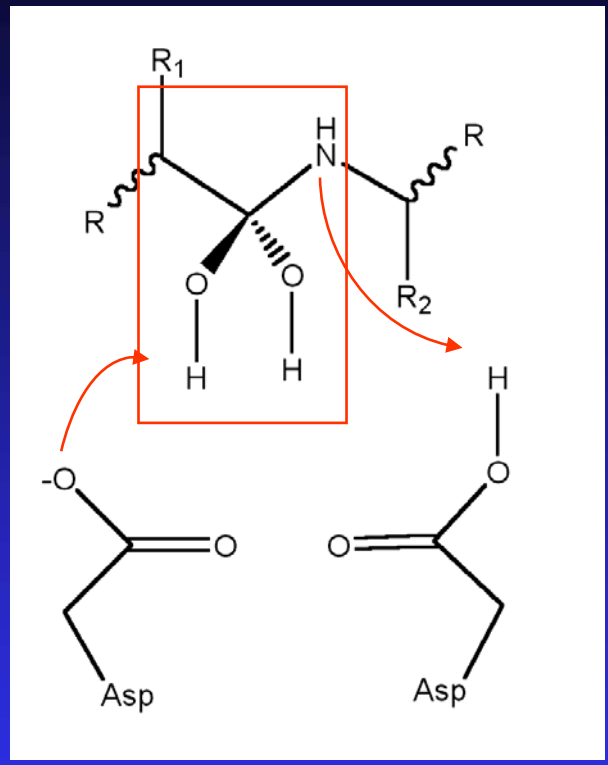
Lien Phe-Pro et aspartate protease ...

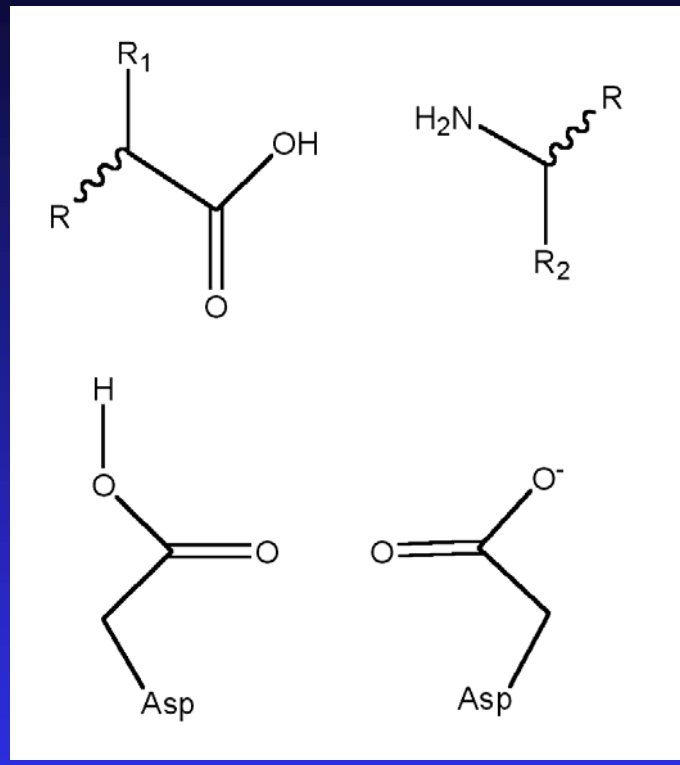




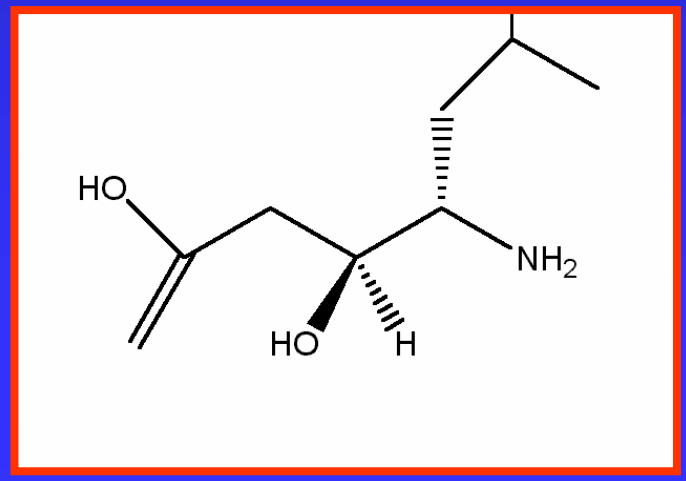
Mechanism of aspartate protease and typical inhibitor (pepstatin)

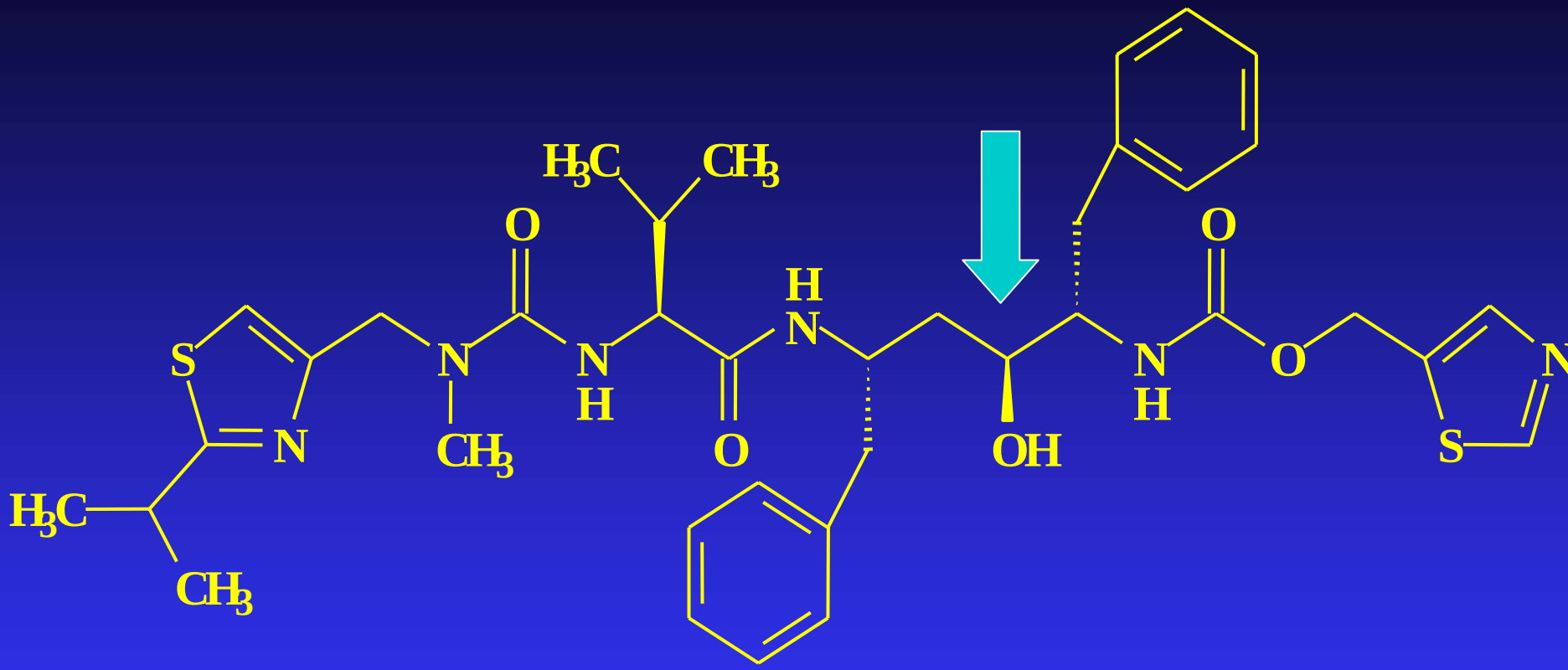




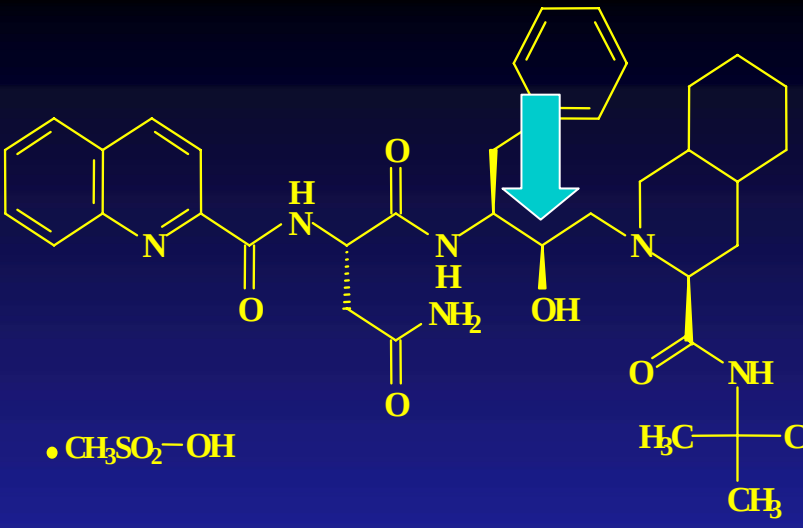


Pepstatine...

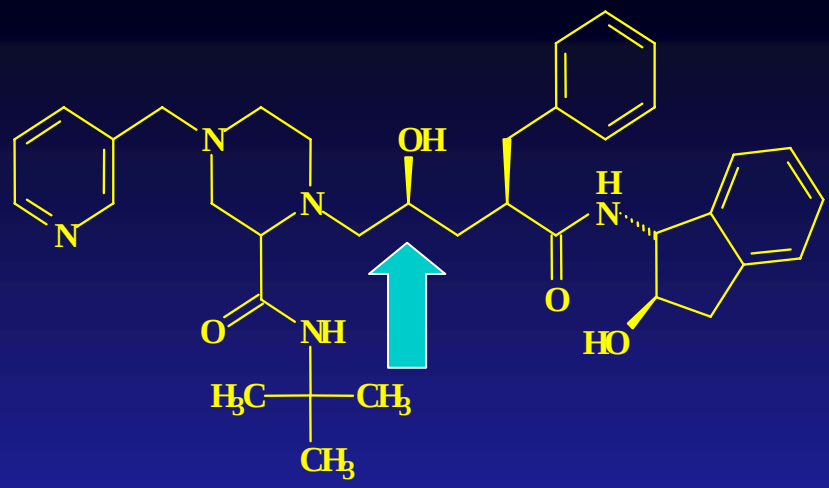




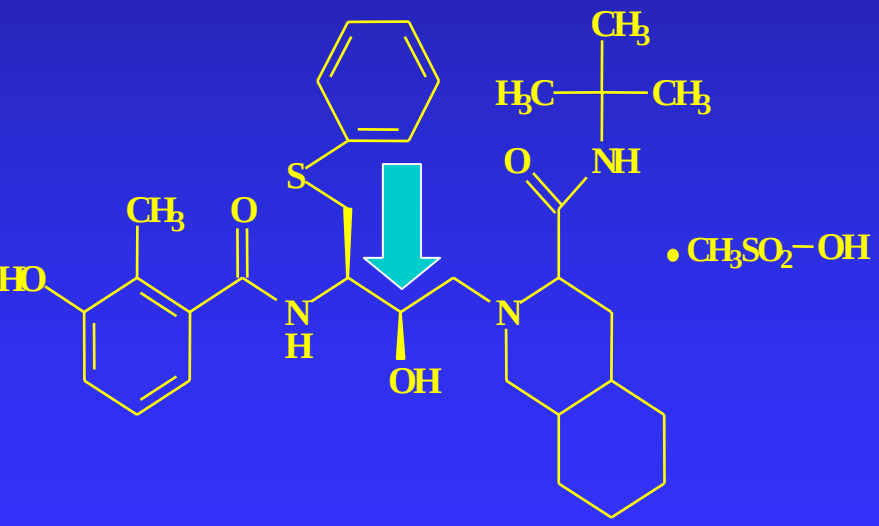
Ritonavir



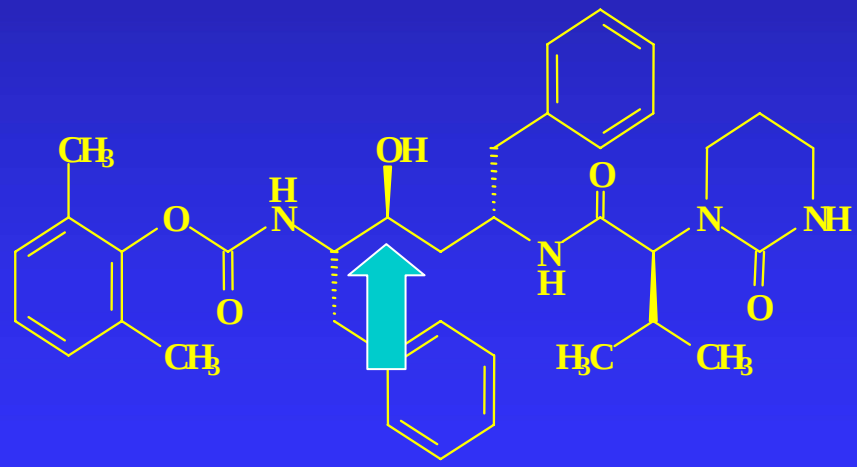
Saquinavir



Indinavir

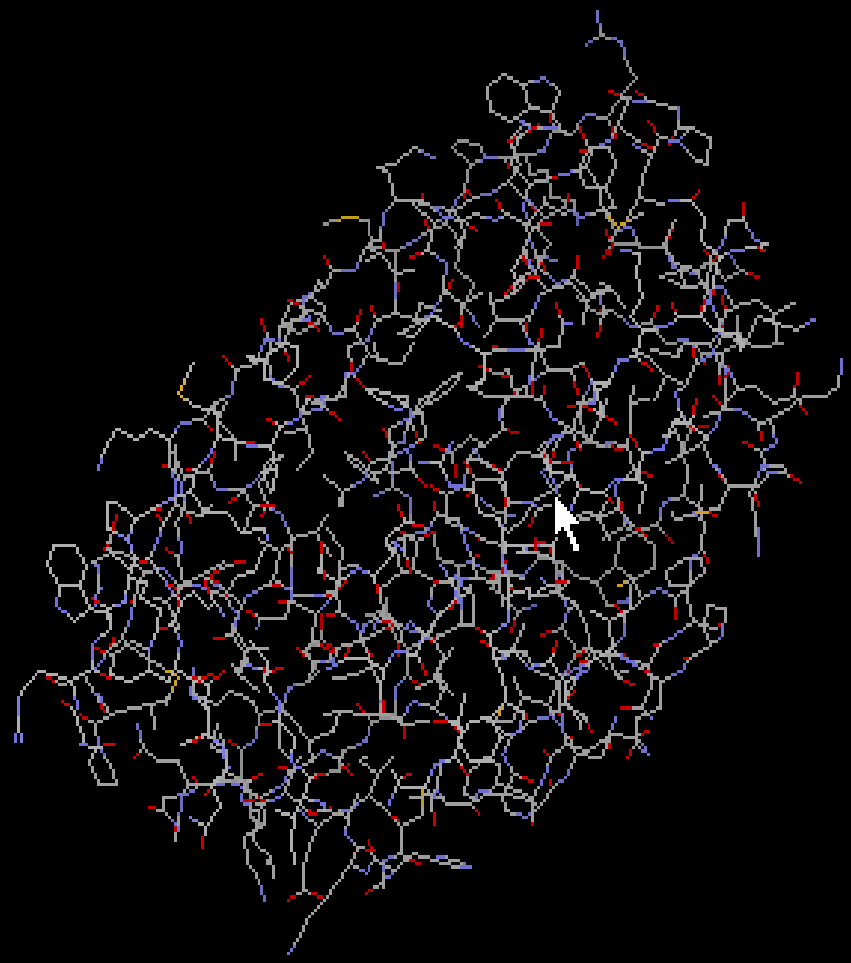


Nelfinavir



Lopinavir

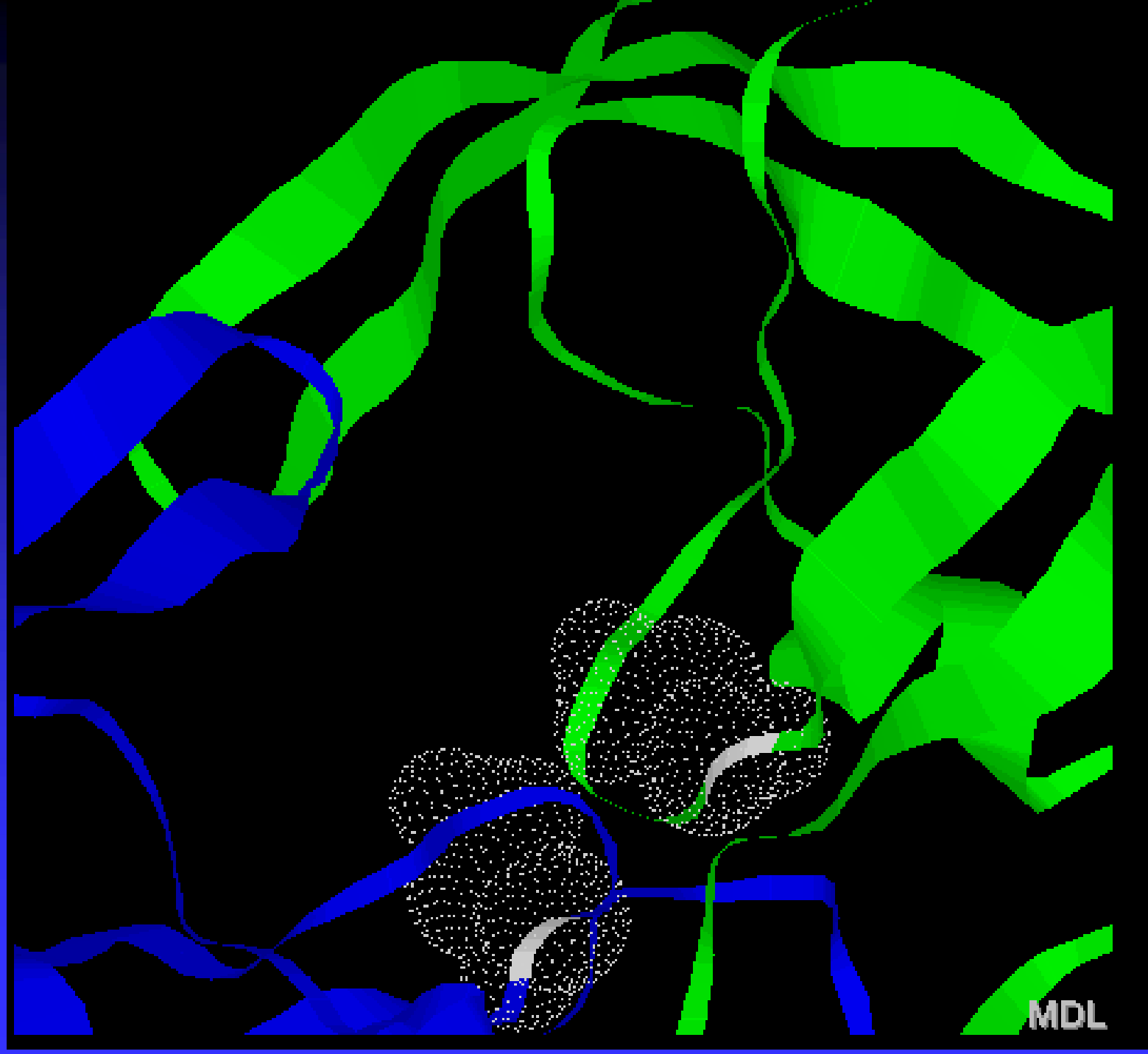
HIV protease



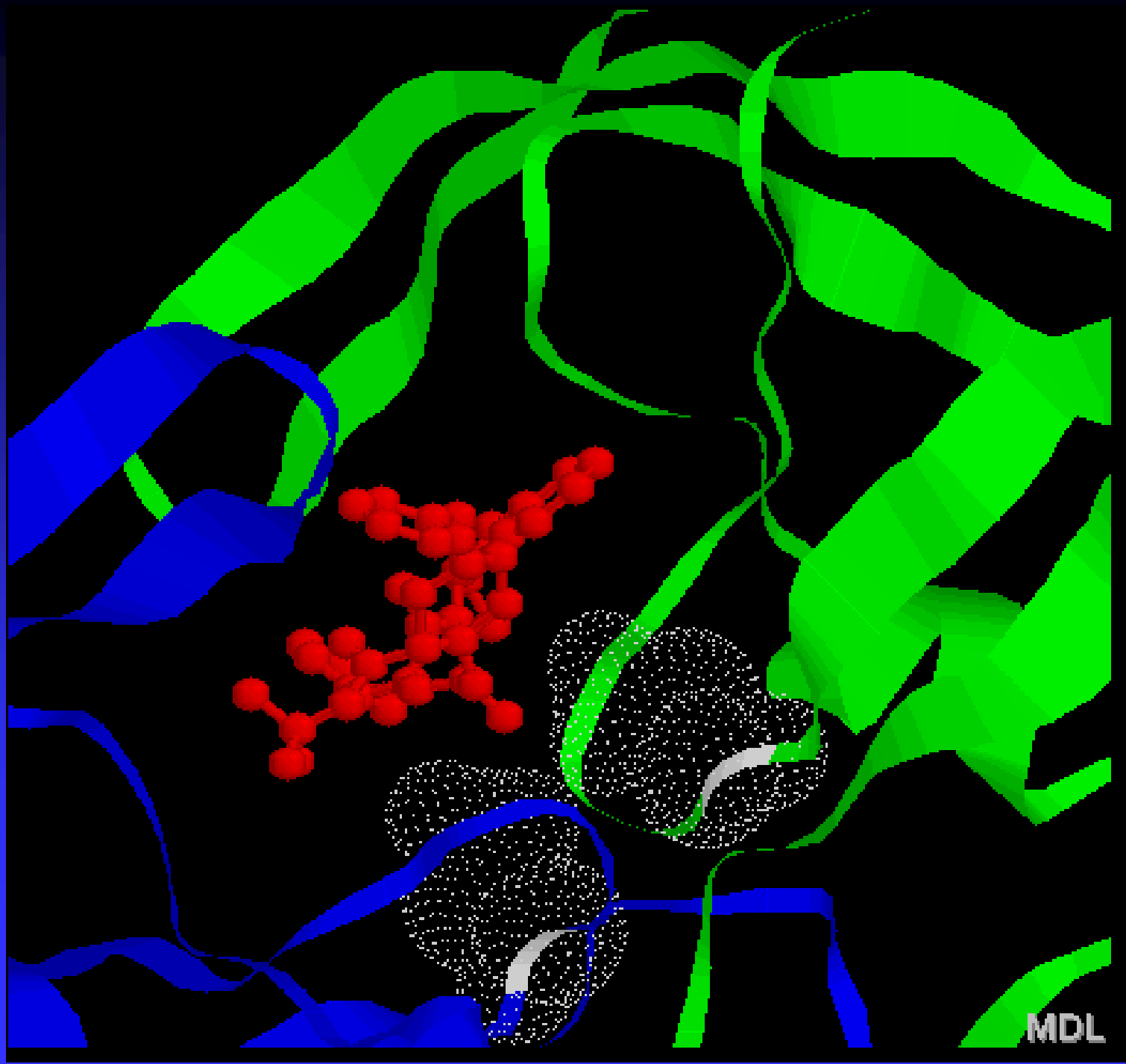
MDL

HIV protease

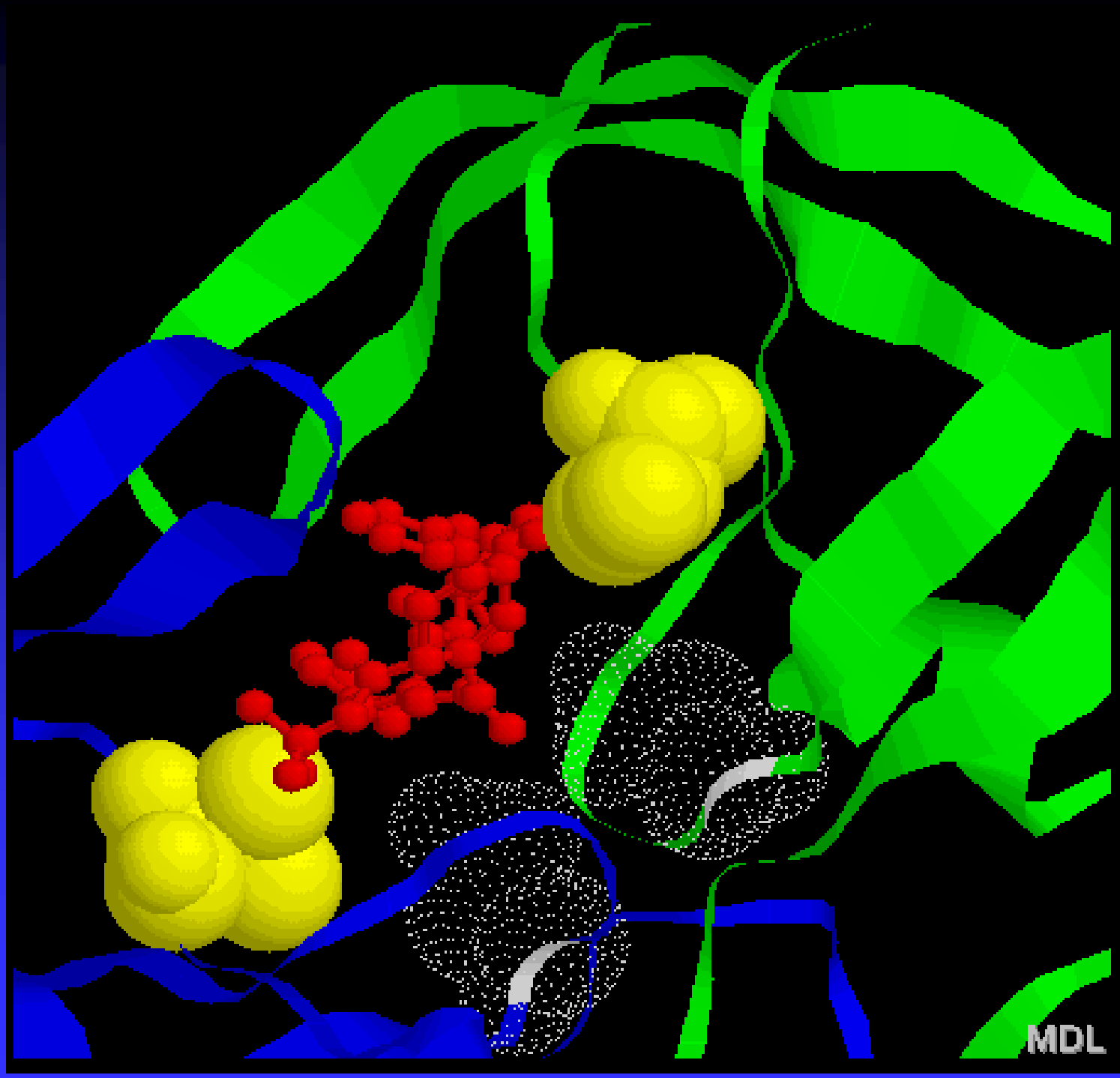
HIV protease



HIV protease



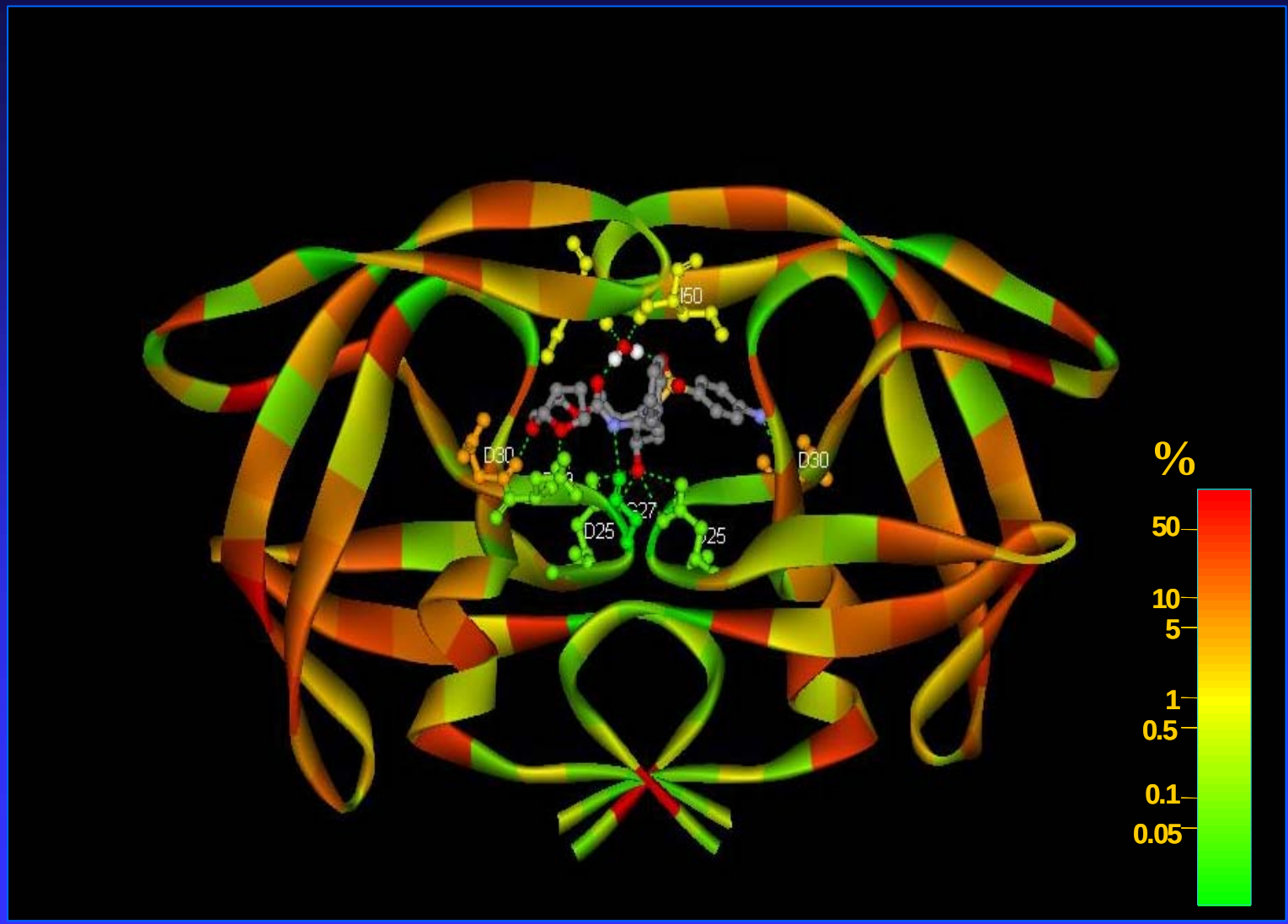
HIV protease



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

	10	20	24	30	32	33	36	46	47	48	50	53	54	63	71	73	77	82	84	88	90
Multi-PI Resistance: Accumulation of Mutations	L → F, I, R, V							M → I, L					I → V, M, L					V → A, F, T, S	I → V		L → M
Indinavir	L → I, R, V	K → M, R	L → I		V → I		M → I	M → I, L					I → V		A → V, T	G → S, A	V → I	V → A, F, T	I → V		L → M
Ritonavir	L → F, I, R, V	K → M, R			V → I	L → F	M → I	M → I, L					I → V, L		A → V, T		V → I	V → A, F, T, S	I → V		L → M
Saquinavir	L → I, R, V									G → V			I → V, L		A → V, T	G → S	V → I	V → A	I → V		L → M
Nelfinavir	L → F, I			D → N			M → I	M → I, L							A → V, T		V → I	V → A, F, T, S	I → V	N → D, S	L → M
Amprenavir	L → F, I, R, V				V → I			M → I, L	I → V		I → V		I → L, V, M			G → S			I → V		L → M
Lopinavir/ Ritonavir	L → F, I, R, V	K → M, R	L → I		V → I	L → F		M → I, L	I → V		I → V	F → L	I → V, L	L → P	A → V, T	G → S		V → A, F, T, S	I → V		L → M
Atazanavir (expanded access)					V → I			M → I			I → L		I → L		A → V			V → A	I → V	N → S	L → M

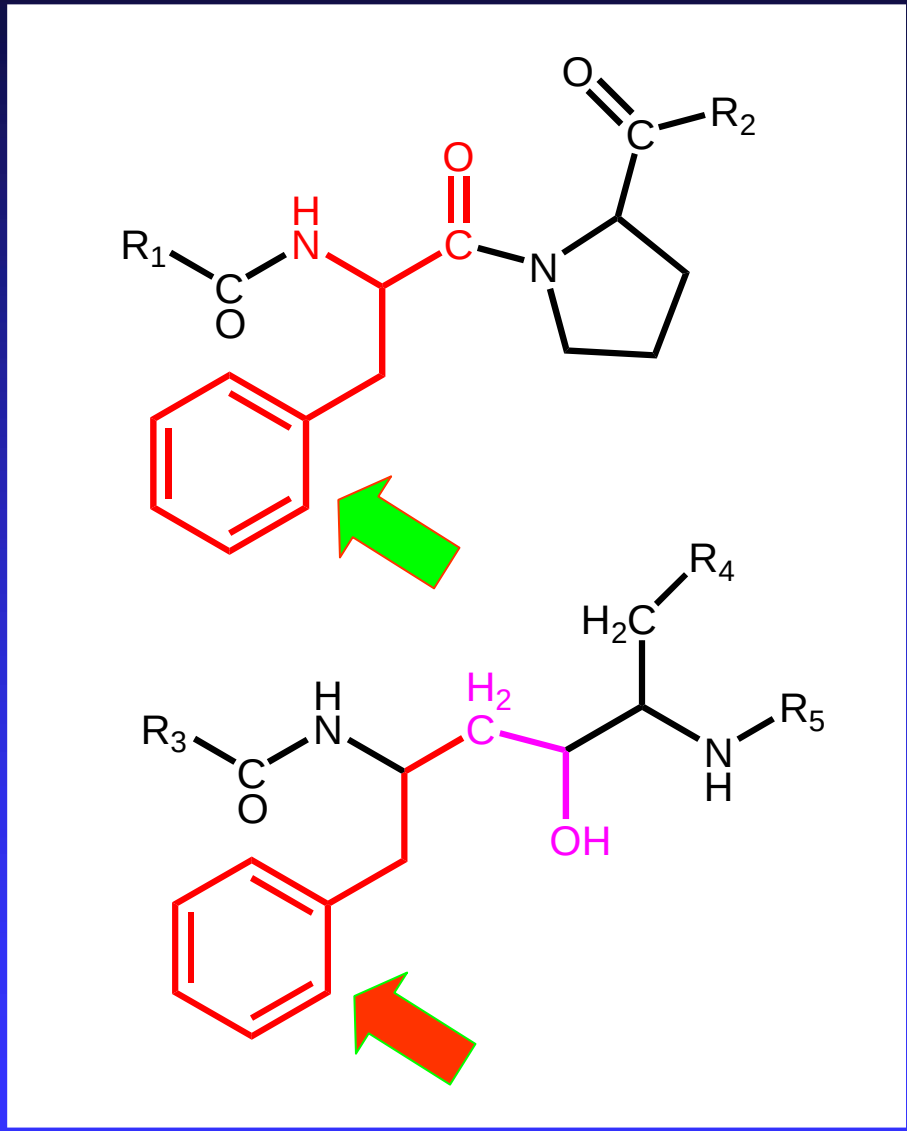
HIV protease genetic variability after PI drug pressure (N = 30,000)



Pauwels - HIV Dart 2002 – December 15-19, Naples, Florida

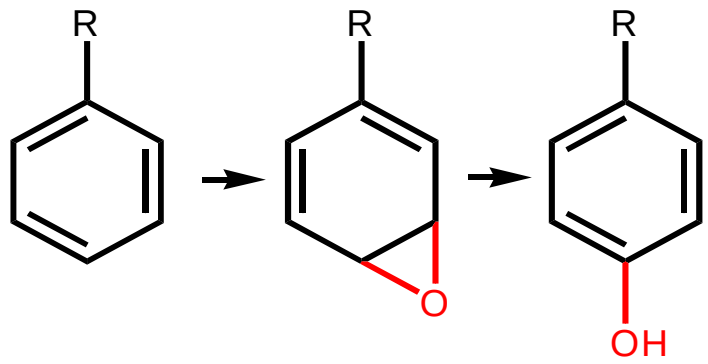
Interférences médicamenteuses et inhibiteurs de protéase …

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

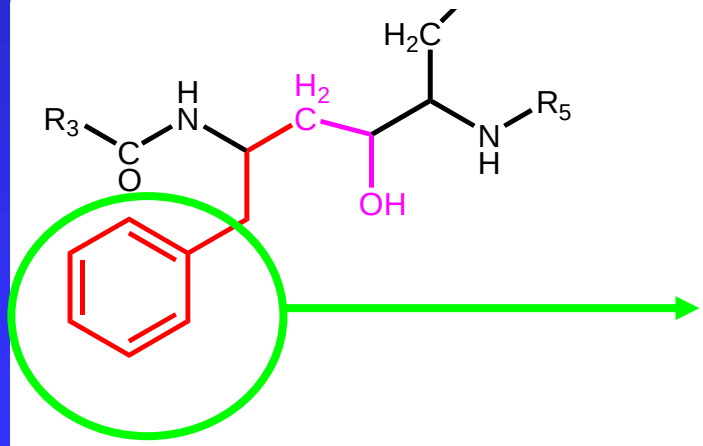


Métabolisme des substances à noyau aromatique…

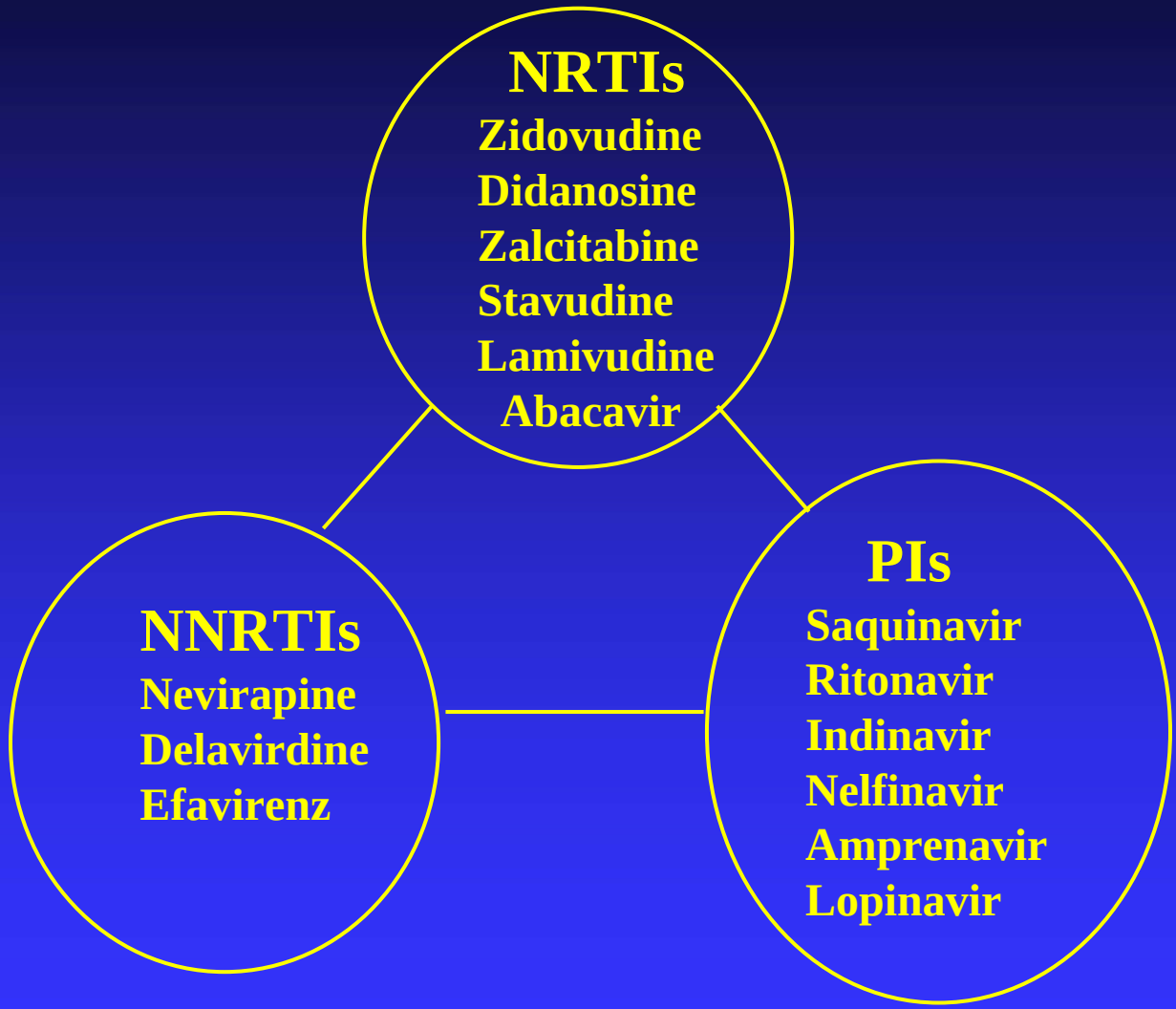
- La plupart des médicaments (et autres substances) à noyau aromatique sont métabolisées en dérivés hydroxylés, ce qui est essentiel pour leur élimination

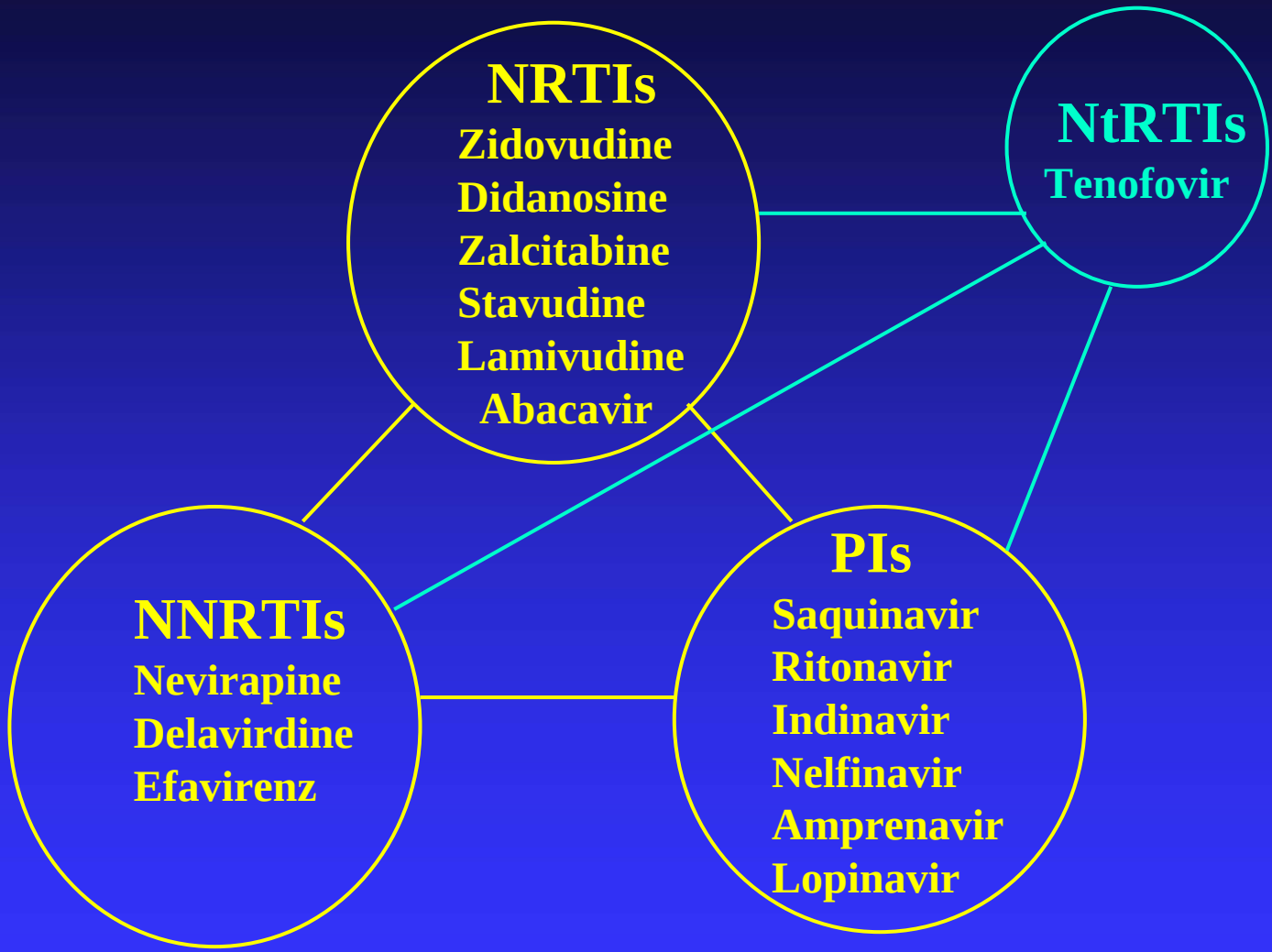


- phénytoïne (antépileptique)
- phénobarvital (sédatif)
- propranolol (antihypertenseur)
- phénylbutazone (antiinflammatoire)
- éthinyloestradiol (hormone)
- dicoumarol (anticoagulant)
- …..



- 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): 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: 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 (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

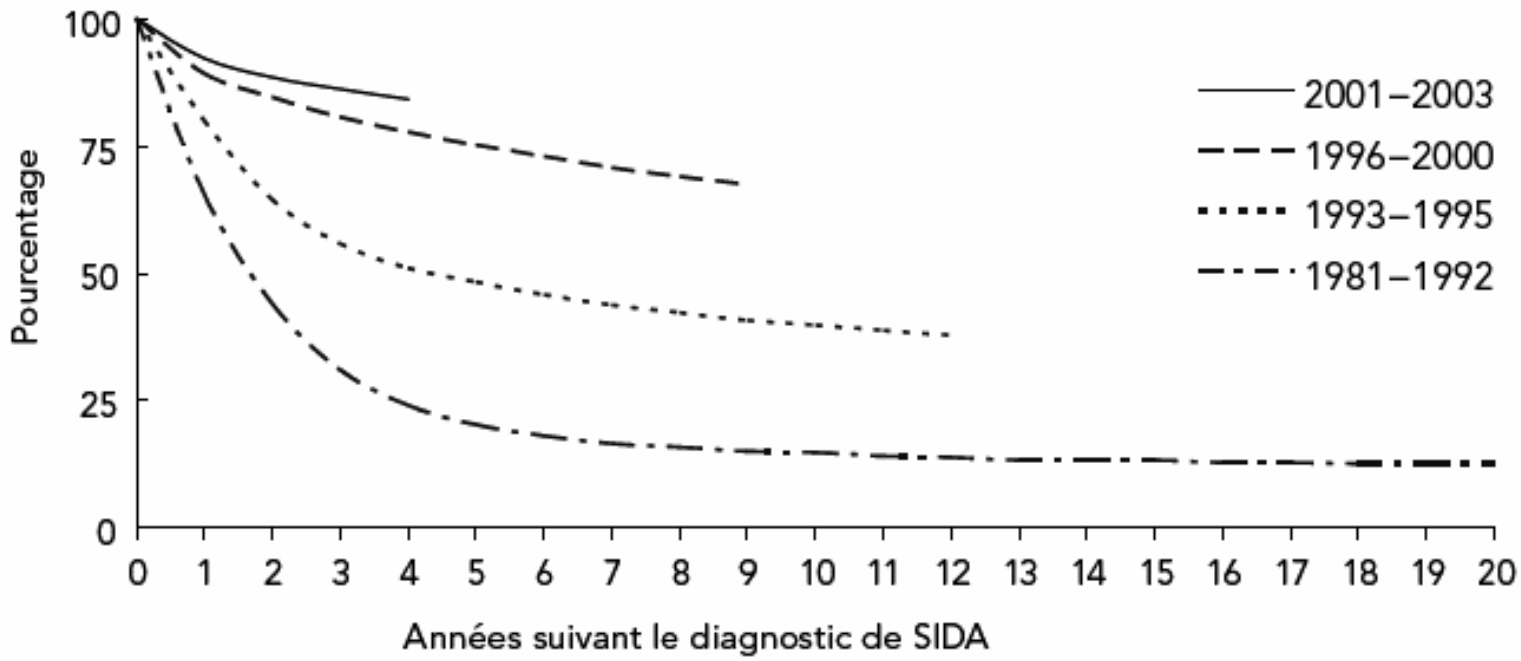
Antiretroviral Therapy Adherence Support

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

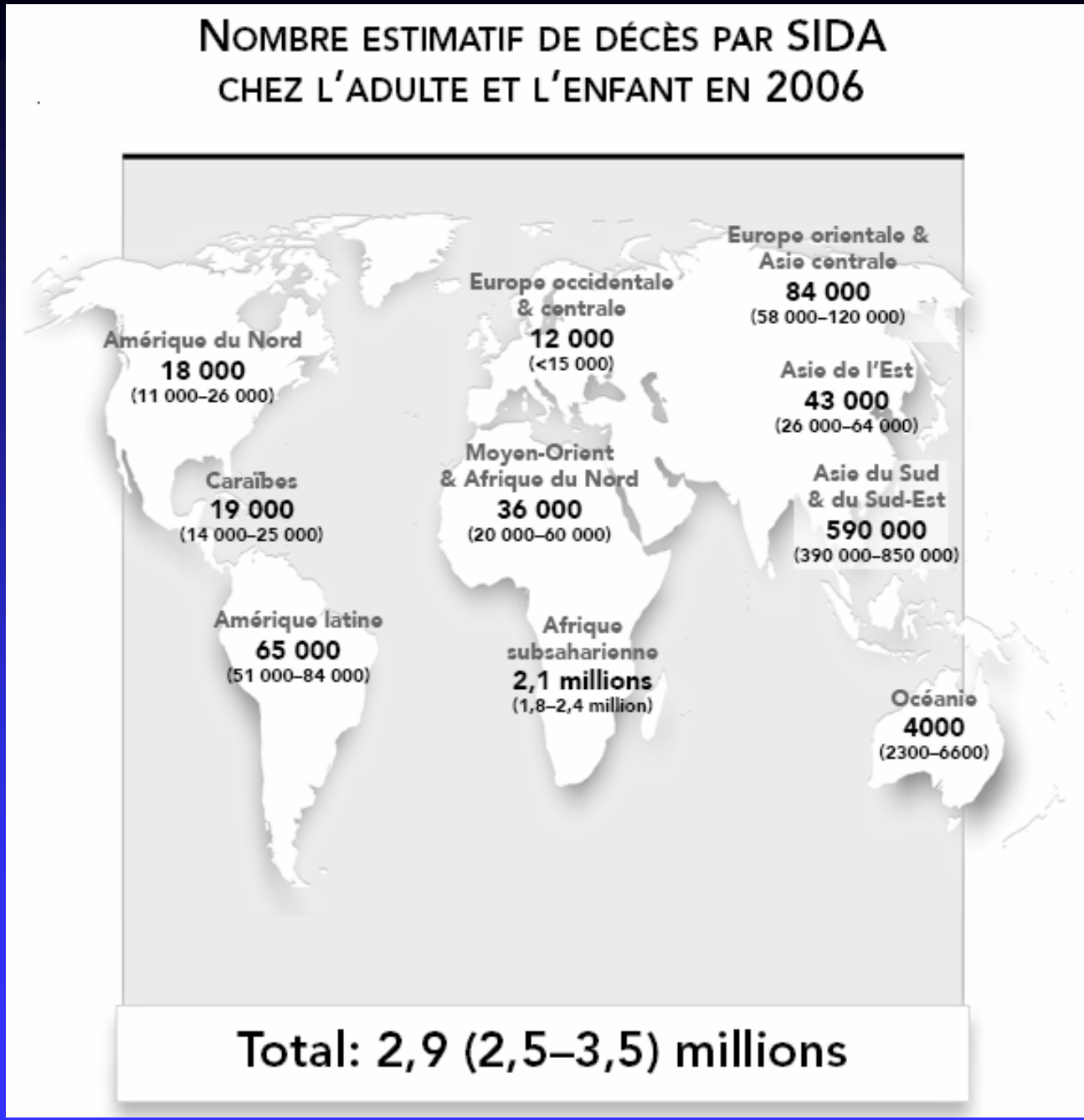
Succès thérapeutiques en Europe et en Amérique du Nord…

Pourcentage de personnes encore en vie en juin 2006,
par cohortes selon les années suivant le diagnostic de SIDA
entre 1981 et 2003 et par année de diagnostic

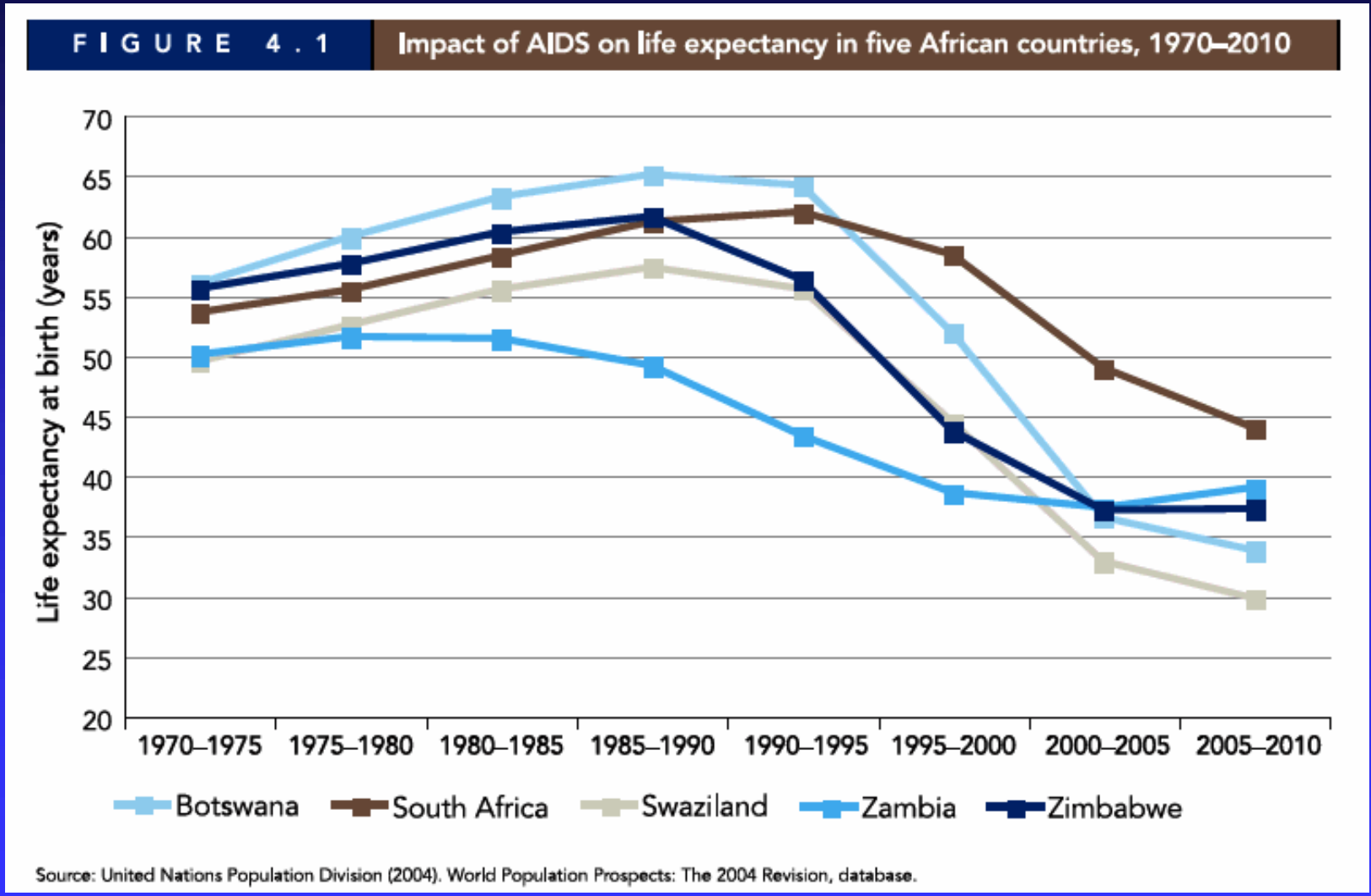


Source : CDC Twenty-five years of HIV/AIDS – Etats-Unis, 1981-2006. MMWR 2006.

Succès thérapeutiques mondiaux ... ??

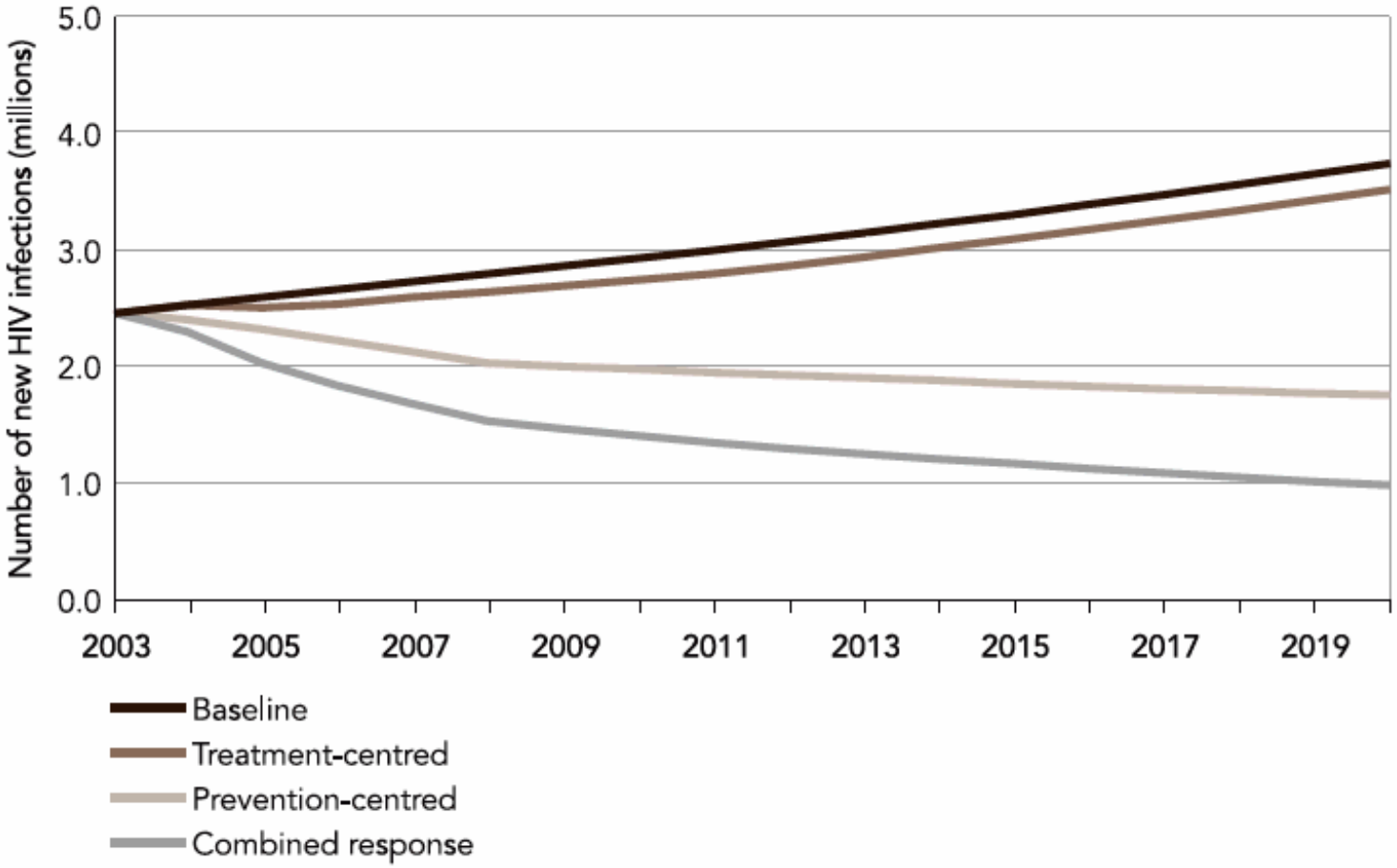


Un des problèmes africain...



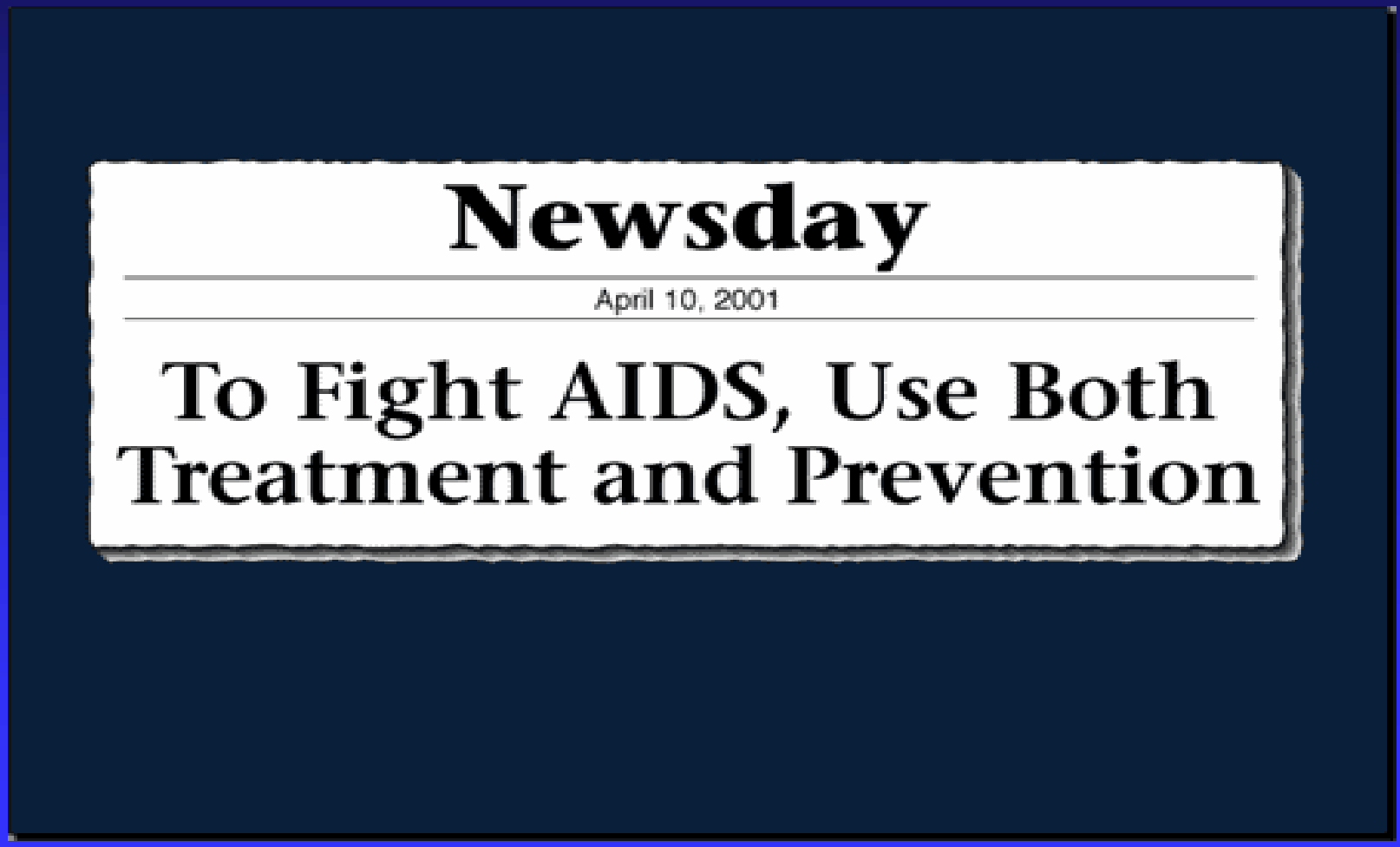
Vers une solution ?

FIGURE 6.1 Impact of three scenarios on HIV infection in sub-Saharan Africa, 2003–2020

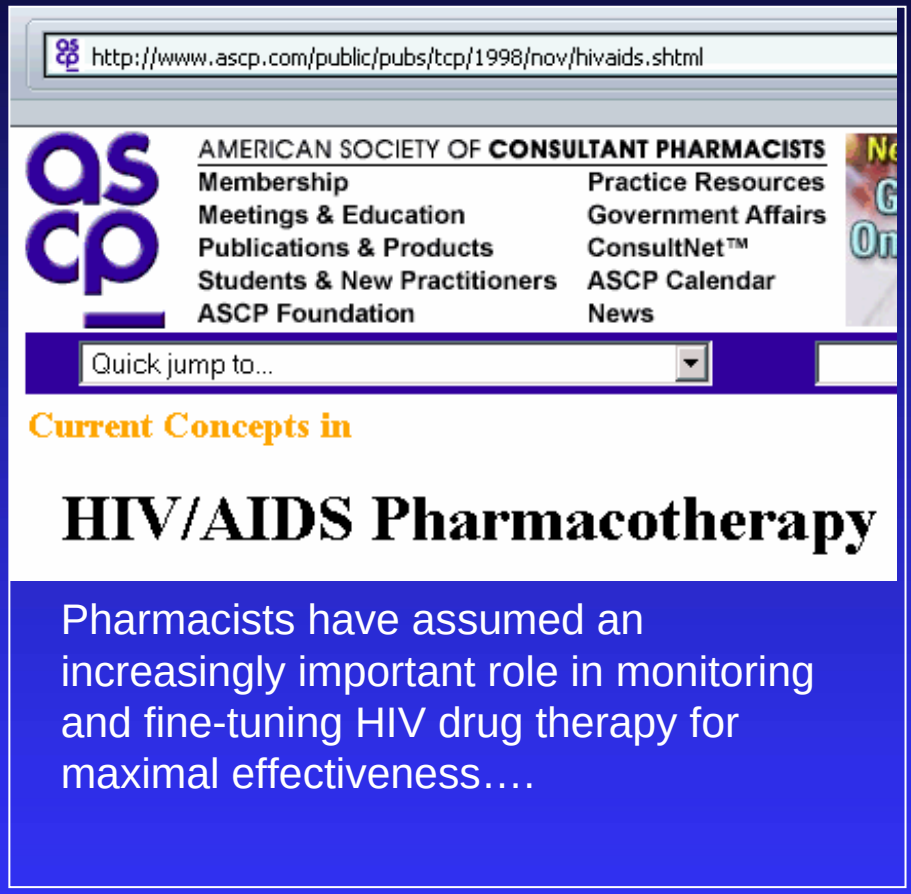


Source: Salomon JA et al. (2005). Integrating HIV prevention and treatment: from slogans to impact.

Prevention vs. Rx



SIDA et Pharmaciens



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