STATE OF THE ART OF THE TREATMENT OF HIV INFECTIONS (AIDS)

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B-3000 Leuven, Belgium

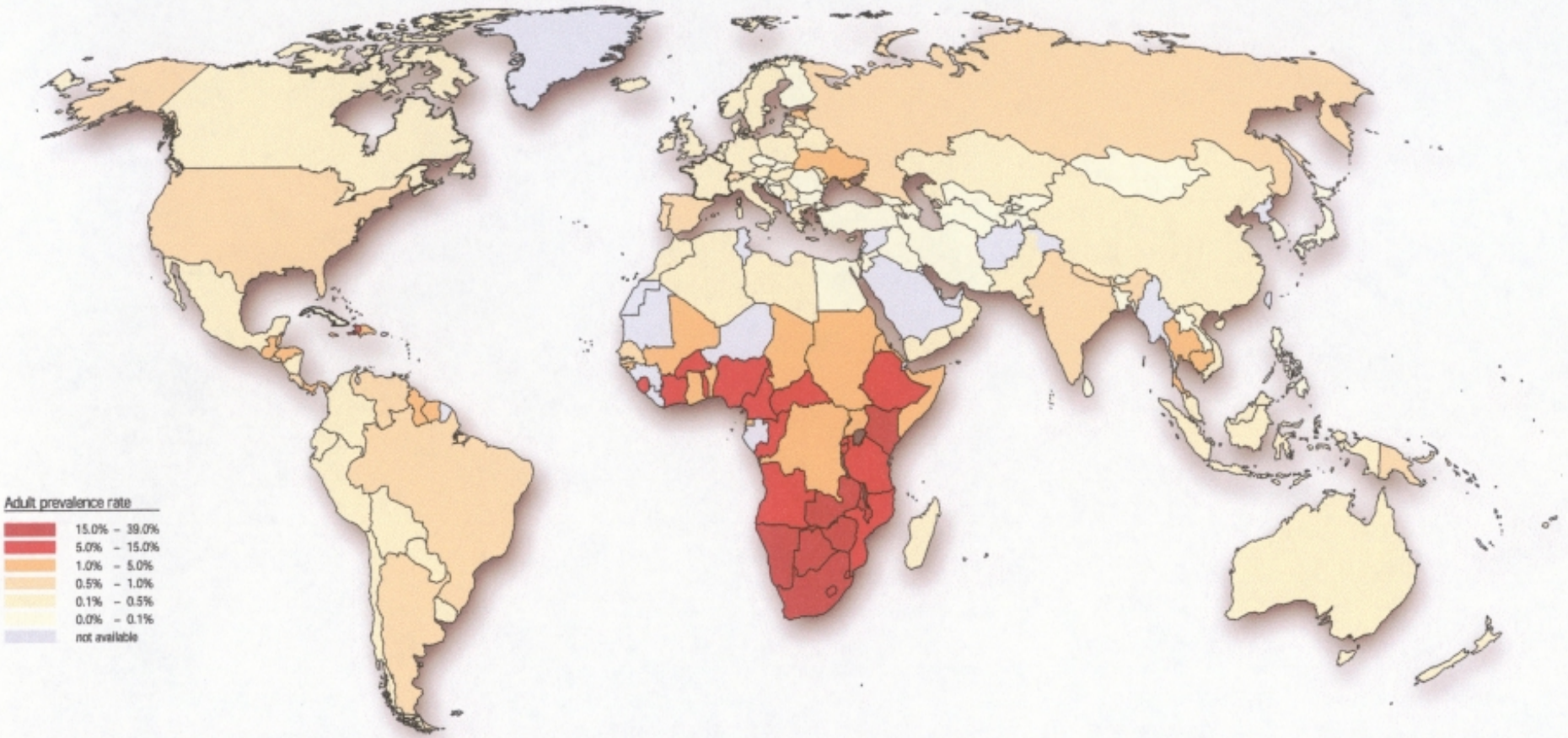
Global estimates of HIV/AIDS epidemic as of end 2001

Total number of adults and children living with HIV/AIDS: 40 million

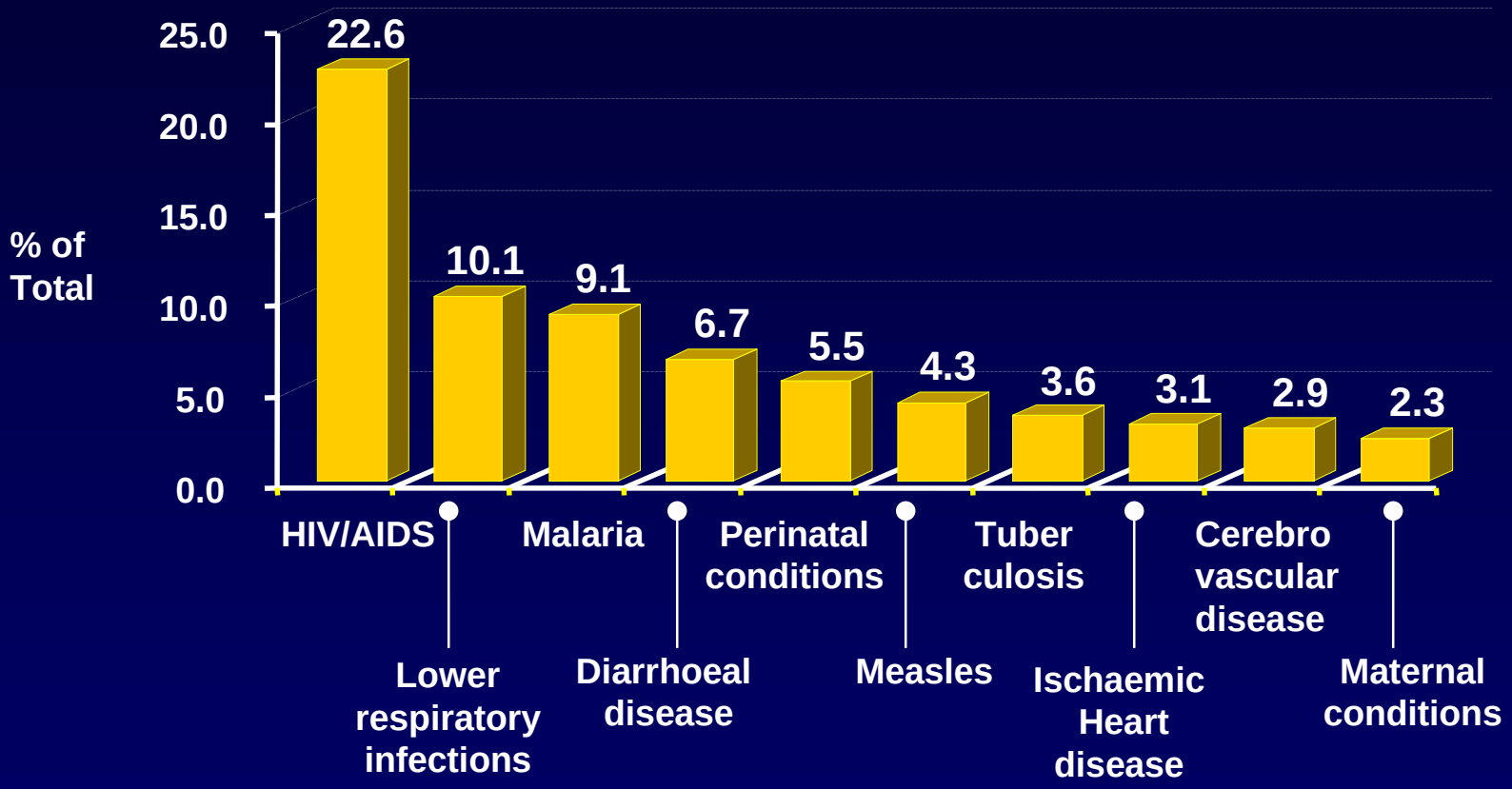
A global view of HIV infection

40 million adults living with HIV/AIDS as of end 2001

UNAIDS
UNICEF • UNDP • UNFPA • UNDCP
ILO • UNESCO • WHO • WORLD BANK

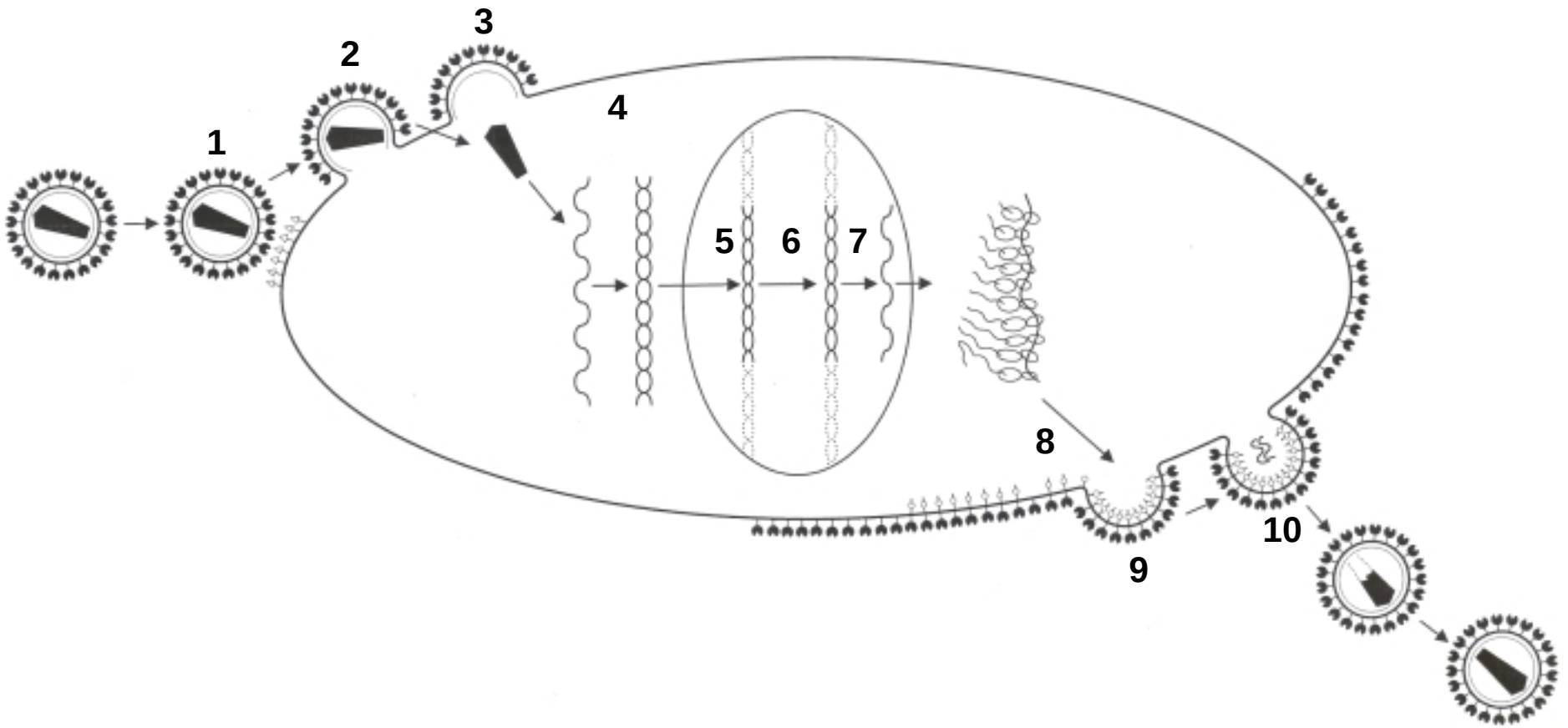


Leading causes of death in Africa, 2000



Source: *The World Health Report 2001, WHO*

HIV REPLICATIVE CYCLE



HIV REPLICATIVE CYCLE

- Virus adsorption
- Virus-cell fusion
- Virus uncoating
- Reverse transcription
- Proviral DNA integration
- Proviral DNA replication
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- Maturation (proteolysis/myristoylation/glycosylation)
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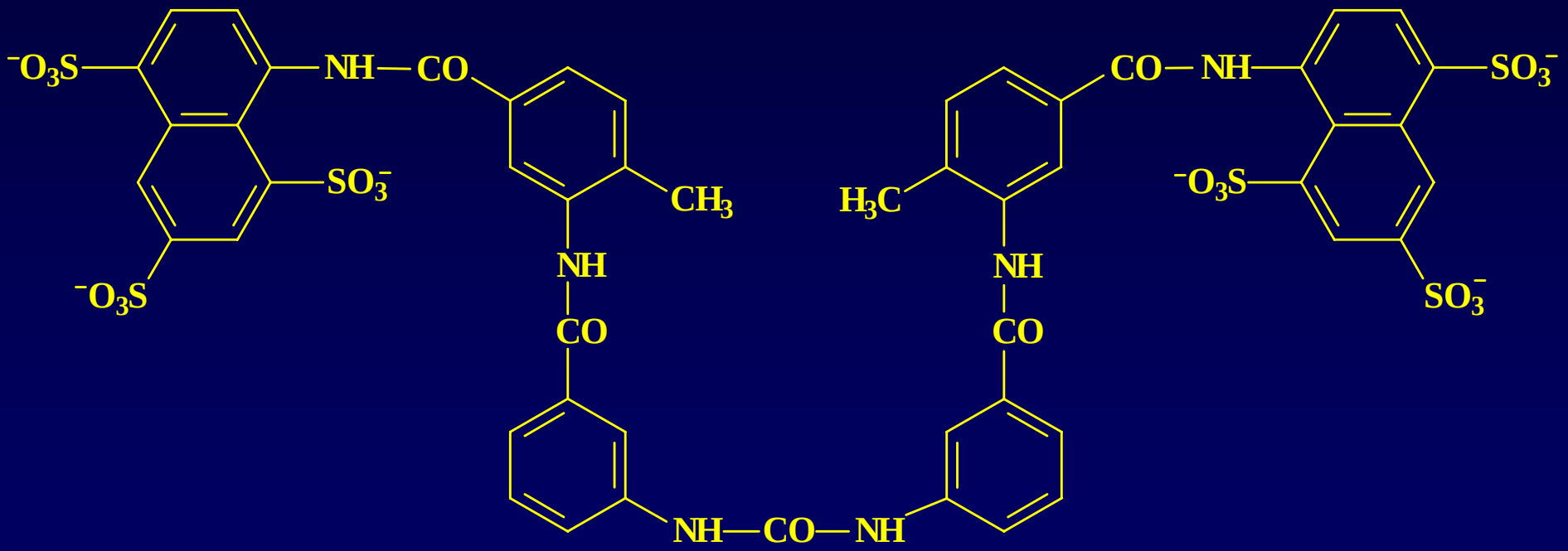
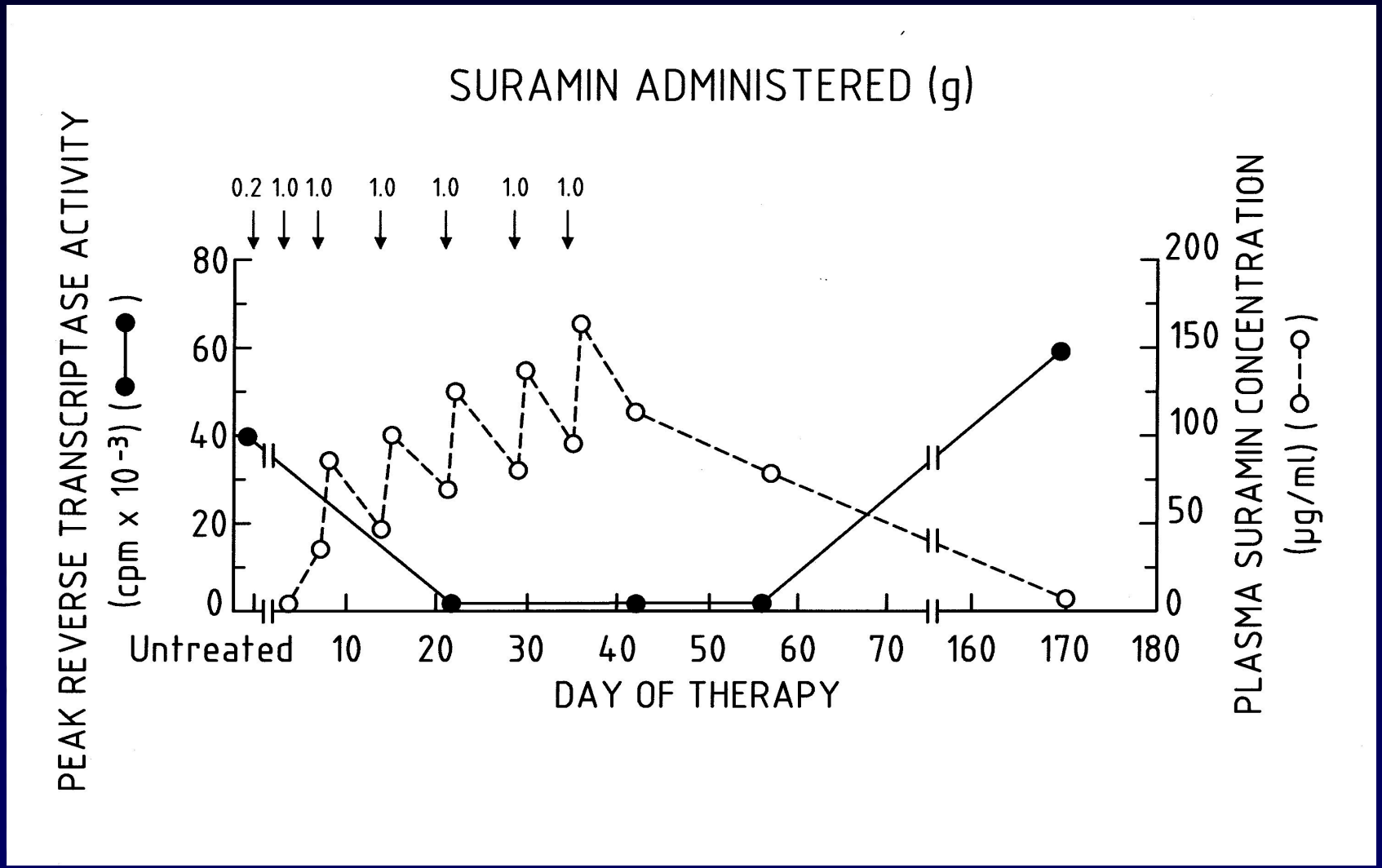
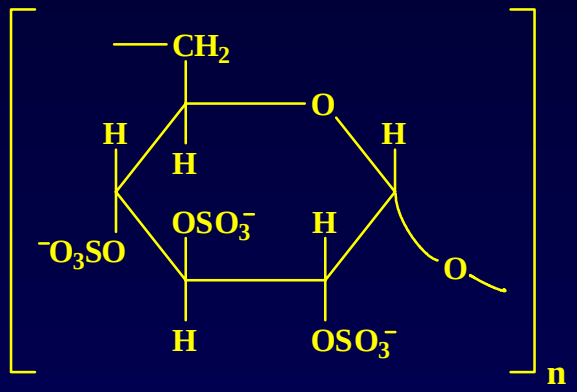
Suramin



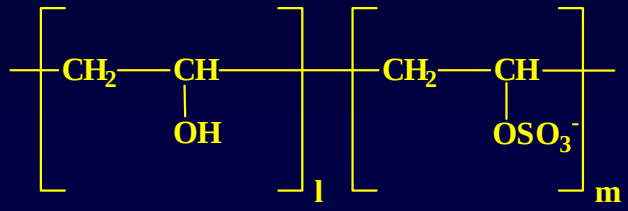


Broder *et al*., Lancet ii, 627-630 (1985)

Polyanions

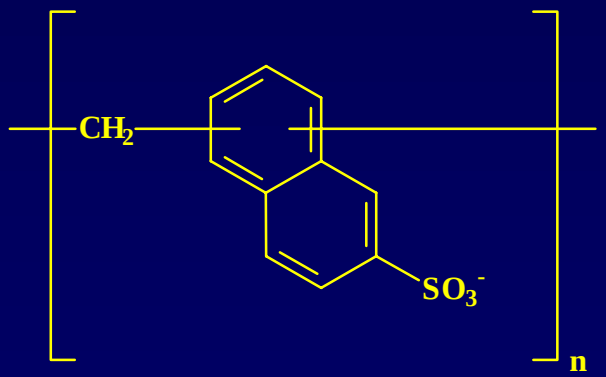


Dextran sulfate

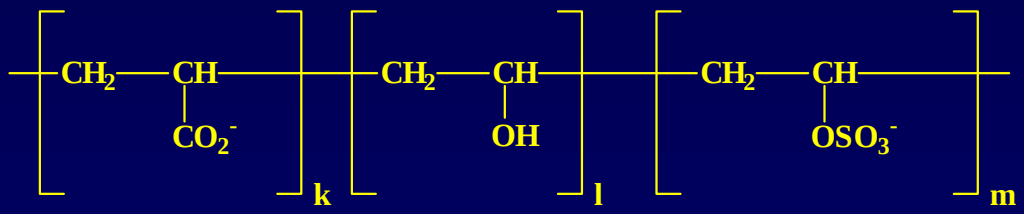


PVAS

PVS



PRO 2000



PAVAS

(H$_2$N)Leu—Gly–Lys—Phe—Ser–Gln—Thr—Cys—Tyr—Asn—Ser–Ala—

—Ile–Gln—Gly—Ser—Val—Leu–Thr—Ser—Thr—Cys—Glu–Arg—Thr—Asn—Gly–Gly—Tyr—Asn—Thr–Ser—

—Ser—Ile—Asp—Leu–Asn—Ser—Val—Ile–Glu–Asn—Val—Asp—Gly—Ser—Leu—Lys—Trp—Gln–Pro—Ser—

—Asn—Phe—Ile–Glu—Thr—Cys—Arg—Asn—Thr—Gln–Leu–Ala—Gly—Ser—Ser—Glu—Leu–Ala—Ala—Glu—

—Cys—Lys—Thr—Arg—Ala—Gln—Gln—Phe—Val—Ser—Thr—Lys—Ile–Asn—Leu–Asp—Asp—His—Ile–Ala—

—Asn—Ile–Asp—Gly—Thr—Leu—Lys—Tyr—Glu(COOH)

Cyanovirin-N

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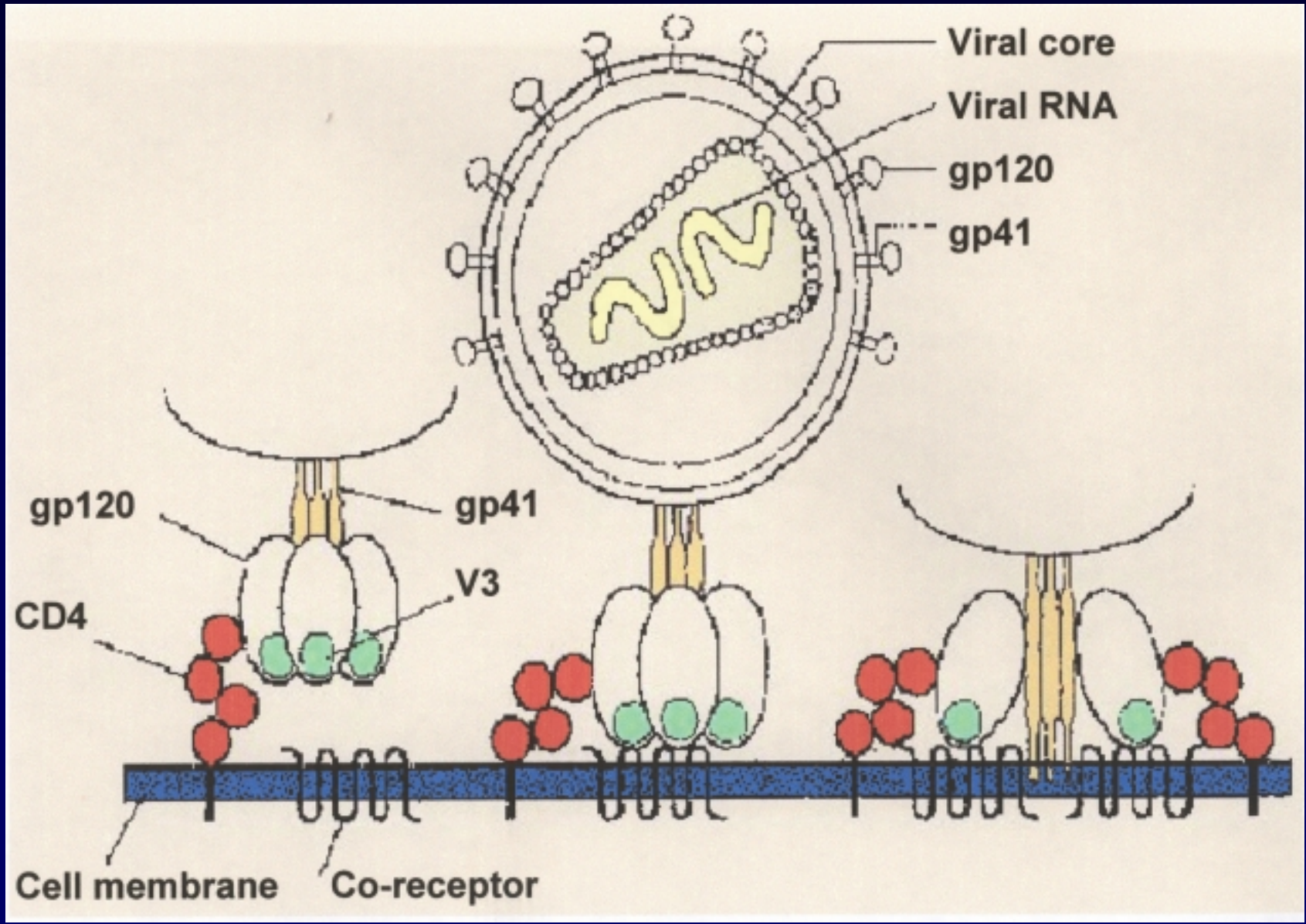
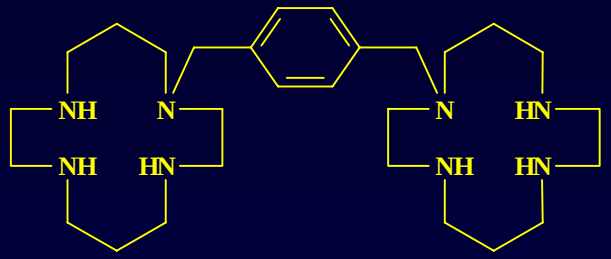
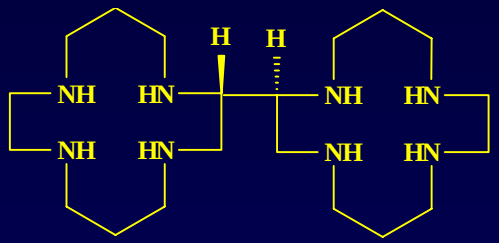
HIV FUSION STEPS

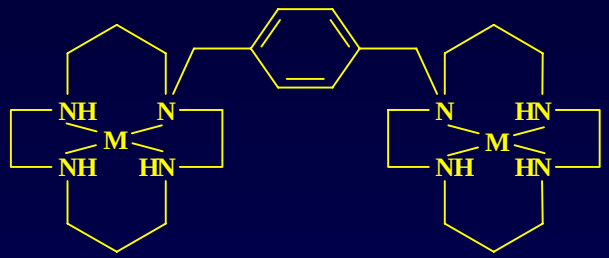




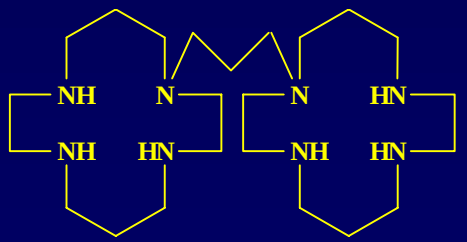
AMD 3100



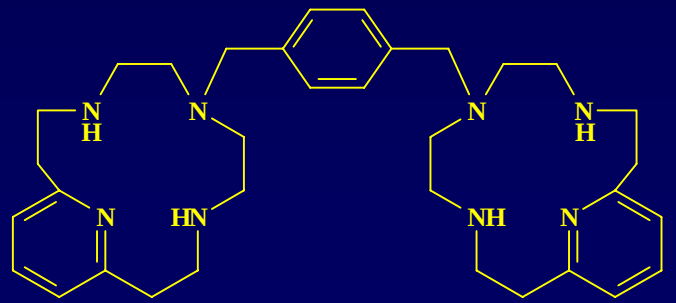
AMD 1657



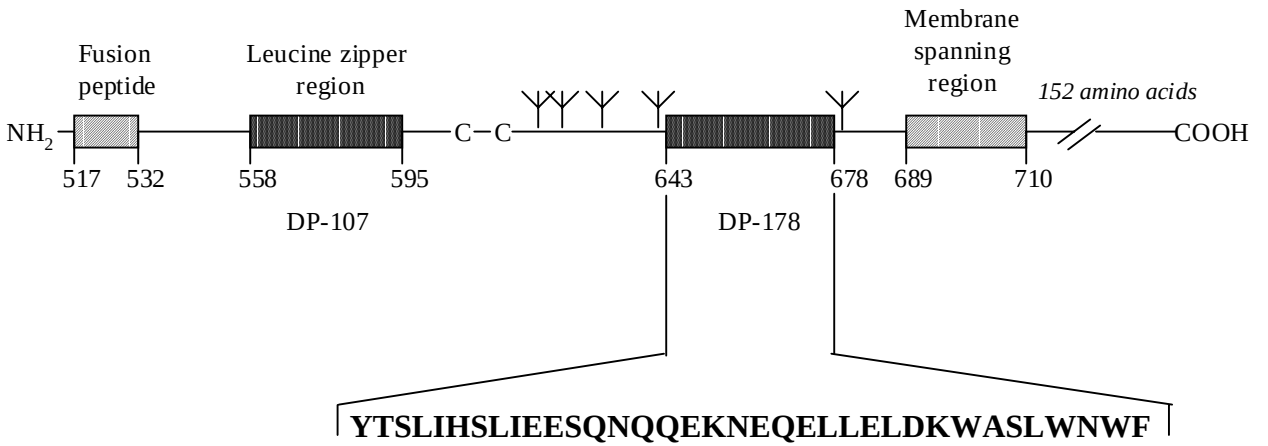
AMD 3479



AMD 2763

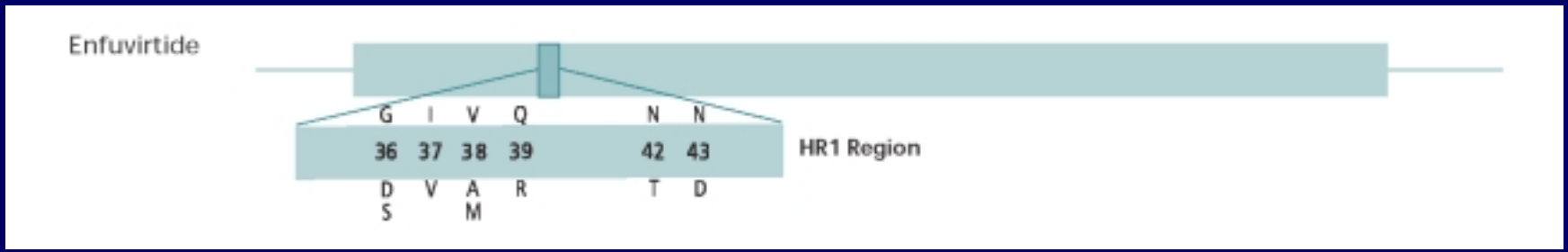


AMD 3329



T-20
(Pentafuside, Enfuvirtide, Fuzeon)

MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



http:/www.iasusa.org/resistance_mutations/index.html

T-20 (enfuvirtide) *versus* Optimized Regimen Only (TORO 1) Study 1

Efficacy at week 24 in the Intention-to-Treat population

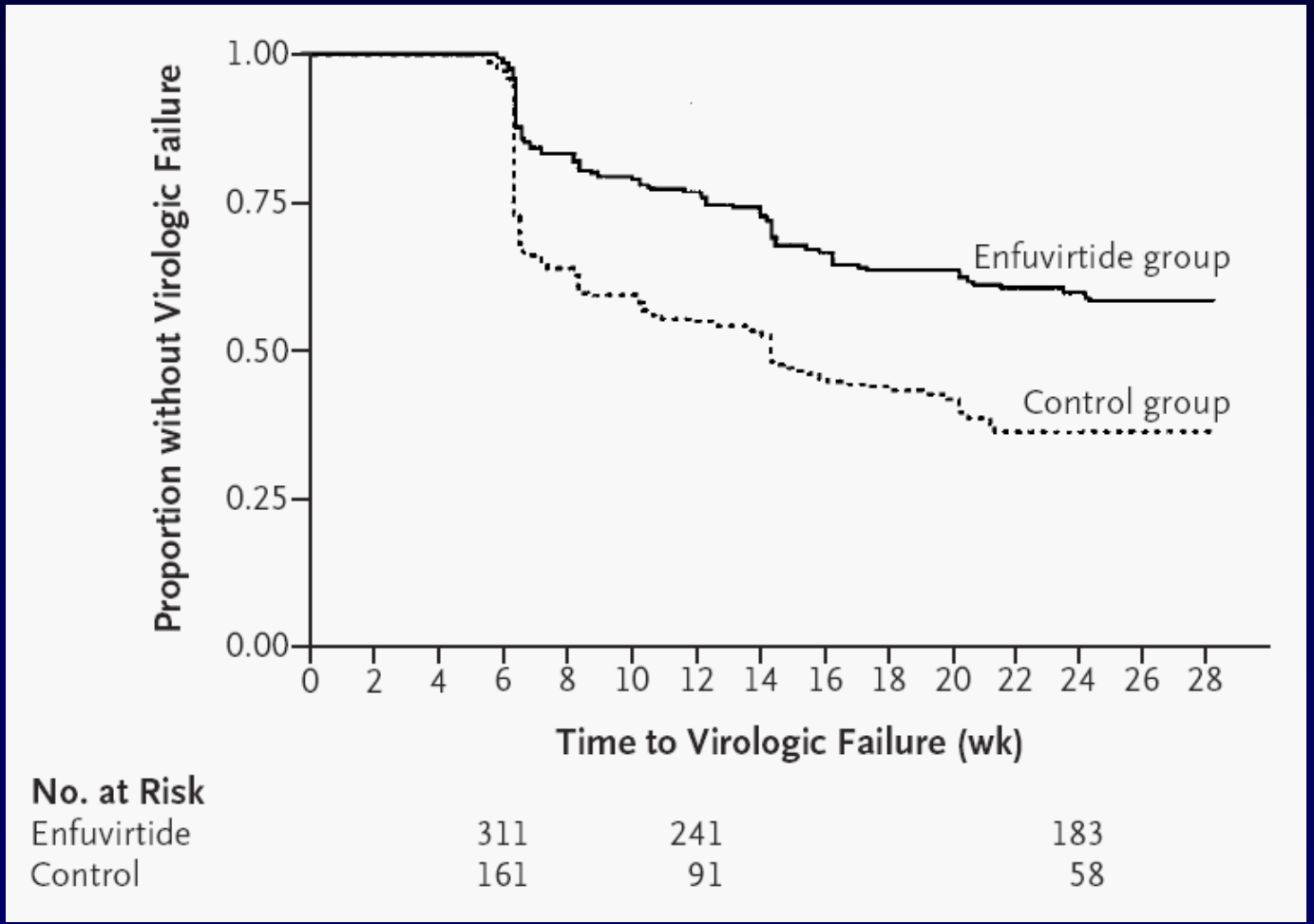
Variable	Enfuvirtide group	Control group	P value
Least-squares mean change from base line in plasma HIV-1 RNA level (log_{10} copies/ml)	-1.696	-0.764	<0.001
<50 Copies of HIV-1 RNA per ml of plasma (% of patients)	19.6	7.3	<0.001
<400 Copies of HIV-1 RNA per ml of plasma (% of patients)	31.7	16.4	<0.001
Reduction from base line of ≥ 1 log_{10} copies of HIV-1 RNA per milliliter of plasma (% of patients)	51.8	29.1	<0.001
Least-squares mean increase in CD4+ cell count (cells/µl)	76.2	32.1	<0.001

Patients from 48 sites in North and South America with at least six months of previous treatment with antiretroviral drugs, and with $\geq$ 5000 copies of HIV-1 RNA per ml of plasma were assigned in a 2:1 ratio to receive enfuvirtide plus an optimized background regimen of 3 to 5 antiretroviral drugs or such regimen alone (control group). Enfuvirtide (90 mg) was administered twice daily by subcutaneous injection.

Lalezari *et al*., N. Engl. J. Med. 348 (29 May 2003)

T-20 (enfuvirtide) *versus* Optimized Regimen Only (TORO 1) Study 1

Time to protocol-defined virologic failures, as of week 24



Lalezari *et al*., N. Engl. J. Med. 348 (29 May 2003)

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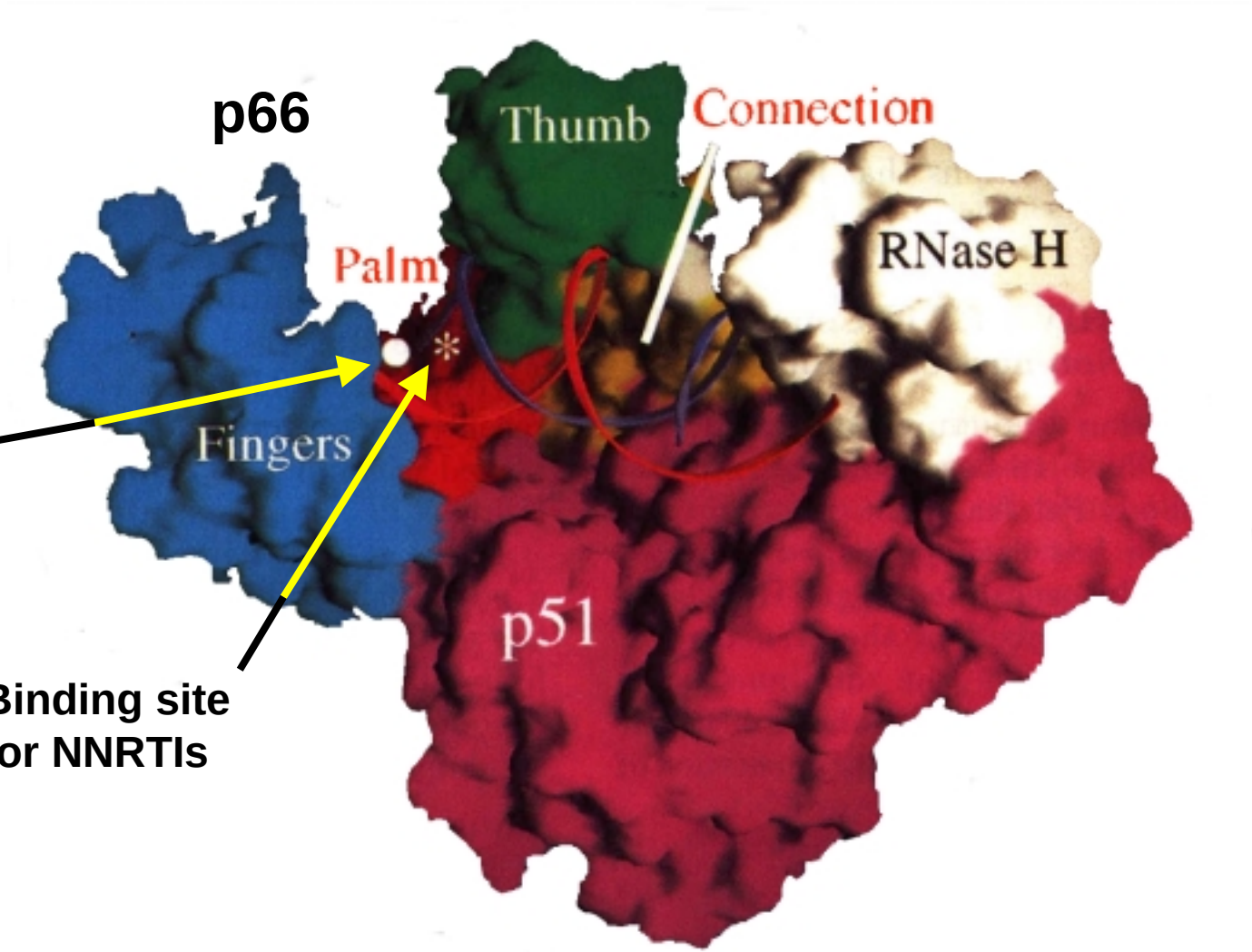
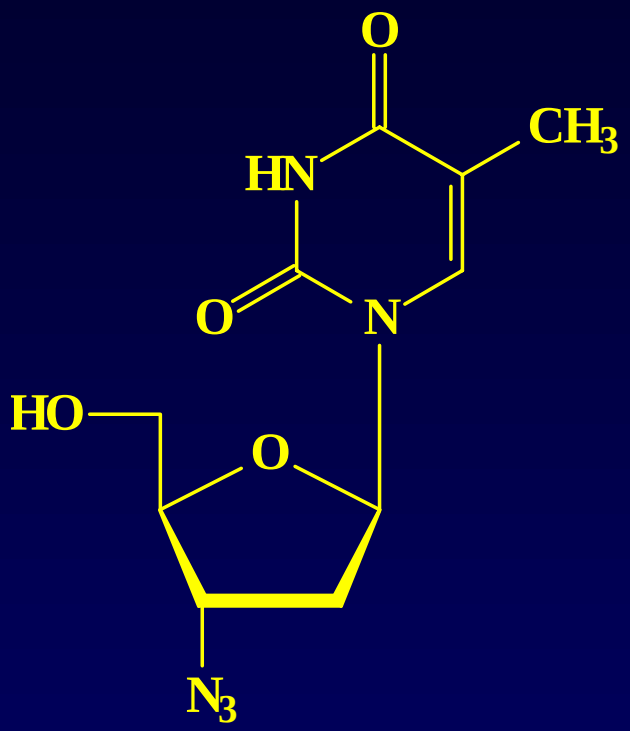
HIV Reverse Transcriptase



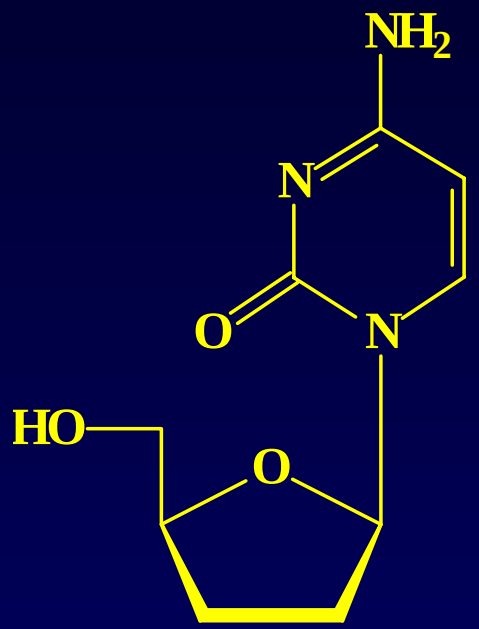


Zidovudine

3’-Azido-2’,3’-dideoxythymidine
AZT
Retrovir®

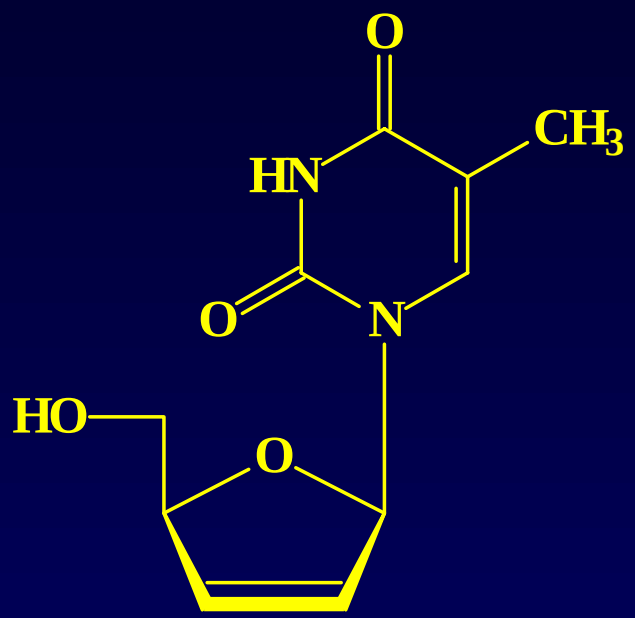
Didanosine

2’,3’-Dideoxyinosine
DDI
Videx®



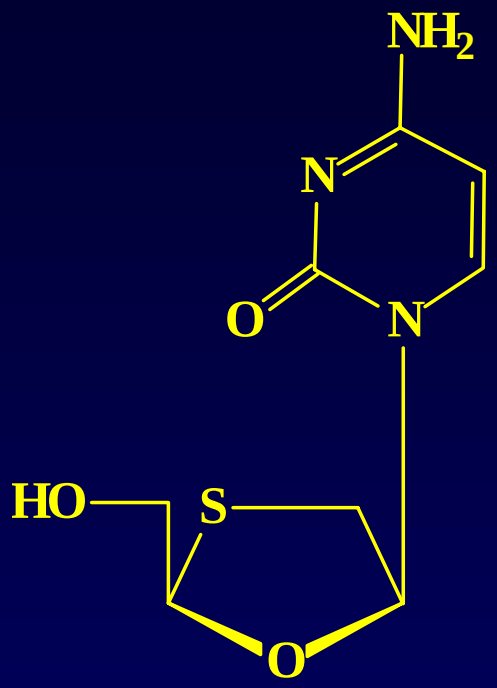
Zalcitabine

2’,3’-Dideoxycytidine
DDC
Hivid®



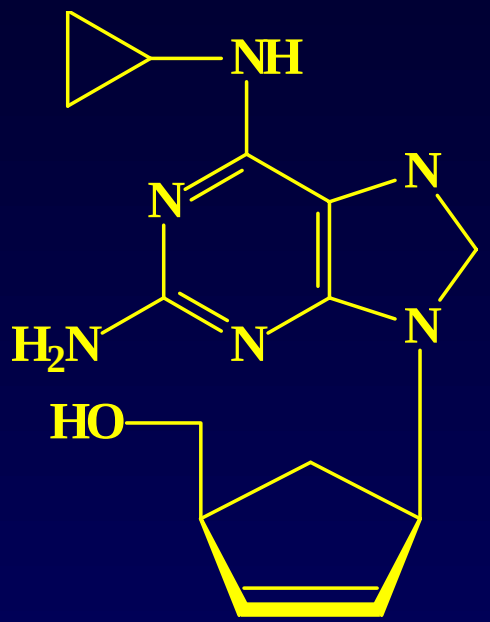
Stavudine

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



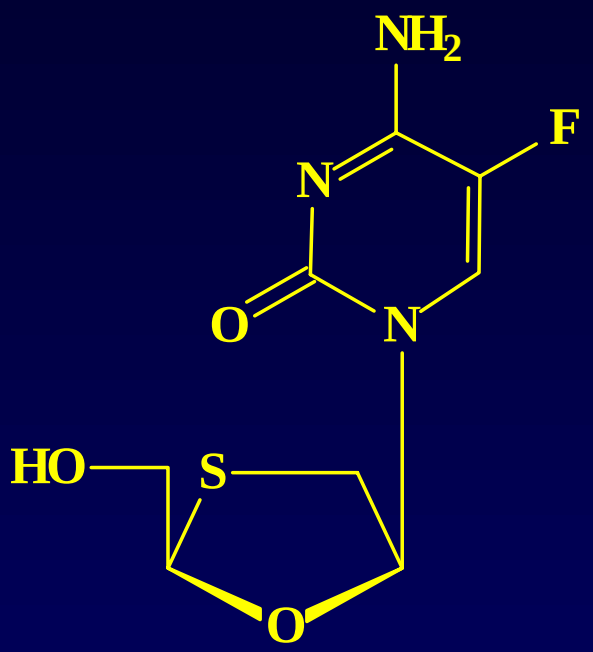
Lamivudine

2’,3’-Dideoxy-3’-thiacytidine
3TC
Epivir®



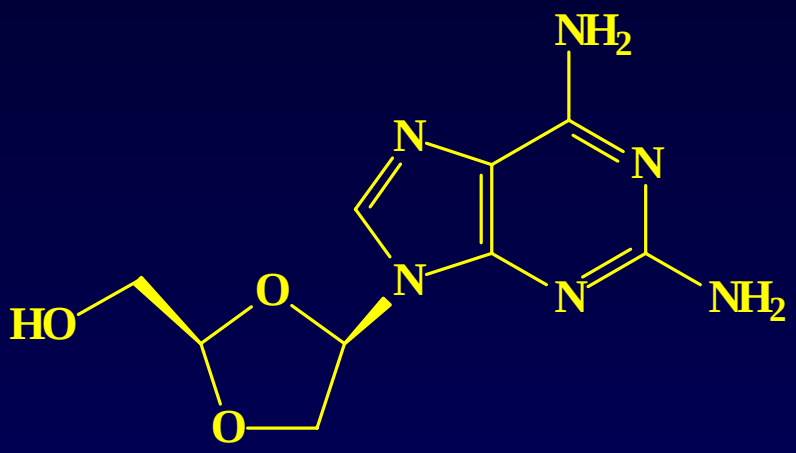
Abacavir

1592U89
Ziagen®



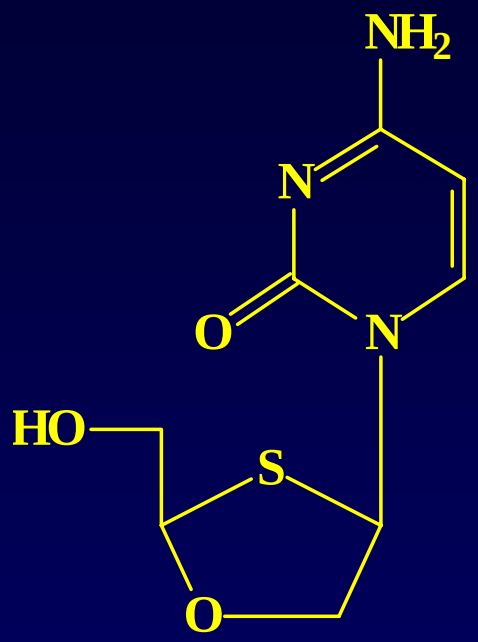
Emtricitabine

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

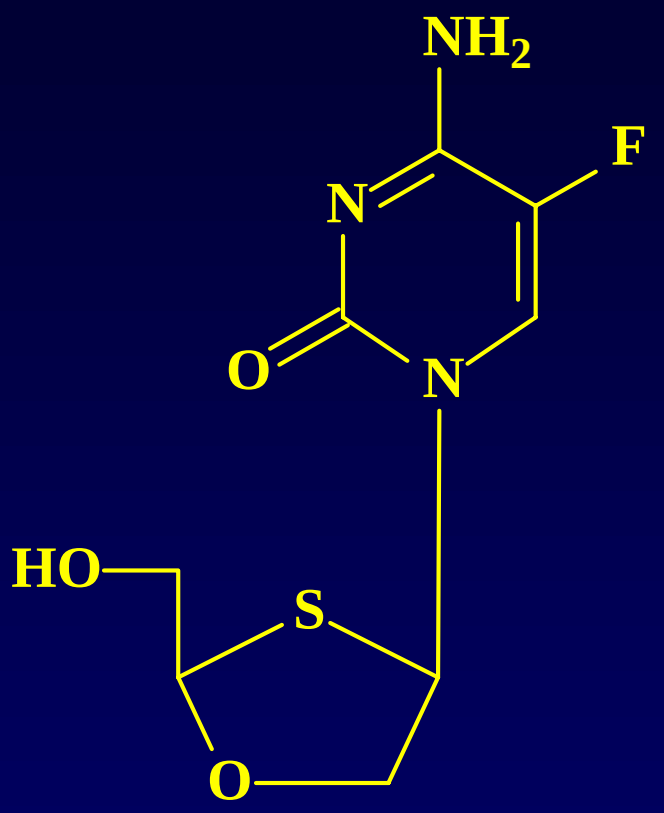


DAPD
Amdoxovir

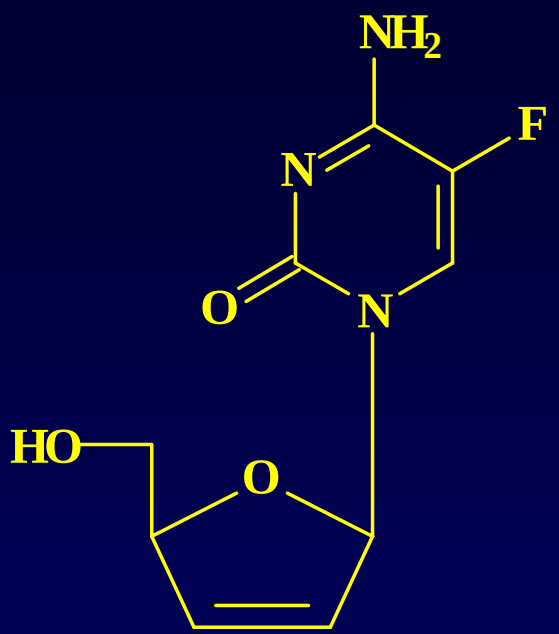
DXG



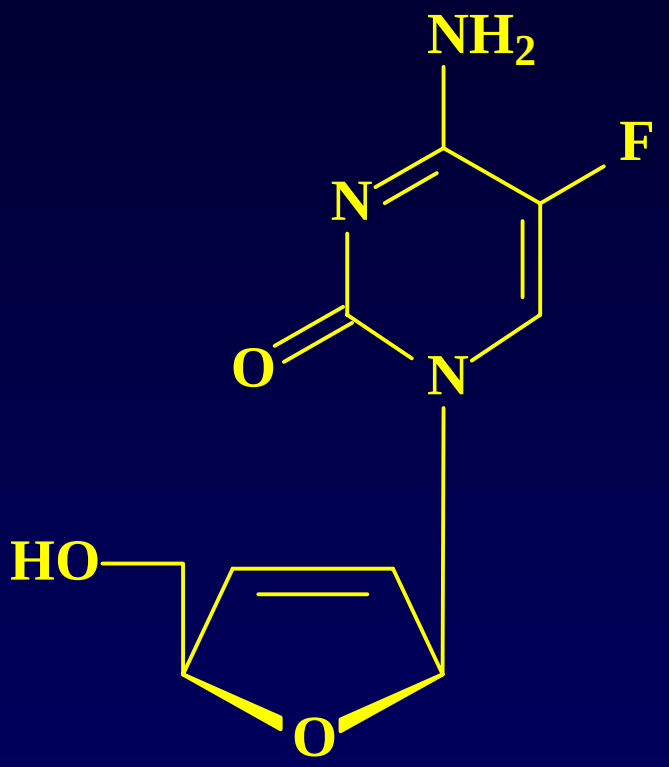
(±)2’-deoxy-3’-oxa-4’-thiacytidine (dOTC)



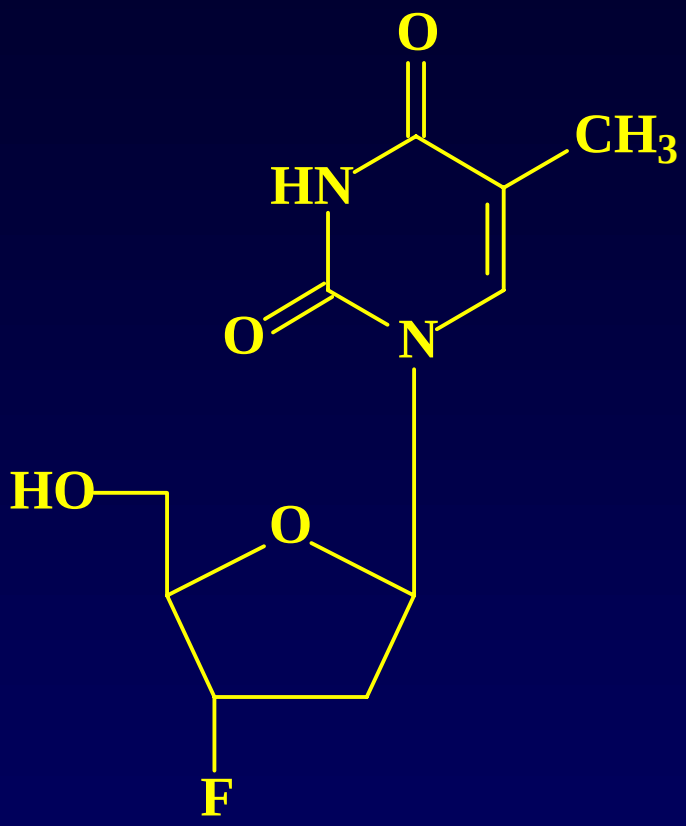
(±)2’-Deoxy-3’-oxa-4’-thiocytidine (FdOTC)
Racivir® (RCV)



DPC 817
D-D4FC
Reverset

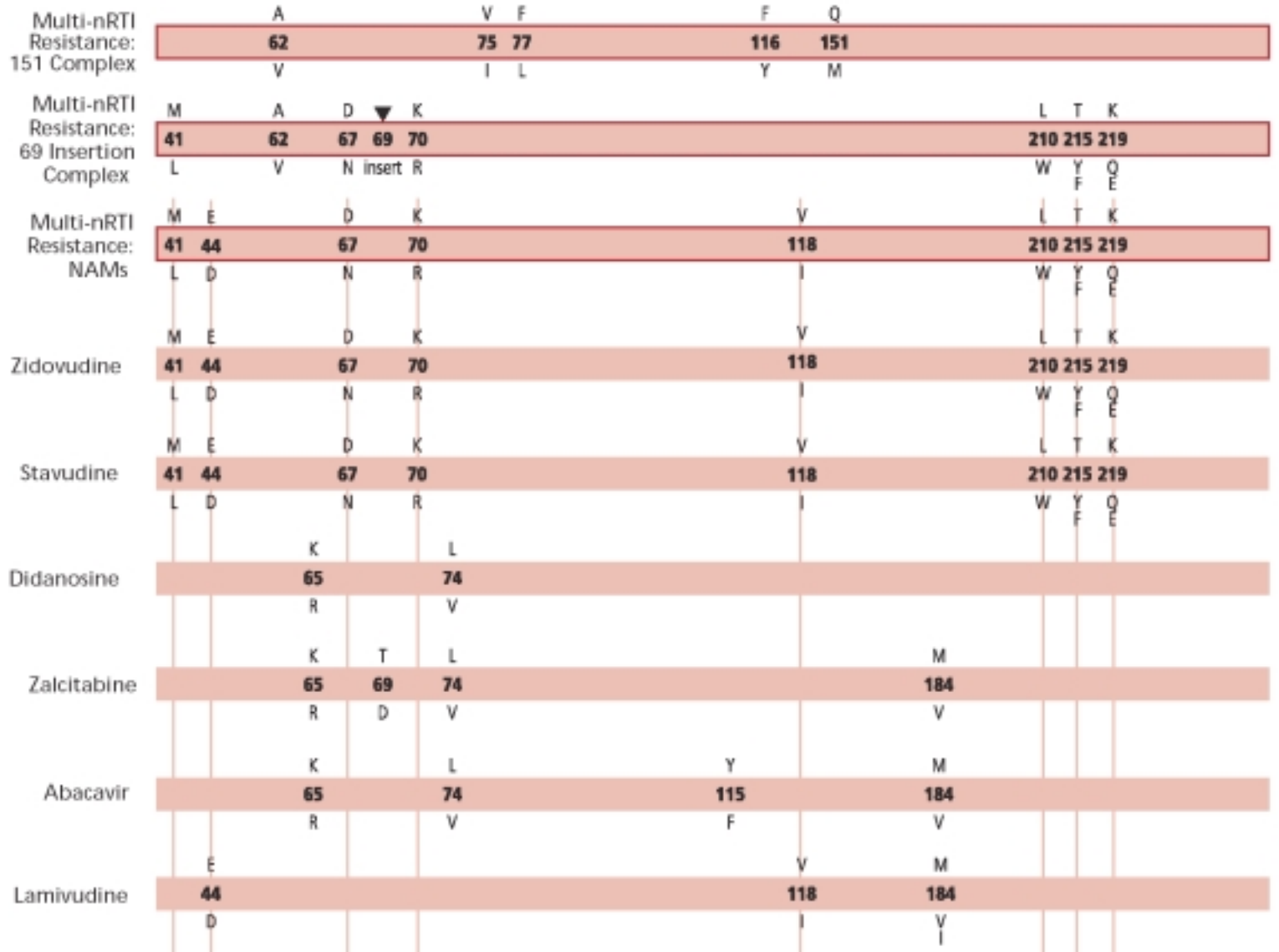


Elvucitabine (ACH-126,443)
β-L-2’,3’-didehydro-2’,3’-dideoxy-5-fluorocytidine
(β-L-d4FC)

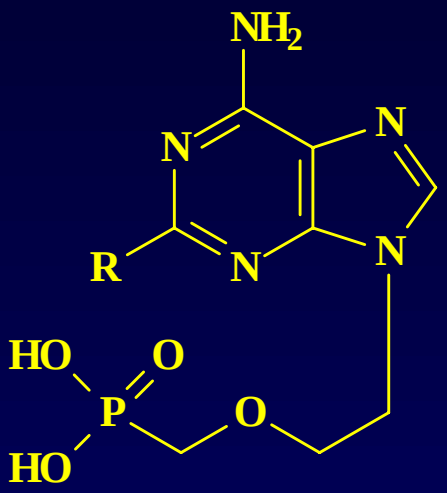


Alovudine (MIV-310)
3’-Fluoro-2’,3’-dideoxythymidine
FddTdhd

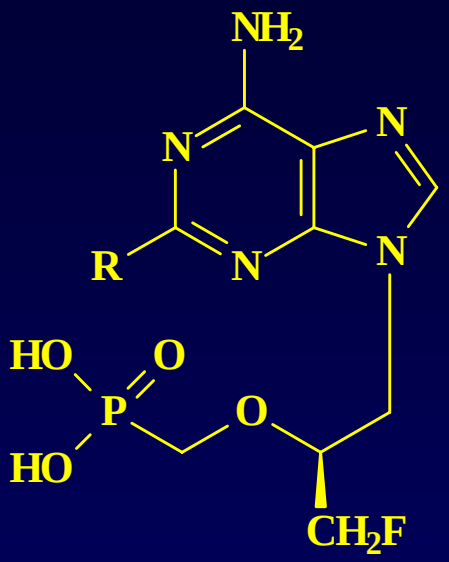
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)



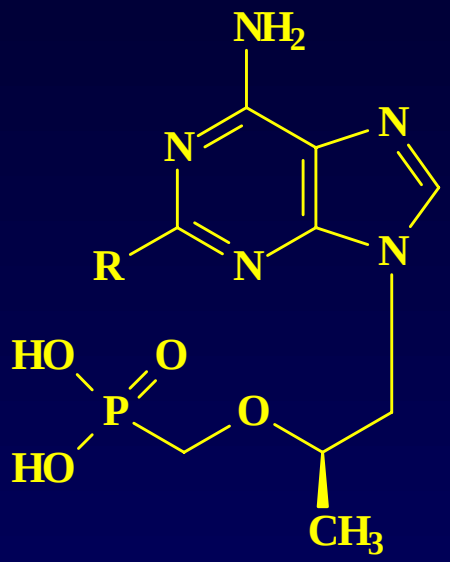
http:/www.iasusa.org/resistance_mutations/index.html



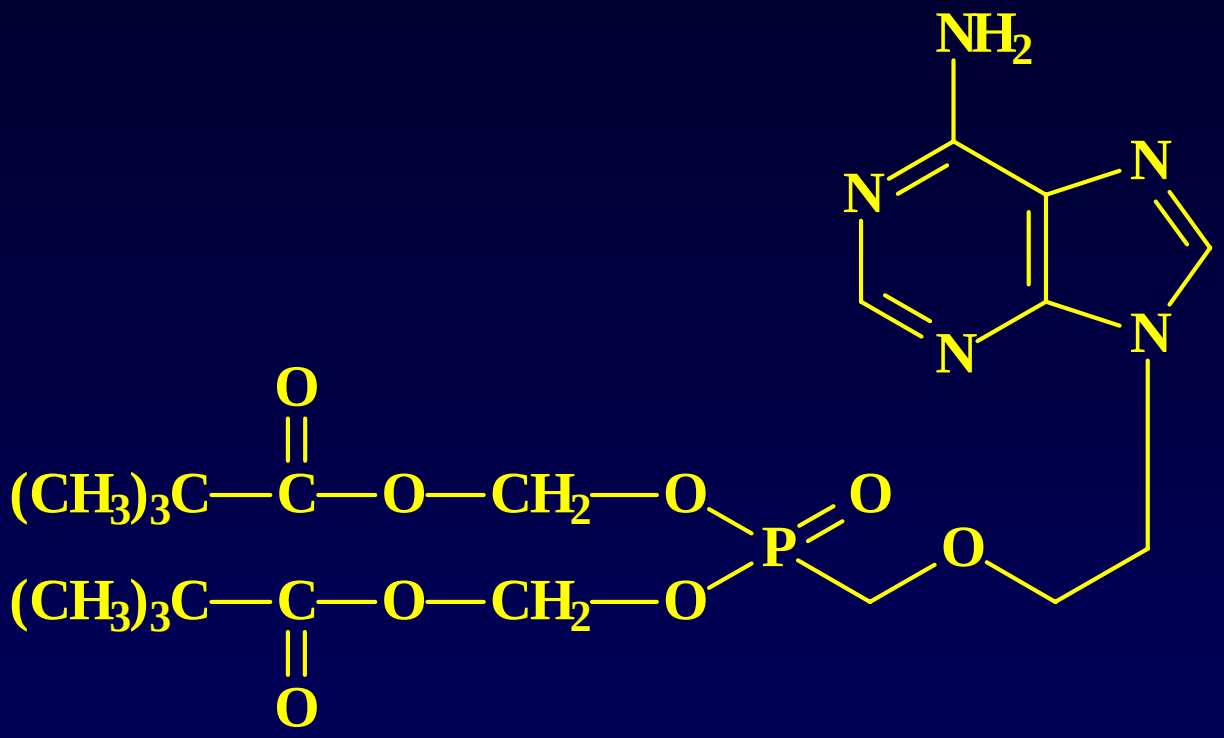
R = H : PMEA
R = NH_2 : PMEDAP



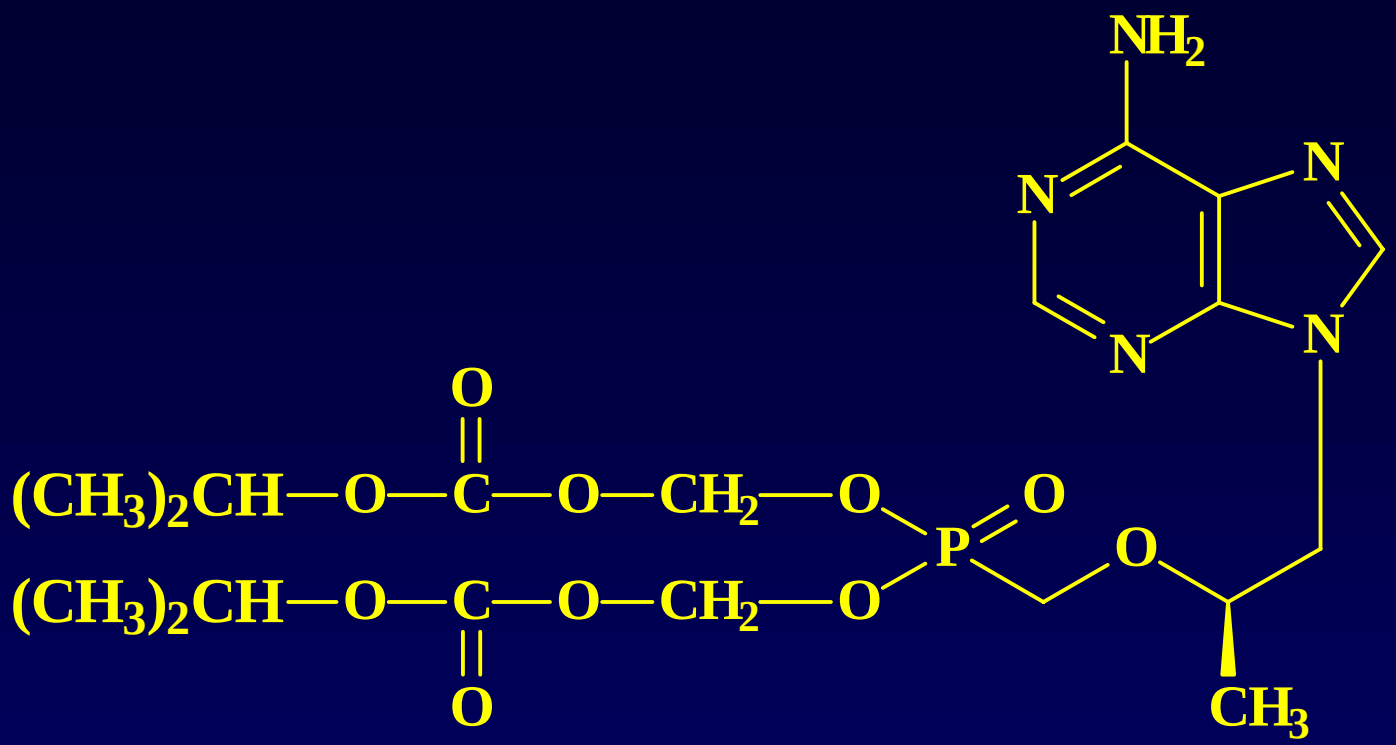
R = H : (*S*)-FPMPA
R = NH_2 : (*S*)-FPMPDAP



R = H : (*R*)-PMPA
R = NH_2 : (*R*)-PMPDAP



bis(POM)-PMEA
Adefovir dipivoxil



fumarate

bis(POC)-PMPA
Tenofovir disoproxil
Viread®

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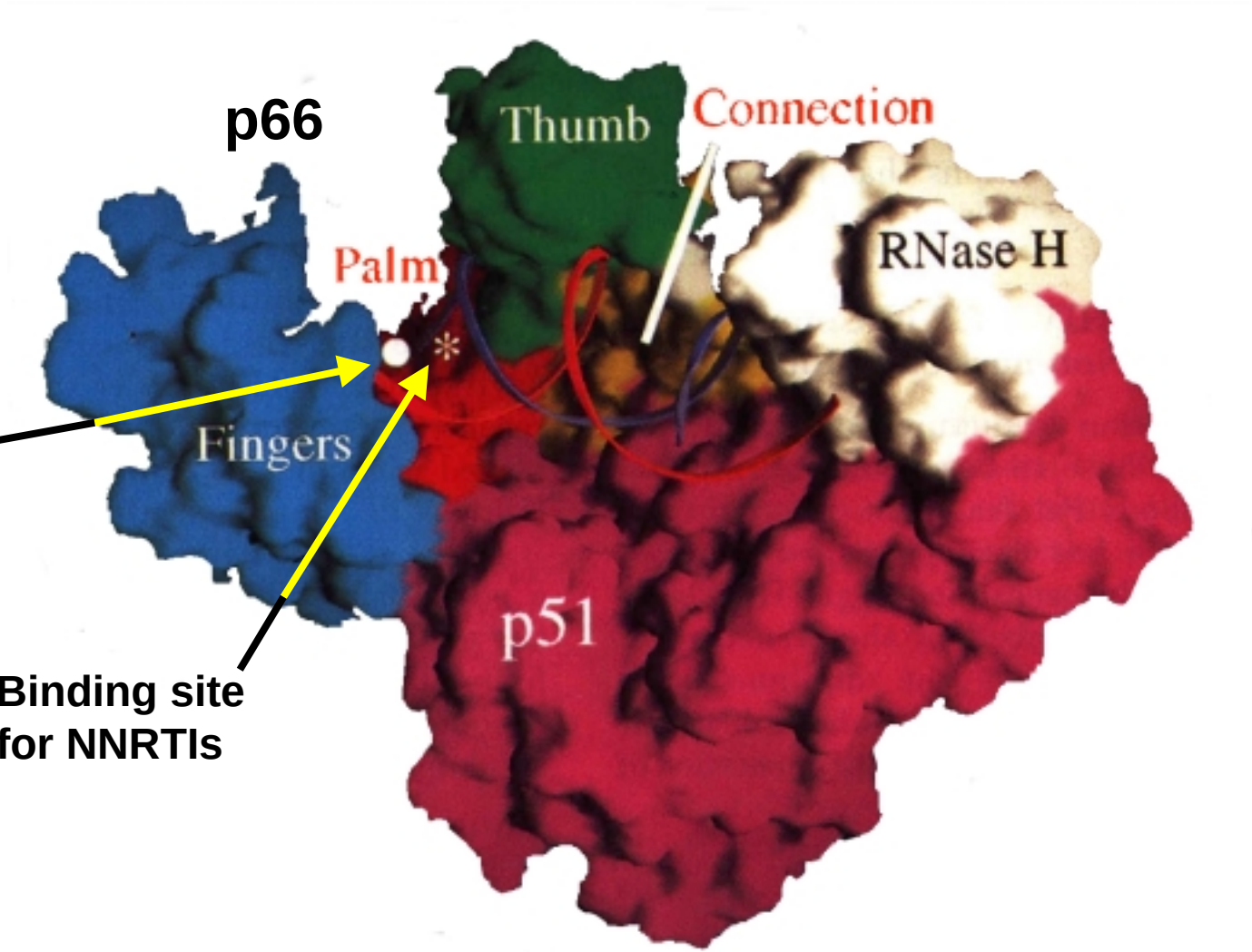
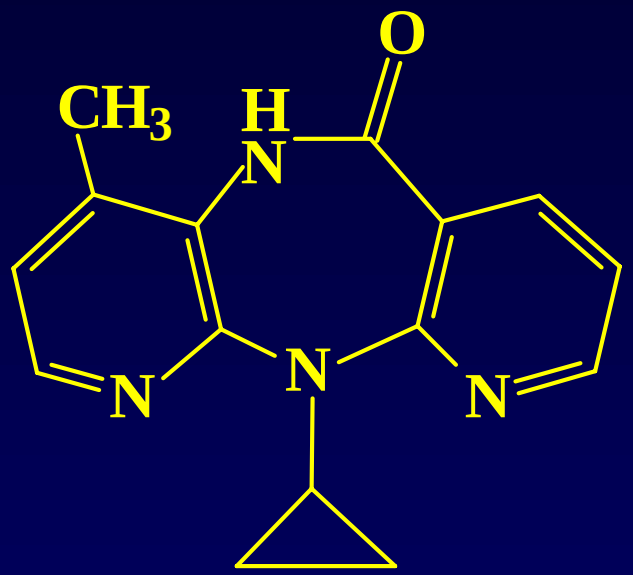
HIV Reverse Transcriptase

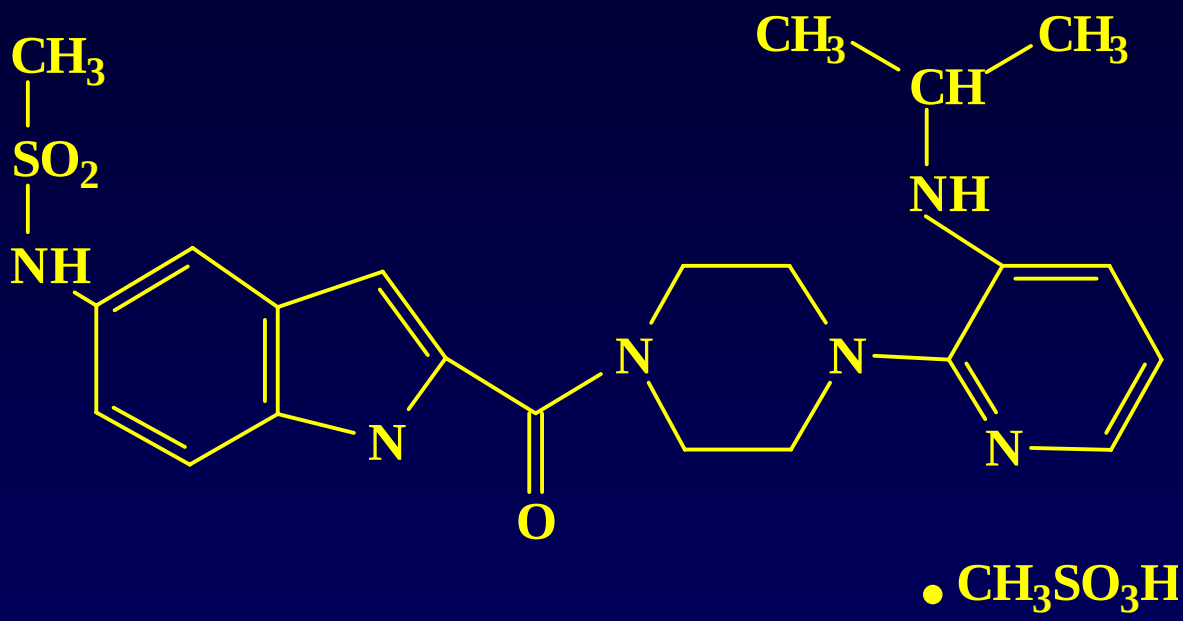




Nevirapine

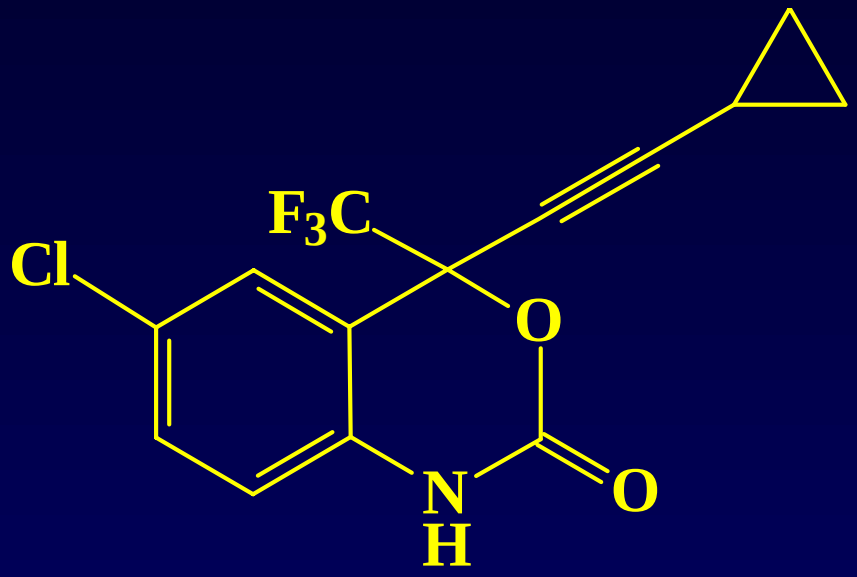
BI-RG-587

Viramune®



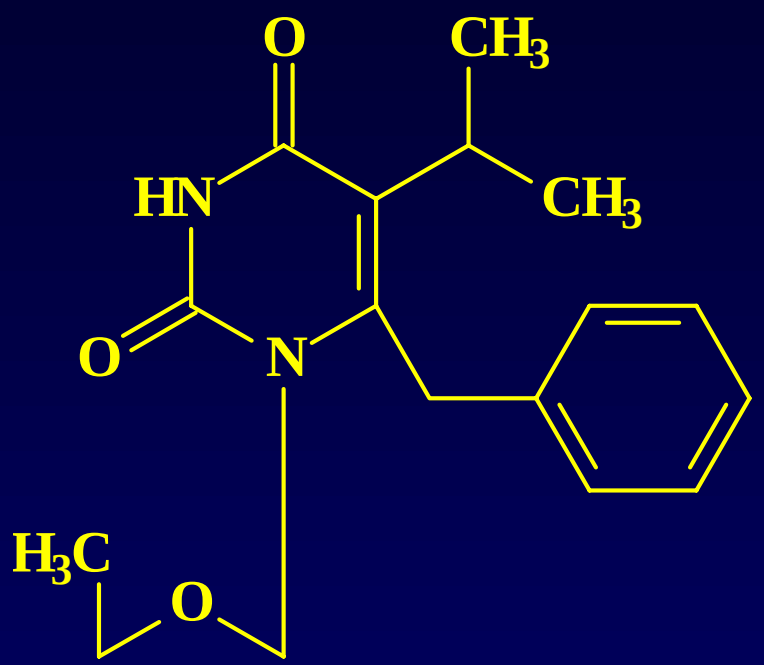
U-90152S

Delavirdine
Rescriptor®



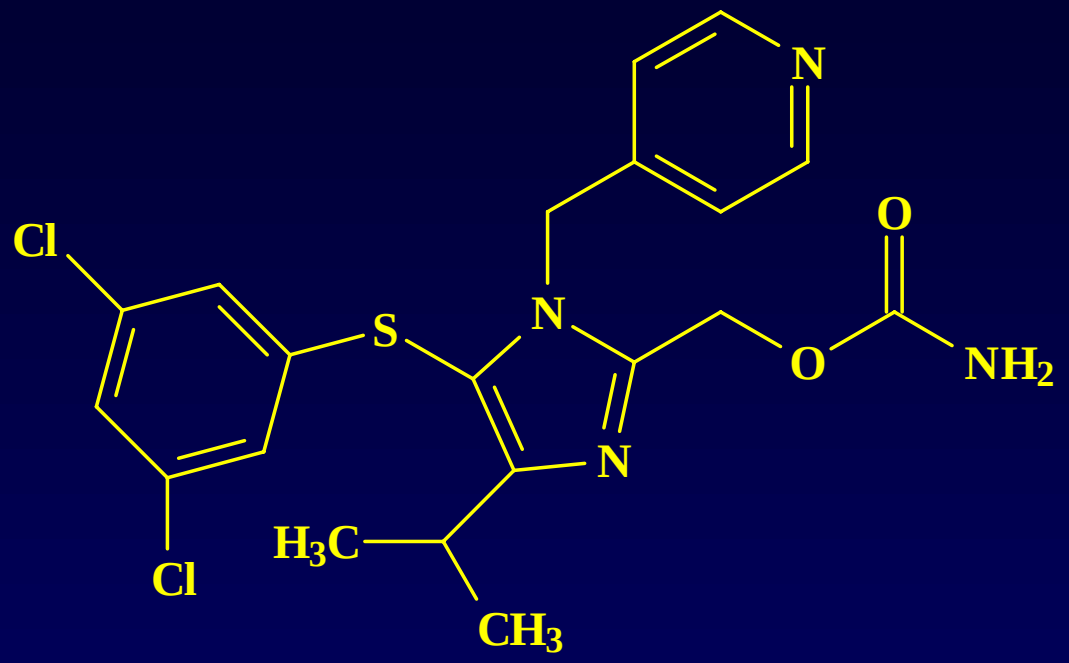
Benzoxazinone DMP 266

Efavirenz
Sustiva®



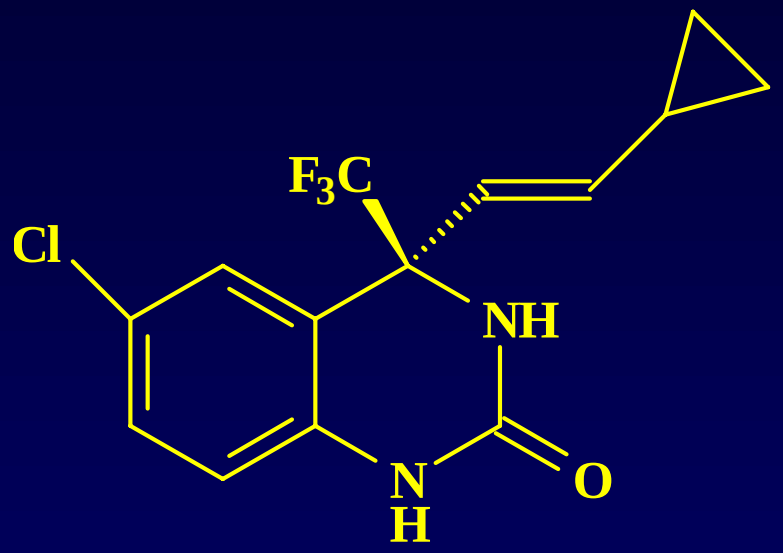
MKC-442

Emivirine
Coactinon®



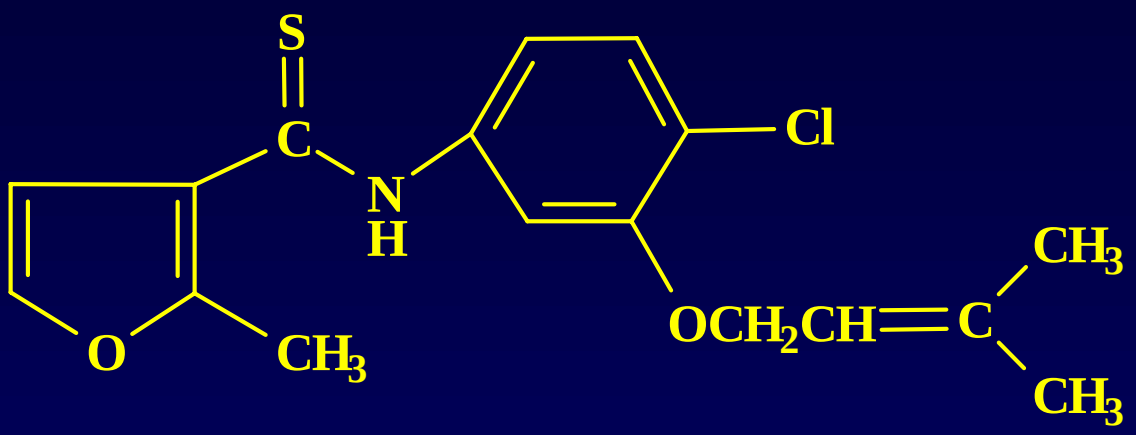
S-1153

AG1549
Capravirine

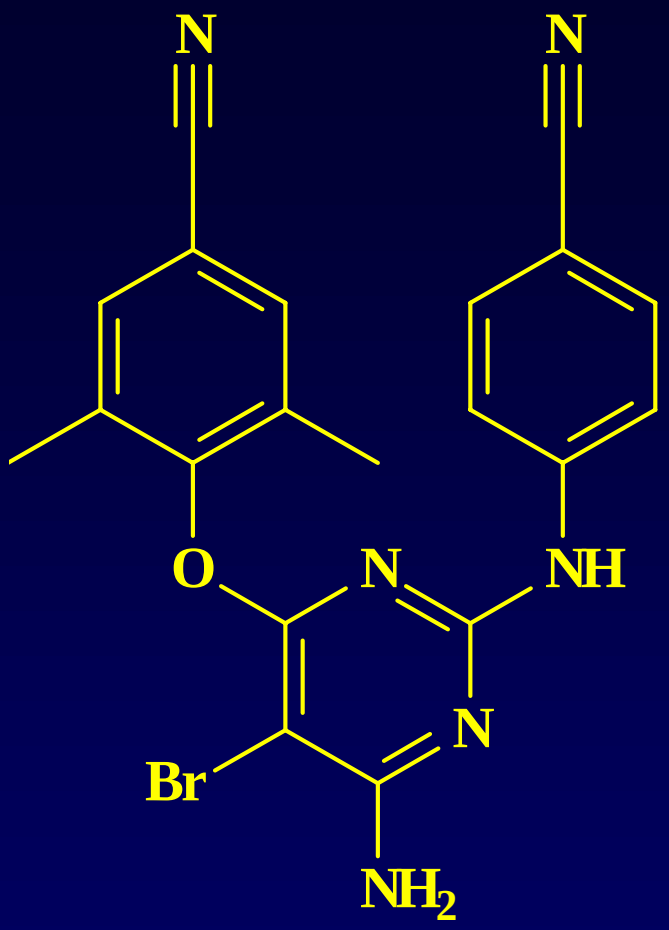


DPC-083

(+)-Calanolide A

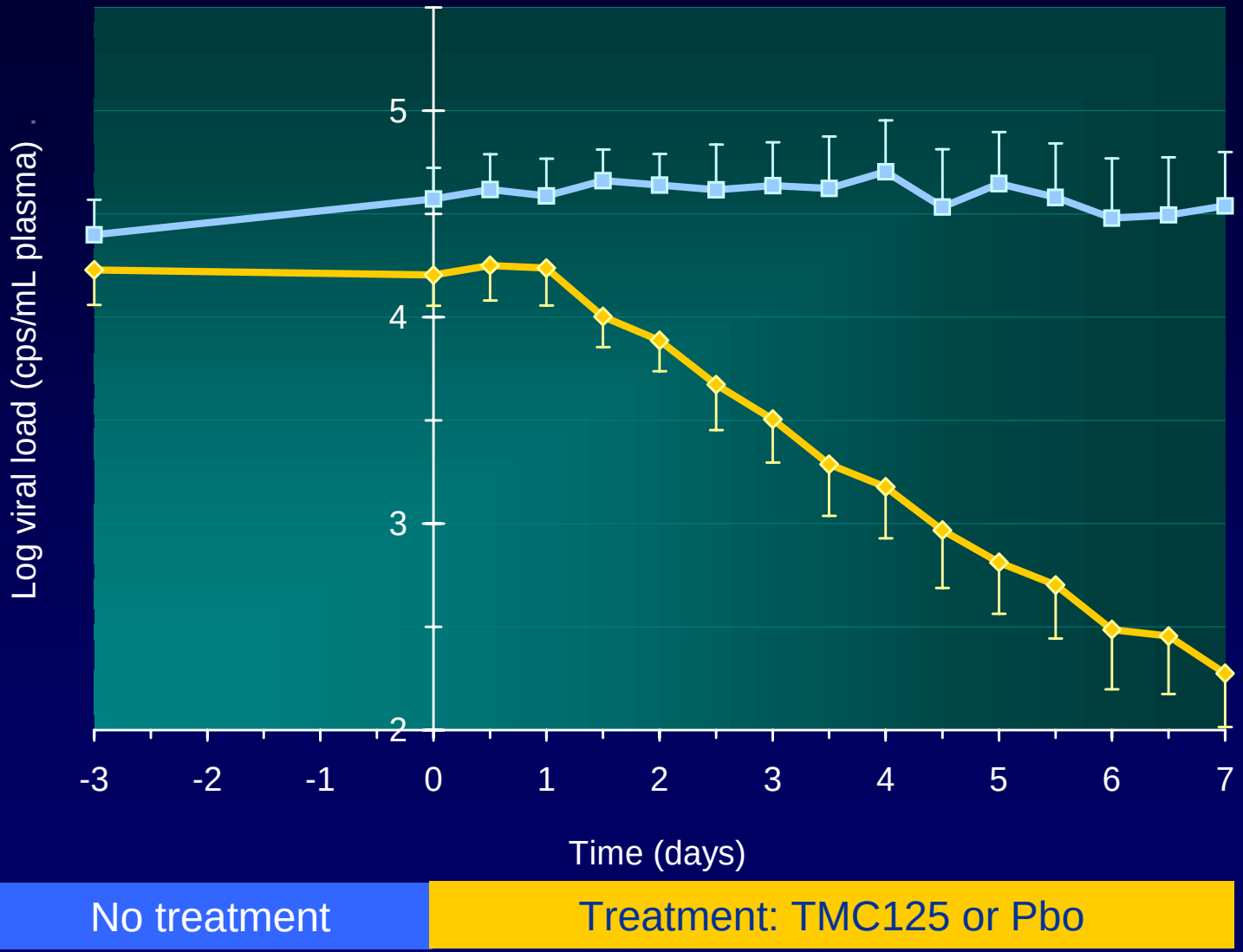


UC-781

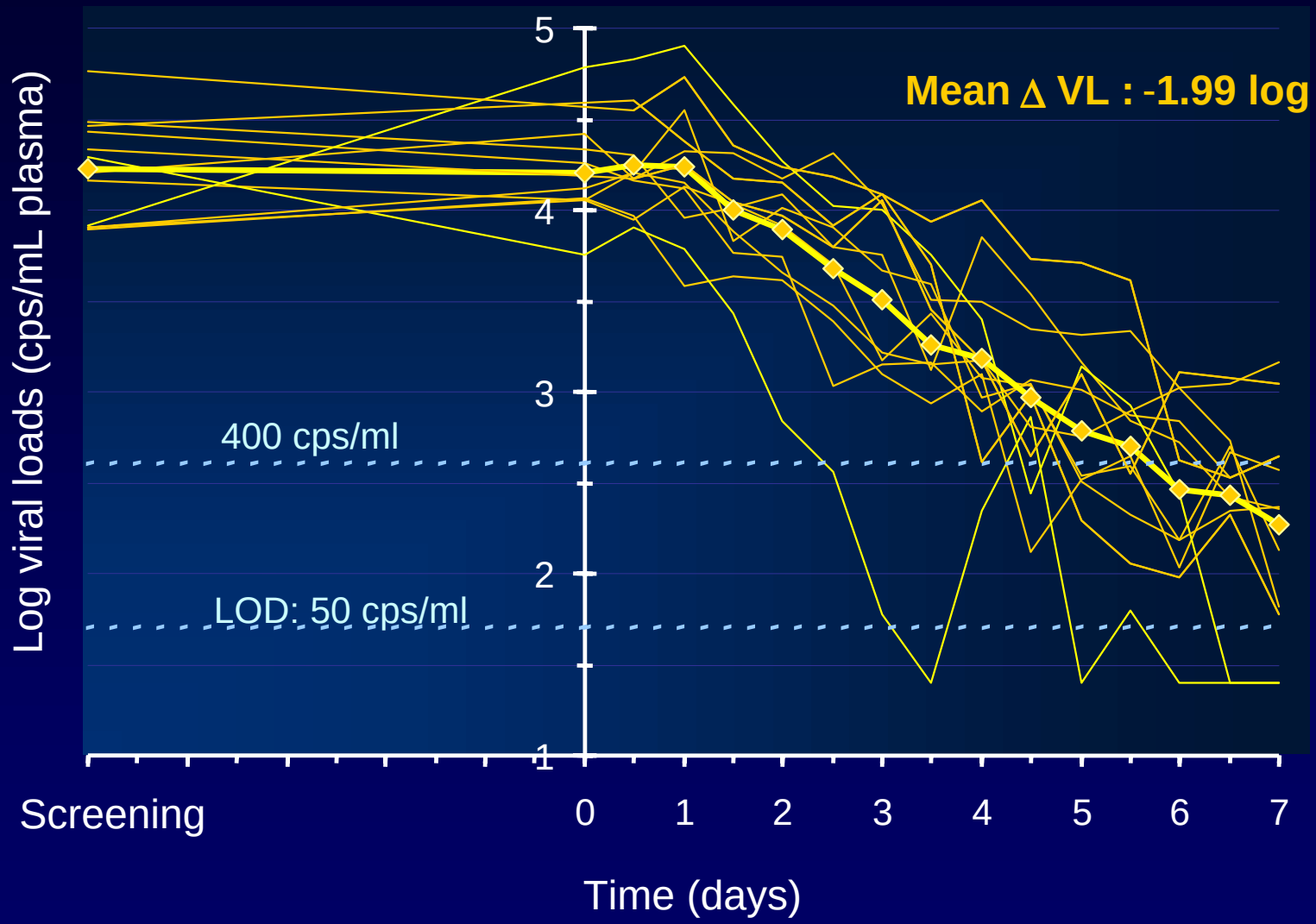


R165335
TMC-125
Dapivirine

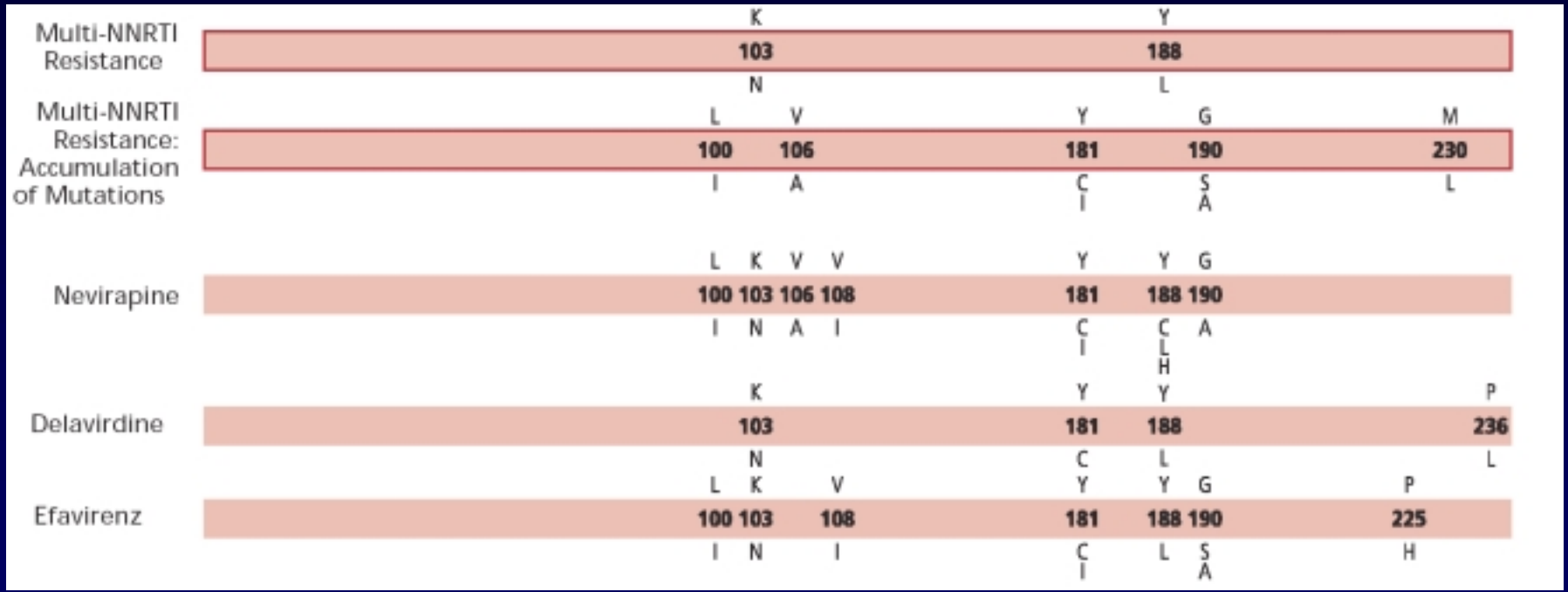
Activity in treatment-naive patients
TMC125 900 mg b.i.d. monotherapy x 7 days (mean ± SE)



TMC125: viral load response in individual patients (n = 12)



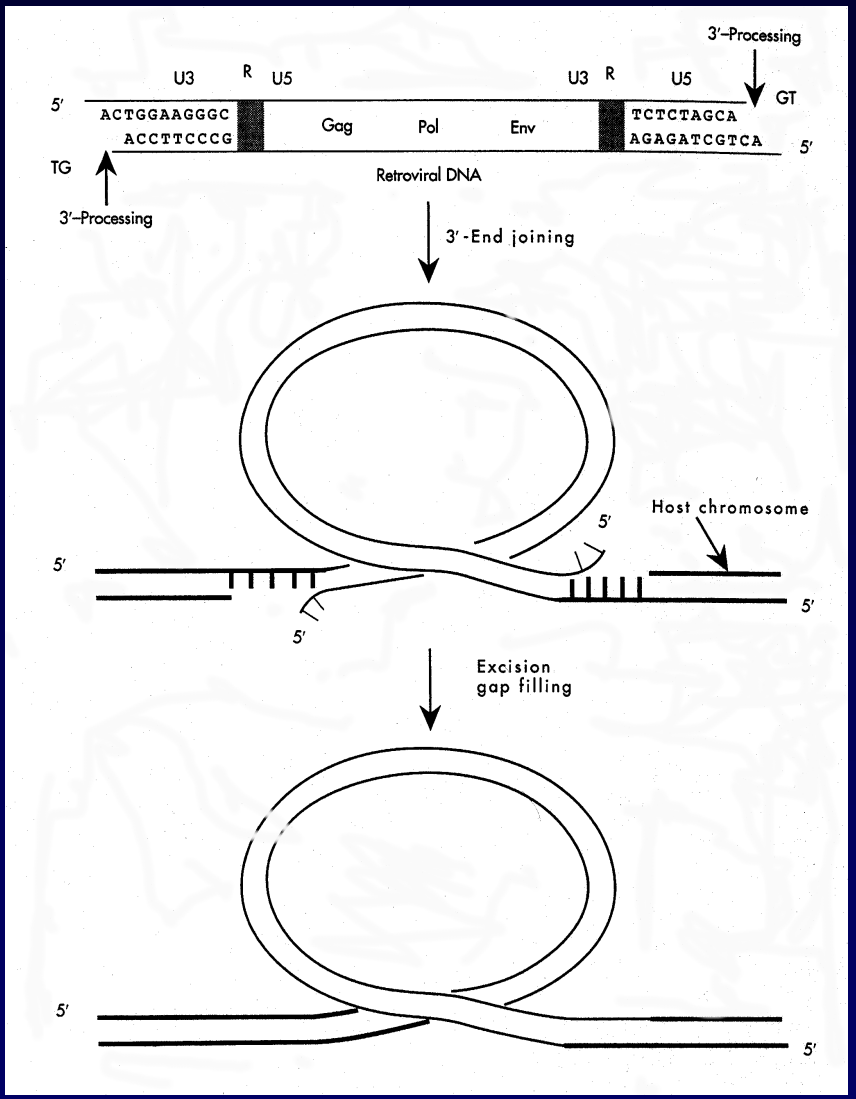
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

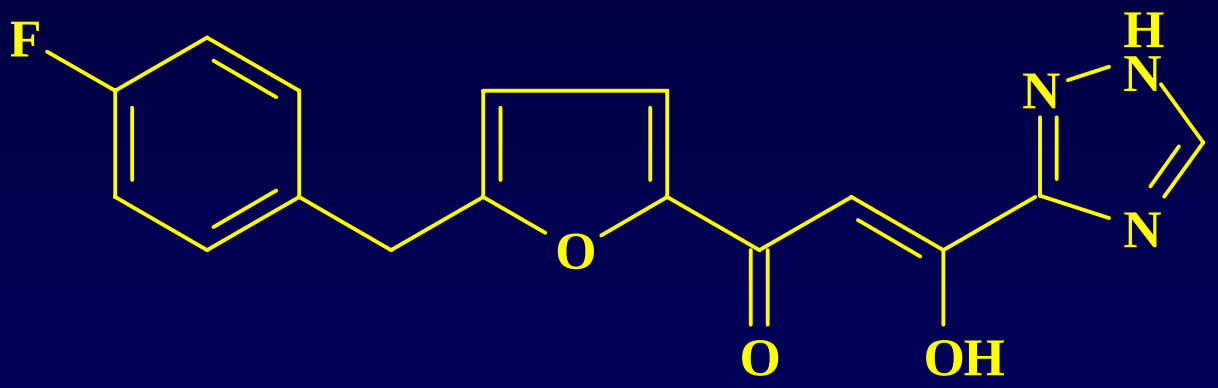


http:/www.iasusa.org/resistance_mutations/index.html

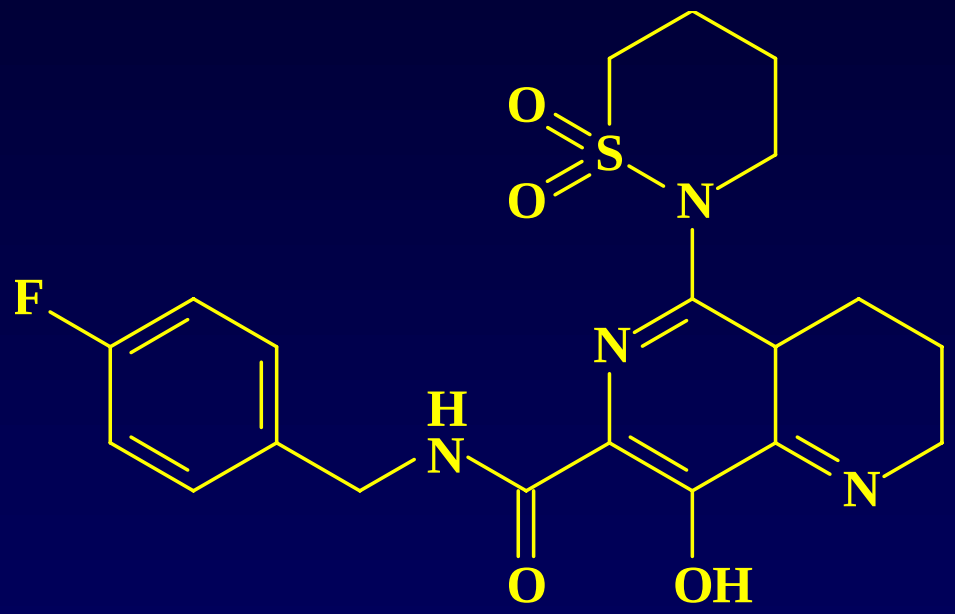
HIV REPLICATIVE CYCLE

- 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)


3′–Processing
U3
R
U5
U3
R
U5
5′
ACTGGAAGGGC
ACCTTCCCG
Gag
Pol
Env
TCTCTAGCA
AGAGATCGTCA
GT
5′
TG
3′–Processing
Retroviral DNA
3′-End joining
Host chromosome
5′
5′
5′
5′
Excision
gap filling
5′
5′



S-1360



1,6-Naphthyridine-7-carboxamide
L-870810

HIV REPLICATIVE CYCLE

- Virus adsorption
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- Proviral DNA replication
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HIV REPLICATIVE CYCLE

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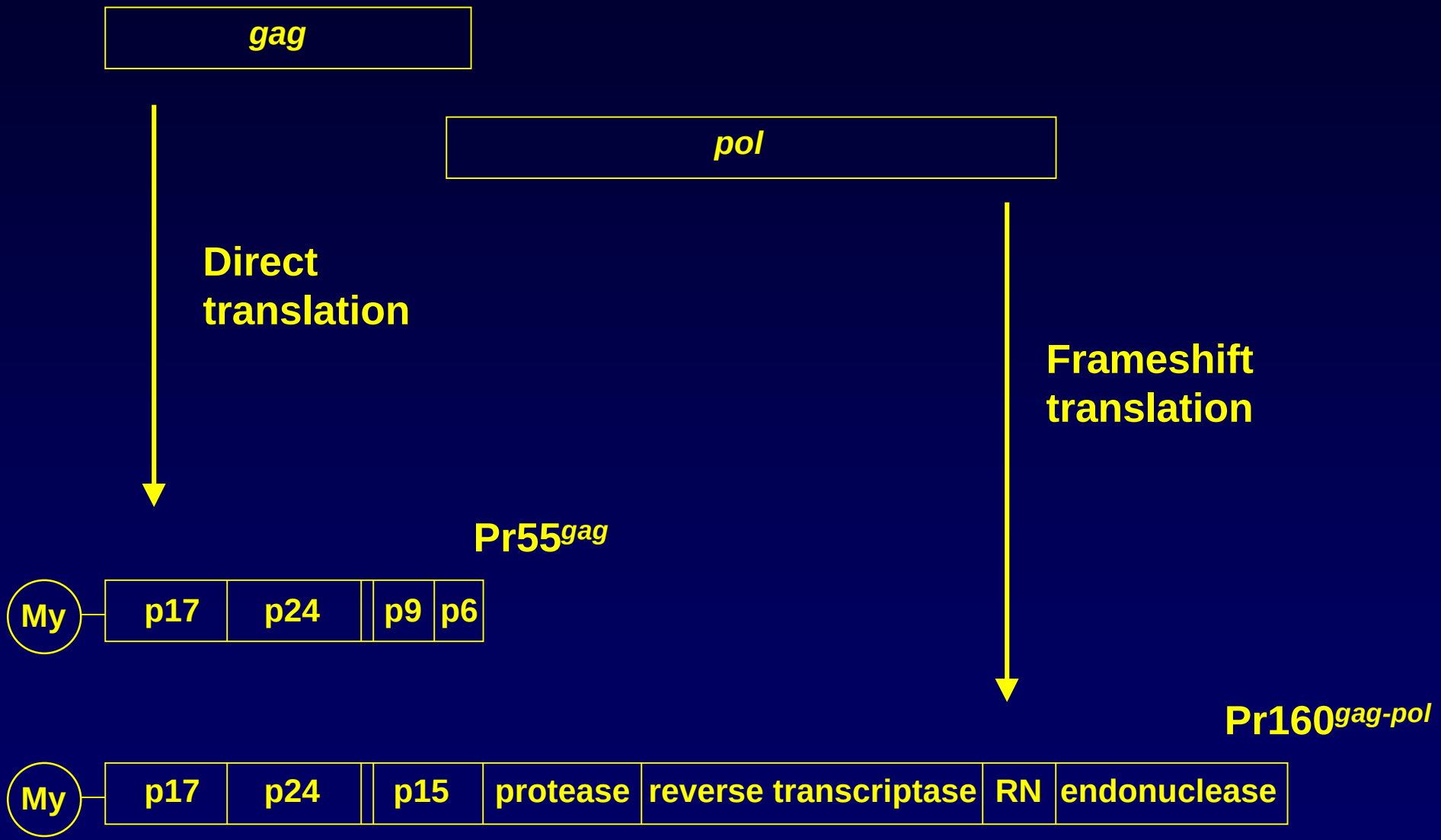
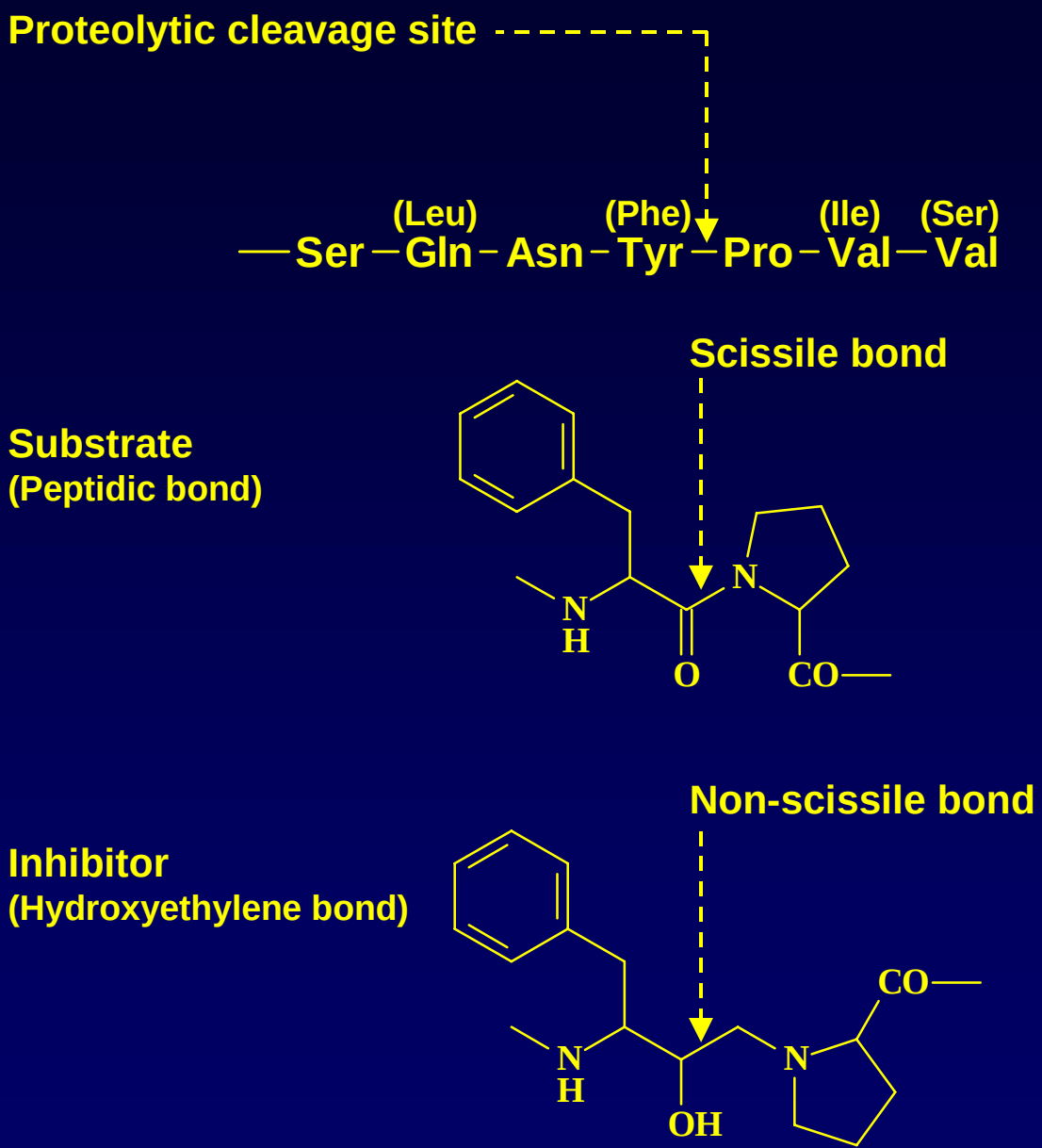
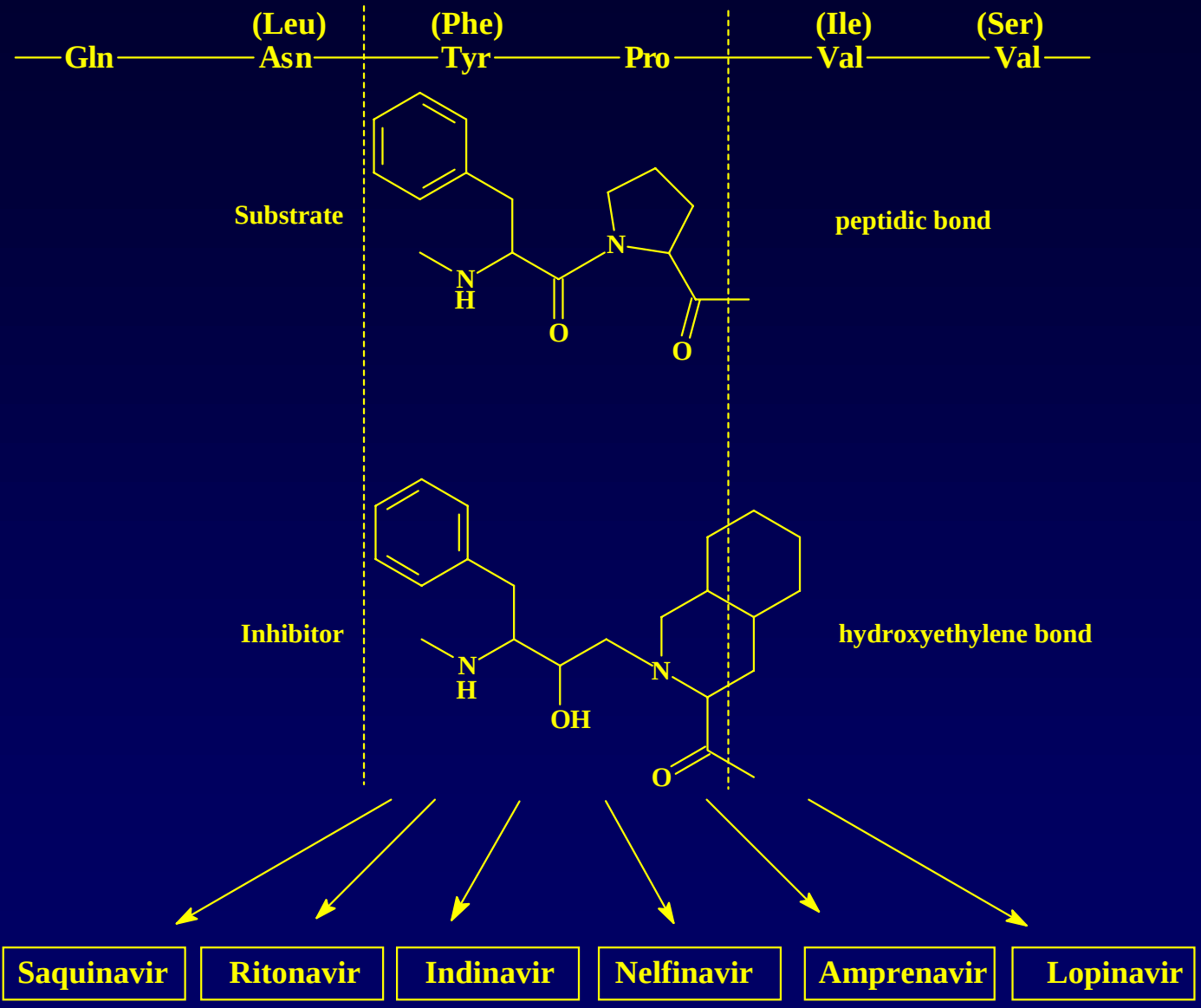
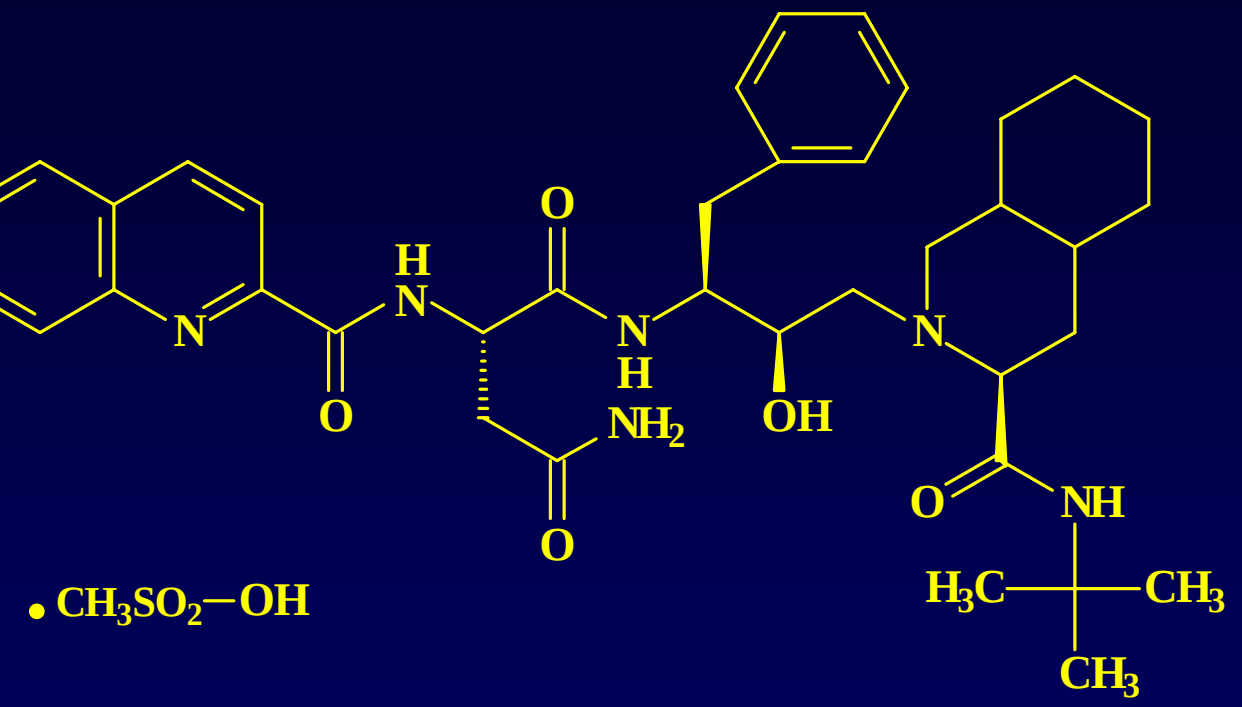
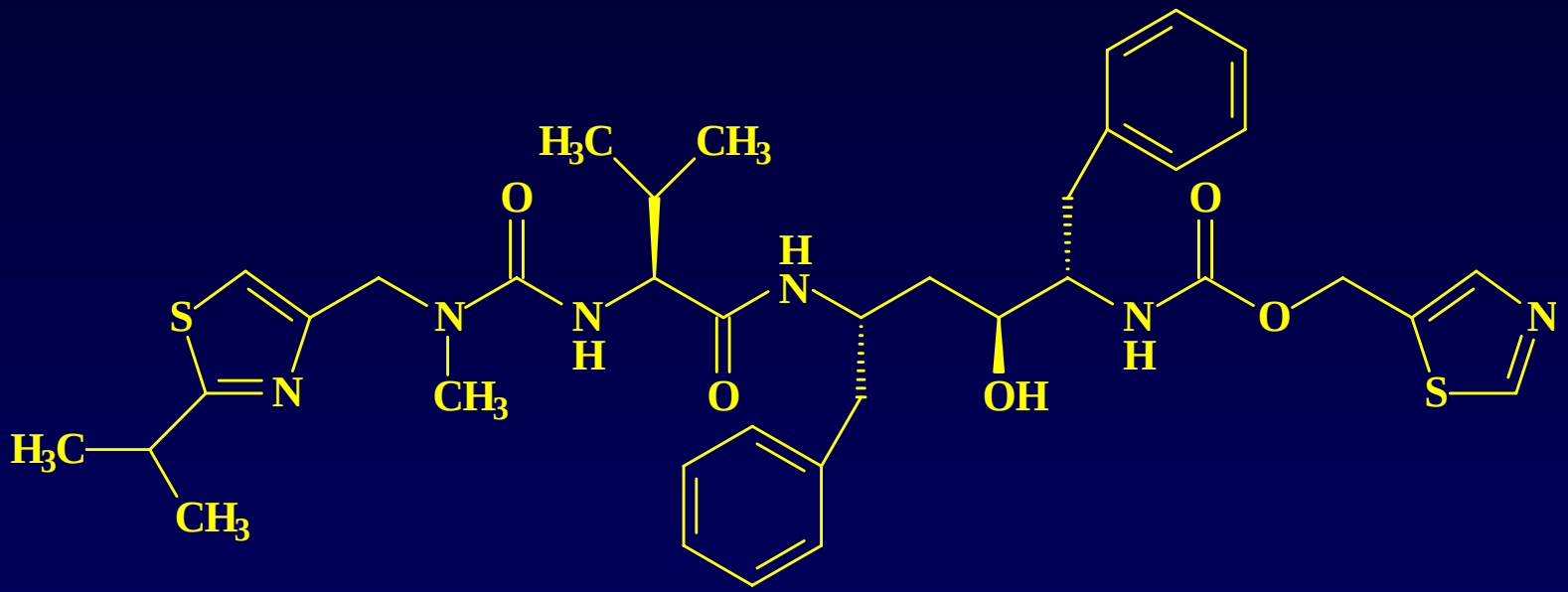

gag
pol
Direct translation
Frameshift translation
Pr55gag
My
p17
p24
p9
p6
Pr160gag-pol
My
p17
p24
p15
protease
reverse transcriptase
RN
endonuclease


Proteolytic cleavage site
(Leu)
(Phe)
(Ile)
(Ser)
Ser Gln Asn Tyr Pro Val Val
Scissile bond
Substrate
(Peptidic bond)
N
H
O
N
CO
Non-scissile bond
Inhibitor
(Hydroxyethylene bond)
CO
N
H
OH
N

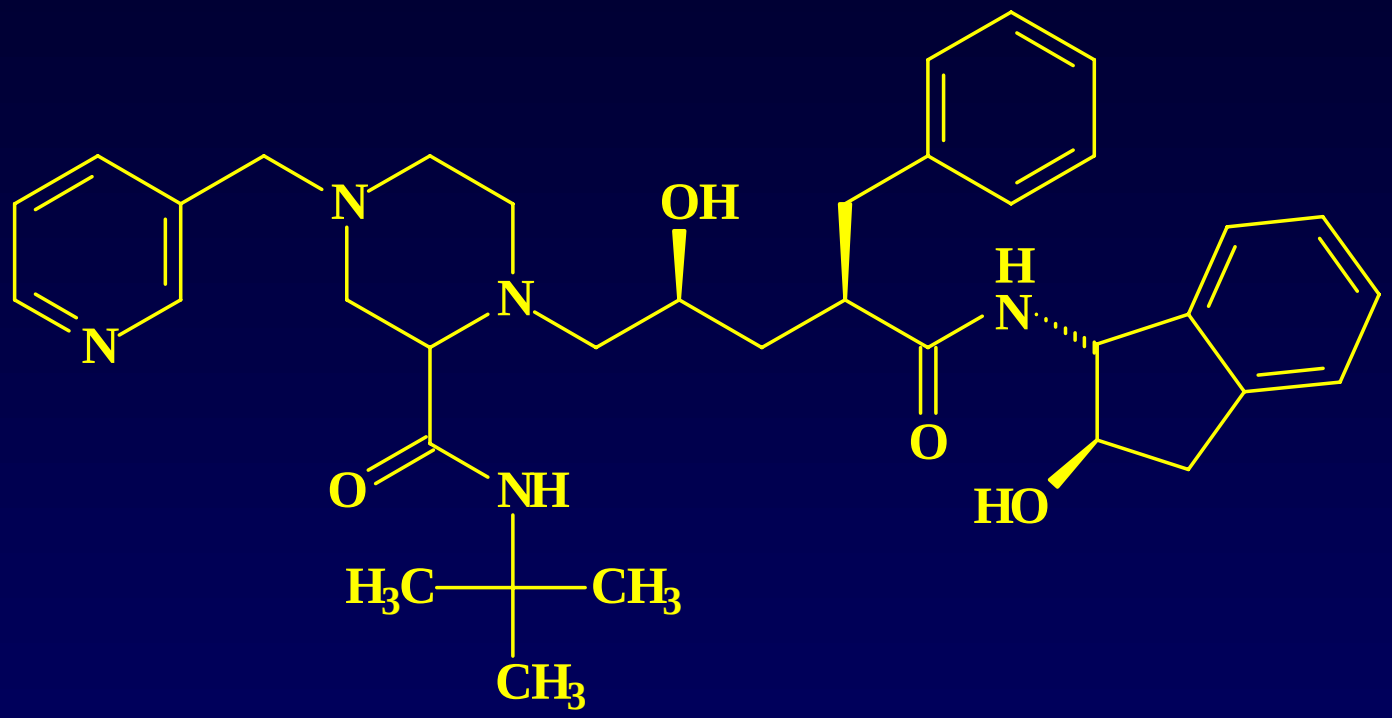

(Leu)
(Phe)
(Ile)
(Ser)
Gln
Asn
Tyr
Pro
Val
Val
Substrate
peptidic bond
N
H
O
N
O
Inhibitor
hydroxyethylene bond
N
H
OH
N
O
Saquinavir
Ritonavir
Indinavir
Nelfinavir
Amprenavir
Lopinavir



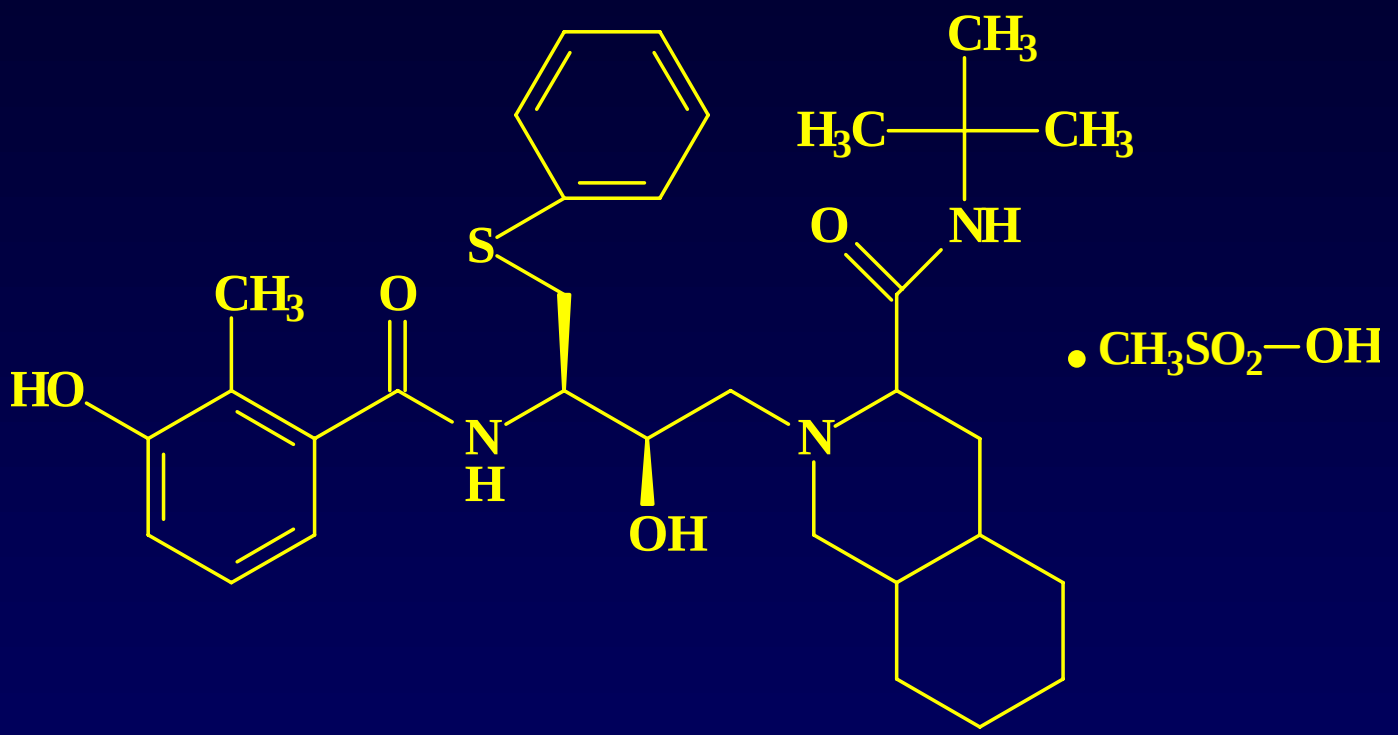
Saquinavir
Invirase®



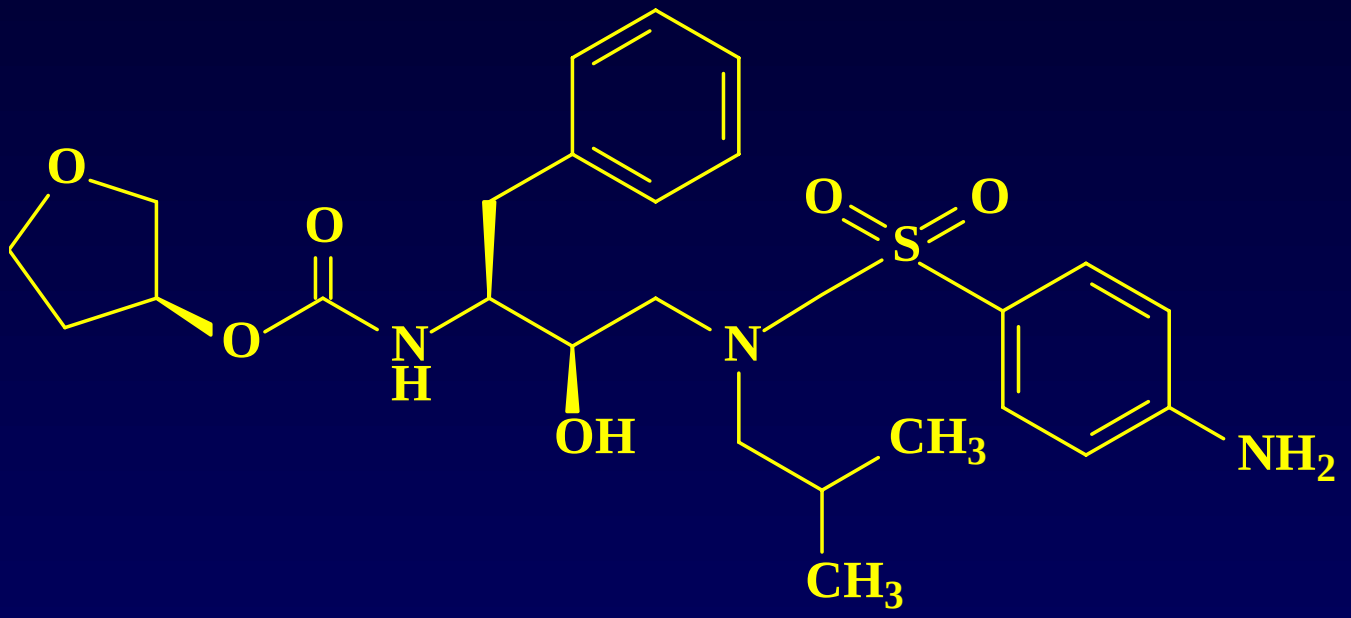
Ritonavir
Norvir®



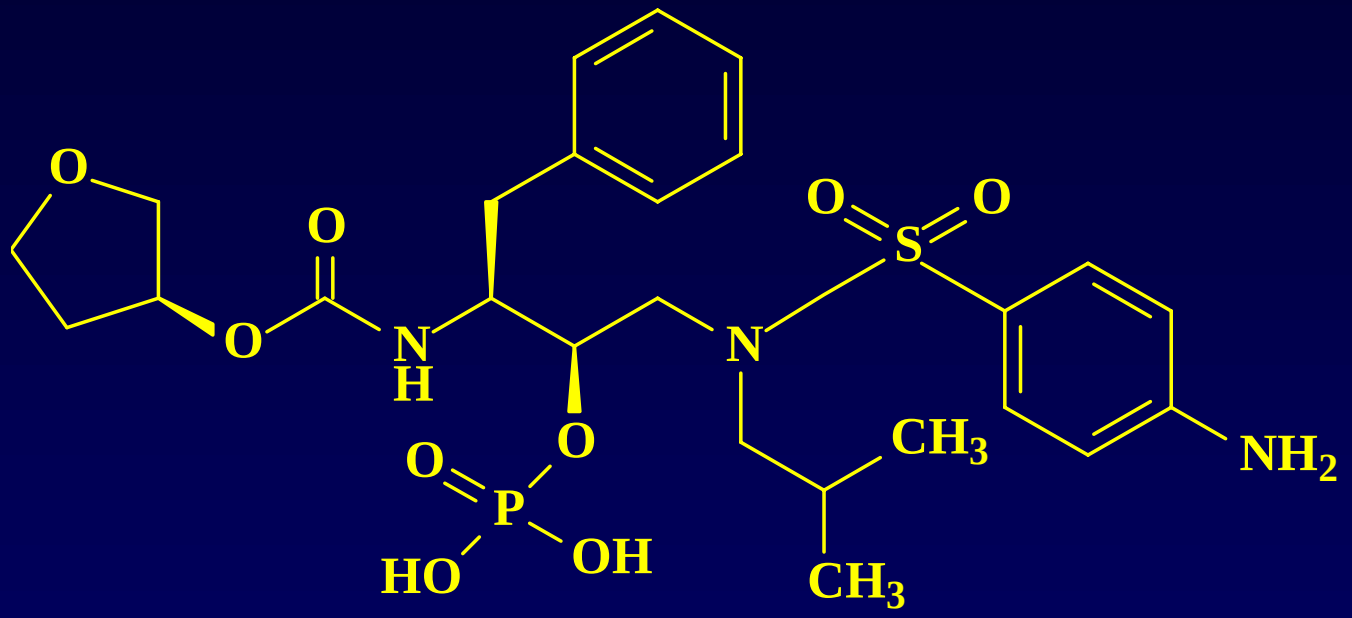
Indinavir
Crixivan®



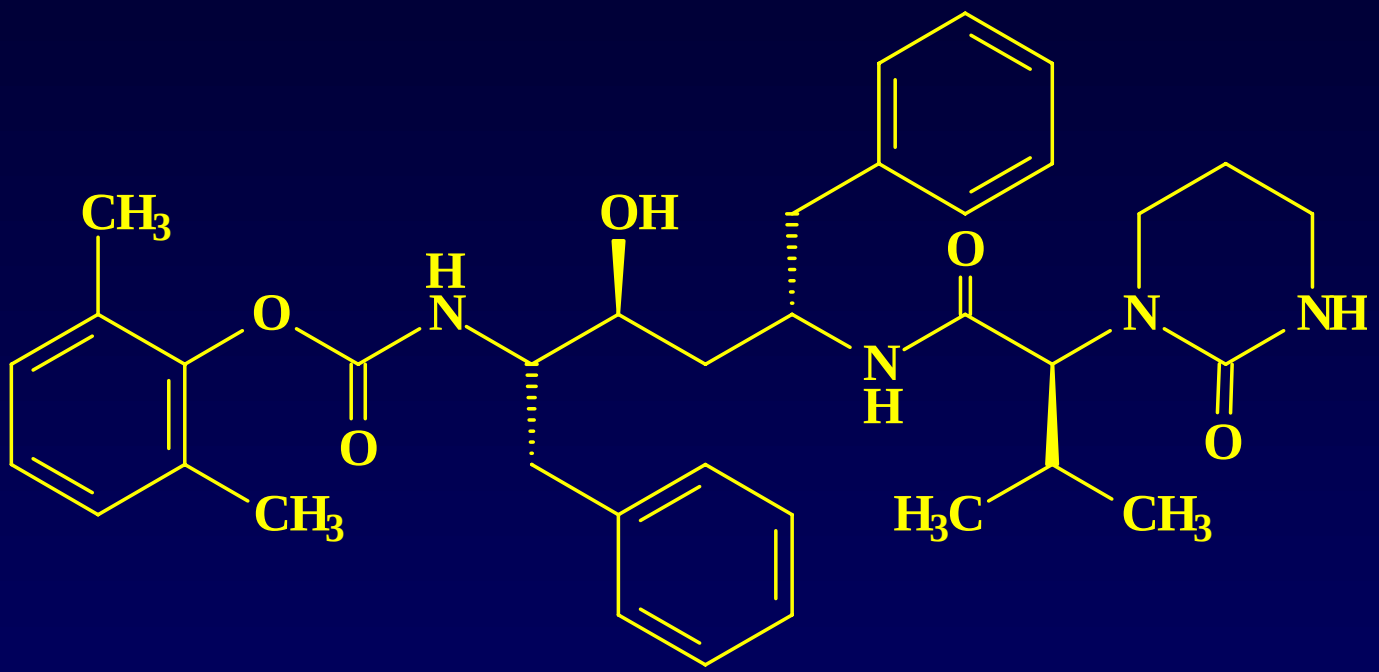
Nelfinavir
Viracept®



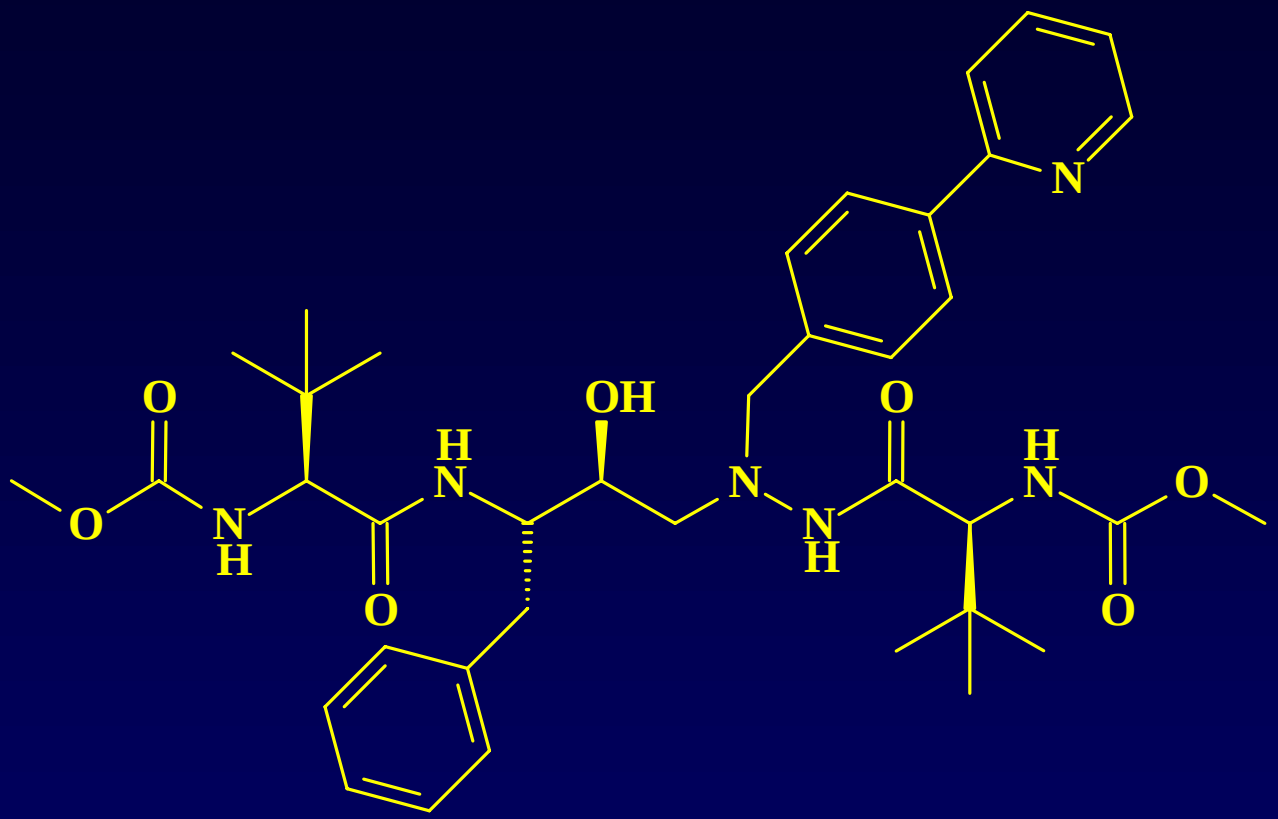
Amprenavir
Agenerase®



Fosamprenavir



Lopinavir
Kaletra®



BMS 232632
Atazanavir

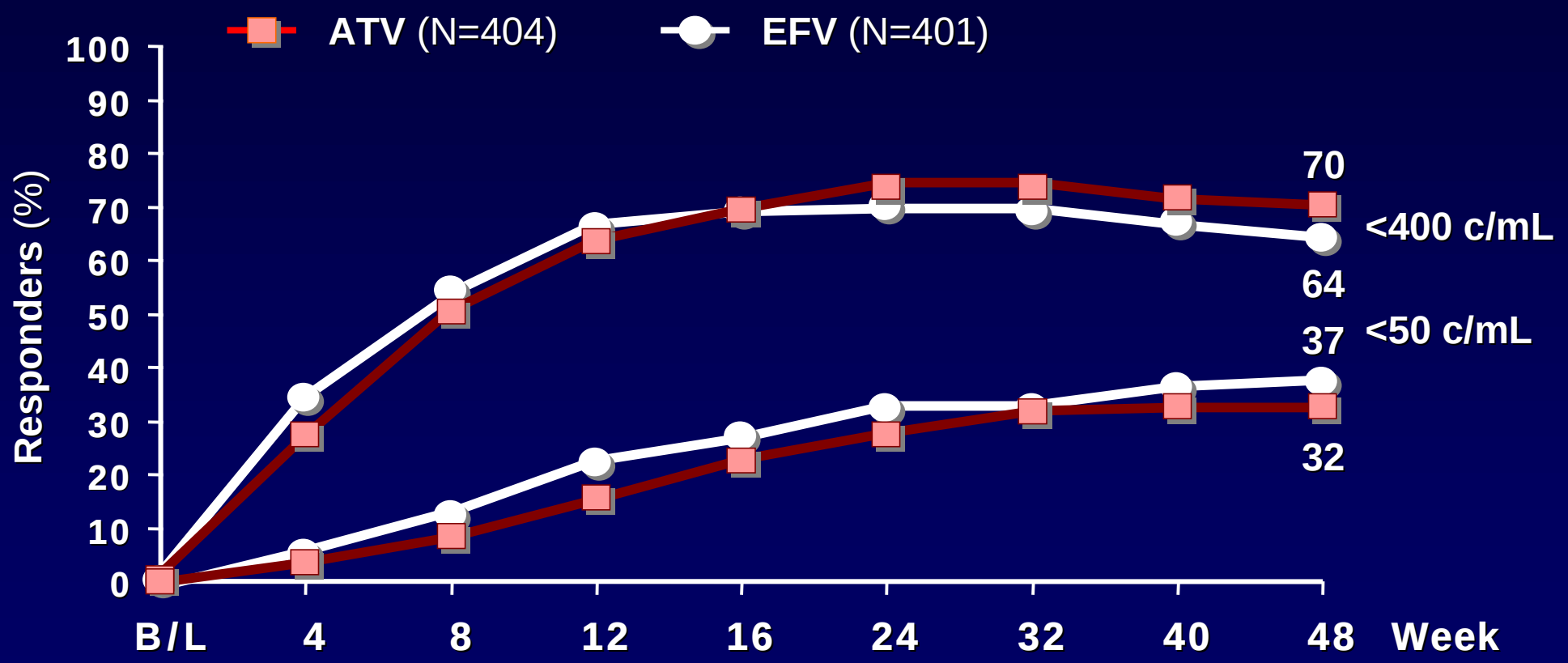
Atazanavir clinical profile

- Once-daily azapeptide PI
- Low pill burden (2 capsules/day)
- Efficacy and durability of response in treatment-naive and –experienced patients
- Atazanavir treatment does not result in clinically relevant increases in total cholesterol, low-density lipoprotein cholesterol, or triglycerides
- Atazanavir does not inhibit insulin-mediated transport of glucose
- I50L is signature mutation in PI-naive patients, and is associated with increased *in vitro* sensitivity to other PIs

Colonno *et al*., Antiviral Ther. 7 (Suppl. 1): S6 (2002)

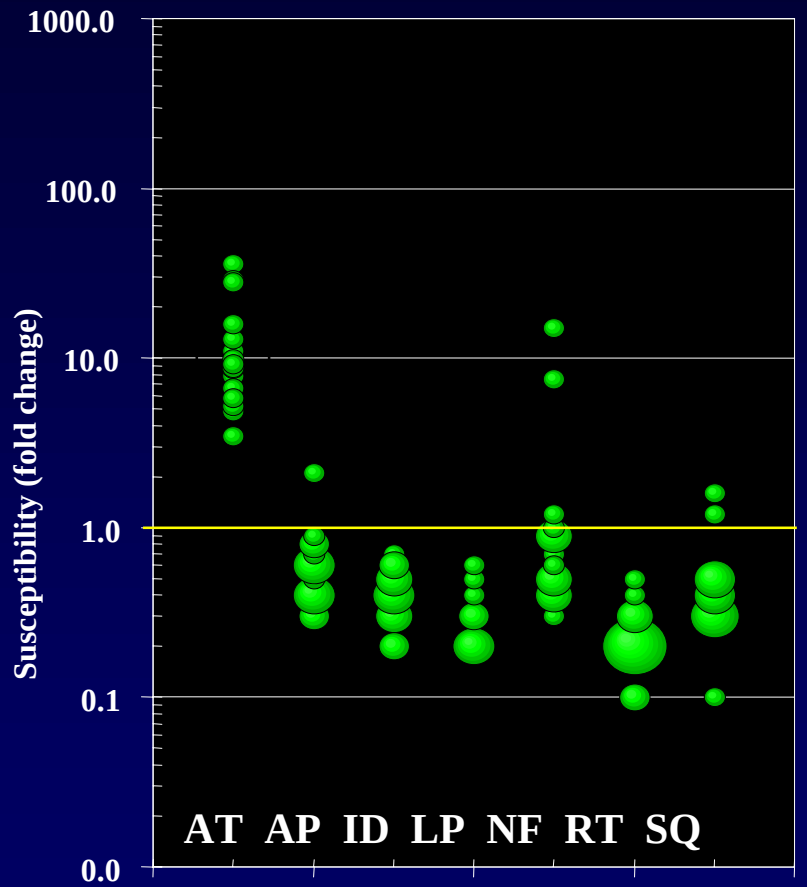
Atazanavir (ATV) qd *versus* efavirenz (EFV) qd with zidovudine plus lamivudine bid in treatment-naive patients

Virologic response through week 48 (ITT)



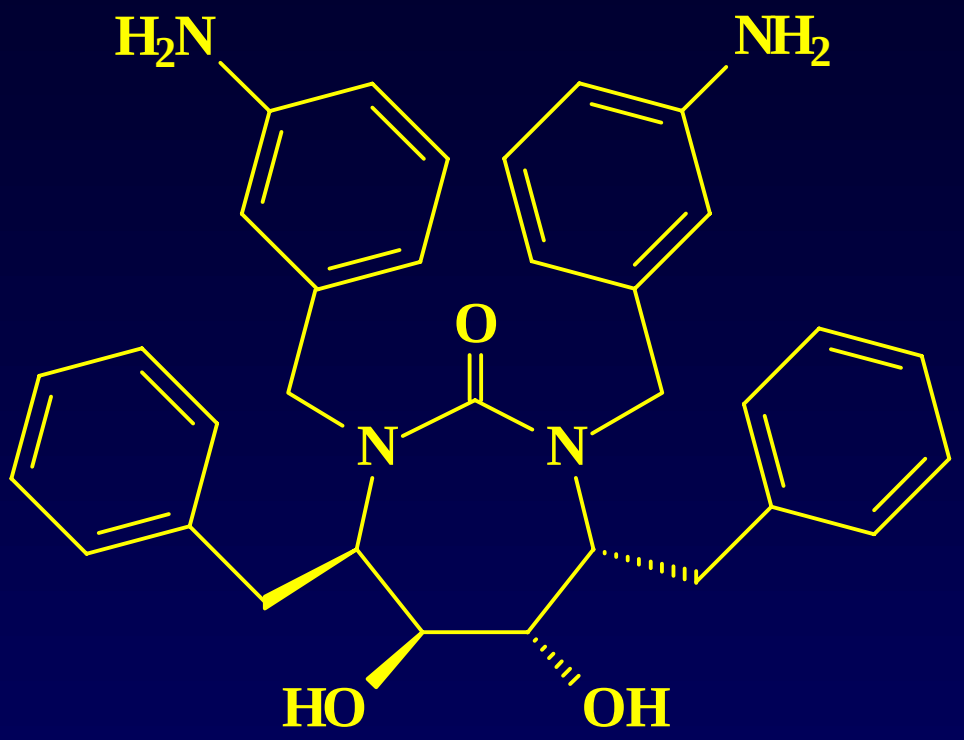
Squires *et al*., 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, USA, 27-30 September 2002. Abstract no. H-1076

Susceptibility profiles of I50L isolates

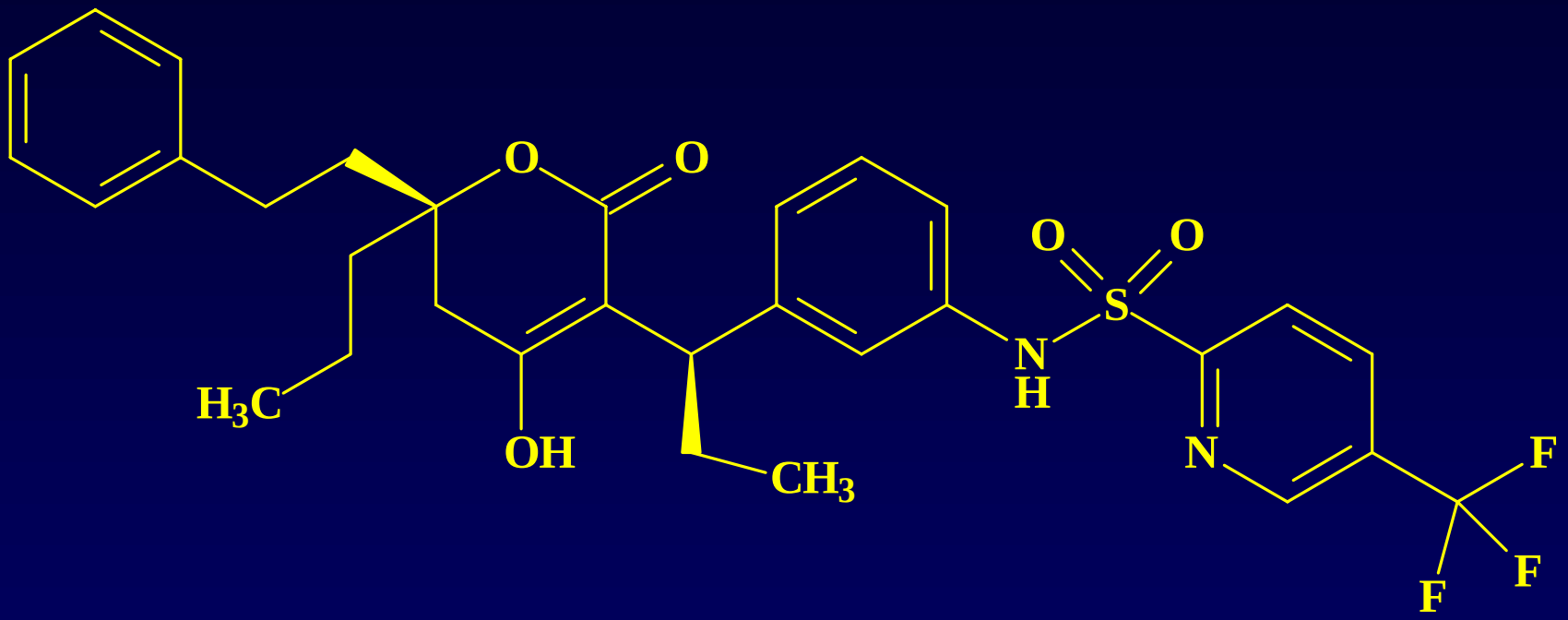


AT = Atazanavir
AP = Amprenavir
ID = Indinavir
LP = Lopinavir
NF = Nelfinavir
RT = Ritonavir
SQ = Saquinavir

Colonno *et al*., 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, USA, 10-14 February 2003. Abstract no 597

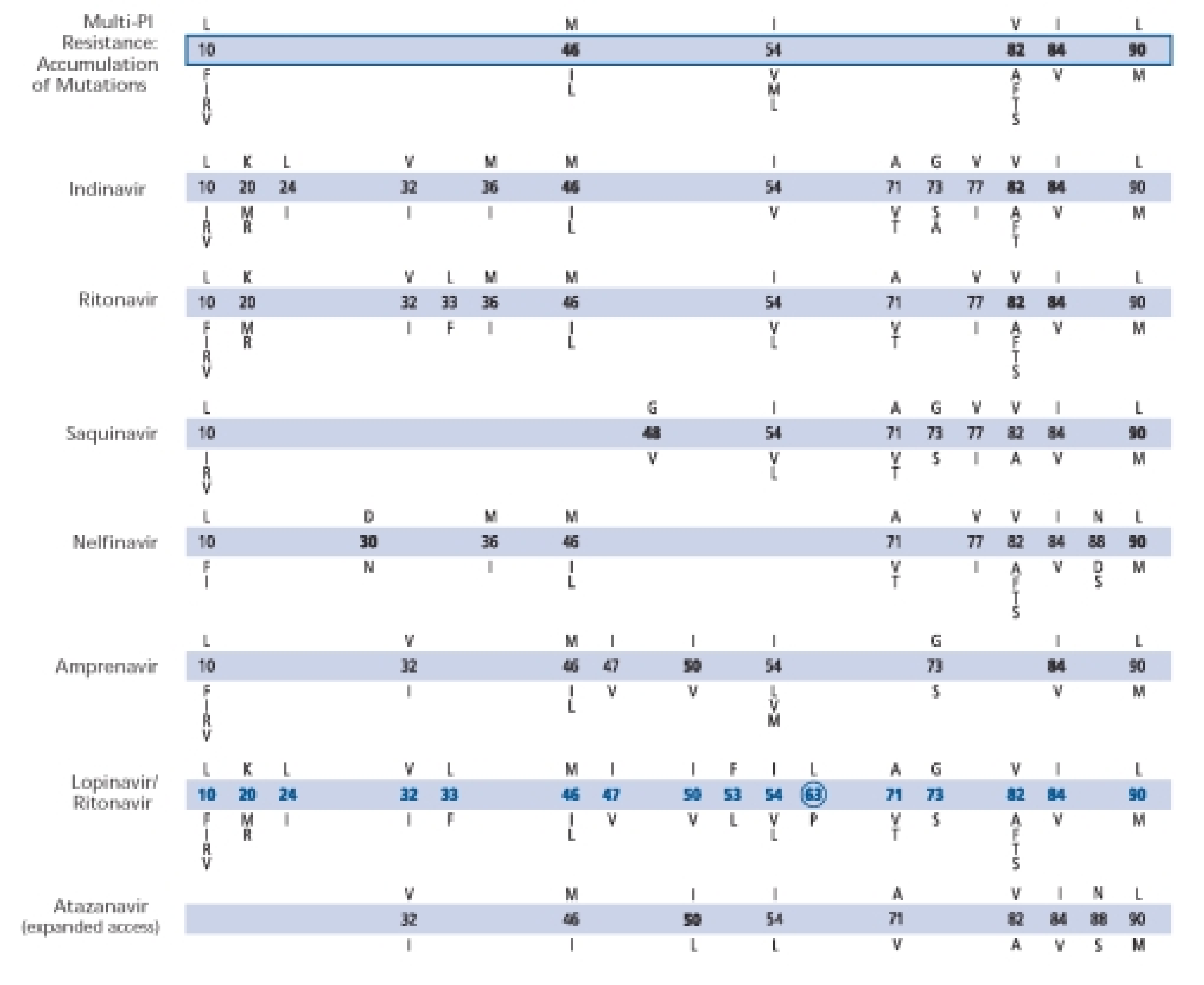


DMP-450
Mozenavir



PNU-140690
Tipranavir

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



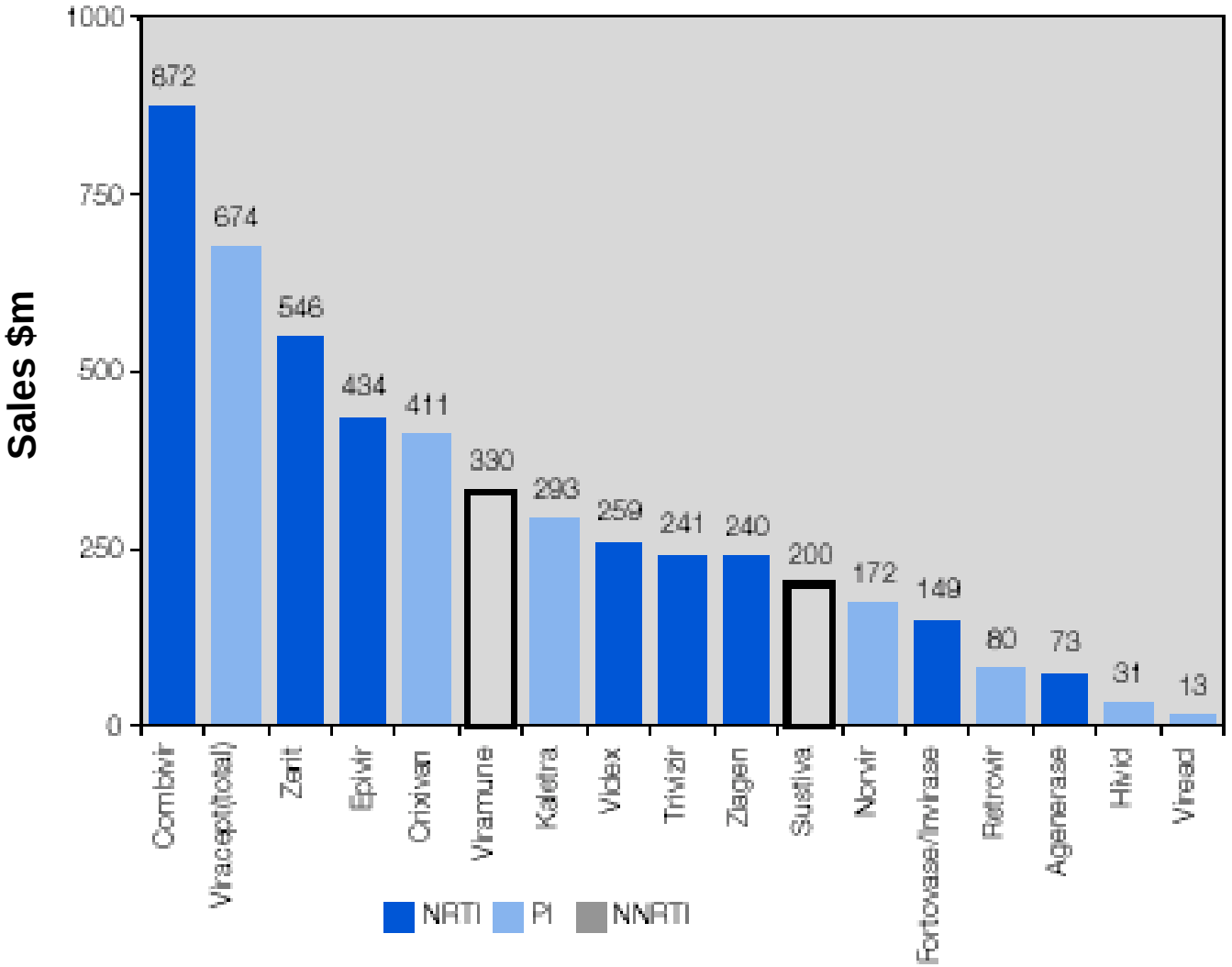
http:/www.iasusa.org/resistance_mutations/index.html

Drugs used to treat HIV infections (AIDS)

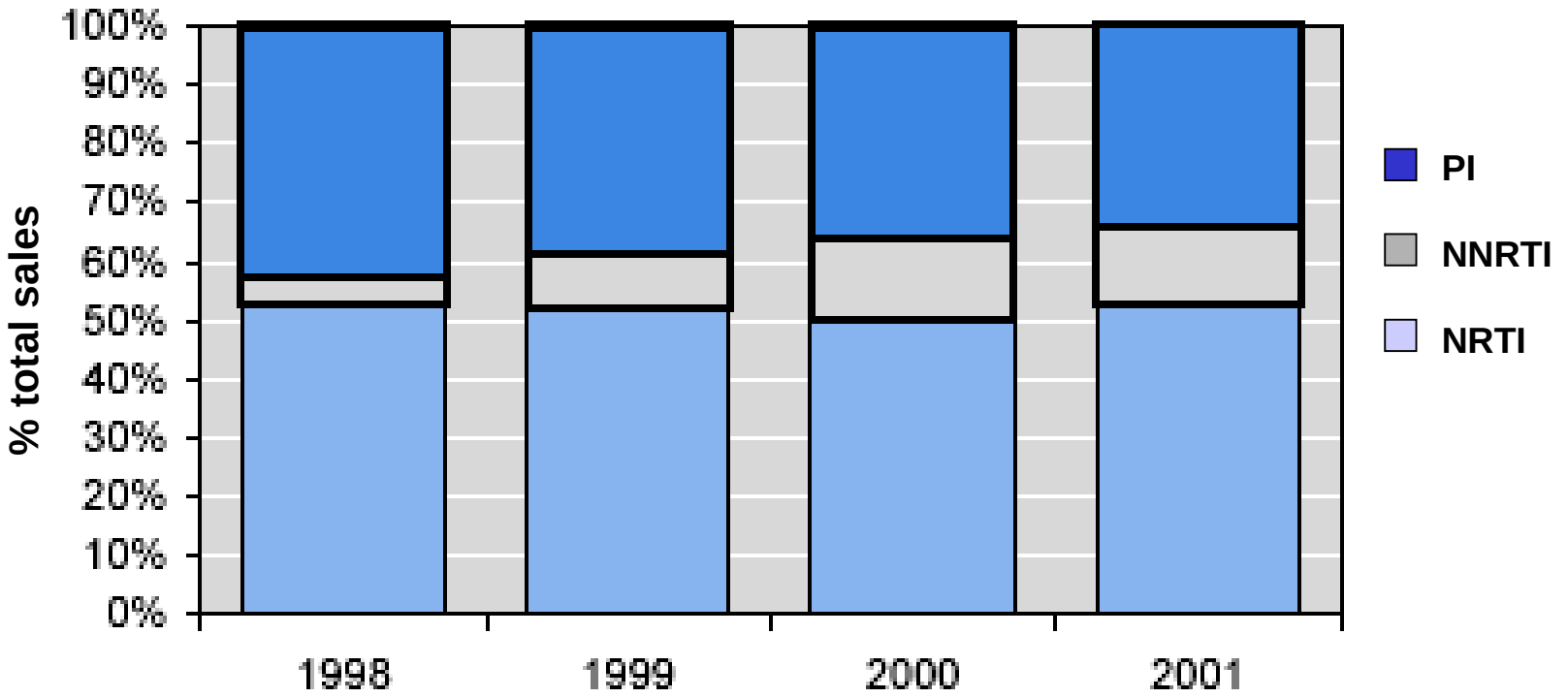
Drug	Brand Name	Manufacturer
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Zidovudine (AZT)	Retrovir	GlaxoSmithKline
Didanosine (ddI)	Videx	Bristol-Myers Squibb
Zalcitabine (ddC)	Hivid	Roche
Stavudine (d4T)	Zerit	Bristol-Myers Squibb
Lamivudine (3TC)	Epivir	GlaxoSmithKline
Abacavir (ABC)	Ziagen	GlaxoSmithKline
Nucleotide reverse transcriptase inhibitors (NtRTIs)		
Tenofovir disoproxil fumarate (TDF)	Viread	Gilead Sciences
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Nevirapine	Viramune	Roxane/Boehringer Ingelheim
Delavirdine	Rescriptor	Pharmacia
Efavirenz	Sustiva, Stocrin	DuPont Merck
Protease inhibitors (PIs)		
Saquinavir	Fortovase, Invirase	Roche
Ritonavir	Norvir	Abbott
Indinavir	Crixivan	Merck
Nelfinavir	Viracept	Agouron/Pfizer
Amprenavir	Agenerase	GlaxoSmithKline
Lopinavir (with ritonavir)	Kaletra	Abbott

Sales of the major anti-retroviral drugs in 2001

Source: Companies, Fortis Bank



Share of the global HIV market by drug type from 1998 to 2001



Source: Companies, Fortis Bank

Currently approved NRTIs

Brand name	Generic	FDA approved	Manufacturer
Retrovir®	Zidovudine	March 1987	GSK
Videx®	Didanosine	October 1991	BMS
Hivid®	Zalcitabine	June 1992	Roche
Zerit®	Stavudine	June 1994	BMS
Epivir®	Lamivudine	November 1995	GSK
Combivir®	Zidovudine + lamivudine	September 1997	GSK
Ziagen®	Abacavir	December 1998	GSK
Trizivir®	Abacavir + lamivudine + zidovudine	November 2000	GSK
Viread®	Tenofovir	October 2001	Gilead

Source: Companies, Fortis Bank

NRTIs in development

Name	Clinical trials	Manufacturer	Description
Epivir® + Ziagen®	Phase III	GSK	New NRTI combination tablet
Coviracil®	NDA	Triangle	
Amdoxovir	Phase II	Triangle	Purine (guanine) nucleoside analogue
MIV-310	Phase II	Medivir	Thymidine mimetic; Phase IIa is complete. Additional Phase IIb trials being planned for 2003
Ach-126443	Phase I	Achillion Pharma	An L-nucleoside with in vitro activity against HIV and HBV. The drug is being positioned as a lamivudine (3TC) replacement

Source: Companies, Fortis Bank

Currently approved NNRTIs

Brand name	Generic	FDA approved	Manufacturer
Viramune®	Nevirapine	June 1996	Boehringer Ingelheim
Rescriptor®	Delavirdine	April 1997	Upjohn/Pharmacia/Pfizer
Sustiva®	Efavirenz	September 1998	DuPont/BMS

Source: Companies, Fortis Bank

NNRTIs in development

Name	Clinical trials	Manufacturer	Description
Coactinon® (MKC-442)	Phase III	Triangle	Terminated
Capravirine (AG1549)	Phase III	Agouron/Pfizer	Appears to be 10 times more effective than nevirapine or delavirdine. HIV requires 2 or 3 mutations to become resistant to this drug (compared to 1 mutation for other NNRTIs). Phase III - reinitiated
TMC125	Phase II	Tibotec/J & J	Achieved a 2-log drop in viral load within 7 days, all patients responded, and the drug was safe and well tolerated. It was active against mutant strains of HIV
DPC083	Phase III	DuPont/BMS	A modified form of efavirenz (Sustiva) that will probably be a once daily formulation with some activity against HIV resistant to other NNRTIs. US submission due 2003
Calanolide A	Phase I/II	Sarawak Medichem	Novel NNRTI based on a natural chemical found in a tropical rainforest tree

Source: Companies, Fortis Bank

Currently approved PIs

Brand name	Generic name	FDA approved	Manufacturer
Invirase®/ Fortovase®	Saquinavir	Dec 1995/Nov 1997	Roche
Norvir®	Ritonavir	March 1996	Abbott
Crixivan®	Indinavir	March 1996	Merck
Viracept®	Nelfinavir	March 1997	Roche (ex-US sales) Pfizer (US sales)
Agenerase®	Amprenavir	April 1999	Vertex/GSK
Kaletra®	Lopinavir (+ ritonavir)	1st quarter 2001	Abbott

Source: Companies, Fortis Bank

PIs in development

Name	Clinical trials	Manufacturer	Description
Atazanavir (BMS-232632)	EMEA filed, Phase III US	BMS	Once daily dosing, pending EU approval, Phase III in the US. Expected to combine a better safety profile with increased potency
Fosamprenavir (GW433908)	Phase III	Vertex/GSK	A prodrug of amprenavir (Agenerase) in a more convenient formulation
Tipranavir (PNU-140690)	Phase III	Boehringer Ingelheim	Better resistance profile, expected to be used for patients who have tried and failed at least on one PI-based combination
DMP450	Phase II/III	Triangle	Terminated

Source: Companies, Fortis Bank

Daily Dosing of Antiretroviral Agents*

	CLASS/DRUG	USUAL ADULT DAILY DOSING†	ACTUAL SIZE
NON-NUCLEOSIDE REVERSE TRANSRIPTASE INHIBITORS	**Viramune®** (Nevirapine)	1 x 200 mg tablet 2 times a day Lead in dosing for first 14 days of therapy : 1 x 200 mg tablet once a day	
	Stocrin® (Efavirenz)	3 x 200 mg capsule Once a day (at bed time)	
NUCLEOSIDE ANALOGUES	**Ziagen®** (Abacavir)	1 x 300 mg capsule 2 times a day	
	Videx® enteric coated (Didanosine – also known as ddI)	1 x 400 mg capsule once a day Patients weighing > 60 kg 1 x 250 mg capsule once a day Patients weighing < 60 kg	
	Epivir® (Lamivudine – also known as 3TC)	1 x 150 mg tablet 2 times a day	
	Combivir® (Lamivudine/zidovudine)	1 x 150 mg / 300 mg tablet 2 times a day	
	Zerit® (Stavudine – also known as d4T)	1 x 40 mg capsule 2 times a day Patients weighing > 60 kg 1 x 30 mg capsule 2 times a day Patients weighing < 60 kg	
	Hivid® (Zalcitabine – also known as ddC)	1 x 0,75 mg tablet 3 times a day	

	Retrovir® (Zidovudine – also known as ZDV or AZT)	2 x 100 mg capsules 3 times a day 1 x 300 mg tablets 2 times a day 1 x 250 mg capsules 2 times a day	
	Trizivir® (Abacavir, Lamivudine, Zidovudine)	1 x 300 mg/150 mg/300 mg tablet 2 times a day	
PROTEASE INHIBITORS	**Agenerase®** (Amprenavir)	8 x 150 mg capsules 2 times a day If in combination with Ritonavir (100-200 mg twice daily), reduced dose of Amprenavir is recommended (600 mg 2 times a day)	
	Crixivan® (Indinavir)	2 x 400 mg capsules 3 times a day For use with Ritonavir, other dosages may be used	
	Viracept® (Nelfinavir mesylate)	5 x 250 mg tablets 2 times a day 3 x 250 mg tablets 3 times a day	
	Norvir® (Ritonavir)	6 x 100 mg capsules 2 times a day As "PI booster" 100–200 mg 2 times a day	
	Fortovase® (Saquinavir Soft Gel Capsule)	6 x 200 mg soft gelatin capsules 3 times a day For use with Ritonavir, other dosages may be used	
	Invirase® (Saquinavir Hard Gel Capsule)	3 x 200 mg hard gelatin capsules 3 times a day For use with Ritonavir, other dosages may be used	
	Kaletra® (Lopinavir/Ritonavir – also known as ABT378/r)	3 x 133/33 mg capsules 2 times a day	

HIV MEDICATION CHART

Community Research Initiative of New England

TOLL FREE: (888) 253-2712 Visit our website at www.crine.org

Nucleoside Analogs (NRTIs)

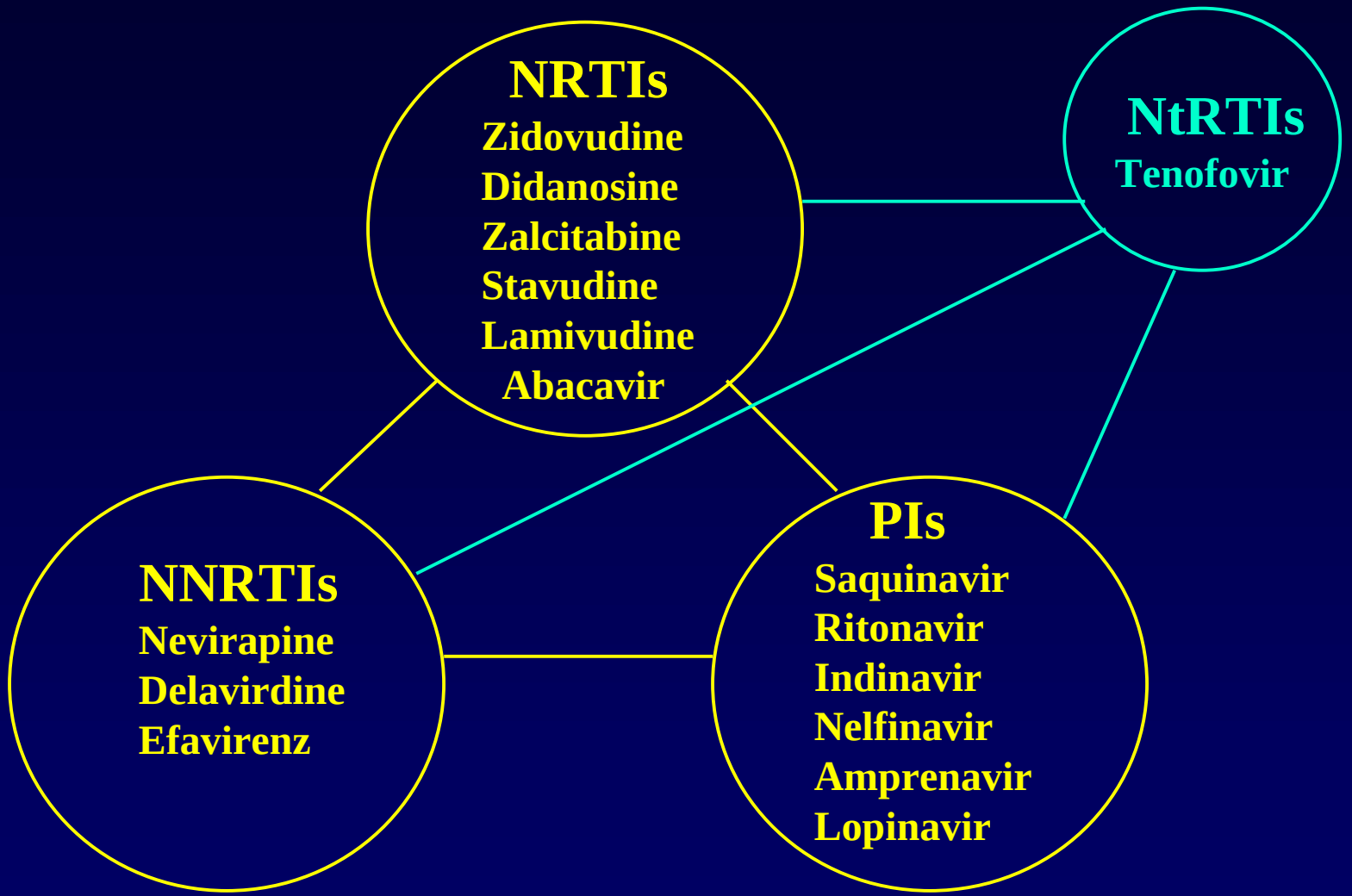
Non-Nucleosides (NNRTIs)

Nucleotide Analog (NtRTI)

Protease Inhibitors (PIs)

cri

Produced with support from the Massachusetts Dept of Public Health HIV/AIDS Bureau. Pills shown actual size.


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

COMBO CARDS

Combivir® Kaletra®

AM ☀

❶

❷

PM ☾

FYI

❶ Name: Combivir (300 mg zidovudine plus 150 mg lamivudine)
Class: Nucleoside (NRTI) • Dose: one tablet twice a day

❷ Name: Kaletra (133.3 mg lopinavir plus 33.3 mg ritonavir)
Class: Protease Inhibitor (PI) • Dose: three capsules twice a day

COMBO CARDS

Viread®
Epivir®
Kaletra®

AM ☀

❷

❸

PM ☾

❶

FYI

❶ Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
Dose: one 300 mg tablet once a day

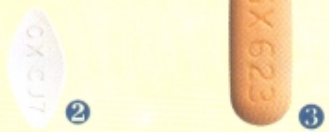
❷ Name: Epivir (3TC) • Class: Nucleoside (NRTI)
Dose: one 150 mg tablet twice a day

❸ Name: Kaletra (133.3 mg lopinavir plus 33.3 mg ritonavir)
Class: Protease Inhibitor (PI) • Dose: three capsules twice a day

COMBO CARDS

Viread®
Epivir®
Ziagen®

AM ☀



❷ ❸

PM ☾

❶

FYI

❶ Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
Dose: one 300 mg tablet once a day

❷ Name: Epivir (3TC) • Class: Nucleoside (NRTI)
Dose: one 150 mg tablet twice a day

❸ Name: Ziagen (abacavir) • Class: Nucleoside (NRTI)
Dose: one 300 mg tablet twice a day

COMBO CARDS

Viread®
Ziagen®
Sustiva®

AM ☀

❶

❷

PM ☾

❸

FYI

❶ Name: **Viread (tenofovir)** • Class: **Nucleotide (NtRTI)**
Dose: **one 300 mg tablet once a day**

❷ Name: **Ziagen (abacavir)** • Class: **Nucleoside (NRTI)**
Dose: **one 300 mg tablet twice a day**

❸ Name: **Sustiva (efavirenz)** • Class: **Non-Nucleoside (NNRTI)**
Dose: **one 600 mg tablet once a day**

COMBO CARDS

Trizivir®
Viread™

AM ☀

❶

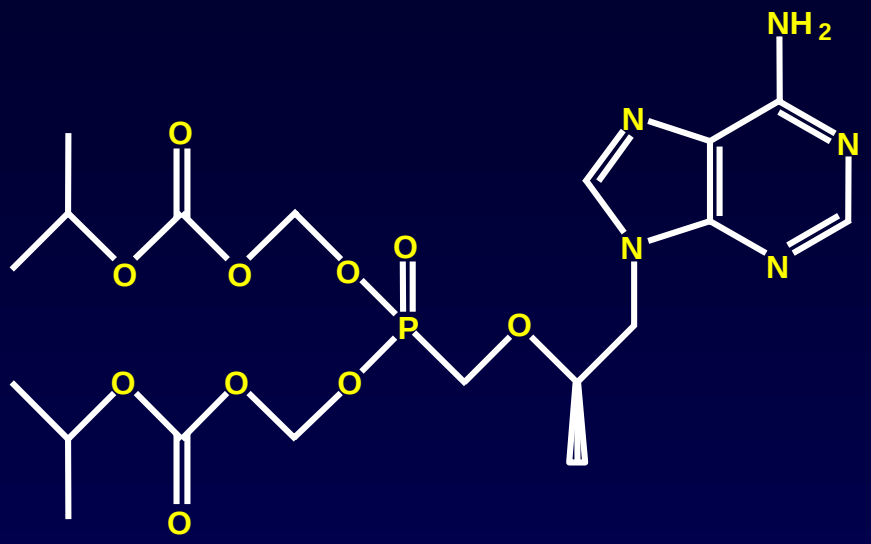
PM ☾

❷

FYI

❶ Name: Trizivir (300 mg zidovudine plus 150 mg lamivudine plus 300 mg abacavir) • Class: Nucleoside (NRTI)
Dose: one tablet twice a day

❷ Name: Viread (tenofovir) • Class: Nucleotide (NtRTI)
Dose: one 300 mg tablet once a day



VIREAD™
(tenofovir disoproxil fumarate)

Study 903

Study Design: Randomization

ART-naive patients

(N = 600)

randomized 1:1

TDF	QD
EFV	QD
3TC	BID
d4T placebo	BID

d4T	BID
EFV	QD
3TC	BID
TDF placebo	QD

144 wks

144 wks

Stratification by:

- **plasma HIV RNA >/< 100000 cop/ml**
- **CD 4 count >/< 200 cells/mm³**

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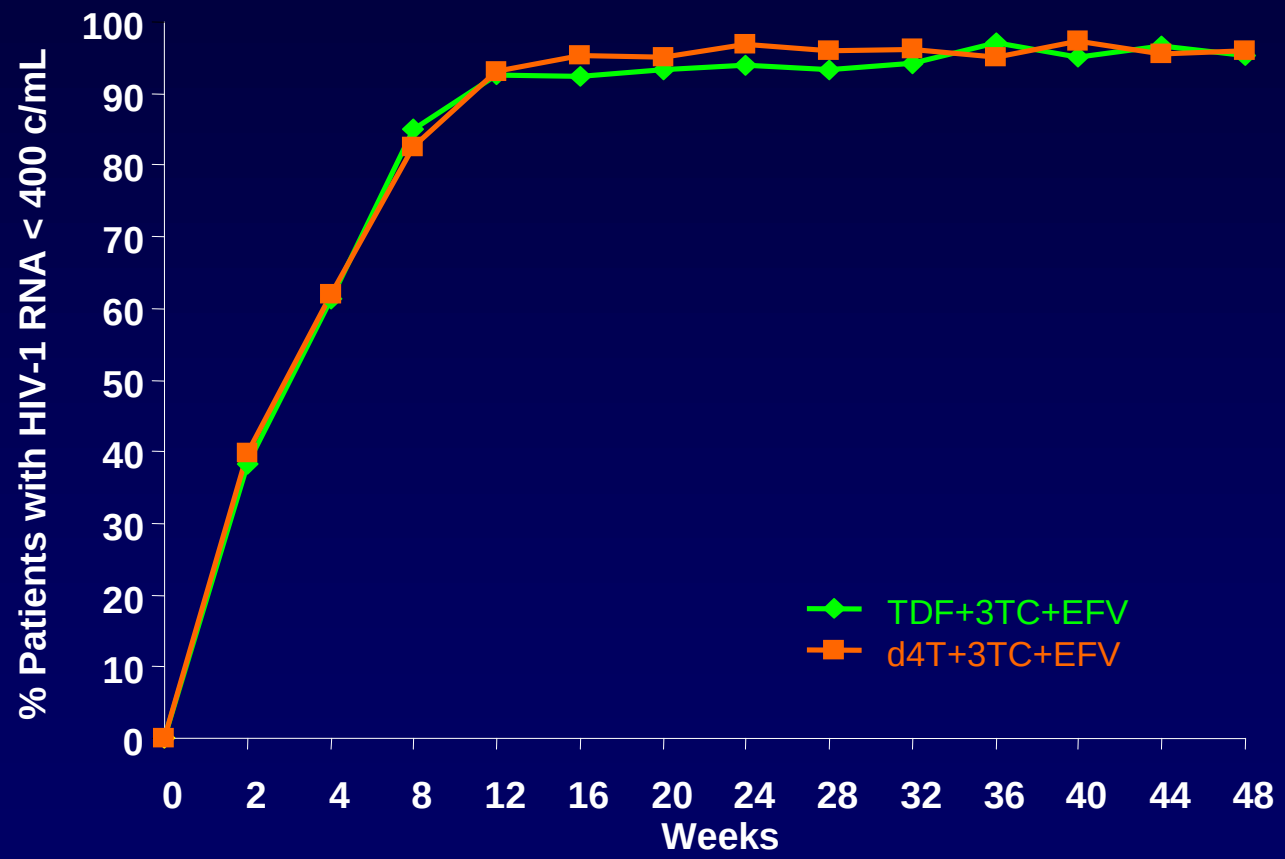
% Patients < 400 Copies/mL

Missing Observations are Excluded



96%

95%

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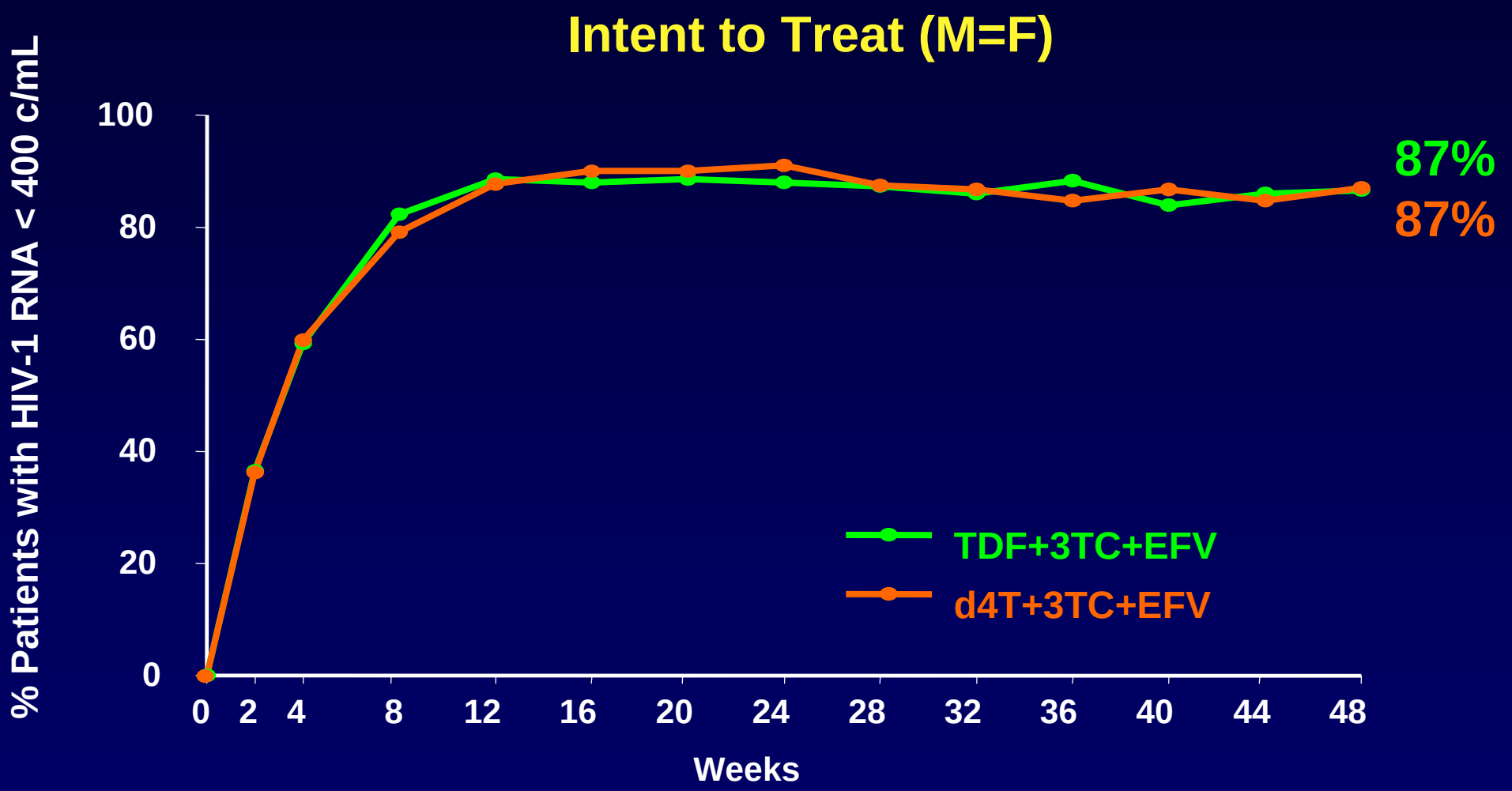
% Patients < 400 Copies/mL



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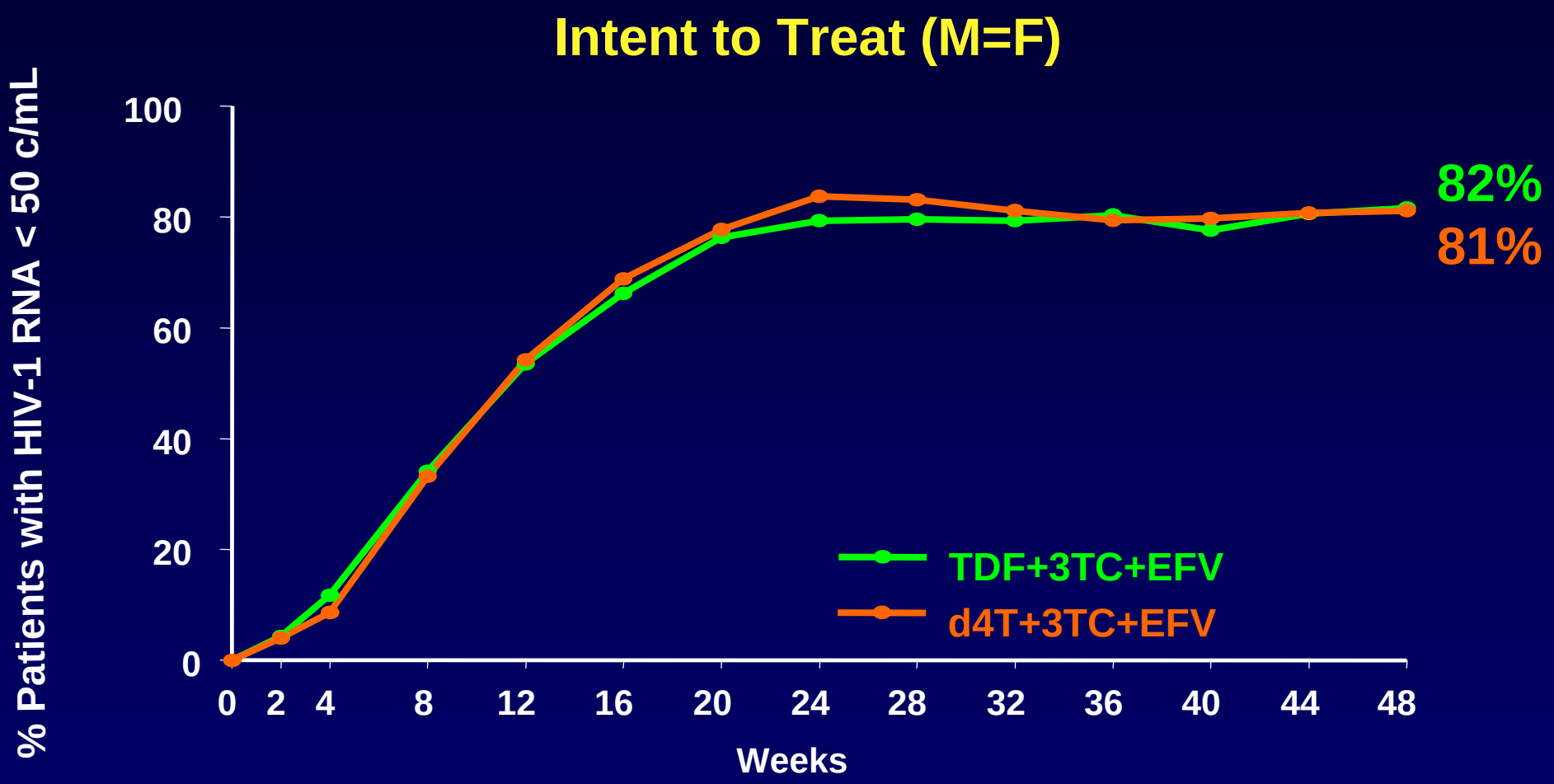
% Patients < 50 Copies/mL



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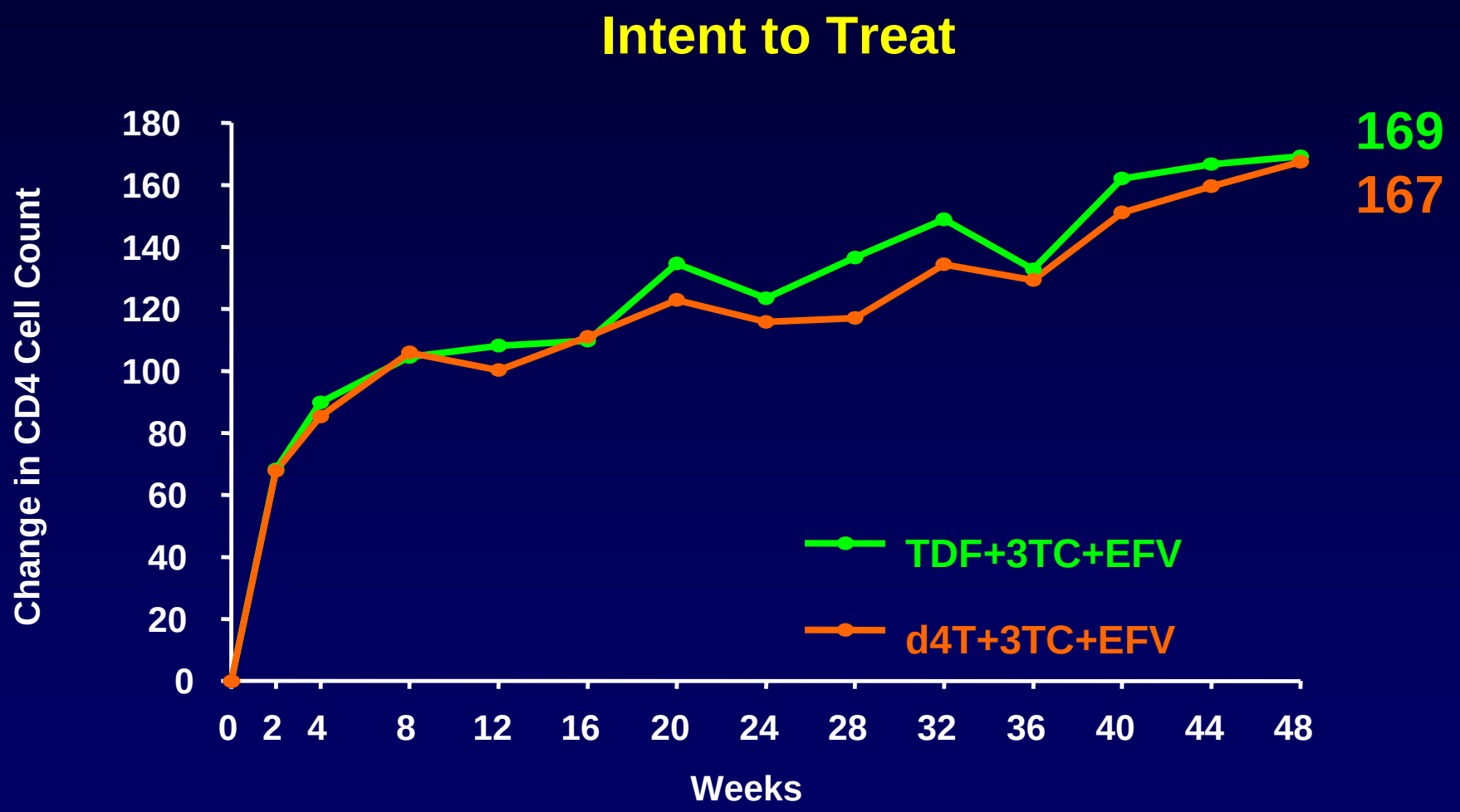
Mean Change from Baseline in CD4



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Nucleoside Associated Toxicities

(All Grades, 0-48 Weeks)	TDF+3TC+EFV (n=299)	d4T+3TC+EFV (n=301)
Patients (%) with Events [a]	9 (3%)	34 (11%)
Peripheral Neuritis/Neuropathy	6 (2%)	20 (7%)
Lipodystrophy	3 (1%)	11 (4%)
Lactic Acidosis	0	3 (<1%)
Pancreatitis	0	0

[a] Investigator Defined

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Grade 3/4 Laboratory Abnormalities[a]

(0-48 Weeks)	TDF+3TC+EFV (n=299)	d4T+3TC+EFV (n=301)
Patients (%) with Abnormalities	85 (28%)	94 (31%)
Creatine Kinase	25 (8%)	26 (8%)
Amylase	21 (7%)	18 (6%)
AST	13 (4%)	16 (5%)
Hematuria	13 (4%)	13 (4%)
ALT	11 (3%)	11 (3%)
Lipase	11 (3%)	9 (3%)
Neutropenia	9 (3%)	2 (<1%)
Triglycerides	7 (2%)	24 (8%)

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[a] ≥ 3% in any group

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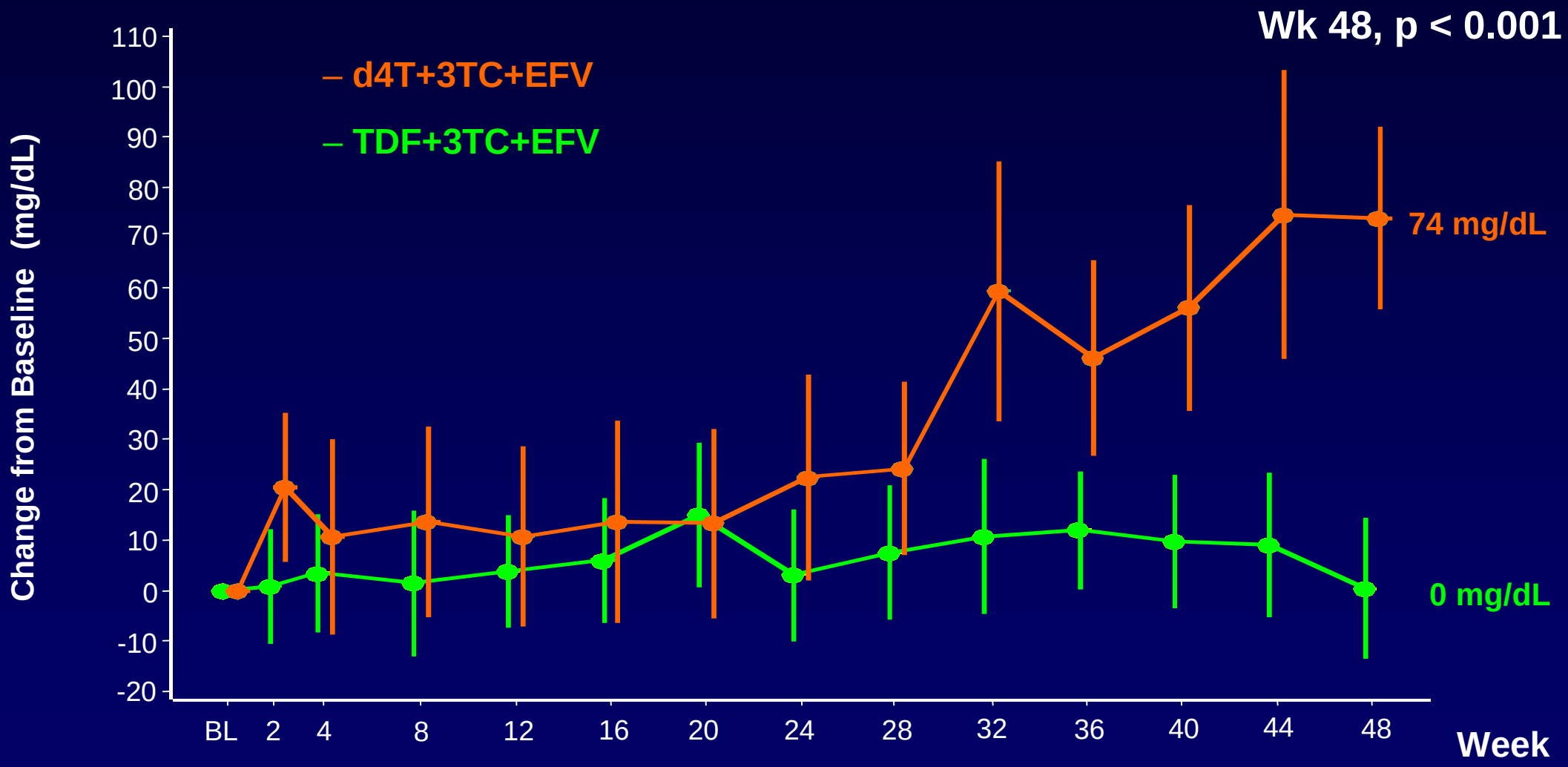
Mean (95%CI) Change from Baseline in Triglycerides



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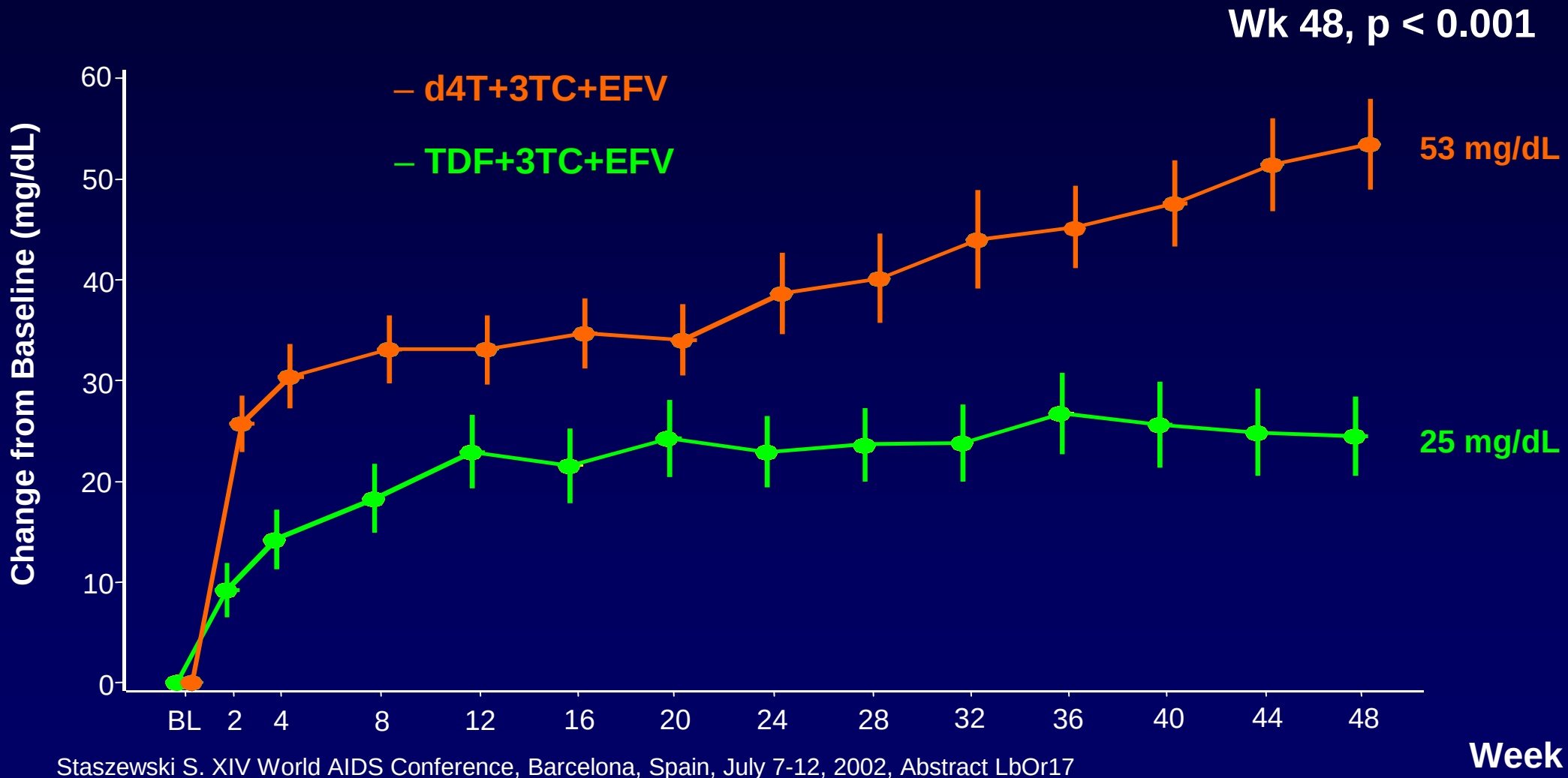
Mean (95% CI) Change from Baseline in Cholesterol



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Serum Creatinine

Maximum Toxicity Grade (0-48 Weeks)

Grade (mg/dL)	TDF+3TC+EF (n=296)	d4T+3TC+EFV (n=296)
1 (≥0.5 from baseline)	3 (1%)	5 (2%)
2 (2.1-3.0)	2 (<1%)	0
3 (3.1-6.0)	0	2 (<1%)
4 (>6.0)	0	0

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Summary

- High proportions of patients in both arms achieved:
  - HIV-RNA <400 and <50 c/mL
  - Significant increases in CD4 cell count
- Both arms had low discontinuation rates
- Compared to the control group the tenofovir DF containing_group showed smaller increases in cholesterol and no change in triglyceride levels

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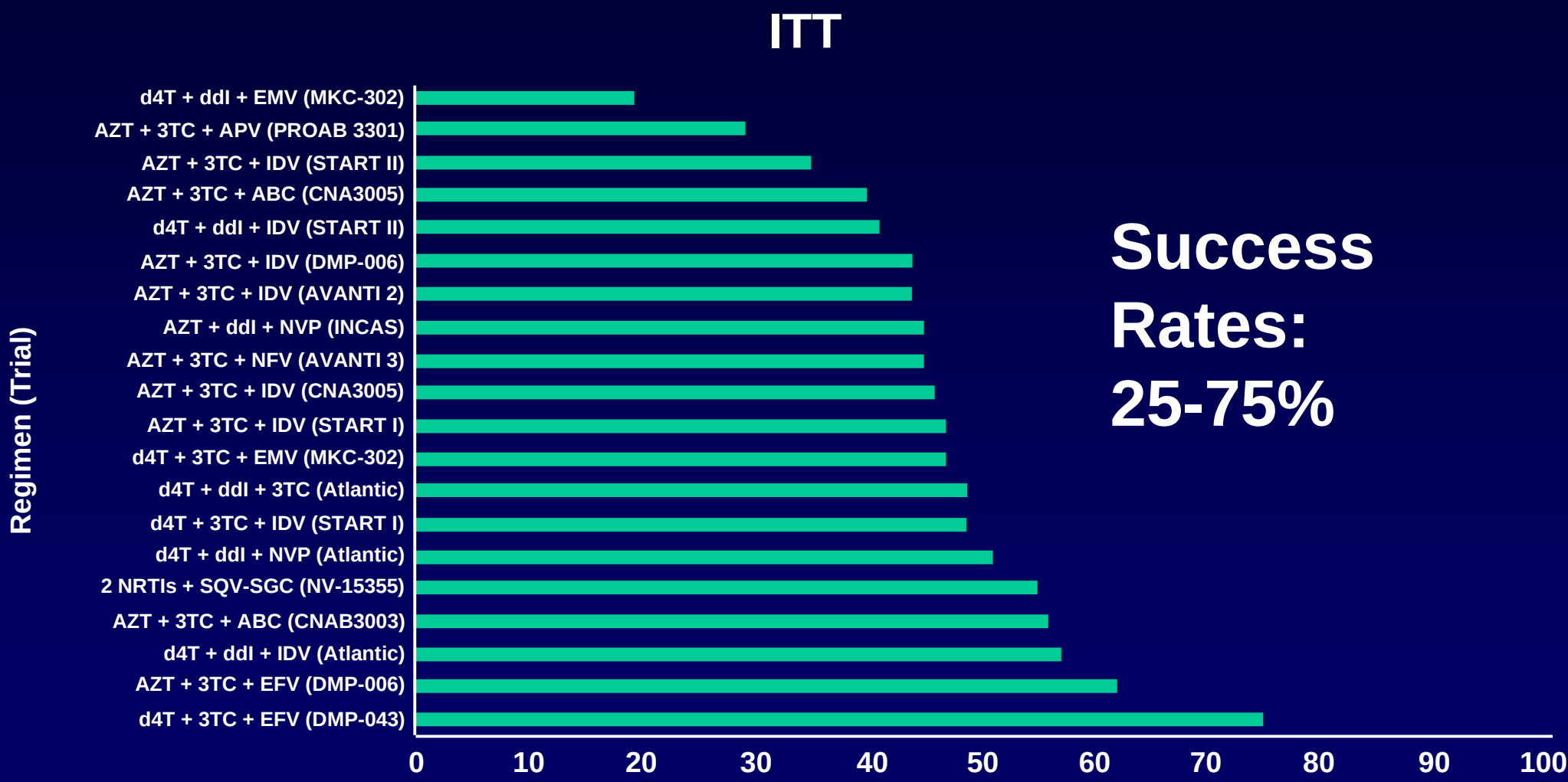
Results from Clinical Trials: Percent With HIV RNA ≤50 at 48 Weeks



Success Rates: 25-75%

Bartlett. 7th CROI; 2000; San Francisco. Poster 519.

Results from Clinical Trials: Percent With HIV RNA ≤50 at 48 Weeks