Antiretroviral Agents

Scott M. Hammer, M.D.

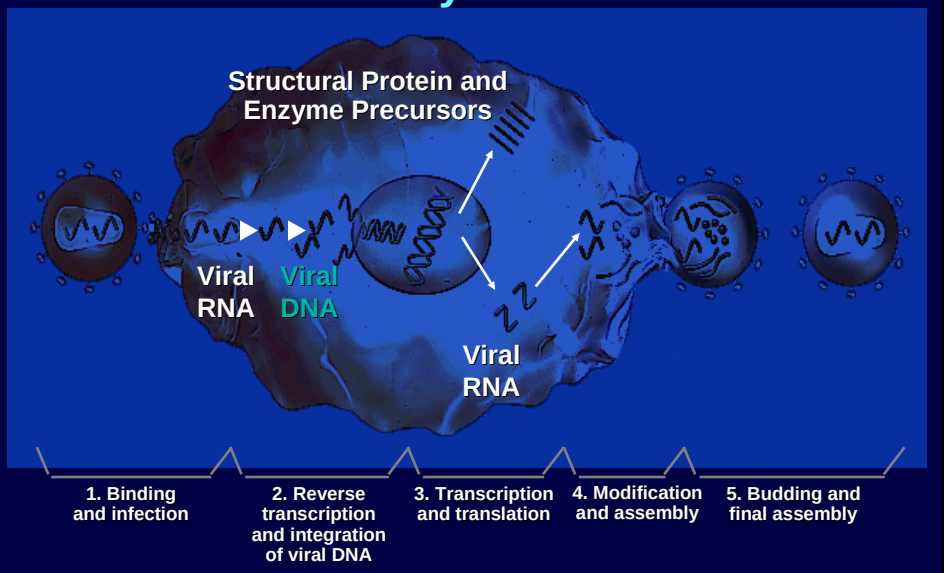
Evolution of Antiretroviral Therapy

1986 → 1990
ZDV monoRx

1990 → 1995
Alternative NRTI monoRx
Combination NRTI Rx
Introduction of NNRTI's
Antiretroviral resistance
Pathogenetic concepts

1995 → 2006
End of ZDV monoRx era
Benefit of combination Rx proven
Introduction of protease inhibitors
Re-emergence of NNRTI's
Introduction of viral load monitoring
Elucidation of viral dynamics
Knowledge of viral reservoirs
Capacity for immune restoration
Importance of chemokine receptors
Reductions in morbidity & mortality
Introduction of resistance testing
Metabolic complications of therapy
Conservative swing in approach to Rx
Reality of new classes of agents
ARV rollout in developing countries

The Life Cycle of HIV-1



Antiretroviral Agents

- Every step in viral life cycle is a potential antiviral target
- Currently there are 5 classes of FDA approved agents
  - Nucleoside analog reverse transcriptase inhibitors (NsRTI's)
  - Nucleotide analog reverse transcriptase inhibitors (NtRTI's)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI's)
  - Protease inhibitors (PI's)
  - Entry (fusion) inhibitors
- Drugs must be used in combination to be effective
  - This has led to dramatic reductions in morbidity and mortality in the developed world
- Current therapies are imperfect
  - Toxicities
  - Drug resistance

Nucleoside (ns) and Nucleotide (nt) Analog RT Inhibitors

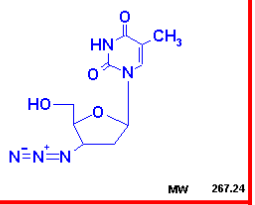
- Zidovudine (ZDV, AZT)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

→ nsRTI's

- Tenofivir disoproxil fumarate (TDF) → ntRTI

N.B.: Four fixed dose combinations are approved: ZDV + 3TC (Combivir®); ZDV + 3TC + ABC (Trizivir®); 3TC + ABC (Epzicom®); FTC + TDF (Truvada®)

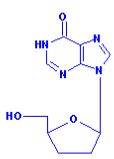
Nucleoside Analog RT Inhibitors



MW 267.24

NAME	3'-Azido-3'-deoxythymidine
SYN	AZT; Azidothymidine; Zidovudine; Retrovir; ZDV
COMP	GLAXO WELLCOME

Zidovudine



MW 236.23

NAME	2',3'-Dideoxyinosine
SYN	DDI; D2I; ddIno; Didanosine; Videx
COMP	BRISTOL-MYERS SQUIBB

Didanosine

Nucleoside Analog RT Inhibitors

- First class of anti-HIV agents developed
- Active vs. HIV-1 and HIV-2
- Need to undergo intracellular anabolic phosphorylation to triphosphate form of the drug or metabolic intermediate to be active vs. HIV
- Mechanism
  - NRTI-TP's inhibit the HIV RT by competing with normal nucleoside triphosphates for incorporation into growing proviral DNA chain
  - Viral DNA chain elongation terminated
    - » Absence of 3'-OH group on sugar moiety prevents addition of another nucleotide
  - Viral replication ceases

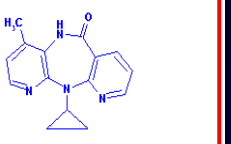
Nucleotide Analog RT Inhibitors

- Tenofovir disoproxil fumarate (TDF)
  - A prodrug
  - Contains a phosphate group so only needs to be diphosphorylated intracellularly to be active
    - » Tenofovir-diphosphate is the active moiety
      - Competiive inhibitor of HIV RT

Non-Nucleoside RT Inhibitors

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)

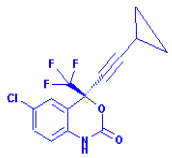
Non-Nucleoside RT Inhibitors



MW 266.31

NAME	N11-Cyclopropyl-4-methyl-5,11-dihydro-6H-dipyrido[3,2-b:2',3'-e]-[1,4]diazepin-6-one
SYN	BI-RG-587; Nevirapine; Viramune
COMP	BOEHRINGER INGELHEIM (ROXANE)

Nevirapine



MW 315.68

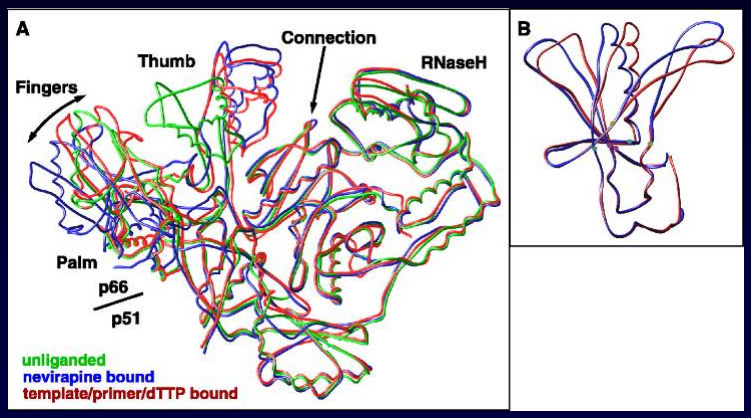
NAME	(-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4,-dihydro-2H-3,1-benzoxazin-one
SYN	Sustiva; Efavirenz; DMP-266; L-743,726
COMP	DUPONT MERCK

Efavirenz

Non-Nucleoside RT Inhibitors

- Second class of anti-HIV agents developed
- Potent but subject to rapid emergence of resistance
- Active vs. HIV-1 (except Group O)
- Inactive vs. HIV-2
- Parent molecules are the active moieties
- Mechanism
  - NNRTI's inhibit the HIV-1 RT by binding to hydrophobic pocket on the enzyme close to the active site
    - » May lock active site in an inactive conformation

HIV RT: Structure



Huang H, Chopra R, Verdine GL & Harrison SC: Science 1998;282:1669-1675

NNRTI's: Drug Interactions

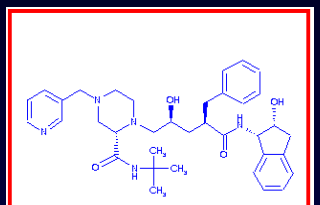
- Metabolized by CYP3A4 isozyme of hepatic p450 system
- NVP and EFZ are inducers of CYP3A4
- DLV is an inhibitor of CYP3A4
- Potential for major drug interactions with numerous HIV (esp. PI's) and non-HIV agents
- Do not prescribe without first checking for potential drug interactions
  - May be contraindications or need for dose adjustment(s)

Protease Inhibitors

- Saquinavir (SQV)*
- Ritonavir (RTV)
- Indinavir (IDV)*
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~*
- Lopinavir/ritonavir (LPV/r)*
- Atazanavir (ATV)*
- Fosamprenavir (fos-APV)*
- Tipranavir (TPV)*
- Darunavir (DRV)*

*Typically prescribed with low-dose ritonavir for pharmacologic "boosting". Lopinavir is coformulated with ritonavir.

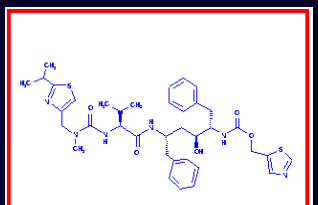
Protease Inhibitors



MW 613.81

NAME	4-Hydroxy-N-(2-hydroxy-2,3-dihydro-1H-1-indanyl)-N'-(1,1-dimethylethyl)-2-phenylmethyl-5-[4-(3-pyridylmethyl)-1-piperzinyl]hexanediamide
SYN	Indinavir; Crixivan; MK-639 L-735,524;
COMP	MERCK

Indinavir



MW 720.96

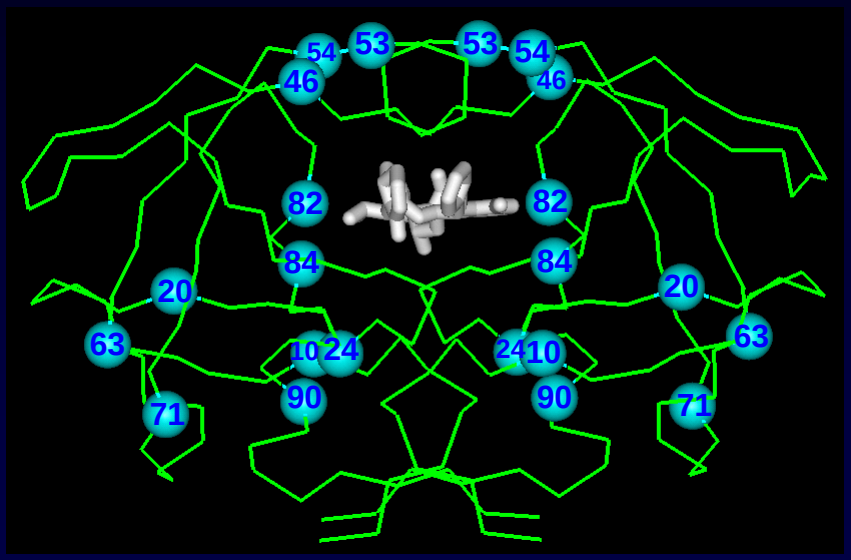
NAME	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]-
SYN	ABT-538; A 84538; Norvir; Ritonavir
COMP	ABBOTT

Ritonavir

Protease Inhibitors

- Third class of anti-HIV agents developed
- Potent
  - Revolutionized therapy following introduction in 1996
- Active vs. HIV-1 and HIV-2
- Mechanism
  - PI's inhibit the HIV protease by binding to active site and preventing the cleavage of gag and gag-pol precursor polyproteins
  - Virions are produced but they are incomplete and non-infectious

Protease Structure: Mutations Associated With Reduced *in vitro* Susceptibility to Lopinavir

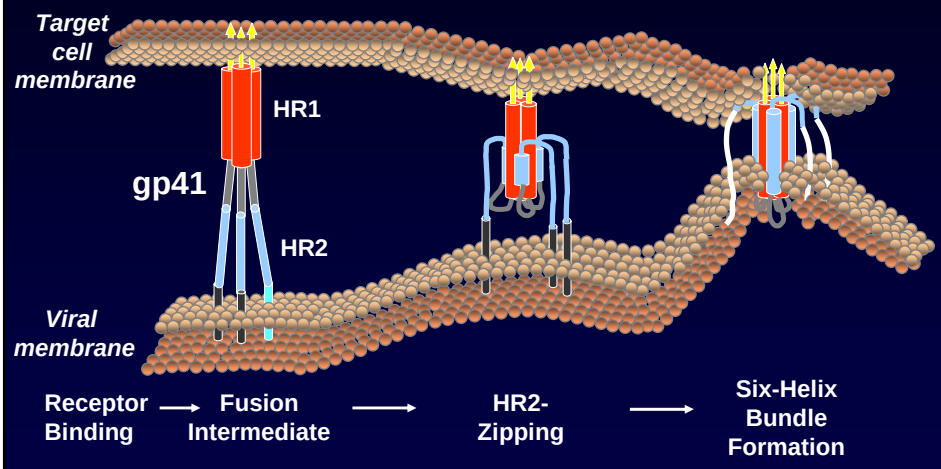


PI's: Drug Interactions

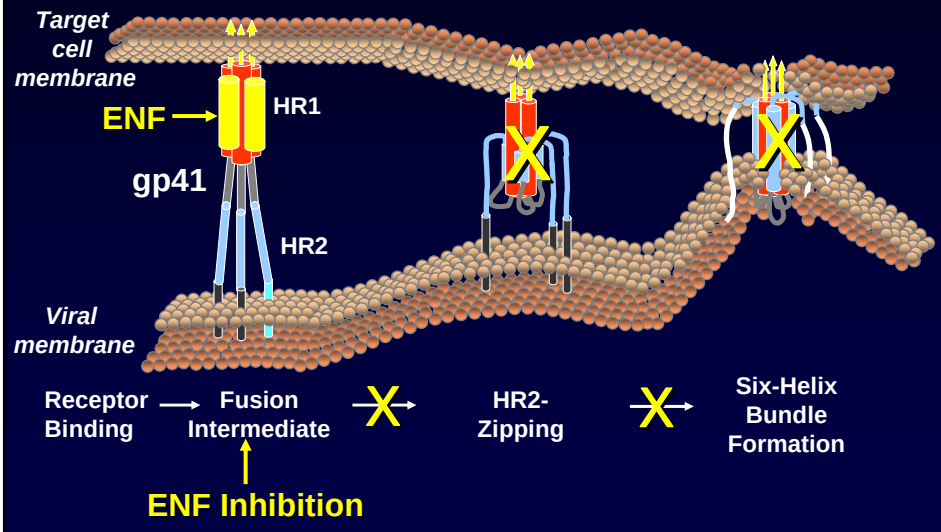
- Metabolized by CYP3A4 isozyme of hepatic p450 system
- Inhibit CYP3A4 to varying degrees
  - Ritonavir is one of the most potent CYP3A4 inhibitors known
    - » Basis for using low-dose RTV as pharmacoenhancer of other PI's
    - » One approved PI, LPV, is coformulated with RTV
- Potential for major drug interactions with numerous HIV (esp. NNRTI's) and non-HIV agents
- Do not prescribe without first checking for potential drug interactions
  - May be contraindications or need for dose adjustment(s)

Enfuvirtide (Fusion Inhibitor): Mechanism of Action

Model for HIV-Cell Fusion



Enfuvirtide Inhibition of HIV Fusion



Antiretroviral Agents Approved in the U.S. as of August 2006

Nucleoside RTI's

- Zidovudine (ZDV)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Nucleotide RTI

- Tenofovir DF (TDF)

Non-Nucleoside RTI's

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

Entry Inhibitor

- Enfuvirtide (T-20)

N.B.: Six fixed-dose combinations are approved:
ZDV + 3TC (Combivir®); ZDV + 3TC + ABC (Trizivir®);
ABC + 3TC (Epzicom®); FTC + TDF (Truvada®);
LPV + RTV (Kaletra®); TDF + FTC + EFV (Atripla®)

When to Start Antiretroviral Therapy: 2006 IAS-USA Guidelines

Measure	Recommendation	Comments
Symptomatic HIV disease	Therapy recommended	
Asymptomatic HIV disease		
CD4 ≤200/µl	Therapy recommended	
CD4 >200 but ≤350/µl	Therapy should be considered and decision individualized	Recommendation to treat stronger as CD4 approaches 200/µl, particularly if viral load high or CD4 declining rapidly
CD4 >350 but ≤500/µl	Therapy generally not recommended	Consider therapy if viral load high (>100,000 copies/ml) or CD4 declining rapidly (>100 cells/µl per year)
CD4 >500/µl	Therapy generally not recommended	

Hammer S et al: JAMA 2006;296:827-843

Choice of Initial Regimen: 2006 IAS-USA Recommendations

- At baseline:
  - Evaluate for hepatitis B or C coinfection, diabetes mellitus, hyperlipidemia, coronary artery disease, renal disease
    - Concomitant medications
  - Consider resistance testing
  - Pregnancy or risk thereof
- Regimen:
  - Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based *or*
  - Ritonavir (r)-boosted protease inhibitor (PI)-based
  - Either (NNRTI or PI/r) combined with a dual nucleoside/nucleotide reverse transcriptase inhibitor (nRTI) component

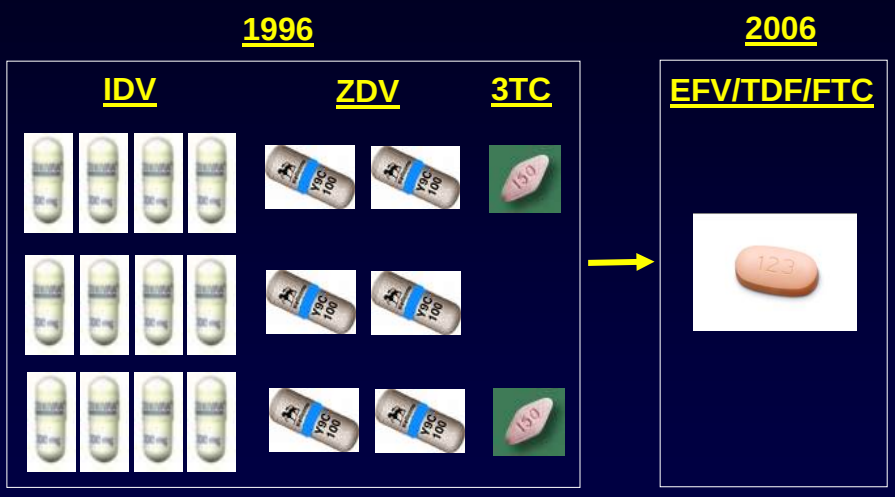
Hammer S et al: JAMA 2006;296:827-843

Choice of Initial Regimen: 2006 IAS-USA Guidelines

Component	Drugs	Comments
NNRTI component	efavirenz or nevirapine	EFV: teratogenic in 1st trimester NVP: increased risk of hepatotoxicity in women with CD4 >250/µl and men with CD4 >400/µl
PI/r component	lopinavir/r, atazanavir/r, fosamprenavir/r, or saquinavir/r	ATV/r: diminished hyperlipidemic potential; hyperbilirubinemia (inc. risk assoc. w/ UGT1A1-28 gt)
Dual nRTI component	tenofovir/emtricitabine, zidovudine/lamivudine, or abacavir/lamivudine	ABC hypersensitivity in 5-8% of unscreened patients (inc. risk assoc. w/ HLA-B5701 gt)

Hammer S et al: JAMA 2006;296:827-843

Simplification of Therapy



Antiretroviral Therapy Failure

- Clinical
  - Disease progression
    - » Needs to be distinguished from immune reconstitution syndrome
- Immunologic
  - CD4 cell count decline
- Virologic
  - Plasma HIV-1 RNA rise

Reasons for Drug Failure

- Resistance
- Adherence
- Pharmacologic factors
- Insufficiently potent regimens
- Sanctuaries
- Cellular mechanisms of resistance
- Host immune status

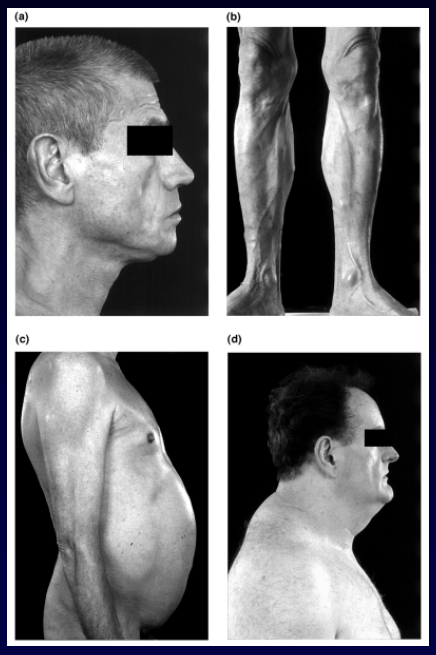
Limitations of Currently Available Agents

- Some regimens remain complex
  - Particularly for treatment experienced patients or those who may have primarily acquired drug resistant virus
    - » Approximately 10% of new infections are with drug resistant virus in the U.S. and Europe
- Negative effects on quality of life
- Toxicities, particularly metabolic
  - Hyperlipidemia, fat redistribution, insulin resistance, decreased bone density, mitochondrial dysfunction
- Drug class cross resistance
- Drug interactions (esp. for NNRTIs and PIs)
- Submaximal potency
- Cost

Antiretroviral Therapy Related Lipodystrophy

Lipoatrophy →

Lipoaccumulation →



Mallon PWG, Cooper DA and Carr A:
HIV Medicine 2001;2:1468-1293

HIV Resistance: Underlying Concepts

- Genetic variants are continuously produced as a result of high viral turnover and inherent error rate of RT
  - Mutations at each codon site occur daily
    - » Survival depends on replication competence and presence of drug or immune selective pressure
  - Double mutations in same genome also occur but 3 or more mutations in same genome is a rare event
  - Numerous natural polymorphisms exist

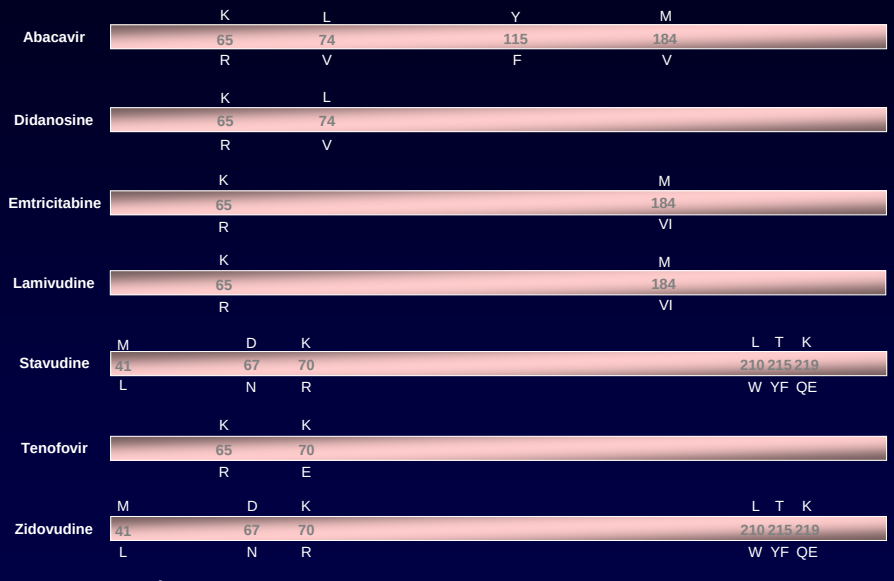
Pre-existence of Resistant Mutants

- Viral replication cycles: 10^{9}-10^{10}/day
- RT error rate: 10^{-4}-10^{-5}/base/cycle
- HIV genome: 10^{4} bp
- Every point mutation occurs 10^{4}-10^{5} times/day

HIV Resistance: Underlying Concepts

- **Implications**
  - **Resistance mutations may exist before drug exposure and may emerge quickly after it is introduced**
  - **Drugs which develop high level resistance with a single mutation are at greatest risk**
    - » **e.g., 3TC, FTC, NNRTI's (nevirapine, efavirenz)**
  - **Resistance to agents which require multiple mutations will evolve more slowly**
  - **Partially suppressive regimens will inevitably lead to emergence of resistance**
  - **A high 'genetic barrier' needs to be set to prevent resistance**
    - » **Potent, combination regimens**

Mutations Selected by nRTIs



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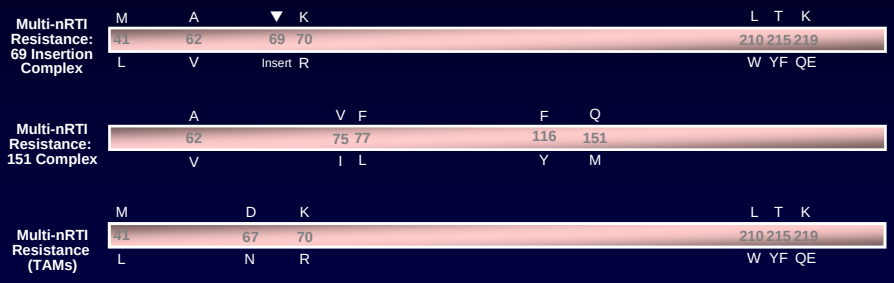
Mutations Selected by nRTIs (cont'd)



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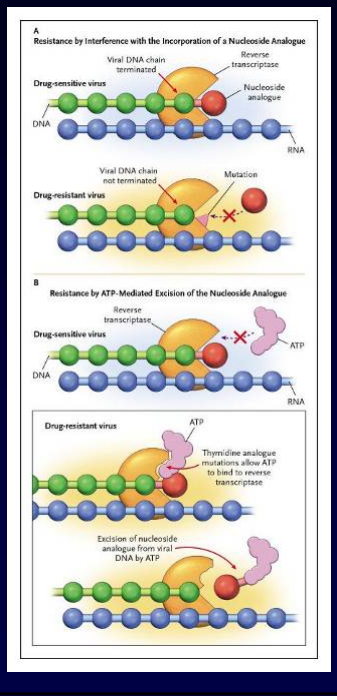
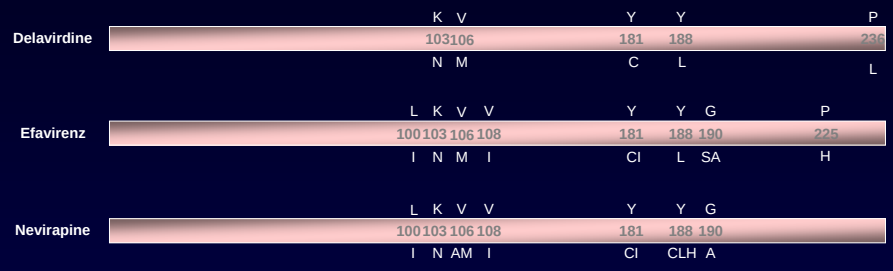
The Two Principal Mechanisms of Resistance of HIV to Nucleoside Analogues



The NEW ENGLAND JOURNAL of MEDICINE

Clavel F et al: N Engl J Med 2004;350:1023-1035

Mutations Selected by NNRTIs



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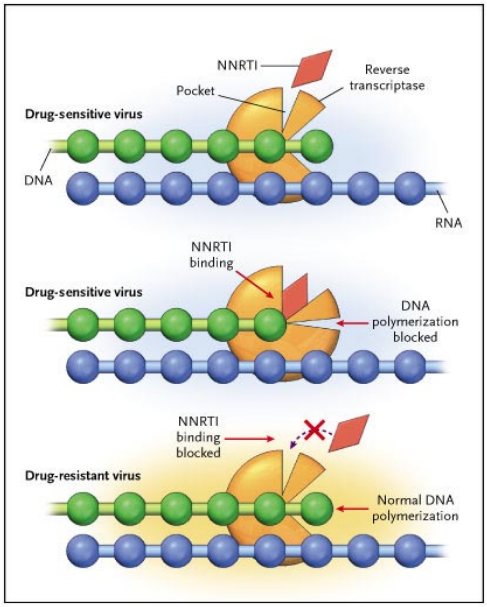
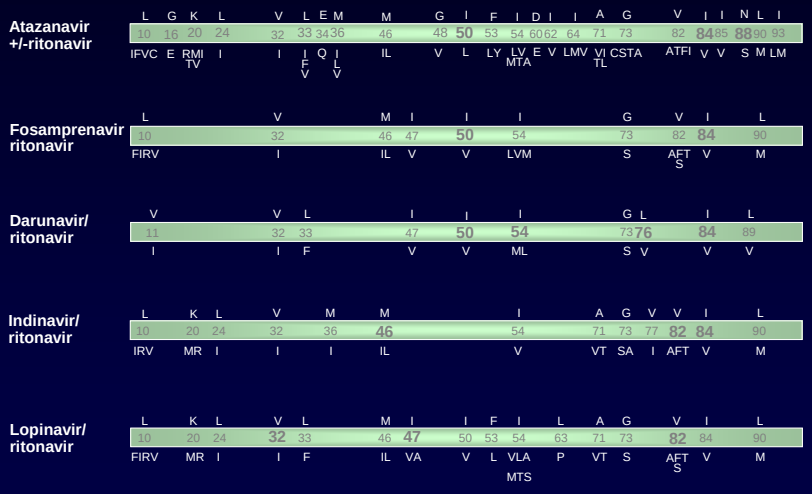
Mechanism of Resistance of HIV to Nonnucleoside Reverse-Transcriptase Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

Clavel F et al:
N Engl J Med 2004;350:1023-1035

Mutations Selected by PIs



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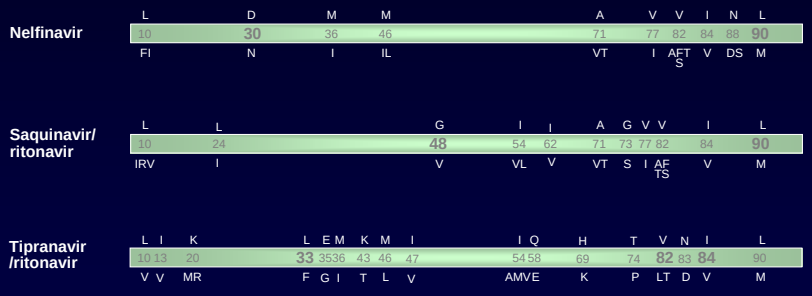
Mutations Selected by PIs (cont'd)



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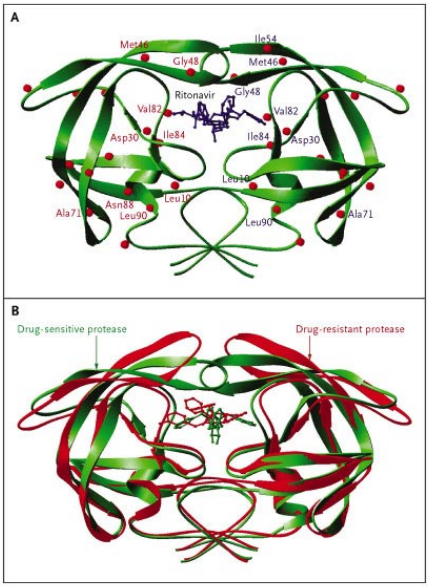
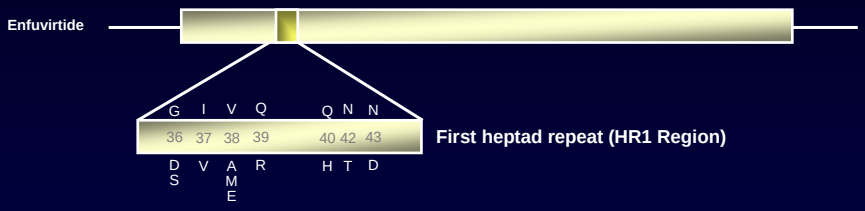
HIV-1 Protease Dimer Binding with a Protease Inhibitor (Panel A) and a Drug-Sensitive (Wild-Type) Protease Juxtaposed against a Drug-Resistant Protease (Panel B)



The NEW ENGLAND JOURNAL of MEDICINE

Clavel F et al:
N Engl J Med 2004;350:1023-1035

Mutations in the gp41 Envelope Gene Associated With Resistance to Entry Inhibitors



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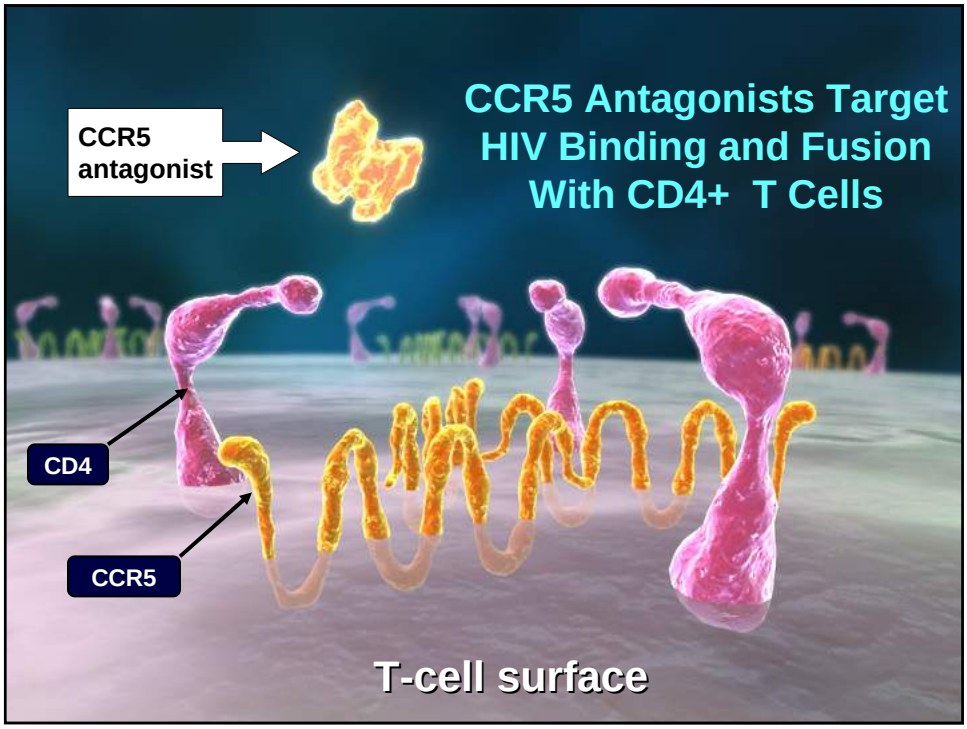
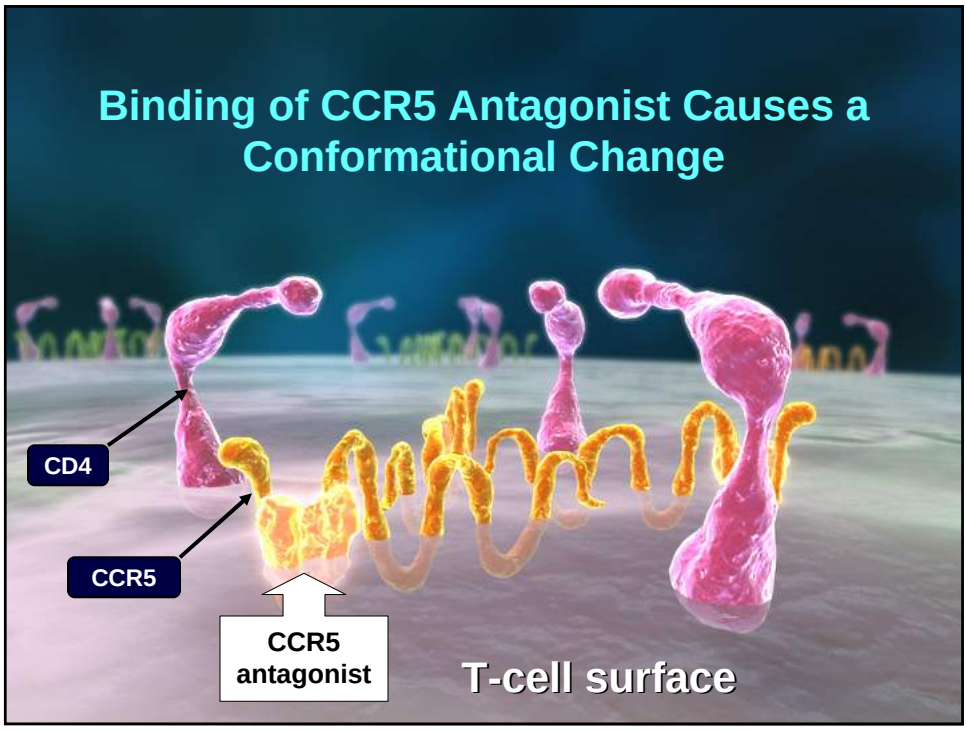
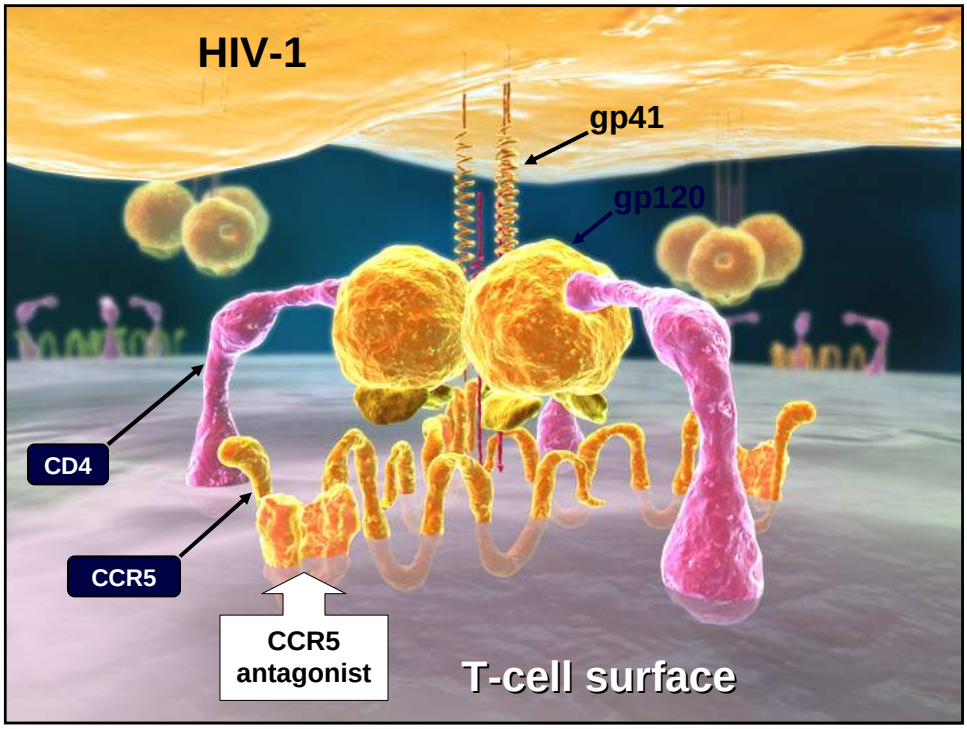
Selected New Classes of Agents

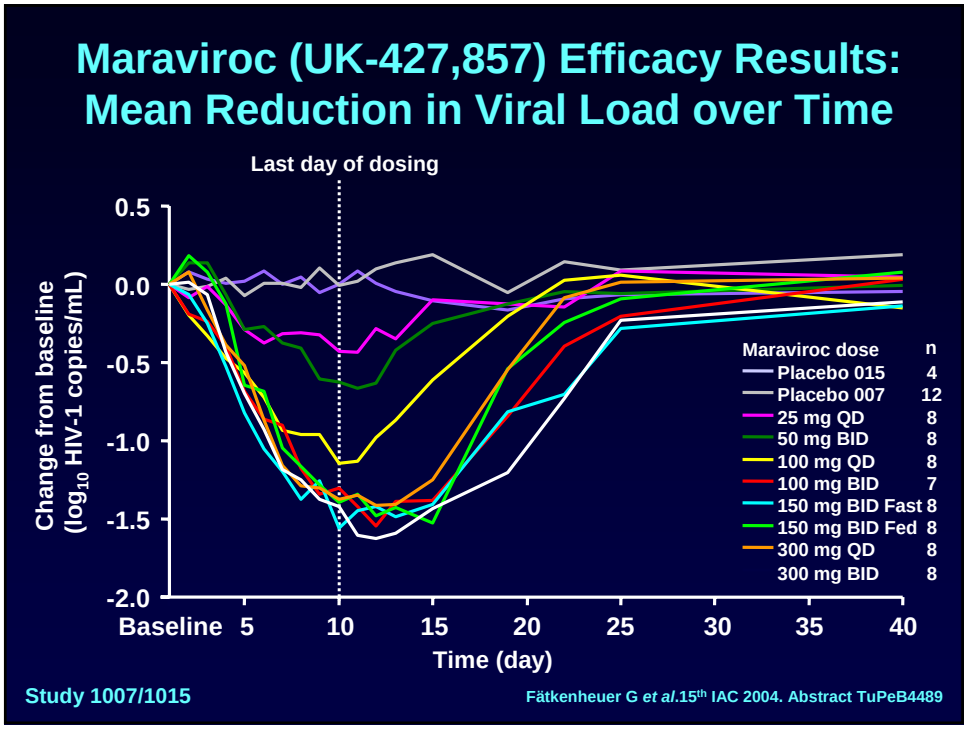
- Entry inhibitors
  - Attachment inhibitors (PRO 542, BMS-488043)
  - Chemokine receptor blockers/antagonists
    - » CCR5 (PRO 140, maraviroc, vicriviroc, TAK 220, AMD 887)
    - » CXCR4 (AMD 070, KRH-2731)
  - Fusion inhibitors (ENF [T-20], 5-Helix)
  - TNX-355
- Integrase inhibitors
  - MK-0518, GS-9137
- Gag processing inhibitor
  - PA-457

CCR5 Blocker: Maraviroc


CCR5 antagonist
CCR5 Antagonists Target HIV Binding and Fusion With CD4+ T Cells
CD4
CCR5
T-cell surface


Binding of CCR5 Antagonist Causes a Conformational Change
CD4
CCR5
CCR5 antagonist
T-cell surface

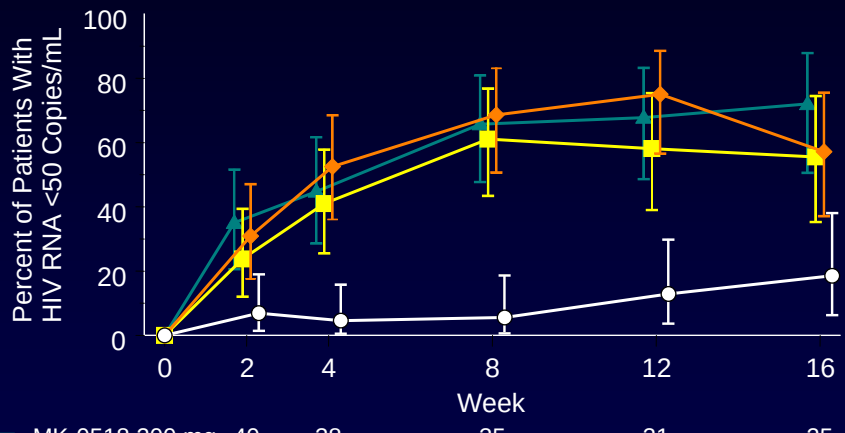

HIV-1
gp41
gp120
CD4
CCR5
CCR5 antagonist
T-cell surface


Maraviroc (UK-427,857) Efficacy Results: Mean Reduction in Viral Load over Time
Last day of dosing
Change from baseline (log10 HIV-1 copies/mL)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
Baseline
5
10
15
20
25
30
35
40
Time (day)
Maraviroc dose n
Placebo 015 4
Placebo 007 12
25 mg QD 8
50 mg BID 8
100 mg QD 8
100 mg BID 7
150 mg BID Fast 8
150 mg BID Fed 8
300 mg QD 8
300 mg BID 8
Study 1007/1015
Fätkenheuer G et al.15th IAC 2004. Abstract TuPeB4489

Integrase Inhibitor: MK-0518

CROI 2006 ABSTRACT #159LB

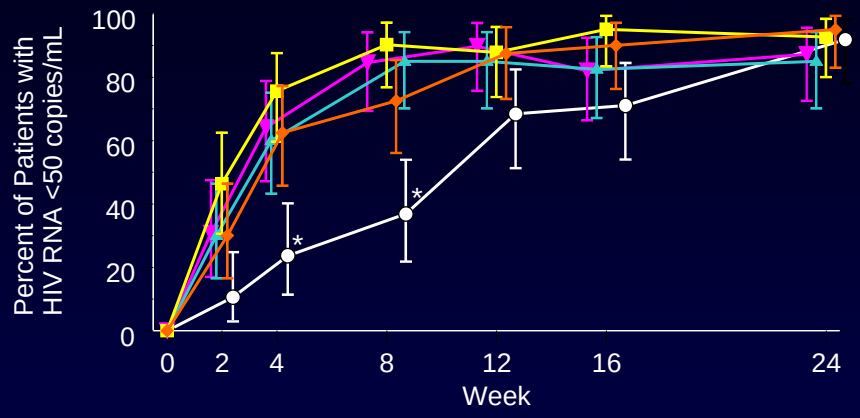
MK-0518 in Tx-Experienced Pts: Proportion with HIV RNA < 50 copies/mL



MK-0518 200 mg	40	38	35	31	25
MK-0518 400 mg	42	39	36	31	27
MK-0518 600 mg	42	40	35	32	28
OBT Alone	43	43	36	31	27

m518p5.r50.1 Jan. 12, 2006

Protocol 004 in Tx-Naïve Pts: Percent with HIV RNA < 50 copies/mL (NC=F)

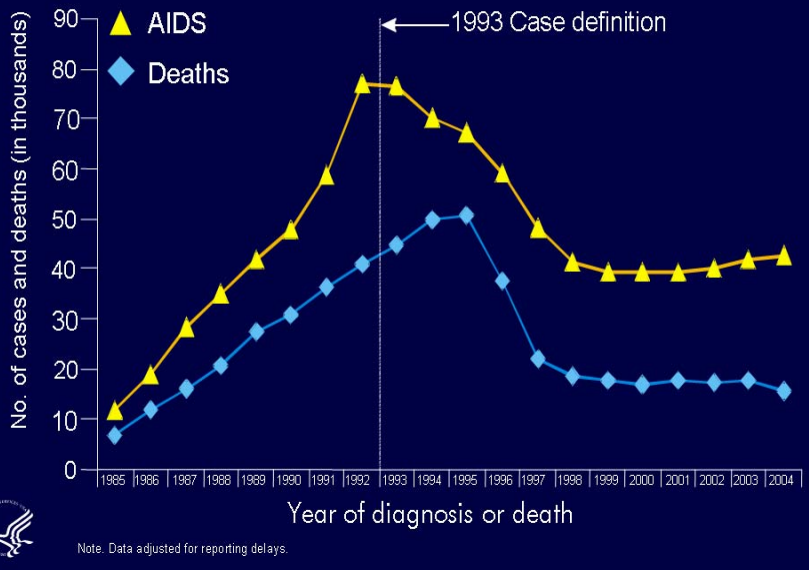


MK-0518 100mg	39	39	39	39	39	39
MK-0518 200mg	40	40	40	40	40	40
MK-0518 400mg	41	41	41	41	41	41
MK-0518 600mg	40	40	40	40	40	40
Efavirenz	38	38	38	38	38	37

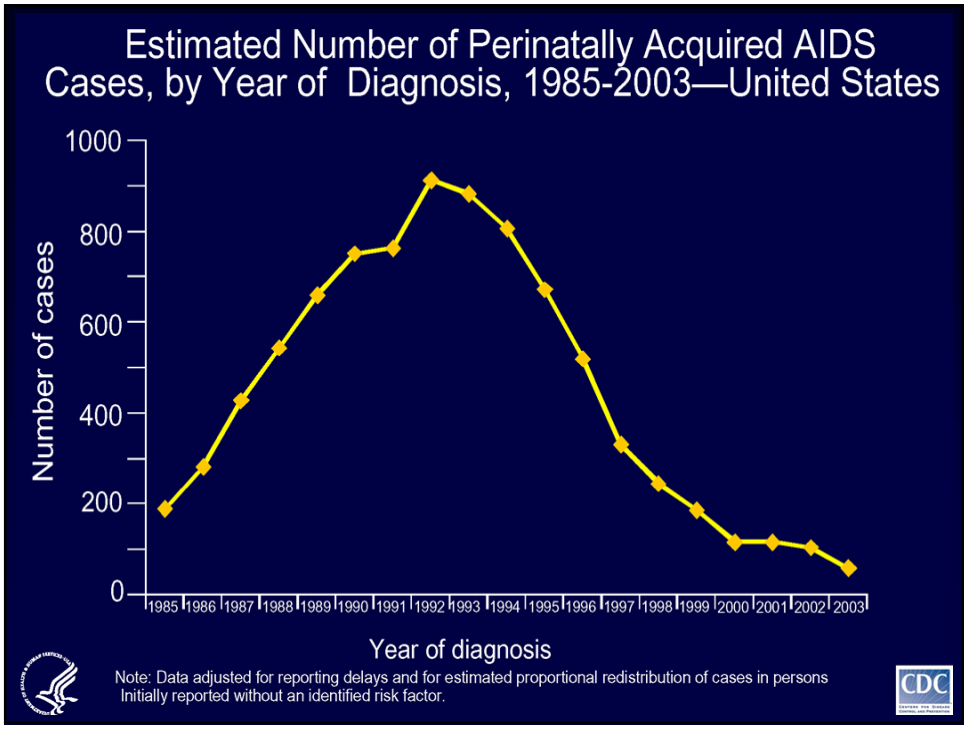
P < 0.001 for MK-0518 at each dose vs. EFV

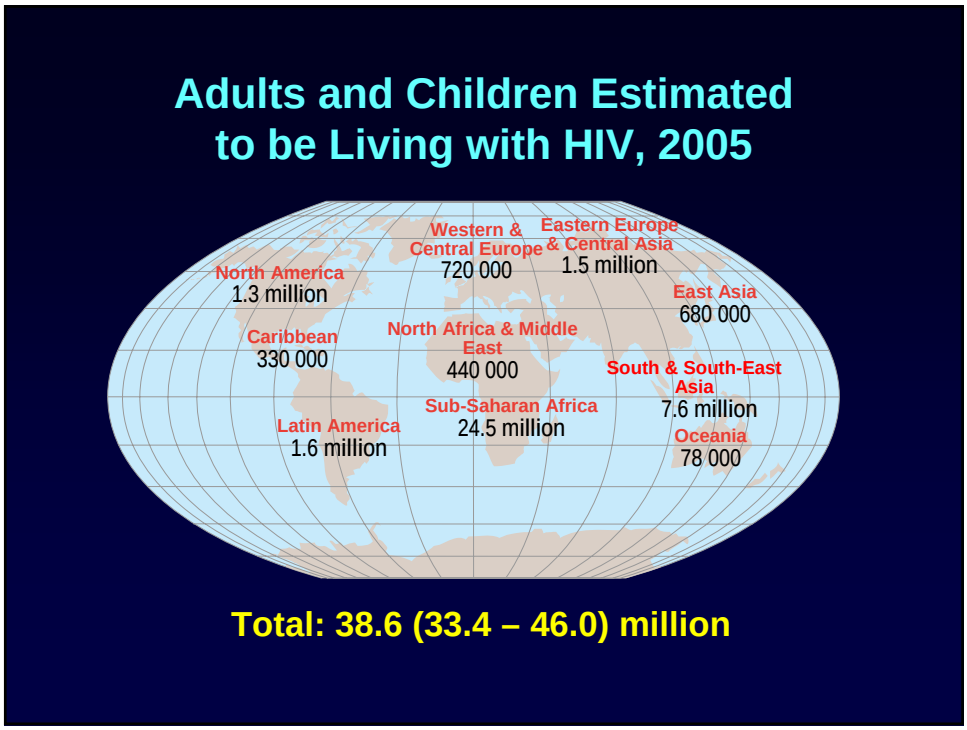
m518p4.r50.5 Aug. 3, 2006

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2004—United States



Note. Data adjusted for reporting delays.


Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985-2003—United States
Number of cases
1000
800
600
400
200
0
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003
Year of diagnosis
Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases in persons Initially reported without an identified risk factor.
CDC


Adults and Children Estimated to be Living with HIV, 2005
North America
1.3 million
Western & Central Europe
720 000
Eastern Europe & Central Asia
1.5 million
East Asia
680 000
Caribbean
330 000
North Africa & Middle East
440 000
South & South-East Asia
7.6 million
Sub-Saharan Africa
24.5 million
Latin America
1.6 million
Oceania
78 000
Total: 38.6 (33.4 – 46.0) million