Antiretroviral Agents

Scott M. Hammer, M.D.

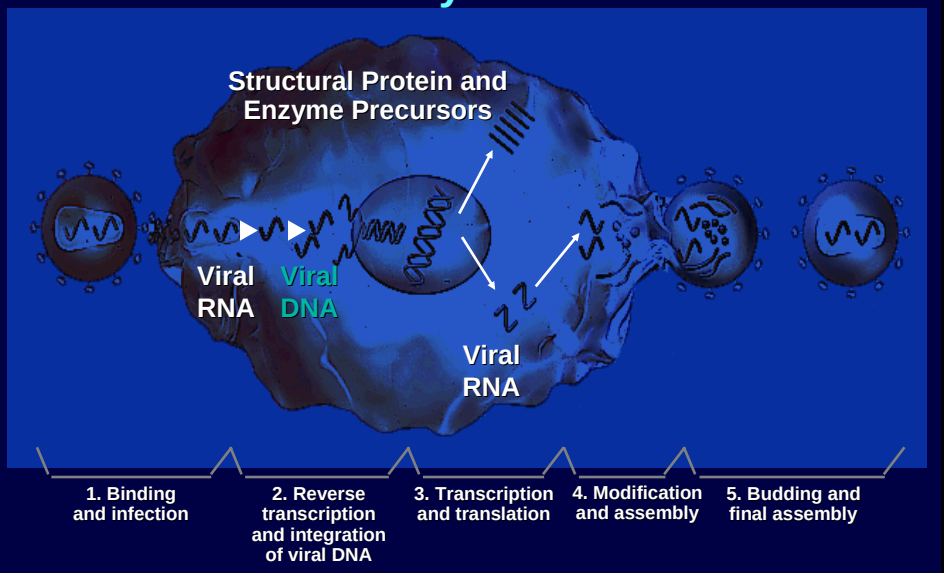
Evolution of Antiretroviral Therapy

1986 → 1990
ZDV monoRx

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

1995 → 2005
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
Introduction of TDM
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

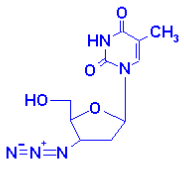
- Every step in viral life cycle is a potential antiviral target
- Currently there are 5 classes of FDA approved agents
  - Nucleoside analog reverse transcriptase inhibitors (NsRTI's)
  - Nucleotide analog reverse transcriptase inhibitors (NtRTI's)
  - Non-nucleoside reverse transcriptase inhibitors (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
  - Regimen complexities
  - Toxicities
  - Drug resistance

Nucleoside Analog RT Inhibitors

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

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

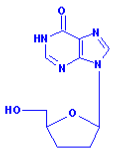
Nucleoside Analog RT Inhibitors



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

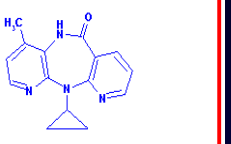
Nucleotide Analog RT Inhibitors

- 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)

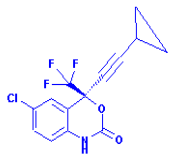
Non-Nucleoside RT Inhibitors



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

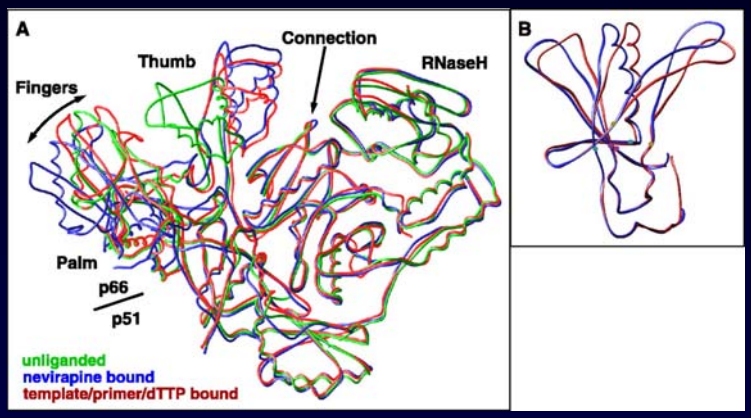
NAME	(-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4,-dihydro-2H-3,1-benzoxazin-one
SYN	Sustiva; Efavirenz; DMP-266; L-743,726
COMP	DUPONT MERCK

Efavirenz

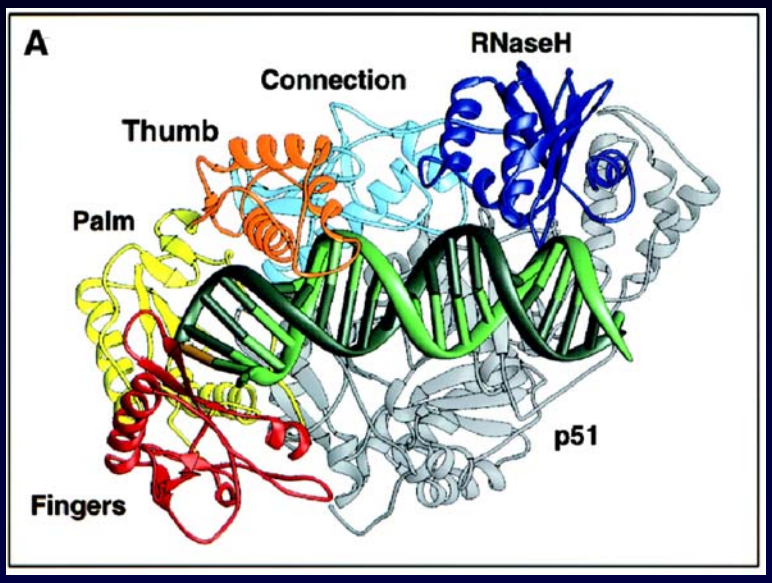
Non-Nucleoside RT Inhibitors

- 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

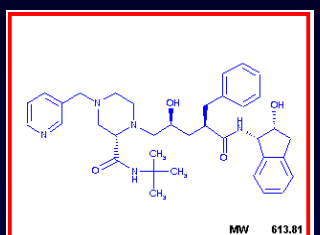
- Metabolized by CYP3A4 isozyme of hepatic p450 system
- NVP and EFZ are inducers of CYP3A4
- DLV is an inhibitor of CYP3A4
- Potential for major drug interactions with numerous HIV (esp. PI's) and non-HIV agents
- Do not prescribe without first checking for potential drug interactions
  - May be contraindications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

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

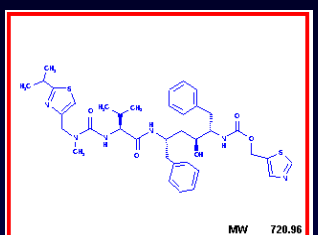
Protease Inhibitors



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

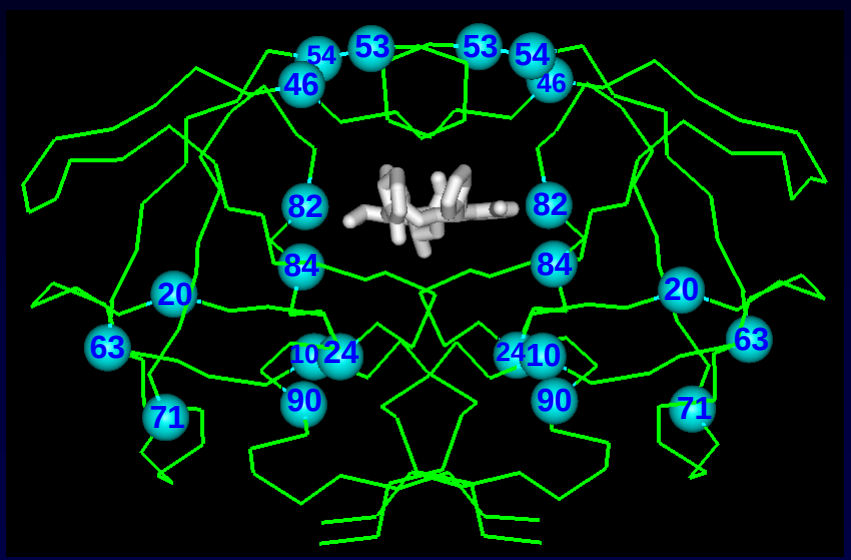
NAME	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]-
SYN	ABT-538; A 84538; Norvir; Ritonavir
COMP	ABBOTT

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

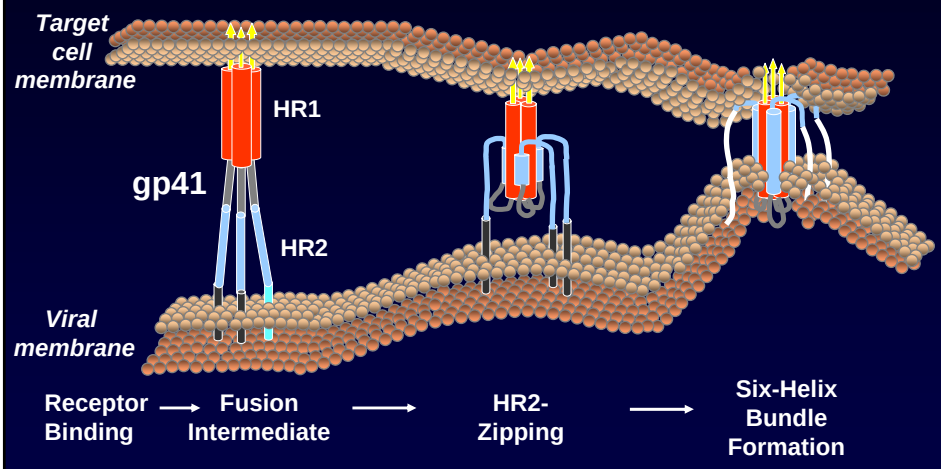
Protease Structure: Mutations Associated With Reduced *in vitro* Susceptibility to Lopinavir



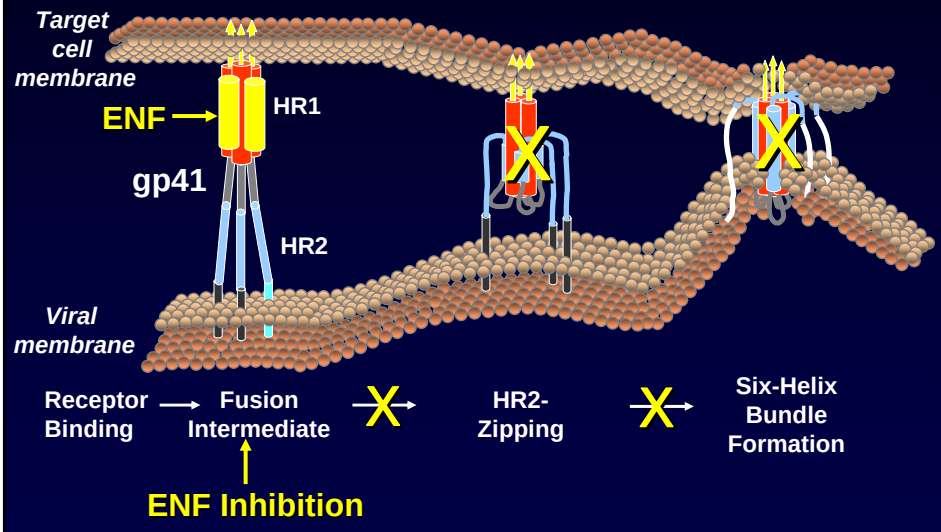
PI's: Drug Interactions

- 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)

Model for HIV-Cell Fusion



Enfuvirtide Inhibition of HIV Fusion



Antiretroviral Agents Approved in the U.S.

Nucleoside RTI's

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

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)
- Fos-amprenavir (Fos-APV)
- Tipranavir (TPV)

Nucleotide RTI

- Tenofovir DF (TDF)

Entry Inhibitor

- Enfuvirtide (T-20)

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

Initiation of Therapy: Regimens

- Non-nucleoside RTI + 2 nucleoside RTI's
  - Newer options
    - » NNRTI + 1 NsRTI + 1 NtRTI
      - Not all such combinations are effective
        - » High virologic failure rate recently reported with NNRTI/ddI-EC/TDF
    - » NNRTI + 3 NsRTI's
  - PI sparing
- Protease inhibitor (+/low-dose RTV) + 2 nucleoside RTI's
  - NNRTI sparing

Initiation of Therapy: Regimens

- 3 Nucleoside RTI's
  - PI and NNRTI sparing
  - No longer a preferred first line option
    - » Data from A5095 have shown ZDV/3TC/ABC to be inferior to two other combined arms (EFZ/ZDV/3TC, EFZ/ZDV/3TC/ABC) – study still ongoing
      - 21% vs. 10% virologic failure rate at 32 wks
  - Data on other triple NRTI options also problematic
    - » e.g, 2 NsRTI's + NtRTI
      - ABC/3TC/TDF as qD regimen – 49% virologic failure rate and high incidence of K65R
      - ddI/3TC/TDF as qD regimen – 91% suboptimal response and high incidence of K65R
- 3 Nucleoside RTI's + NtRTI??
  - PI and NNRTI sparing
  - Response suboptimal in patients with RNAs >100,000

Initiation of Therapy: Regimens

- 1-2 Protease inhibitors + NNRTI + 1-2 NRTI's
  - Consideration only in special circumstances
    - » e.g., acquisition of drug resistant virus
- Protease inhibitor/low-dose RTV + NNRTI
  - NRTI sparing
  - Currently in clinical trials

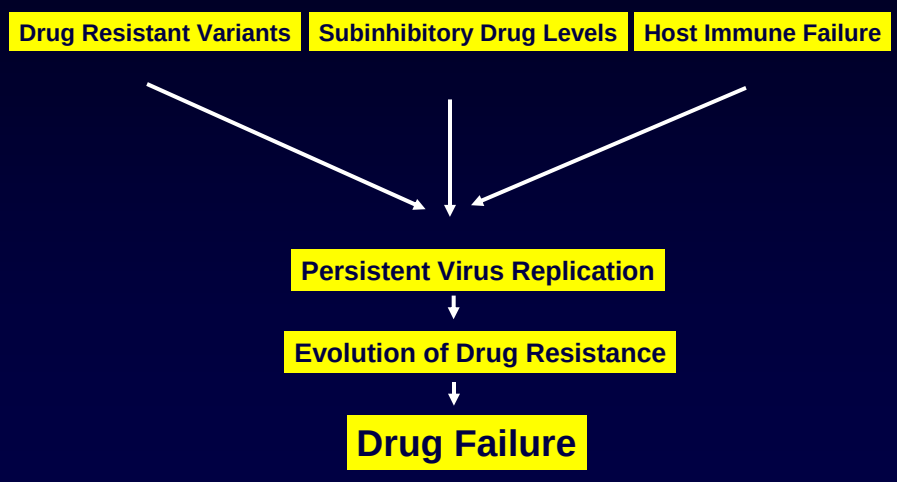
Antiretroviral Therapy Failure

- 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

Drug Failure



Adapted from J Mellors

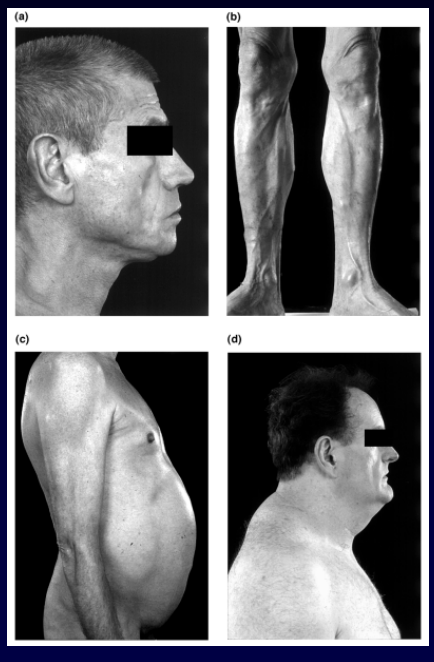
Limitations of Currently Available Agents

- Some regimens remain complex
  - Particularly for treatment experienced patients
- 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
  - In drug naïve individuals
    - » Single and double mutants pre-exist
    - » Triple and quadruple mutants would be predicted to be rare

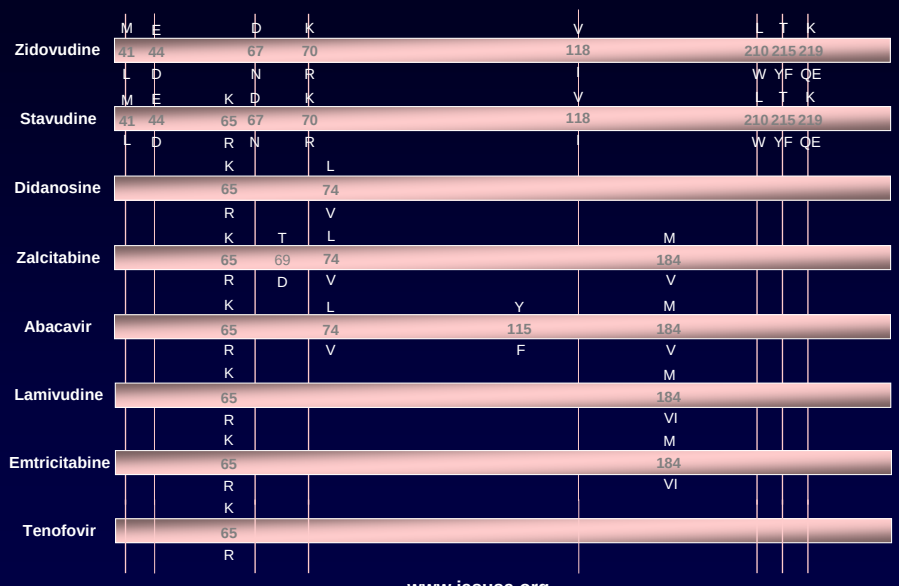
HIV Resistance: Underlying Concepts

- 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, 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

HIV Drug Resistance: Definitions

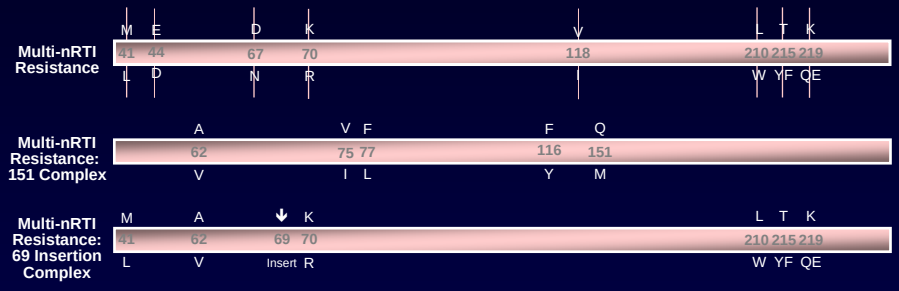
- Genotype
  - Determines phenotype
  - Major and minor mutations for PIs
- Phenotype
  - Drug susceptibility
- 'Virtual phenotype' or Vircotype®
  - Variant of a genotypic test
  - Result of large relational genotype and phenotype database

Mutations Associated with nRTIs/ntRTIs



www.iasusa.org

Mutations Associated with nRTIs/ntRTIs



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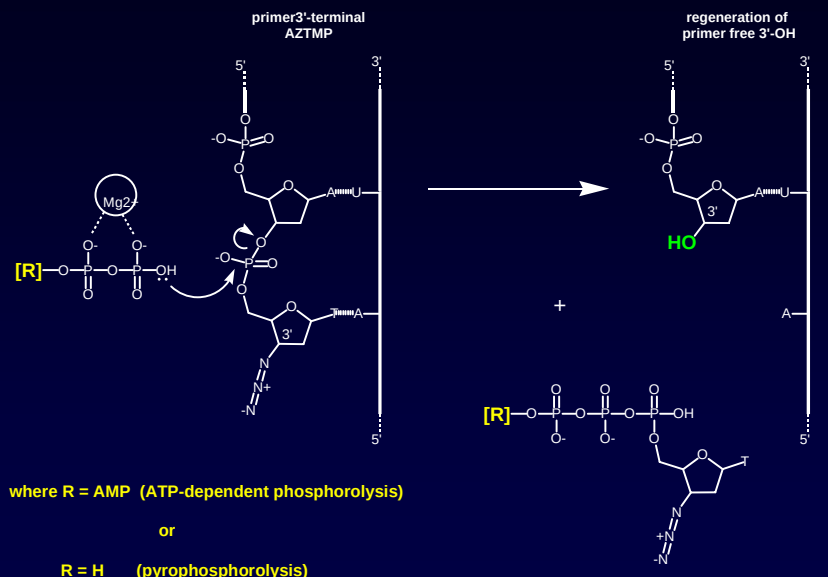
Nucleoside Analog Resistance

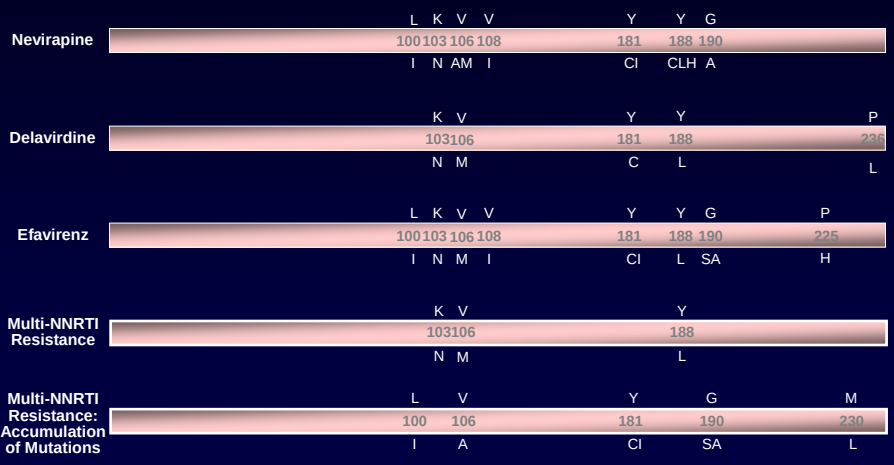
TAM's (M41L, D67N, K70R, L210W, T215F/Y, K219Q/E/N)	M184V	K65R
Confer ZDV resistance thru ZDV-MP excision	Confers 3TC resistance thru decreased 3TC-TP incorporation	Confers non-ZDV NRTI resistance thru decreased analog incorporation
Antagonize K65R	Decreases ZDV resistance thru decreased ZDV-MP excision	Decreases ZDV resistance thru decreased ZDV-MP excision

Pyrophosphorolysis



Courtesy M. Parniak
Mellors, 9th CROI, 2002

Mutations Selected by NNRTIs



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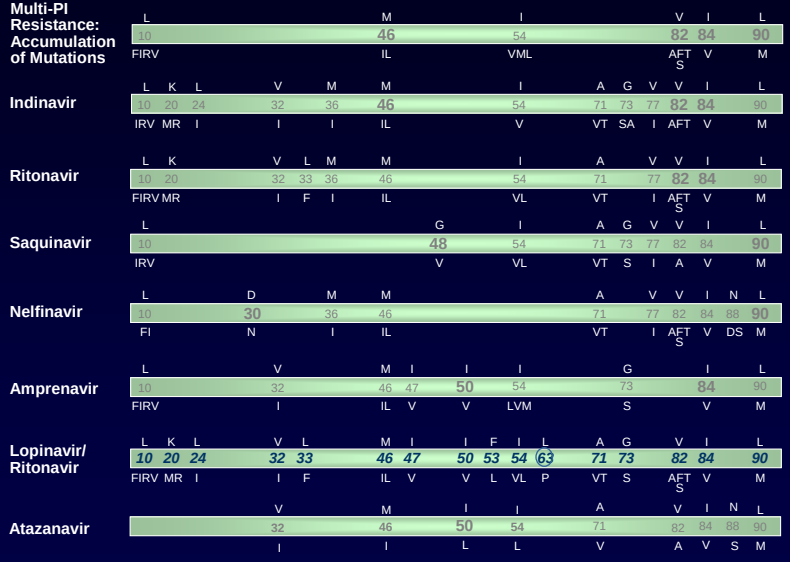
Mutations Selected by PIs



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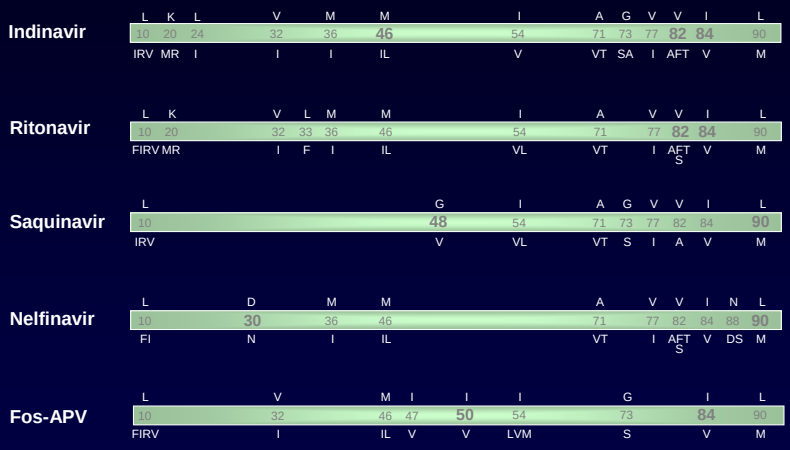
Mutations Selected by PIs



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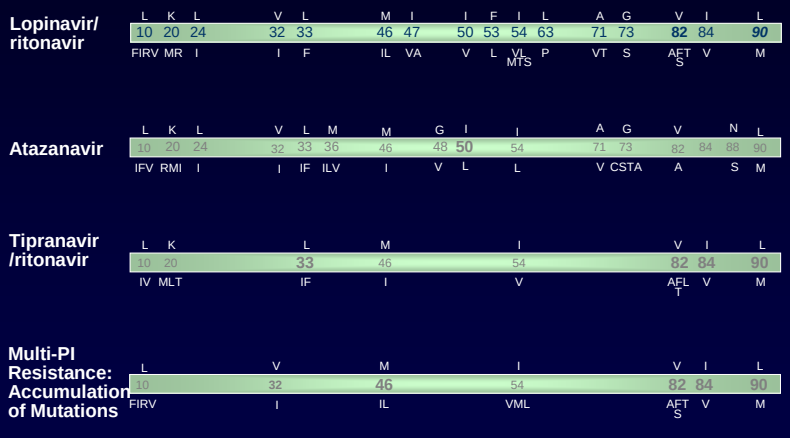
Mutations Selected by PIs



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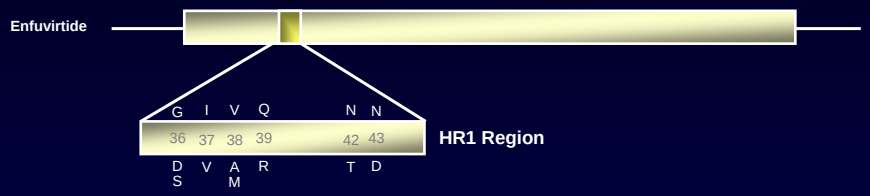
Mutations in the gp41 Envelope Gene Associated With Resistance to Enfuvirtide



Selected Experimental Agents Within Existing Drug Classes

Nucleoside RTI's

- Amdoxovir (DAPD)
- SPD-754
- D-D4FC
- Others

Non-Nucleoside RTI's

- TMC 125
- TMC 278
- GW678248/GW695634
- Others

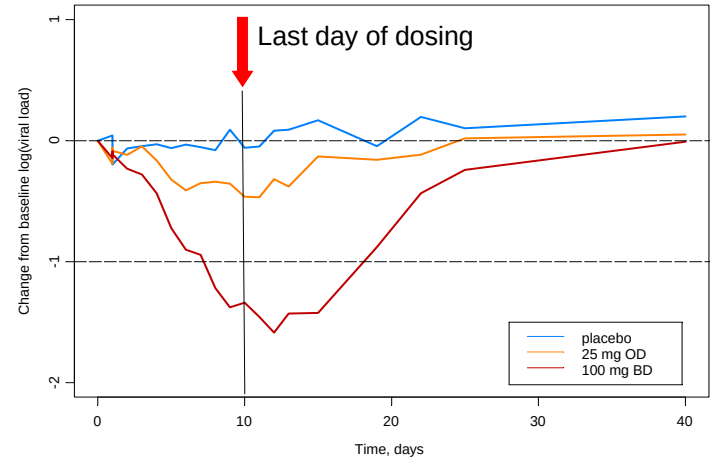
Protease Inhibitors

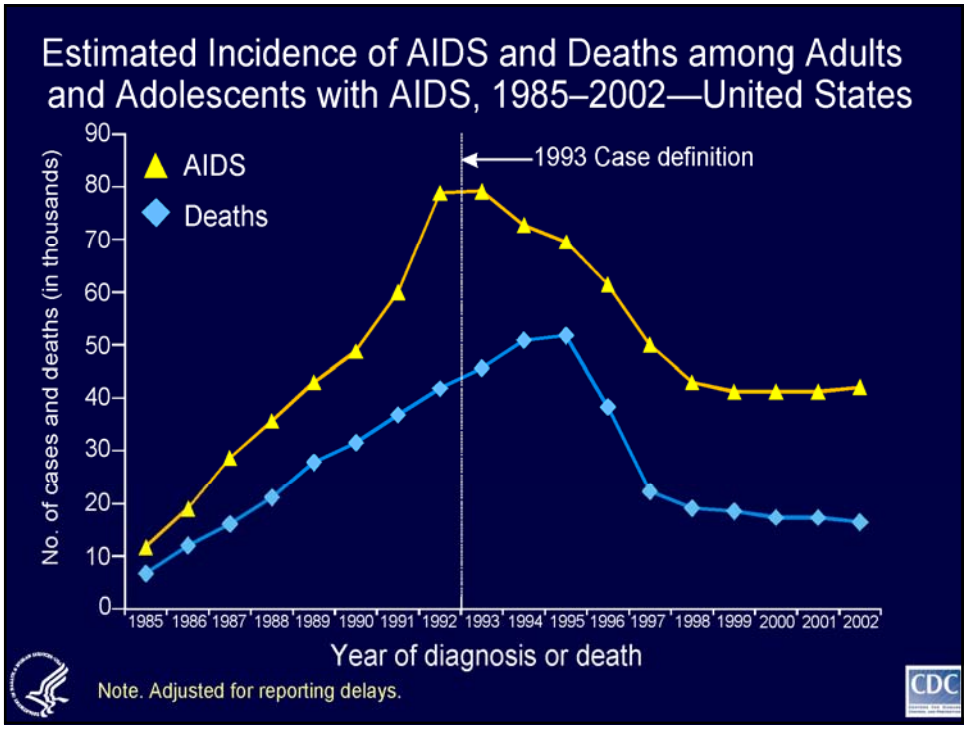
- TMC 114
- AG-1859
- RO-033-4649
- Others

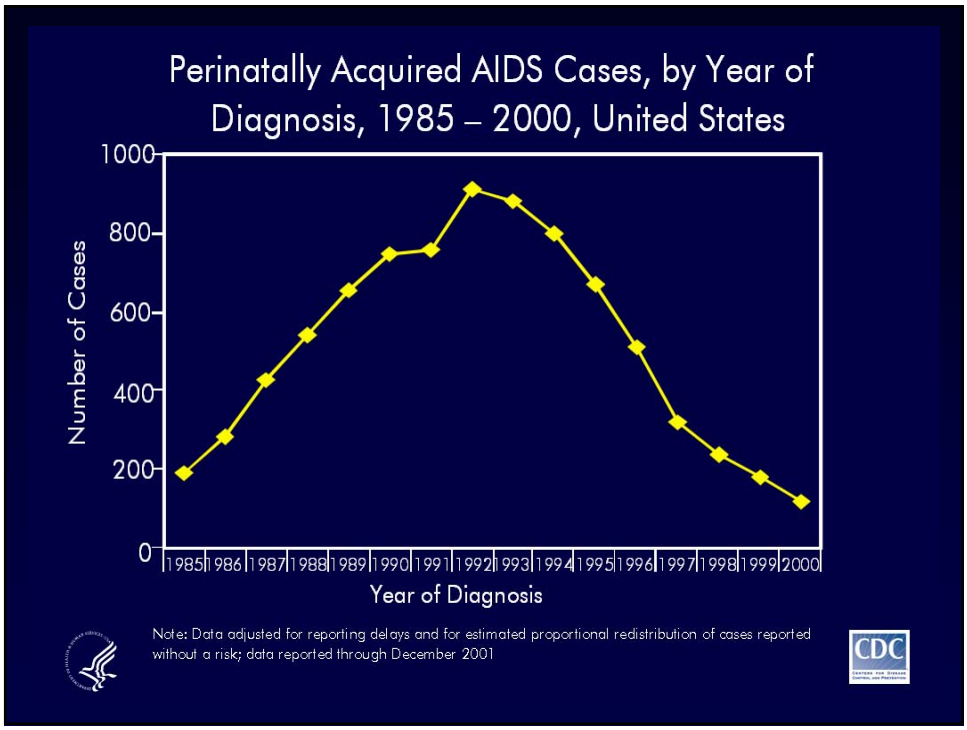
Selected New Classes of Agents

- Entry inhibitors
  - Attachment inhibitors (PRO 542, BMS-488043)
  - Chemokine receptor antagonists
    - » CCR5 (PRO 140, SCH-D, UK 427857, TAK 220, GW873140/AK-602, AMD887)
    - » CXCR4 (AMD 070, KRH-2731)
  - Fusion inhibitors (ENF [T-20], T-1249, 5-Helix)
  - TNX-355
- Integrase inhibitors
  - MK-0518, RSC-1838, V-165
- Gag processing inhibitor
  - PA-457

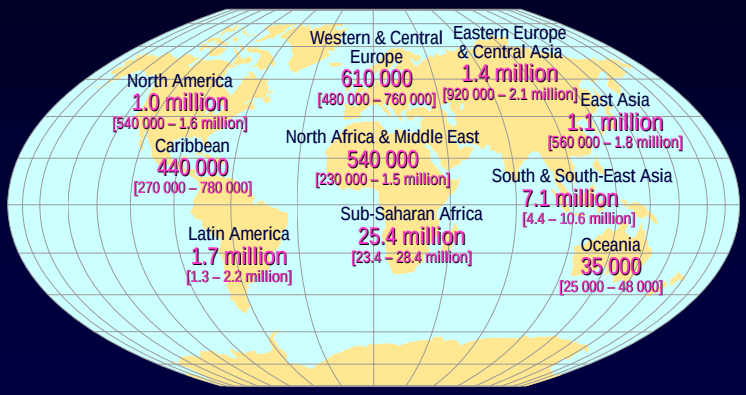
CCR5 Inhibitor: Maraviroc Trial
Viral Load Decline in CCR5 Tropic Patients




Estimated Incidence of AIDS and Deaths among Adults and Adolescents with AIDS, 1985–2002—United States
No. of cases and deaths (in thousands)
90
80
70
60
50
40
30
20
10
0
AIDS
Deaths
1993 Case definition
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002
Year of diagnosis or death
Note. Adjusted for reporting delays.
CDC


Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985 – 2000, 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
Year of Diagnosis
Note: Data adjusted for reporting delays and for estimated proportional redistribution of cases reported without a risk; data reported through December 2001
CDC

Adults and Children Estimated to be Living with HIV as of End 2004



Total: 39.4 (35.9 – 44.3) million

Source: UNAIDS