Antiretroviral Therapy

Scott M. Hammer, M.D.

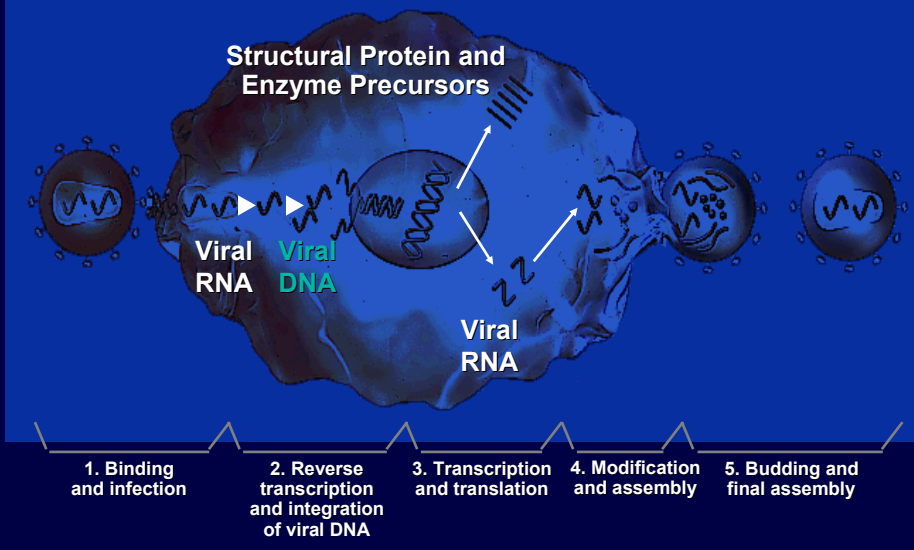
Evolution of Antiretroviral Therapy

1986 – 1990
ZDV monoRx

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

1995 – 2008
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
Reality of new classes of agents
Swings in approach to Rx
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 7 classes of FDA approved agents
  - Nucleoside analog reverse transcriptase inhibitors (NsRTIs)
  - Nucleotide analog reverse transcriptase inhibitor (NtRTI)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs)
  - Fusion inhibitor (enfuvirtide)
    - » Entry inhibitor which targets the virus
  - CCR5 antagonist inhibitors (maraviroc)
    - » Entry inhibitor which targets the host
  - Integrase inhibitors (raltegravir)
- Drugs must be used in combination to be effective
  - This has led to dramatic reductions in morbidity and mortality where ART has been introduced effectively
- Current therapies are imperfect
  - Toxicities
  - Drug resistance

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

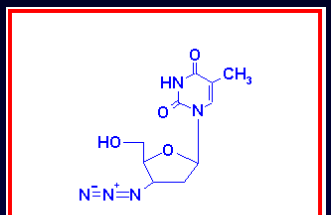
- Zidovudine (ZDV, AZT)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

→ nsRTI's

- Tenofovir disoproxil fumarate (TDF) → ntRTI

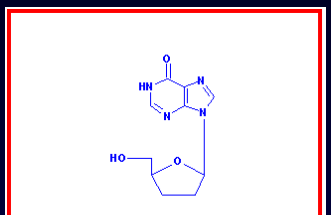
N.B.: Four fixed dose combinations are approved:
ZDV + 3TC (Combivir®); ZDV + 3TC + ABC (Trizivir®);
3TC + ABC (Epzicom®); FTC + TDF (Truvada®)

Nucleoside Analog RT Inhibitors



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

Zidovudine



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

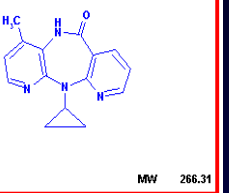
Nucleotide Analog RT Inhibitors

- 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)
- Etravirine (ETV)

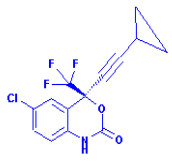
Non-Nucleoside RT Inhibitors



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

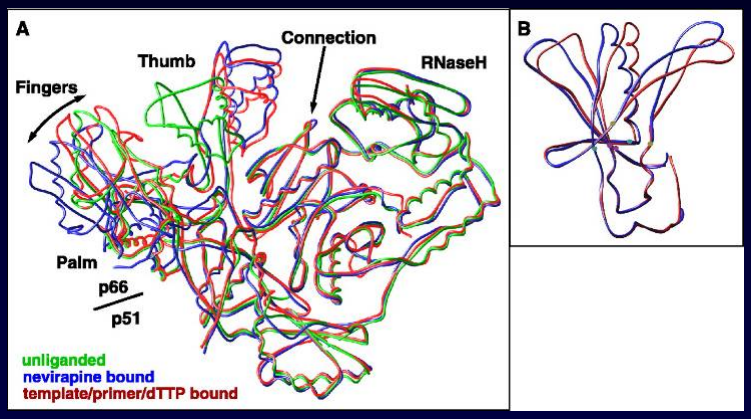
NAME	(-)-6-Chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4,-dihydro-2H-3,1-benzoxazin-one
SYN	Sustiva; Efavirenz; DMP-266; L-743,726
COMP	DUPONT MERCK

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

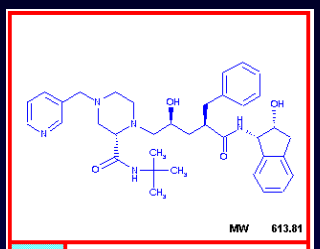
- Metabolized by CYP3A4 isozyme of hepatic p450 system
- NVP and EFZ are inducers of CYP3A4
- DLV is an inhibitor of CYP3A4
- Potential for major drug interactions with numerous HIV (esp. PI's) and non-HIV agents
- Do not prescribe without first checking for potential drug interactions
  - May be contraindications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

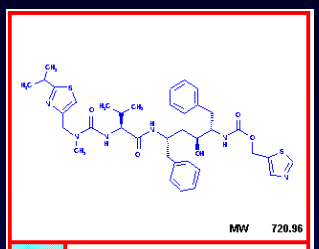
Protease Inhibitors



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

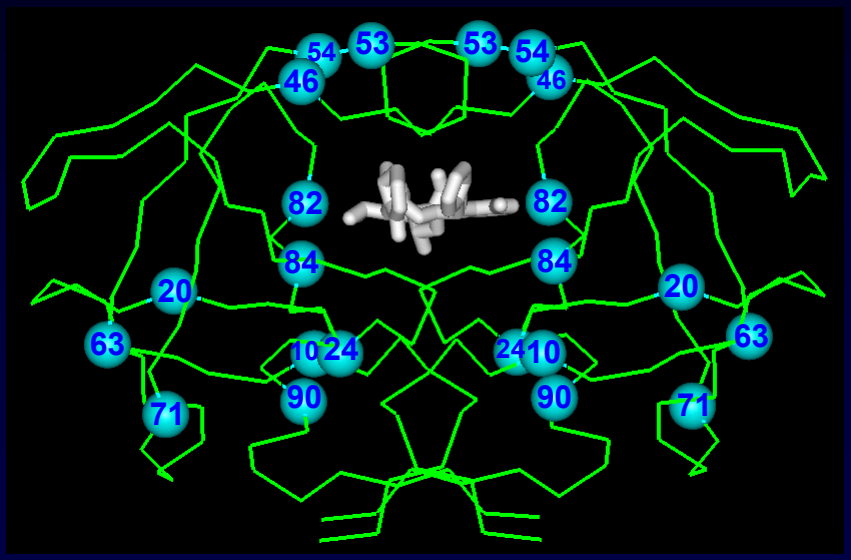
NAME	2,4,7,12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]-
SYN	ABT-538; A 84538; Norvir; Ritonavir
COMP	ABBOTT

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



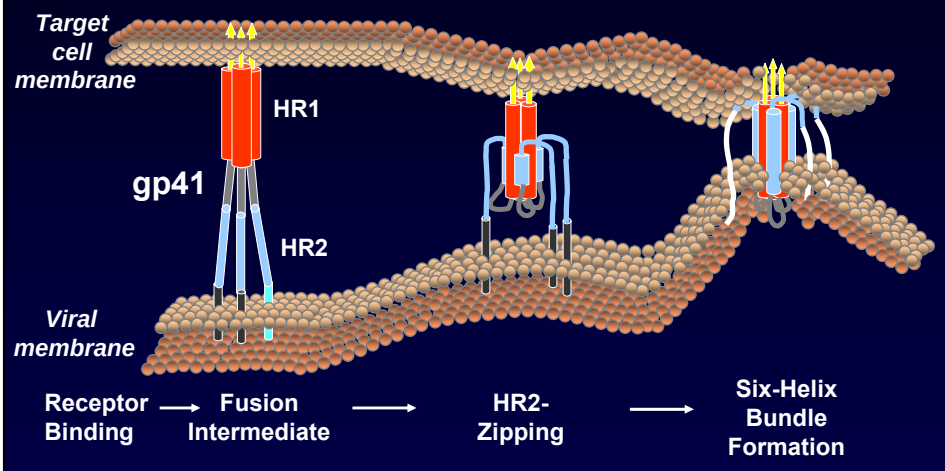
PI's: Drug Interactions

- 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)

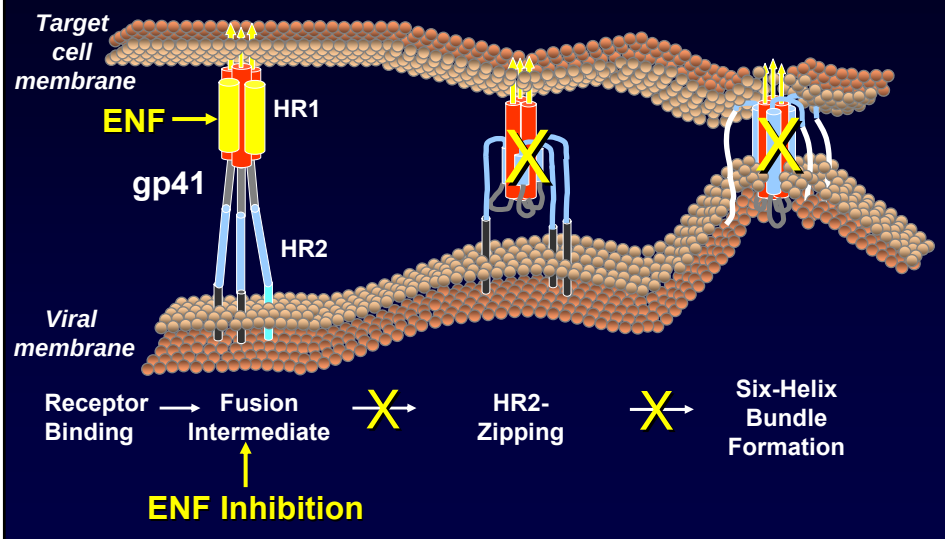
HIV Entry

Enfuvirtide (Fusion Inhibitor): Mechanism of Action

Model for HIV-Cell Fusion



Enfuvirtide Inhibition of HIV Fusion



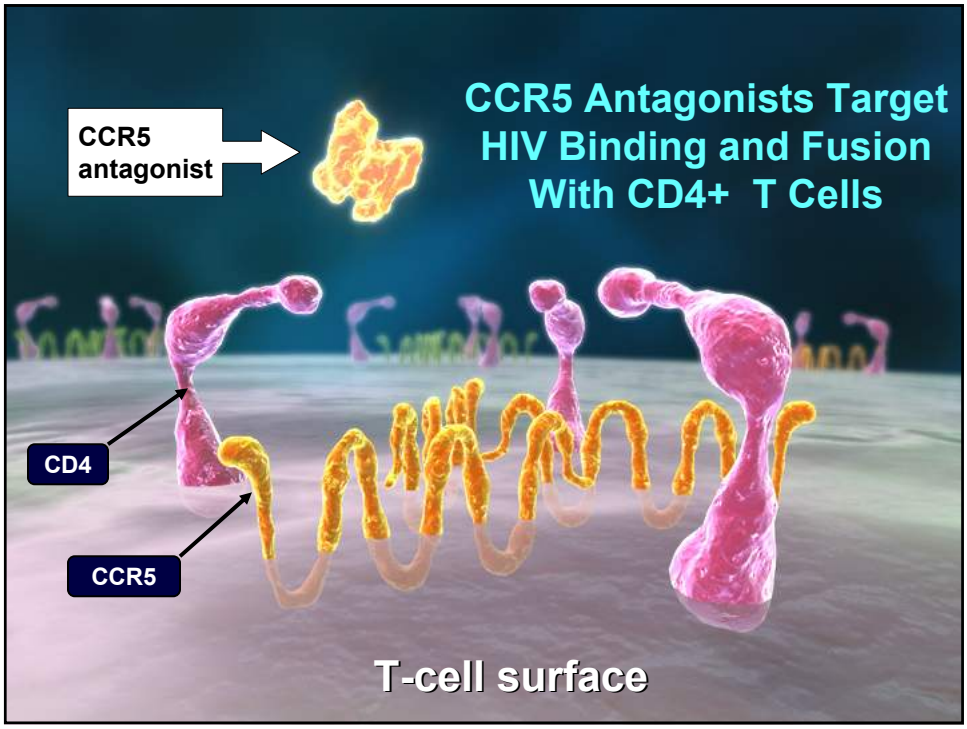
CCR5 Antagonist: Maraviroc

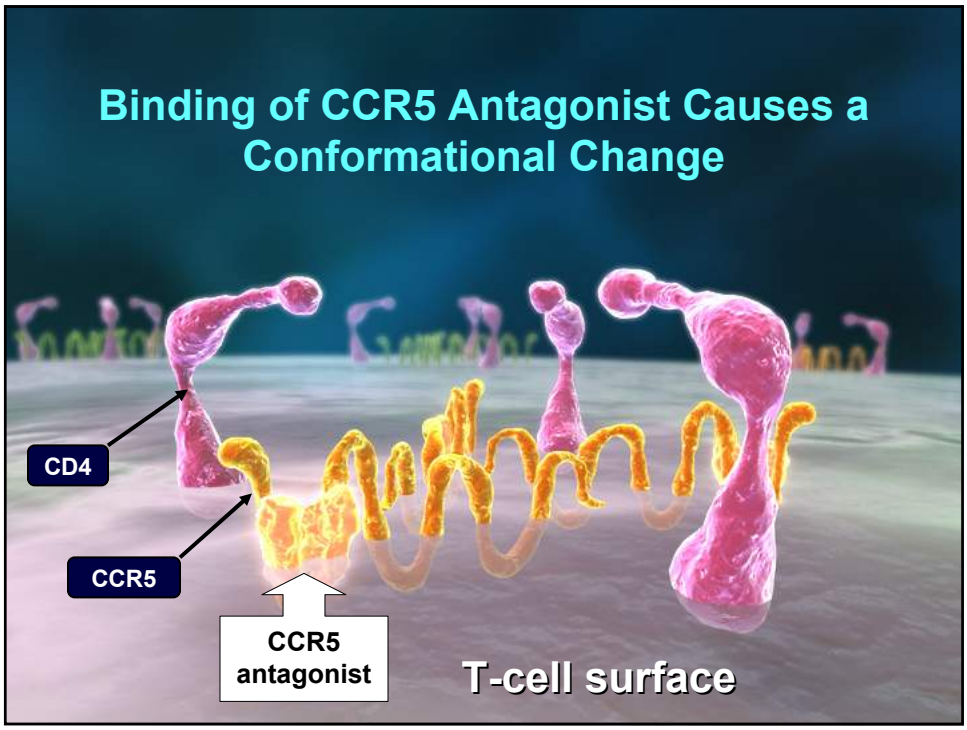
Percentage of HIV Co-receptor Usage

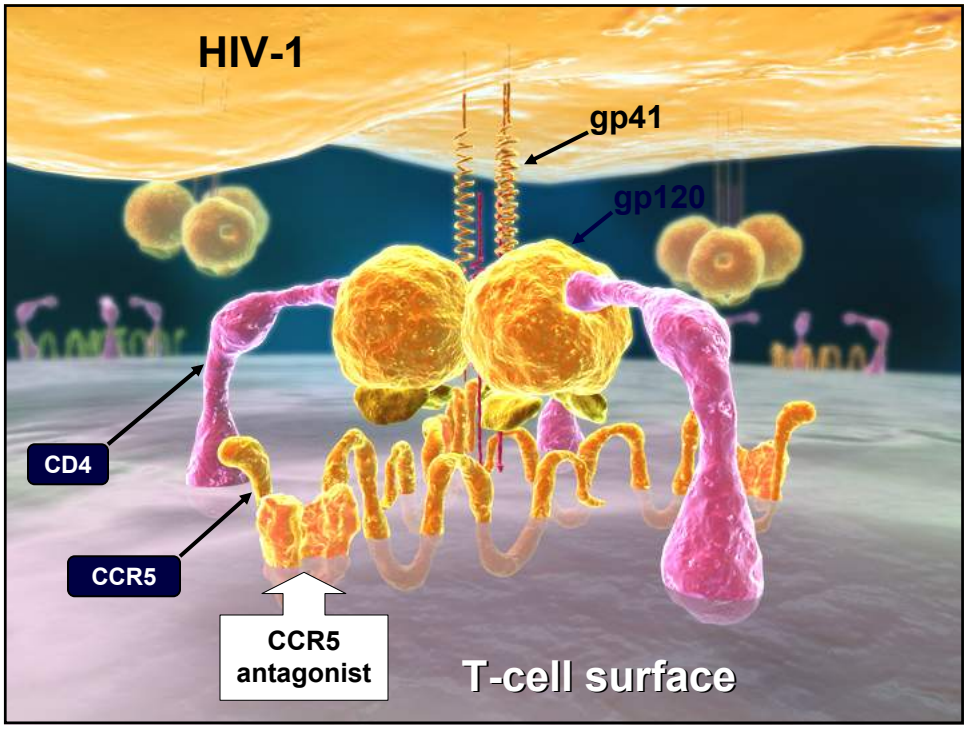
Study/Source	Population	N	R5	X4	R5/X4
Homer cohort[1]	Naive	979	82%	<1%	18%
C & W cohort[2]	Naive	402	81%	<1%	19%
Demarest[3]	Naive	299	88%	0%	12%
TORO 1/2[4]	Experienced	612	62%	4%	34%
ViroLogic[5]	Experienced	>2000	48%	2%	50%
ACTG 5211[6]	Experienced	391	49%	4%	47%

*This table may not include all available reported data.
Majority of data are generated in the developed world (subtype B)

[1]Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474.
[2]Moyle GJ, et al. *J Infect Dis*. 2005;191:866-872.
[3]Demarest J, et al. *ICAAC* 2004. Abstract H-1136.
[4]Whitcomb JM, et al. *CROI* 2003. Abstract 557.
[5]Paxinos EE, et al. *ICAAC* 2002. Abstract 2040.
[6]Wilkin T, *et al. CROI* 2006. Abstract 655.


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

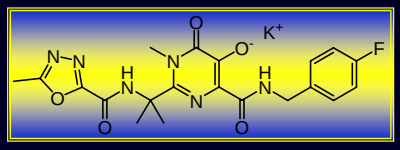

Binding of CCR5 Antagonist Causes a Conformational Change
CD4
CCR5
CCR5 antagonist
T-cell surface



Integrase Inhibitor: Raltegravir

HIV Integration

Raltegravir: An HIV-1 Integrase Inhibitor



- Mechanism of action
  - Inhibits DNA strand transfer from provirus into host cell genome – a key step in viral integration process
- Potent *in vitro* activity
  - » IC_{95} = 33 nM ± 23 nM in 50% human serum
  - » Active against:
    - multi-drug resistant HIV-1
    - CCR5 and CXCR4 HIV-1
  - » HIV resistant to raltegravir remains sensitive to other ARTs
  - » Synergistic *in vitro* with all ARTs tested

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)
- Etravirine (ETV)

Integrase Inhibitor
- Raltegravir (RAL)

Nucleotide RTI
- Tenofovir DF (TDF)

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)

Fusion Inhibitor
- Enfuvirtide (T-20)

CCR5 Antagonist
- Maraviroc (MVC)

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®)

"Non-AIDS" Conditions

- Since 2006, a number of "non-AIDS" conditions have been described to be associated with uncontrolled HIV-1 viremia, even in persons with relatively well preserved CD4 cell counts (e.g., >350/mm^3)
  - Cardiovascular events
  - Hepatic disease
  - Renal disease
  - Malignancies
- Direct effect of HIV-1 on organ systems, associated immune activation and/or other mechanisms may be involved
- Active area of investigation
- Redefining HIV-related disease progression and influencing decision of when to start ART

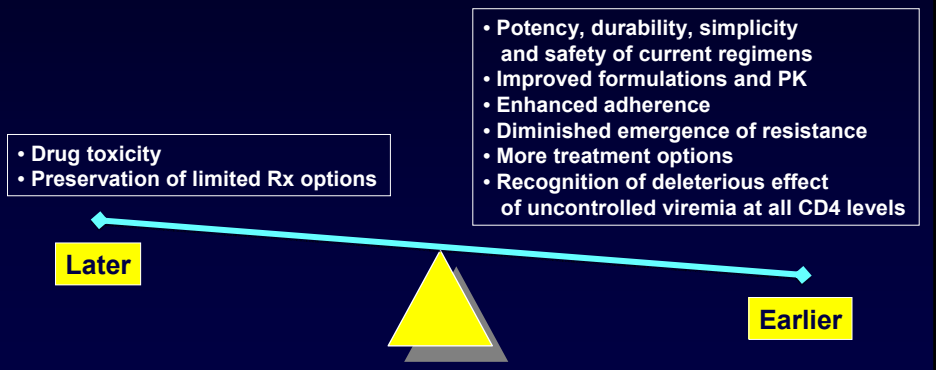
Initiation of Therapy in Established HIV Infection: Considerations

- Patient's disease stage
  - Symptomatic status
  - CD4 cell count
  - Plasma HIV-1 RNA level
  - Presence of, or risk factors for, "non-AIDS" conditions
    - » Cardiovascular, hepatic and renal disease
- Patient's commitment to therapy
- Philosophy of treatment
  - Pros and cons of 'early' intervention

Rationale for Initiation of Therapy Before CD4 Cell Counts Fall to 350/µL

- Uncontrolled HIV replication and resultant immune activation associated with 'non-AIDS' illnesses
  - » Cardiovascular
  - » Hepatic
  - » Renal
  - » Malignancies
- Patients with CD4 counts >350/µL and HIV-1 RNA levels >400 copies/mL have greater morbidity and mortality than those with viral suppression
  - » Definition of HIV-related disease progression should be revisited
- Potential for decreased horizontal HIV-1 transmission

When to Start Therapy: Balance Tipping in Favor of Earlier Initiation



When to Start Antiretroviral Therapy

Measure	Recommendation	Comments
Symptomatic HIV disease	Therapy recommended	
Asymptomatic HIV disease		
CD4 <350/µl	Therapy recommended	Recommendation strengthened since 2006
CD4 ≥350	Therapy should be considered and decision individualized Examples →	Correlates of faster HIV disease progression: • High viral load (>100,000 RNA copies/ml) • Rapidly declining CD4 (>100/µl per year) Coexistent conditions influenced by uncontrolled viremia: • Presence of, or high risk for, cardiovascular disease • Active HBV or HCV coinfection • HIV-associated nephropathy

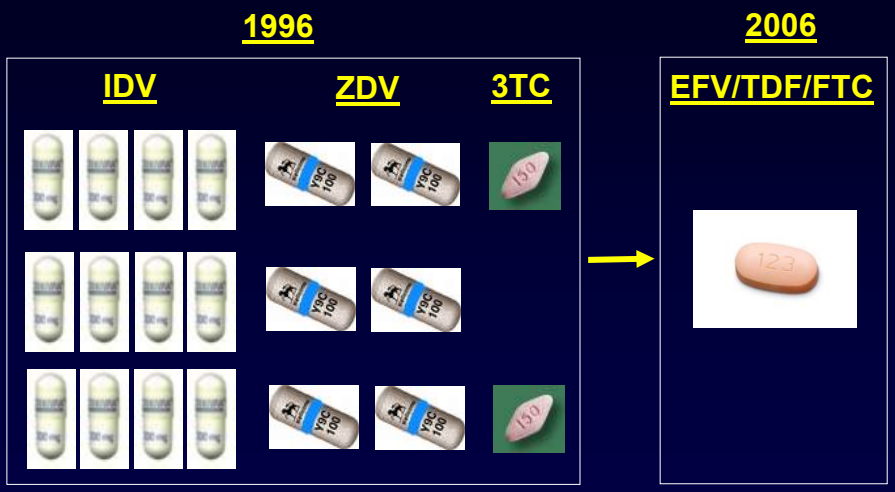
Choice of Initial Regimen

- At baseline:
  - Evaluate for hepatitis B or C coinfection, diabetes mellitus, hyperlipidemia, coronary artery disease, renal disease, other comorbid conditions and medications
  - Perform resistance testing
  - Assess for pregnancy or risk thereof
- Regimen:
  - Nonnucleoside 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

Choice of Initial Regimen (cont'd)

Component	Drugs	Comments
NNRTI component	efavirenz	• EFV: teratogenic in 1st trimester • NVP (alternative): 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, darunavir/r *or* saquinavir/r	• ATV/r: diminished hyperlipidemic potential; care with antacids • DRV/r: important role in treatment-experienced patients
Dual nRTI component	tenofovir/emtricitabine *or* abacavir/lamivudine	• ZDV/3TC: alternative • ABC: Screen for HLA-B*5701 to decrease risk of HSR; ?increased risk of cardiovascular disease • ABC/3TC: ?efficacy when viral load >100,000 c/ml

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

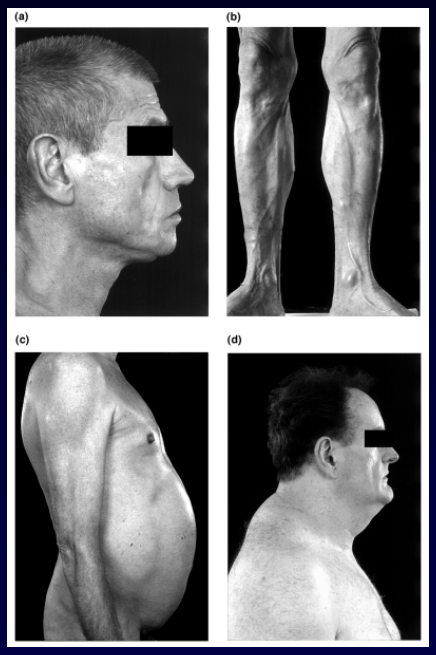
Limitations of Currently Available Agents

- 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

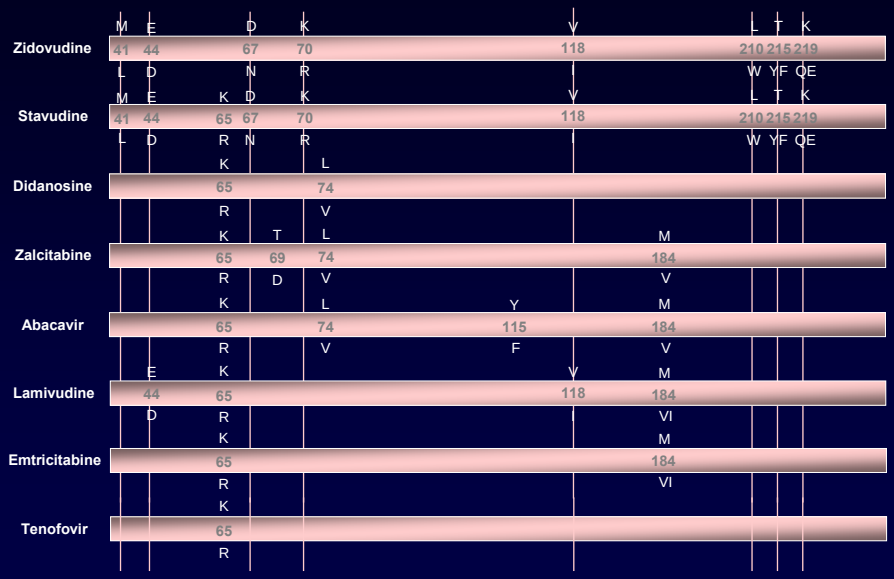
Pre-existence of Resistant Mutants

- 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

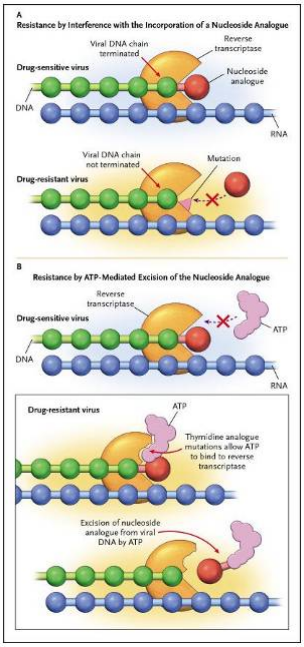
- Implications
  - Resistance mutations may exist before drug exposure and may emerge quickly after it is introduced
  - Drugs which develop high level resistance with a single mutation are at greatest risk
    - » e.g., 3TC, FTC, NNRTI's (nevirapine, efavirenz)
  - Resistance to agents which require 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/ntRTIs I



www.iasusa.org

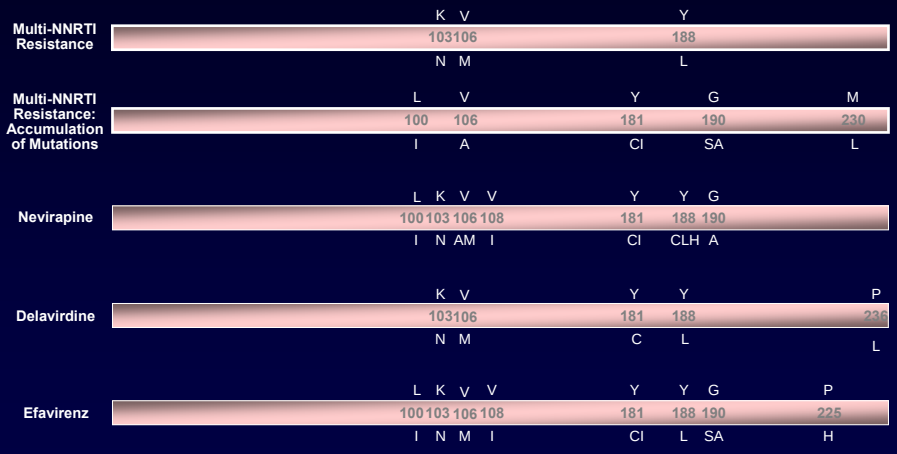
The Two Principal Mechanisms of Resistance of HIV to Nucleoside Analogues



The NEW ENGLAND JOURNAL of MEDICINE

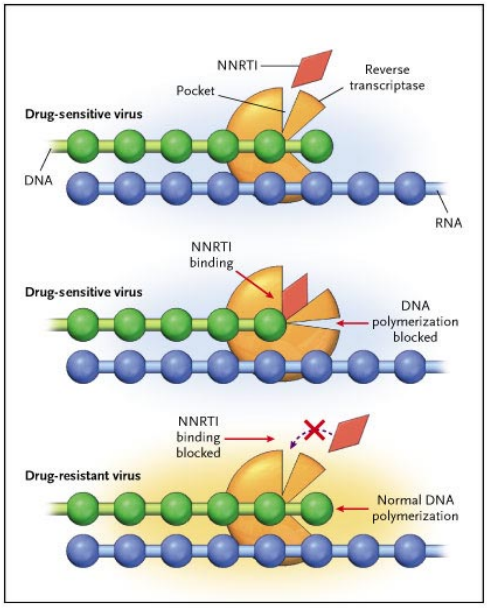
Clavel F et al: N Engl J Med 2004;350:1023-1035

Mutations Selected by NNRTIs



www.iasusa.org

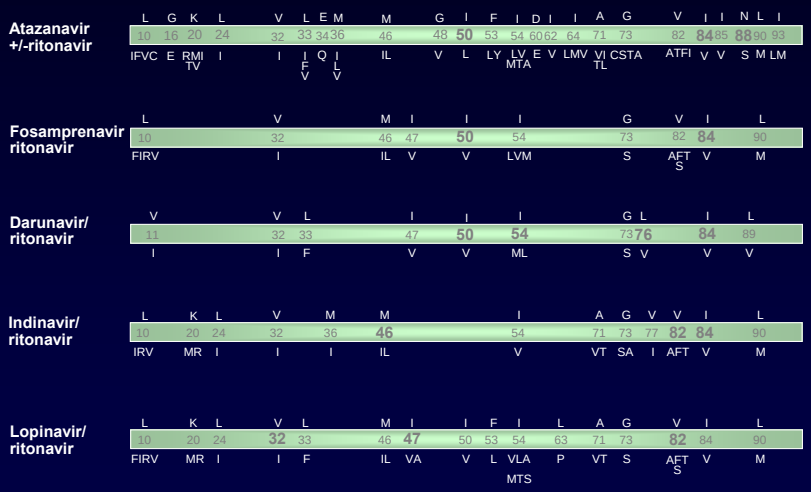
Mechanism of Resistance of HIV to Nonnucleoside Reverse-Transcriptase Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

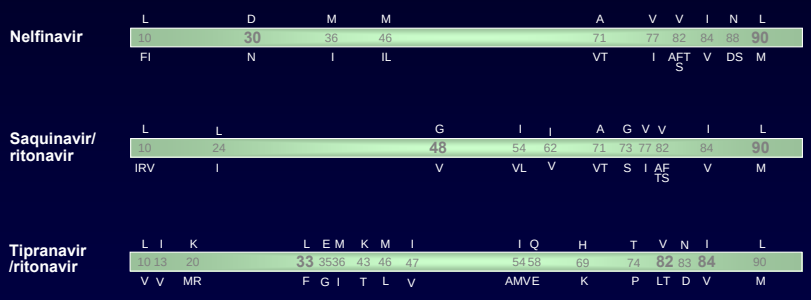
Clavel F et al:
N Engl J Med 2004;350:1023-1035

Mutations Selected by PIs



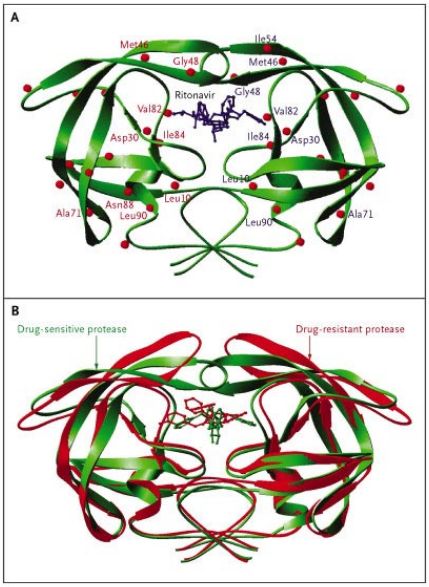
www.iasusa.org

Mutations Selected by PIs (cont'd)



www.iasusa.org

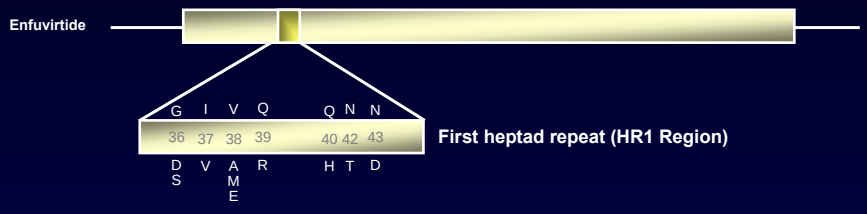
HIV-1 Protease Dimer Binding with a Protease Inhibitor (Panel A) and a Drug-Sensitive (Wild-Type) Protease Juxtaposed against a Drug-Resistant Protease (Panel B)



The NEW ENGLAND JOURNAL of MEDICINE

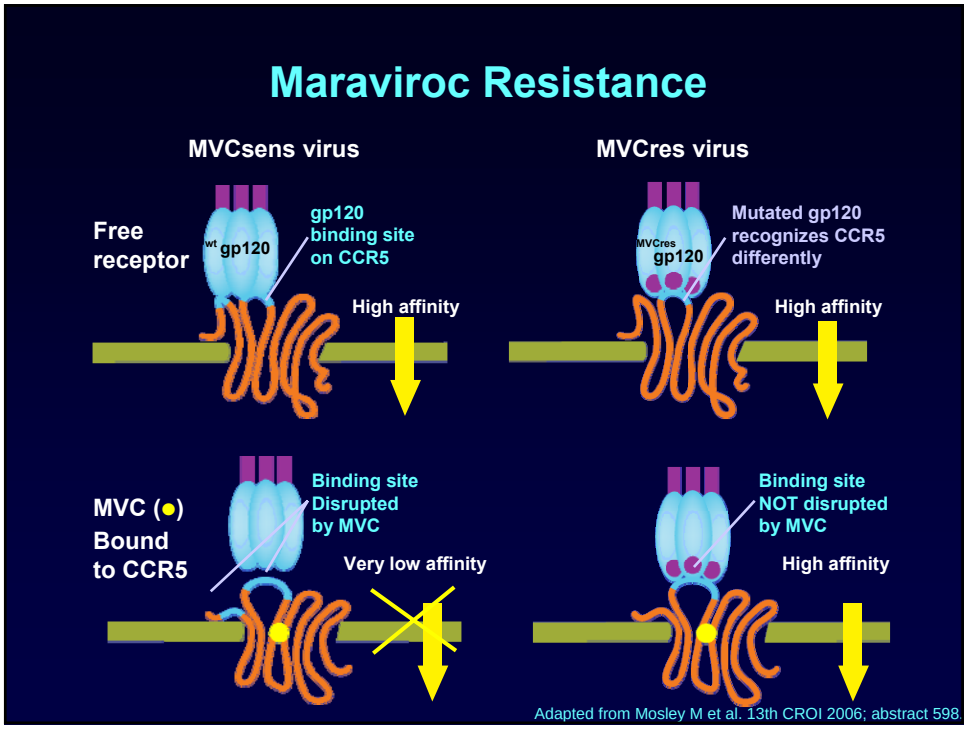
Clavel F et al:
N Engl J Med 2004;350:1023-1035

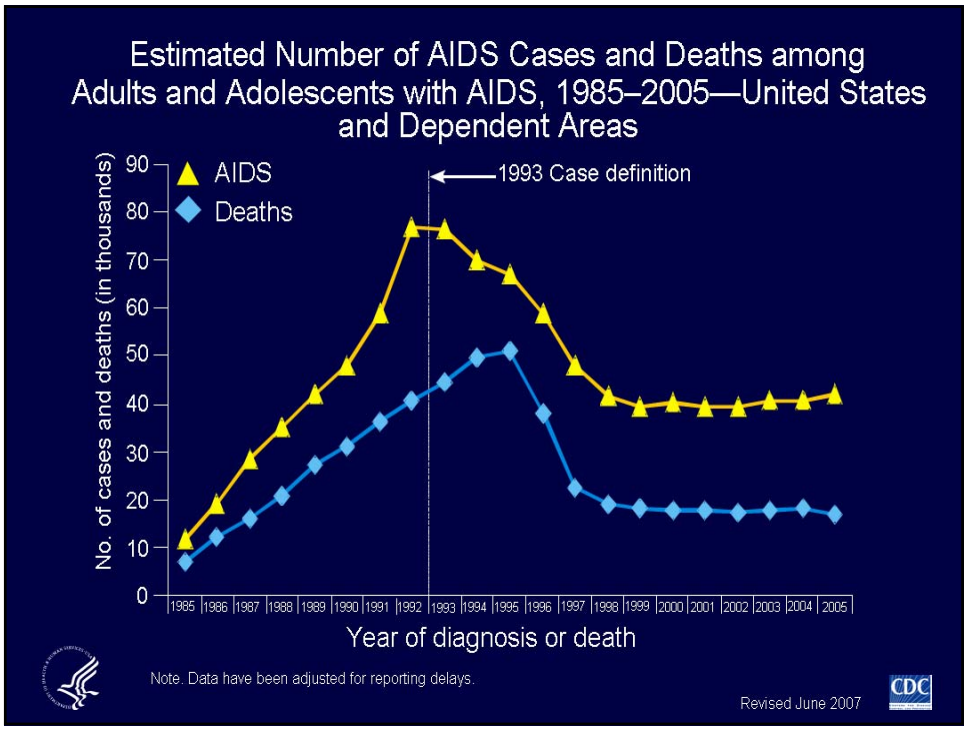
Mutations in the gp41 Envelope Gene Associated With Resistance to Enfuvirtide



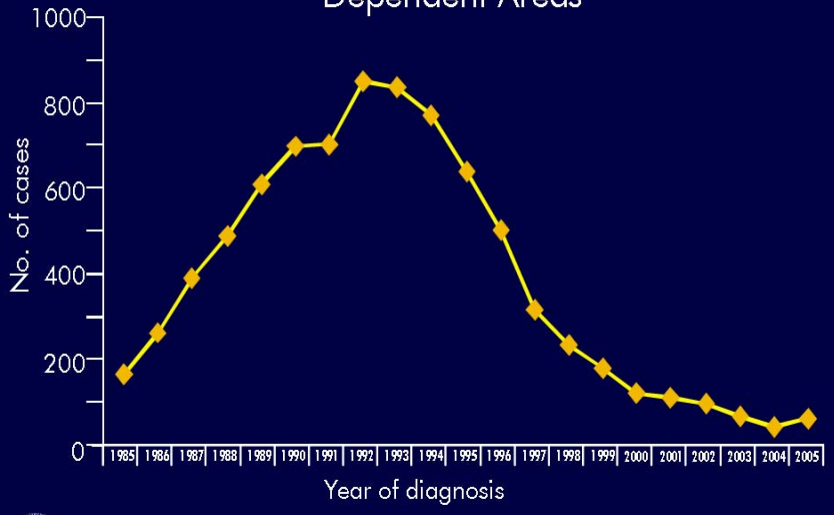
First heptad repeat (HR1 Region)

www.iasusa.org


Maraviroc Resistance
MVCsens virus
MVCres virus
Free receptor
wt gp120
gp120 binding site on CCR5
High affinity
MVCres gp120
Mutated gp120 recognizes CCR5 differently
High affinity
MVC (●) Bound to CCR5
Binding site Disrupted by MVC
Very low affinity
Binding site NOT disrupted by MVC
High affinity
Adapted from Mosley M et al. 13th CROI 2006; abstract 598

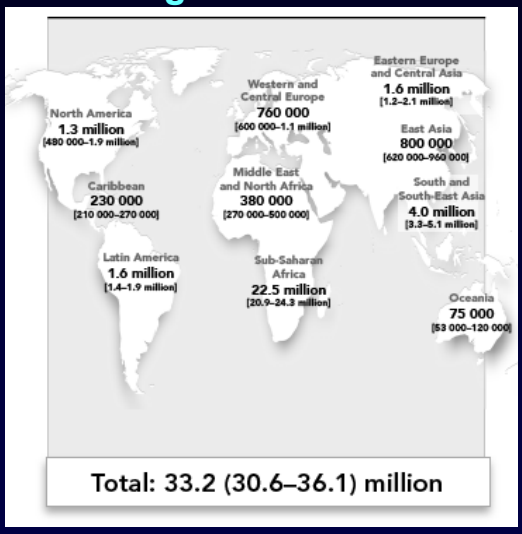

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2005—United States and Dependent Areas
AIDS
Deaths
1993 Case definition
No. of cases and deaths (in thousands)
0
10
20
30
40
50
60
70
80
90
1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005
Year of diagnosis or death
Note. Data have been adjusted for reporting delays.
Revised June 2007
CDC

Estimated Number of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2005—United States Dependent Areas



Note: Data adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

Adults and Children Estimated to be Living with HIV in 2007



UNAIDS World Health Organization