Antiretroviral Therapy

Scott M. Hammer, M.D.

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

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

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

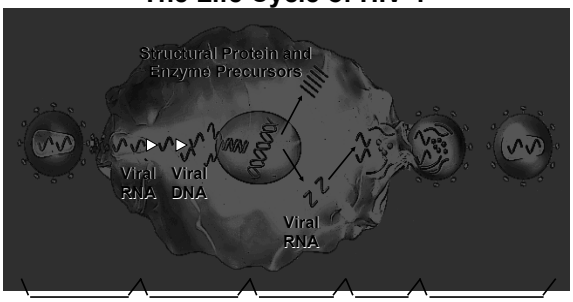
- Zidovudine (ZDV, AZT)
- Didanosine (ddI)
- ~~Zalcitabine (ddC)~~
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

→ nsRTI's

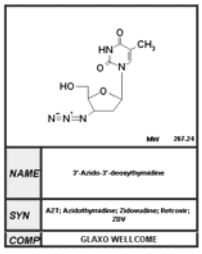
- Tenofovir disoproxil fumarate (TDF) → ntRTI

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

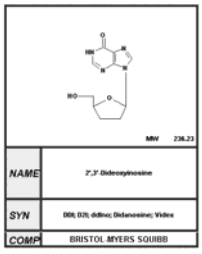
The Life Cycle of HIV-1



Nucleoside Analog RT Inhibitors



Zidovudine

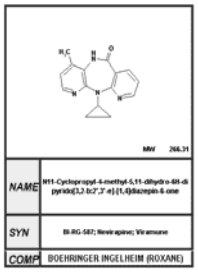


Didanosine

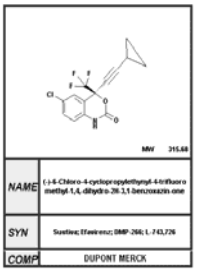
Nucleoside Analog RT Inhibitors

- 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

Non-Nucleoside RT Inhibitors



Nevirapine



Efavirenz

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

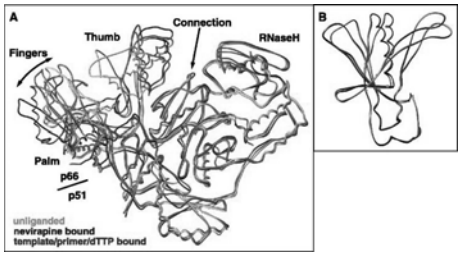
Non-Nucleoside RT Inhibitors

- 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

Non-Nucleoside RT Inhibitors

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

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

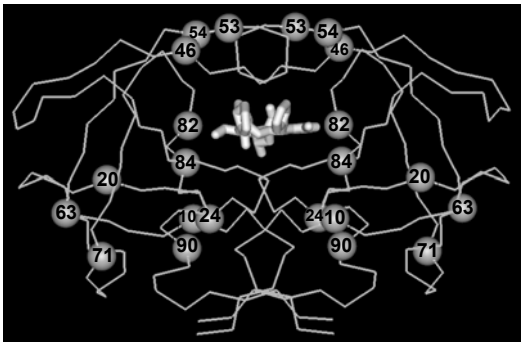
- Third class of anti-HIV agents developed
- Potent
  - Revolutionized therapy following introduction in 1996
- Active vs. HIV-1 and HIV-2
- Mechanism
  - PI's inhibit the HIV protease by binding to active site and preventing the cleavage of gag and gag-pol precursor polyproteins
  - Virions are produced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

Protease Inhibitors

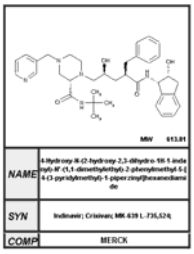
- Saquinavir (SQV)*
- Ritonavir (RTV)
- Indinavir (IDV)*
- Nelfinavir (NFV)
- ~~Amprenavir (APV)~~*
- Lopinavir/ritonavir (LPV/r)*
- Atazanavir (ATV)*
- Fosamprenavir (fos-APV)*
- Tipranavir (TPV)*
- Darunavir (DRV)*

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

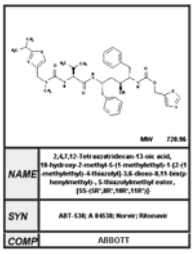
Protease Structure: Mutations Associated With Reduced *in vitro* Susceptibility to Lopinavir



Protease Inhibitors



Indinavir



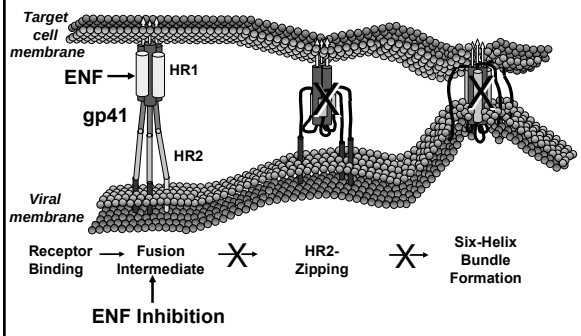
Ritonavir

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

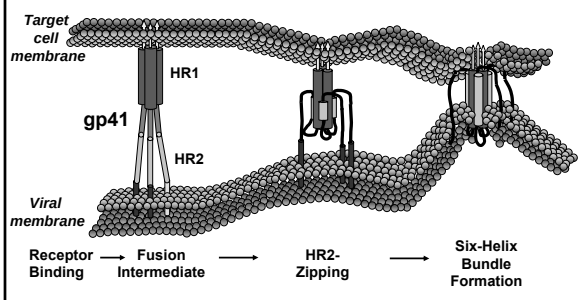
Enfuvirtide Inhibition of HIV Fusion



Enfuvirtide (Fusion Inhibitor): Mechanism of Action

CCR5 Antagonist: Maraviroc

Model for HIV-Cell Fusion

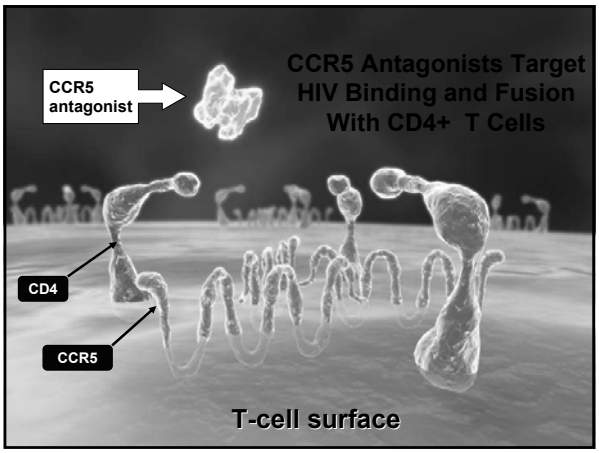


Percentage of HIV Co-receptor Usage

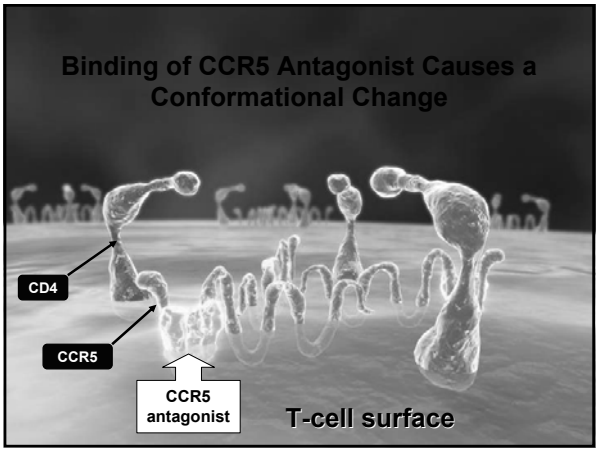
Study/Source	Population	N	R5	X4	R5/X4
Homer cohort[1]	Naive	979	82%	<1%	18%
C & W cohort[2]	Naive	402	81%	<1%	19%
Demarest[3]	Naive	299	88%	0%	12%
TORO 1/2[4]	Experienced	612	62%	4%	34%
ViroLogic[5]	Experienced	>2000	48%	2%	50%
ACTG 5211[6]	Experienced	391	49%	4%	47%

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

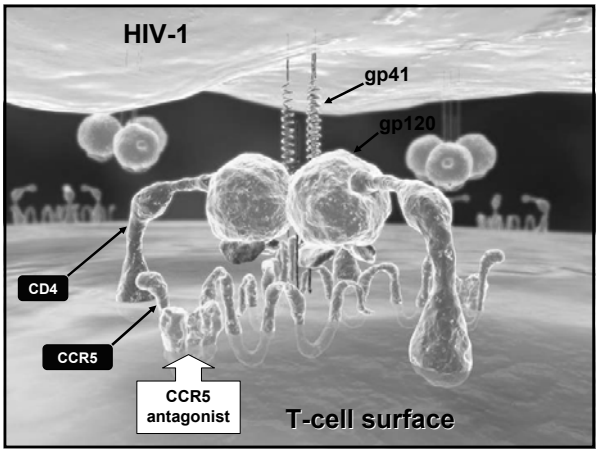
[1]Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474.
[2]Moyle GJ, et al. *J Infect Dis.* 2005;191:866-872.
[3]Demarest J, et al. *ICAAC* 2004. Abstract H-1136.
[4]Whitcomb JM, et al. *CROI* 2003. Abstract 557.
[5]Paxinos EE, et al. *ICAAC* 2002. Abstract 2040.
[6]Wilkin T, *et al. CROI* 2006. Abstract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



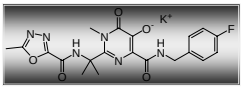
Integrase Inhibitor: Raltegravir



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®)

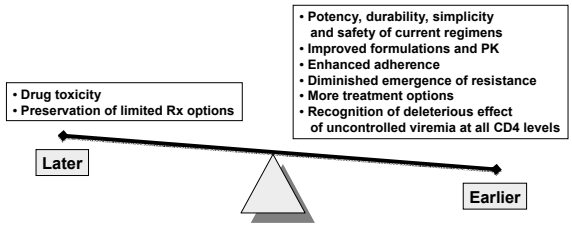
Rationale for Initiation of Therapy Before CD4 Cell Counts Fall to 350/µL

- 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

"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

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



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

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

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

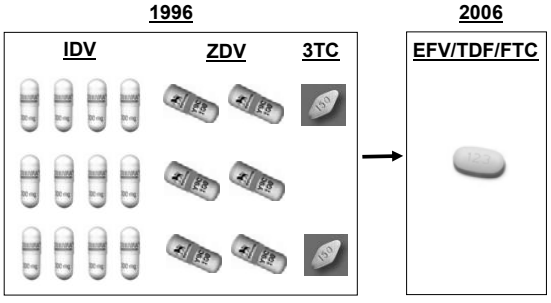
Choice of Initial Regimen (cont'd)

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

Reasons for Drug Failure

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

Simplification of Therapy



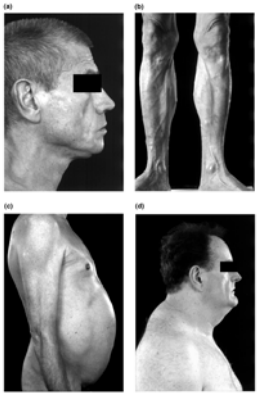
Limitations of Currently Available Agents

- 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

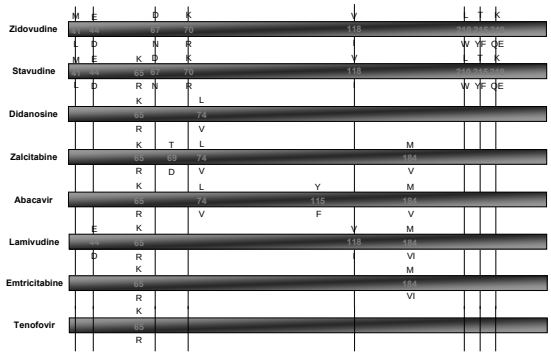
HIV Resistance: Underlying Concepts

- 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

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

Mutations Selected by nRTIs/ntRTIs I

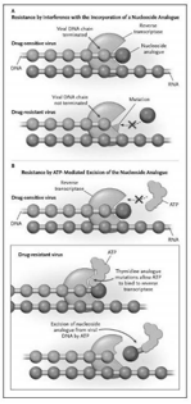


www.iasusa.org

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

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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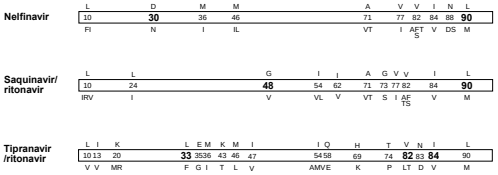
Mutations Selected by PIs (cont'd)



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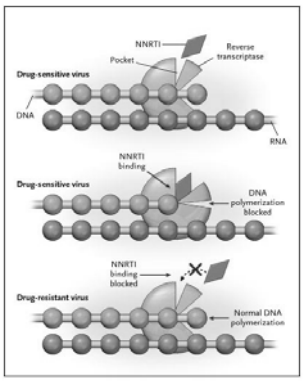
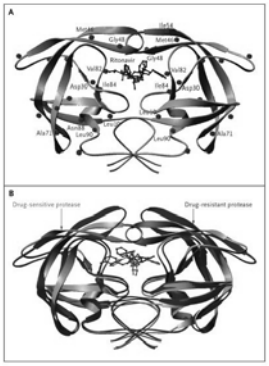
Mechanism of Resistance of HIV to Nonnucleoside Reverse-Transcriptase Inhibitors



The NEW ENGLAND JOURNAL of MEDICINE

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

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)



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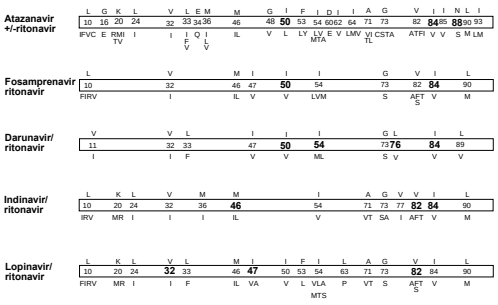
Mutations Selected by PIs



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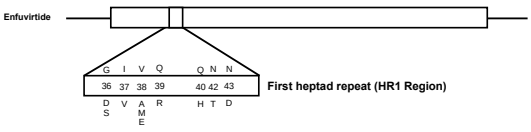
Mutations in the gp41 Envelope Gene Associated With Resistance to Enfuvirtide



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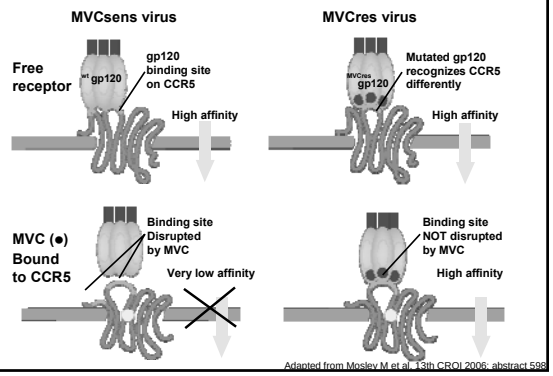
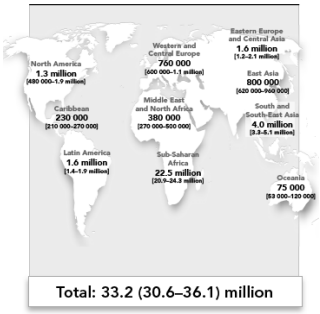
Maraviroc Resistance



Adapted from Mosley M et al. 13th CROI 2006; abstract 598

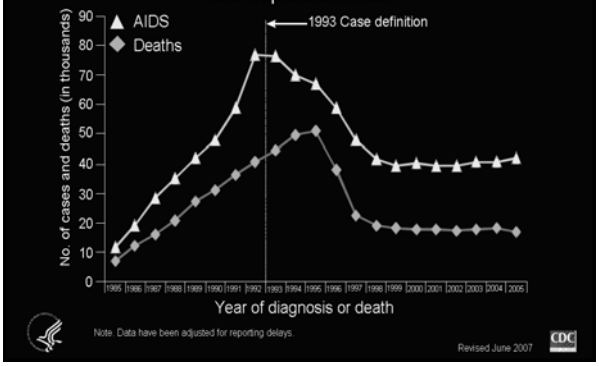
Adults and Children Estimated to be Living with HIV in 2007



Total: 33.2 (30.6–36.1) million

UNAIDS

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2005—United States and Dependent Areas

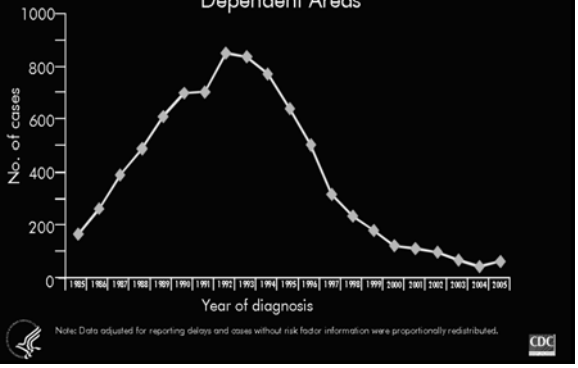


Note: Data have been adjusted for reporting delays.

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.

CDC