

Antiretroviral Drugs in the Treatment and Prevention of HIV Infection

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Uses of Antiretroviral Agents

- Treatment of chronic HIV infection
- Prevention of mother-to-child transmission [PMTCT]
- Occupational and non-occupational post-exposure prophylaxis [PEP]
- Acute HIV infection
- Pre-exposure prophylaxis [PrEP]
- Epidemiological control

Antiretroviral Drugs: General Principles

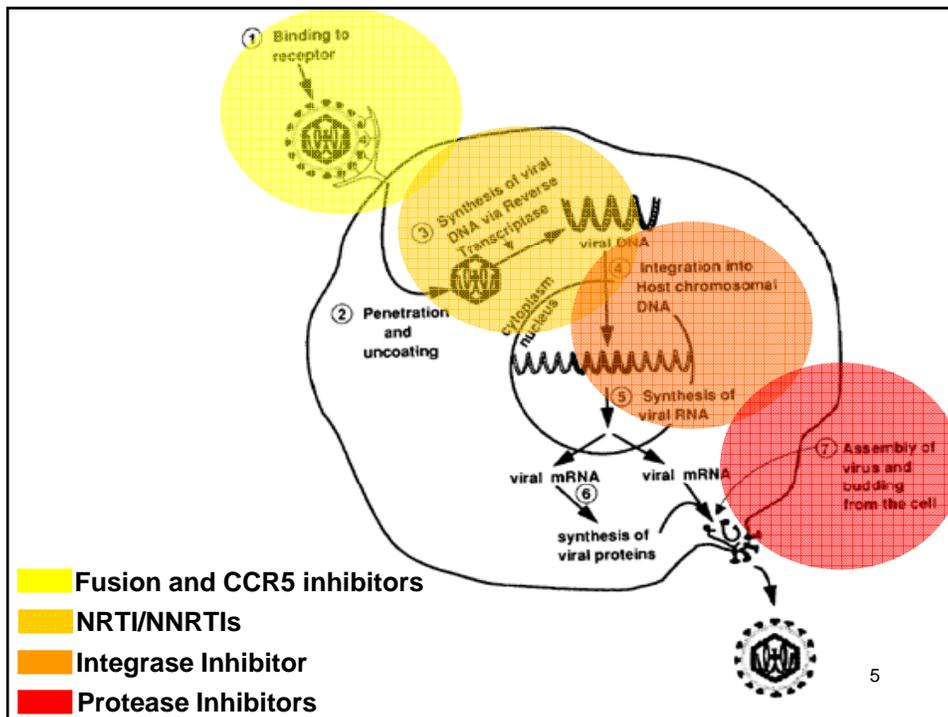
- There are 7 classes of FDA-approved antiretroviral agents and 22 individual drugs
- Antiretroviral agents must be used in combination for effective treatment of HIV infection
- Highly Active Antiretroviral Therapy [HAART] has led to life expectancies approaching the general population
- Drug toxicities and the emergence of drug resistance compromise the efficacy of antiretroviral agents

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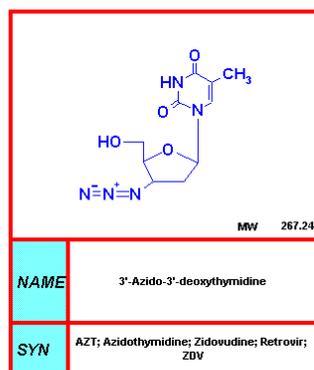
FDA-approved Antiretroviral Classes

- Nucleoside reverse transcriptase inhibitors (NsRTIs)
- Nucleotide reverse transcriptase inhibitor (NtRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Fusion inhibitor
- CCR5 antagonist
- Integrase inhibitor

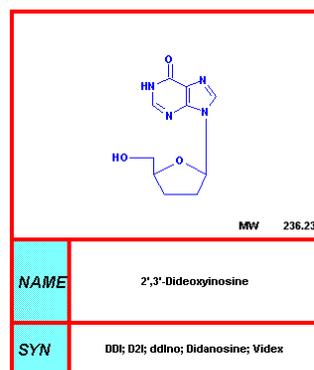
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Nucleoside Reverse Transcriptase Inhibitors



Zidovudine



Didanosine

Nucleoside Reverse Transcriptase Inhibitors

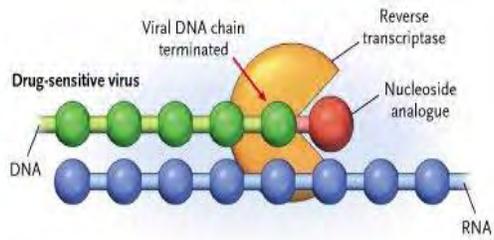
- First class of antiretrovirals developed
- Must undergo intracellular triphosphorylation to become active against HIV
- Mechanism of action
 - NRTI's compete with host nucleotides to serve as the substrate for reverse transcriptase chain elongation
 - Absence of 3'-OH group on sugar moiety prevents the addition of another nucleotide resulting in chain termination
 - Viral DNA chain elongation is aborted and viral replication ceases
- Adverse effects: nausea, headache, lactic acidosis, anemia (AZT), peripheral neuropathy, pancreatitis, lipodystrophy

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Nucleotide Reverse Transcriptase Inhibitor

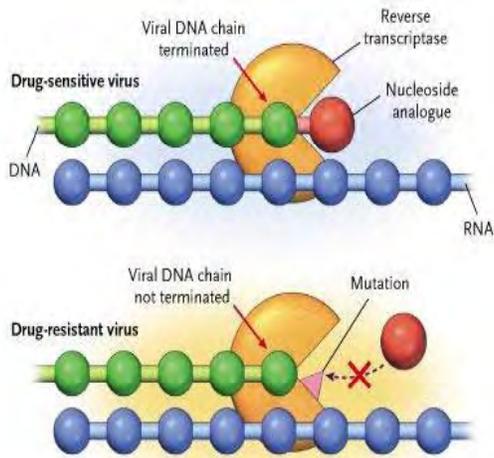
- One drug in class: tenofovir disoproxil fumarate (TDF)
- NtRTI is similar in its mechanism of action to the NsRTI's: it acts as a DNA chain terminator
- Tenofovir contains a phosphate group and therefore only requires diphosphorylation to become active
- Adverse effects: nephrotoxicity, Fanconi's syndrome, bone mineralization disorders

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Clavel F. *N Engl J Med* 2004



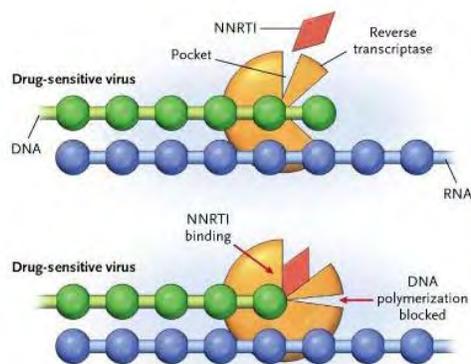
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Clavel F. *N Engl J Med* 2004

Non-Nucleoside Reverse Transcriptase Inhibitors

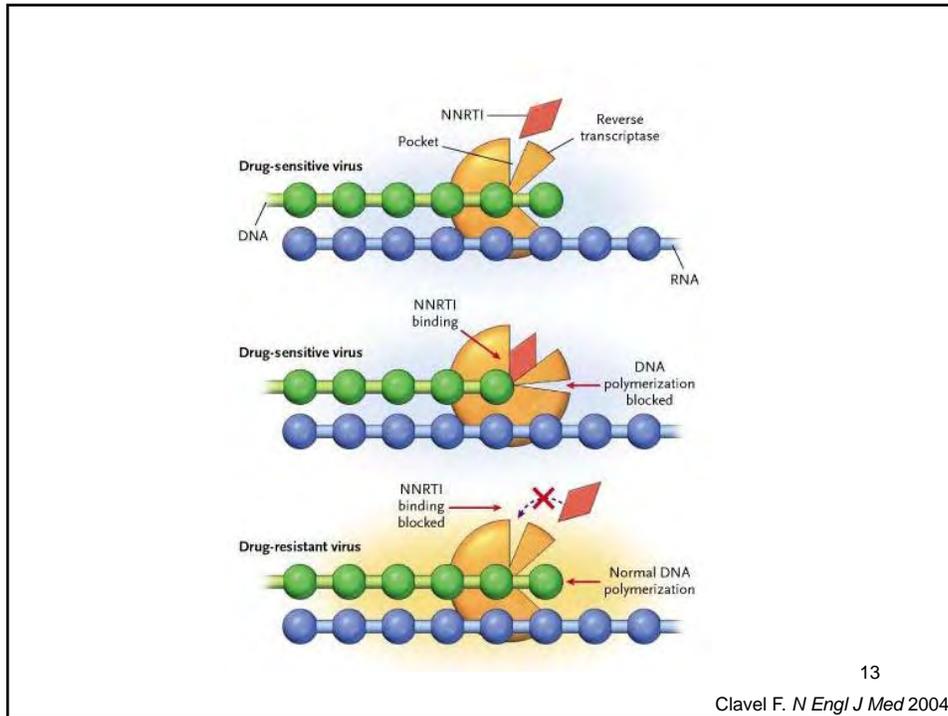
- Second class of antiretroviral agents developed
- Mechanism of action:
 - NNRTI's inhibit the HIV reverse transcriptase by binding a hydrophobic pocket close to the active site
 - Lock the enzyme's active site in an inactive conformation
- Potent but subject to rapid emergence of resistance
- Active against HIV-1 but NOT active against HIV-2

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Clavel F. *N Engl J Med* 2004



NNRTI's: Drug Interactions and Adverse Effects

- Metabolized by CYP3A4 isoenzyme of the hepatic cytochrome p450 system
- Are *either* potent inducers or inhibitors of CYP3A4
- Potential for major drug interactions with HIV and non-HIV agents, including antimycobacterials
- Adverse effects: rash, hepatotoxicity, neurocognitive impairment (efavirenz), teratogenicity (efavirenz)

Protease Inhibitors

- Third class of antiretroviral agents developed
- Revolutionized therapy following introduction in 1995
- Mechanism of action:
 - Inhibit HIV protease by binding to its active site, preventing the cleavage of gag and gag-pol precursor proteins
 - Virions are produced but they are incomplete and non-infectious
- Side effects: abdominal upset, diarrhea, dyslipidemia, lipodystrophy, atherosclerosis

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Protease Inhibitors: Drug Interactions

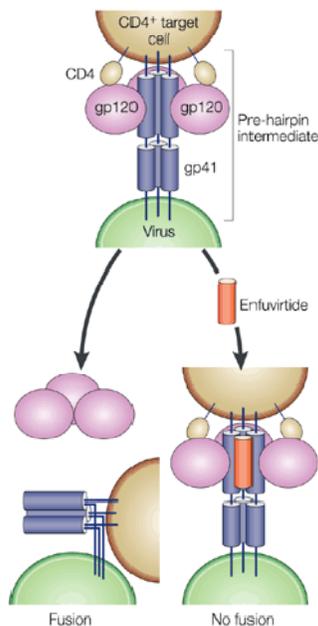
- Metabolized by the CYP3A4 isoenzyme of the hepatic p450 system
- Are inhibitors of CYP3A4 to varying degrees
- Ritonavir is one of the most potent CYP3A4 inhibitors known and is used to “boost” levels of other PI’s
- Potential for major drug interactions with numerous HIV and non-HIV drugs

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Entry Inhibitors

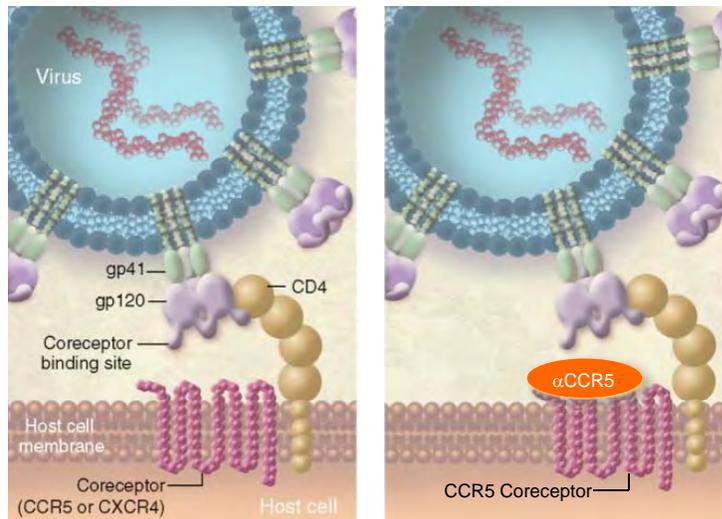
- Fusion inhibitor prevents entry by binding to glycoprotein on the viral envelope
 - One in a class: Enfuvirtide, T20
 - Binds to the gp41 envelope glycoprotein
 - Injectable only
- CCR5 antagonist prevents entry by binding to the chemokine coreceptor on the host CD4+ cell
 - One in a class: Maraviroc
 - Binds to CCR5 coreceptor
 - Active against CCR5 tropic virus only

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LaBonte J. *Nat Rev Drug Dis* 2003



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Percentage of HIV Co-receptor Use

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%

¹Brumme ZL *J Infect Dis.* 2005

²Moyle GJ *J Infect Dis.* 2005

³Demarest J *JCAAC* 2004. Abstract H-1136

⁴Whitcomb JM, *CROI* 2003. Abstract 557

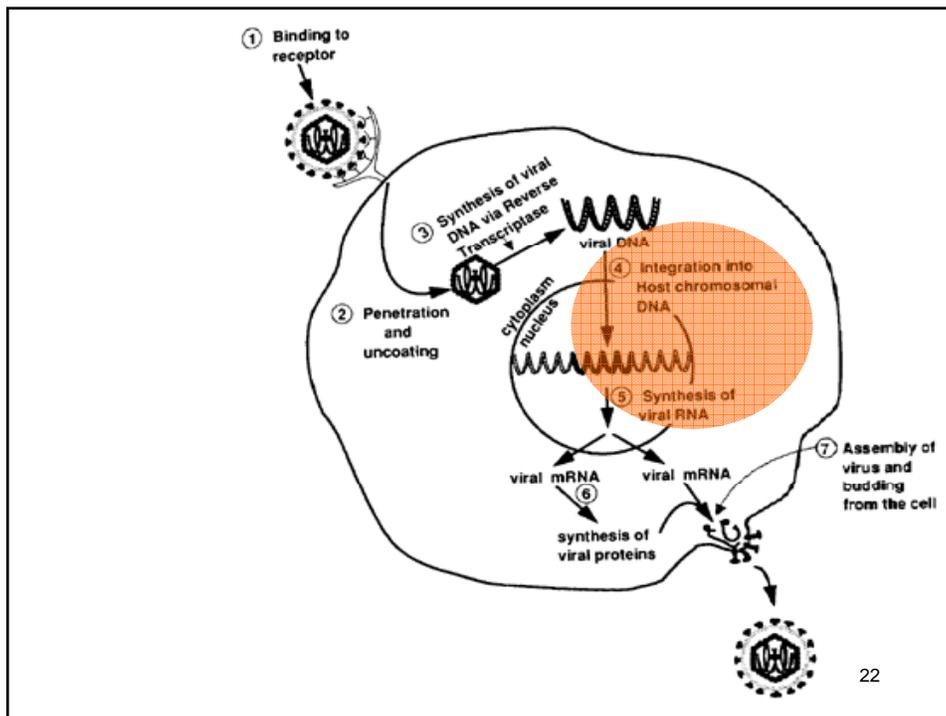
⁵Paxinos EE, *ICAAC* 2002. Abstract 2040

⁶Wilkin T, *et al.* *CROI* 2006. Abstract 655

Integrase Inhibitor

- One drug in class: Raltegravir
- Mechanism of action
 - Inhibits DNA strand transfer into host-cell genome and thus prevents viral integration
 - Very potent in-vitro and in-vivo
- Does not confer resistance to other ART classes
- Works synergistically with all ART's studied
- Has few side effects and drug interactions

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Treatment of Chronic HIV Infection: When to Start?

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Treatment of Chronic HIV Infection: When to Start?

- Patient's disease stage
 - Symptomatic status
 - CD4 cell count <350
 - Plasma HIV RNA level
 - Presence of, or risk factors for, "non-AIDS" conditions such as cardiovascular, hepatic and renal disease
- Patient's commitment to therapy
- Philosophy of treatment
 - Pros and cons of 'early' intervention
 - Treatment is for lifetime

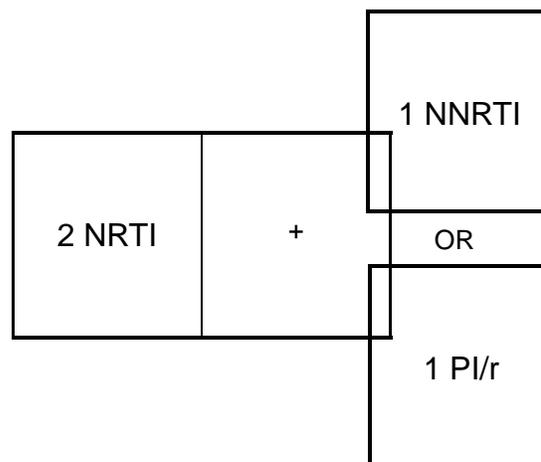
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Treatment of Chronic HIV Infection: What to Start?

- Resistance testing is now recommended at baseline due to high prevalence of primary drug resistance
- Assess for pregnancy, desire for, or potential for pregnancy
- Evaluate for viral co-pathogens, namely hepatitis B or C co-infection
- Determine presence of comorbid conditions such as diabetes, hyperlipidemia, coronary artery disease and renal disease

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What to Start? First Line Antiretroviral Therapy



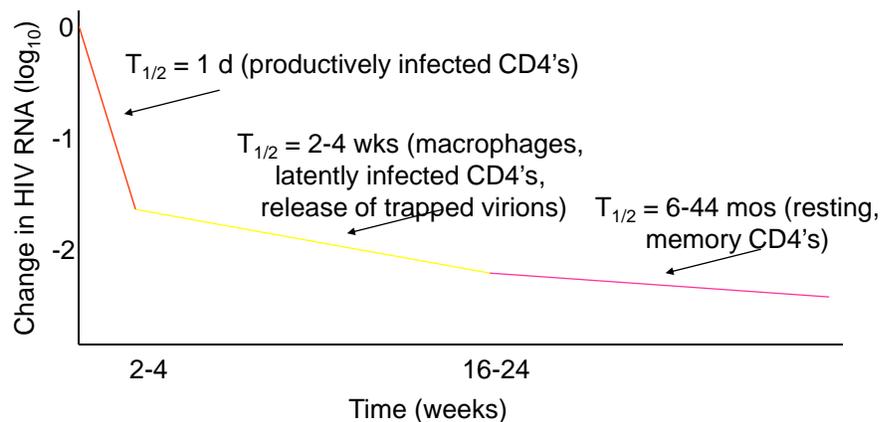
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Goals of Antiretroviral Treatment and Definition of Treatment Failure

- Goals:
 - Virological suppression as measured by an undetectable viral load
 - Immune reconstitution as measured by a rise in CD4+ count
 - Clinically, a decrease in HIV associated morbidity and mortality
- Failure:
 - Virological failure is defined as a rise in VL or failure to achieve virological suppression
 - Immunological failure is defined as a decline in CD4 cell count or a failure of the CD4+ cell count to rise
 - Clinical failure to prevent opportunistic, neoplastic and other HIV-related complications

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Phases of Viral Decay with Antiretroviral Therapy



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Limitations of Currently Available Agents

- Toxicities and adverse effects
- Emergence of resistance
- Negative effects on quality of life, “treatment fatigue”
- Drug-class cross resistance
- Drug interactions (esp NNRTIs, PIs and CCR5 blocker)
- Complexity of “salvage regimens”
- Cost, especially in “resource limited” settings

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Causes of Treatment Failure

- Emergence of or baseline drug resistance
- Incomplete adherence
- Variable pharmacologic metabolism
- Insufficiently potent regimens
- Viral sanctuaries
- Host immune status

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HIV Resistance: Underlying Concepts

- Genetic variants are continuously produced due to the high error rate of reverse transcriptase
- Mutations at each codon site occur daily and numerous natural polymorphisms exist
- Resistance mutations exist before drug exposure and are selected for when drug is introduced
- In general, resistance mutations do not persist in the absence of drug because they are associated with decreased viral fitness

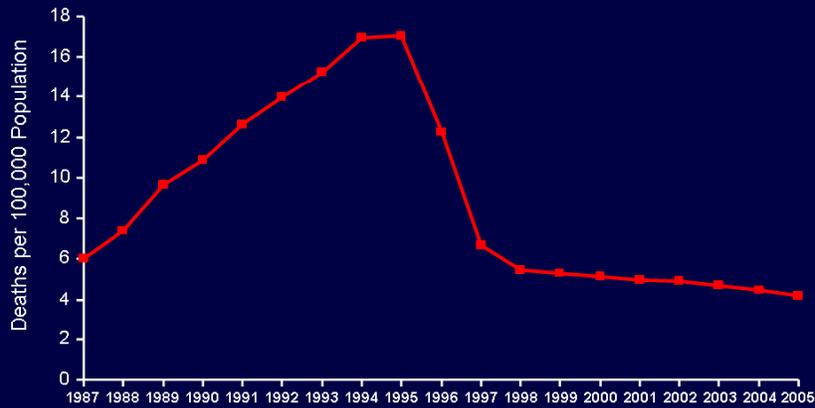
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HIV Resistance: Implications

- Survival of drug mutants depends on *replication competence* and the presence of *selective pressure*
- Drugs to which high-level resistance emerges due to a single mutation with minimal impact on replication capacity are most vulnerable
- Resistance to agents which require multiple mutations will evolve more slowly
- Partially suppressive regimens will inevitably lead to emergence of resistance

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Trends in Annual Age-Adjusted* Rate of Death due to HIV Disease, United States, 1987–2005



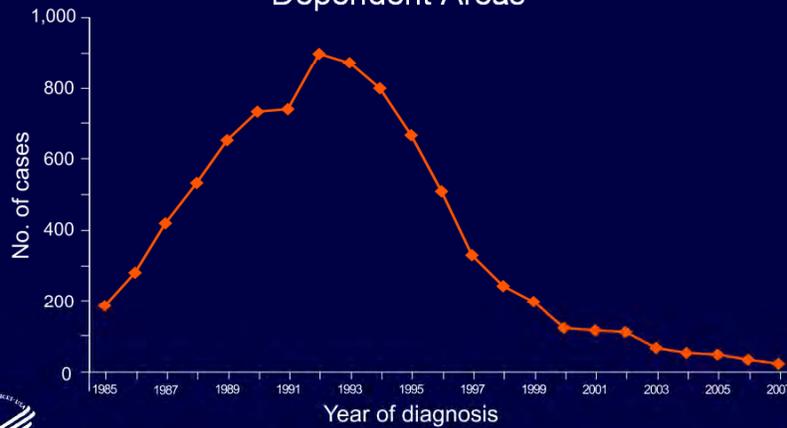
Note: For comparison with data for 1999 and later years, data for 1987–1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
*Standard: age distribution of 2000 US population



Prevention of Mother to Child Transmission

- In 1994, PACTG 076 showed a reduction in HIV transmission from 25% to 8% in women and infants treated with zidovudine monotherapy vs placebo
- Subsequently, trials of HAART have shown reductions in transmission to rates as low as 1-2%
- Use of monotherapy or dual therapy continues in resource-poor settings and is associated with reduced transmission but high rates of resistance
- All pregnant women should be offered HIV treatment for PMTCT if not already receiving treatment

Estimated Numbers of Perinatally Acquired AIDS Cases by Year of Diagnosis, 1985–2007—United States and Dependent Areas



Note. Data have been adjusted for reporting delays and missing risk-factor information.



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Post-exposure prophylaxis [PEP]

- Occupational
 - Data is limited to a case-control trial and epidemiological surveillance
 - Zidovudine monotherapy reduced the rates of HIV transmission by ~80% in health care workers
 - Rates of transmission for percutaneous exposure are low, estimated at 0.3%
 - Current guidelines in the State of New York recommend combination antiretroviral therapy in cases of exposure
- Non-occupational:
 - Sexual assault, barrier protection breakage, IDU
 - Time is of the essence! nPEP recommended within 72 hours

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Cardo DM, *N Engl J Med* 1997

Treatment of Acute HIV Infection

- Acute HIV infection [AHI] refers to the event of exposure to and acquisition of HIV infection
- AHI is associated with extremely high levels of viremia and infectiousness
- Irreversible damage to the CD4+ T cell compartment occurs during AHI, especially in gut-associated lymphatic tissue
- It has been suggested that treatment of HIV during acute infection may:
 - Protect CD4+ T cells from destruction
 - Reduce the viral load set point and slow disease progression
 - Prevent transmission of HIV

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Pre-Exposure Prophylaxis [PrEP]

- PrEP refers to the use of antiretrovirals prior to an exposure to HIV
- This strategy involves the timed use of antiretrovirals prior to sexual intercourse
- Mathematical models have shown this to be a potentially useful strategy but no RCT's have been published
- Antiretroviral containing microbicides are another use of ART in the prevention of sexual transmission

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Antiretroviral Treatment in the Control of the HIV Epidemic

- The propagation of an epidemic depends on the reproduction number (R_0) being ≥ 1
- A higher mean HIV RNA in a community is associated with a higher R_0
- Universal treatment would lower mean viral loads and reduce HIV transmission and incidence
- A recent mathematical model suggests that a “test and treat” strategy may lead to the elimination of a generalized HIV epidemic

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Granich M. *Lancet* 2009

Summary

- Antiretroviral therapy has led to a sustained decline in HIV-associated mortality
- Where HAART is available life expectancy is now approaching the general population
- The efficacy of antiretrovirals is compromised by toxicity, resistance and incomplete adherence
- Antiretroviral use is not limited to treatment of chronic infection and indications may continue to expand
- Antiretrovirals do not replace active and multifaceted efforts at HIV prevention

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