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

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
Nucleoside Reverse Transcriptase Inhibitors

- **NAME**: Zidovudine
  - **SYN**: AZT, Aciviradine; ZDV

- **NAME**: Didanosine
  - **SYN**: ddI, Dideoxinosine; Videx

**Diagram Notes:**
- Fusion and CCR5 inhibitors
- NRTI/NNRTIs
- Integrase Inhibitor
- Protease Inhibitors
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

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
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
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

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
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
### Percentage of HIV Co-receptor Use

<table>
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<tr>
<th>Study/Source</th>
<th>Population</th>
<th>N</th>
<th>R5</th>
<th>X4</th>
<th>R5/X4</th>
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<tr>
<td>Homer cohort¹</td>
<td>Naive</td>
<td>979</td>
<td>82%</td>
<td>&lt;1%</td>
<td>18%</td>
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<tr>
<td>C &amp; W cohort²</td>
<td>Naive</td>
<td>402</td>
<td>81%</td>
<td>&lt;1%</td>
<td>19%</td>
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<tr>
<td>Demarest³</td>
<td>Naive</td>
<td>299</td>
<td>88%</td>
<td>0%</td>
<td>12%</td>
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<td>TORO 1/2⁴</td>
<td>Experienced</td>
<td>612</td>
<td>62%</td>
<td>4%</td>
<td>34%</td>
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<tr>
<td>ViroLogic⁵</td>
<td>Experienced</td>
<td>&gt;2000</td>
<td>48%</td>
<td>2%</td>
<td>50%</td>
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<tr>
<td>ACTG 5211⁶</td>
<td>Experienced</td>
<td>391</td>
<td>49%</td>
<td>4%</td>
<td>47%</td>
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</tbody>
</table>

1Brumme ZL. J Infect Dis. 2005
2Moyle GJ. J Infect Dis. 2005
3Demarest J. ICAAC 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
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
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

What to Start? 
First Line Antiretroviral Therapy

2 NRTI + 1 NNRTI
OR 1 PI/r
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

Phases of Viral Decay with Antiretroviral Therapy

- $T_{1/2} = 1 \text{ d (productively infected CD4's)}$
- $T_{1/2} = 2-4 \text{ wks (macrophages, latently infected CD4's, release of trapped virions)}$
- $T_{1/2} = 6-44 \text{ mos (resting, memory CD4's)}$
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

Causes of Treatment Failure

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

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
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
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

*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

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
Antiretroviral Treatment in the Control of the HIV Epidemic

- The propagation of an epidemic depends on the reproduction number (R0) being ≥ 1
- A higher mean HIV RNA in a community is associated with a higher R0
- 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

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