Antiretroviral Agents

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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 (NRTI’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
  - Toxocities
  - 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

Zidovudine
Didanosine

The Life Cycle of HIV-1

1. Binding and infection
2. Reverse transcription and integration of viral DNA
3. Transcription and translation
4. Modification and assembly
5. Budding and final assembly
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
  - Competitive 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)

HIV RT: Structure

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)*

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

Antiretroviral Agents Approved in the U.S.

<table>
<thead>
<tr>
<th>Nucleoside RTI's</th>
<th>Non-Nucleoside RTI's</th>
<th>Protease Inhibitors</th>
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<tbody>
<tr>
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<td>Tenofovir DF (TDF)</td>
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<td>Enfuvirtide (T-20)</td>
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</table>

Model for HIV-Cell Fusion

Initiation of Therapy: Regimens

- Non-nucleoside RTI + 2 nucleoside RTI's
  - Newer options
    - NNRTI + 1 NtRTI + 1 NsRTI
      - Not all such combinations are effective
      - High virologic failure rate recently reported with NNRTI+2 NsRTI+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 has shown ZDV+3TC/ABC to be inferior to two other combined arms (EFZ+ZDV/3TC, EFZ+ZDV/3TC/ABC) - study still ongoing
    - 27% vs. 10% virologic failure rate at 24 wks
  - Data on other triple NRTI options also problematic
    - e.g., 2 NtRTI + NsRTI
      - 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 + NRTI??
    - PI and NNRTI sparing
    - Response suboptimal in patients with RNAa >100,000

Enfuvirtide Inhibition of HIV Fusion

- 3 Nucleoside RTI's
  - PI and NNRTI sparing
    - No longer a preferred first line option
    - Data from A5095 has shown ZDV+3TC/ABC to be inferior to two other combined arms (EFZ+ZDV/3TC, EFZ+ZDV/3TC/ABC) - study still ongoing
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    - PI and NNRTI sparing
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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

Drug Failure

- Drug Resistant Variants
- Subinhibitory Drug Levels
- Host Immune Failure

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

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

Reasons for Drug Failure

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

Antiretroviral Therapy Related Lipodystrophy

- Lipoatrophy
- Lipoaccumulation

Mallon FWG, Cooper DA, and Carr A: HIV Medicine 2001;2:1488-1293
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 naive individuals
    - Single and double mutants pre-exist
    - Triple and quadruple mutants would be predicted to be rare

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

- Zidovudine
- stavudine
- Didanosine
- Zalcitabine
- Abacavir
- Lamivudine
- Stavudine
- Emtricitabine
- Tenofovir

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, NNRTIs (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
**Nucleoside Analog Resistance**

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<tr>
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<tbody>
<tr>
<td>Confer ZDV resistance thru ZDV-MP excision</td>
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<tr>
<td>Confers 3TC resistance thru decreased 3TC-TP incorporation</td>
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**Pyrophosphorolysis**

\[
\text{R} = \text{H} \quad \text{or} \quad \text{AMP} \quad \text{(ATP-dependent phosphorolysis)}
\]

\[
\begin{align*}
&\text{Antagonize K65R} \\
&\text{Decreases ZDV resistance thru decreased ZDV-MP excision} \\
&\text{Decreases ZDV resistance thru decreased ZDV-MP excision}
\end{align*}
\]

**Mutations Selected by NNRTIs**

**Mutations Selected by PIs**
Mutations in the gp41 Envelope Gene Associated With Resistance to Enfuvirtide

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-6, UK-427857, TAK 220, GW873140/AK-602, AMD887)
    - CXCR4 (AMO 070, KRD-2731)
  - Fusion inhibitors (ENF [T-20], T-1249, 5-Helix)
  - TNX-355

- Integrase inhibitors
  - MK-0918, RSC-1838, V-165

- Gag processing inhibitor
  - PA-457

Estimated incidence of AIDS and Deaths among Adults and Adolescents with AIDS, 1985–2002—United States

Note: Adjusted for reporting delays.
## Adults and Children Estimated to be Living with HIV as of End 2004

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated HIV+ Population</th>
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<tbody>
<tr>
<td>West &amp; Central Europe</td>
<td>610,000 (480,000 – 760,000)</td>
</tr>
<tr>
<td>North Africa &amp; Middle East</td>
<td>540,000 (230,000 – 1.5 million)</td>
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<tr>
<td>Sub-Saharan Africa</td>
<td>25.4 million (23.4 – 28.4 million)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>1.4 million (920,000 – 2.1 million)</td>
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<tr>
<td>Latin America</td>
<td>1.7 million (1.1 – 2.6 million)</td>
</tr>
<tr>
<td>South &amp; South East Asia</td>
<td>7.1 million (6.8 – 7.5 million)</td>
</tr>
<tr>
<td>Oceania</td>
<td>35,000 (25,000 – 48,000)</td>
</tr>
<tr>
<td>North America</td>
<td>1.0 million (540,000 – 1.6 million)</td>
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<tr>
<td>Caribbean</td>
<td>440,000 (270,000 – 780,000)</td>
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<tr>
<td>South Asia</td>
<td>1.1 million (0.9 – 1.3 million)</td>
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<tr>
<td>Total</td>
<td>39.4 (35.9 – 44.3) million</td>
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*Source: UNAIDS*