Antiretroviral Therapy

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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 (NRTIs)
  - Nucleotide analog reverse transcriptase inhibitors (NtRTIs)
  - 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

1986 1990
ZDV monoRx
Alternative NRTI monoRx
Combination NRTI Rx
Antiretroviral resistance
Pathogenetic concepts

1990 1995
End of ZDV monoRx era
Benefit of combination Rx proven
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
Sweings in approach to Rx
ARV rollout in developing countries

Evolution of Antiretroviral Therapy

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 (ns) and Nucleotide (nt) Analog RT Inhibitors

- Zidovudine (ZDV, AZT)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir disoproxil fumarate (TDF) → ntRTI

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

Antiretroviral Therapy

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

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
**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 \textit{in vitro} Susceptibility to Lopinavir**

**Protease Inhibitors**

- 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

<table>
<thead>
<tr>
<th>Study/Source</th>
<th>Population</th>
<th>N</th>
<th>RS</th>
<th>R5</th>
<th>X4</th>
<th>RS/X4</th>
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<tr>
<td>Homer cohort</td>
<td>Naive</td>
<td>979</td>
<td>82%</td>
<td>&lt;1%</td>
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<td>C &amp; W cohort</td>
<td>Naive</td>
<td>402</td>
<td>81%</td>
<td>&lt;1%</td>
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<td>Demarest</td>
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<td>299</td>
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<td>0%</td>
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<tr>
<td>TORO 1/2*</td>
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<td>612</td>
<td>62%</td>
<td>4%</td>
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<td>ViroLogic</td>
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<td>&gt;2000</td>
<td>48%</td>
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<tr>
<td>ACTG 5211</td>
<td>Experienced</td>
<td>391</td>
<td>49%</td>
<td>4%</td>
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*This table may not include all available reported data. Majority of data are generated in the developed world (subtype B)

CCR5 Antagonists Target HIV Binding and Fusion With CD4+ T Cells

Binding of CCR5 Antagonist Causes a Conformational Change

HIV-1

Integrase Inhibitor: Raltegravir

HIV Integration

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
  - IC50 = 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)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

Non-Nucleoside RTI's
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)
- Etravirine (ETV)

Integrase Inhibitor
-Raltegravir (RAL)

Nucleoside RTI
- Tenofovir DF (TDF)

Non-Nucleoside RTI's
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- 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 (Stribild®); 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/µm³)
  - 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 Antiretroviral Therapy

<table>
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<tr>
<th>Measure</th>
<th>Recommendation</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Symptomatic HIV disease</td>
<td>Therapy recommended</td>
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</tr>
<tr>
<td>Asymptomatic HIV disease</td>
<td>Therapy recommended</td>
<td>Recommendation strengthened since 2006</td>
</tr>
<tr>
<td>CD4 &lt;350/µL</td>
<td>Therapy recommended</td>
<td></td>
</tr>
<tr>
<td>CD4 ≥350</td>
<td>Therapy should be considered and decision individualized</td>
<td>Examples:</td>
</tr>
</tbody>
</table>

- Presence of, or high risk for, cardiovascular disease
- Active HIV or HCV coinfection
- HIV-associated nephropathy

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 Therapy: Balance Tipping in Favor of Earlier Initiation
- Drug toxicity
- Preservation of limited Rx options

- Early
- Drug toxicity
- Preservation of limited Rx options

Later
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 
  - 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)

<table>
<thead>
<tr>
<th>Component</th>
<th>Drugs</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI component</td>
<td>efavirenz</td>
<td>- EFV: teratogenic in 1st trimester</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- NVP (alternative): increased risk of hepatotoxicity in women with CD4 &gt;250/µl and men with CD4 &gt;400/µl</td>
</tr>
<tr>
<td>PI/r component</td>
<td>lopinavir/r, atazanavir/r, fosamprenavir/r, darunavir/r or saquinavir/r</td>
<td>- ATV/r: diminished hyperlipidemic potential; care with antacids</td>
</tr>
<tr>
<td></td>
<td>abacavir/lamivudine</td>
<td>- DRV/r: important role in treatment-experienced patients</td>
</tr>
<tr>
<td>Dual nRTI</td>
<td>tenofovir/emtricitabine</td>
<td>- ZDV/3TC: alternative to decrease risk of HSR:</td>
</tr>
<tr>
<td></td>
<td>or abacavir/tamivudine</td>
<td>- Increased risk of cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ABC/3TC: efficacy when viral load &gt;100,000 c/ml</td>
</tr>
</tbody>
</table>

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

Simplification of Therapy

<table>
<thead>
<tr>
<th>1996</th>
<th>2006</th>
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<tbody>
<tr>
<td>IDV</td>
<td>ZDV</td>
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<tr>
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MID 41
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: $10^6$-$10^{10}$/day
- RT error rate: $10^{-4}$-$10^{-5}$/base/cycle
- HIV genome: $10^4$ bp
- Every point mutation occurs $10^4$-$10^8$ times/day
Mutations Selected by NNRTIs

Mutations Selected by PIs (cont'd)

Mechanism of Resistance of HIV to Nonnucleoside Reverse-Transcriptase Inhibitors

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)

Mutations in the gp41 Envelope Gene Associated With Resistance to Enfuvirtide
Maraviroc Resistance

MVCsens virus

- gp120 binding site on CCR5
- High affinity

MVCres virus

- Mutated gp120 recognizes CCR5 differently
- High affinity

Free receptor

MVC (•) Bound to CCR5

- Binding site disrupted by MVC
- Very low 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

Years of diagnosis or death

Note: Data have been adjusted for reporting delays.

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

No. of cases

Note: Data include only the first AIDS diagnosis in a person's medical record.

MID 41