Treatment of HIV-1 in Adults and Adolescents: Part 1

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Lecture Outline
- FDA approved antiretroviral agents
- Clinical evaluation strategies
- Initiating treatment
- Case discussion

Approved Antiretroviral Agents
- Entry inhibitors (1)
  - Fusion inhibitors (1)
- Reverse transcriptase inhibitors (11)
  - Nucleoside and nucleotide analogs (8)
  - Non-nucleosides (3)
- Protease inhibitors (7)
- Fixed-dose combination products (5)

Entry Inhibitors
- Enfuvirtide (Fuzeon; T-20)
  - Fusion inhibitor
- Adult dose: 90 mg (1mL) SC bid
- Only injectable antiretroviral agent available
- Used in treatment experienced patients

"The HIV-1 Life-cycle"
### Reverse Transcriptase Inhibitors

#### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Acronym</th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th>#/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>ABC</td>
<td>300 or 600</td>
<td>bid or qd</td>
<td>2</td>
</tr>
<tr>
<td>didanosine</td>
<td>ddi</td>
<td>≥ 60 kg; 400 or 250</td>
<td>qd</td>
<td>1 (EC) or 2 (buff)</td>
</tr>
<tr>
<td></td>
<td>ddI EC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>emtricitabine</td>
<td>FTC</td>
<td>200</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>lamivudine</td>
<td>3TC</td>
<td>150 or 300</td>
<td>bid or qd</td>
<td>1-2</td>
</tr>
</tbody>
</table>

#### Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Acronym</th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th>#/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>tenofoviv</td>
<td>TDF</td>
<td>300</td>
<td>qd</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Acronym</th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th>#/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>delavirdine</td>
<td>DLV</td>
<td>400</td>
<td>tid</td>
<td>6</td>
</tr>
<tr>
<td>efavirenz</td>
<td>EFV</td>
<td>600</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>nevirapine</td>
<td>NVP</td>
<td>200</td>
<td>qd x 14d then bid 1 x 14d then 2</td>
<td></td>
</tr>
</tbody>
</table>

**Fixed-Dose Combination N/NtRTIs**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Acronym</th>
<th>Dose (mg)</th>
<th>Schedule</th>
<th>#/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine</td>
<td>Combivir©</td>
<td>300/150</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td>lamivudine</td>
<td>Trizivir©</td>
<td>300/150/300</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td>abacavir</td>
<td>Epzicom©</td>
<td>600/300</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>lamivudine</td>
<td>Truvada©</td>
<td>300/200</td>
<td>qd</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Protease Inhibitors and Pharmacokinetic Enhancement**

- Protease inhibitors (PIs) are substrates and inhibitors of the hepatic cytochrome P450 (CYP) enzyme system.
- Ritonavir (RTV) is a potent inhibitor of hepatic CYP 3A4.
  - Full dose (600 mg q12h) is poorly tolerated.
  - A low or booster dose (usually 100 or 200 mg) is often prescribed with one or two other PIs.
  - Avoids standard dosing of the co-administered PIs.

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*“The HIV-1 Life-cycle” Wolinsky et al. NEJM 1999, 340:1614-1622*
Example: Lopinavir + Ritonavir

Pharmacokinetic Enhancement

- **PK Advantages**
  - Improved drug exposure (AUC) of co-administered PI(s)
  - Increased half-life of co-administered PI(s) allows q12h or q24h dosing
  - Positive drug-drug interaction

- **Adherence Advantages**
  - Reduced pill burden
  - Reduced dosing frequency

Protease Inhibitors (PIs)

<table>
<thead>
<tr>
<th>Generic &amp; Acronym</th>
<th>PI Dose (mg)</th>
<th>RTV Dose (mg)</th>
<th>Schedule</th>
<th>#Pills /Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>atazanavir (ATV)</td>
<td>300</td>
<td>100</td>
<td>q24h</td>
<td>3</td>
</tr>
<tr>
<td>(150 or 200 mg)</td>
<td>400</td>
<td>-</td>
<td>q24h</td>
<td>2</td>
</tr>
<tr>
<td>fosamprenavir (FPV)</td>
<td>700</td>
<td>100</td>
<td>q24h</td>
<td>4</td>
</tr>
<tr>
<td>(700 mg)</td>
<td>1400</td>
<td>100</td>
<td>q24h</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>1400</td>
<td>-</td>
<td>q12h</td>
<td>4</td>
</tr>
<tr>
<td>indinavir (IDV)</td>
<td>800</td>
<td>100 or 200</td>
<td>q12h</td>
<td>6-8</td>
</tr>
<tr>
<td>(400 mg)</td>
<td>800</td>
<td>-</td>
<td>q8h</td>
<td>6</td>
</tr>
</tbody>
</table>

*Saquinavir once daily dosing is currently being studied.

Protease Inhibitors (PIs)

<table>
<thead>
<tr>
<th>Generic &amp; Acronym</th>
<th>PI Dose (mg)</th>
<th>RTV Dose (mg)</th>
<th>Schedule</th>
<th>#Pills /Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>lopinavir/ritonavir</td>
<td>400</td>
<td>100</td>
<td>q12h</td>
<td>4-6</td>
</tr>
<tr>
<td>(LPV/RTV)</td>
<td>800</td>
<td>200</td>
<td>q24h</td>
<td>4-6</td>
</tr>
<tr>
<td>nefavirin (NFV)</td>
<td>750</td>
<td>-</td>
<td>q8h</td>
<td>9</td>
</tr>
<tr>
<td>(250 or 750 mg)</td>
<td>1250</td>
<td>-</td>
<td>q12h</td>
<td>4</td>
</tr>
<tr>
<td>saquinavir (SQV)</td>
<td>1000</td>
<td>100</td>
<td>q12h</td>
<td>6</td>
</tr>
<tr>
<td>(500 mg)</td>
<td>2000</td>
<td>100 or 200</td>
<td>q24h*</td>
<td>5-6</td>
</tr>
</tbody>
</table>

DHHS: Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents

- Reviewed monthly by the “Panel on Clinical Practices for Treatment of HIV”
- Utilize scientific evidence & expert opinion
- Last updated: October 6, 2005
- Other guidelines exist for: pregnant women, pediatrics, occupational exposures

- Newest FDA approved ARV
- Limited to use for patients with PI resistant virus
- Synergy demonstrated with enfuvirtide
- Significant CYP3A4 and p-glycoprotein inducer
- Not to be combined with other PIs
Initiating Antiretroviral Therapy in a Treatment Naïve Patient

Primary Goals of Therapy

- **Virologic endpoints:**
  - Suppress HIV-1 RNA as much as possible (e.g., < 50 copies/mL) for as long as possible (durability)
  - Prevent development of drug resistance

- **Immunologic endpoints:**
  - Restore and preserve CD4 lymphocyte count

- **Clinical endpoints:**
  - Reduce morbidity/mortality; improve quality of life

**Prognostic Markers**

- CD4 count - most important consideration in the decision to start antiretroviral therapy
- HIV-1 RNA - additional factor to consider
- 2 baseline measurements of CD4 count and HIV-1 RNA should be evaluated before initiating treatment
- Better assessment of patient’s clinical status

**Indications for Initiating Therapy in Treatment Naïve Persons**

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4 Count cells/mm³</th>
<th>HIV RNA copies/mL</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>symptomatic* AIDS</td>
<td>any</td>
<td>any</td>
<td>treat</td>
</tr>
<tr>
<td>asymptomatic AIDS</td>
<td>&lt; 200</td>
<td>any</td>
<td>treat</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt; 200 but ≤ 350</td>
<td>any</td>
<td>offer treatment</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt; 350</td>
<td>≥ 100,000</td>
<td>defer (more likely)</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt; 350</td>
<td>&lt; 100,000</td>
<td>offer treatment</td>
</tr>
</tbody>
</table>

* AIDS-defining illness; unexplained fever/diarrhea >2-4 wks; oral candidiasis; >10% unexplained weight loss

**Asymptomatic Patients**

- In patients with a CD4 count >200 but ≤350 cells/mm³ there must also be a balance:
  - Patient readiness
    - 90-95% adherence may be needed to maintain suppression of viral replication (Paterson DL, et al. Ann Int Med 2000; 21-30)
  - Risks and benefits of therapy
  - Prognosis for disease-free survival determined by baseline (pre-treatment) CD4 count and HIV-1 RNA

**Recommended Regimens: Treatment Naïve Patients**

**Non-nucleoside Reverse Transcriptase Inhibitor-Based**

| Preferred | EFV + (3TC or FTC) + (AZT or TDF) | 2-3 pills/d |
| Alternatives | EFV + (3TC or FTC) + (ABC or ddI or d4T) | 2-4 pills/d |
|             | NVP + (3TC or FTC) + (AZT or d4T or ddI or ABC or TDF) | 3-6 pills/d |

**Notes:**
- EFV - teratogenic; not recommended in women who are pregnant or at a high risk of becoming pregnant; NVP - high incidence of symptomatic hepatic events in women with CD4 >250 (11%) and men with CD4 >400 (6.3%); not recommended as initial therapy in these individuals; DLV - not recommended

**Recommended Dual Nucleoside/tide Backbones**

| Preferred | zidovudine (AZT) or tenofovir (TDF)) + lamivudine (3TC) or emtricitabine (FTC) |
| Alternatives | stavudine (d4T) or didanosine (ddI) or abacavir (ABC) + (3TC or FTC) |

* Choice is made on the basis of:
  - potency and durability (AZT + 3TC; FTC + TDF; d4T + 3TC)
  - short- and long-term toxicities (mitochondrial toxicity)
  - drug-drug interaction potential (TDF; ↑ ATV and ↓ ddI)
  - propensity to select for resistance mutations
  - dosing convenience

**Recommended Regimens: Treatment Naïve Patients**

**Protease Inhibitor-Based**

| Preferred | LPV/RTV (co-formulated) | (3TC or FTC) + AZT |
| Alternatives | LPV/RTV | (3TC or FTC) + d4T, ABC, TDF or ddI |
|             | ATV | (3TC or FTC) + (AZT, d4T, ABC or ddI) |
|             | FPV ± RTV* | (3TC or FTC) + (AZT, d4T, ABC, TDF or ddI) |

*Refers to low-dose RTV

**Recommended Regimens: Treatment Naïve Patients**

**NNRTI-Based Regimens**

- **Advantages:**
  - Virologic/immunologic efficacy well documented
  - Low pill burden and dosing frequencies
  - Spares PI-associated side effects
  - Preserves PIs for future use

- **Disadvantages:**
  - Resistance can be conferred by a single point mutation
  - Resistance usually leads to cross-class resistance
  - Potential for drug-drug interactions (CYP 450 induction)
  - Side effects - rash (all NNRTIs), CNS (EFV), liver (NVP)

**Which PI Do I Choose?**

- **Once daily dosing**
  - LPV/RTV; ATV ± RTV; FPV + RTV; SQV + RTV

- **Food or fluid requirements**
  - LPV/RTV; ATV; NFV; SQV (all taken with food)
  - IDV (empty stomach when not boosted by RTV)
  - IDV (1.5-2.0 liters of water/fluid per day)
  - FPV (taken without regard to food)

- **Co-formulated product**
  - LPV/RTV

**Dual Nucleoside/tide Backbones**

- Co-formulated products
  - AZT and 3TC; TDF and FTC; ABC and 3TC

- Once daily dosing
  - TDF and FTC; ABC and 3TC

- Specific potential toxicities
  - AZT - anemia, GI upset
  - TDF - rare renal toxicity
  - ABC - hypersensitivity reaction (2.9%)
  - d4T - lipoatrophy, peripheral neuropathy
  - ddI - peripheral neuropathy, rare pancreatitis
  - 3TC and FTC - well tolerated
Other Considerations

- Known side effects
  - Most cause GI intolerance (NFV > diarrhea)
  - Dyslipidemias (LPV/RTV; RTV containing; ATV has less effect on lipids versus other PIs)
  - Hyperbilirubinemia (ATV; IDV)
  - Nephrolithiasis (IDV)
  - Rash (FPV)
- Dosing frequency and pill burden
- Co-morbidities

PI-Based Regimens

- Advantages
  - Clinical/virologic/immunologic efficacy well documented
  - Resistance requires multiple mutations
  - Avoids NNRTI-associated side effects
  - Targets HIV at 2 steps of viral replication (RT and PRO)
  - Preserves NNRTIs for future use
- Disadvantages
  - Some regimens are difficult to use/adhere to
  - Long-term side effects include lipodystrophy, dyslipidemias, and insulin resistance
  - Potential for drug-drug interactions (CYP 450 inhibition)

Recommended Regimens: Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Triple Nucleoside Reverse Transcriptase Inhibitor-Based</th>
<th>2 pills/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only when a NNRTI- or PI-based regimen can’t be used</td>
<td>ABC + 3TC + AZT</td>
</tr>
</tbody>
</table>

- Several clinical trials have shown many 3-NRTI regimens to have less potent virologic activity than comparator NNRTI or PI-based regimens. Some trials have also reported virologic failure or early virologic non-response using 3-NRTI regimens.

Not Recommended

- monotherapy
- dual nucleoside/tide regimens
- atazanavir + indinavir (hyperbilirubinemia and jaundice)
- didanosine + stavudine (peripheral neuropathy, pancreatitis, lactic acidosis)
- emtricitabine + lamivudine (similar resistance profiles)
- stavudine + zidovudine (in vitro and in vivo antagonism)

Case Presentation