An Update on HIV Therapy: Protease Inhibitors for Treatment Experienced Patients

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Program Overview:
This program will enhance the pharmacists understanding of HIV therapy and the use of protease inhibitors for treatment experienced patients. The program includes information on pharmacologic treatments, patient counseling and a question/answer period.

Objectives:
1. Describe the mechanism of action, efficacy, safety, and tolerability profiles for protease inhibitors and rationale for prescribing combination therapy when using them.
2. Outline the pharmacist’s role in counseling and educating HIV patients on drug treatment strategies to improve the patient’s medication adherence.

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**HIV/AIDS**

- Human Immunodeficiency Virus
- Acquired Immune Deficiency Syndrome

**AIDS**

- CD4 count below 200
- AIDS defining illness (regardless of CD4 count)

A partial list includes …

- Pneumocystis carinii pneumonia
- Cytomegalovirus
- Toxoplasmosis of the brain
- Cryptosporidiosis
- Mycobacterium Avium
- Kaposi's sarcoma
- Candidiasis of the esophagus, trachea, bronchi or lungs

**Global estimates for adults and children, 2007**

- People living with HIV
  - 33.2 million [30.6 – 36.1 million]

- New HIV infections in 2007
  - 2.5 million [1.8 – 4.1 million]

- Deaths due to AIDS in 2007
  - 2.1 million [1.9 – 2.4 million]
Over 6,800 new HIV infections a day in 2007

- More than 96% are in low and middle income countries
- About 1,200 are in children under 15 years of age
- About 5,800 are in adults aged 15 years and older of whom:
  - almost 50% are among women
  - about 40% are among young people (15-24)

Adults and children estimated to be living with HIV, 2007

Total: 33.2 (30.6 – 36.1) million

Cost of HIV/AIDS in the USA

“The Centers for Disease Control and Prevention (CDC) estimate that about 40,000 people become infected with HIV every year in the United States. Under current care standards, these infections will result in $12.1 billion annually in future treatment costs.”

(Schackman, Freedberg, Gebo & Moore)
Costs

- Costs per individual
  - Monthly average is $2,100
  - Life expectancy increased to 24.2 years
  - Lifetime HIV care cost $618,900

- Medication Costs
  - more than 70% of cost of treatment
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Estimated Number of Persons Living with HIV/AIDS, by Race/Ethnicity, 2003–2006—33 States

Race/ethnicity of persons (including children) with HIV/AIDS diagnosed during 2006

[Graph showing race/ethnicity distribution]

[Diagram showing HIV structure]
HAART Therapy

- Highly Active Antiretroviral Therapy
- Protease Inhibitors are a cornerstone of the effective triple drug HAART therapy

Trends in Annual Rates of Death due to the 9 Leading Causes among Persons 25–44 Years Old, United States, 1987–2005

- Unintentional Injury
- Cancer
- Heart disease
- Suicide
- Homicide
- HIV disease
- Chronic liver disease
- Stroke
- Diabetes

CD4 - Track Length
Virus Load – Speed of Train
Mortality

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CD4 - Track Length
Virus Load – Speed of Train
Mortality
Therapy Goals

• Increase CD4 cell count
  – protect the body’s immune system
  – prevent the occurrence of opportunistic infections

• Decrease viral load count to undetectable

• Maintain quality of life for patient

Compliance with Medications!!!

• Compliance
• Compliance
• Compliance
• Compliance

Compliance issues
  – 2.6 days changes virus

Adherence and Viral Response

<table>
<thead>
<tr>
<th>Level of Adherence</th>
<th>% pts viral load &lt;400</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;95%</td>
<td>81</td>
</tr>
<tr>
<td>90-95%</td>
<td>64</td>
</tr>
<tr>
<td>80-90%</td>
<td>50</td>
</tr>
<tr>
<td>70-80%</td>
<td>25</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>6</td>
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</table>

Adherence and CD4 response

<table>
<thead>
<tr>
<th>Level of Adherence</th>
<th>Mean change in CD4 Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;95%</td>
<td>+60</td>
</tr>
<tr>
<td>80-95%</td>
<td>+54</td>
</tr>
<tr>
<td>&lt;80%</td>
<td>-13</td>
</tr>
</tbody>
</table>
The complicating variables…

- Limited number of medications
- Cost of medications
- Side effects of the medications
- Ability of the virus to mutate: develop resistance to medications

Fusion

**Fusion Inhibitor** Prevents binding of HIV virus to the host cell by blocking a particular domain located on the gp41 portion of the outer membrane gp120.

| Fuzeon® (Enfuviritide) | T-20 | dose 90mg SQ BID | 60 = $2,552.74 |

Entry

**CCR5 Co-Receptor Antagonist** Binds to CCR5 chemokine co-receptor located on the host cell membrane, blocking interaction between HIV-1 gp120 and CCR5 needed for internalization of the virus.

| Selzentry® maraviroc | 300mg BID (adjust for P450) | $900.00/month |

Overview of Drug Therapy

*(Reverse transcription inhibitors)*

**NRTI**: Competes with endogenous deoxynucleotides for the reverse transcriptase. NRTI prematurely stop DNA elongation. Stops virus from changing its genes from RNA to DNA.

Drug Therapy: Epivir® (lamivudine) ; Viread® (tenofovir)

**NNRTI**: Directly bind reverse transcriptase in a noncompetitive manner. Stops virus from changing its genes from RNA to DNA.

Drug Therapy: Sustiva® (efavirenz) ; Intelence® (etravirine)
Overview of Drug Therapy

**HIV INTEGRASE INHIBITOR:** Blocking integrase prevents the integration of HIV-1 DNA into the host’s genomic sequence. Integrase inhibitors prevent HIV from taking over the CD4 cell’s command center (nucleus).

Drug Therapy: Insentress® raltegravir

| Insentress® | raltegravir | 400mg BID + or - food | 60 = $810.00 |

**Protease Inhibitors**

**Mechanism:** reversible inhibitors of HIV aspartyl protease, a viral enzyme responsible for the cleavage of the viral polyprotein into a number of essential enzymes and several structural proteins.

**Adverse reactions:** Lipodystrophy, hyperglycemia, lipid metabolism, osteonecrosis, osteopenia, osteoporosis, avascular necrosis of the hips.

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Abbr</th>
<th>Dosage</th>
<th>COST (AWP) 4/08</th>
</tr>
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<tbody>
<tr>
<td>Viracept®</td>
<td>Nelfinavir</td>
<td>NFV</td>
<td>1250mg q12</td>
<td>120 = $788.95</td>
</tr>
<tr>
<td>Norvir®</td>
<td>Ritonavir</td>
<td>RTV</td>
<td>100-400mg with other PI for intensification</td>
<td>50 = $321.00</td>
</tr>
<tr>
<td>Crixivan®</td>
<td>Indinavir</td>
<td>IDV</td>
<td>800mg q 8 hrs</td>
<td>180 = $570.96</td>
</tr>
<tr>
<td>Agenerase®</td>
<td>Amprenavir</td>
<td>APV</td>
<td>1200mg q12 hrs</td>
<td>Withdrawn: 2007</td>
</tr>
<tr>
<td>Invirase®</td>
<td>Saquinavir (hard gelcap)</td>
<td>SQV-HGC</td>
<td>400mg q12 with 400mg Ritonavir</td>
<td>120 = $906.91</td>
</tr>
<tr>
<td>Fortovase®</td>
<td>Saquinavir (softgel cap)</td>
<td>SQV-SGC</td>
<td>1100mg every 8 hrs Withdrawn: 2005</td>
<td></td>
</tr>
<tr>
<td>Reyataz®</td>
<td>Atazanavir</td>
<td>TAZ</td>
<td>400mg daily</td>
<td>60 = $1,028.55</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Lopinavir/ Ritonavir</td>
<td>LPV/r</td>
<td>400mg/100mg BID 60 = $876.98</td>
<td></td>
</tr>
<tr>
<td>Aptivus®</td>
<td>Tipranavir</td>
<td>TPV</td>
<td>500mg BID give with ritonavir</td>
<td>120 = $1,137.50</td>
</tr>
<tr>
<td>Lexiva®</td>
<td>fosamprenavir</td>
<td>FPV</td>
<td>1.4gm BID 60 = $765.16</td>
<td></td>
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</table>
Preferred Protease Inhibitors
(for initial PI therapy) Nov 3, 2008

1. Ritonavir-boosted Atazanavir (REYATAZ®)
2. Ritonavir-boosted Darunavir (Prezista®)
3. Ritonavir-boosted Fosamprenavir (Lexiva®)
4. Lopinavir/Ritonavir (co-formulated: twice daily)(Kaletra®)

Ritonavir-boosted Atazanavir (REYATAZ®)

- **Dosage:** 400mg every 24 hours with food (unboosted)
- **Boosted:** 300mg every 24 hours + Ritonavir 100mg every 24 hours
- **Advantages:** once daily dosing concentrations of Atazanavir are enhanced with Ritonavir boosting Low pill burden (2 daily)

Low risk for PI resistance with failure.

Ritonavir-boosted Atazanavir (REYATAZ®)

**Adverse Effects**

- Elevations in LDL, HDL and total cholesterol
- Indirect hyperbilirubinemia (with or without jaundice)
- Nephrolithiasis (causal relationship not yet demonstrated)
- Headache, rash GI upset, prolonged PR interval (1st degree AV block)
- Requires acidic environment avoid antacids, H2 receptor antagonists, Proton pump inhibitors. Separate doses from Atazanavir as far as possible.
Ritonavir-boosted Fosamprenavir (Lexiva®)

- **Dosage:** 1400mg (2 x 700mg tablets) twice daily (unboosted)
- **Boosted:** 1400mg (2x700mg tablets) + Ritonavir 200mg every 24 hours
- **Advantages:** Twice daily dosing, No food effect

**Disadvantages:** Skin rashes including Stevens-Johnson syndrome, dyslipidemia, insulin resistance

Lopinavir/Ritonavir (co-formulated) (Kaletra®)

- **Dosage:** 400mg + 100mg Ritonavir 2 tablets twice daily
  - Twice daily dosing
  - Preferred PI for pregnant women
    - (don’t use once daily if pregnant)
  - Low risk for PI resistance with failure
  - No food restrictions with tablet formulations

**Disadvantages:**
- GI intolerance especially if using once daily therapy
- Dyslipidemia and insulin resistance
- Increase ALT and AST
- Pancreatitis

Prezista® darunavir (Tibotec Labs)

- For treatment-experienced adults, such as those with HIV-1 resistant to more than one Protease Inhibitor (PI)
- No PREZISTA dose adjustment required in patients with mild or moderate hepatic impairment

Prezista® darunavir (Tibotec Labs)

- Ritonavir boosting increases systemic exposure to darunavir by an approximately 14-fold increase
- Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir
Ritonavir Boosting

Ritonavir (Norvir®) by Abbott Labs

- Most potent inhibitor of the Cytochrome P450 enzyme system
- ALL PI are substrates of CYP450-3A4
  - metabolic rate may be altered in the presence of CYP inducers or inhibitors

Tests of HIV drug resistance

- **Genotypic Assays**
  - **Benefits**: cheaper, quicker, may detect the emergence of resistance earlier.
  - **Drawbacks**: predictive, not demonstrative

- **Phenotypic Assays**
  - **Benefits**: Useful in highly HAART-experienced patients needing salvage, may be able to semi-quantitate resistance
  - **Drawbacks**: Long turn-around, expensive

Testing “Genotype”

- Looks at the HIV present in a patients blood and examines it to see what mutations if any exist.
  - Certain drugs are known for causing certain genetic mutations.

- If a specific genetic mutation is present, doctors can select which drugs or class of drugs a particular virus may be resistant to.

- Genotypic testing is relatively fast, inexpensive test that is available to most patients.
Testing “Phenotype”

- Virus is exposed it to different concentrations of HIV medications to determine which drugs are effective.
- Generally used in early stages of drug development long before they are given to humans.
- Phenotypic testing is a slow & expensive. Few patients have access to.
- Currently reserved for patients with multiple drug resistant HIV

When to Start HAART????

Source: Sanford Guide 2008 p.152

<table>
<thead>
<tr>
<th>HIV symptoms?</th>
<th>CD4 count</th>
<th>Start Treatment?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Any</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>&lt;200</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>200-350</td>
<td>Yes*</td>
<td>New DHHS recommendation</td>
</tr>
<tr>
<td>No</td>
<td>350&lt;</td>
<td>No**</td>
<td>Maybe if CD4 decreasing rapidly or viral load &gt;100,000 copies/ml</td>
</tr>
</tbody>
</table>

NNRTI options

- Preferred: Efavirenz (Sustiva®)
  - Dosage: 600mg at bedtime
  - Caution: 1st trimester pregnancy
  - Caution: unstable psychiatric disease

- Alternative: Nevirapine (Viramune®)
  - Dosage: 200mg daily for 14 days; then 200mg BID

Dual NRTI options

- Preferred: Tenofovir + emtricitabine (Truvada®)
  - Avoid: in unboosted atazanavir regimens
  - Caution: nevirapine (early virologic failure)
  - Caution: renal insufficiency

- Alternative: Abacavir + Lamivudine (Epzicom®)
To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B
(as of Nov 3, 2008)

<table>
<thead>
<tr>
<th>COLUMN A</th>
<th>COLUMN B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred components</td>
<td>Preferred components</td>
</tr>
<tr>
<td>(NNRTI or PI options</td>
<td>(Dual-NRTI options - in</td>
</tr>
<tr>
<td>in alphabetical order)</td>
<td>alphabetical order)</td>
</tr>
<tr>
<td>NNRTI – efavirenz OR PI</td>
<td>Tenofovir/emtricitabine</td>
</tr>
<tr>
<td>– (Atazanavir + ritonavir)</td>
<td>(co-formulated)</td>
</tr>
<tr>
<td>or (Darunavir + ritonavir)</td>
<td></td>
</tr>
<tr>
<td>or (Fosamprenavir +</td>
<td></td>
</tr>
<tr>
<td>ritonavir) or (Lopinavir</td>
<td></td>
</tr>
<tr>
<td>+ ritonavir)</td>
<td></td>
</tr>
</tbody>
</table>

Alternative to preferred components

| Preferred components      | Alternative to preferred     |
|----------------------------| components                  |
| PI – atazanavir or Fosamprenavir or (Saquinavir + ritonavir) | Abacavir/lamivudine (co-formulated) OR Didanosine + (emtricitabine or lamivudine) OR Zidovudine/lamivudine (co-formulated) |

IMMUNOLOGIC FAILURE
(defined as failure to achieve and maintain adequate CD4 t-cell response in spite of virological suppression)

Defined as suppressed viremia and reached a CD4 count greater than 500.
- CD4 count less than 200 (42%)
- CD4 200-350 (66%)
- CD4 greater than 350 (85%)
- May expect increase of CD4 count of 150 over the first year in treatment naïve patients.
- A CD4 t-cell count plateau may occur after 4-6 years of treatment with suppressed viremia.

Goals of HAART
1. Lower viral loads to undetectable levels
2. Elevate CD4 counts
3. Eradication difficult due to:
   - latent HIV reservoirs
   - poor patient compliance as well as to mutations with the HIV virus

Successful HAART Therapy
1. Need to have at least two (preferably 3) active drugs from MULTIPLE drug classes.
2. When maximal suppression is NOT achieved or LOST changing to a new regimen with at least two active drugs is required.
   - NEVER change only 1 drug in a failing regimen.
Successful HAART Therapy

3. Viral load reduction to below limits of assay detection in a treatment naïve patient usually occurs within the first 12 to 24 weeks of therapy.

4. Predictors of virologic success include:
   • High potency of HAART regimen
   • Excellent adherence (compliance) to treatment
   • Low baseline viremia
   • Higher baseline CD4 counts
   • Rapid reduction of viremia

Strategies for Improving Adherence

1. Complex medication regimens
2. Active substance abuse by patients
3. Depression
4. Health system issues
   – Interruptions in medications access
   – Inadequate education, treatment and support

Pill Box Reminders

- Use of a pillbox increased adherence to HIV therapy by more than 4%
- Use of pillbox increased the probability of achieving a viral load of less than 400 copies/ml by 15%

Source: APhA DrugInfoLine (Oct-2007)

The Role of the Pharmacist

1. Get familiar with the newest treatment advances of HIV therapy.
2. Work tightly with patients so you can provide product as well as control inventory.
3. Use of pill reminders.
4. Spend the necessary time with this special patient population group to encourage compliance.