HIV/AIDS Update 2007

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Objectives

1. List the modes of transmission of HIV and describe methods of prevention of transmission
2. Discuss the current Florida Law on AIDS and its impact on testing, confidentiality of test results, and treatment
3. Identify combinations of antiretroviral agents (ARVs) that are not recommended according to the most recently approved Department of Health and Human Services Guidelines
4. Review important aspects of recently approved antiretroviral agents
HIV Transmission

• Modes of Transmission
  – Sexual Contact
    • Anal, vaginal, oral
  – Blood to blood
    • Sharing needles
    • Needle stick injury
  – Mother-to-child
    • In utero
    • During birth
    • Breastfeeding

• Non-transferable Modes
  – Casual contact
    • Shaking hands
    • Hugging
    • Doorknobs
    • Toilet seats
    • Drinking behind
    • Swimming pools
  – Insects
Prevention of Vertical Transmission

- Rapid HIV testing recommended by CDC for all HIV-infected pregnant women who do not have an HIV test result available at the time of delivery
- Goal is to reduce the number of infants infected perinatally in US from 200-300/year to 0/year

Postexposure Prophylaxis Guidelines

• U.S. Public Health Service Guidelines for the Management of Occupational Exposure to HIV and Recommendations for Postexposure Prophylaxis-September 30, 2005

• Available online at www.aidsinfo.nih.gov

  • PEPLine
    National Clinicians’ Postexposure Prophylaxis Hotline
    – 1-888-HIV-4911
    – Consultation available 24 hours per day
Nonoccupational Exposure Guidelines

• Management of Possible Sexual, Injecting-Drug-Use, or Other Nonoccupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy - January 21, 2005 (Available online at www.aidsinfo.nih.gov)

• Nonoccupational Postexposure Prophylaxis (nPEP) recommended for persons presenting ≤ 72 hours following nonoccupational exposure to person known to be HIV-infected

• Other exposures should be evaluated on a case by case basis
Legal/Legislative Issues: HIV Testing

Florida Statutes
Title XXIX
Chapter 381.004
Surrogate Markers

• CD4\(^+\) Cell Count
  – Measures extent of immune destruction
  – Reported as absolute number (cells/mm\(^3\)) or percent
  – Percent is more stable over time
  – Normal level is 500-1400 cells/mm\(^3\)

• Viral load
  – Measures magnitude of viral replication
  – Reported as viral copies/mL
### Guidelines for Opportunistic Infection Prophylaxis in HIV-infected Patients

<table>
<thead>
<tr>
<th>Infection</th>
<th>CD4+ Count</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pneumocystis jiroveci</em> (formerly <em>carinii</em>) pneumonia (PCP)</td>
<td>&lt; 200 cells/mm³</td>
<td>TMP/SMX DS 1 po qd or MWF</td>
</tr>
<tr>
<td>Toxoplastic encephalitis (TE)*</td>
<td>&lt; 100 cells/mm³</td>
<td>TMP/SMX DS 1 po qd</td>
</tr>
<tr>
<td><em>Mycobacterium avium</em> complex (MAC)</td>
<td>&lt; 50 cells/mm³</td>
<td>Azithromycin 1200 mg po qweek</td>
</tr>
</tbody>
</table>

*Patient positive Toxoplasma IgG antibody

Vaccines

- Hepatitis B vaccine if not infected or immune (HepBsAg-, HepBsAB-)
- Hepatitis A vaccine for MSM, sex workers, patients with other liver disease
- Pneumovax®
- Influenza vaccine yearly (inactivated, not Flumist®)
- Tetanus/diphtheria (Td) q10years
- Note: Live virus vaccines (e.g. MMR, Varicella), are not absolutely contraindicated—it depends!
HIV Life Cycle

- CCR5 Inhibitors
- Fusion Inhibitors
- Integrase Inhibitors
- Protease inhibitors (PIs)
- NRTIs and NNRTI

From The Immunodeficiency Clinic - University Health Network Website, www.tthhivclinic.com

Florida/Caribbean AIDS Education and Training Center
# Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTI’s)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT, ZDV, Retrovir®)</td>
<td>3/87</td>
</tr>
<tr>
<td>Didanosine (ddl, Videx®, Videx EC®)</td>
<td>10/91</td>
</tr>
<tr>
<td>Stavudine (d4T, Zerit®)</td>
<td>6/94</td>
</tr>
<tr>
<td>Lamivudine (3TC, Epivir®)</td>
<td>11/95</td>
</tr>
<tr>
<td>Abacavir (ABC, Ziagen®)</td>
<td>12/98</td>
</tr>
<tr>
<td>Combivir® (AZT/3TC)</td>
<td>9/97</td>
</tr>
<tr>
<td>Trizivir® (AZT/3TC/ABC)</td>
<td>11/00</td>
</tr>
<tr>
<td>Tenofovir (TDF, Viread®)*</td>
<td>10/01</td>
</tr>
<tr>
<td>Emtricitabine (FTC, Emtriva®)</td>
<td>7/03</td>
</tr>
<tr>
<td>Epzicom® (ABC/3TC)</td>
<td>8/04</td>
</tr>
<tr>
<td>Truvada® (FTC/TDF)</td>
<td>8/04</td>
</tr>
</tbody>
</table>

* *A nucleotide reverse transcriptase inhibitor*
## Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI’s)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine (NVP, Viramune®)</td>
<td>6/96</td>
</tr>
<tr>
<td>Delavirdine (DLV, Rescriptor®)</td>
<td>4/97</td>
</tr>
<tr>
<td>Efavirenz (EFV, Sustiva®)</td>
<td>9/98</td>
</tr>
</tbody>
</table>
# Protease Inhibitors (PI’s)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir-HGC (SQV-HGC, Invirase®)</td>
<td>12/95</td>
</tr>
<tr>
<td>Ritonavir (RTV, Norvir®)</td>
<td>3/96</td>
</tr>
<tr>
<td>Indinavir (IDV, Crixivan®)</td>
<td>3/96</td>
</tr>
<tr>
<td>Nelfinavir (NFV, Viracept®)</td>
<td>3/97</td>
</tr>
<tr>
<td>Saquinavir-SGC (SQV-SGC, Fortovase®)</td>
<td>11/97</td>
</tr>
<tr>
<td>Amprenavir (APV, Agenerase®)</td>
<td>4/99</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (KAL, Kaletra®)</td>
<td>9/00</td>
</tr>
<tr>
<td>Atazanavir (ATV, Reyataz®)</td>
<td>6/03</td>
</tr>
<tr>
<td>Fosamprenavir (fos-APV, Lexiva®)</td>
<td>10/03</td>
</tr>
<tr>
<td>Tipranavir (TPV, Aptivus®)</td>
<td>6/05</td>
</tr>
<tr>
<td>Darunavir (DRV, Prezista®)</td>
<td>6/06</td>
</tr>
</tbody>
</table>
Fusion Inhibitor

- Enfuvirtide (T-20, Fuzeon®)
- Approved March 2003
Initial Treatment: Preferred Components

**NNRTI Option**
- *Efavirenz*

**OR**

**PI Options**
- Atazanavir + ritonavir
- Fosamprenavir + ritonavir (BID)
- Lopinavir/ritonavir (BID)

**NRTI Options**
- Tenofovir + emtricitabine**
- Zidovudine + lamivudine**

*Avoid in pregnant women and women with significant pregnancy potential.

**Emtricitabine can be used in place of lamivudine and vice versa.*

http://www.aidsetc.org
Initial Treatment: Alternative Components

**NNRTI Option**
- Nevirapine*

**OR**

**PI Options**
- Atazanavir**
- Fosamprenavir
- Fosamprenavir + ritonavir (QD)
- Lopinavir/ritonavir (QD)

**NRTI Options**
- Abacavir + lamivudine
  *Or*
- Didanosine + (emtricitabine or lamivudine)

* Nevirapine should not be initiated in women with CD4 counts > 250 cells/mm³ or men with CD4 counts > 400 cells/mm³

**Atazanavir must be boosted with ritonavir if used in combination with tenofovir**

http://www.aidsetc.org
• Tipranavir (Aptivus®)
  – Approved June 2005
• Darunavir (Prezista®)
  – Approved June 2006
• Emtricabine/tenofovir/efavirenz (Atripla™)
  – Approved August 2006
• Maraviroc
  – Approved August 6th, 2007
• Raltegravir (Isentress™)
  – Approved October 2007
• TMC-125 (Etravirine)
  – Investigational NNRTI-available via expanded access program (EAP)
Tipranavir (Aptivus®)

- **Dosage Form**
  - 250 mg capsules

- **Adult Dose**
  - 500 mg po bid **WITH** ritonavir 200 mg po bid

- **Patient Counseling Points**
  - Take with food (high fat meal preferred)
  - Antacids may decrease TPV/RTV absorption (25-29%), consider separating dosing
  - Keep in refrigerator or store at room temperature for up to 60 days
  - AEs: Hepatotoxicity-monitor LFTs, closely, rash (8-14%) of patients, diarrhea, nausea, vomiting, rare cases of intracranial hemorrhage
  - Caution with sulfa allergy
Darunavir (Prezista®)

• **Dosage Form**
  – 300 mg capsules

• **Adult Dose**
  – 600 mg po bid **WITH** ritonavir 100 mg po bid

• **Patient Counseling Points**
  – Take with food
  – AEs: Rash (7%), abdominal pain, constipation, headache
  – Caution with sulfa allergy
One Pill Once Daily!

- **Atripla™**
  (emtricitabine/tenofovir/efavirenz)
  - Emtricitabine/tenofovir (Truvada®) + efavirenz (Sustiva®)
- Approved July 12, 2006
- First collaborative effort between 2 companies to develop combination pill for HIV treatment
- Not new drugs!
Maraviroc (Selzentry™)

• First in new class of agents, CCR5 inhibitors
• Approved August 6th, 2007
• Maraviroc binds to the CCR5 receptor on the membrane of human cells such as CD4 cells. This binding prevents the interaction of HIV-1 gp120 and human CCR5 which is necessary for entry into the cell. Maraviroc does not prevent HIV-1 entry into CXCR4-tropic or dual-tropic cells.
Maraviroc (Selzentry™)

- Maraviroc is indicated (in combination with other ARVs) treatment-experienced adult HIV-infected patients
- Maraviroc is not recommended in patients who have dual/mixed tropic or CXCR4-tropic virus
- Use of maraviroc should be based on treatment history and tropism assay results
- The tropism assay is available from Monogram Biosciences, Inc. (For more information go to monogramhiv.com)
## Maraviroc (Selzentry™)

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Maraviroc Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A inhibitors (with or without a CYP3A inducer)</td>
<td>150 mg po bid</td>
</tr>
<tr>
<td>▪ Protease inhibitors (except tipranavir/ritonavir)</td>
<td></td>
</tr>
<tr>
<td>▪ Delavirdine</td>
<td></td>
</tr>
<tr>
<td>▪ Ketoconazole, itraconazole, clarithromycin</td>
<td></td>
</tr>
<tr>
<td>▪ Other strong CYP3A inhibitors (e.g. telithromycin, nefazodone)</td>
<td></td>
</tr>
</tbody>
</table>

Source: www.selzentry.com

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**Florida/Caribbean AIDS Education and Training Center**
# Maraviroc (Selzentry™)

<table>
<thead>
<tr>
<th>Concomitant Medications</th>
<th>Maraviroc Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other meds including tipranavir/ritonavir, nevirapine, all NRTIs, enfuvirtide (T-20)</td>
<td>300 mg po bid</td>
</tr>
<tr>
<td>CYP 3A inducers (WITHOUT a strong CYP3A inhibitor)</td>
<td></td>
</tr>
<tr>
<td>• Efavirenz</td>
<td>600 mg po bid</td>
</tr>
<tr>
<td>• Rifampin</td>
<td></td>
</tr>
<tr>
<td>• Carbamazepine, phenobarbital, phenytoin</td>
<td></td>
</tr>
</tbody>
</table>
Maraviroc (Selzentry™)

- **Adverse effects/precautions**
  - Hepatotoxicity
    - may be preceded by a systemic allergic reaction (pruritic rash, eosinophilia)
  - Dizziness/postural hypotension
  - Increased risk of CV events (MI, ischemic events)
Raltegravir (Isentress™)

• First in novel class of agents, integrase inhibitors
  – Inhibits the integrase enzyme which is necessary for the virus to incorporate viral DNA into host cell DNA

• Adverse effects
  – Generally well-tolerated, GI adverse effects, increased CPK can be seen
DHHS Adult/Adolescent HIV Guidelines: Updated December 1st, 2007

Laboratory Testing
Resistance Testing

- Resistance testing (genotype) should be performed in all treatment-naïve patients when they enter into clinical care regardless of plans to initiate ARV therapy
  - Rationale: More likely to detect resistance mutations closer to time of infection
- For those for whom treatment is deferred, repeat testing should be considered at the time that therapy is initiated
- Resistance testing is recommended for all pregnant women prior to initiation of therapy and for those who are on therapy with a detectable viral load
# vircoTYPE HIV-1

## SUMMARY REPORT

### NRTI / NNRTI mutations: 20wt/R, 41wt/L, 211wt/K, 215C/N/S/Y

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Fold Change</th>
<th>Cut-Off</th>
<th>Resistance Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrovir®</td>
<td>6.2</td>
<td>1.9</td>
<td>REDUCED RESPONSE</td>
</tr>
<tr>
<td>Epivir®</td>
<td>1.8</td>
<td>1.1</td>
<td>REDUCED RESPONSE</td>
</tr>
<tr>
<td>Videx®</td>
<td>0.9</td>
<td>1.3</td>
<td>MAXIMAL RESPONSE</td>
</tr>
<tr>
<td>Hivid®</td>
<td>0.9</td>
<td>3.0</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>Zerit®</td>
<td>1.1</td>
<td>1.1</td>
<td>MAXIMAL RESPONSE</td>
</tr>
<tr>
<td>Ziagen®</td>
<td>1.1</td>
<td>2.1</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>Emtriva®</td>
<td>2.3</td>
<td>3.7</td>
<td>SUSCEPTIBLE</td>
</tr>
<tr>
<td>Viread®</td>
<td>1.7</td>
<td>1.0</td>
<td>REDUCED RESPONSE</td>
</tr>
</tbody>
</table>

### NNRTI mutations: 103N, 135L, 179I, 188L

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Fold Change</th>
<th>Cut-Off</th>
<th>Resistance Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viramune®</td>
<td>66.5</td>
<td>5.2</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Rescriptor®</td>
<td>135.6</td>
<td>7.7</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Sustiva® , Stocrin®</td>
<td>574.7</td>
<td>3.4</td>
<td>RESISTANT</td>
</tr>
</tbody>
</table>

### PI mutations: 10I, 24I, 33F, 46L, 54V, 58E, 63P, 71T, 73wt/A, 75I, 77I, 82A

<table>
<thead>
<tr>
<th>PI</th>
<th>Fold Change</th>
<th>Cut-Off</th>
<th>Resistance Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crixivan®</td>
<td>27.6</td>
<td>0.8</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Crixivan® @; boosted</td>
<td>27.6</td>
<td>4.1</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Norvir®</td>
<td>144.3</td>
<td>2.4</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Viracept®</td>
<td>29.7</td>
<td>1.0</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Invirase®</td>
<td>4.6</td>
<td>0.7</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Invirase®@; boosted</td>
<td>4.6</td>
<td>1.1</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Agenerase®</td>
<td>10.0</td>
<td>0.7</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Agenerase®@; boosted</td>
<td>10.0</td>
<td>0.9</td>
<td>MINIMAL RESPONSE</td>
</tr>
<tr>
<td>Lexiva®@, Telzir®</td>
<td>10.0</td>
<td>1.8</td>
<td>RESISTANT</td>
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<tr>
<td>Kaletra®</td>
<td>47.7</td>
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<td>REDUCED RESPONSE</td>
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<td>Reyataz®</td>
<td>70.2</td>
<td>2.0</td>
<td>RESISTANT</td>
</tr>
<tr>
<td>Aptivus®</td>
<td>1.6</td>
<td>1.6</td>
<td>SUSCEPTIBLE</td>
</tr>
</tbody>
</table>

### Notes

1. Note 1
HLA-B*5701 Screening

• HLA-B*5701 testing should be performed prior to initiating abacavir therapy to reduce the risk of hypersensitivity reaction

• If patients test positive for HLA-B*5701, abacavir-containing regimens should not be prescribed and abacavir should be added to the patient’s medication allergy list (in the medical record and at the pharmacy)
  – Abacavir contained in Ziagen® (abacavir), Epzicom® (abacavir/lamivudine), Trizivir® (abacavir/lamivudine/zidovudine)
Abacavir Hypersensitivity

- Occurs in 5% of patients (range of 3-8% in clinical trials)
- Onset
  - Usually within first 2 weeks; rarely > 6 weeks
  - Worsens as therapy continued
  - Resolves relatively quickly upon discontinuation
Abacavir Hypersensitivity

- Symptoms
  - Rash (not always present, can be very mild if present) OR at least 1 or more symptoms from at least 2 of the following groups:
    1. Fever
    2. Nausea, vomiting, diarrhea, stomach pain
    3. Extreme fatigue, achiness
    4. Sore throat, shortness of breath, cough
Abacavir Hypersensitivity

- Discontinue abacavir and NEVER rechallenge
- Note allergies to abacavir products (Ziagen®, Epzicom®, Trizivir®) in patient’s medical record
- Decreased risk of HSR
  - Male gender, African ethnicity, advanced HIV
- Genetic testing to determine risk for HSR
Abacavir Hypersensitivity

• Screening for HLA-B*5701
  – Predict Study
    • Screening significantly ↓ the incidence of both clinically suspected HSR (from 7.8% to 3.4%) and immunologically confirmed HSR (from 2.7% to 0%). Sensitivity for immunologically confirmed HSR was 100%, and negative predictive value was also 100%.

Abacavir Hypersensitivity

Co-receptor Tropism Assay

• A co-receptor tropism assay should be performed prior to initiating a CCR5 antagonist
  – Maraviroc (Selzentry™) is currently the only CCR5 antagonist available
  – Currently, the only tropism assay available is Trofile™ from Monogram Biosciences
  – Each clinic needs to set up a direct account with Monogram and directly ship samples to them
  – More information is available online at monogramhiv.com and by calling 1-800-777-0177
When To Initiate Therapy

• Viral load (ie > 100,000 copies/mL) no longer used as a determinant of when to initiate therapy

• ARV therapy should be initiated in patients with AIDS-defining illness or those with CD4 < 350 cells/mm$^3$
  – Data are strongest for those with AIDS-defining illness or CD4 < 200 cells/mm$^3$
When to Initiate Therapy

• ARV therapy should be initiated in the following groups regardless of CD4 cell count
  – Pregnant women
  – Patients with HIV-associated nephropathy
  – Patients with hepatitis B co-infection who require hepatitis B treatment
When to Initiate Therapy

• Initiation of therapy in those with CD4 > 350 cells/mm$^3$ should be done on a case by case basis weighing the potential benefits and risks
  – Earlier initiation of ARV therapy (i.e. CD4 cell > 350 cells/mm$^3$ may be reasonable in patients who benefits outweigh risks
    • Discordant relationships (HIV-infected patient with negative partner)
    • Those who continue to engage in risky behaviors
Managing Virologic Failure

• Construct new regimens with at least 2 (preferably 3) fully active agents based on past resistance testing and treatment history

• In treatment-experienced patients with suppressed viral load, assess adherence regularly and consider attempting to simplify regimen as new agents become available
Antiretroviral Agents: Counseling Points, Adverse Effects
NRTI’s

• Mainly undergo renal excretion EXCEPT
  – Zidovudine (AZT) undergoes glucuronidation
  – Abacavir metabolized by alcohol dehydrogenase

• Do not have P-450 drug interactions

• Limited food restrictions
  – Take without regards to meals: zidovudine, lamivudine, stavudine, tenofovir, emtricitabine
  – Take on empty stomach: didanosine (except when given with tenofovir)

• Class adverse effects
  – Lactic acidosis with hepatic steatosis
Lactic Acidosis with Hepatic Steatosis

• Rare complication of NRTI therapy
• Signs/Symptoms:
  – Abdominal distention, abdominal pain, nausea, vomiting, diarrhea, weight loss, difficulty breathing, generalized weakness, myalgias
• Risk Factors:
  – Stavudine and didanosine use during pregnancy
  – Female gender
  – Obesity
  – Prolonged use of NRTIs
## NRTI Adverse Effects

<table>
<thead>
<tr>
<th>Zidovudine</th>
<th>Abacavir</th>
<th>Lamivudine</th>
<th>Emtricitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bone marrow suppression</td>
<td>• Hypersensitivity reaction: fever, rash,</td>
<td>• Generally well-tolerated</td>
<td>• Hyperpigmentation of palms</td>
</tr>
<tr>
<td>(anemia/neutropenia)</td>
<td>fatigue, malaise, nausea, vomiting, diarrhea,</td>
<td></td>
<td>and soles</td>
</tr>
<tr>
<td>• Nausea</td>
<td>loss of appetite, pharyngitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nail discoloration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# NRTI Adverse Effects

<table>
<thead>
<tr>
<th>Stavudine</th>
<th>Didanosine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Peripheral neuropathy</td>
<td>• Pancreatitis</td>
<td>• GI upset</td>
</tr>
<tr>
<td>• Pancreatitis</td>
<td>• Peripheral neuropathy</td>
<td>• Flatulence</td>
</tr>
<tr>
<td>• Increased triglycerides</td>
<td>• Diarrhea</td>
<td>• Nephrotoxicity</td>
</tr>
</tbody>
</table>

*Stavudine side effects*:
- Peripheral neuropathy
- Pancreatitis
- Increased triglycerides

*Didanosine side effects*:
- Pancreatitis
- Peripheral neuropathy
- Diarrhea

*Tenofovir side effects*:
- GI upset
- Flatulence
- Nephrotoxicity

*Florida/Caribbean AIDS Education and Training Center*
Agents with Hepatitis B Activity

- Lamivudine, emtricitabine, tenofovir

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED _______. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE _______ AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).
NNRTI’s-General Statements

• Hepatic metabolism-no renal dosage adjustments required
• Single mutation confers cross resistance to all available NNRTIs
• Due to pill burden and lack of potency, delavirdine is rarely used
• Many P-450 drug interactions
• Class adverse effects:
  – increased transaminase levels
  – rash (nevirapine > delavirdine > efavirenz)
Nevirapine Adverse Effects

• Rash (7%)
  - To ↓ risk of rash, a 14 day "lead-in" dose of one 200 mg tablet daily is used for adults (in combination with other ARVs); dose can then be ↑ to 1 tablet bid (if no rash, hepatitis, or other serious adverse effect)
Nevirapine (NVP, Viramune®)

• Severe, life-threatening hepatotoxicity
  – Often associated with rash
  – Greatest risk in women with CD4 >250 (12-fold greater risk)
  – Increased risk for men with CD4 > 400 (3-fold greater risk)
  – Greatest risk during 1st 6 weeks (continued risk through 18 weeks)
    • Monitor LFTs closely (e.g. baseline, at 2 weeks, 4 weeks, then monthly for first 3 months)
Efavirenz (EFV, Sustiva®)

- Rash (1.7%),
- Increased transaminase levels,
- CNS side effects
  - vivid dreams (sometimes disturbing), dizziness, insomnia
  - Usually mild to moderate and usually resolve after 2-4 weeks
  - Take at bedtime
  - Use with caution in patients with history of psychiatric illness
PI’s-General Statements

• Hepatic metabolism-no renal dosage adjustments
• Resistance usually requires multiple mutations
• Many drug interactions
PI’s-General Statements

• Food restrictions
  – Take all with food EXCEPT:
    • Indinavir: take on empty stomach when not combined with ritonavir
    • Fosamprenavir: can take with or without food
    • Lopinavir/ritonavir tablets: take with or without food

• Class adverse effects
  – Hyperglycemia, lipodystrophy, hyperlipidemia (less with atazanavir), increased transaminases
<table>
<thead>
<tr>
<th>PI Drug</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Amprenavir/fos-amprenavir</td>
<td>GI intolerance, rash, oral paresthesias</td>
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<tr>
<td>Atazanavir</td>
<td>Hyperbilirubinemia</td>
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<tr>
<td>Indinavir</td>
<td>Nephrolithiasis, hyperbilirubinemia</td>
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<tr>
<td>Lopinavir/ritonavir</td>
<td>Nausea, diarrhea, pancreatitis</td>
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<tr>
<td>Nelfinavir</td>
<td>Diarrhea</td>
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<tr>
<td>Ritonavir</td>
<td>GI intolerance, paresthesias, asthenia, taste perversion, hepatitis</td>
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<tr>
<td>Saquinavir</td>
<td>GI intolerance</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>GI intolerance, hepatitis, rash, intracranial hemorrhage</td>
</tr>
<tr>
<td>Darunavir</td>
<td>GI intolerance, rash</td>
</tr>
</tbody>
</table>
PIs Containing Sulfa Moieties

- Darunavir (Prezista®)
- Fosamprenavir (Lexiva®)
- Tipranavir (Aptivus®)
  - Above agents are not contraindicated with sulfa allergy
  - History of sulfa allergy did not correlate with rash in studies and patients with history of sulfa allergy were not excluded
  - Use with caution
Questions?
Web Sources of HIV Information

- www.aidsinfo.nih.gov
- www.hiv-druginteractions.org
- www.cdc.gov
- http://hivinsite.ucsf.edu
- www.hopkins-aids.edu
- www.thebodypro.com
- www.faetc.org