Pharmacology: Hormones and ART

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HIV-Related Drug Interactions

Image: thebody.com
Drug Metabolism

- Metabolism of some drugs occurs along cytochrome P-450 iso-enzyme pathway (most common = 3A4 and 2D6)

- Two or more drugs using this pathway will interact
  - Affecting potency, side effects, & effectiveness
  - Drug concentrations may go up or down
  - Difficult to predict the effects of multiple drug interactions

- Enzyme Inducers
  - Increase metabolism
  - Decrease amount of drug in bloodstream
    - unless it’s a pro-drug

- Enzyme Inhibitors
  - Decrease metabolism
  - Increase the amount of drug in bloodstream
    - Unless it’s a pro-drug
Cytochrome (CYP) P450 metabolism

- **Common inducers**
  - Smoking
  - St. John’s Wort
  - All Protease Inhibitors
  - NNRTI’s

- **Common inhibitors**
  - Grapefruit
  - Statins
  - Azoles (anti-fungals)

- **Mixed inducer/inhibitor**
  - Efavirenz
Chanelle

- 28 year old trans woman with HIV
- +THC (no cigarettes), non-drinker
- Taking Delestrogen on the street whenever she can get it. Unsure of dose.
  - CD4 count 250 & VL 173,000
  - ALT 60, Cr 1.0, Hep C+, Hep A&B immune
  - Rest of CBC and CMP are unremarkable
- Feels ready to start ARVs

- What are her options?
- What else might you want to do?
Available Antiretroviral Agents: June 2011

### NRTIs
- Abacavir (Ziagen)
- Didanosine (Videx)
- Emtricitabine (Emtriva)
- Lamivudine (Epivir)
- Stavudine (Zerit)
- Tenofovir (Viread)
- Zidovudine (Retrovir)
- 3TC/ABC (Epzicom)
- 3TC/ABC/ZDV (Trizivir)
- 3TC/ZDV (Combivir)
- FTC/TDF (Truvada)

### NNRTIs
- Delavirdine (Rescriptor)
- Efavirenz (Sustiva)
- Nevirapine (Viramune)
- Etravirine (Intelence)
- Rilpivirine (Edurant)

### PIs
- Atazanavir (Reyataz)
- Darunavir (Prezista)
- Fosamprenavir (Lexiva)
- Indinavir (Crixivan)
- Lopinavir/ritonavir (Kaletra)
- Nelfinavir (Viracept)
- Ritonavir (Norvir)
- Saquinavir (Invirase)
- Tipranavir (Aptivus)

### Fusion Inhibitors (FIs)
- Enfuvirtide (Fuzeon)

### Integrase Inhibitor
- Raltegravir (Isentress)

### CCR5 Inhibitor
- Maraviroc (Selzentry)

### Multiple Class
- Atripla (EFV/FTC/TDF)
Chanelle - 3 months later

- Switched to oral estradiol 4mg daily plus 100mg twice daily of spironolactone.
- Started on TDF/FTC + ATV + RTV
- Denies any side effects
  - CD4 increased to 400, UDVL
  - ALT increased to 100, Cr 1.45
  - Complains of hot flashes

- What drug interactions may be at play?
- What might you want to do?
## PI’s and Hormonal Contraceptives

### DHHS Guidelines – January 10, 2011

#### Ritonavir-boosted Protease Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>EE Effect</th>
<th>Progestogen</th>
<th>Contraceptive Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/r</td>
<td>↓</td>
<td>↑ norgestimate</td>
<td>Use OCP &gt;35mcg EE</td>
</tr>
<tr>
<td>Darunavir/r</td>
<td>↓</td>
<td>↓ norethindrone</td>
<td>Use alternative method</td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>↓</td>
<td>↓ norethindrone</td>
<td>Use alternative method</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>↓</td>
<td>↓ norethindrone</td>
<td>Use alternative method</td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td>↓</td>
<td></td>
<td>Use alternative method</td>
</tr>
<tr>
<td>Tipranavir/r</td>
<td>↓</td>
<td></td>
<td>Use alternative method</td>
</tr>
</tbody>
</table>

#### Protease Inhibitors without Ritonavir

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Progestogen</th>
<th>Contraceptive Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>↑</td>
<td>↑ norethindrone</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>APV ↑</td>
<td>EE and norethindrone Use alternative method</td>
</tr>
<tr>
<td></td>
<td>EE ↓</td>
<td>APV by 20%</td>
</tr>
</tbody>
</table>
### NNRTI’s and Hormonal Contraceptives

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Interaction</th>
<th>Consequences</th>
</tr>
</thead>
</table>
| **Efavirenz**  | $\leftrightarrow$ EE  
                 | ↓ Levenorgestrel  
                 | ↓ Norelgestromin | Use alternative methods. Norelgestromin & levonorgestrel are active metabolites of norgestimate. |
| **Etravirine** | ↑ EE  
                 | No $\Delta$ Norethindrone | No dose adjustment necessary |
| **Nevirapine** | ↓ EE  
                 | ↓ Norethindrone  | Use alternative methods |
|                | No $\Delta$ DMPA | No dose adjustment necessary |
### Other ARVs & Hormonal Contraception

<table>
<thead>
<tr>
<th></th>
<th>CCR5 Antagonist</th>
<th>Integrase Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maraviroc</strong></td>
<td>No Δ EE or levonorgestrel</td>
<td>Safe to use together</td>
</tr>
<tr>
<td><strong>Integrase Inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Raltegravir</strong></td>
<td>No clinically significant effect</td>
<td>Safe to use together</td>
</tr>
</tbody>
</table>

DHHS Guidelines – January 10, 2011
Chanelle - 6 months later

- Pt was switched back to Delestrogen at 40mg IM every other week and continues spironalactone at previous doses.
- She returns with resolution of symptoms
- Stable on ARVs and hormone therapy
- Wants to address her Hepatitis C
  - CD4 count 500, UDVL, Hep C genotype 1
  - HCV RNA 750,000; ALT 80; Cr 1.2
  - No known contraindications to treatment
- What drug interactions concern you?
Drug Interaction

Estradiol levels are **DECREASEd** by:

- Rifampin
- Dexamethasone
- Naphthoflavone
- Smoking cigarettes
- Carbamazepine
- Phenytoin
- Phenobarbital
- Telaprevir
Chanelle – 4 weeks later

- She has started Peg-IFN, RBV, and Telaprevir*
- She complains of depressive symptoms; denies suicidal ideation
- She doesn’t want to take pharmaceuticals and wants to try something natural like St. John’s Wort.

- What do you recommend?

*Telaprevir has not been FDA-approved for use in HIV-HCV co-infected patients. This is an off-label use of this medication.
Cytochrome (CYP) P450 metabolism

- **Common inducers**
  - Smoking
  - St. John’s Wort
  - All Protease Inhibitors
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- **Common inhibitors**
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- **Mixed inducer/inhibitor**
  - Efavirenz
Drug Interaction

Estradiol levels are **INCREASED** by:

- Isoniazid
- Fluvoxamine
- **Fluoxetine**
- **Sertraline**
- **Paroxetine**
- Diltiazem
- Verapamil
- Cimetidine
- Astemizole
- Itraconazole
- Ketoconazole
- Fluconazole
- Miconazole
- Clarythromycin
- Erythromycin
- Grapefruit

www.hivwebstudy.org
Chanelle – 8 weeks later

- She was started on citalopram and depressive symptoms have improved
- Her labs are stable and she continues on the following medications:
  - Peg-IFN, RBV, and Telaprevir
  - Tenofovir/Emtricitabine, Atazanavir, Norvir
  - Delestrogen, Spironolactone
- While she doesn’t like the pill burden, she is tolerating meds well and happy to be able to get her all her care in the same place.
Summary: Estrogens & Antiretrovirals

- DHHS evidence based on oral contraceptives
  - Oral contraceptives use ethinyl estradiol at contraceptive doses
  - Hormones for transgender patients usually are 17-β estradiol or conjugated equine estrogen (CEE)

- Most PI interactions decrease estrogen levels
  - If estrogen is continued and antiretrovirals are stopped, this may lead to dangerously high estrogen levels with associated risk of adverse effects

- Non-nucleosides (NNRTI)
  - Nevirapine decreases estrogen levels
  - Efavirenz may increase or decrease estrogen levels
Amprenavir and Fosamprenavir are the only antiretrovirals that should **not** be co-administered with estrogen due to risk of virologic failure.

Several HIV medications change the levels of estrogens, therefore estrogen dose adjustment may be necessary.

Gender confirming hormone therapy is not contraindicated with antiretroviral therapy.
Web Resources for Drug Interactions

http://www.healthline.com/druginteractions


http://www.drugs.com/drug_interactions.html
Expert Advice at Your Fingertips

HIV/AIDS Clinical Consultation
1-800-933-3413
Mon-Fri 8am to 8pm EST
www.ucsf.edu/hivcntr