AETC AIDS Education & Training Center Program Southeast

Watch Out! Drug Drug Interactions with Antiretrovirals

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Objectives

1. Review basic principles of pharmacokinetics
2. Describe interaction potential of common antiretrovirals
3. Identify common drug-drug interactions with antiretrovirals

Disclaimer

- This is a review of selected drug-drug interactions (DDI) with antiretrovirals (ARVs) and proposed management. Always consider the risk vs. benefit for individual therapies.

What's the goal of medications?

- My motto:

"If I have to take a medication, it better work"

- What is the ultimate goal of utilizing drugs?
  - Maximal effect, minimal toxicities
  - Balancing the decision to use a drug between potential effect and potential adverse effects/complication/toxicity

Polling Question - 1

Which of the following are potential outcomes of a drug-drug interaction?

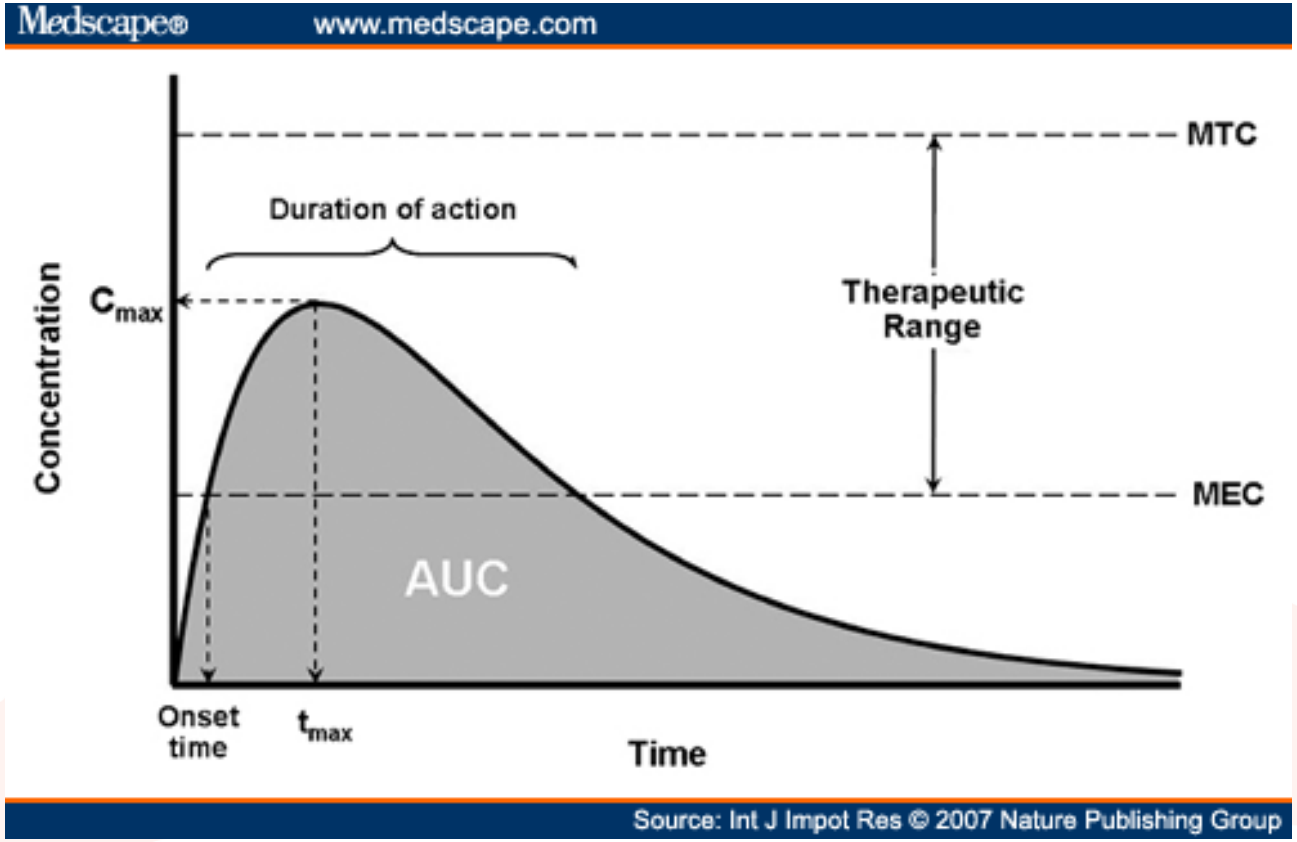
a. Viral breakthrough
b. Night terrors
c. Hypotension
d. Rash
e. A & C

Pharmacokinetic Basics

- Pharmacokinetics: “What a body does to a drug”
  - Onset, duration, intensity of drug’s effect
- Pharmacodynamics “What a drug does to the body”
  - Observed effect of drug

Pharmacokinetic Basics

- Clinical Pharmacokinetics:
  - Enhancing efficacy, decreasing toxicity
  - Determining optimal concentration of drug for desired effect



Pharmacokinetic Basics

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**

Depends on patient specific factors + chemical properties

- Ex: renal function

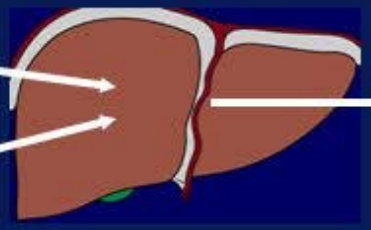
Pharmacokinetic Basics

- Metabolism
  - CYP450 System
  - Substrate
    - Substance/drug that is metabolized by a certain enzyme
  - Inducer
    - Usually means: Drug is being metabolized faster, and will leave the body quicker, having less time to exert it's effects
    - Ex: efavirnez moderately induces CYP3A4
  - Inhibitor
    - Usually means: Drug is NOT being metabolized at usual rate…will stay in body longer, will have increased effects/side effects
      - Different if drug is pro-drug.
    - Ex: cobicistat, ritonavir are both strong CYP3A4 inhibitors

Drug Metabolism Interactions

CYP SUBSTRATE

CYP INHIBITOR



↑ SUBSTRATE [ ]

– RISK OF TOXICITY

CYP SUBSTRATE

CYP INDUCER

↓ SUBSTRATE [ ]

↓ SUBSTRATE EFFICACY

CYP SUBSTRATE

CYP SUBSTRATE

↑, ↓, ↔ SUBSTRATE [ ]

↑, ↓, ↔ IN EFFICACY OR TOXICITY

Potential Consequences of DDI

- Increased concentration = potentially increased toxicity/side effects
- Decreased concentration = potentially reduced efficacy
  - Viral breakthrough

Polling Question - 2

Patient DC is a male to female transgender patient who is new to your clinic. You bring up the topic of starting ARVs and she immediately states that she doesn't want to take ARVs because she will be starting hormone replacement therapy (HRT) soon at the Equality Clinic. Her CD4 count is 576 and VL is 56,000. How do you respond?

a. Tell her she's right to not want to start ARV therapy because it is contraindicated with HRT
b. Tell her we can wait to start her ARV therapy until after she's completed her transition
c. Tell her the current recommendations support starting antiretroviral therapy, and we can work around her HRT.

Hormone Replacement Therapy & ARVs

- Aging population and transgender population
  - Also – hormonal contraception!
- HIV treatment is not a contraindication to hormone replacement therapy (HRT)
  - HRT may be a motivation for them to adhere to HIV therapy
- Always important to fully reconcile patient's medication list!

Hormone Replacement Therapy & ARVs

Hormone or related therapy	Interaction w/ ARV?
Spironolactone	No major DDI w/ ARVs Caution w/ Bactrim – risk of hyperkalemia
Progesterone -major 3A4 substrate	↓progesterone d/t EFV (3A4 inducer) May ↑ ritonovir concentrations
Testosterone	No major DDI
Estrogen / Estradiol	See following slides

Hormone Replacement Therapy & ARVs

ARV	Effect on Contraceptive	Recommendation with Oral Contraceptive	Recommendation with DMPA	Recommendation with Etonogestrel Implant
NNRTIs				
Efavirenz 	**Ethinyl Estradiol/ Norgestimate:** • No change in ethinyl estradiol • ↓ active metabolites of norgestimate • levonorgestrel AUC ↓ 83%; • norelgestromin AUC ↓ 64% **Implant:** • ↓ etonogestrel **Emergency Contraception:** • Levonorgestrel AUC ↓ 58%	**Use alternative contraceptive method.**	**No additional contraceptive needed.**	**Use alternative or additional contraceptive method.**
Etravirine	**Ethinyl estradiol:** • AUC ↑ 22% **Norethindrone** • No significant change	**No additional contraceptive needed.**	**No additional contraceptive needed.**	**No additional contraceptive needed.**
Nevirapine	**Ethinyl estradiol:** • AUC ↓ 20% **Norethindrone:** • AUC ↓ 19% **DMPA:** • No significant change	**Consider alternative method or reliable barrier contraception in addition**	**No additional contraceptive needed.**	**Consider alternative method or reliable barrier contraception in addition.**
Rilpivirine	**Ethinyl estradiol:** • AUC ↑ 14% **Norethindrone:** • No significant change	**No additional contraceptive needed.**	**No additional contraceptive needed.**	**No additional contraceptive needed.**

Faragon, J. **Drug Interactions with Oral Contraceptives and HIV Medications. NYNJ AETC , 2015.**

Hormone Replacement Therapy & ARVs

ARV	Effect on Contraceptive	Recommendation with Oral Contraceptive	Recommendation with DMPA	Recommendation with Etonogestrel Implant
Ritonavir Boosted Protease Inhibitors				
Atazanavir/rtv	Ethinyl estradiol: • AUC ↓ 19% ↑ Norgestimate: • AUC ↑ 85%	Use alternative or additional contraceptive method.	No additional contraceptive needed.	Consider alternative method or reliable barrier contraception in addition.
Darunavir/rtv	Ethinyl estradiol: • AUC ↓ 44% Norethindrone: • AUC ↓ 14%	Use alternative or additional contraceptive method.	No additional contraceptive needed.	Consider alternative method or reliable barrier contraception in addition.
Fosamprenavir/rtv	Ethinyl estradiol: • AUC ↓ 37% Norethindrone: • AUC ↓ 34%	Use alternative or additional contraceptive method.	No additional contraceptive needed.	Consider alternative method or reliable barrier contraception in addition.
Lopinavir/rtv	Ethinyl estradiol: • AUC ↓ 42% Norethindrone: • AUC ↓ 17%	Use alternative or additional contraceptive method.	No additional contraceptive needed.	Consider alternative method or reliable barrier contraception in addition.

Faragon, J. **Drug Interactions with Oral Contraceptives and HIV Medications. NYNJ AETC , 2015.**

Hormone Replacement Therapy & ARVs

ARV	Effect on Contraceptive	Recommendation for Oral Contraceptive	Recommendation for DMPA	Recommendation for Etonogestrel Implant
Integrase Inhibitors				
Raltegravir	No significant effect	No additional contraceptive needed.	No additional contraceptive needed.	No additional contraceptive needed
Dolutegravir	No significant effect on norgestimate or ethinyl estradiol	No additional contraceptive needed.	No additional contraceptive needed.	No additional contraceptive needed
Elvitegravir/cobicistat	Ethinyl Estradiol: • AUC ↓ 25% Noregstimate: • AUC ↑ 230%	No additional contraceptive needed.	No additional contraceptive needed.	No additional contraceptive needed

Faragon, J. **Drug Interactions with Oral Contraceptives and HIV Medications. NYNJ AETC , 2015.**

Hepatitis C

- Hepatitis C therapy recommendations do not differ for HIV positive patients
- Always check for interactions when first considering a hepatitis C regimen, may need to change antiretrovirals.
  - Hep C therapy is temporary.

Hepatitis C

- “Combined treatment of HIV and HCV can be complicated by drug-drug interactions, increased pill burden, and toxicities. Although ART should be initiated for all HCV/HIV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until HCV treatment is completed **(CIII)**.”

	Sofosbuvir	Ledipasvir	Velpatasvir	Simeprevir	Daclatasvir	Elbasvir/ grazoprevir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)
Ritonavir-boosted atazanavir	No data	Ledipasvir ↑; atazanavir ↑[a]	Velpatasvir ↑; atazanavir ↑[a]	No data	Daclatasvir ↑[b]	Elbasvir ↑; grazoprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↑	Paritaprevir ↑; atazanavir ↔
Ritonavir- boosted darunavir	Sofosbuvir ↑; darunavir ↔	Ledipasvir ↑; darunavir ↔[a]	Velpatasvir ↔; darunavir ↔[a]	Simeprevir ↑; darunavir ↔	Daclatasvir ↑; darunavir ↔	Elbasvir ↑; grazoprevir ↑; darunavir ↔	Paritaprevir ↓/↑; darunavir ↓	Paritaprevir ↑; darunavir ↔
Ritonavir-boosted lopinavir	No data	No data[a]	Velpatasvir ↔; lopinavir ↔[a]	No data	Daclatasvir ↑; lopinavir ↔	Elbasvir ↑; grazoprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔	Paritaprevir ↑; lopinavir ↔
Ritonavir-boosted tipranavir	No data	No data	No data	No data	No data	No data	No data	No data
Efavirenz	Sofosbuvir ↔; efavirenz ↔	Ledipasvir ↓; efavirenz ↓[a]	Velpatasvir ↓; efavirenz ↓	Simeprevir ↓; efavirenz ↔	Daclatasvir ↓[b]	Elbasvir ↓; grazoprevir ↓; efavirenz ↓	No pharmacokinetic data[c]	No data
Rilpivirine	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	Velpatasvir ↔; rilpivirine ↔	Simeprevir ↔; rilpivirine ↔	No data	elbasvir ↔; grazoprevir ↔; rilpivirine ↔	Paritaprevir ↑; rilpivirine ↑	No data
Etravirine	No data	No data	No data	No data	Daclatasvir ↓[b]	No data	No data	No data

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

hcvguidelines.org – "Unique Patient Populations: Patients with HIV/HCV Coinfection

Raltegravir	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	Velpatasvir ↔; raltegravir ↔	Simeprevir ↔; raltegravir ↔	No data	Elbasvir ↔; grazoprevir ↔; raltegravir ↑	PrOD ↔; ↑ raltegravir	PrO ↔; raltegravir ↑
Cobicistat-boosted elvitegravir	Sofosbuvir ↑[a]; cobicistat ↑	Ledipasvir ↑; cobicistat ↑[a]	Velpatasvir ↑; cobicistat ↑	No data	No data	Elbasvir ↑; grazoprevir ↑; cobicistat ↑	No data	No data
Dolutegravir	No data	Ledipasvir ↔; dolutegravir ↔	Velpatasvir ↔; dolutegravir ↔	No data	Daclatasvir ↔; dolutegravir ↑	Elbasvir ↔; grazoprevir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data
Maraviroc	No data	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Velpatasvir ↔; tenofovir ↑	Simeprevir ↔; tenofovir ↔	Daclatasvir ↔; tenofovir ↔	Elbasvir ↔; grazoprevir ↔; tenofovir ↑	PrOD ↔; tenofovir ↔	Pro ↔; tenofovir ↔
Tenofovir alafenamide	Sofosbuvir ↑; tenofovir ↑[d]	Ledipasvir ↔; tenofovir ↑[d]	Velpatasvir ↔; tenofovir ↑[d]	No data	No data	No data	No data	No data

[a] Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.

[b] Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.

[c] PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

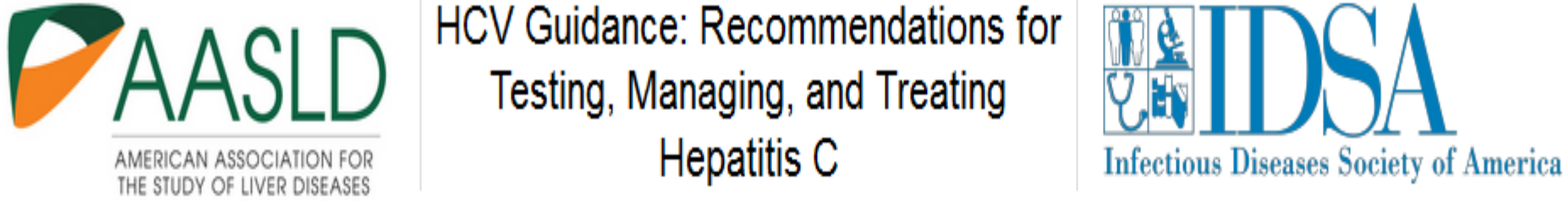
[d] Studied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Table. Drug Interactions Between Direct-Acting Antivirals and Antiretroviral Drugs

hcvguidelines.org – "Unique Patient Populations: Patients with HIV/HCV Coinfection

Hepatitis C Therapy & ARVs

- Great reference:
  - hcvguidelines.org
    - Information is being constantly being updated



Polling Question - 3

Which of the following is contraindicated?

a. Fluticasone and Reyataz (atazanavir)
b. Metformin and Tivicay (dolutegravir)
c. Ibuprofen and Viread (tenofovir)
d. Ranitidine and Edurant (rilpivirine)

Over-the-Counter Meds & ARVs

- Fluticasone and norvir
  - Potentially severe drug interaction, often overlooked
  - Flonase is quite popular, particularly during allergy season
  - Many people end up taking chronically
  - Now, OTC!

Over-the-Counter Meds & ARVs

- Fluticasone and Norvir
  - Likely mechanism of this drug interaction is via CYP450 enzyme system
    - Fluticasone = CYP3A4 substrate
    - Ritonavir = strong CYP3A4 inhibitor
  - Fluticasone **AUC increased > 300-fold** when intranasal spray (200mg) used daily with ritonavir (100mg) for 7 days.
  - Plasma cortisol decreased ~86% (adrenal gland suppression d/t exogenous fluticasone?)
  - Cushing's – like – syndrome

Over-the-Counter Meds & ARVs

- Fluticasone and Norvir
  - Other potential interactions:
    - Prezista = strong CYP3A4 inhibitor
    - Cobicistat = strong CYP3A4 inhibitor
  - Ritonavir is the drug with the strongest warning, really a contraindication
  - Others from above require caution, monitoring
  - A significant interaction is not anticipated with moderate CYP3A4 inhibitors

Over-the-Counter Meds & ARVs

- Fluticasone containing products:
  - Intranasal
    - Flonase
    - Veramyst
  - Inhaled
    - Flovent
    - Advair - fluticasone + salmeterol (also 3A4 substrate)

Over-the-Counter Meds & ARVs

- Fluticasone – Alternative Options
  - Beclomethasone
    - Beconase (nasal)
    - Qvar (inhaled)
  - Triamcinolone
    - Nasacort (nasal)
  - Budesonide – still has drug interaction potential!
    - Rhinocort AQ (nasal)
    - Pulmicort (inhaled)

Polling Question -

JJ is here for a regular ID follow-up appointment. He reports he's been wonderful, and remains stable on atazanavir, ritonavir, and emtricitabine/tenofovir. His only complaint today is that he's been having heartburn lately and asks you what he should take. Which of the following is not an appropriate recommendation for your patient?

a. Tums
b. Omeprazole
c. Ranitidine
d. None of the above are appropriate

Interactions with Acid Reducing Agents

- Widely used, widely available, not widely reported on med list
- Many, varying interactions with ARVs.

Acid Reducing Agents and ARVs

Medication	Antacids	H2 Blockers	Proton Pump Inhibitors
	Tums Maalox	Zantac (ranitidine) Pepcid (famotidine)	Prilosec (omprazole) Nexum (esomeprazole)
Rilpivirine	Give antacids 2 hours before or 4 hours after RPV	RPV AUC ↓ 76% 2H after famotidine 40mg dose Give H2-blocker 12 hours before or 4 hours after RPV	**CONTRAINDICATED!** RPV AUC ↓ 40% w/ omeprazole 20mg daily

Can get confusing and cumbersome for patients. Also consider that rilpivirine needs to be taken with a full meal.
Counsel on avoiding trigger foods, not eating too close to bedtime, etc.

Acid Reducing Agents and ARVs

Medication	Antacids	H2 Blockers	Proton Pump Inhibitors
	Tums Maalox	Zantac (ranitidine) Pepcid (famotidine)	Prilosec (omprazole) Nexum (esomeprazole)
Atazanavir/r	Give ATV at least 2 hours before or 2 hours after antacid, do not give simultaneously	Take ATZ/r simultaneously or 10 hours after *Do not exceed 40mg famotidine BID in naïve pts or 20mg BID in experienced pts	ATZ ↓ 94% ATZ/r ↓ 76% *must use boosted ATZ. If medically necessary, separate by 12 hours. Do not exceed omeprazole 20mg dose equivalent.
Darunavir	No significant effect, no dosing adjustment needed	No significant effect, no dosing adjustment needed	w/ ritonavir: omeprazole AUC ↓ 42% No significant effect, no dosing adjustment needed

Acid Reducing Agents and ARVs

Medication	Antacids	H2 Blockers	Proton Pump Inhibitors
	Tums Maalox Al, Mg, Ca salts	Zantac (ranitidine) Pepcid (famotidine)	Prilosec (omprazole) Nexum (esomeprazole)
Raltegravir	Al-Mg Hydroxide Antacid: RAL C_{min} ↓ 54% to 63% $CaCO_3$ Antacid: RAL C_{min} ↓ 32% DO NOT COADMINISTER Al/Mg ANTACIDS CACO3 Antacids Ok	No significant effect, no dosing adjustment needed	RAL AUC ↑ 212% and C_{min} ↑ 46% No dosing adjustment needed
Dolutegravir	DTG AUC ↓ 74% if given simultaneously with antacid; DTG AUC ↓ 26% if given 2 hours before antacid Take DTG 2h before or 6h after Or, take at the same time with food.	No significant effect, no dosing adjustment needed	No significant effect, no dosing adjustment needed
Elvitegravir/c	Separate by at least 2h	No significant effect, no dosing adjustment needed	No significant effect, no dosing adjustment needed

Miscellaneous Interactions -

- Medications for erectile dysfunction
  - Sildenafil
    - w/ Pis: start with 25mg every 48hours
  - Tadalafil
    - w/ Pis: Do not exceed 10mg every 72 hours
- Statins
  - Lovastatin
    - Contraindicated with PIs due to significantly increased levels of lovastatin
  - Simvastatin
  - Atorvastatin – usually OK, start at lowest dose, and titrate
  - Rosuvastatin

Miscellaneous Interactions -

- Interactions w/ other ARVs?
  - Ritonovir & cobicistat: pharmacokinetic boosters
- Illicit drugs?
  - Methadone
- Dolutegravir
  - Carbamazepine – induces dolutegravir metabolism, increase to BID dosing
  - Metfromin – Do Not Exceed 500mg BID of metformin

Tips and Tricks

- Always check for drug-drug interactions with ARVs
  - Counsel patients to inform their other providers of all the meds they are on
  - Include OTC products!
- Get to know interaction profile
  - i.e. cobicistat is a strong CYP3A4 inhibitor = many interactions!
- Utilize your resources
- Regularly reconcile med list in your EMR
- **Not all interactions require adjustment/change**

Where to find information

- Your pharmacist ☺
- DHHS Guidelines
  - www.aidsinfo.gov
- Package Inserts
- Drug Information Database
  - Ex: Lexi-Comp
- Drug Interaction Checkers
  - Micromedex, Lexi-Comp, Epocrates
- University of Liverpool
  - HIV: http://www.hiv-druginteractions.org/
  - Hep C: http://www.hep-druginteractions.org/

Questions?


That's all Folks!