Common Drug Interactions in HIV practice

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Disclosure/Disclaimer

- I have no financial relationships with any organizations or commercial supporters.
- Trade names will be used on occasion for ease of presentation.
- This is a selective review of HIV drug interactions and not comprehensive in scope.
- A risk versus benefit analysis should be used for all potential interactions.

Objectives

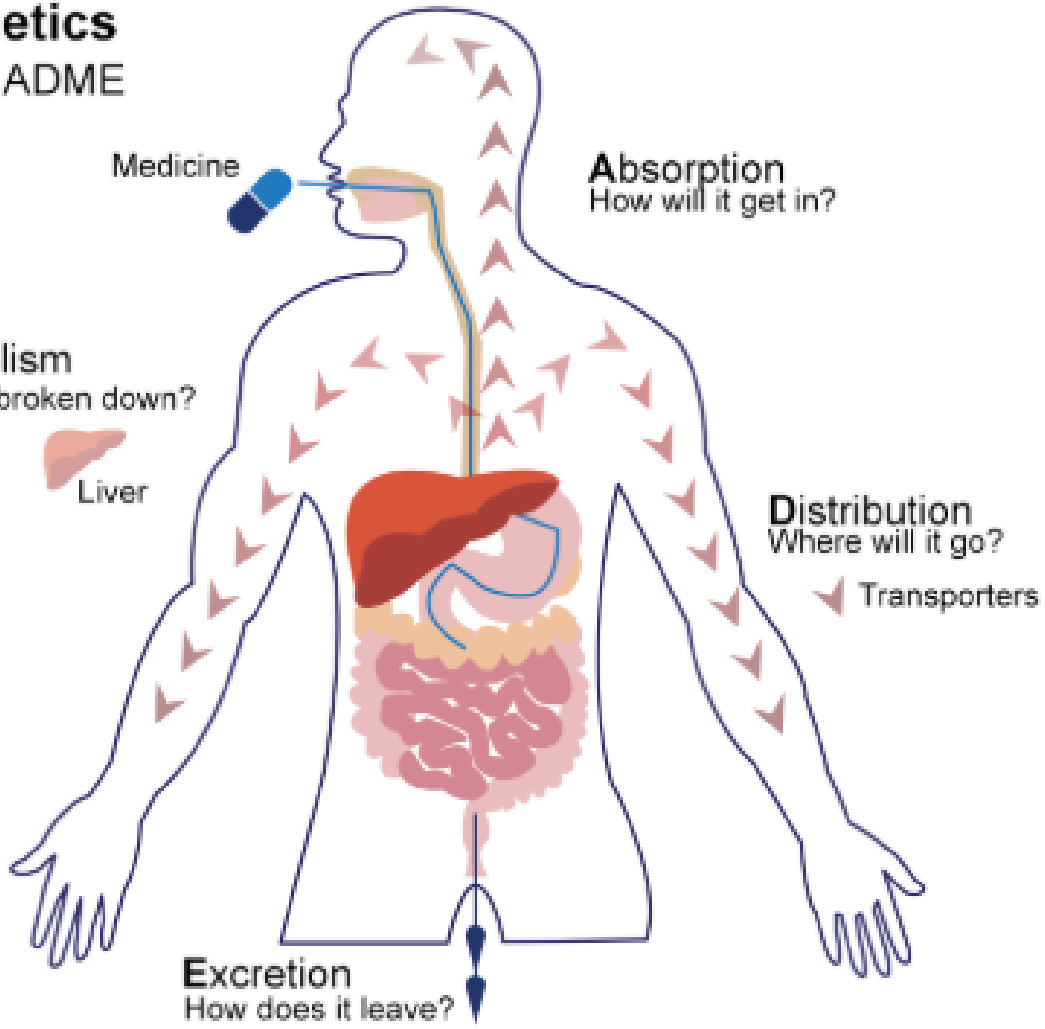
- Review the basics of drug metabolism and the significance of drug interactions in HIV therapy.
- Identify common clinically significant interactions that occur with HIV medications.
- Discuss alternative therapies to prevent complications from drug interactions.

Abbreviations

- Antiretrovirals (ARVs)
- Cytochrome P-450 enzyme pathway (CYP450)
- Human Immunodeficiency Virus (HIV)
- H_2 Receptor Antagonists (H2RAs)
- Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Integrase Strand Transfer Inhibitors (INSTIs)
- Proton Pump Inhibitors (PPIs)
- Phosphodiesterase-5 Inhibitors (PDE-5 inhibitors)
- Benign Prostatic Hyperplasia (BPH)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- People living with HIV (PLWH)

Pharmacokinetics

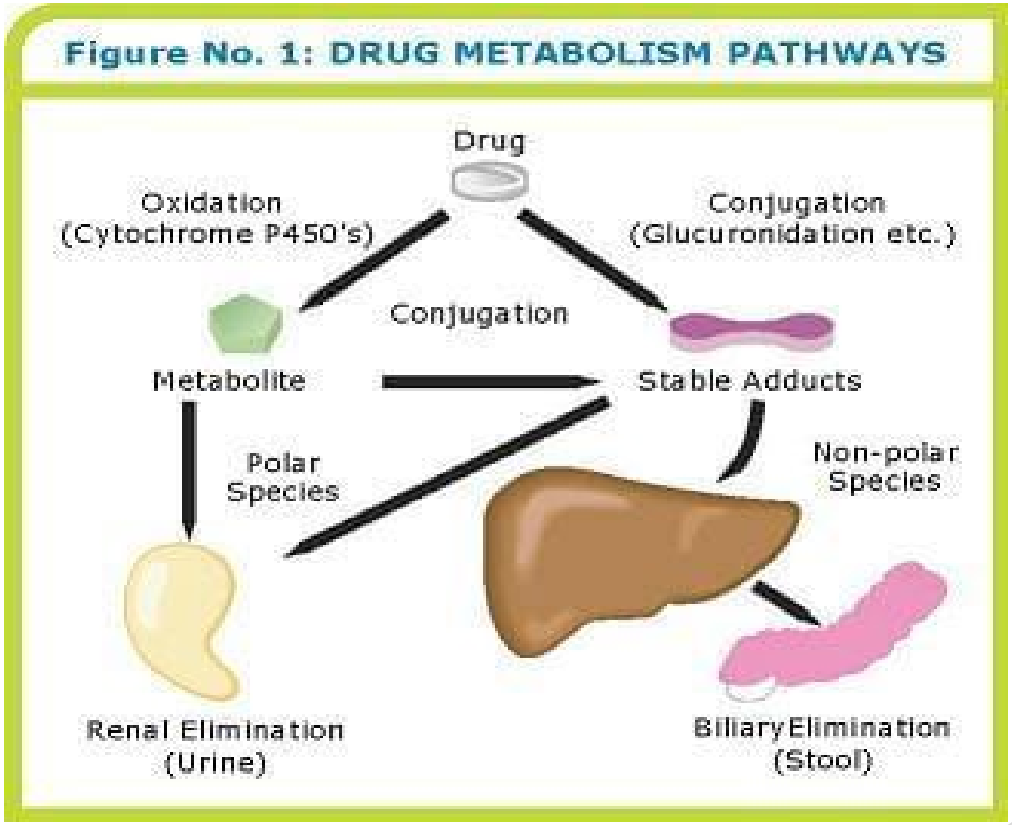
The principles of ADME



www.medicosite.com

Drug metabolism:

Biotransformation of drugs in the body so that they can be eliminated more easily.



Important Terms

- **Cytochrome P450 enzyme system:**
  - A group of enzymes which facilitate the reactions of drug metabolism and are found in high levels in the liver. They change many drugs into less toxic forms that are easier for the body to excrete.
- **Substrate**: Drug/substance that is being metabolized by a certain enzyme
- **CYP450 Inducer**: Drug will leave the body faster with little time for its intended effect
- **CYP450 Inhibitor:** Drug is not metabolized at usual rate and can cause potential toxicities
- **Glucuronidation:**
  - A metabolic process by which drugs are combined with glucuronic acid to form more water-soluble compounds, which are more readily excreted by the kidneys or in bile.
- **Hydrolysis:**
  - A chemical reaction where drugs react with water and are changed into a new substance.

Background

- Advances in HIV drug development have lead to longer lifespans
- An increase in comorbid conditions have lead to the potential for drug-drug interactions
- Many HIV drugs are CYP450 inducers and/or inhibitors
  - Inducers can reduce effectiveness of HIV medications
    - Possible virologic failure
  - Inhibitors can increase toxicities of HIV medications or other medication classes
- The magnitude/significance of interactions are difficult to predict when several drugs with competing metabolic pathways are prescribed together

Mechanisms of Interactions

- Pharmacokinetic interactions affecting **drug absorption**
  - Acid reducing agents, Polyvalent cations (calcium, iron, magnesium, aluminum)
- Pharmacokinetic interactions (drugs that share a common pathway) affecting **hepatic metabolism**
  - CYP3A4, UGT1A1, CYP2D6
- Pharmacokinetic Enhancers **(i.e. Boosters)**
  - Ritonavir, Cobicistat

Metabolism of HIV Drugs

- Nucloside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)- Renally eliminated
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)- Primarily CYP3a inducers
- Protease Inhibitors (PIs)- CYP3a Inhibitors
- Integrase Strand Transfer Inhibitors (INSTIs)-UGT glucuronidation (some have contribution from CYP3a)
- Pharmacokinetic boosters (Cobi/RTV) - CYP3a Inhibitors
- *Fusion inhibitors- Hydrolysis
- *Cell entry inhibitors- CYP3a inducer
- *Attachment Inhibitors-**Organic anion transporting polypeptide (OATP)1B1/3 inhibition/ affected by CYP Induction**
- *Monoclonal Antibodies- drug-drug interactions are not expected

**rarely used in clinical practice*

NRTIs	NNRTIs
Retrovir® (Zidovudine)	Viramune® (Nevirapine) or XR
Videx® (Didanosine)	Pifeltro® (Doravirine)
Zerit® (Stavudine)	Sustiva® (Efavirenz)
Epivir® (Lamivudine)	Intelence® (Etravirine)
Ziagen® (Abacavir)	Edurant® (Rilpivirine)
Viread® (Tenofovir disoproxil fumarate or TDF)	INTEGRASE INHIBITORS
Emtriva® (Emtricitabine)	Isentress® (Raltegravir)
Combivir® (Lamivudine/Zidovudine)	Tivicay® (Dolutegravir)
Truvada® (Emtricitabine/TDF)	Biktarvy® (Emtrictabine/TAF/Bictegravir)
Epzicom® (Abacavir/Lamivudine)	ENTRY INHIBITORS/ MONOCLONAL ABS
Trizivir® (Abacavir/Lamivudine/Zidovudine)	Fuzeon® (Enfuvirtide)/Trogarzo® (ibaluzimab)
Descovy® (Emticitabine/Tenofovir alafenamide or TAF)	Selzentry® (Maraviroc)

Protease Inhibitors	Pharmacokinetic Enhancers/ Attachment Inhibitor
Invirase® (Saquinavir)	Norvir® (Ritonavir) / (Rukobia®) Fostemsavir
Aptivus® (Tipranavir)	Tybost ® (Cobicistat)
Crixivan® (Indinvavir)	**Single Tablet Regimens**
Viracept® (Nelfinavir)	Atripla® (Emtricitabine/TDF/Efavirenz)
Reyataz® (Atazanavir)	Complera® (Emtricitabine/TDF/Rilpivirine)
Kaletra® (Lopinavir/Ritonavir)	Stribild® (Emtricitabine/TDF/Elvitegravir/Cobicistat)
Lexiva® (Fosamprenavir)	Triumeq® (Abacavir/Lamivudine/Dolutegravir)
Prezista® (Darunavir)	Odefsey® (Emtricitabine/TAF/Rilpivirine)
Kaletra® (Lopinavir/Ritonavir)	Genvoya® (Emticitabine/TAF/Elvitegravir/Cobicistat)
Prezcobix® (Darunavir/Cobicistat)	Biktarvy® (Emtrictabine/TAF/Bictegravir)
Evotaz® (Atazanavir/Cobicistat)	Juluca® (Dolutegravir/rilpivirine)

Medication Class	Adverse Event
HMG-CoA Reductase Inhibitors (Statins)	Increased risk of rhabdomyolysis
Acid Reducing Agents (H2RAs/PPIs/antacids)	Virologic failure (decreased absorption)
Corticosteroids	Cushing syndrome and adrenal insufficiency
Benzodiazepines	Possible fatal respiratory depression
Sedative Hypnotics	Increased sedation
Opioids	Possible fatal respiratory depression
Anticonvulsants	Virologic failure (increased metabolism)
Anticoagulants and Antiplatelet Agents	Increased risk of bleeding or decreased antiplatelet activity
PDE5 Inhibitors	Increased risk of hypotension/priapism
Antifungals	Increased toxicity of antiretrovirals and antifungals or reduced efficacy of antifungals
Polyvalent Cations	Virologic failure (decreased absorption)
Antipsychotics	Increased concentrations of antipsychotics
Antimycobacterial Agents	Virologic failure (increased metabolism)

HMG-CoA Reductase Inhibitors (statins)

- **Effect: Statins are CYP3A4 substrates. Increased statin levels can cause myopathy and rhabdomyolysis.**
- Lovastatin and simvastatin are **contraindicated** with PIs and cobicistat
- Atorvastatin and rosuvastatin concentrations are increased but **acceptable to use**
  - Use lower dosages:
    - 10mg Rosuvastatin and 20mg Atorvastatin
- Pravastatin and pitavastatin have minimal CYP 450 metabolism and are **acceptable to use**
- Efavirenz can reduce levels of statins
- Fostemsavir can increase all statin levels
- **Caution:** External PCPs may prescribe in addition to HIV providers

Knowledge Check Question #1

- Which statin(s) are contraindicated with Protease inhibitors and Cobicistat?
  - A) Simvastatin
  - B) Rosuvastatin
  - C) Lovastatin
  - D) Atorvastatin
  - E) Both A and C

Knowledge Check Question #1

- Which statin(s) are contraindicated with protease inhibitors and cobicistat?
  - A) Simvastatin
  - B) Rosuvastatin- max dose 10mg
  - C) Lovastatin
  - D) Atorvastatin- max dose 20mg
  - **E) Both A and C**

- Rationale: simvastatin and lovastatin have significant CYP450 metabolism, PIs/Cobi are strong CYP450 inhibitors, which can lead to severe or fatal muscle toxicity

Proton Pump Inhibitors (acid blockers)

- **Effect: PPIs can cause virologic failure due to decreased absorption**
- Atazanavir absorption is substantially decreased by Omeprazole 40 mg
  - Equivalent of omeprazole 20 mg can be given 12 hours apart only in **treatment naïve patients**
  - Darunavir is a good PI alternative
- Rilpivirine levels are significantly decreased by PPIs
  - **Contraindicated**
  - **Caution:** Complera®, Odefsey ® and Juluca® **ALL contain rilpivirine** and PPIs are **available OTC!**

H_2 Receptor Antagonists (acid blockers)

- **Effect: H2RAs can cause virologic failure with atazanavir and rilpivirine due to decreased absorption**
- Atazanavir (boosted):
  - Give ATV 300 mg (plus COBI 150 mg **or** RTV 100 mg) simultaneously with and/or ≥10 hours after the dose of H2RA.
  - ARV Treatment naïve: do not exceed famotidine equivalent up to 40 mg BID
  - ARV Treatment experienced: do not exceed famotidine equivalent up to 20 mg BID
- Rilpivirine:
  - Give H2RAs at least 12 hours before or at least 4 hours after rilpivirine
- **Caution:** Another OTC available class!

Knowledge Check Question # 2

- Which drug(s) should not be given with high dose proton pump inhibitors?
  - A) Atazanavir
  - B) Rilpivirine
  - C) Dolutegravir
  - D) A and B

Knowledge Check Question # 2

- Which drug(s) should not be given with high dose proton pump inhibitors?
  - A) Atazanavir
  - B) Rilpivirine
  - C) Dolutegravir
  - **D) A and B**

- Rationale: atazanavir/rilpivirine levels are decreased by PPIs leading to a loss of ARV efficacy

Corticosteroids

- **Effect: Corticosteroids are CYP3A4 substrates. Increased steroid levels can result in adrenal insufficiency, Cushing syndrome, osteoporosis, and immunosuppression**
- Protease inhibitors and cobicistat inhibit the metabolism of corticosteroids
- Effect is not limited to just systemic steroids
  - ADRs reported with inhaled, intranasal, local and ophthalmic steroids
- **Avoid fluticasone, mometasone, budesonide, betamethasone**
  - **Intranasal**: flunisolide or beclomethasone as alternative to fluticasone
  - **Inhaled**: beclomethasone as alternative or lowest budesonide doses
- **Caution**: Beware of **combos** with fluticasone-i.e. Advair®, Breo®, Trelegy® and **OTC** use potential!
- **Caution:** External PCPs may prescribe in addition to HIV providers

Benzodiazepines (sedatives)

- **Effect: Benzodiazepines are metabolized by CYP3A4. Increased Benzodiazepine levels result in increased sedation and respiratory depression**
- Oral Midazolam and Triazolam are **contraindicated** with cobicistat and PIs
- Parenteral Midazolam- use with caution
  - Single dose use for procedural sedation ok
- Alprazolam and Diazepam levels can be increased
  - Consider alternative agents/ lowest doses
- **Use "LOT":**
  - Lorazepam, Oxazepam and Temazepam are metabolized by non-CYP450 pathways and are preferred

Sedatives/Opioids

- **Effect: Increased sedation/ possible fatal respiratory depression**
- **Zolpidem:**
  - Increased concentrations possible with PIs and cobicistat
  - Start at lowest dose, dose reduction may be necessary
- **Buprenorphine:**
  - PIs and cobicistat can increase concentrations
  - Start at lowest dose, dose reduction may be necessary
- **Fentanyl:**
  - PIs and cobicistat may increase concentrations
  - Start at lowest dose, dose reduction may be necessary
- **Methadone:**
  - Boosted PIs can slightly decrease concentrations
    - Monitor for withdrawal
  - Efavirenz and nevirapine can reduce concentrations
    - Opioid withdrawal can occur, consider slightly increasing dose

Rx practice: What is wrong?

- Truvada (FTC/TDF)® 200mg/300mg daily
- Evotaz (ATV/cobi)® 300mg/150mg daily
- Omeprazole 40mg daily
- HCTZ 25mg daily
- Multivitamin 1 daily
- Fluticasone 1 spray each nostril BID

Rx practice: What is wrong?

- Truvada (FTC/TDF)® 200mg/300mg daily
- Evotaz (ATV/cobi)® 300mg/150mg daily
- Omeprazole 40mg daily-*contraindicated*
- HCTZ 25mg daily
- Multivitamin 1 daily
- Fluticasone 1 spray each nostril BID-*contraindicated*

Anticonvulsants (seizures)

- **Effect: Carbamazepine, phenobarbital, and phenytoin are CYP 3A4 inducers. Coadministration is contraindicated due to the potential for reduced plasma concentrations of ARVs.**
  - Loss of therapeutic effect and development of resistance to ARVs especially cobicistat /PIs, NNRTIs, fostemsavir
- **Newer anticonvulsants** should be used to avoid major interactions
  - Levetiracetam, lacosamide, gabapentin, and pregabalin are recommended
    - Eliminated renally

Antiplatelet Agents (prevent clots)

- **Effect: decreased antiplatelet activity**
- Clopidogrel:
  - Do not administer clopidogrel with PIs and cobicistat
  - Clopidogrel active metabolite AUC decreases by 320% with a booster, leading to insufficient inhibition of platelet aggregation
- Ticagrelor:
  - Coadministration has not been studied but ticagrelor use with strong inhibitors of CYP3A4 is contraindicated
- Prasugrel:
  - **Preferred in boosted regimens**

Rx practice : What is wrong?

- Symtuza (DRV/Cobi/FTC/TAF)® 800/150/200/10mg daily
- Atorvastatin 40mg daily
- Clopidogrel 75mg daily
- Lisinopril 20mg daily

Rx practice : What is wrong?

- Symtuza (DRV/Cobi/FTC/TAF)® 800/150/200/10mg daily
- Atorvastatin 40mg daily- *max dose 20mg*
- Clopidogrel 75mg daily- *contraindicated*
- Lisinopril 20mg daily

Anticoagulants (blood thinners)

- **Effect: Increased risk of bleeding**
- Warfarin is generally the anticoagulant of choice for patients taking regimens including a PI or cobicistat
  - PIs and cobicistat inhibit warfarin metabolism
  - NNRTIs can induce warfarin metabolism
  - Closely monitor INR when initiating or discontinuing a PI, cobicistat, or NNRTI
- Avoid use of rivaroxaban and apixaban with PIs and cobicistat
  - US label gives the option to use apixaban at a reduced dose (i.e., 2.5 mg BID) if needed.
  - Potential for increased risk of bleeding (category X) due to increased concentrations
- Dabigatran with PIs and cobicistat
  - 110 mg BID with normal renal function
  - 75 mg BID with moderate renal impairment
  - coadministration should be avoided in case of severe renal impairment

Phosphodiesterase 5 Inhibitors (erectile dysfunction)

- **Effect: PIs and cobicistat increase levels of PDE-5 inhibitors leading to hypotension/priapism**
- Sildenafil 25 mg given with darunavir/ritonavir = 100 mg sildenafil alone
  - Not to exceed 25 mg every 48 hours with PIs and cobicistat
  - Treatment of pulmonary arterial hypertension with sildenafil is contraindicated with PIs and cobicistat
- Tadalafil for erectile dysfunction
  - Dosing should start at 5 mg and not exceed 10 mg in 72 hours
- Tadalafil for BPH
  - Maximum recommended dose is 2.5 mg daily with PIs/cobicistat

Antifungals

- **Effect: Increased toxicity of antiretrovirals and antifungals or reduced efficacy of antifungals**
- Itraconazole and posaconazole levels may be increased with cobicistat and PIs
  - Itraconazole dose should not exceed 200 mg daily unless closely monitored
  - Monitor posaconazole levels at steady state
- Voriconazole
  - Cobicistat can increase levels of voriconazole and voriconazole can increase Cobi levels
  - Ritonavir can potentially increase and decrease voriconazole levels due to ritonavir-mediated induction of CYP2C19, which is responsible for voriconazole metabolism.
  - Efavirenz is contraindicated with voriconazole at standard doses
- Fluconazole does not have any significant interactions with the PIs, cobicistat, or efavirenz

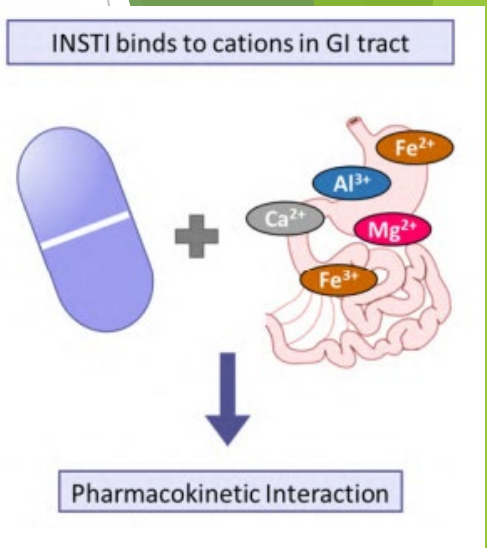
Rx practice : What is wrong?

- Truvada (FTC/TDF)® 200/300mg 1 daily
- Prezista® (darunavir) 600mg BID
- Norvir® (ritonavir) 100mg BID
- Sildenafil 100mg Q48 hours prn
- Apixaban 5mg BID

Rx practice : What is wrong?

- Truvada (FTC/TDF)® 200/300mg 1 daily
- Prezista® (darunavir) 600mg BID
- Norvir® (ritonavir) 100mg BID
- Sildenafil 100mg Q48 hours prn- *max dose 25mg*
- Apixaban 5mg BID –*reduce dose to 2.5mg BID*

Polyvalent Cations (Al, Mg, Ca, Fe)



- **Effect: Polyvalent cations (Al, Mg, Ca, FeSo4) can reduce the absorption of INSTIs**
- Antacids can decrease levels by decreasing pH or binding
  - Atazanavir and rilpivirine need acidic environment
  - Raltegravir and dolutegravir bound by antacids
  - **General rule: give 2 hours before or 4 hours after**
- Administer Bictegravir and calcium or Iron together with food
- Administer Dolutegravir and calcium or iron together with food or separate administration by 2 hours prior to Dolutegravir or 6 hours after
- **Caution:** Another **OTC** available class!

Knowledge Check Question # 3

- When counseling a patient starting on Calcium and Bictegravir, which of the following is **not** true?
  - A) Take them together
  - B) Take them with food
  - C) Take them on an empty stomach

Knowledge Check Question # 3

- When counseling a patient starting on Calcium and Bictegravir, which of the following is **not** true?
  - A) Take them together
  - B) Take them with food
  - **C) Take them on an empty stomach**

- Rationale: when coadministered with calcium under fed conditions, the bictegravir AUC was not significantly altered

Antimycobacterial Agents (TB,MAC)

- **Effect: Virologic failure (increased metabolism)**
- Rifampin:
  - Potent inducer
  - Not recommended with PIs and cobicistat
  - Not recommended with fostemsavir
  - Contraindicated with rilpivirine
  - Contraindicated with bictegravir/TAF
    - reduced concentrations can lead to decreased efficacy or resistance
- Rifampin can be administered with dolutegravir and raltegravir if dose adjusted
  - Dolutegravir: 50 mg BID with rifampin
  - Raltegravir: 800 mg BID with rifampin
- Rifampin can induce efavirenz metabolism

Antimycobacterial Agents (TB,MAC)

- **Effect: Virologic failure (increased metabolism)**
- Rifabutin:
  - less potent CYP inducer
  - Can be given at doses of 150 mg daily or 300 mg 3x/week with PIs
  - Significantly reduces concentrations of agents boosted by cobicistat (avoid)
  - No adjustment with dolutegravir or raltegravir with rifabutin
- Rifabutin levels are decreased by efavirenz
  - Give rifabutin 450mg to 600 mg daily or 600 mg 3x/week
- Rifabutin is contraindicated with rilpivirine and Biktarvy®
- If etravirine is given with a PI/ritonavir avoid rifabutin

Antipsychotics

- **Effect: Concentrations are increased with PIs and cobicistat leading to toxicities**
- Quetiapine:
  - Initiate at lowest dose and monitor closely
  - Patients stable on quetiapine adding a PI or cobicistat:
    - Reduce dosage to 1/6 dose and monitor
- Lurasidone:
  - Contraindicated
- Aripiprazole:
  - Administer 50% of the usual aripiprazole dose.
  - Titrate dose based on clinical monitoring for efficacy/adverse events.

Knowledge Check Question # 4

A patient is maintained on Genvoya® (TAF/FTC/EVG/cobi). This patient is newly diagnosed with Bipolar disorder and is going to be started on quetiapine 300mg daily. Which of the following actions can be taken to reduce the likelihood of a drug interaction occurring?

A. Increase dose to 400mg daily

B. Decrease dose to 150mg daily

C. Increase dose to 800mg daily

D. Decrease dose to 50mg daily

Knowledge Check Question # 4

A patient is maintained on Genvoya®. This patient is newly diagnosed with Bipolar disorder and is going to be started on Quetiapine 300mg daily. Which of the following actions can be taken to reduce the likelihood of a drug interaction occurring?

A. Increase dose to 400mg daily

B. Decrease dose to 150mg daily

C. Increase dose to 800mg daily

D. Decrease dose to 50mg daily

Rationale: **Concentrations are increased with PIs and cobicistat, reduce dose by 1/6 and monitor**

Danger- Will Robinson!

Google Image: Lost In Space

"Red Flag Classes" in Practice

Medication Class	ARVS interacting	Adverse Event
HMG-CoA Reductase Inhibitors (Statins)	PIs and boosters/Fostemsavir	Increased risk of rhabdomyolysis
Acid Reducing Agents (H2RAs/PPIs/antacids)	Atazanavir/Rilpivirine	Virologic failure (decreased absorption)
Corticosteroids	PIs and boosters	Cushing syndrome and adrenal insufficiency
Benzodiazepines	PIs and boosters	Increased sedation/possible fatal respiratory depression
Sedatives/Opioids	PIs and boosters	Increased sedation/possible fatal respiratory depression
Anticonvulsants	PIs and booster/Fostemsavir/NNRTIs	Virologic failure (increased metabolism)
Anticoagulants and Antiplatelet Agents	PIs and boosters/NNRTIs	Increased risk of bleeding or decreased antiplatelet activity
PDE5 Inhibitors	PIs and boosters	Increased risk of hypotension/priapism
Antifungals	PIs and boosters/NNRTIs	Increased toxicity of ARVS/antifungals or reduced efficacy of antifungals
Polyvalent Cations	INSTIs	Virologic failure (decreased absorption)
Antipsychotics	PIs and boosters	Increased concentrations of antipsychotics leading to toxicities
Antimycobacterial Agents	PIs/boosters/ NNRTIs/Fostemsavir/INSTIs	Virologic failure (increased metabolism)

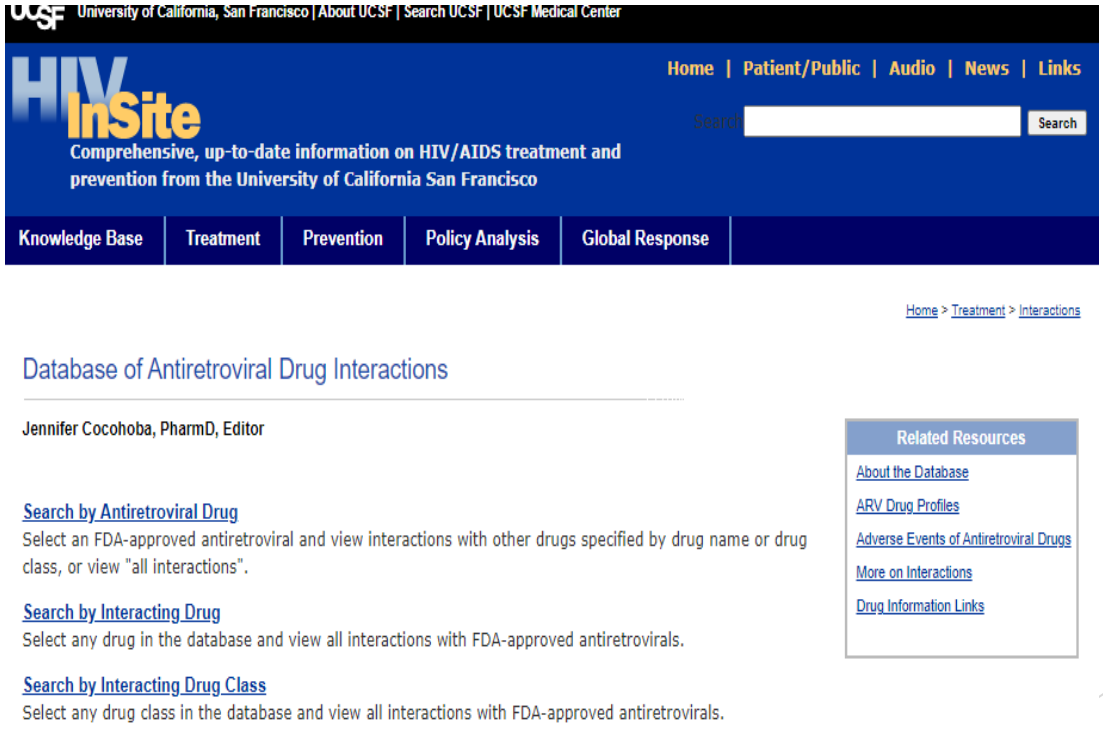
Summary

- PLWH are living longer resulting in more comorbidities, polypharmacy, and an increased risk of drug-drug interactions
- Counseling, medication reconciliation and interviewing patients is key (i.e. OTC or herbal use)
- Important ARVs to monitor → **PIs, Cobicistat, Ritonavir, NNRTIs**
- **ALWAYS COMPLETE A DRUG INTERACTION CHECK** if a new medication is being started- (i.e. Up to Date, Liverpool)

Helpful Resources

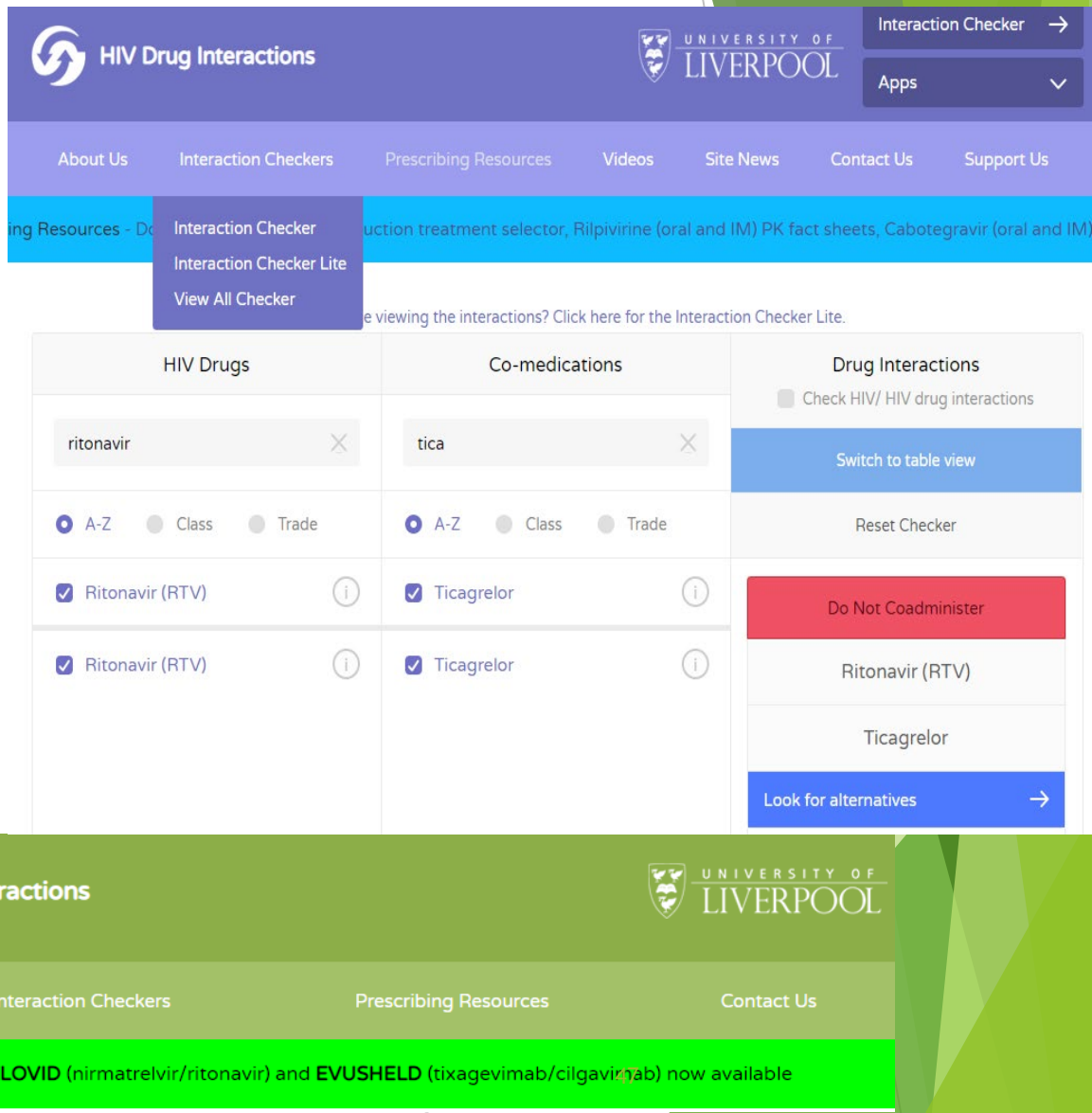
HIVInsite-UCSF :

www.hivinsite.ucsf.edu



Helpful Resources

Liverpool Drug Interactions:
www.hiv-druginteractions.org



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