



Antiretroviral Pharmacotherapy Issues

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Disclosures

No financial interests to disclose



Objectives

- Review side effects and complications of commonly used antiretrovirals
- Define Drug-Drug Interactions
- Define Pharmacokinetics
- Review Significant ART Drug Interactions
- Apply information to antiretroviral drug interaction cases



Side Effects

- Benefits of effective ART far outweigh risk of side effects/toxicity
- Previous era – common reason for switching and poor medication adherence
- New medications – more tolerable



Side Effects

Considerations to Reduce the Risk

- Concomitant use of other medications
 - Overlapping /additive toxicities
 - Drug-drug interactions
- Co-morbid conditions increasing risk
- Genetic factors that predispose patients toxicity



NRTIs: Side Effects

- Nausea/vomiting/diarrhea
- Headache
- Lipoatrophy
- Mitochondrial toxicities
 - Peripheral neuropathy
 - Pancreatitis, lactic acidosis, and hepatic steatosis
 - d4T > ddI & AZT > others



Abacavir (ABC)

Ziagen ®, Epzicom ®, Triumeq®

- HLA-B*5701 screening required
- No renal adjustment required
- Cardiovascular risk?



Lamivudine (3TC) or Emtricitabine (FTC)

Epzicom®, Triumeq®
Genvoya,

Truvada®, Descovy®, Stribild®,
Odefsy®, Complera®

- Well tolerated
- Nausea/Vomiting (unusual)
- Hyperpigmentation of skin (FTC)



Tenofovir (TDF or TAF)

Truvada®, Descovy®, Stribild®, Genvoya,
Odefsy®, Complera®

- **Kidney Issues (with TDF)**
 - Proximal tubular dysfunction/Fanconi's
 - May result in AKI or CKD

- **BMD decrease (with TDF)**

- **TAF**
 - New salt formulation
 - Results in 90% less tenofovir in the plasma
 - Allows for lower doses/fewer side effects



NNRTI Class Side Effects

- Rash
- Hepatotoxicity
- Neuropsychiatric symptoms
 - Efavirenz
 - Rilpivirine



PI Class Side Effects

- Nausea, vomiting, diarrhea
- Metabolic
 - Hyperlipidemia
 - Lipodystrophy
 - Hyperglycemia & insulin resistance
 - Decreased bone mineral density
- QT prolongation (minimal)



Darunavir (DRV)

Prezista®, Prezcobix®

- Sulfa drug- but not necessarily a sulfa allergy
- No issues with bilirubin



Atazanavir (ATV)

Reyataz® , Evotaz®

- Hyperbilirubinemia
- Nephrolithiasis/Cholelithiasis (rare)
- Not a sulfa drug

Integrase Inhibitors (INSTI)



Elvitegravir (EVG)

Genvoya®, Stribild®, Vitekta®

Dolutegravir (DTG)

Tivicay®, Triumeq®

- Side Effects: Common
 - Nausea, diarrhea
 - Headache
 - Insomnia
 - Rash
- Side Effects: Rare (serious)
 - Rhabdomyolysis
 - Hepatotoxicity
 - Mental Health concerns (DTG)



Questions/Comments

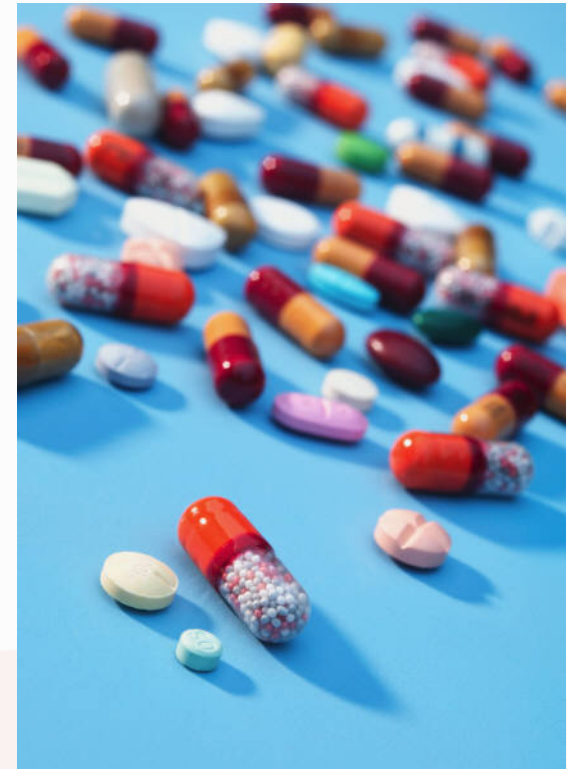


Antiretroviral Drug-Drug Interactions



What is a Drug-Drug Interaction?

- A drug interaction occurs when a drug interferes in a negative (or positive) way with another drug
- Can increase or lower drug levels
- Can occur between:
 - Two drugs (prescription, over the counter, vitamins, supplements and illegal drugs)
 - Drugs and foods/drinks





The Problem of Polypharmacy

Drug Interactions

Increased risk for drug interactions with increasing number of concomitant medications

Potential # of interactions =

$$\frac{n!}{2!(n-2)!}$$

Example:

# of drugs (n)	Potential # of interactions
1	0
2	1
3	3
4	6
5	10

What is Pharmacokinetics (PK)?



- Means movement of drugs
- Study of the relationship between dose, amount of drug in the body and therapeutic or toxic effects of a drug
- Pharmacokinetic data help us understand:
 - dose and schedule (once a day vs. twice a day, etc)
 - dose adjustments due to drug interactions and other issues.



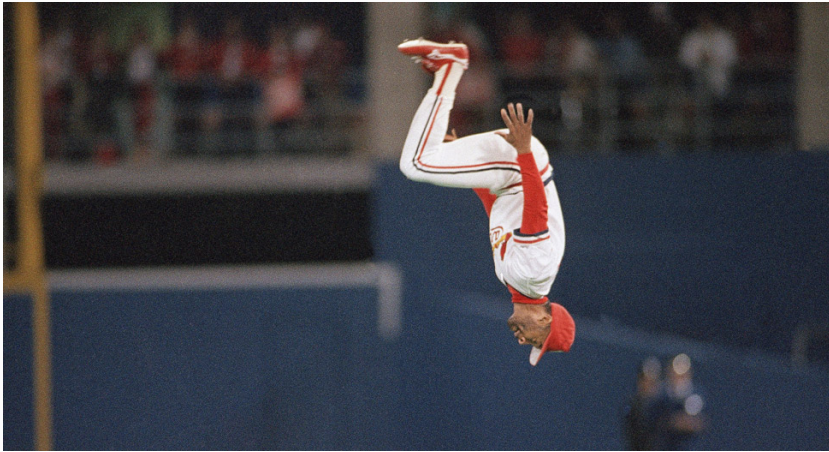
Processes that Determine Drug PK

Absorption: how the drug enters the blood

Distribution: how the drug travels in the blood and how it goes into and out of other areas of the body

Metabolism: how the body changes a drug usually in intestine and liver

Elimination: how the body gets the drug out
via kidneys through urine
via liver through stool



Case #1





Case #1

58 yo newly diagnosed pt presents to your clinic ready to start ART. Based on pt's presentation you decide on the using dolutegravir/abacavir/lamivudine combination tablet.

Medication List	
Pravastatin	40mg tablet daily
Lisinopril	40mg tablet daily
Cetirizine	10mg daily
Calcium/Vitamin D	1200mg/800mg daily
Tums E-X	750mg prn heart burn



Case #1

- Which of the following is true regarding pt's ART initiation?
 - A. By inhibiting HMG-CoA Reductase, pravastatin reduces the activity of the drug transporter responsible for dolutegravir absorption
 - B. Antihistamine (cetirizine) will decrease the risk for abacavir hypersensitivity
 - C. Calcium/Vit D supplement will bind to dolutegravir decreasing absorption
 - D. Tums-Ex will reduce dolutegravir levels



Absorption:

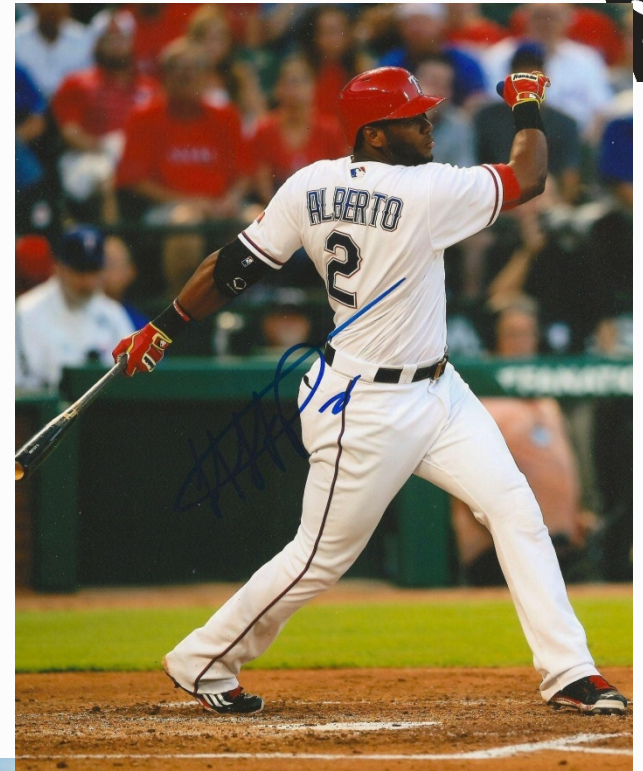
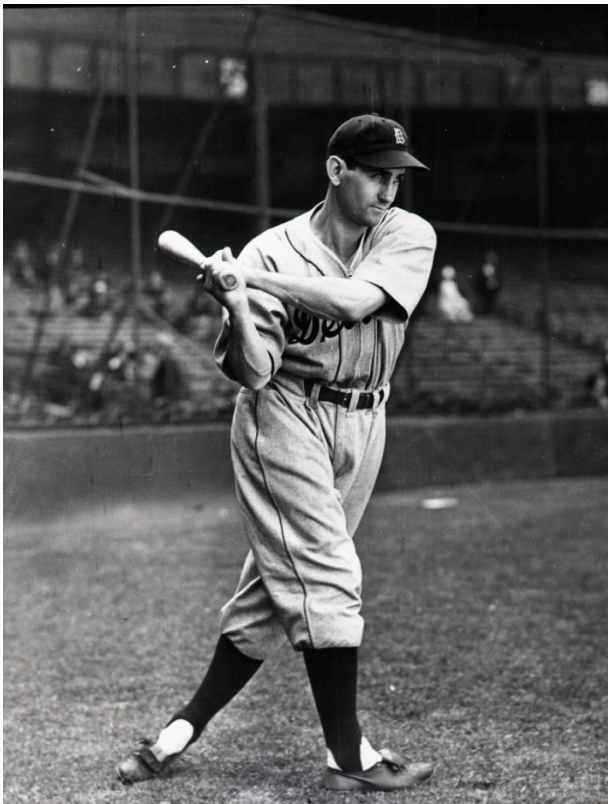
ART Drug Interactions

- Atazanavir : Needs acid to be absorbed
 - Proton Pump Inhibitors- Generic names all end in “-prazole”
 - Prilosec ® - omeprazole
 - Nexium ® - esomeprazole
 - Protonix ® - pantoprazole
 - Prevacid ® - lansoprazole
 - H2 blocker- Generic names end in “-tidine”
 - Zantac ® - ranitidine
 - Tagamet ® - cimetidine
 - Pepcid ® - famotidine
 - Axid ® -nizatidine
- Integrase Inhibitors: easily bound by polyvalent cations
 - Calcium
 - Iron
 - Magnesium



Distribution

- Limited drug interactions in this category
- None for ART(that we know)





Case #2

Pt with hx of allergic rhinitis presents to clinic with complaints of sneezing, postnasal drip, cough, and fatigue.

Medication List	
Pravastatin	40mg tablet daily
Aspirin	81mg tablet daily
Metformin	500mg tablet twice daily
Lisinopril	40mg tablet daily
Atazanavir	300mg capsule daily
Ritonavir	100mg tablet daily
Tenofovir DF/emtricitabine	300mg/200mg daily
Cetirizine	10mg daily



Case #2

Which of the following is concerning regarding patients current medication and potential treatment?

- A. Pt is at a higher risk of renal dysfunction with his tenofovir DF and the antihistamine
- B. Azelastine nasal spray is contraindicated with pt's meds
- C. Antihistamine drug levels are reduced by ritonavir making it less effective
- D. Fluticasone nasal spray is contraindication with pt's meds
- E. None of the above



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Case #3

Pt presents to your clinic for routine f/u. Pt has been on DRV/c, TAF/FTC for 1 year. VL has been <50 since 6 weeks after initiation. Pt reports that he recently had a seizure and was started on a new medication.

Medication List	
Rosuvastatin	10mg tablet daily
HCTZ	25mg tablet daily
Darunavir/cobicistat	300mg capsule daily
Tenofovir AF/emtricitabine	300mg/200mg daily
phenytoin	300mg capsule daily



Case #3

Which of the following is concerning regarding patients current medication and potential treatment?

- A. Phenytoin may decrease levels of DRV
- B. Phenytoin may increase levels of DRV
- C. DRV may increase levels of phenytoin
- D. DRV may decrease levels of phenytoin

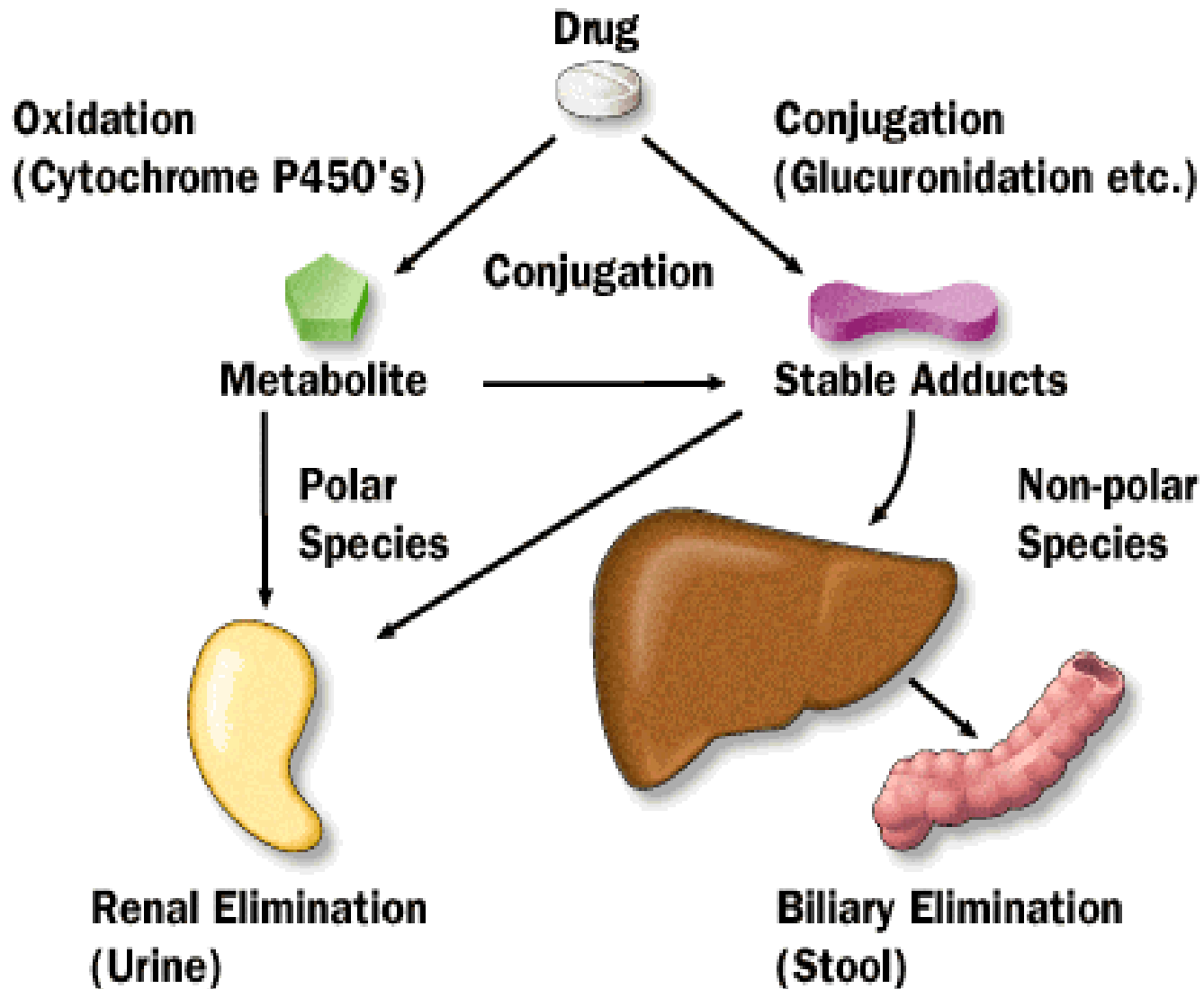


Metabolism

Most common pharmacokinetic step for drug interactions related to ART

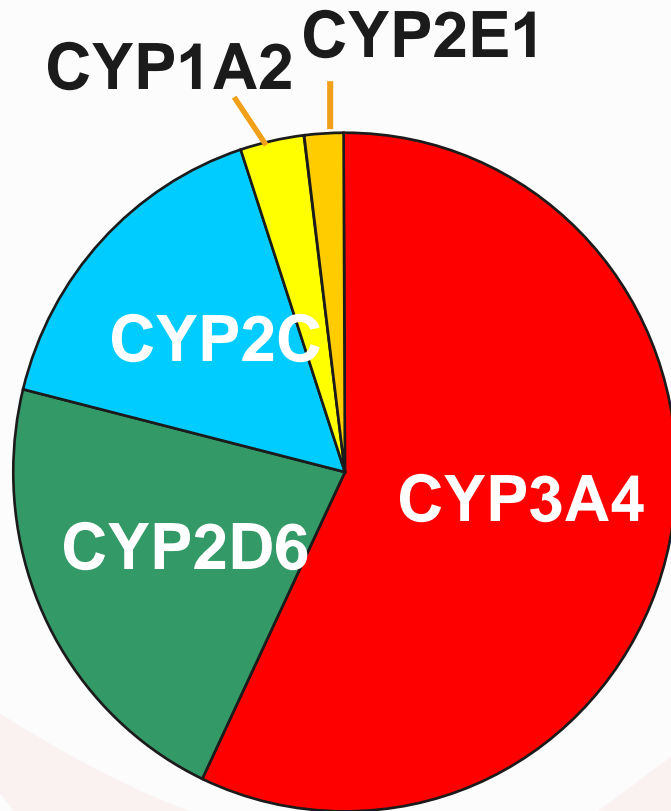


Drug Metabolism: Overview





CYP450 and Drug Metabolism



Key points

- Majority of drugs metabolized by CYP3A4 and CYP2D6
- CYP3A4 and CYP2D6 extensively involved with PI/NNRTI metabolism
- Enzymes can be induced or inhibited



Metabolism

- **Hepatic Metabolism Induction**
 - Results in decreased drug levels
 - Examples: efavirenz (Sustiva ®) induces metabolism of atazanavir (Reyataz ®)

- **Hepatic Metabolism Inhibition**
 - Results in increase drug levels
 - Example: Protease Inhibitors inhibit metabolism of simvastatin (Zocor ®) and lovastatin (Mevacor ®)



Metabolism

Common meds involved in ART Drug-Drug Interactions

Interactions can occur between different ART agents

- Efavirenz induces metabolism
 - PIs
 - Maraviroc
 - Dolutegravir and elvitegravir
- Etravirine only to be used with DRV, LPV/r, or SQV
- PIs inhibit metabolism
 - Each other
 - NNRTIs
 - Maraviroc



Metabolism

Common meds involved in ART Drug-Drug Interactions

- **Statins** – with Protease Inhibitors (PIs), cobicistat
 - Lovastatin (Mevacor ®) contraindicated
 - Simvastatin (Zocor ®) contraindicated
- **Steroids** – with PIs, cobicistat
 - PO
 - IV, IM, Intrabursal, Intrarticular
 - Inhalers/Nasal sprays – fluticasone products are the worst
- **Phosphodiesterase 5 Inhibitors (ED meds)**
- **Oral contraceptives**
- **Methadone**



Metabolism

Common meds involved in ART Drug-Drug Interactions

- Azole antifungals- with PIs, coBI, and NNRTIs
- Antiepileptic medications
 - Phenytoin, phenobarbital - with PIs and NNRTIs
 - Carbamazepine, Oxcarbazepine – PIs, NNRTIs, TAF, INSTI
- Rifampin – PIs, NNRTIs, coBI, INSTI



Metabolism

Mental Health Medications and ARVs

- Numerous interactions with ARVs
- Few truly contraindicated meds
 - Lurasidone and ritonavir or cobicistat
 - Some BZDs and protease inhibitors or cobicistat
 - Pimozide and PIs or cobi
- May require close monitoring for side effects
- May require dose adjustment or drug level monitoring



Excretion

- No interaction examples with ART
(that we know)



Strategies for Limiting Drug-Drug Interactions

- Real med reconciliation with each patient visit
- Assess medication list for interactions with any medication change
- Pt education related to drug interaction potential (including to OTCs, herbals, etc)
- Encourage use of one pharmacy
- Hire a pharmacist 😊



Antiretroviral Interaction Resources

- www.hivinsite.ucf.edu
- www.hiv-druginteractions.org
- www.aidsinfo.nih.org – interaction tables in DHHS guidelines



Conclusion

- Side effects and drug interactions occur but are generally manageable
- Drug interactions may increase morbidity and mortality
- The potential for drug interactions increases the complexity of treating HIV



Questions/Comments