Antiretroviral Drug-Drug Interactions

3 Part Case-Based Review

Case #1

“A Study in Clotting”

Case #1

Pt with new onset deep vein thrombosis (DVT) initiated on rivaroxaban (Xarelto®) at local hospital with instructions to follow-up with you.

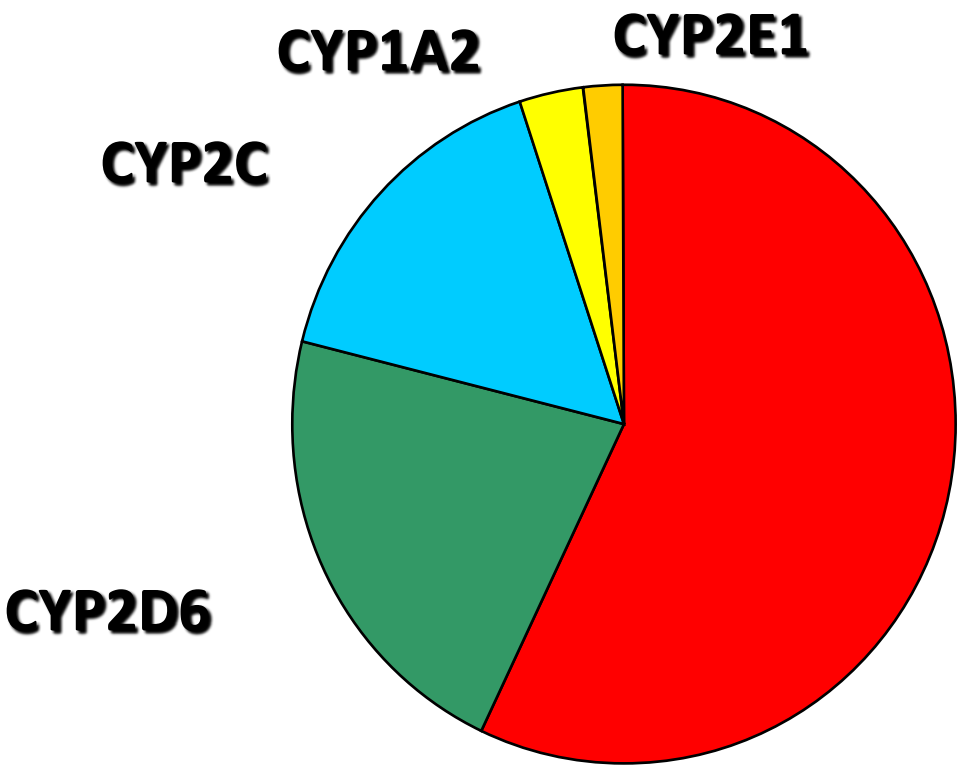
Medication List	
rivaroxaban	15mg tablet twice daily for 21 days then 20mg daily
HCTZ	25mg tablet daily
atorvastatin	20mg tablet daily
lisinopril	20mg tablet daily
sertraline	100mg tablet daily
Darunavir/cobicistat	800mg/150mg tablet daily
tenofovir AF/emtricitabine	25mg/200mg tablet daily

Case #1

Which of the following is concerning regarding patients new anticoagulant?

A. Pt is at a higher risk of bleeding d/t an interaction with cobicistat
B. Pt is at a higher risk of clotting d/t an interaction with cobicistat
C. Pt is at a higher risk of hypertensive emergency d/t an interaction with HCTZ and lisinopril
D. Pt is at a higher risk of hypotension d/t and interaction with HCTZ and lisinopril
E. None of the above

Super Quick Review!
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

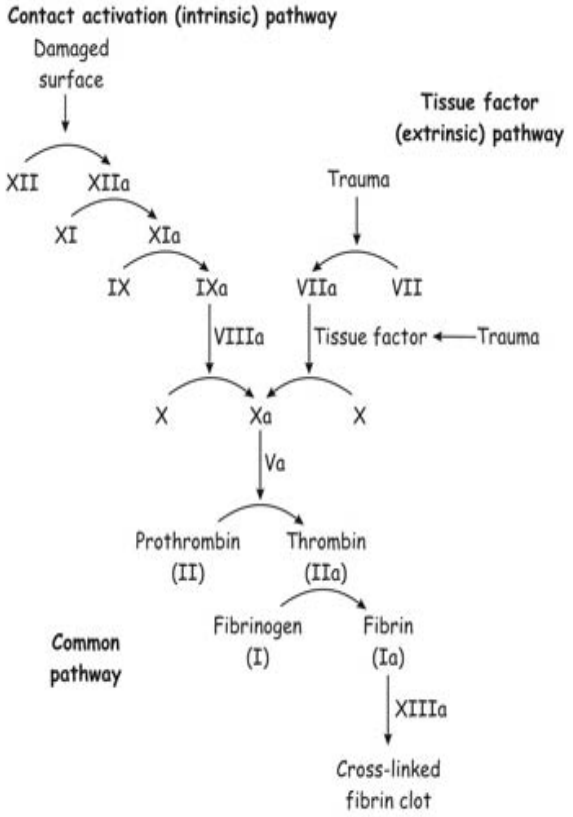
Super Quick Review! Metabolism

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

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

Factor Xa Inhibitors

- Directly inhibit FXa preventing the cleaving of prothombin to thrombin
- Meds that end in –xaban
- Require no INR monitoring
- No dietary restrictions
- Drug-drug interactions
- Bleeding risk



Factor Xa Inhibitos

- Rivaroxaban (Xarelto®)
  - Metabolized by CYP3A4 and P-gp
  - Contraindicated with CYP3A4 inhibitors/inducers
- Apixaban (Eliquis®)
  - Metabolized by CYP3A4 and other CYP enzymes
  - Dosing changes required if given with CYP3A4 inhibitors
  - Contraindicated with strong 3A4 inducers

Questions

Case # 2

“The man with the seasonal allergies”

Case #2

Pt with hx of allergic rhinitis presents to clinic with complaints of sneezing, postanasal 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

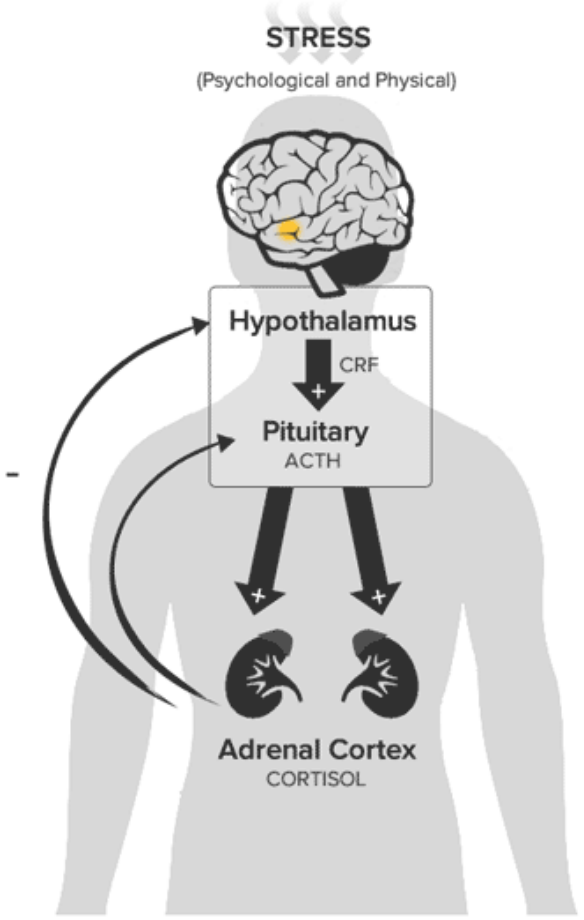
Which of the following is concerning regarding patients current medication and potential treatment?

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

Antiretrovirals and glucocorticoids

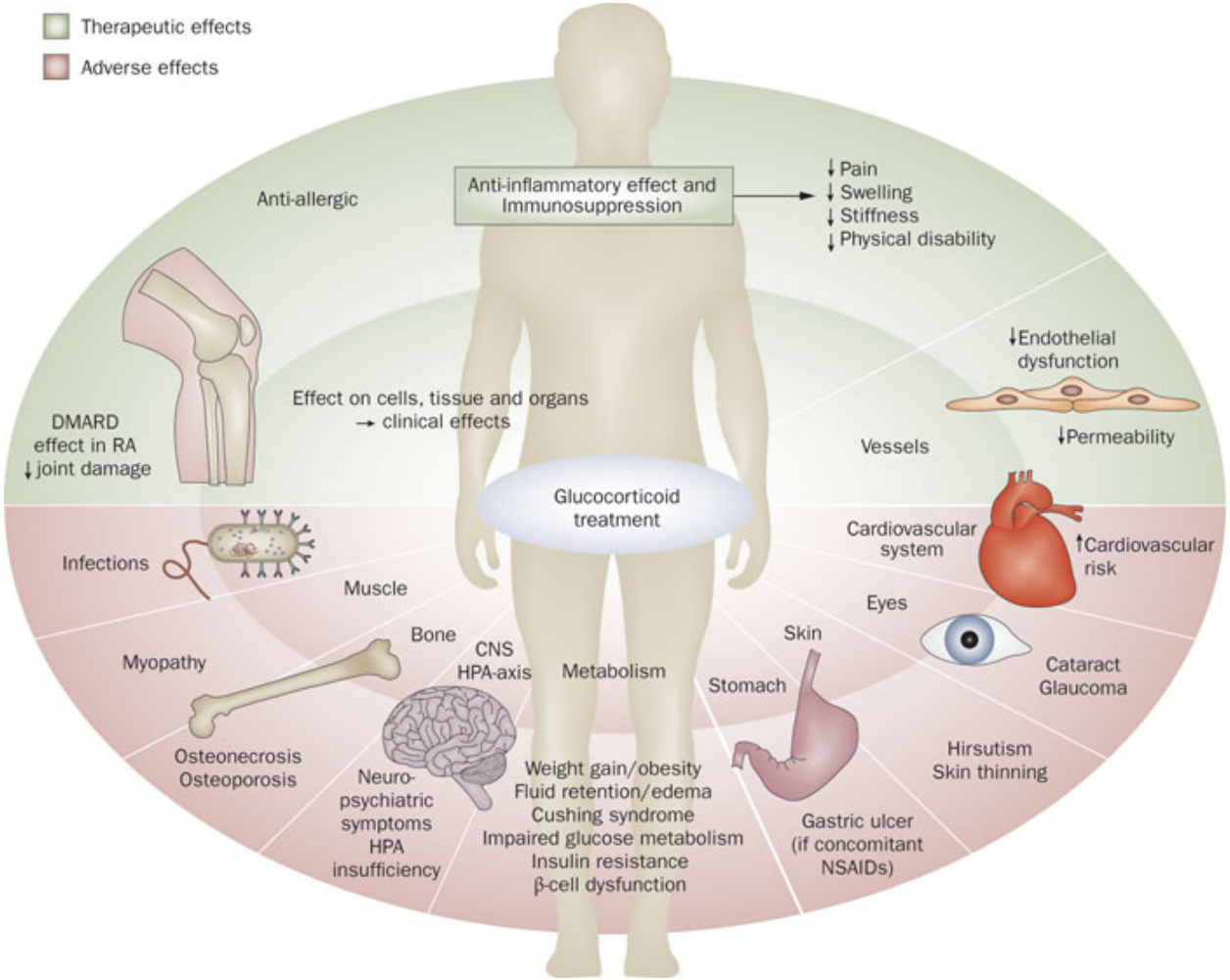
- Quick Reminder
  - Protease inhibitors (PIs) inhibit CYP3A4 metabolism
  - NNRTIs induce CYP3A4 metabolism
- Steroids
  - metabolized by CYP3A4
  - PIs may lead to HPA-axis dysfunction
  - NNRTIs may cause normal doses to be ineffective

HPA-Axis



http://www.integrativepro.com/Resources/Integrative-Blog/2016/The-HPA-Axis

Clinical effects spectrum of glucocorticoids



Hoes, J. N. *et al.* (2010) Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2010.179

Oral Glucocorticoids

- Prednisolone
  - AUC increase by ~30%
  - Increase risk of systemic toxicity
- Above is true for all oral glucocorticoids
  - May need lower than standard dosing
  - Will need close monitoring for adverse effects

Inhaled/Intranasal Glucocorticoids

- Fluticasone: contraindicated with PIs
  - Plasma AUC increased 350 fold
  - Plasma cortisol AUC decrease by 86%
  - Numerous case reports of Cushing's and adrenal suppresion
- Others (mometasone, beclamethasone, budesonide, triamcinolone, flunisolide)
  - Still have risk for increase levels
  - Lower affinity for glucocorticoid receptors
  - Short half-life

Glucocorticoid Injections

- Case reports of Cushing's and adrenal suppression
  - Epidural triamcinolone
  - Intrabursal triamcinolone
  - Intra-articular triamcinolone
  - Cortisone injections just about everywhere
- Benefit should far outweigh the risk before using

Topical Glucocorticoids

- No documented cases with topical steroids and ART

- Eye drops/ointment – one case of toxicity

Questions

Case #3

"The Five Orange Pills"

Case #3

Pt with newly diagnosed HIV. Has been managed for other co-morbidities by a PCP and a mental health provider and is unaware of medications other than taking 5 orange pills a day. After calling pt's pharmacy you find the following list:

Medication List	
Metformin	500mg tablet twice daily
Glipizide	10mg XR tablet daily
Oxcarbazepine	600mg twice daily
Quetiapine	400mg tablet daily
Rosuvastatin	10mg tablet daily

Case #3

Which of the following drug-drug interactions should be considered when selecting the patient's new antiretroviral regimen?

A. Rosuvastatin and protease inhibitors are contraindicated

B. Metformin is contraindicated with dolutegravir

C. Quetiapine doses should not exceed 200mg daily with protease inhibitors

D. Oxcarbazepine is contraindicated with almost all of the initial ART options recommended by the DHHS

E. All of the Above

Mental Health Medications and ARVs

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

Selective Serotonin Reuptake Inhibitors

- Fluoxetine and Paroxetine levels decreased by darunavir/rtv and fosamprenavir/rtv (about 50%)
- Citalopram, escitalopram , & sertraline have fewest interactions
- Vilazodone: reduce dose to 20mg when used with HIV PIs or cobicistat

Tricyclic Antidepressants

- All boosted PIs and cobicistat expected to increase levels of TCAs
- Desipramine levels increased 59% with ritonavir 65% by cobi
- Similar increases likely for amitriptyline, imipramine, nortripyline
- Monitor for anticholinergic side effects, EKG, TCA levels

Other Antidepressants

- SNRIs:
  - Mirtazapine (Remeron®) & duloxetine (Cymbalta®): Generally well tolerated
  - Venlafaxine (Effexor®) and desvenlafaxine (Pristiq®): PIs and Cobicistat may increase levels use caution
- Bupropion (Wellbutrin®, Zyban®)
  - AUC decreased 57% with lopinavir/rtv
  - AUC decreased 46% with tipranavir/rtv
- Trazodone (Deseryl®)
  - With ritonavir-boosted PIs and cobicistat, start low, titrate
- Avoid nefazodone, fluvoxamine

Benzodiazepines

- **CONTRAINDICATED with COBI and RTV**
  - Triazolam and oral midazolam with PIs or cobicistat
  - Midazolam– Single dose for sedation acceptable if in a controlled environment
- Safest to use glucuronidated benzodiazepines (LOT)
  - **Lorazepam**
  - **Oxazepam**
  - **Temazepam**
- Use at lower doses & titrate with all PIs and cobicistat:

  Alprazolam, clonazepam, diazepam

Antipsychotics

- Contraindicated with PIs or Cobicistat
  - Pimozide
  - Lurasidone
- Often have CYP3A4 metbolism
  - Start low and go slow with ritonavir or cobicistat
  - Aripiprazole, ziprasidone, quetiapine, iloperidone
- Other metabolized by CYP2D6
  - Levels may be decrease by ritonavir
  - Olanzapine, risperidone

Carbamazepine/Oxcarbazepine

- Antiepileptics sometimes used for mood stabilization in hard to treat bipolar disorder
- Significant ART interaction implications

  LOWERS ART LEVELS!!!
  - CYP3A4 inducers
  - P-gp inducers
  - UGT1A1 inducers
- Contraindicated
  - Dolutegravir (CBZ can be given with BID DTG)
  - Elvitegravir
  - Tenofovir AF
  - Rilpivirine
- Major interaction
  - Protease Inhibitors
  - NNRTIs (besides riplivirine)
  - Maraviroc (dose adjust)

Antiretroviral Interaction Resources

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

Any Questions?

"The potential for drug interactions is extremely common, given the increasing complexity of managing patients infected with HIV. To avoid compromising therapeutic efficacy or increasing drug toxicity, practitioners need to be aware of potential interactions and are encouraged to use a systematic approach when managing patient drug therapy."

-Alice Tseng, Pharm.D. and Michelle Foisy, Pharm.D.