Clinically Relevant Drug Interactions in HIV Treatment

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Objectives
- Review mechanisms behind drug interactions with antiretroviral drugs (ARVs)
- Discuss recently approved ARV agents and key interactions of concern
- Identify interactions between ARVs and commonly prescribed medications and OTC products

Mechanisms of ARV Interactions

HIV Overview
- HIV is a retrovirus that infects essential cells within the immune system
  - Single stranded, positive sense, enveloped RNA virus
  - Infects CD4+ T cells, macrophages, and dendritic cells
- Chronic, untreated HIV infection progresses to acquired immunodeficiency syndrome (AIDS)
  - AIDS status defined by
    - CD4 count <200 cell/mm³
    - Development of ≥1 opportunistic infection
- No effective cure has been discovered → lifelong treatment with antiretroviral drugs (ARVs) is necessary

HIV Infection Course
Fundamentals of HIV Management

- All HIV-infected patients should be treated with ARV therapy
  - No longer based on CD4 count thresholds
  - Need 2-3 fully active agents from different drug classes
- Treatment goals
  - Suppress plasma HIV RNA
  - Restore and preserve immunologic function
  - Reduce HIV-associated morbidity and mortality
  - Prevent transmission of HIV

Drug Interactions in HIV

- ARVs are substrates, inhibitors, and inducers of several metabolic enzymes and transporters
  - ARV-ARV interactions very common
- Other concomitant non-HIV medications are also affected
- Increased longevity of HIV-infected patients → shifted need to management of comorbid conditions
  - Estimated that >50% of HIV-infected persons are 50 years of age or older
  - CV disease, metabolic disorders, non-HIV malignancies, and renal/liver dysfunction now more of a concern
Types of Drug Interactions

**Pharmacodynamic**
- Additive
- Synergistic
- Antagonistic

**Pharmacokinetic**
- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacokinetic Interactions


Absorption

- pH dependence for drug dissolution
  - Ex: atazanavir, ripirvirine
- Chelation of drugs that bind to cationic active sites
  - Ex: integrase inhibitors
- Expression of CYP enzymes in the small intestine
- Intestinal transporters
  - Efflux: P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)
  - Uptake: organic anion transporter (OAT)

Transporters

Image from: [http://www.pnas.org/content/109/7/2251/F1.large.jpg](http://www.pnas.org/content/109/7/2251/F1.large.jpg) (top), [http://www.nature.com/nrd/journal/v9/n3/images/nrd3028-f1.jpg](http://www.nature.com/nrd/journal/v9/n3/images/nrd3028-f1.jpg) (bottom)

Distribution

Transporters

**Substrates**

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
<th>Efflux</th>
<th>Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OATP</strong></td>
<td>Lipid-lowering agents (statins, ezetimibe), glyburide, rifampin, valsartan, olmesartan</td>
<td>Atazanavir, cobicistat, cyclosporine, gemfibrozil, lopinavir, ritonavir, saquinavir, tipranavir/ritonavir</td>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAT1</strong></td>
<td>Captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zidovudine</td>
<td>Probenecid</td>
<td>Not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OAT3</strong></td>
<td>Acyclovir, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, penicillin G, some statins</td>
<td>Probenecid, cimetidine, diclofenac</td>
<td>Not known</td>
<td></td>
<td></td>
</tr>
</tbody>
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**Inhibitors**

- Aliskiren, colchicine, dabigatran etexilate, digoxin, DPP4-inhibitors, fexofenadine, immunosuppressants, maraviroc, posaconazole, ranolazine, talinolol, tolvaptan

**Inducers**

- Cardiac medications (ACEIs, ARBs, antiarrhythmics, CCBs), cobicistat, macrolides, cyclosporine, itraconazole, ketoconazole, lopinavir, ritonavir

**Efflux**

- P-gp: Aliskiren, colchicine, dabigatran etexilate, digoxin, DPP4-inhibitors, fexofenadine, immunosuppressants, maraviroc, posaconazole, ranolazine, talinolol, tolvaptan
- BCRP: Many antineoplastics (topotecan), rosuvastatin, sulfasalazine

**Uptake**

- OATP1B1: Lipid-lowering agents (statins, ezetimibe), glyburide, rifampin, valsartan, olmesartan
- OATP1B3: Atazanavir, cobicistat, cyclosporine, lopinavir, ritonavir, saquinavir, tipranavir/ritonavir
- OCT2: H2RAs, metformin, NMDA-antagonists, pindolol
- OAT1: Captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zidovudine
- OAT3: Acyclovir, ciprofloxacin, famotidine, furosemide, methotrexate, zidovudine, penicillin G, some statins

Metabolism

Elimination
- NRTIs primarily renally eliminated
  - Require dose adjustments in patients with renal insufficiency
    - Exception: abacavir
- Creatinine secretion inhibited by some ARVs → transient SCR increase
  - MATE1 by cobicistat
  - OCT2 by dolutegravir, rilpivirine, ritonavir
- Inhibition of renal uptake transporters can increase drug levels
  - P-gp and OATP1B1/3 by cobicistat, ritonavir

ARV Interaction Overview

Cobicistat (COBI)
- Newer PK enhancer without HIV activity
  - Dose of 150 mg once daily
  - Strong inhibitor of 3A4 > 2D6
  - Similar AEs to RTV-boosted regimens
- Coformulated into fixed dose combinations (FDCs)
  - EVG/c/TDF/FTC (Stribild) – approved Nov 2012
  - ATV/c (Evotaz) – approved Jan 2015
  - DRV/c (PrezCISION) – approved Jan 2015
  - EVG/c/TAF/FTC (Genvoya) – approved Nov 2015
COBI Interactions

- Potent inhibitor of CYP3A4
- Similar potency of 3A4 inhibition, weaker 2D6 vs. RTV
- Similar interactions to RTV assumed with 3A4 substrates
  - P-gp, BCRP, OATP1B1/3, MATE

- Interaction profile between RTV and COBI may vary
  - No induction of CYP enzymes
  - Substrates for enzymes induced by RTV may not be affected with a transition to COBI
  - COBI may yield stronger MATE inhibition than RTV
  - Similar IC50, but higher intracellular accumulation via OCT2 uptake into renal tubular cells
- Drug interaction studies comparing differences between RTV- and COBI-boosted atazanavir and darunavir are lacking at this time

Tenoforv alafenamide (TAF)

- Newly available prodrug form of tenofovir (TFV)
  - Converted inside target cell by cathepsin A
  - 90% lower systemic concentrations of TFV \( \rightarrow \) less renal and bone toxicity vs. TDF

TAF Formulations

- TAF available at two different doses depending on concomitants ARVs
  - 10 mg \( \rightarrow \) boosted with RTV or COBI
  - 25 mg \( \rightarrow \) unboosted regimens
- Four FDC formulations at various stages of development
  - Genvoya\textsuperscript{®} (EVG/c/TAF/FTC) – approved Nov 2015
    - Alternative for Stribild
  - Odefsey\textsuperscript{®} (RPV/TAF/FTC) – approved March 2016
    - Alternative for Complera
  - Descovy\textsuperscript{®} (TAF/FTC) – application submitted
    - Alternative for Truvada
  - DRV/c/TAF/FTC – Ph3 trials, possible approval later in 2016

TAF Interactions

- TAF is increased 2.5-fold by boosted ARVs
  - Use 10 mg dose (\textbf{not} 25 mg)
- Intracellular metabolism by cathepsin A
  - TAF also inhibits cathepsin A \textbf{in vitro} \( \rightarrow \) contraindicated with certain hepatitis C protease inhibitors
- Substrate for P-gp, BCRP, OATP1B1/3
  - Inhibitors may increase TAF levels
  - Inducers may decrease TAF levels
- Weak inhibitor of OCT1 and MATE1
  - In vitro studies show weak inhibition of CYP3A

Common Interactions with ARVs

- 53 yo HIV-infected male presents to clinic with complaints of dizziness, disturbing dreams after restarting therapy with Atripla
  - Contains efavirenz/tenofovir/emtricitabine
- Current medication list
  - Atorvastatin 40 mg po daily
  - Atripla 1 tab po q HS
  - Lisinopril 20 mg po daily
  - Metformin 1000 mg BID with food
- The patient would like to change his ARV regimen
  - What would you recommend?
  - What interactions are you concerned about?

Patient Case #1
Antacids & Acid Suppressants

- Cautioned use with dolutegavir (DTG) specifically
  - DTG alone (Tivicay®)
  - DTG/abacavir/lamivudine (Triumeq®)
- DTG inhibits the renal transporter responsible for eliminating metformin (OCT2)
  - 79% increase in metformin AUC with DTG 50 mg q 24 hrs
  - vs. metformin 500 mg bid alone
  - 145% increase in metformin AUC with DTG 50 mg q 12 hrs
- Maximum metformin dose = 1,000 mg/day with concomitant use of DTG

Patient Case #1

- Regimen change from Atripla (efavirenz/tenofovir/emtricitabine)?
  - Atorvastatin 40 mg daily
    - 40 mg = 20 mg due to 3A4 induction by efavirenz
    - Efavirenz → dolutegravir or raltegravir?
      - Reduce dose to 20 mg to achieve similar effects
      - Efavirenz → darunavir/cobicistat or elvitegravir/cobicistat?
        - Reduce dose to 10 mg daily due to 3A4 inhibition
  - Lisinopril 20 mg daily
    - No change necessary
  - Metformin 2000 mg daily with food
    - Efavirenz → dolutegravir?
      - Maximum daily dose of 2000 mg
  - Pravastatin 20 mg daily
    - No adjustment
  - Pitavastatin 20 mg daily
    - No adjustment
  - Bupropion 150 mg bid
    - No adjustment
  - Simvastatin 40 mg daily
    - No data
  - Statins

Mineral Supplements

- Cationic minerals can reduce integrase inhibitor (INSTI) levels by 40-74% when coadministered
  - INSTIs are the only ARV drug class of concern → binds to Mg²⁺ in the HIV integrase enzyme
  - Applies to Ca²⁺, Fe²⁺, Al³⁺, Mg²⁺, and Zn²⁺ supplements
  - Sulfate and liquid bismuth subsalicylate can also interact
  - Extent of interaction with daily multivitamins unclear
- INSTIs must be taken 2 hrs before or 6 hrs after mineral supplements
  - Exception: dolutegavir can be given at the same time as Fe²⁺ or Ca²⁺ supplements if given with food

Statins

- PIs and elvitegravir/Cobi (EVG/c) can increase statin exposure
  - Efavirenz (EFV), etravirine (ETR), nevirapine (NVP) primarily decrease exposure
  - Do not exceed maximum statin doses to overcome induction

Anticoagulants & Antiplatelets

- Warfarin: CYP2C9 > 3A4
  - Monitor INR and adjust warfarin dose accordingly
  - Decreased warfarin levels possible with RTV-boosted PIs
  - Increased warfarin levels possible with etravirine
  - Avoid with 3A4 inhibitors & inducers
  - Rivaroxaban, apixaban, edoxaban: CYP3A4 and Pgp
    - Avoid with 3A4 inhibitors & inducers
  - Dabigatran: P-gp and MATE1
    - No induction of MATE1
    - Increases NO, may inhibit
    - INR increases
    - No adjustment
  - Clopidogrel: 2C9/19
    - Etravirine may prevent activation → do not coadminister
  - Warfarin: CYP2C9/19
    - Monitor INR and adjust warfarin dose accordingly
    - Decreased warfarin levels possible
    - No adjustment

- Antiplatelets
  - Apixaban, rivaroxaban, edoxaban: CYP3A4 and Pgp
    - Avoid with 3A4 inhibitors & inducers
Patient Case #2

- 34 yo male with recent diagnosis of HIV/AIDS
  - Initiated on Stribild (elvitegravir/cobicistat/tenofovir/emtricitabine)
  - Presented with cryptococcal meningitis, CMV encephalopathy
    - Neurological changes, agitation present despite effective therapy
    - Medical team decides to add on an antipsychotic
- What agent would you recommend?

Anticonvulsants

- Phenytoin, phenobarbital, carbamazepine, oxcarbazepine metabolized via CYP450 system
  - All are capable of CYP induction ➔ dual interaction with RTV-boosted PIs and NNRTIs
  - Many combinations are contraindicated or cautioned against
  - Consider alternatives if boosted PIs or NNRTIs required
    - Levetiracetam, lacosamide
    - Agents that undergo glucuronidation may be decreased by RTV-boosted PIs ➔ monitor drug levels
    - Valproic acid (+90% by UGT and beta-oxidation)
    - Lamotrigine (UGT1A4)

Antidepressants

- SSRIs, SNRIs, and TCAs metabolized via CYP2D6
  - Boosted PIs: start with lowest dose and titrate to effect
  - Darunavir/RTV: decreases paroxetine and sertraline AUC by 39-49%
    - Effects with Cobi unknown
  - Bupropion via 2B6
    - Efavirenz decreases levels by 55% ➔ titrate to effect
  - Trazodone via CYP3A4
    - 3-4 fold AUC increase with RTV administration
    - No data with Cobi but increased levels expected
    - May be used at low dose for sleep, titrate to effect
    - Mirtazapine could be considered as an alternative
  - Modifications to ARV regimen may require further dose adjustments in psych medications

Antipsychotics

- PIs and PK enhancers can alter concentrations of atypical antipsychotics
  - Nearly all are substrates for CYP3A4 and/or 2D6, some for 1A2, 2C19
  - Ritonavir (RTV)
    - Inhibits CYP3A4, 2D6 ➔ increased levels
    - Decreases levels of clarithromycin
  - Cobicistat
    - Inhibits CYP3A4, 2D6 ➔ increased levels expected, no data available
  - Numerous case reports documenting AEs following coadministration of antipsychotics + RTV-boosted PIs
    - EPS side effects, sedation, disorientation, significant weight gain develop quickly
    - Reversal of symptoms accomplished with discontinuation of antipsychotic or boosted PI

Anxiolytics & Hypnotics

- Anxiolytics
  - Alprazolam: avoid with PIs, no data with NNRTIs
  - Midazolam and triazolam: do not coadminister oral dose with efavirenz, or Cobi or RTV-boosted ARVs
  - Low interaction potential with lorazepam, oxazepam, temazepam ➔ alternative treatment options
- Hypnotics
  - Suvorexant (Belsomra®): contraindicated with 3A4 inhibitors
  - Zolpidem (Ambien®): 3A4 and other pathways ➔ increased levels possible with boosted PIs

Patient Case #2

- Treatment was initiated with quetiapine 50 mg daily
  - Partial response, further dose increases desired
  - Concern over boosting by Cobi ➔ guideline recommendation to use 1/6th dose
- Transitioned to olanzapine 12.5 mg daily
  - Metabolized by UGT, 1A2, 2D6 ➔ lower interaction risk
    - No data with Cobi-boosted regimens
  - Changed ARV regimen to Triumeq (dolutegravir/abacavir/tenofovir)
  - Reduce risk of drug interactions with future psych medications
Azole Antifungals

- Low dose fluconazole can be used with ARV regimens
- Itraconazole, ketoconazole, and itraconazole are 3A4 substrates and inhibitors → bi-directional interactions with PIs and NNRTIs
  - Certain combinations should be avoided or require dose adjustments
  - Consult guidelines and monitor azole levels
  - PIs increased azole and PI levels may result, monitor for PI toxicity
  - NNRTIs: decreased azole and increased NNRTI levels possible
  - Exception: ritonavir
- Voriconazole metabolized by CYP 3A4
  - RTV decreases AUC by 39% → monitor levels or consider alternatives
  - COBI-boosted ARVs may increase levels
  - Efavirenz decreases AUC by 77%: increase voriconazole to 400 mg BID
  - Decrease efavirenz from 600 mg to 300 mg daily (bi-directional interaction)

Corticosteroids

- Systemic corticosteroids altered by boosted PIs and NNRTIs
  - Prednisone AUC changes by 30% with 3A4 inhibition/induction
  - Dexamethasone decreases NNRTI AUCs → consider alternatives if >1-fold increase in AUC
  - COBI-boosted ARVs may increase levels
  - Inhaled and nasal corticosteroids are boosted by RTV and COBI → do not coadminister, concern for iatrogenic Cushion’s syndrome
  - Inhaled fluticasone + PI/r = 36-fold increase in AUC
  - Beclomethasone is currently the only alternative if a boosted regimen is necessary
  - Metabolized by esterases (not CYP450) → 2-fold increase with RTV alone (not clinically significant), unchanged with darunavir/RTV
- Intraarticular steroid injections can also be boosted with RTV or COBI-containing regimens → do not coadminister

Patient Case #3

- 35 yo male received epidural injections of triamcinolone acetonide (x2) for lumbosacral back pain at outside facility
  - ARV regimen: lopinavir/RTV BID + tenofovir/emtricitabine
  - Reported facial swelling within 1 week of injection
  - 1 month post-injection: BP 157/100, weight gain of 1.4 kg, “moon face” and “buffalo hump”, poor wound healing

Oral contraceptives can be affected
- Barrier methods needed if levels are decreased
- Depomedroxyprogesterone and IUDs do not appear to have significant interactions with ARVs
- May be preferred methods, but further studies are needed

Hormones

- Oral contraceptives can be affected
  - Barrier methods needed if levels are decreased
  - Depomedroxyprogesterone and IUDs do not appear to have significant interactions with ARVs
- Ethinyl estradiol (EE)
  - Decreased with PI/r, EFV, and NVP, (?)COBI
  - ATV/r use 0C with 35+ mcg EE
  - Increased with ATV 400 mg daily → max dose 30 mcg
- Progestins
  - Increased with ATV/r, (?)COBI
  - Monitor for acne, decreased HDL, and insulin resistance
  - Decreased with EFV and NVP
References

Resources for HIV Drug Interactions

- Liverpool: www.hivdruginteractions.org
- Toronto General Hospital: http://www.hivclinic.ca/main/drugs_interact.html
- Micromedex: www.micromedexsolutions.com

Conclusions

- Drug interactions can pose significant problems for HIV-infected patients on ARV therapy
- Aging HIV population is requiring chronic medication therapy for non-HIV-associated conditions
- Several drug interactions have been identified and characterized
- Many more are based on known interactions mediated by similar mechanisms → not always clear if similar or different
- Further research is still needed
- Full evaluations of all concomitant medications need to be conducted at every patient encounter

Questions?

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