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Connecting the Dots: Recognizing the Impact of Antiretroviral Therapy on Concomitant Therapies

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Disclosures

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Session Objectives

1) Given a patient case, evaluate the medication profile for potentially significant drug interactions.

2) Recommend appropriate therapeutic alterations to minimize harm to patients on antiretroviral therapy.

3) Predict drug interaction potential in situations where data is unavailable or unclear.

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Mechanistic Understanding of Antiretroviral Drug Interactions

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Learning Objectives

1) Evaluate medication profiles for potential drug-drug interactions involving antiretroviral agents

2) Apply knowledge of an antiretroviral agent's transporter and isoenzyme effects to determine potential drug-drug interaction mechanisms

3) Perform appropriate evaluation of pharmacokinetic studies to determine potential drug-drug interaction risks

Drug Interaction Mechanism Types

- Pharmacokinetic
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Pharmacodynamic
  - Synergistic
  - Antagonistic

JK Case

JK is a 45 year old male with HIV virologically- and immunologically-controlled on an antiretroviral regimen of dolutegravir/abacavir/lamivudine 50/600/300 mg once daily is admitted to your internal medicine floor with diverticulitis and you are profiling the following medications as part of his admission order set:

Piperacillin/tazobactam 3.375 gm intravenously q6 hours	Dextrose 5% with 0.45% NaCl 75 ml/hr
Acetaminophen 650 m orally q6 hours prn pain	Famotidine 20 mg intravenously twice daily
Magnesium hydroxide 30 mL daily as needed for constipation	Prochlorperazine 5 mg intramuscularly every 4 hours as needed for nausea/vomiting
Ondansetron 4 mg intravenously every 8 hours as needed for nausea/vomiting	Diphenhydramine 25 mg orally three times daily as needed for itching
Temazepam 15 mg qHS prn sleep	Calcium carbonate 500 mg chewable tablet 2 tablets orally every 2 hours as needed for heartburn
Dolutegravir/abacavir/lamivudine 50/600/300 mg orally once daily	

Absorption

- Binding interactions (e.g. cholestyramine)
- Chelation (e.g. dolutegravir and calcium)
- Stomach acid alterations (e.g. atazanavir and proton pump inhibitors)

JK Case Question #1

- Which of the following admission orders do you expect to cause a potential drug-drug interaction with JK's antiretroviral regimen?

  A. Famotidine
  B. Prochlorperazine
  C. Ondansetron
  D. Calcium carbonate

JK Question #2

- JK's nurse tells you he has been complaining of heartburn despite his famotidine and she would like to give him some calcium carbonate. He received his dolutegravir/abacavir/lamivudine 4 hours ago. Which of the following do you recommend?

  A. It is okay to give calcium carbonate now
  B. He cannot have calcium carbonate at all since he is receiving dolutegravir/abacavir/lamivudine. You should call his medical team and asked for this to be changed to Aluminum hydroxide/magnesium carbonate 31.7/119.3 mg/5 Ml
  C. Its okay to give calcium carbonate now
  D. Calcium carbonate can only be administered 2 hours prior to administering dolutegravir/abacavir/lamivudine

Distribution/Metabolism/Excretion

Drug-Drug Pharmacokinetic Interaction Studies

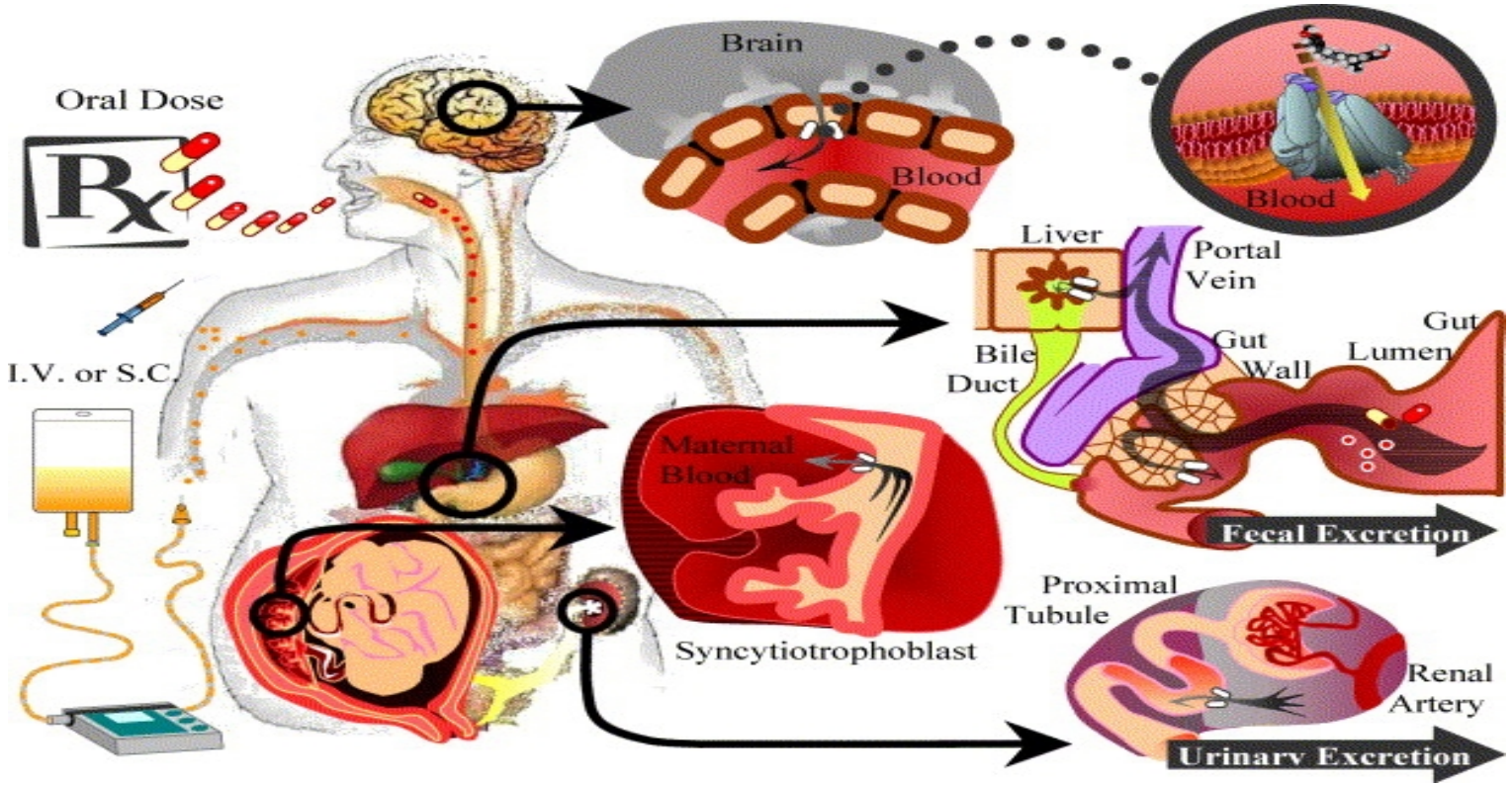
- *In vitro* studies intended to guide clinical DDI studies
- FDA has established definitions for clinical substrates, inhibitors and inducers as it relates to CYP-based interactions
  - Sometime pharmacogenetic alterations considered in lieu of clinical substrate alterations
- Results from CYP substrate-inhibitor studies can be extrapolated to other CYP inhibitors of similar magnitude (e.g. strong CYP3A4 inhibitor – substrate study can be applied to other strong CYP3A4 inhibitors)
  - Cannot extrapolate for transporters
- Drug-drug interactions can be difficult to predict with fixed dose combination (FDC) products, also when multiple mechanisms potentially at play

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf; Accessed 9/26/18
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport; Accessed 9/26/18

Transporters

- ATP-binding cassette (ABC) family transporters
  - P-glycoprotein (P-gp)/Multi-Drug Resistance 1 (MDR1)
  - Breast cancer resistance protein (BCRP)
  - MRP
- Solute carrier family transporters
  - Organic anion transporting polypeptides (OATP)
  - Organic anion transporters (OAT)
  - Organic cation transporters (OCT)

P-glycoprotein



Endres CJ et al: Eur J Pharm Sci 2006; 27(5): 501-17.

YM Case

- YM is a 67 year old female with past medical history significant for atrial fibrillation for which she has been maintained on digoxin 0.25 mg daily for the last 4 years and recent diagnosis of HIV for which she was initiated on an antiretroviral regimen of tenofovir alafenamide/emtricitabine and darunavir 800 mg daily and ritonavir 100 mg daily approximately 1 month ago. She is admitted to the hospital following presentation with anorexia, nausea, vomiting, and weight loss and found to have a digoxin level was found to be >6.8 mmol/L.

P-glycoprotein

- Inhibitors (≥ 2-fold increase in digoxin AUC)

Antiretrovirals	Other
Lopinavir/ritonavir	Amiodarone
Ritonavir	Carvedilol
Saquinavir/ritonavir	Clarithromycin
Tipranavir/ritonavir	Itraconazole

- Substrates (≥ 2-fold increase in AUC with verapamil or quinidine)

Antiretrovirals	Other
Tenofovir AF/DF	Dabigatran
Maraviroc	Digoxin
	Fexofenadine

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport; Accessed 9/26/18

Other Transporters

Transporters	Substrates	Inhibitor Criteria	Inhibitors	Example Interaction(s)
OATP (OATP1B1, OATP1B3)	Atorvastatin Cerivastatin Glyburide Paclitaxel Pravastatin Repaglanide	≥ 2-fold AUC increase with clinical substrate	Atazanavir/ritonavir Lopinavir/ritonavir Saquinavir	Repaglanide x atazanavir/ritonavir*
OAT (OAT1/OAT3)	Zidovudine	≥ 1.5-fold AUC increase with clinical substrate	Probenecid Teriflunomide	Zidovudine x probenecid
OCT (OCT2/MATE)	Dofetilide Metformin	≥ 1.5-fold AUC increase in metformin	Dolutegravir	Dolutegravir x metformin Dolutegravir x dofetilide

*CYP-based mechanisms also involved

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport; Accessed 9/26/18

YM Case Follow-Up

- Her medical team asks for your assistance in determining if any component of her antiretroviral regimen could be responsible for her increased digoxin levels. Which of the following do you think is the likely culprit?

  A. Tenofovir AF
  B. Darunavir
  C. Emtricitabine
  D. Ritonavir

Ding R et al: Clin Pharmacol Ther 2004; 76 (1): 73-84.

- Design: double-blind, randomized, crossover prospective study
- Subjects: 12 healthy males
- Methods: received ritonavir (300 mg twice daily) or placebo for 11 days, digoxin 0.5 mg given intravenously on day 3
- Results:
  - Effects on digoxin pharmacokinetic parameters

Parameter	Placebo	Ritonavir
$AUC_{0-\infty}$ (h x ng/mL)	22 ± 9	41 ± 17
CL_r (mL/min)	194 ± 23	126 ± 21

Metabolism

- Cytochrome P450 (CYP)-mediated
  - Mixed-function oxidation (MFO): NDAPH + H^+ + O_2 + RH (oxidizable drug substrate) → $NADP^+$ + H_2O + ROH (hydroxylated metabolite)
  - Nomenclature: number-letter-number (family-subfamily-gene)
  - 90% of drug oxidation occurs by 6 enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5

- Non-CYP mediated
  - UDP-glucoronosyl transferases and esterases
  - Minor pathways: monoamine oxidases, aldehyde or alcohol dehydrogenases, N-acetyltransferases

Tanaka E et al: J Clin Pharm Ther 1998; 23: 403-16.

FB Case

- FB is a 42 year old male with HIV recently initiated on an initial antiretroviral regimen of darunavir 800 mg once daily, ritonavir 100 mg daily, and tenofovir AF/emtricitabine 25/200 mg daily with a good decrease in viral load from 257,000 copies/mL to 1,225 copies/ml and increase in CD4 from 57 cells/mcL to 149 cells/mcL after 4 weeks. After being admitted to the hospital with severe shortness of breath, cough and fever, the patient is found to have upper lobe cavitation on chest xray and positive AFB smear.

CYP450-Based Antiretroviral Interactions

	Inhibitors	Inducers	Substrate
3A4	Ritonavir* Cobicistat* Itraconazole*, Ketoconazole*, Fluconazole$ Clarithromycin*	Efavirenz$ Etravirine$ Rifampin	Efavirenz, Etravirine, Nevirapine, Rilpivirine, Doravirine Darunavir, Atazanavir, Ritonavir Elvitegravir, Cobicistat Maraviroc
2C9	Fluconazole$	Carbamazepine$ Rifampin$ Ritonavir$	Etravirine
2C19	Fluoxetine* Fluconazole*	Rifampin*	Etravirine
2B6		Efavirenz$, Ritonavir$ Rifampin$ Carbamazepine*	Efavirenz Buproprion

*Strong, $Moderate

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport; Accessed 9/26/18

Ketoconazole effects on Rilpivirine and Doravirine

- Pharmacokinetic study: ketoconazole x doravirine
  - ketoconazole (400 mg daily) and doravirine (100 mg single dose)
  - doravirine AUC, Cmax and Cmin increased by 3.1-fold, 1.3-fold, and 2.8-fold, respectively

- Pharmacokinetic study: ketoconazole x rilpivirine
  - Ketoconazole (400 mg daily) and rilpivirine (150 mg daily)
  - Rilpivirine AUC, Cmax and Cmin increased by 1.49-fold, 1.3-fold and 1.76-fold, respectively

- Results from both studies determined not to be clinically significant

Official package labeling for Pifeltro (doravirine). Merck & Co, Inc; Whitehouse Station, NJ (2018).
Official package labeling for Edurant (rilpivirine). Janssen Products; Titusville, NJ (2018).

FB Case – Question #1

- The medical team would like to empirically initiate an anti-tibuberculous regimen of ethambutol, isoniazid, rifampin and pyrazinamide. Which of the following of these medications is most likely to cause drug-drug interactions with the patients antiretroviral regimen?

A. Ethambutol
B. Isoniazid
C. Rifampin
D. Pyrazinamide

FB Case – Question #2

- Which of the following antiretroviral agents poses an interaction concern with rifampin?

  A. Tenofovir AF
  B. Emtricitabine
  C. Darunavir
  D. Ritonavir

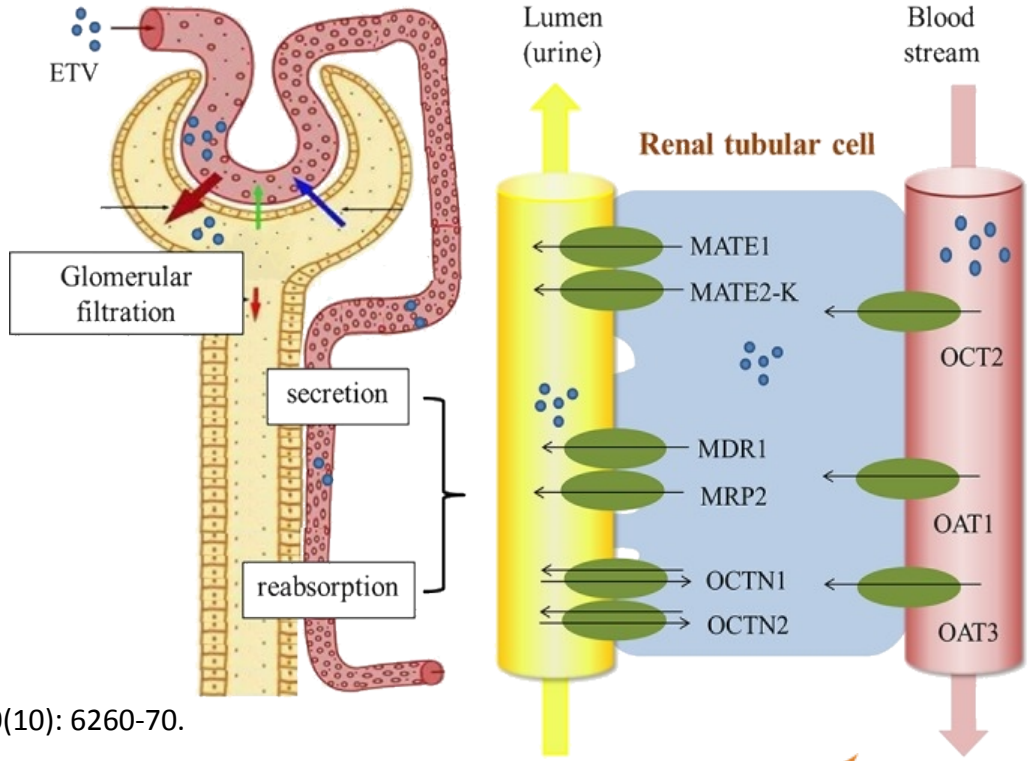
FB Case – Question #3

- Which of the following would be a potential drug-drug interaction strategy to recommend for FB?

A. Increase darunavir dose to 600 mg twice daily and ritonavir dose to 100 mg twice daily
B. Change rifampin to rifabutin
C. Change darunavir and ritonavir to efavirenz
D. Change darunavir and ritonavir to dolutegravir

(renal) Elimination

- Glomerular Filtration
- Proximal tubular secretion
- Distal tubular reabsorption



Yang X et al: Antimicrob Agents Chemother 2016; 60(10): 6260-70.

KEY TAKEAWAYS

1) DRUG-DRUG INTERACTIONS CAN OCCUR AT VARIOUS POINTS IN THE PHARMACOKINETIC PROCESS (ADME)

2) STATISTICALLY SIGNIFICANT PHARMACOKINETIC CHANGES NOTED IN CLINICAL STUDIES DO NOT ALWAYS TRANSLATE TO CLINICALLY SINGIFICANT OUTCOMES

3) TRANSPORTER EFFECTS HAVE TO BE CONSIDERED, ALONG WITH CYP-BASED MECHANISMS, WITH MIXED EFFECTS BEING UNPREDICTABLE

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Impact of HIV Pharmacotherapy On Key Therapeutic Areas

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Objectives

1. Based on a patient case, evaluate a medication list for potential drug-drug interactions involving antiretrovirals
2. Based on a patient case, design a therapeutic plan to manage drug-drug interactions
3. List resources to help identify drug-drug interactions with antiretrovirals

Some Abbreviations Throughout

ART: Antiretroviral

NRTI: Nucleoside reverse transcriptase inhibitor

NNRTI: Non-NRTI

PI: Protease inhibitor

INSTI: Integrase strand inhibitor

DRV/r: Darunavir/ritonavir

EVG/c: Elvitegravir/cobicistat

PK: Pharmacokinetic

PD: Pharmacodynamic

SABA: Short-acting beta$_2$-agonist

LABA: Long-acting beta$_2$-agonist

ICS: Inhaled corticosteroid

RTG: Raltegravir

DTG: Dolutegravir

Potential Drug-Drug Interactions in a Swiss HIV Cohort

- Observational cohort
- Prospective analysis of medications use between Apr-2008 and Jan-2009
- Assessed the prevalence of potential drug-drug interactions with antiretrovirals assessed with customized version of drug interaction database of University of Liverpool. Classified as:

Red flag interactions	Contraindicated, co-administration may lead to serious adverse events or decrease ART efficacy
Orange flag interactions	Potential drug-drug interaction that may require dose adjustment or close monitoring

Marzolini et al. *Antivir Ther*, 2010;15:413–23.

Potential Drug-Drug Interactions in a Swiss HIV Cohort

N = 1,497 patients treated with ART
68% (1,013/1,497) with concomitant medications
40% (599/1,497) with ≥1 potential drug-drug interaction

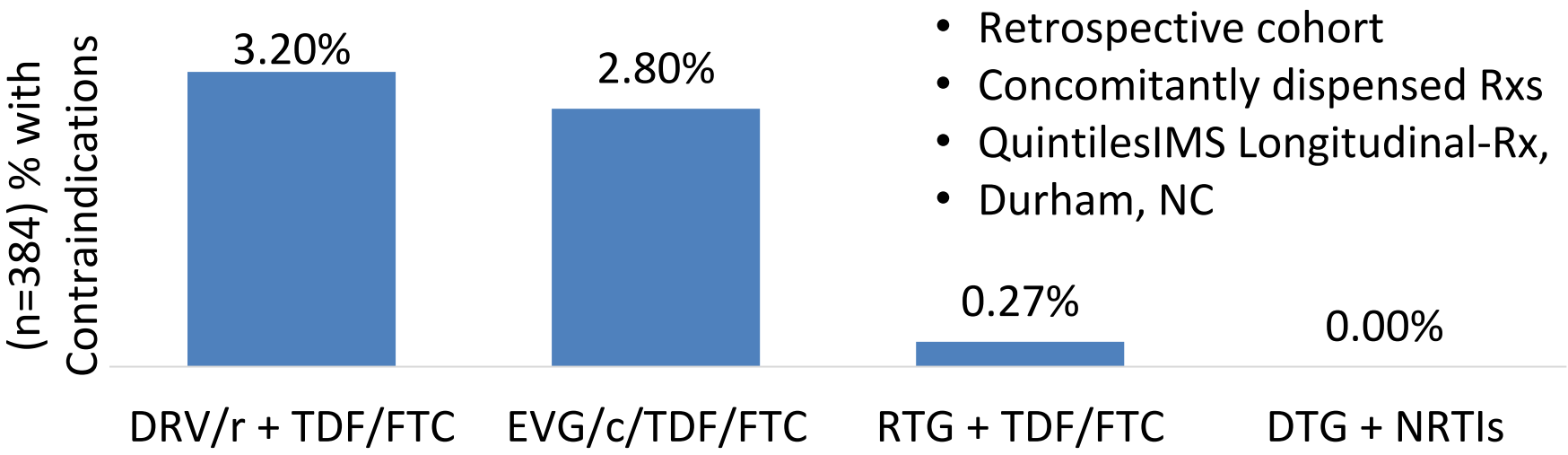
Red flag interactions	2% (21/1,013)
Orange flag interactions	59% (597/1,013)

Independent factors associated with potential drug-drug interactions:
Combinations with PIs and NNRTIs, OR=3.06 (95% CI, 1.44–6.48)
≥2 concomitant medications, OR=1.89 (95% CI, 1.32–2.70)
Current illicit drug use, OR=2.00 (95% CI, 1.29–3.10)
HCV co-infection, OR=1.74 (95% CI, 1.19–2.56)

Marzolini et al. *Antivir Ther*, 2010;15:413–23.

Drug Contraindications in a Large US Database

N = 25,919 ART-Naïve Patients Between April 2014 and March 2015



- Retrospective cohort
- Concomitantly dispensed Rxs
- QuintilesIMS Longitudinal-Rx,
- Durham, NC

DRV/r: darunavir/ritonavir; EVG/c: elvitegravir/cobicistat; RTG: raltegravir; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; NRTIs: nucleoside reverse transcriptase inhibitors

Patel et al. *Am J Health-Sys Pharm*, 2018;75(5):1132–9.

Drug Contraindications in a Large US Database

N = 25,919 ART-Naïve Patients Between April 2014 and March 2015

ART Regimen	DRV/r + TDF/FTC (*n*=3,386)	EVG/c/TDF/FTC (*n*=8,783)	RTG + TDF/FTC (*n*=10,508)	DTG + NRTIs (*n*=3,246)
Contra-indicated drugs	Salmeterol (44) Simvastatin (24) Phenytoin (12) Rivaroxaban (8) Rifampin (3) Apixaban (2) ED agents (4)	Salmeterol (80) Simvastatin (53) Phenytoin (19) Rivaroxaban (17) Rifabutin (15) Rifampin (13) Carbamazepine (13) Triazolam (10) ED agents (11)	Al^{2+} or Mg^{2+} antacids (28)	None

Patel et al. *Am J Health-Sys Pharm*, 2018;75(5):1132–9.

Drug-Drug Interactions: Why It Matters

- Retrospective case-control study
- US Military HIV Natural History Study, 1986 to 2011
- ≥18 years of age
- On NNRTI- or PI-based + 2 NRTIs, for ≥ 6 months
- All episodes of antiepileptic drugs for ≥28 days

CYP 450 Inducers	phenytoin, carbamazepine, phenobarbital
CYP 450 Non-Inducers	levetiracetam, lamotrigine, zonisamide, pregabalin, ethosuxamide, topiramate, gabapentin, tiagabine

Okulicz et al. *AIDS Res Ther*, 2011;8:18.

Drug-Drug Interactions: Why It Matters

US Military HIV Natural History Study, 1986 to 2011

Outcome	CYP 450 Inducer	CYP 450 Non-Inducer	OR (95% CI)
HIV-1 RNA ≥400 c/mL	63.3% (19/30)	27.9% (34/122)	4.29 (1.51 - 12.21) P = 0.006
HIV-1 RNA <400 c/mL at 6 months	28.6% (8/28)	69.4% (84/121)	0.17 (0.06 - 0.53) P = 0.002
HIV-1 RNA <400 c/mL at 12 months	39.1% (9/23)	74.0% (71/96)	0.21 (0.07 - 0.61) P = 0.004

Virologic failure more common in patients with periods of taking enzyme inducers

Okulicz et al. *AIDS Res Ther*, 2011;8:18.

My Approach to Identifying and Solving Drug-Drug Interactions in Patients Taking ARTs

ARTs
- Possible interaction pathways? PK or PD?
- Their reputation? NNRTIs (inducers), PIs (inhibitors)

Concomitant Drugs
- Possible interaction with ARTs?
- Any data demonstrate interaction?
- Use a drug-interaction checker!

Indication
- Is concomitant medication needed?
- Is it consistent with disease state guidelines?
- Medication reconciliation process

Guidance
- Any guidance about drug-drug interaction?
- Any alternatives to concomitant medication?
- Any alternatives to interacting ARTs?

Or use your own system

Patient Case: CYP 3A4 Inhibition

JD is a 48 yo male with medical history significant for HIV since 1998, asthma since childhood, DM Type 2, HTN, vitamin D deficiency, and allergic rhinitis.

Home Medication List

- Tenofovir/emtricitabine/elvitegravir/cobicistat 300/200/150/150 mg po daily
- Darunavir 800 mg po daily
- Metformin 500 mg po daily
- Hydrochlorothiazide 25 mg po daily
- Ergocalciferol 50,000 International Units po weekly
- Fluticasone/salmeterol 100/50 mcg 2 puffs bid
- Albuterol MDI 2 puff q6h prn wheezing
- Fluticasone nasal spray to each nostril daily

Patient Case: CYP 3A4 Inhibition

During interview you discover that JD complains of frequent heart palpitations. A possible drug-drug interaction that could likely explain his cardiac symptoms is:

A. Fluticasone and metformin
B. Hydrochlorothiazide and boosted darunavir
C. Albuterol and boosted darunavir
D. Albuterol and boosted elvitegravir
E. Salmeterol with boosted darunavir and elvitegravir

Guidelines from the National Asthma Education and Prevention Program Expert Panel Report 3 (2012 Revision)

Severity	Intermittent	Mild	Moderate	Severe		
Step	1	2	3	4	5	6
Preferred Treatment	SABA	Low-ICS	Low-ICS + LABA Or Med-ICS	Med-ICS + LABA	High-ICS + LABA	High-ICS + LABA + oral steroid (consider omalizu-mab if allergies)
Alternative Treatment	SABA	Cromolyn, LTRA, or theophylline	Low-ICS + LTRA, theophylline or zileuton	Med-ICS + LTRA, theophylline or zileuton	(consider omalizu-mab if allergies)	

NIH & NHLBI. *Asthma Guidelines: Expert Panel Report 3*, 2012. https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma (accessed 2018 Sep 24).

Patient Case: CYP 3A4 Inhibition

Salmeterol use has been associated with increased risk of cardiovascular events, including **heart palpitations**, acute coronary syndrome, blood pressure alteration, hypertension, **cardiac dysrhythmia**, heart failure, prolonged QT interval, **tachycardia**.

Ullman et al. *Thorax*, 1988;43:674-678.
Ullman et al. *Am Rev Respir Dis*, 1990;142:571-575.
Fitzpatrick et al. *BMJ*, 1990;301:1365-1368.
Maconochie et al. *Br J Clin Pharmacol*, 1994;37:199-204.
Gershon et al. *JAMA Intern Med*, 2013;173(13):1175-1185.

Patient Case: CYP 3A4 Inhibition

Inhibition of CYP 3A4 by darunavir, elvitegravir, cobicistat (theoretically) increase concentrations of salmeterol (substrate of CYP 3A4).

CYP 3A4 Substrate	CYP 3A4 Inhibitor	Effect	Recommendation
Salmeterol	Darunavir Elvitegravir Cobicistat All protease inhibitors	Increased salmeterol exposure	Do not co-administer due to potential salmeterol toxicity

Formoterol metabolized primarily by glucuronidation. No interaction expected.

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).
Rittweger et al. *Clin Pharmacokinet*, 2007;46(9):739-756.

Patient Case: CYP 3A4 Inhibition

During interview you discover that JD complaints of frequent heart palpitations. A possible drug-drug interaction that could likely explain his cardiac symptoms is:

A. Fluticasone and metformin
B. Hydrochlorothiazide and boosted darunavir
C. Albuterol and boosted darunavir
D. Albuterol and boosted elvitegravir
E. Salmeterol with boosted darunavir and elvitegravir

Patient Case: CYP 3A4 Inhibition

What would be an appropriate inhaler substitution for the long-term management of JD's asthma?

A. Budesonide/formoterol MDI
B. Mometasone/formoterol MDI
C. Beclomethasone MDI + formoterol DPI
D. Beclomethasone MDI + tiotropium MDI
E. Albuterol MDI

Patient Case: CYP 3A4 Inhibition

Inhibition of CYP 3A4 by darunavir, elvitegravir, cobicistat increases concentrations of corticosteroids (substrate of CYP 3A4), including topical, inhaled, intranasal, eyedrops, and systemic corticosteroid preparations.

CYP 3A4 Substrate	CYP 3A4 Inhibitor	Effect	Recommendation
All corticosteroids, except beclomethasone, flunisolide	Darunavir Elvitegravir Cobicistat All protease inhibitors	Increased cortico-steroid exposure	Do not co-administer unless benefits outweighs risk. Monitor for adrenal insufficiency

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).
Tseng et al. *Curr Infect Dis Rep,2012;14:67–82.*

Patient Case: CYP 3A4 Inhibition

Numerous case reports in patients on ritonavir-boosted protease inhibitors

Corticosteroid	Effect	Reference
Fluticasone, intranasal	Cushing's syndrome	Foisy et al. *HIV Med*, 2008;9(6):389–96.
Fluticasone, inhaled	Cushing's syndrome	Valin et al. *J Int Assoc Physicians AIDS Care (Chic),* 2009;8(2):113–21.
Fluticasone, inhaled	Avascular necrosis	Pollett et al. *Int J STD AIDS*, 2014;25:458-60.
Triamcinolone, injectable	Adrenal insufficiency	Dort et al. *AIDS Res Ther,* 2009;6:10. Danaher et al. *Orthopedics*, 2009;32(6):450.
Budesonide, inhaled, oral	Cushing's syndrome	Kedem et al. *J Asthma,* 2010;47(7):830–1. Gray et al. *S Afr Med J*, 2010;100(5):296–7.
Dexamethasone, betamethasone, ophthalmic	Cushing's syndrome, avascular necrosis	Molloy et al. *AIDS*, 2011;25:1337–9. Reinsburg et al. *Pediatr Infect Dis J*, 2017;36(5):502-503.

Patient Case: CYP 3A4 Inhibition

Corticosteroid	Effect	Reference
Beclomethasone, inhaled	No adrenal suppression observed No significant increase in active metabolite, 17-BMP	Boyd et al. *J Acquir Immune Defic Syndr, 2013;63(3):355-61*.
Flunisolide, inhaled, intranasal	None described	Saberi et al. *HIV Med, 2013;14(9): 519–529.*

Beclomethasone and **flunisolide;** least potential for accumulation and adrenal suppression and corticosteroid toxicity in general.

Patient Case: CYP 3A4 Inhibition

What would be an appropriate inhaler substitution for the long-term management of JD's asthma?

A. Budesonide/formoterol MDI
B. Mometasone/formoterol MDI
C. Beclomethasone MDI + formoterol DPI
D. Beclomethasone MDI + tiotropium MDI
E. Albuterol MDI

Patient Case: CYP 3A4 Inhibition

LS is a 40 yo female with h/o HIV since 2010, HTN, and with a recent diagnosis of dyslipidemia and unstable angina (NSTEMI), status post placement of drug-eluding stent. You are consulted for initiation of a statin on this patient.

Home Medication List

- Abacavir/lamivudine 600/300 mg po daily
- Darunavir 800 mg po daily
- Ritonavir 100 mg po daily
- ASA 325 mg po daily
- Prasugrel 10 mg po daily
- Lisinopril 10 mg po daily

Patient Case: CYP 3A4 Inhibition

What would be an appropriate initial statin dose for LS?

A. Simvastatin 10 mg po daily
B. Lovastatin 20 mg po daily
C. Rosuvastatin 10 mg po daily
D. Pravastatin 40 mg po daily
E. Atorvastatin 40 mg po daily

Statin Recommendations for Primary Prevention

	ACC/AHA	CCS	ESC/EAS	USPSTF	VA-DoD
Threshold	Age 40–75: if risk ≥7.5% Age ≥ 21: if LDL-C ≥190	Age 40–75: if risk ≥20% Any age and LDL-C ≥193	Age 40–65: if risk 5-10% and LDL-C ≥ 100 Risk ≥ 10% and LDL-C ≥ 70	Age 40-75: risk ≥ 10% and one other atherosclerotic CVD risk factor	Men age > 35 and women age > 45 with risk ≥ 12% LDL-C > 190
Recommend	Risk ≥7.5%: M or H Risk >5% but <7%: M	Target ≥ 50% reduction or LDL-C < 77	Max tolerated dose to achieve goal	Risk > 10%: L to M Risk 7.5-10%: L to M in some	Risk > 12%: M Risk 6-12%: M in some

ACC. *Major Dyslipidemia Guidelines and Their Discrepancies, 2018*. https://www.acc.org/latest-in-cardiology/articles/2018/04/24/08/56/major-dyslipidemia-guidelines-and-their-discrepancies (accessed 2018 Sep 24).

Statin Recommendations for Secondary Prevention

	ACC/AHA	CCS	ESC/EAS	USPSTF	VA-DoD
Recommend:	Age ≤ 75: H Age > 75, contraindications or safety concerns: M	Target LDL-C < 77 or ≥ 50% reduction If LDL-C ≥ 193, reduce by ≥ 50%	Max tolerated dose to achieve goal	Not addressed	Generally M, but H if ACS, multiple uncontrolled risk factors or recurrent CV events

ACC. *Major Dyslipidemia Guidelines and Their Discrepancies, 2018*. https://www.acc.org/latest-in-cardiology/articles/2018/04/24/08/56/major-dyslipidemia-guidelines-and-their-discrepancies (accessed 2018 Sep 24).

Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and statins

Statin	Effect/Recommendation	Reference
Atorvastatin	10 mg + DRV/r similar to 40 mg alone, max dose 20 mg/day	Hoetelmans et al. *ICAAC*, 2004;Poster H-865.
Lovastatin	Significant increase in lovastatin, **contraindicated**	Theoretical
Pitavastatin	No significant interaction Decreased pitavastatin AUC by 26%	Malvestutto et al. *J Acquir Immune Defic Syndr. 2014;67(4):390-6*. Yu et al. *Clin Drug Investig,* 2014;34(7):475-82.

Many interactions between other protease inhibitors and statins: Consult DHHS or other references for guidance

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and statins

Statin	Effect/Recommendation	Reference
Pravastatin	Increase in pravastatin AUC, 81% single-dose, 23% steady state. Titrate dose, lowest dose	Sekar et al. *8th Interntl Workshop Clin Pharmacol,* 2007;Abstract 54.
Rosuvastatin	Increase in rosuvastatin AUC by 48% steady state. Titrate dose	Samineni et al. *J Clin Pharmacol*, 2012;52(6):922-31.
Simvastatin	Significant increase in simvastatin, **contraindicated**	Theoretical

Many interactions between other protease inhibitors and statins: Consult DHHS or other references for guidance.

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

Patient Case: CYP 3A4 Inhibition

What would be an appropriate initial statin dose for LS?

A. Simvastatin 10 mg po daily
B. Lovastatin 20 mg po daily
C. Rosuvastatin 10 mg po daily
D. Pravastatin 80 mg po daily
E. Atorvastatin 40 mg po daily

Patient Case: CYP 3A4 Inhibition

Which of the following statements are true regarding antiplatelet agents in combination with darunavir/ritonavir in this patient?

A. Prasugrel may not be effective
B. It may increase plasma concentration of ticagrelor
C. No interaction is expected with clopidogrel
D. Clopidogrel would be a preferred $P2Y_{12}$ inhibitor for this patient
E. All of the above are true statements

ACC/AHA Guidelines for Adjunctive Antithrombotic Therapy for Primary PCI for NSTEMI, 2014

Recs	Before PCI		After PCI with stent	
Class I	Aspirin 81–325 mg	One $P2Y_{12}$ inhibitor loading dose: Clopidogrel Prasugrel Ticagrelor (All level B)	Aspirin 81–325 mg daily indefinitely (Level B)	One $P2Y_{12}$ for at least 12 months: Clopidogrel 75 mg daily Prasugrel 10 mg daily Ticagrelor 90 mg bid (All level B)
Class IIa		Prasugrel > clopidrogel if not at high risk of bleeding (Level B)	Aspirin 81 mg daily (Level B)	

Amsterdam et al. *JACC,* 2014;64(4):e138–228.

Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and antiplatelet agents

Statin	Effect/Recommendation	Reference
Prasugrel	Decrease in prasugrel AUC, 38% by CYP 3A4 inhibition of conversion to active metabolite. Potential for reduced efficacy of prasugrel	Ancrenaz et al. *Basic Clin Pharmacol Toxicol, 2013; 112(2):132-137.*
Ticagrelor	Increase in ticagrelor plasma concentrations. Coadministration not recommended.	Theoretical
Clopidrogel	No significant interactions expected	n/a

Many interactions between other protease inhibitors and antiplatelet agents: Consult references for guidance

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

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Patient Case: CYP 3A4 Induction

TW is a 30 yo male with h/o HIV/AIDS since 2010, HTN, major depression and a smoking history of 12 pack-years. He was started on depression treatment with bupropion 6 months ago, and reports ongoing depression symptoms as well as ongoing tobacco use.

Home Medication List

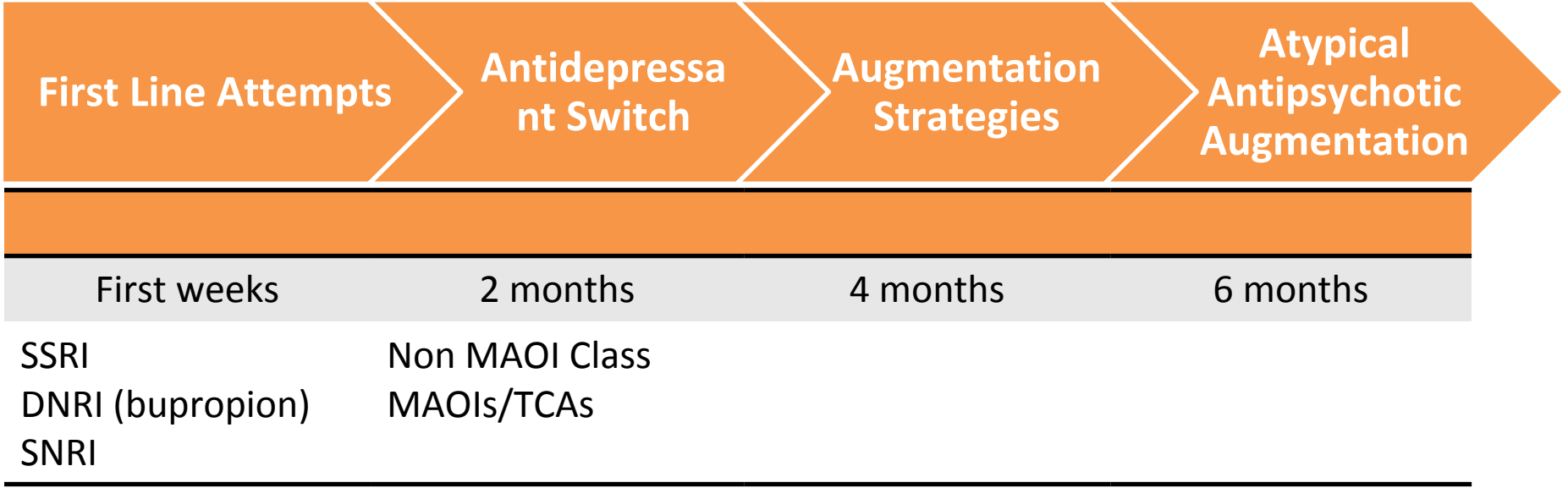
- Tenofovir/emtricitabine/efavirenz 300/200/600 mg po daily
- Lisinopril 40 mg po daily
- Bupropion 300 mg XL po daily

Patient Case: CYP 3A4 Induction

What are possible explanations for TW's ongoing depression symptoms?

A. Decreased adherence to bupropion
B. Efavirenz induction of bupropion metabolism
C. Depression is a known side effect of efavirenz
D. All of the above are possible explanations

2010 APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder



APA. *Guidelines for Treatment of Major Depression, 3rd Edition,* 2010. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf (accessed 2018 Sep 20).

Patient Case: CYP 3A4 Induction

Drug interactions between NNRTIs and bupropion

NNRTI	Effect/Recommendation	Reference
Efavirenz Nevirapine	Single dose of bupropion 150 mg SR after 2 weeks of efavirenz 600 mg daily (a CYP 2B6 inducer) resulted in 55% decrease in bupropion AUC (a CYP 2B6 substrate) in 13 healthy adults. Titrate bupropion based on clinical response.	Robertson et al. *J Acquir Immune Defic Syndr, 2008;49(5):513-519.*

Many interactions between NNRTIs and antidepressants:
Consult DHHS or other references for guidance

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

Patient Case: CYP 3A4 Induction

What are possible explanations for TW's ongoing depression symptoms?

A. Decreased adherence to bupropion
B. Efavirenz induction of bupropion metabolism
C. Depression is a known side effect of efavirenz
D. All of the above are possible explanations

Patient Case: Other Mechanisms

MJ is a 59 yo male with h/o HIV/AIDS since 1997, HTN, uncontrolled diabetes mellitus type 2, diabetic neuropathy. He has poor adherence with his insulin.

Home Medication List

- Tenofovir/emtricitabine 25/200 mg po daily
- Dolutegravir 50 mg po daily
- ASA 81 mg po daily
- Lisinopril 40 mg po daily
- Metformin 1000 mg po bid *(recently increased from 500 mg po bid)*
- Insulin detemir 50 Units sc qhs
- Insulin aspart 10 Units sc tid with meals
- Pregabalin 150 mg po bid

Patient Case: Other Mechanisms

MJ is a 59 yo male with h/o HIV/AIDS since 1997, HTN, uncontrolled diabetes mellitus type 2, diabetic neuropathy. He has poor adherence with his insulin.

Pertinent Laboratories

	9/20/2018	6/14/2018	3/14/2018
• CD4+ T-cell count:	451 cells/mm^3	636 cells/mm3	461 cells/mm^3
• HIV-1 RNA:	<20 copies/mL	<20 copies/mL	<20 copies/mL
• Metabolic panel:	within normal	within normal	within normal
• Hgb A1c:	10.9	9.3	11.7

ADA Standards of Medical Care in Diabetes (DM 2), 2018

Hgb A1C < 9	Hgb A1C ≥9	Hgb A1C ≥10 + metabolic complications
Monotherapy: Lifestyle modifications + metformin	Dual therapy: Lifestyle modifications + metformin ± additional agent	Combination injectable therapy: Initiate basal insulin + metformin ± other non-insulin agent
Consider dual therapy if A1C not at goal after 3 months	Consider triple therapy if A1C not at goal after 3 months: Lifestyle modifications + metformin + two agents	

ADA. *Diabetes Care,* 2018;41(Suppl 1).

Patient Case: Other Mechanisms

Which of the following are true statements regarding MJ's recent increase in metformin dose:

A. The maximum dose of metformin while on DTG is 1000 mg/day
B. MJ will almost certainly develop lactic acidosis
C. Metformin should be discontinued in this patient
D. It is reasonable to up titrate metformin with careful monitoring
E. None of the above are true

Patient Case: Other Mechanisms

Drug interaction between dolutegravir (DTG) and metformin

Effect	Reference
With DTG 50 mg daily + metformin 500 mg bid, increased metformin AUC by 79%.	Song et al. *J Acquir Immune Defic Syndr,* 2016;72(4):400-7.
With DTG 50 mg bid + metformin 500 mg bid, increased metformin AUC 2.45-fold	Zong et al. *J Int AIDS Soc*, 2014;17(4 Suppl 3):19584.

Clear interaction between DTG and metformin, partly explained by DTG inhibition of organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1).

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

Patient Case: Other Mechanisms

Drug interaction between dolutegravir (DTG) and metformin: How significant?

Effect	Reference
With DTG 50 mg daily + metformin >1000 mg/day, increased GI distress, hypoglycemia in retrospective analysis (*n*=19)	Masich et al. *Int J STD AIDS*, 2017;28(12):1229-1233.
On DTG + metformin (ranging doses), no adverse events in retrospective analysis (*n*=15)	Cattaneo et al. *AIDS*, 2018;32(4):532-3.
Case report: hyperlactemia while on DTG + metformin	Naccarato et al. *AIDS*, 2017;31(15):2176-2177.

In patients on DTG: Up titrate metformin based on glycemic control. In patients on metformin: May need to dose-adjust metformin when starting or stopping DTG.

DHHS. *Adult & Adolescent Antiretroviral Guidelines*. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0 (accessed 2018 Sep 20).

Patient Case: Other Mechanisms

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E. None of the above are true

Drug Interaction Resources

- **www.aidsinfo.nih.gov** 
  DHHS HIV Treatment Guidelines with drug interaction tables and guidance
- **http://hivinsite.ucsf.edu/interactions**
  Interactive tool and database, University of California, San Francisco
- **www.hiv-druginteractions.org/checker**
  Drug interaction checker, interactive tool, University of Liverpool
- **www.hivmedicationguide.com**
  Medication guide and drug interaction database
- **Micromedex**: Comprehensive drug database (subscription required)
- **Lexicomp**: Comprehensive drug database (subscription required)

KEY TAKEAWAYS

1) **DRUG INTERACTIONS WITH ANTIRETROVIRALS ARE COMMON**
   Particularly among patients taking NNRTIs and PIs.
   Drug-drug interactions may have serious consequences.

2) **IMPOSSIBLE TO MEMORIZE ALL DRUG-DRUG INTERACTIONS**
   Develop your own systematic approach for checking.
   Often guidance/data on interaction available.

3) **USE A DRUG INTERACTION CHECKER**
   Many resources available online or by subscription