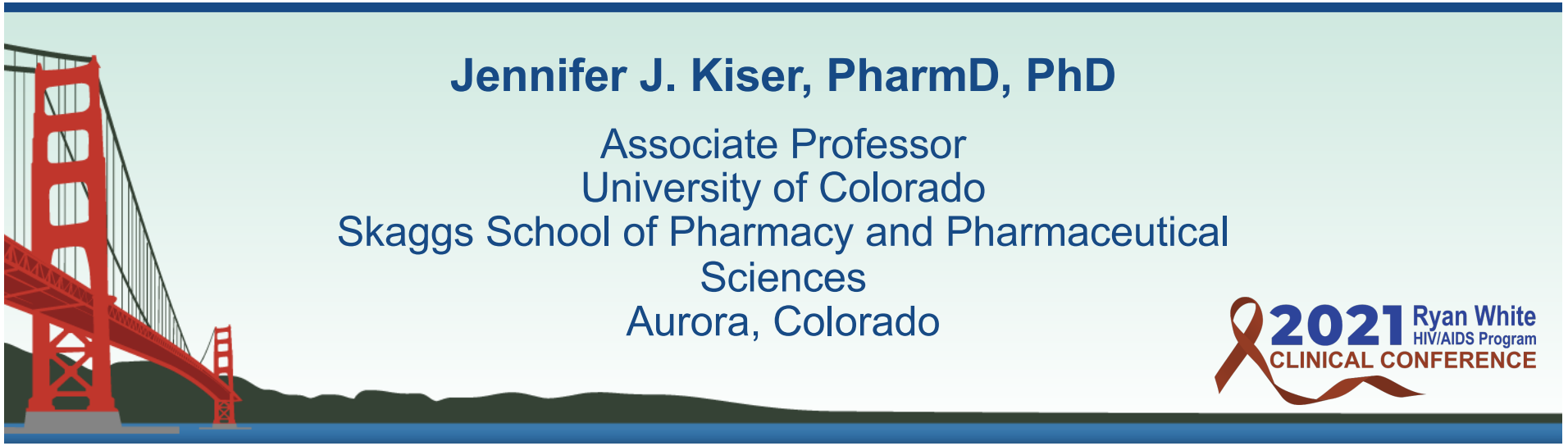
Managing Polypharmacy and Drug-Drug Interactions



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2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Kiser has no relevant financial affiliations to disclose. (Updated 9/30/21)

Learning Objectives

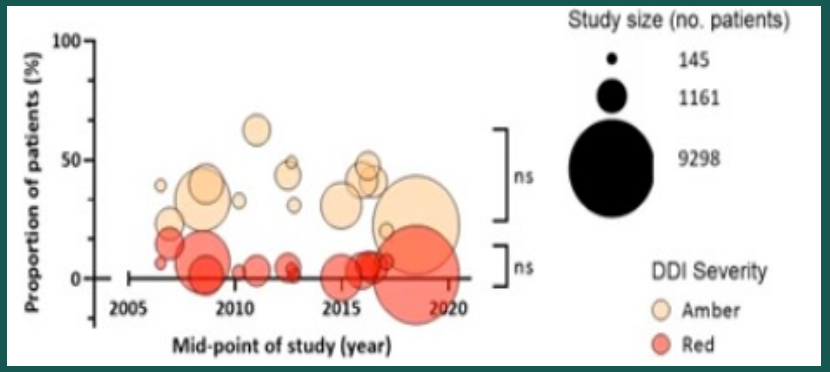
After attending this presentation, learners will be able to:

- Describe common mechanisms for drug interactions with contemporary ART
- Identify therapeutic classes of drugs with high interaction potential with ART
- Distinguish oral vs intramuscular cabotegravir/rilpivirin interactions
- Compare the clinical pharmacology and drug interaction potential of tenofovir alafenamide vs tenofovir disoproxil fumarate

DDI Remain a Critical Consideration in Treatment of PWH

Modern ARV, including unboosted integrase inhibitors and newer NNRTIs, have a decreased potential for clinically significant drug interactions.

Despite this, there has been no change in overall prevalence of clinically significant DDI over past 15 years.



DDI severity based on www.hiv-druginteractions.org
Amber = precautionary and Red=contraindicated

The pharmacologic advantages of newer ARV are offset by polypharmacy and an aging population of PWH.

Deutschmann E, et al. CID Epub, Hodge D, et al. Int Workshop of Clin Pharmacol Antiviral Therapy 9/21/21

Types of Drug Interactions

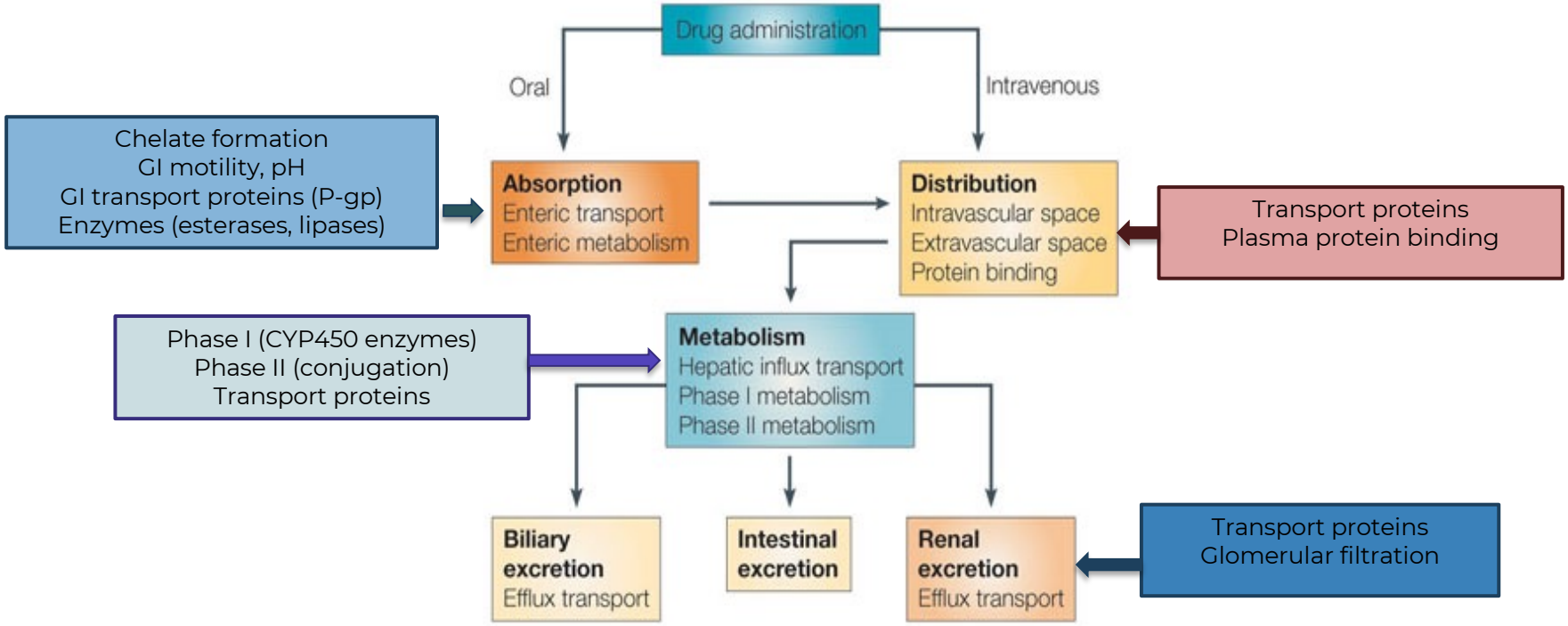
Pharmacodynamic

- Additive
- Synergistic
- Antagonistic

Pharmacokinetic

- Absorption
- Distribution
- Metabolism
- Elimination

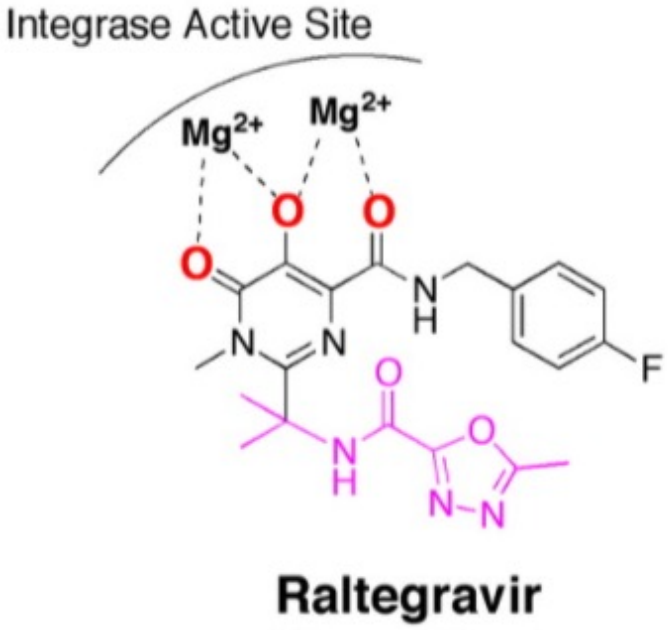
Pharmacokinetic Interactions



Undevia SD, et al. Nature Reviews Cancer 2005;5(6):447-458

1. Chelation Interactions

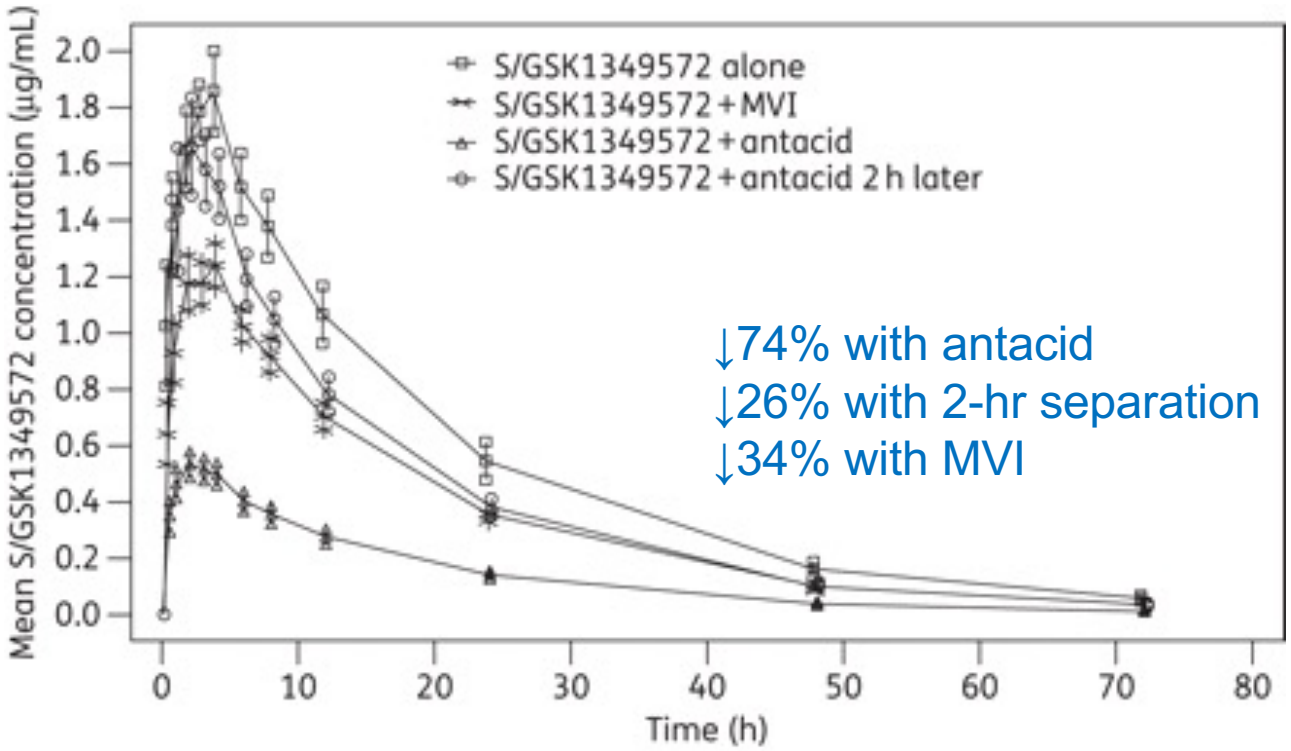
- Inhibition of the viral integrase enzyme is regulated by complexing between the integrase inhibitors and Mg^{+2} ions in the integrase active site.
- Thus, a chelation between integrase inhibitors and polyvalent cations can occur, leading to decreased drug absorption from the gastrointestinal tract.
- Al^{3+}, Ca^{2+}, Fe^{3+}, Mg^{2+}, and Zn^{2+} can chelate with INSTIs.



Raltegravir

Pommier Y, et al. Nature Reviews 2005;4:236-48.

Effects of Polyvalent Cations on Dolutegravir



Patel P, et al. JAC 2011;66:1567-1572.

Chelation Interactions Highly Relevant

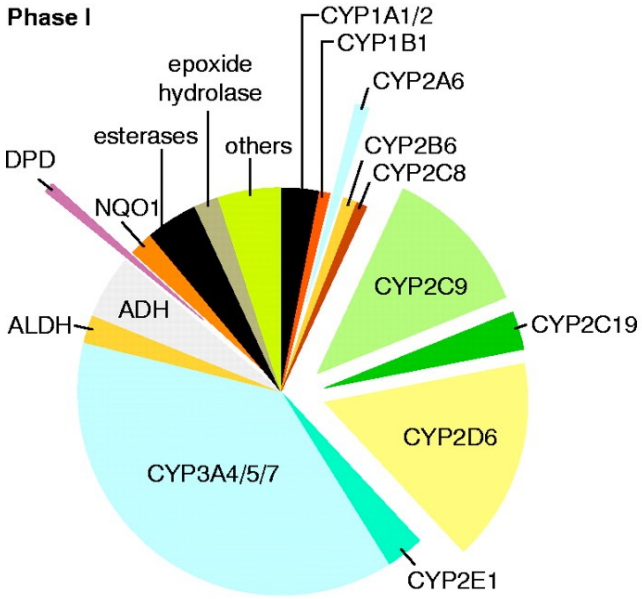
- Polyvalent cation use is common.
  - 42% of PWH on INSTIs in a recent retrospective analysis
- Vitamins, antacids, and other supplements may not be considered "medications" by patients.
  - Education and thorough medication reconciliation are needed
- The odds of viral failure were 2.3 times higher (95% CI 1.2-4.4) among PWH receiving polyvalent cations with INSTIs.
- Avoidance of the combination or strict adherence to temporal separation is critical.

James CW, et al. AIDS 2020;34:487-491

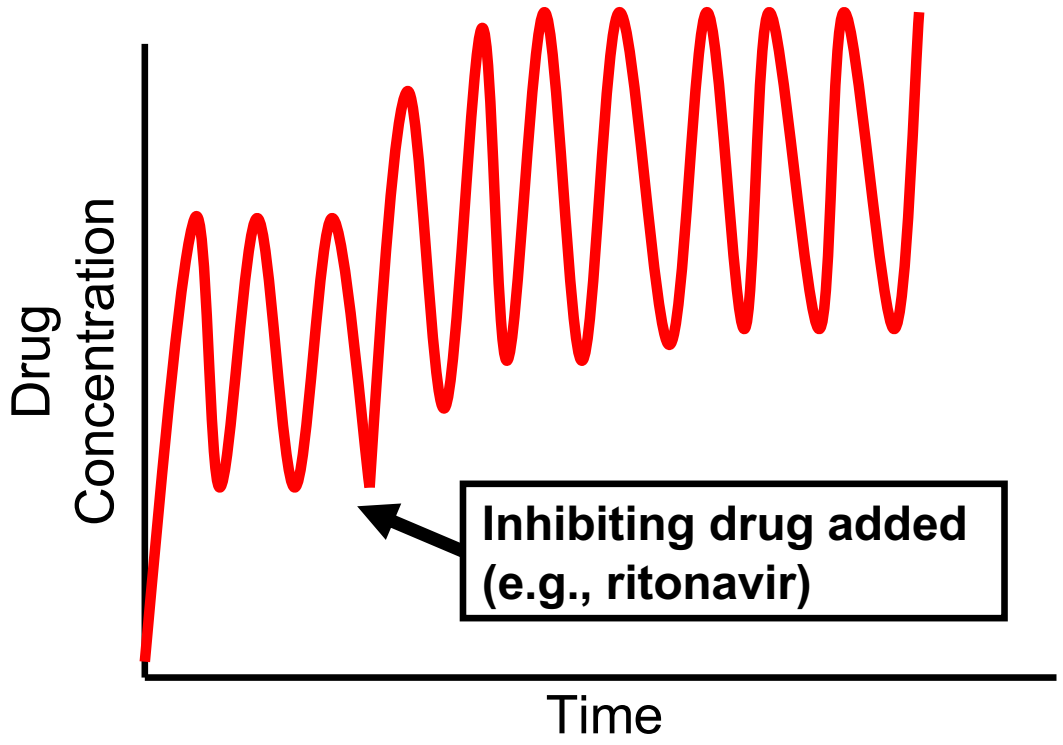
Temporal Separation with INSTIs and Polyvalent Cations

	Al-, Mg-, Ca-containing Antacids	Mg, Al, Fe, Ca, Zn supplements including multivitamins with minerals
TAF/emtricitabine/ bictegravir	Take BIC at least 2 hours before or at least 6 hours after antacids containing Al/Mg Take BIC + Ca-containing antacids with food	Take INSTI at least 2 hours before or at least 6 hours after OR Take supplements containing calcium or iron simultaneous with BIC with food
Dolutegravir	Take DTG at least 2 hours before or at least 6 hours after antacids containing polyvalent cations	Take INSTI at least 2 hours before or at least 6 hours after OR Take supplements containing calcium or iron simultaneous with DTG with food
Elvitegravir/cobicistat	Separate by more than 2 hours	Take INSTI at least 2 hours before or at least 6 hours after
Raltegravir	Avoid Al and Mg-containing antacids, do not use Ca-containing antacids with QD RAL (only BID)	Take INSTI at least 2 hours before or at least 6 hours after

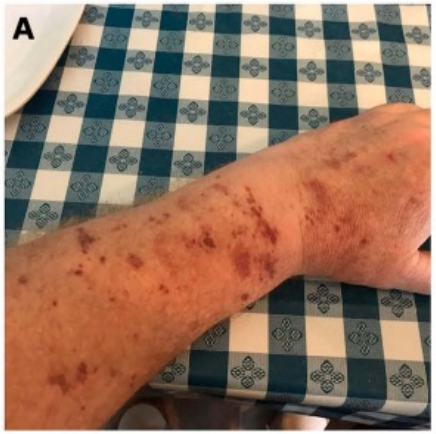
2. CYP Inhibition

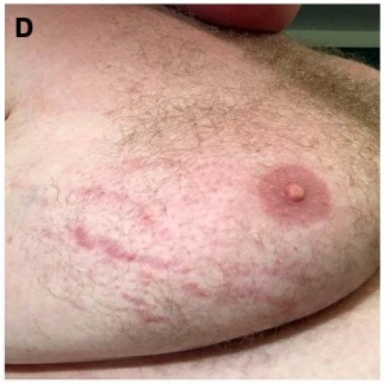


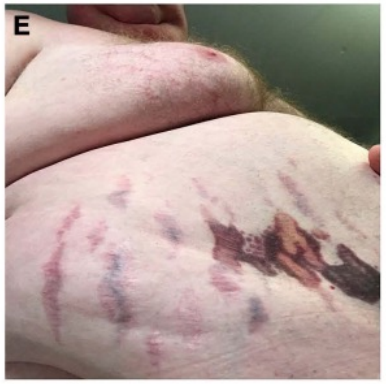
ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; NQO1, NADPH:quinone oxidoreductase or DT diaphorase.



What Caused This?







Alidoost M, et al. Int Med Case Reports J 2020;I3:229-235.

Iatrogenic Cushing's with Corticosteroids and Boosters

Can occur with inhaled, intranasal, intra-articular, and ocular administration of corticosteroids in PWH on boosters.

Whenever possible, switch to an unboosted regimen.

If a booster is essential, use corticosteroids with lowest potential for DDI and frequent monitoring.

Bad with Boosters	Alternatives
Fluticasone Budesonide Ciclesonide Mometasone	beclomethasone
Triamcinolone	Methylprednisolone?
Betamethasone Budesonide	Prednisone? Prednisolone?

Educate PWH on boosters about the risk with both oral and non-oral routes.

Direct Oral Anticoagulants and Boosters

Higher risk of venous thromboembolism and ischemic stroke in PWH

Use of DOACs can be challenging in PWH on boosters, data are limited

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

Results Key

	ATV/c	ATV/r	DRV/c	DRV/c/FTC/TAF	DRV/r	EVG/c/FTC/TAF
Apixaban	●	●	●	●	●	●
Dabigatran	■	■	■	■	■	■
Edoxaban	■	■	■	■	■	■
Rivaroxaban	●	●	●	●	●	●
Warfarin	■	■	■	■	■	■

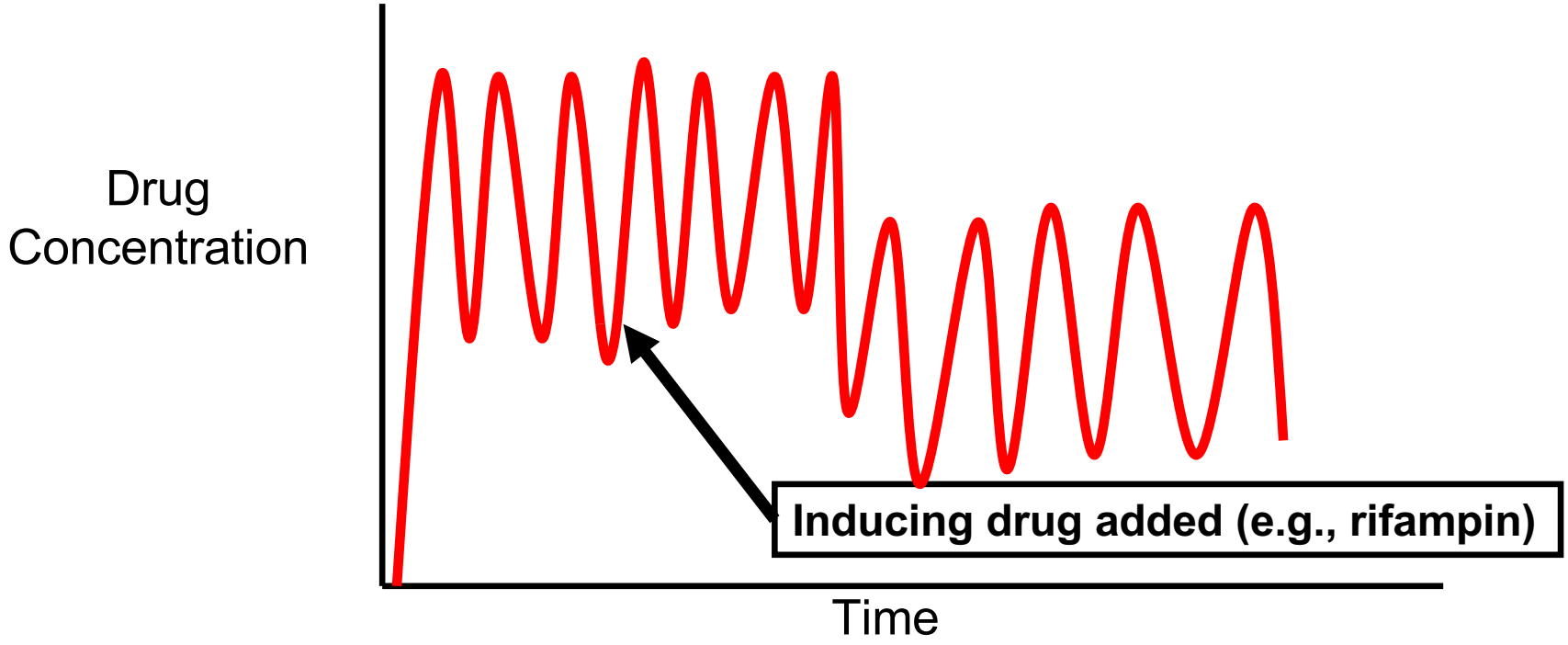
www.hiv-druginteractions.org

DOAC and Booster Management

- Rivaroxaban is not recommended.
  - Cases of bleeding with rivaroxaban and darunavir/ritonavir have been reported.
- No adverse outcomes were observed in 6 PWH receiving boosters with apixaban 2.5mg twice daily.
- Based on pharmacology, edoxaban is a good option, but data are lacking.
- Dabigatran appears okay with ritonavir, but dose must be reduced to 100mg twice daily with cobicistat.
- Monitor anti factor Xa levels if possible
- If warfarin is used, careful monitoring and dose adjustment is needed if switching from ritonavir to cobicistat.

Nhean S, et al. Curr Opin HIV AIDS 2021;16(6):292-302.

3. Enzyme and Transporter Induction



Strong/Moderate Inducers (not an exhaustive list)

Table 3-3: Examples of clinical inducers for P450-mediated metabolisms (for concomitant use clinical DDI studies and/or drug labeling) (12/03/2019)

	Strong inducers	Moderate inducers
CYP1A2		phenytoin[a] rifampin(b), ritonavir[c,d], smoking, teriflunomide
CYP2B6	carbamazepine[e]	efavirenz[e], rifampin[a]
CYP2C8	-	rifampin[a]
CYP2C9	-	enzalutamide[g], rifampin[a]
CYP2C19	rifampin[a]	apalutamide, efavirenz[e,f], enzalutamide[g], phenytoin[b]
CYP3A	apalutamide, carbamazepine[e], enzalutamide[g], mitotane, phenytoin[b], rifampin[a], St. John's wort[h]	bosentan, efavirenz[f], etravirine, phenobarbital, primidone

RIFAMYCINS – rifampin, rifapentine, rifabutin

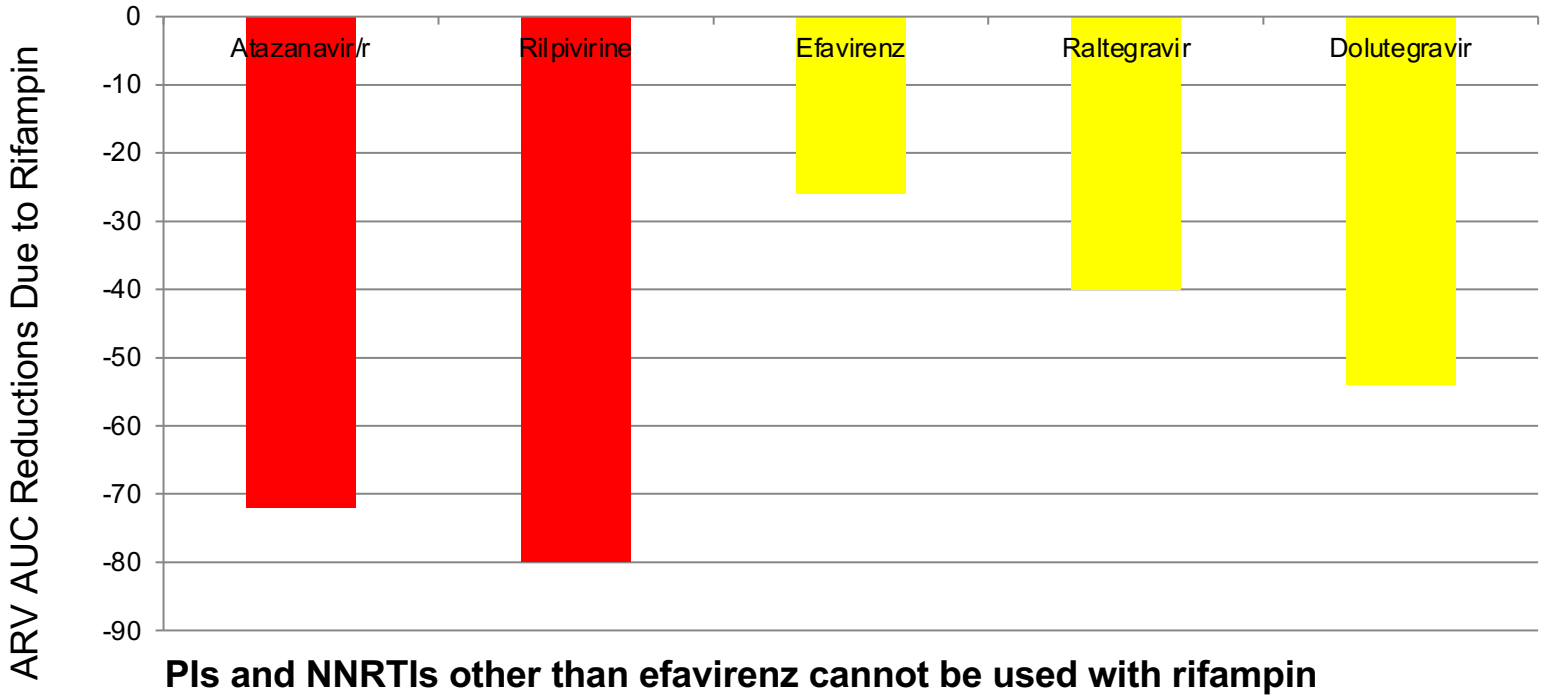
"OLD SCHOOL" ANTIEPILEPTICS

NNRTIs

St Johns Wort

FDA Drug Development and Drug Interactions": Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Rifampin Effects on ARVs



PIs and NNRTIs other than efavirenz cannot be used with rifampin
Efavirenz may be used at 600mg once daily (not 400mg), monitor HIV RNA
Twice daily raltegravir and dolutegravir can be used, but doses should be doubled

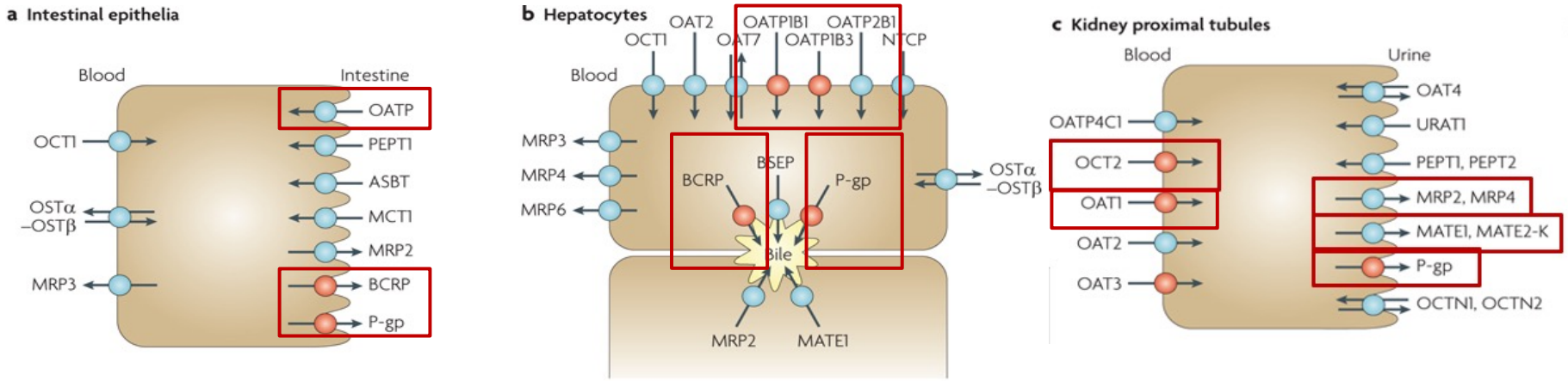
Rifapentine Use with ARV

ARV anchor	Rifabutin dosing
NNRTIs (without PIs)	
Doravirine	don't use
Etravirine	don't use
Efavirenz	no adjustment needed
Nevirapine	don't use
Rilpivirine	don't use
PIs	contraindicated
Integrase	
Bictegravir	don't use
Dolutegravir	only use once weekly rifapentine (not daily), only QD DTG eligible
Elvitegravir/cobi	don't use
Raltegravir	only use once weekly rifapentine (not daily), RAL 400mg BID

Rifabutin Use with ARV

ARV	Rifabutin dosing
NNRTIs (without PIs)	
Doravirine	↑ DOR to 100 BID
Etravirine	300mg/d (no change)
Efavirenz	450mg-600mg/d
Nevirapine	300mg/d (no change)
Rilpivirine IM	don't use, RPV ↓
PIs	
RTV- boosted PIs	150mg QD
Cobi-boosted PIs	don't use, cobi ↓
Integrase	
Bictegravir	don't use, BIC ↓
Dolutegravir	300mg/d (no change)
Elvitegravir/cobi	don't use, ELV ↓
Raltegravir	300mg/d (no change)

4. Transporter Inhibition

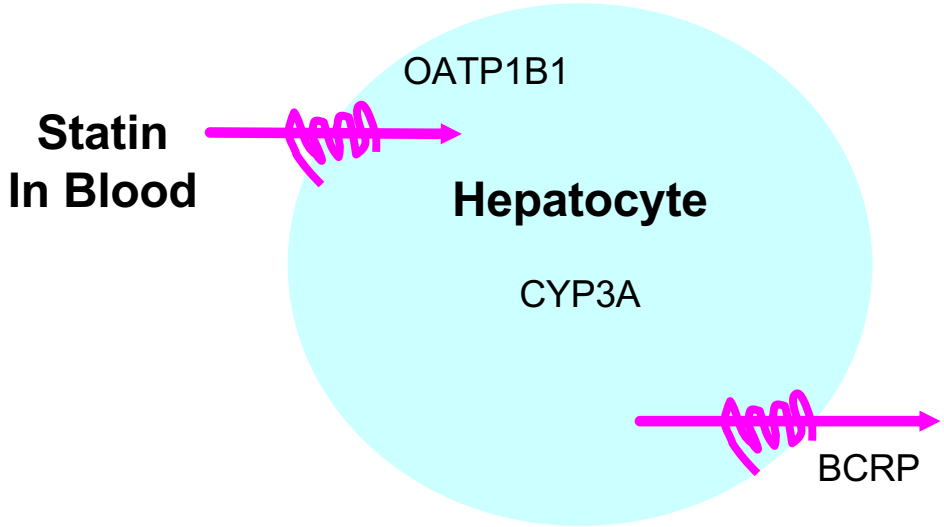


Selected transporters relevant to HIV treatment

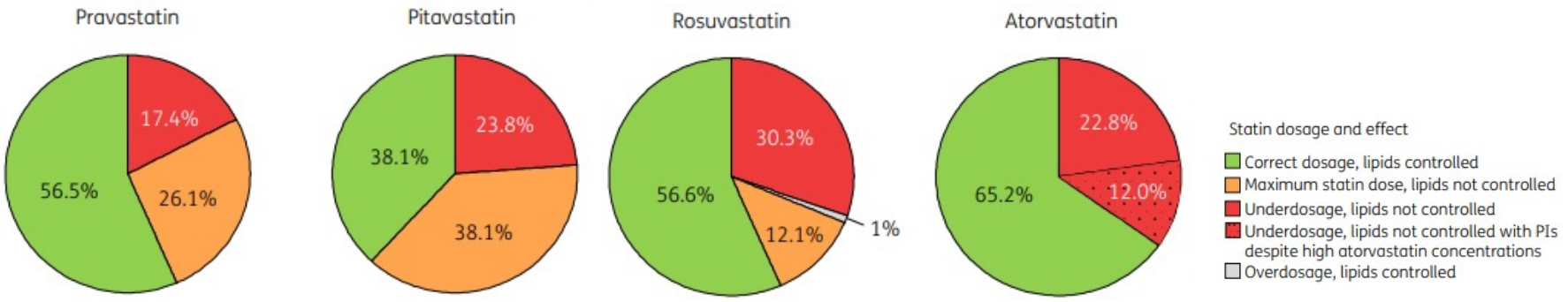
International Transporter Consortium Nat Rev Drug Discov 2010;9(3):215-36.

Statins Interact with PIs and Boosters

Statins have transporter-mediated interactions and some have CYP interactions



Statin Dosing and Lipid Control in PWH



- Insufficient lipid control despite MAX doses (orange)
- Use more potent statins (not PRAVA or PITAVA)

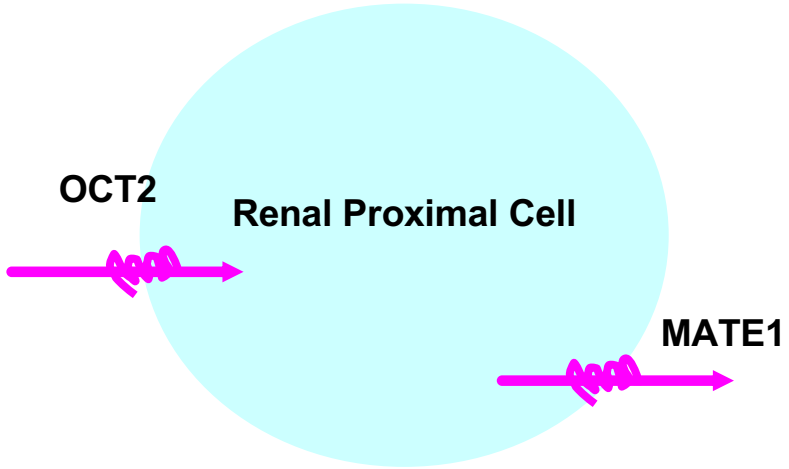
- 1/3 underdosed with insufficient lipid control (red)
- Push dose to lipid control, but caution with b/PI + ATORVA
- Avoid b/PI, and use unboosted INSTIs whenever possible

Courlet P, et al. JAC 2020;75:1972-1980.

Some INSTIs Increase Metformin Exposures

Metformin AUC ↑ 79% with DTG 50mg QD

Metformin AUC ↑ 2.4-fold with DTG 50mg BID



Start with lowest metformin dose and titrate based on glycemic control.

Monitor for gastrointestinal AEs (diarrhea, N/V), renal function, lactic acidosis

Not unique to DTG, bictegravir and elvitegravir/cobicistat may also increase metformin

5. Considerations with Long Acting

- Entering a new era in treatment (and prevention) of HIV with long-acting agents
- Cabotegravir (integrase) and rilpivirine (NNRTI) are given as a 28-day oral lead-in then monthly intramuscular injections
- Drug interaction profiles differ during the oral lead-in vs. intramuscular injections

Interactions Limited to the Oral CAB/RPV Lead-In

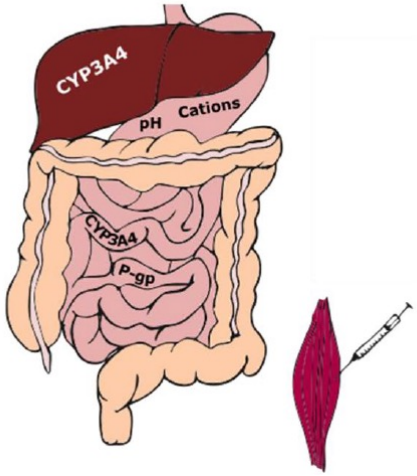
ORAL administration

Stomach/intestine
Change gastric pH
e.g. proton pump inhibitor

Chelation divalent cations
e.g. magnesium, iron, calcium

Inhibition/induction of CYP3A4, drug transporters
e.g. ritonavir, rifampicin

Liver
Inhibition/induction of CYP3A4, UGTs, drug transporters
e.g. ritonavir, rifampicin



INTRAMUSCULAR administration

Stomach/intestine
Bypassed

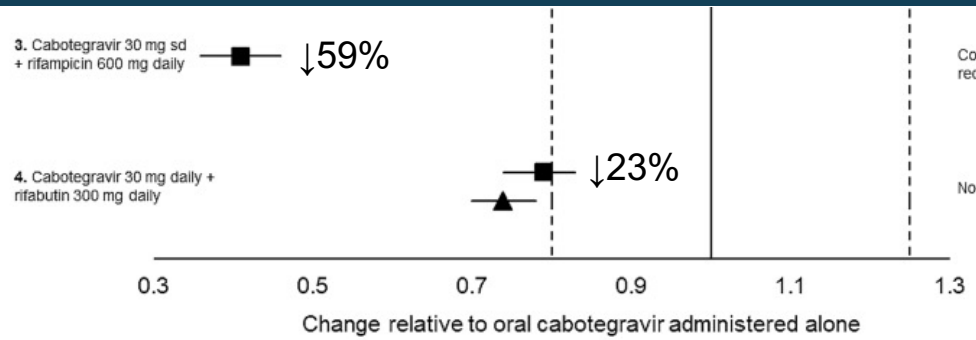
Liver
Inhibition/induction of CYP3A4, UGTs, drug transporters
e.g. ritonavir, rifampicin

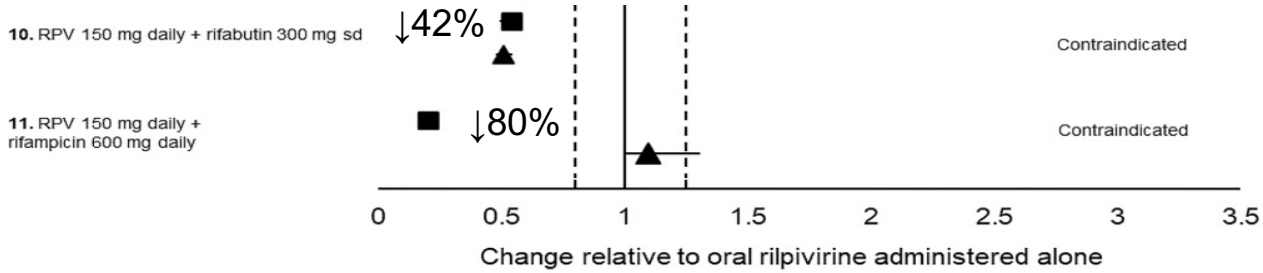
Examples of drugs that interact with oral, but not IM – table courtesy of Catia Marzolini

Cabotegravir	Rilpivirine
Antacids Calcium Iron Magnesium Multivitamins containing divalent cations Orlistat	Antacids Famotidine Lansoprazole Liraglutide Omeprazole Orlistat Pantoprazole Rabeprazole Ranitidine

Hodge D, et al. Clin Pharmacokinetics 2021;60:835-853

Interactions with Oral and IM CAB/RPV





- Strong inducers significantly reduce CAB exposures
- Moderate inducers have a modest effect on CAB
- Both strong and moderate inducers significantly reduce RPV

Avoid older anticonvulsants, rifamycins, dexamethasone, St. Johns Wort with CAB/RPV

Hodge D, et al. Clin Pharmacokinetics 2021;60:835-853

6. Interaction Potential of TDF vs. TAF

- TAF is more stable in plasma than TDF and less is converted to tenofovir (90% lower with TAF vs. TDF).
- Tenofovir-diphosphate (TFV-DP) concentrations in PBMCs are ~7-fold higher with TAF.
- TAF more susceptible to P-gp inducers vs. TDF.

Ray AS, et al. Antiviral Res 2016;125:63-70
Mills A, et al. JAIDS 2015;69(4):429-445

Potent P-gp Inducers Not Recommended with TAF

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected

Results Key

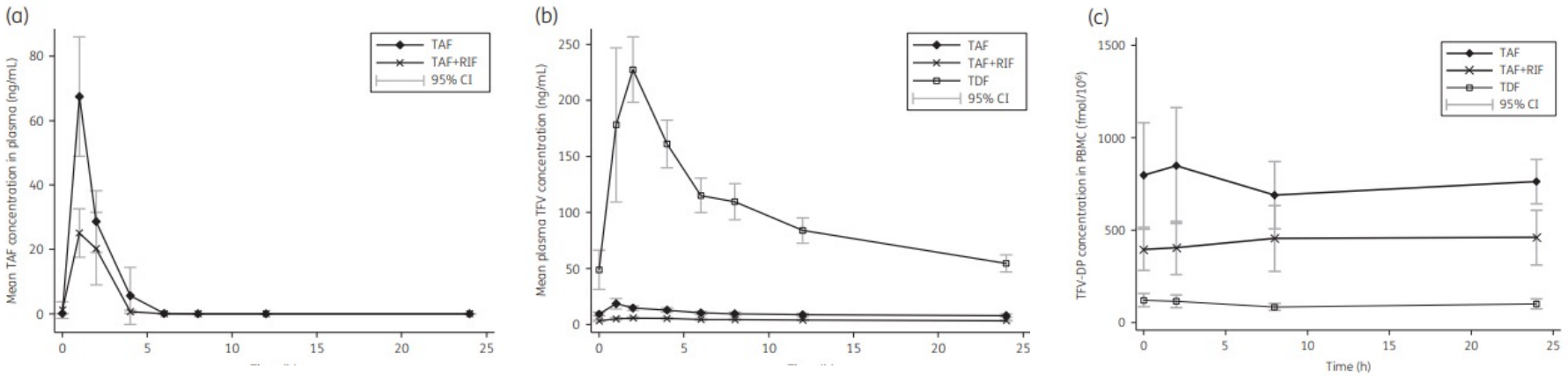
	FTC/TAF	FTC/TDF
Carbamazepine	●	◆
Oxcarbazepine	●	◆
Phenytoin	●	◆
Rifabutin	■	◆
Rifampicin	■	◆
Rifapentine	■	◆
St John's Wort	●	◆
Tipranavir (TPV)	●	■

www.hiv-druginteractions.org

Rifampin May Still be Effective, but Need Data

Plasma TAF and Tenofovir ↓ 55% with Rifampin

TFV-DP in PBMC still ~4-fold higher vs. TDF



Cerrone M, et al. JAC 2019;74:1670-1678

Conclusions

Drug interactions remain an important consideration in PWH

Chelation, enzyme induction, and transporter-mediated interactions are common mechanisms for interactions with contemporary ARV

A thorough medication reconciliation that includes assessment of OTC and dietary/herbal supplements is required

Reputable resources are required for accurate screening and management of potential DDI

Consider deprescribing strategies to reduce polypharmacy

Resources

Resources	Use	Access
Drug–Drug Interaction Management		
University of Liverpool HIV Drug Interaction Checker	This website/app provides current and evidence-based information on HIV drug interactions with recommendations and references. Users can switch to table view to see summary table of interactions. There are separate websites for HCV drug interactions and COVID-19 drug interactions with comedications	https://www.hiv-druginteractions.org
University Health Network HIV/HCV Drug Therapy Guide	This website/app provides up-to-date and evidence-based data on both HIV and HCV drug interactions with recommendations and references. It also provides a link to interaction checks with medications from similar classes	https://hivclinic.ca/wp-content/plugins/php/app.php
Interaction Tables within the Department of Health and Human Services HIV Treatment Guidelines	This website/app provides evidence-based guidelines regarding the management of people living with HIV with a section on useful HIV drug interactions	https://clinicalinfo.hiv.gov/en/guidelines

Nhean S, Tseng A, Back D. Curr Opin HIV AIDS 2021 EPub

Narrow Therapeutic Index Drugs Possible "Victims" of ARVs

A small difference in dose or blood concentration of these compounds may lead to therapeutic failure and/or adverse drug reactions – screen and manage potential interactions with these drugs

Essential NTI Drugs	
Warfarin	Sirolimus
Levothyroxine	Tacrolimus
Carbamazepine	Quinidine
Lithium	Methotrexate
Digoxin	Sodium valproate
Phenytoin	Amiodarone
Theophylline	Flecainide
Cyclosporine	

'Important to know' NTI Drugs	
Apixaban	Amitryptyline
Dabigatran	Imipramine
Endoxaban	Trimipramine
Rivaroxaban	Clozapine
Clopidogrel	Quetiapine
Prasugrel	Aminoglycosides
Ticagrelor	MDMA
Acenocoumarol	GHB

Slide courtesy of Professor David Back, University of Liverpool, founder www.hiv-druginteractions.org

Question-and-Answer Session

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