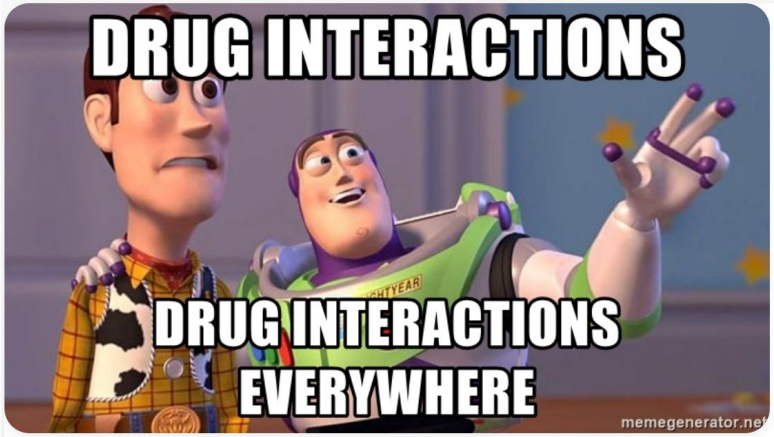
AETC AIDS Education & Training Center Program Southeast



Common Drug-Drug Interactions with Antiretroviral Therapy

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Southeast AETC Champions Academy
January 27, 2022

Learning Objectives

By the end of this module, the learner will:

- Describe the contribution of polypharmacy to the risk of drug interactions in persons with HIV (PWH)
- List common mechanisms for drug interactions with antiretrovirals (ARVs)
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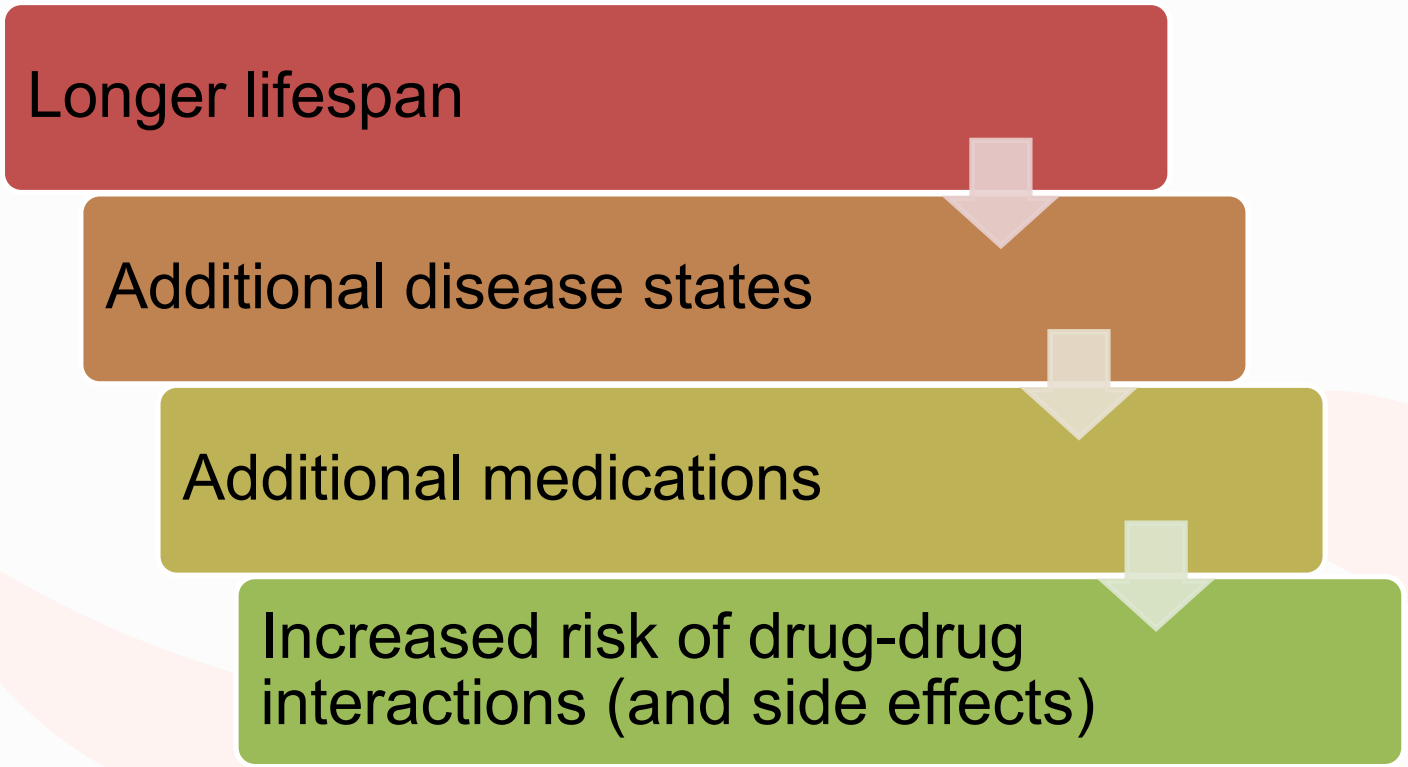
Polypharmacy and HIV Infection

- Polypharmacy is “many drugs”
  - Typically refers to 5+ medications
- Polypharmacy occurs in 20%-50% of people with HIV
  - Adverse drug reactions more common and serious in older patients
- Regular drug interaction screening is essential

Polypharmacy & Aging in People with HIV

Antiretroviral therapy (ART) transformed HIV into complex chronic disease with multimorbidity



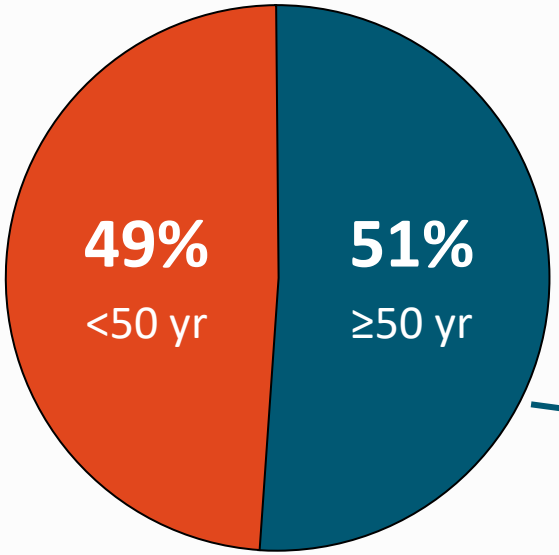
Patient Case

- 75-year-old male who comes in for follow up
- Living with HIV for 25 years:
  - Currently on BIC/FTC/TAF for 3 years
  - Multiple prior ART, no virologic failure
- Current medications: atorvastatin, aspirin, lisinopril, hydrochlorothiazide, amlodipine, omeprazole, metformin, glipizide, calcium carbonate, multiple vitamin, diphenhydramine
- Exam is normal

Labs	Value
CD4+ cell count, cells/mm^3	534
HIV-1 RNA, copies/mL	< 20
HLA-B*5701	Negative
BMI	28.5
Blood pressure, mm Hg	134/78
Total cholesterol, mmol/L	201
HDL cholesterol, mmol/L	35
ALT, IU/L	24
eGFR, mL/min	44
A1C, mmol/mol (%)	7.6

Older Persons with HIV (PWH) in the US in 2018

- Over half of people with diagnosed HIV are ≥ 50 years old



This segment rapidly increasing as PWH age

- 17% of new HIV diagnoses are among people ≥ 50 years old

HealthHIV Second Annual National Survey: State of Aging With HIV

- Survey consisting of 102 qualitative and quantitative questions distributed online summer of 2020
  - Included in analysis: persons with HIV ≥50 years old (N = 479)

Survey Results	Respondents, %
Taking ART	99
Achieved viral suppression	94
Concerned about viral suppression or resistance	11
Reported side effects of their medications	33

- **Average overall physical health on scale of 1-10: 3.4**

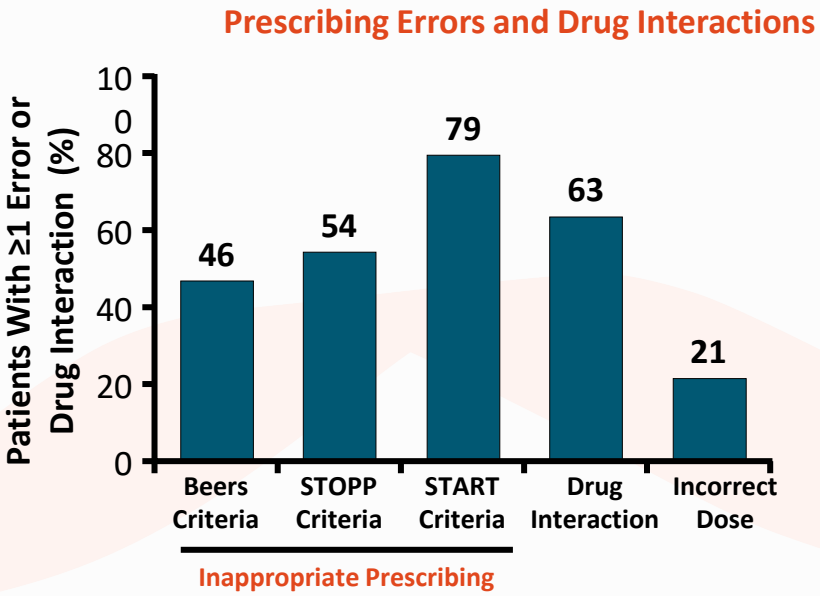
Survey Question	Respondents, %
≥1 comorbidity	60
Elevated cholesterol	57
Hypertension	57
Joint or back pain	56
Arthritis	41
Neuropathy	40
Take medication for chronic condition	81
Use alternative/holistic therapies	40

Slide credit: clinicaloptions.com

HealthHIV Second Annual State of Aging With HIV National Survey. 2021. https://healthhiv.org/wp-content/uploads/2021/07/HealthHIV_Second_Annual_State_of_Aging_with_HIV.pdf

Polypharmacy and Inappropriate Prescribing in Older Persons with HIV

- US PWH ≥65 years old from Jan 2015 - Aug 2018 (N = 112)
  - 87% with HIV-1 RNA <20 copies/mL
- Polypharmacy: ≥5 medications
  - **95% considering all drugs; 84% considering only non-HIV drugs**
- Average number of medications: 12.3, including 9.0 non-HIV medications
- Risk of serious drug interactions correlated with polypharmacy (*P* <.01) and inappropriate prescribing (*P* <.01)



Slide credit: clinicaloptions.com

Cabanilla. IAS 2019. Abstr WEPEB314

Potential Consequences of Polypharmacy

- Decreased adherence/pill fatigue
- Drug–drug interactions
- Increased risk of adverse drug reactions
- Overlapping adverse events
- Use of another medication to treat adverse events of treatments
- Drug–disease interactions
- One medication worsens another condition
- Difficulties in de-prescribing or stopping medications that harm or no longer provide benefit (ART included)

Back. J Int AIDS Soc. 2020;23:e25449.

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- **List common mechanisms for drug interactions with antiretrovirals (ARVs)**
- Identify and mitigate clinically significant drug interactions for PWH

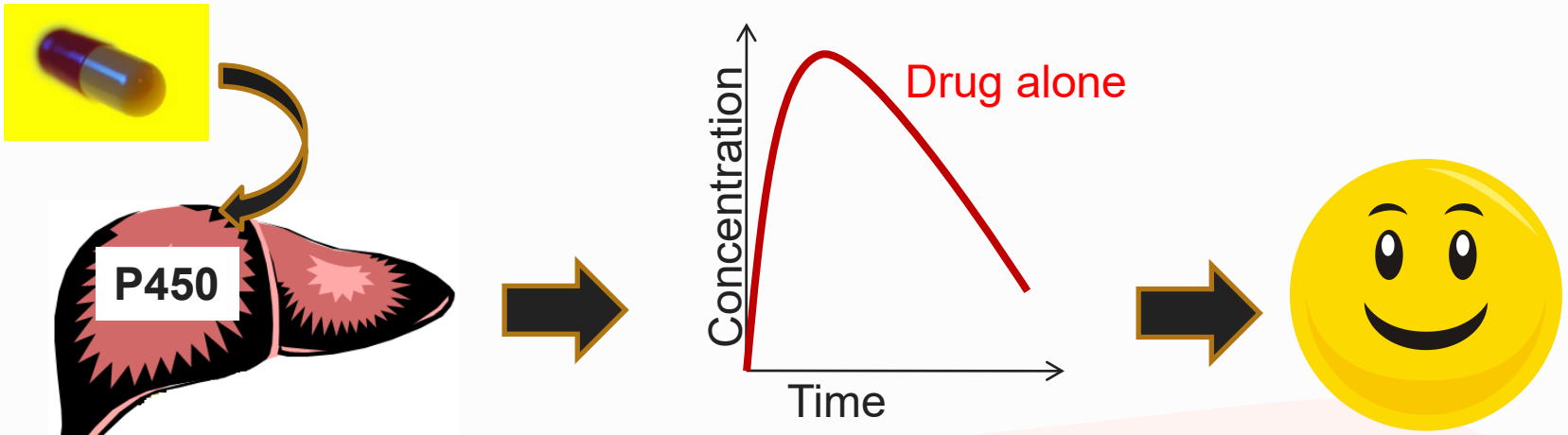
ART Undergoes Pharmacokinetic Transformation

1. Absorption
2. Distribution
3. Metabolism
4. Elimination

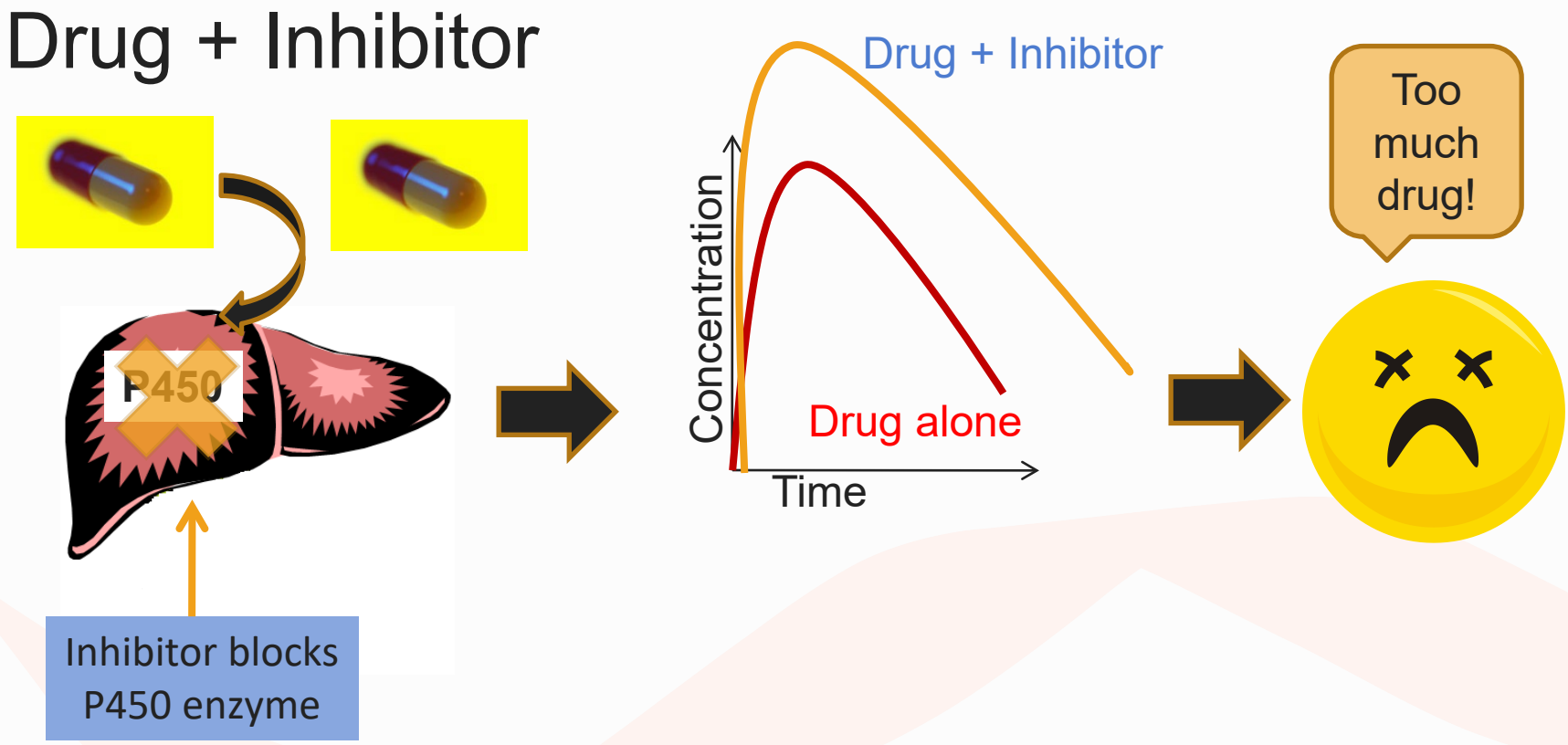
- Setting for most ARV drug interactions
- Cytochrome P450 and/or UGT drug metabolizing enzyme influences/influenced by many ARVs and many other drugs
- PIs, NNRTIs, INSTIs, entry inhibitors & cobicistat can be P450 or UGT substrates, inducers, or inhibitors

Normal Metabolism of a Drug That is a P450 Substrate

Drug alone

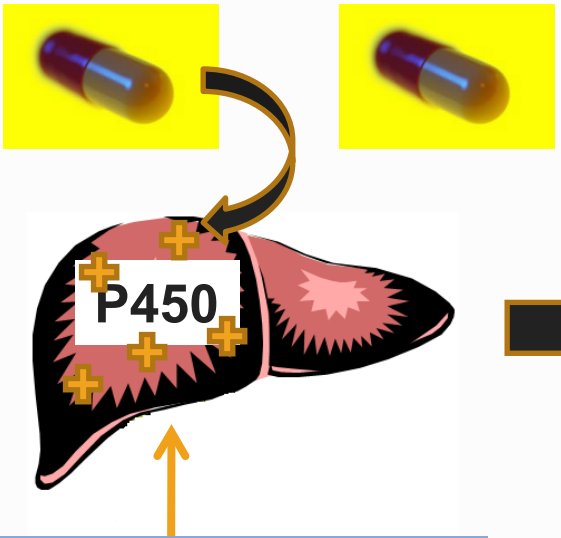


Metabolism of a Drug That Inhibits P450 With a Drug That is a P450 Substrate

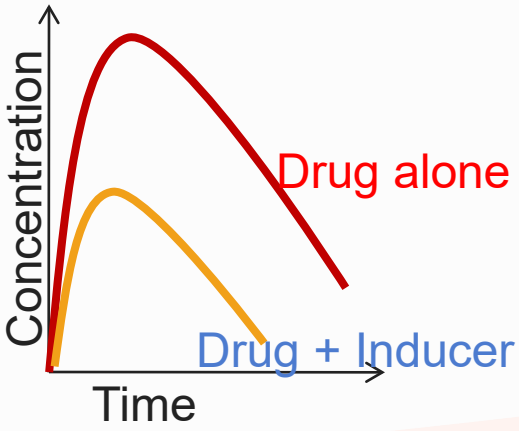


Metabolism of a Drug That Induces P450 With a Drug That is a P450 Substrate

Drug + Inducer



Inducer increases P450 enzyme production



Antiretroviral Metabolism and Drug Interaction Potential

Antiretroviral Drug Class	Route of Metabolism	Drug Interaction Potential
NRTI	Mostly renal	Medium
NNRTI	Liver metabolism: P450 substrates, some are P450 inducers/inhibitors	High
Protease Inhibitors	Liver metabolism: P450 substrates, most are P450 inhibitors	High
Integrase Inhibitors	Liver metabolism: UGT1A1 enzyme and/or P450 substrates	Medium-High
Entry Inhibitors	•Maraviroc & fostemsavir: P450 substrate •Enfuvirtide & ibalizumab: Undergoes catabolism, no known drug interactions	Low-Medium

Antiretrovirals Have Drug Interactions With Multiple Medications

- Statins (HMG Co-A reductase inhibitors)
- Anti-acid therapies
- Antimycobacterials
- Antiepileptics
- Corticosteroids
- Antiplatelets & anticoagulants
- Hepatitis C medications
- Hormonal contraceptives
- Antifungals
- Benzodiazepines
- Phosphodiesterase inhibitors
- Antiarrhythmics, calcium channel blockers
- Antipsychotics and antidepressants
- Herbal and dietary supplements

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ARV Interactions with Statins

- Statins (HMG Co-A reductase inhibitors)
  - P450 substrates
    - Degree of enzyme metabolism varies:

      simva, lova >> rosuva > atorva > pitava > pravastatin
  - May be affected by NNRTIs, PIs, & cobicistat
- NNRTIs can ↓ statin levels
  - Monitor statin efficacy, ↑ dose as necessary
- Protease inhibitors and cobicistat ↑ statin levels
  - Avoid simvastatin, lovastatin (2000% ↑)
  - Myopathy including rhabdomyolysis

Managing ARV Interactions with Statins

Statin	Interacting Antiretroviral(s)	Prescribing Recommendation
Atorvastatin	•Atazanavir ± ritonavir	Titrate atorvastatin dose carefully and use lowest effective dose while monitoring for toxicities
	•Darunavir/cobicistat •Darunavir + ritonavir •Elvitegravir/cobicistat •Lopinavir/ritonavir	Do not exceed 20 mg atorvastatin daily
	•Atazanavir/cobicistat •Tipranavir + ritonavir	Do not co-administer
Lovastatin	•HIV protease inhibitors •Elvitegravir/cobicistat	CONTRAINDICATED
Pitavastatin	•HIV protease inhibitors	No dose adjustment necessary
	•Elvitegravir/cobicistat	No data; no dosage recommendation
Pravastatin	•Atazanavir + ritonavir; Atazanavir/cobicistat •Darunavir + ritonavir; Darunavir/cobicistat	Titrate pravastatin dose carefully while monitoring for toxicities
	•Lopinavir + ritonavir	No dose adjustment needed
	•Elvitegravir/cobicistat	No data; no dosage recommendation
Rosuvastatin	•Darunavir + ritonavir •Elvitegravir/cobicistat	Titrate rosuvastatin dose carefully and use lowest effective dose while monitoring for toxicities
	•Darunavir/cobicistat	Do not exceed 20 mg rosuvastatin daily
	•Atazanavir/cobicistat •Atazanavir + ritonavir •Lopinavir/ritonavir	Do not exceed 10 mg rosuvastatin daily
	•Tipranavir + ritonavir	No dose adjustment needed
Simvastatin	•HIV protease inhibitors •Elvitegravir/cobicistat	CONTRAINDICATED

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/

ARV Interactions with Anti-acid Medications

- Indicated for GERD, peptic ulcer disease to decrease gastric acidity
  - Antacids: aluminum, magnesium hydroxide, or calcium carbonate
  - H2 receptor antagonists
  - Proton pump inhibitors
- Medications decreasing stomach acidity can interfere with ARVs requiring an acidic environment for absorption (e.g., atazanavir, rilpivirine)
- INSTI absorption is decreased by binding with di/trivalent cations

Managing ARV Interactions with Anti-Acid Therapy

Anti-acid	Atazanavir (ATV) Interactions	Oral Rilpivirine (RPV) Interactions	Oral INSTI Interactions
Al, Mg, Ca Antacids	ATV 2 hrs before or 1-2 hour after antacids	Antacids 2 hours before or 4 hours after RPV	•Separate EVG by ≥ 2 hours •RAL/RAL HD not recommended with Al or Mg •RAL no dose adjustment with Ca; RAL HD contraindicated with Ca •BIC, DTG ≥ 2 hours before or ≥ 6 hours after antacids •Oral CAB 4 hours before or 2 hours after antacid
H2 Receptor Antagonists (H2RA)	•Atazanavir with ritonavir or cobicistat: ATV with or 10 hours after H2RA (max famotidine 40mg BID for treatment naïve; 20mg BID for treatment experienced) •Atazanavir alone: ATV 2 hours before or 10 hours after H2RA (max famotidine 20mg dose for treatment naïve; CONTRAINDICATED for treatment experienced)	H2RA 12 hours before or 4 hours after RPV	No dose adjustment
Proton Pump Inhibitors (PPI)	Atazanavir must be boosted with ritonavir or cobicistat: PPI 12 hours prior to ATV (max omeprazole 20mg for treatment naïve; CONTRAINDICATED for treatment experienced)	CONTRAINDICATED	No dose adjustment

ARV Interactions with Rifamycins

- Rifamycins used in tuberculosis and other mycobacterial treatment
- Rifampin
  - Strong CYP3A4, UGT1A1, Pgp inducer
  - ↓ ARV levels
- Rifabutin
  - Weak CYP inducer & substrate
  - ARV levels stay same or slight ↓
  - Often substituted for rifampin in HIV+

Managing ARV Interactions with Rifamycins

Rifampin (RFP)

- NRTI + RFP
  - ↓TAF 55%: **AVOID**
  - Other NRTIs: Okay to use
- Protease inhibitors + RFP
  - ↓PI 75%; **AVOID**
- NNRTIs + RFP
  - NVP,ETR,RPV,DOR: **AVOID**
  - EFV: Okay to use
- INSTI + RFP ↓INSTIs 70%
  - Stribild®,Genvoya®, Biktarvy®, Cabenuva®: **AVOID**
  - ↑ RAL dose to 800mg BID; **AVOID** with RAL HD
  - ↑DTG to 50mg BID; avoid if INSTI-experienced or resistance

Rifabutin (RFB)

- NRTI + RFB
  - ↓TAF: **AVOID**
  - Other NRTIs: Okay to use
- Protease Inhibitors + RFB
  - PIs inhibit RFB metabolism, ↑RFB levels, recommend ↓RFB dose: RFB 150mg QD
- NNRTIs +RFB
  - EFV: use RFB 450-600mg QD
  - Rilpivirine AUC ↓46%: ↑RPV dose to 50mg QD
  - DOR AUC ↓50%: ↑DOR dose to 100mg BID
- INSTI + RFB
  - DTG, RAL: Okay to use
  - Stribild®,Genvoya®, Biktarvy®, Cabenuva®: **AVOID**

ARV Interactions with Macrolides

- Macrolides used in treatment and prevention of mycobacterial infections
- CYP 3A substrates and inhibitors
  - Potential for bidirectional interactions
    - Macrolides are P450 substrates: ARVs that are P450 inducers or inhibitors (PI, NNRTI, cobicistat) may affect macrolide efficacy/toxicity
    - Macrolides are P450 inhibitors: may decrease levels of ARVs that are P450 substrates (PI, NNRTI, INSTIs, entry inhibitors)
  - Degree of 3A4 inhibition varies:

erythromycin >> clarithromycin > azithromycin

Managing ARV Interactions with Macrolides

Clarithromycin

- PIs ↑/same, but ↑clarithro levels
  - ATV: ↓ clarithro dose by 50%
  - Other PIs: ↓ clarithro dose if CrCl < 60 ml/min
- NNRTI ↓ clarithro 30-40%; clarithro ↑ NNRTI
  - Consider alt macrolide
- INSTI
  - Stribild®, Genvoya®: Reduce clarithro dose if CrCl < 60 ml/min
  - BIC, DTG, RAL, CAB: Okay to use

Azithromycin

- No drug interactions with ART
- Preferred macrolide

ARV Interactions with Antiepileptics

- Antiepileptic drugs: Carbamazepine, phenytoin, phenobarbital have two-way drug interactions
  - They are P450 substrates: ARVs that are P450 inducers/inhibitors (PI, NNRTI, cobicistat) may affect antiepileptic efficacy/toxicity
  - They are P450 and p-glycoprotein inducers: may decrease levels of ARVs that are substrates (TAF, PI, NNRTI, INSTIs, entry inhibitors) leading to virologic failure
- Levetiracetam not metabolized by P450, recommend as alternative

Managing ARV Interactions with Antiepileptics: Carbamazepine, Phenytoin, & Phenobarbital

Antiretroviral	Effect on ARV/Antiepileptic Drug	Clinical Management
NRTI	•Antiepileptics induce Pgp, causing lower TAF levels	Avoid with TAF (all other NRTIs ok)
PI	•PIs inhibit P450, causing increased antiepileptic levels •Antiepileptics induce P450, causing lower PI levels	Avoid; or monitor PI efficacy (viral load) & antiepileptic toxicity (drug levels)
NNRTI	•NNRTIs induce P450, causing lower antiepileptic levels •Antiepileptics induce P450, causing lower NNRTI levels	EFV and NVP require close monitoring of ARV levels/efficacy; ETR, RPV, DOR: CONTRAINDICATED
INSTIs	•Antiepileptics induce P450, causing lower INSTI levels •Cobicistat inhibits P450, causing increased antiepileptic levels	Coadministration not recommended

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/

ARV Interactions with Corticosteroids

- Inhaled/intranasal corticosteroids used for allergic rhinitis, asthma, COPD
  - Mostly P450 substrates with potential to interact with PIs and cobicistat
    - Ritonavir & COBI can ↑ fluticasone AUC 36,697%
    - Can result in steroid accumulation, adrenal suppression, and Cushing's syndrome
- Fluticasone: longest glucocorticoid receptor binding t½ and very lipophilic (most potential for drug interactions)
- Beclomethasone likely safest (least potential for interactions)

Cushing's Syndrome Following Lumbar Medial Branch Block

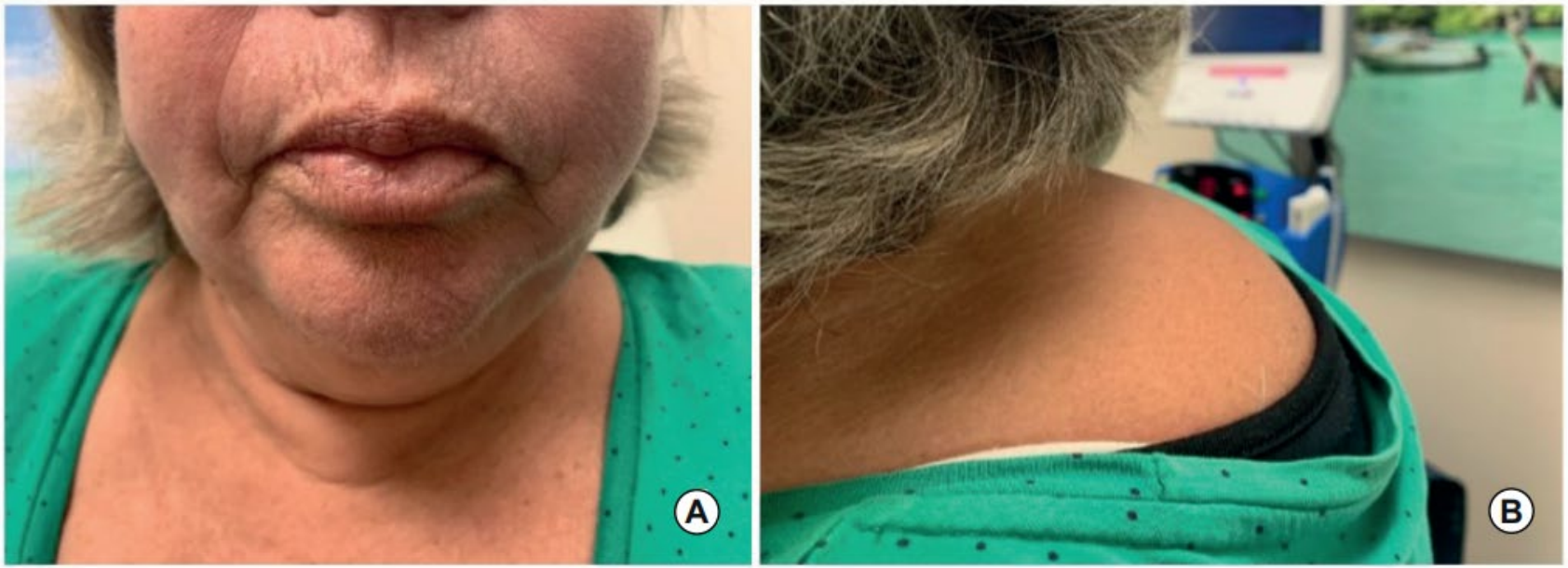


Figure 1. Images of the patient taken at an encounter 4 weeks after the lumbar medial branch block procedure. Noted are moon facies with plethora **(A)** and marked 'buffalo hump' deformity **(B)**.

Mohan A, et al. Pain Manag. 2021 Apr;11(4):381-387.

ARV Interactions with Oral Anticoagulants and Antiplatelets

- **Direct oral anticoagulants** eliminated by hepatic drug metabolizing enzymes including P450
- **Platelet aggregation inhibitors** metabolized by P450
- **Warfarin** metabolized by P450

Managing ARV Interactions with Direct Oral Anticoagulants (DOACs)

DOAC	Antiretroviral	Clinical Effect, Dosing Recommendation
Dabigatran	Darunavir/ritonavir Darunavir/cobicistat	No data, consider alternative
	Atazanavir/ritonavir Atazanavir/cobicistat Elvitegravir/cobicistat	↑ dabigatran, dosing depends on indication and renal function
	NNRTIs	No dose adjustment needed
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed
Rivaroxaban	Boosted PIs Elvitegravir/cobicistat	↑ rivaroxaban, do not coadminister
	Efavirenz, Etravirine, Nevirapine	↓ rivaroxaban, consider alternative
	Doravirine, Rilpivirine	No dose adjustment needed
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed

Managing ARV Interactions with Direct Oral Anticoagulants (DOACs)

DOAC	Antiretroviral	Clinical Effect, Dosing Recommendation
Edoxaban	Darunavir/ritonavir Darunavir/cobicistat	No data, consider alternative
	Atazanavir/ritonavir Atazanavir/cobicistat Elvitegravir/cobicistat	↑ edoxaban, if used for nonvalvular a fib then no dose adjustment needed, if used for DVT/PE then edoxaban 30 mg daily
	NNRTIs	No dose adjustment needed
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed
Apixaban	Boosted PIs Elvitegravir/cobi	↑ apixaban, reduce apixaban dose by 50% (do not coadminister in patients requiring apixaban 2.5mg BID)
	Efavirenz, Etravirine, Nevirapine	↓ apixaban, consider alternative
	Doravirine, Rilpivirine	No dose adjustment needed
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed

Managing ARV Interactions with Antiplatelets

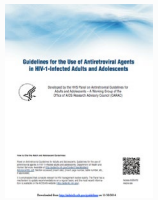
Antiplatelet	Antiretroviral	Clinical Effect, Dosing Recommendation
Clopidogrel	Efavirenz, Etravirine	↓ clopidogrel, consider alternative
	Doravirine, Nevirapine, Rilpivirine	No dose adjustment needed
	All boosted PIs, Elvitegravir/cobicistat	↓ clopidogrel, impaired platelet inhibition, do not co-administer
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed
Ticagrelor	All PIs, Elvitegravir/cobicistat	↑ ticagrelor, do not co-administer
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed
	Efavirenz, Etravirine, Nevirapine	↓ ticagrelor, consider alternative
	Doravirine, Rilpivirine	No dose adjustment needed

Managing ARV Interactions with Antiplatelets

Antiplatelet	Antiretroviral	Dosing Recommendation
Vorapaxar	All PIs Elvitegravir/cobicistat	↑ vorapaxar, do not co-administer
	Bictegravir, Cabotegravir, Dolutegravir, Raltegravir	No dose adjustment needed
	Efavirenz, Etravirine	↓ vorapaxar, insufficient data to make dose recommendation
	Doravirine, Nevirapine, Rilpivirine	No dose adjustment needed
Prasugrel	All NNRTIs All boosted PIs All INSTIs	No dose adjustment needed

Resources: ART & Drug Interactions

- Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. [**clinicalinfo.hiv.gov/guidelines**]
  - **Tables 23-25**



- University of Liverpool HIV iChart app for iPhone and Android [**www.hiv-druginteractions.org**]

- Southeast AETC Pocket Cards

[**www.seaetc.com/provider-resources/reference/**]

ART in Adults & Adolescents

AETC AIDS Education & Training Center Program Southeast

August 2021

Patient Case Revisited

- 75-year-old male who comes in for follow up
- Living with HIV for 25 years:
  - Currently on BIC/FTC/TAF for 3 years
  - Multiple prior ART, no virologic failure
- Current medications: atorvastatin, aspirin, lisinopril, hydrochlorothiazide, amlodipine, omeprazole, metformin, glipizide, calcium carbonate, multiple vitamin, diphenhydramine
- Exam is normal

Labs	Value
CD4+ cell count, cells/mm^3	534
HIV-1 RNA, copies/mL	< 20
HLA-B*5701	Negative
BMI	28.5
Blood pressure, mm Hg	134/78
Total cholesterol, mmol/L	201
HDL cholesterol, mmol/L	35
ALT, IU/L	24
eGFR, mL/min	44
A1C, mmol/mol (%)	7.6

Patient Case Revisited: Recommendations

- BP is at goal—can antihypertensive regimen be consolidated?
- Advise patient to separate ART dosing from multivitamin (if it contains iron or magnesium) or calcium carbonate
- Monitor renal function carefully
- Consider reducing diabetic medications to decrease risk of hypoglycemia
  - Glipizide not recommended in older persons
- Use Beers criteria to screen for potentially inappropriate medications

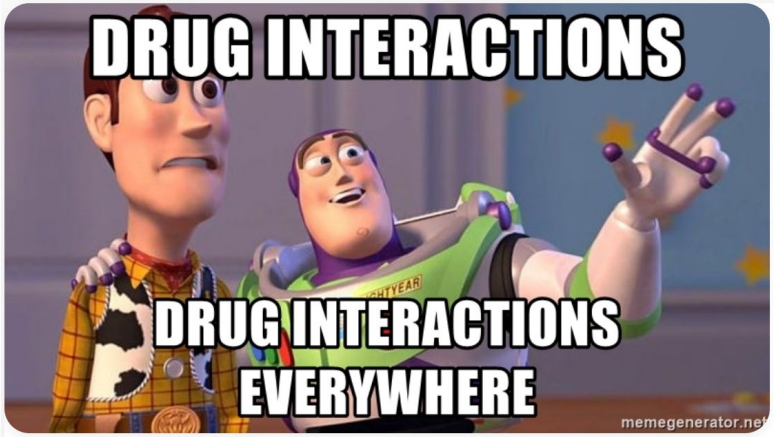
Managing Polypharmacy: A Clinician Checklist

- Establish a complete and accurate medication list by regularly reviewing medications at each visit
  - Include medications from all sources (primary care providers, specialty care providers, and over the counter)
- Consolidation to combination tablets
- Simplifying HIV medications
  - On a stable regimen and virally suppressed with no history of resistance? Inquire within!
- Simplifying non-HIV medications (a.k.a. deprescribing)
- Lowering medication dosages
- Assisting with medication logistics and pharmacy

Summary: The Importance of Drug Interactions

- Drug interactions occur between ART and medications used to manage common comorbidities (polypharmacy consequence)
- ART presents high potential for drug interactions due to the way the medications are absorbed and metabolized
- Clinicians providing care to patients with HIV must be cognizant of potential drug interactions
- Ask about all medications: prescription, over-the-counter, herbal, recreational
  - INSTIs have the fewest drug interactions
  - Regimens containing cobicistat or ritonavir as boosters have a high potential for drug interactions

AETC AIDS Education & Training Center Program Southeast



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