LMAP 2020
LIVERPOOL MASTERCLASS IN ANTIVIRAL PHARMACOLOGY

DDIs (Yesterday's problem?)

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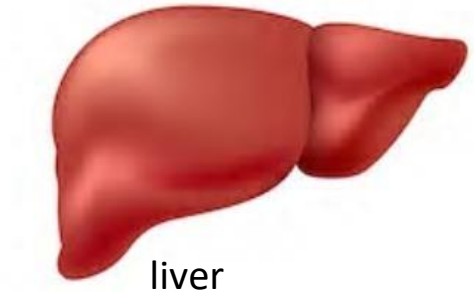
Mechanisms of DDIs with antiretroviral agents

Inhibition/induction of hepatic cytochromes, glucuronidation, or drug transporters

Metabolism

victim	perpetrator
doravirine	PI/r
rilpivirine	PI/c
bictegravir	elvitegravir/c
dolutegravir	efavirenz
raltegravir	etravirine
maraviroc	nevirapine

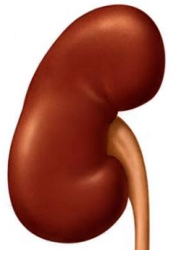


liver

Inhibition of renal drug transporters

Excretion

victim	perpetrator
tenofovir	bictegravir
	dolutegravir
	cobicistat
	ritonavir

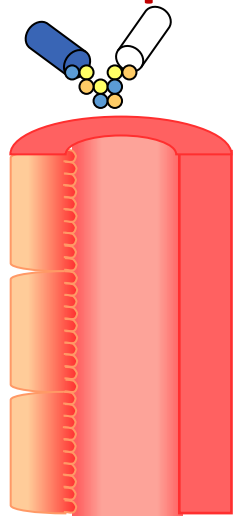


kidney

Inhibition/induction intestinal cytochromes or drug transporters

victim	perpetrator
doravirine	PI/r
rilpivirine	PI/c
bictegravir	elvitegravir/c
Tenofovir (TDF, TAF)	
maraviroc	

Absorption



small intestine

Change gastric pH

victim
atazanavir
rilpivirine

Chelation with mineral supplements

victim
bictegravir
dolutegravir
elvitegravir/c
raltegravir

Back D & Marzolini C. J Int AIDS Soc 2020

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Assessment of DDIs potential and clinical relevance

Step 1: evaluation of likelihood of having DDI

- PK/PD characteristics of coadministered drugs
- clinical DDI studies
- case reports

No DDI

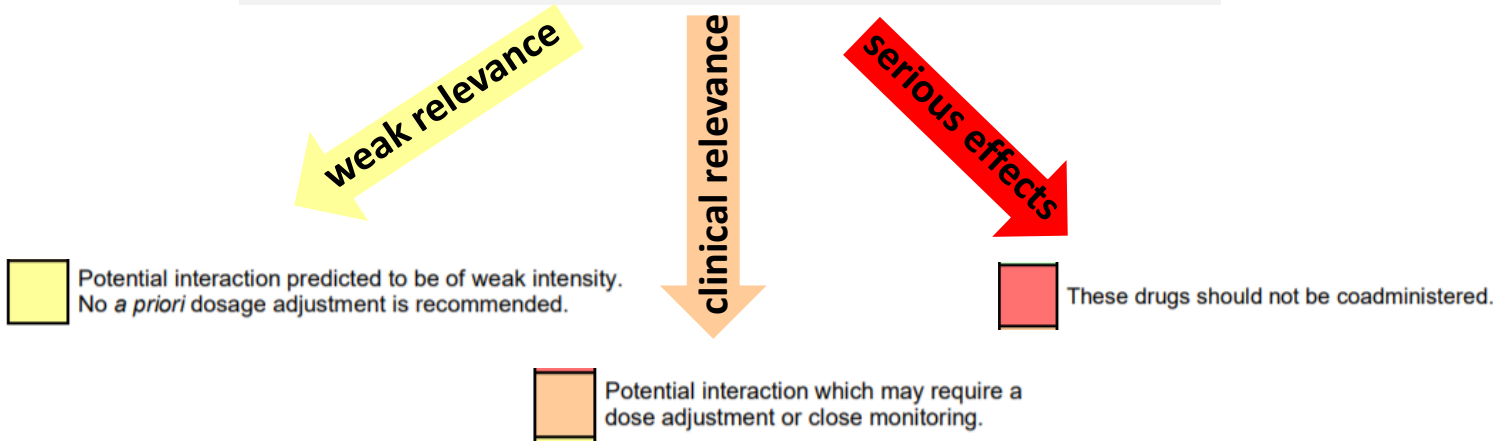
- different elimination pathways
- no significant PK change
- no safety concern

evidence that DDI may occur

Step 2: evaluation of clinical relevance

- magnitude of PK change
- therapeutic index
- possibility to monitor the drug effect
- recommendation on dose adjustment
- length of treatment required

\+ recommendations of product label



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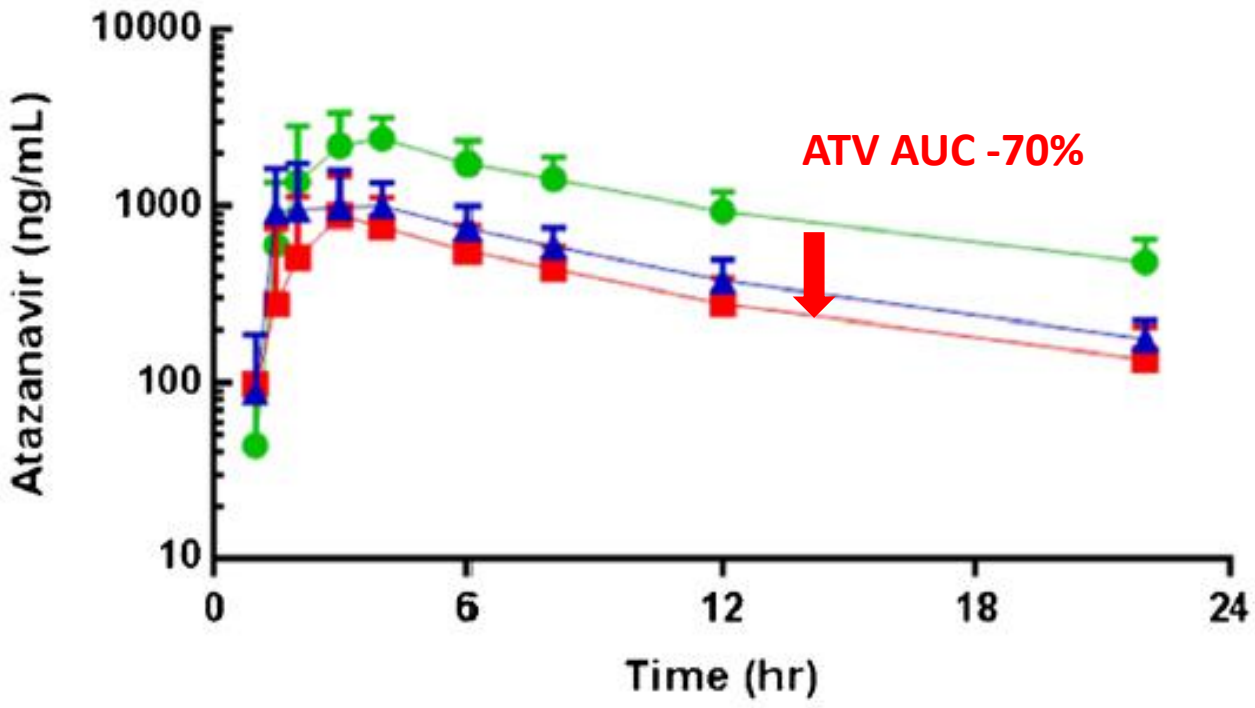
Change in gastric pH and atazanavir absorption



Atazanavir/ritonavir (300/100 mg QD) alone

Atazanavir/ritonavir (300/100 mg QD) + rabeprazole (20 mg BID)

PPIs

Atazanavir & rilpivirine require a low pH for their solubility

Do Not Coadminister
Rilpivirine
Omeprazole

Do Not Coadminister
Atazanavir
Omeprazole

Alternatives for rilpivirine

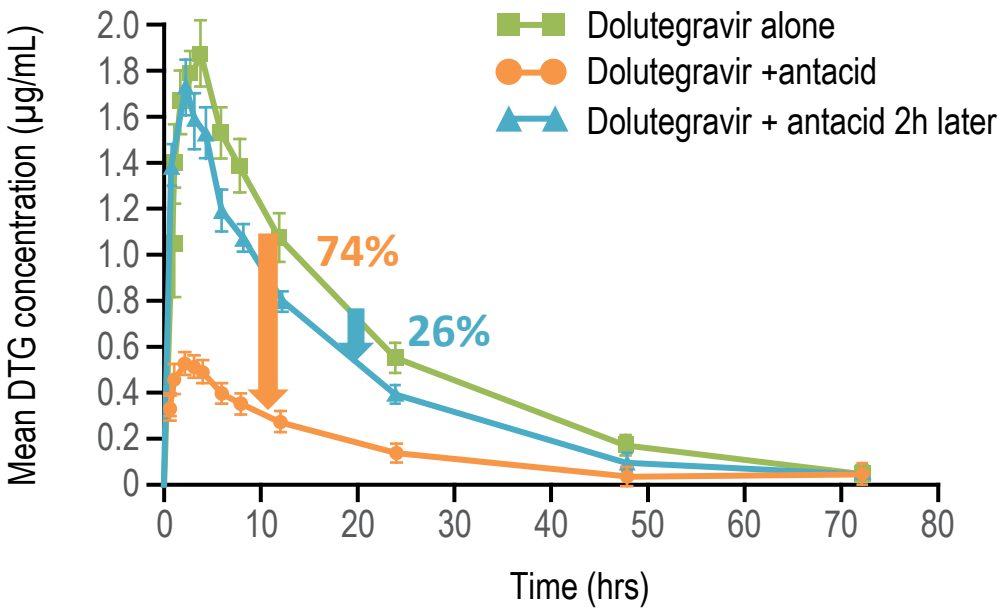
antacids: 2 h before or 4 h after RPV
H2 blockers: 12 h before or 4 h after RPV

Alternatives for atazanavir

antacids: ATV 2 h before or after antacid
H2 blockers: ATV: max equiv. 20 mg BID famotidine
ATV/r: max equiv. 40 mg BID famotidine (ttt naive) or 20 mg BID famotidine (ttt experienced).
Administer simultaneous or >10h after H2 blocker

Faber K et al. Pharm Res 2017, www.hiv-druginteractions.org

Chelation of HIV integrase inhibitors with divalent cations



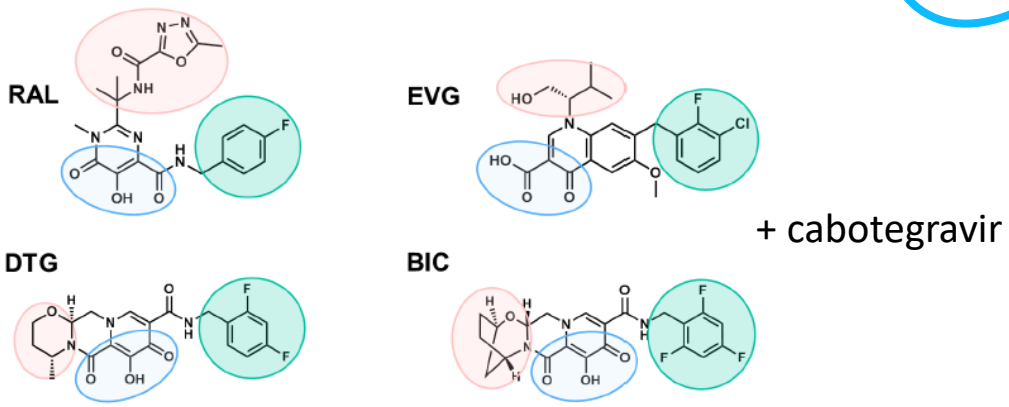
Chelation of integrase inhibitors with divalent cations (magnesium, calcium, iron, aluminium)

Cave: mineral supplements, antacids

Potential Interaction
Dolutegravir (DTG)
Antacids

Administer dolutegravir 2 hours before or 6 hours after taking medications containing polyvalent cations such as antacids

All integrase inhibitors contain a diketo acid motif which binds to Mg at the level of the active site of the HIV integrase



+ cabotegravir

www.hiv-druginteractions.org

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Integrase Inhibitors and Cations

Produced February 2020 *Page 1 of 2*

Drug Interactions between Integrase Strand Transfer Inhibitors and Cations

Administration Recommendations for Antacids

INSTI	Product	Antacids (containing aluminium/magnesium or calcium)
Bictegravir	**Biktarvy** (BIC/FTC/TAF)	Al/Mg antacids: take Biktarvy at least 2 h before antacids. OR take with food 2 h after antacids (European label). OR take 6 h after antacids (USA label). Calcium antacids: take together with food (USA label).
Dolutegravir	**Tivicay** (DTG)	Al/Mg antacids: take Tivicay at least 2 h before or 6 h after antacids. Avoid in the presence of integrase class resistance (European label). Calcium antacids: *take Tivicay at least 2 h before or 6 h after antacids

Patel P et al. JAC 2011, www.hiv-druginteractions.org

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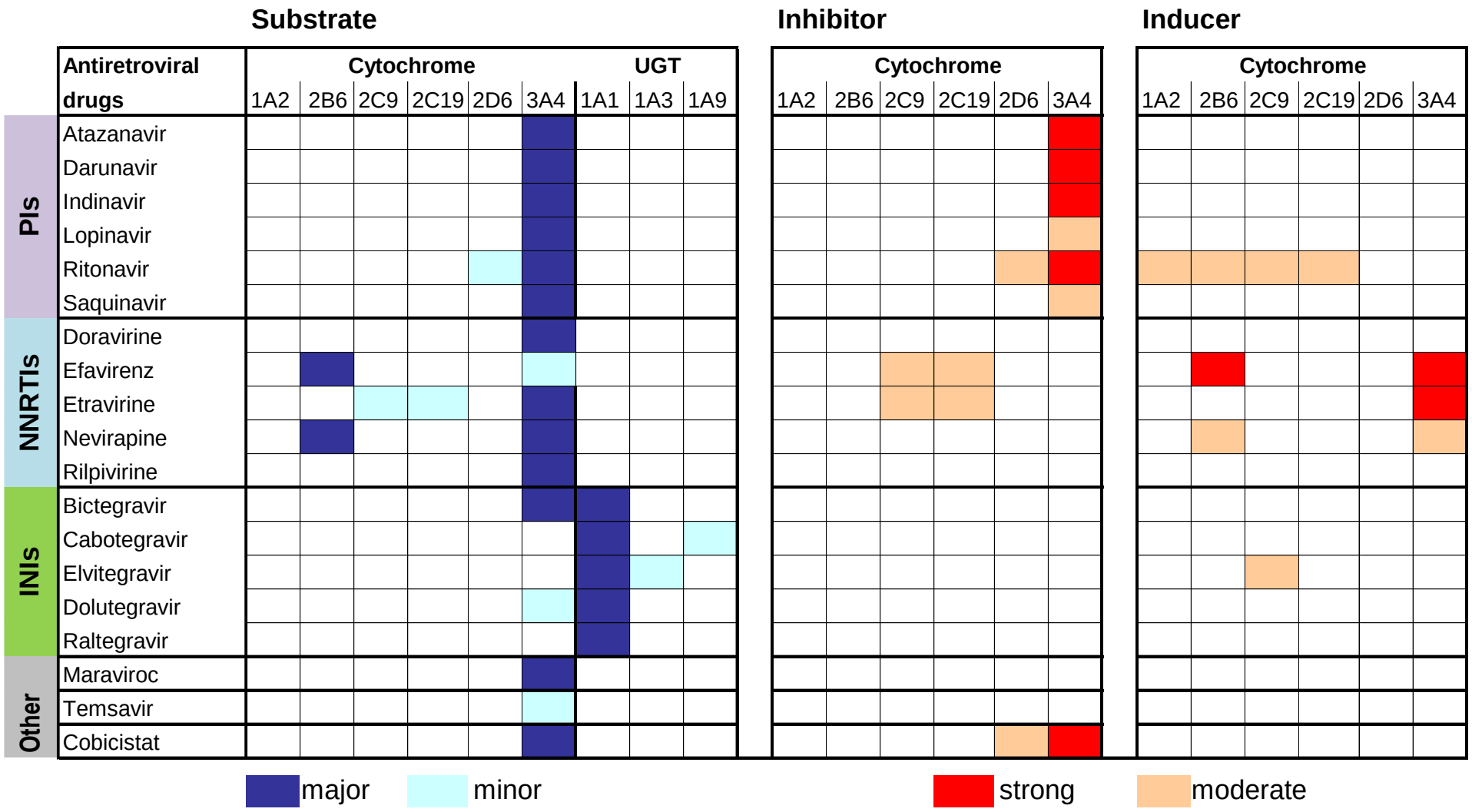
Antiretroviral drugs and drug metabolizing enzymes



Product labels

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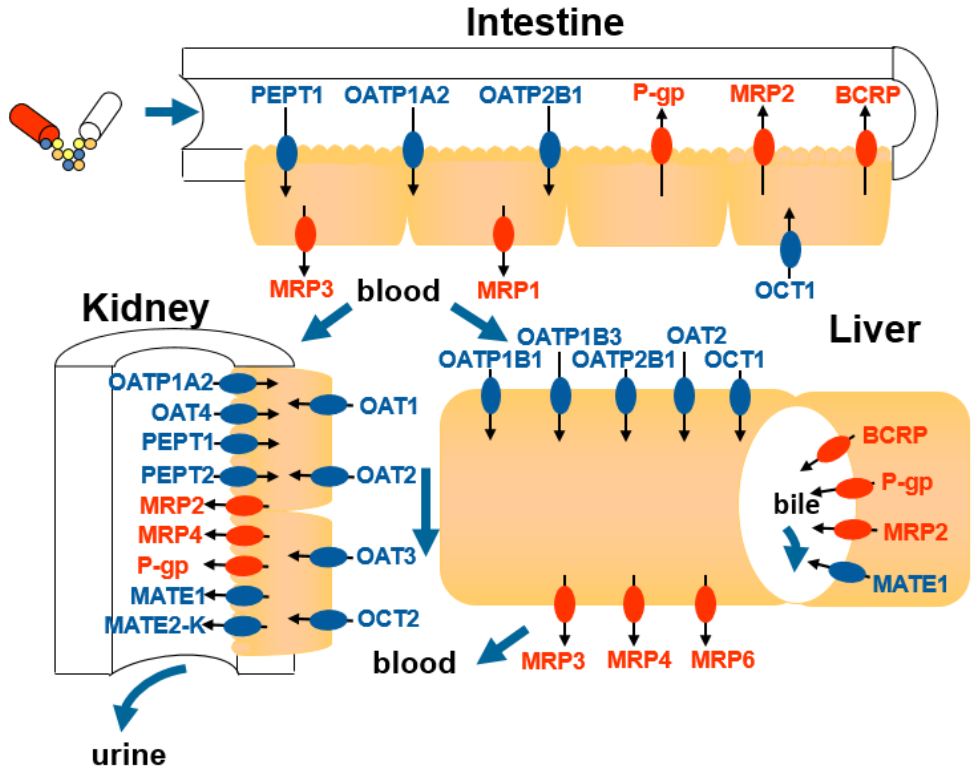
Antiretroviral drugs and drug transporters

	Antiretrovirals	OATP1B1	OAT1	OCT2	MATE1	P-gp	BCRP	MRP4
PIs	Atazanavir	X				X	X	
	Darunavir	X				X	X	
	Lopinavir	X				X	X	
	Ritonavir	X			X	X	X	
	Saquinavir	X				X	X	
NNRTIs	Doravirine							
	Efavirenz							
	Etravirine					x		
	Nevirapine							
	Rilpivirine							
NRTIs	Abacavir							
	Emtricitabine							
	Lamivudine							
	TDF		TFV					TFV
	TAF		TFV		x			TFV
	Zidovudine							
INIs	Bictegravir			x	x			
	Cabotegravir		x					
	Dolutegravir			X				
	Elvitegravir							
	Raltegravir							
Other	Maraviroc							
	Temsavir	x					X	
	Cobicistat	X			X	X	X	

substrate X inhibitor x weak inhibitor



Moss D & Marzolini C In: Drug Interactions in Infectious Diseases 2018

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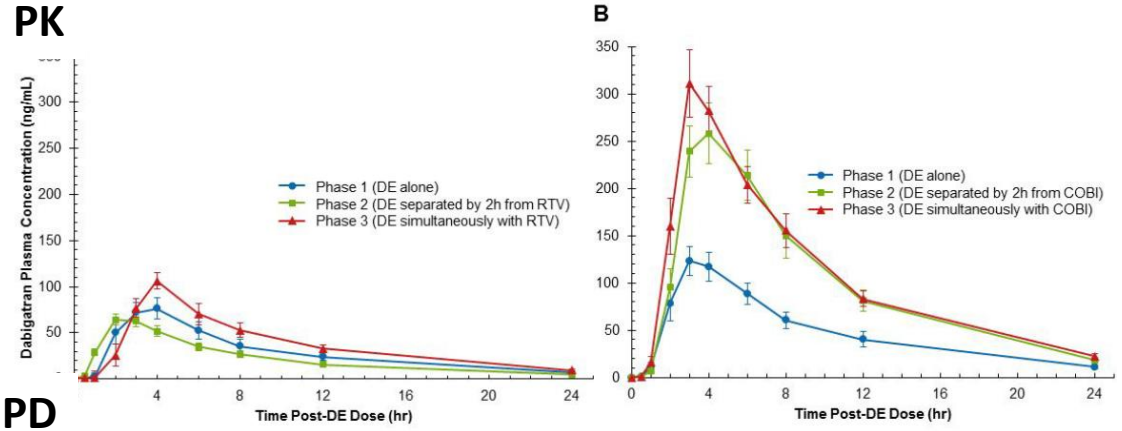
Effect of boosted antiretroviral drugs on dabigatran absorption

Dabigatran: no CYP metabolism, substrate of P-gp

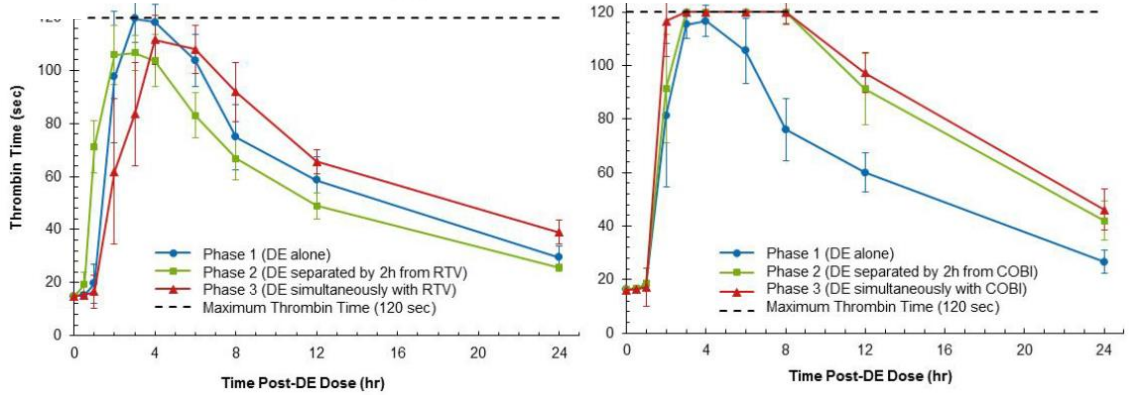
+ Ritonavir
dabigatran alone
dabigatran adm 2 h before RTV
dabigatran adm together with RTV

+ Cobicistat
dabigatran alone
dabigatran adm 2 h before Cobi
dabigatran adm together with Cobi

PK



PD



RTV: mixed inhibitory/inducing effect on P-gp

Cobi: only inhibitory effect on P-gp

Potential Interaction	Do Not Coadminister
Darunavir + ritonavir (DRV/r)	Darunavir/cobicistat (DRV/c)
Dabigatran	Dabigatran

Dabigatran can be administered simultaneously with PI/r. Caution in case of mild or moderate renal function as dabigatran dose may need to be reduced.

when switching pharmacokinetic booster: ritonavir has inhibitory/inducing effects whereas **cobicistat does not**

Chelsea and Westminster Hospital NHS | University of Liverpool | Royal Free London NHS

Effect on key drug-drug interactions of switching from ritonavir- to cobicistat-boosted DRV or ATV

(Refer to Product Labels and/or www.hiv-druginteractions.org for full list of DDIs)

Drug class	Non-ARV Drug	Potential impact of switch on non-ARV	Recommendations *In all cases review risks versus benefit of switch, and liaise closely with other prescribers*
Analgesics	Methadone	Exposure ↑	Consider counselling patient on potential need for reduction in methadone dose. Advise methadone prescriber of potential for dose modification.
	Diamorphine, morphine, hydromorphone, pethidine	Exposure ↑	Consider dose reduction and re-titration and/or monitor for signs of opiate toxicity.
	Dihydrocodeine	Unclear, may ↑ or remain unchanged	Counsel patient that may need to re-titrate dose.
Anti-microbials	Atovaquone, proguanil, sulfadiazine	Exposure ↑	Monitor for side effects.
	Rifabutin	Unclear	Caution or avoid; Consult HIV/TB co-infection guidelines.

Kumar P et al. AAC 2017; www.hiv-druginteractions.org

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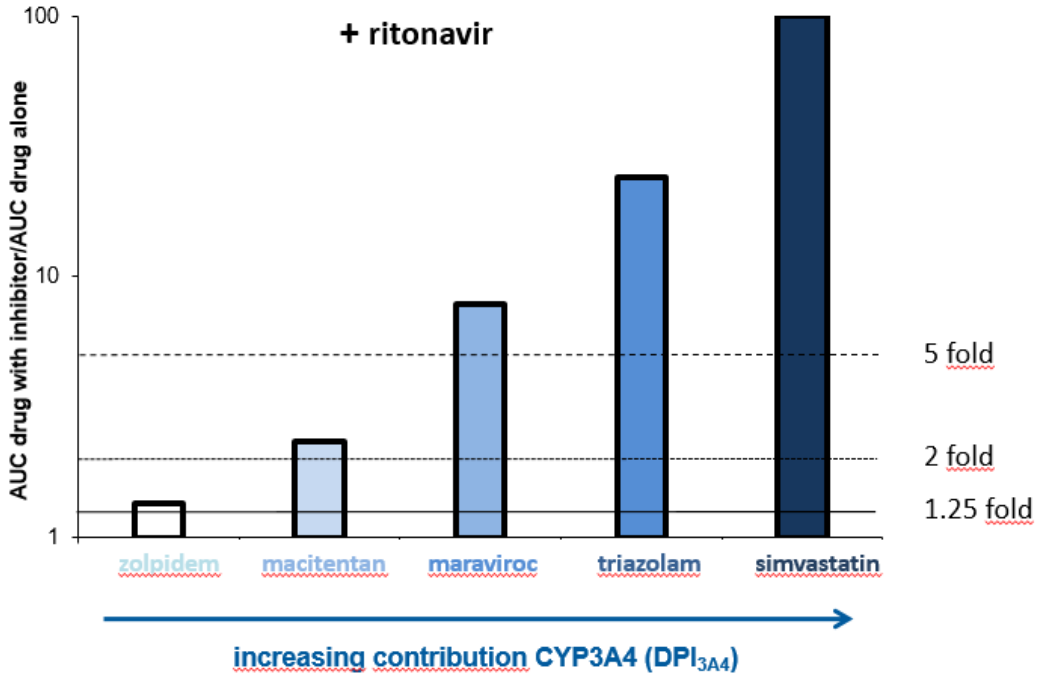
Magnitude of DDIs with CYP inhibitors/inducers

Magnitude of drug-drug interaction depends on:

- **Strength of CYP inhibitor or inducer**
- **Fraction of metabolism via given CYP (DPI)**

Drug	DPI $_{CYP3A4}$	
simvastatin	1.0	exclusively metabolized by CYP3A4
zolpidem	0.26	CYP3A4 contributes to 26% of the overall metabolism

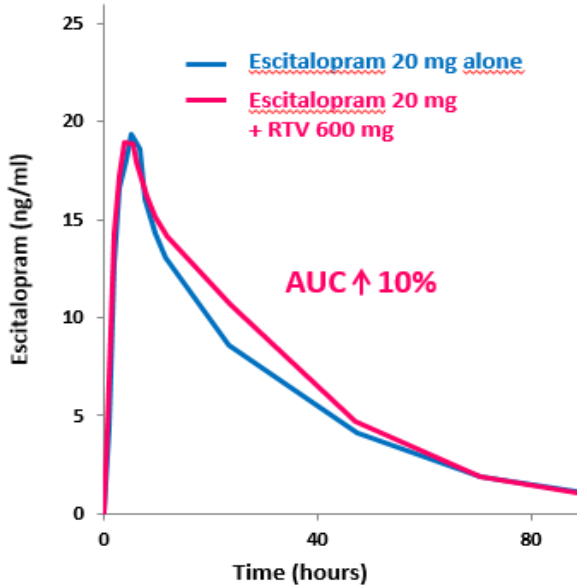


Antidepressants are metabolized by several CYPs

Antidepressants	Cytochrome 1A2	2B6	2C9	2C19	2D6	3A4
citalopram				minor	minor	minor
escitalopram				minor	minor	minor
fluvoxamine	minor				major	
fluoxetine			major	minor	major	minor
paroxetine					major	minor
sertraline		major	minor	minor	minor	minor
duloxetine	major				major	
venlafaxine			minor	minor	major	minor
amitriptyline	minor		minor	major	major	minor
clomipramine	major			minor	major	major
imipramine	major			minor	major	major
nortriptyline	minor			minor	major	minor
trimipramine			minor	minor	major	
maprotiline	minor				major	
mianserine	major				major	minor
mirtazapine	minor				major	major
bupropion		major				
lamotrigine*						
trazodone					minor	major

major minor

➔ mitigate DDIs magnitude



➔ overestimation of DDI risk leading to treatment underdosing. Study found larger proportion of PLWH with subtherapeutic antidepressants levels compared to uninfected individuals suggesting deliberate lower dosing of antidepressants as clinicians fear DDIs with ARV.

Stader F et al. Antimicrob Agent Chemother 2018; Gutierrez MM et al. Clin Ther 2003; Cattaneo D et al. World J Biol Psychiatry 2018

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Combined inhibitory effect of CYP and drug transporters

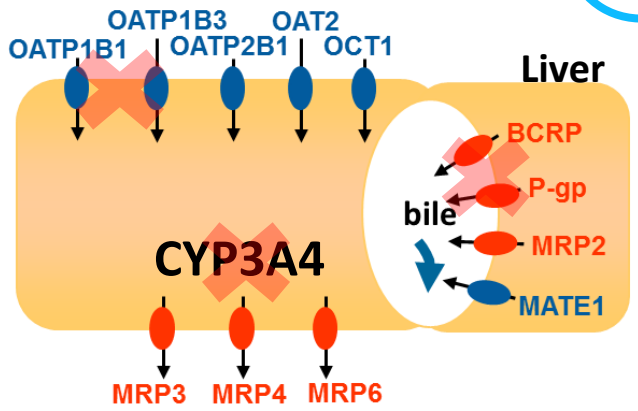
	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EVG/c
Atorvastatin + (CYP3A4 + transporters)	↑822%	↑	↑290%	↑	↑490%	↑
Rosuvastatin + (transporters)	↑242%	↑213%	↑93%	↑48%	↑107%	↑38%

OATP1B1 inhibition: **ATV > LPV > DRV > RTV, Cobi**

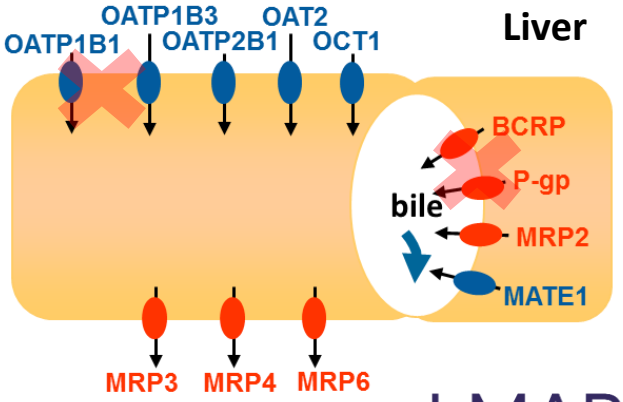
Recommendations

	ATV/c	DRV/c
Atorvastatin	NR/lowest dose Max: 10 mg/d	lowest dose Max: 40 mg/d (US label: 20 mg/d)
Rosuvastatin	lowest dose Max: 10 mg/d	lowest dose Max: 20 mg/d

Atorvastatin + DRV/r



Rosuvastatin + DRV/r



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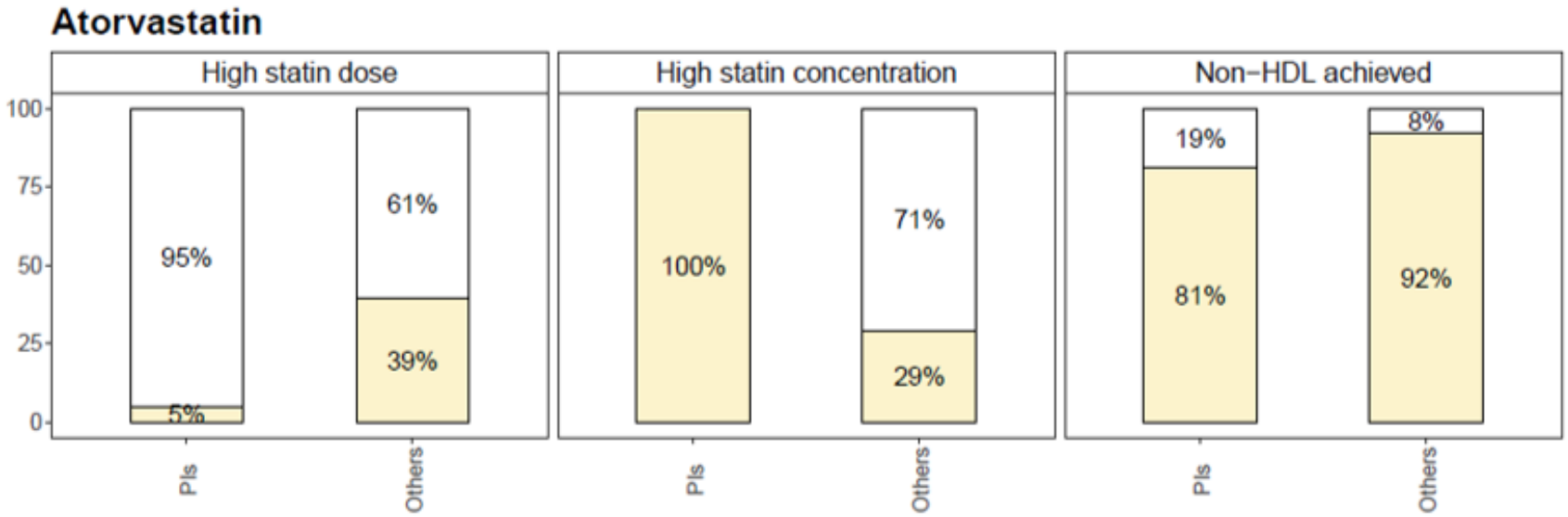
Response to statin treatment

Response to statin treatment was evaluated in patients of the SHCS. Analysis took into account statin dosage, statin plasma concentrations and achievement of lipid targets.



Yellow bars = % statin prescriptions with high statin dose, high statin plasma concentration and achievement of non-HDL-cholesterol targets. Others = dolutegravir, raltegravir or rilpivirine.

Protease inhibitors cause large DDIs with atorvastatin. Despite high concentrations, non-HDL targets were less often achieved with PIs likely due to both their inhibitory effects on OATP1B1 and their unfavourable effects on lipids.

Courlet P et al. J Antimicrob Chemother 2020

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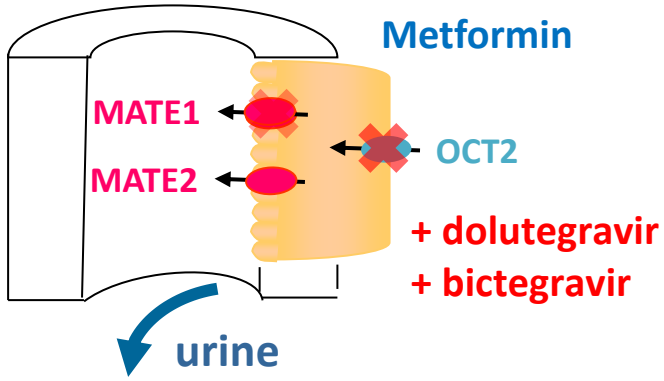
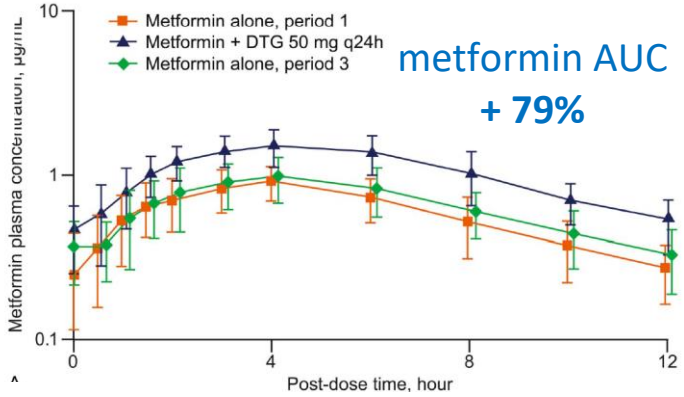
DDIs at renal level

Metformin is excreted unchanged in urine via active secretion

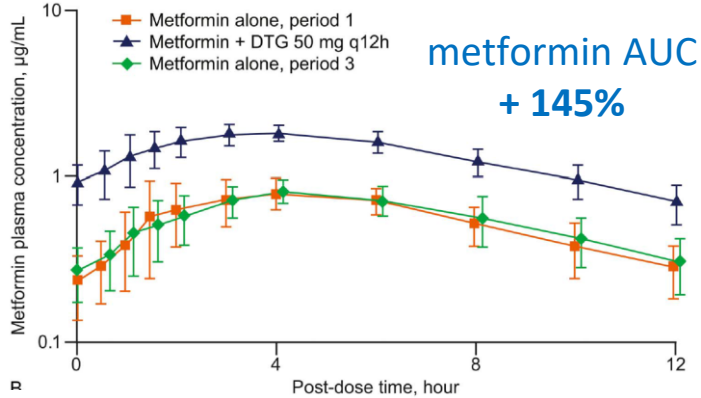


- Metformin-induced lactic acidosis rare
- Cases: related to underlying conditions
- Risk increased with impaired renal function (eGFR < 60) and high dose metformin (>2 gr/day)

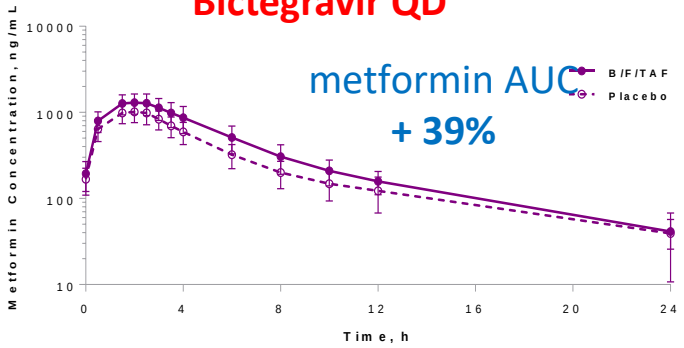
Dolutegravir QD



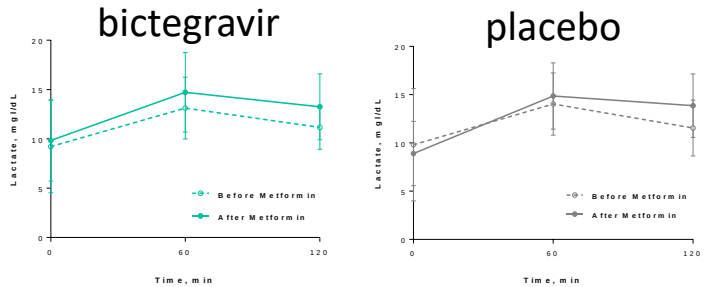
Dolutegravir BID



Bictegravir QD



Plasma lactate concentrations



Potential Interaction	
Dolutegravir (DTG)	
Metformin	
Potential Interaction	
Bictegravir/ Emtricitabine/Tenofovir alafenamide (BIC/FTC/TAF)	
Metformin	

- DTG: close monitoring and consider dose adjustment when starting/stopping DTG (avoid high dose metformin)
- BIC: no dose adjustment in patients with normal renal function, close monitoring and consider dose adjustment in patients with moderate renal impairment

Stades AM et al. J Intern Med 2004, Eppenga WL et Al. Diabetes Care 2014, Song I et al. JAIDS 2016, Zhang H et al. IWCPT 2017

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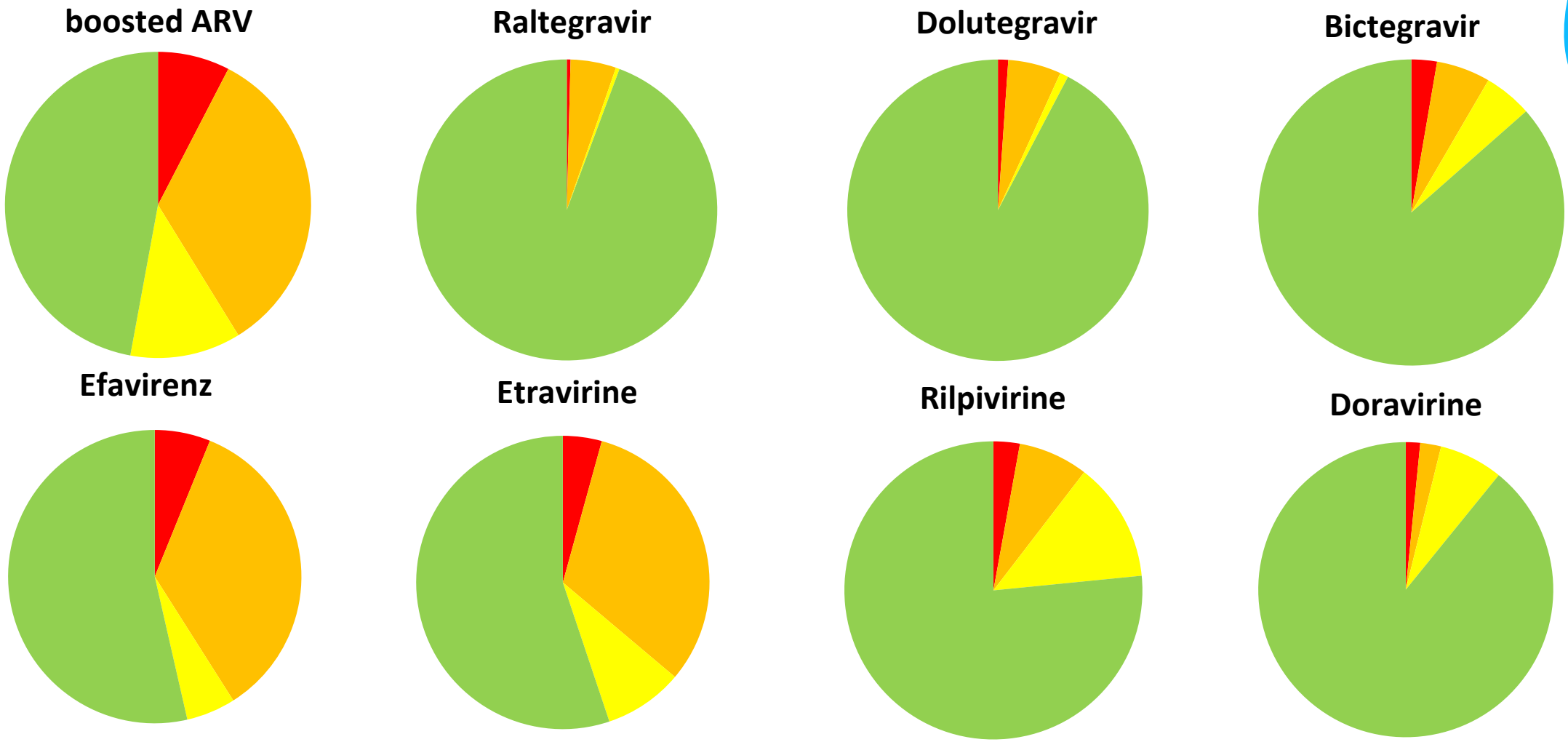
DDIs profiles of antiretroviral drugs

n ≈ 750 comedications



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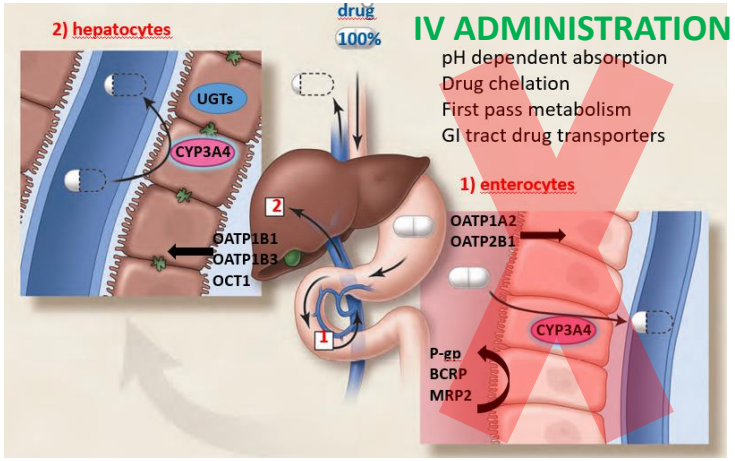
DDIs risk with intramuscular administration of antiretroviral agents

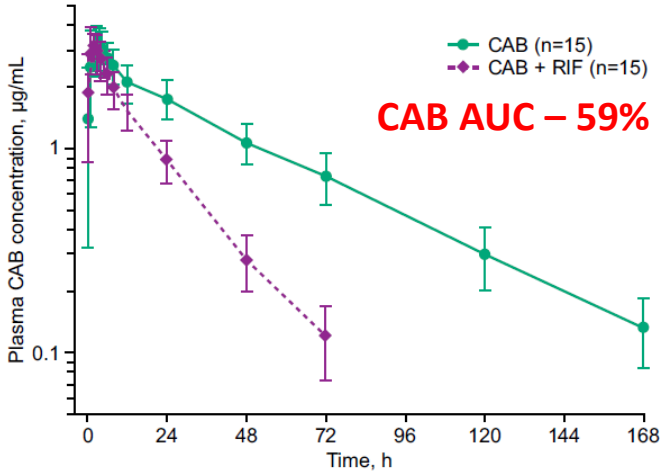


Potential Interaction
Cabotegravir [oral] (CAB oral)
Antacids

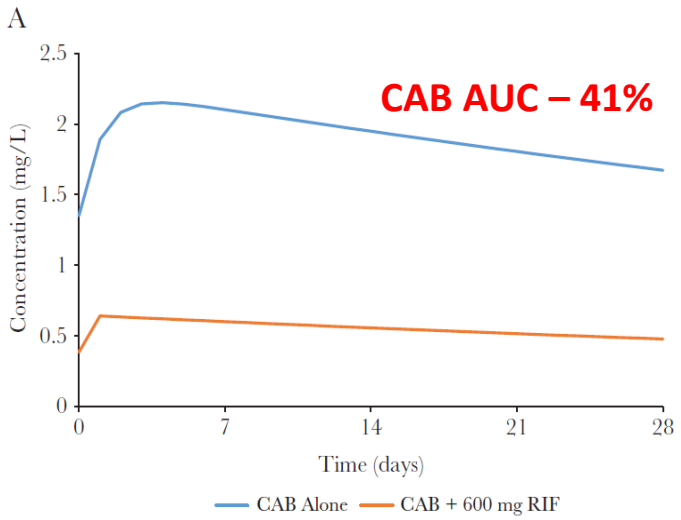
Potential Interaction
Rilpivirine (RPV)
Antacids

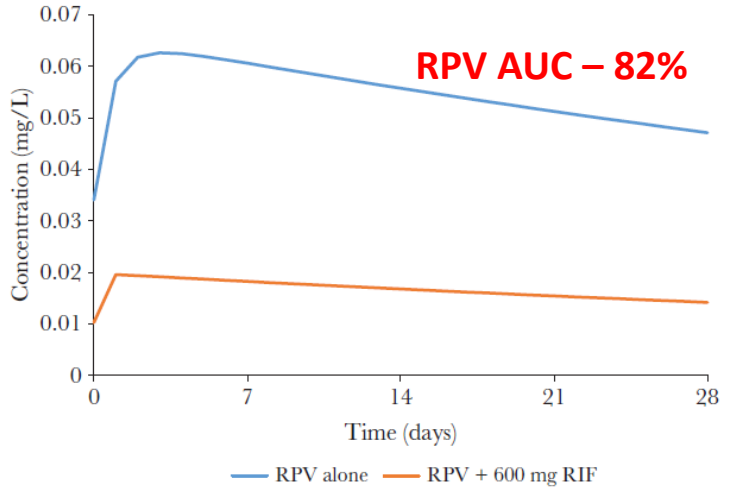
No Interaction Expected
Cabotegravir/rilpivirine [long acting] (CAB/RPV LA)
Antacids

Oral cabotegravir + rifampicin



Cabotegravir (400 mg)/rilpivirine (600 mg) 1x/month im + rifampicin





Ford SL et al. AAC 2017, Rajoli R et al. J Infect Dis 2019

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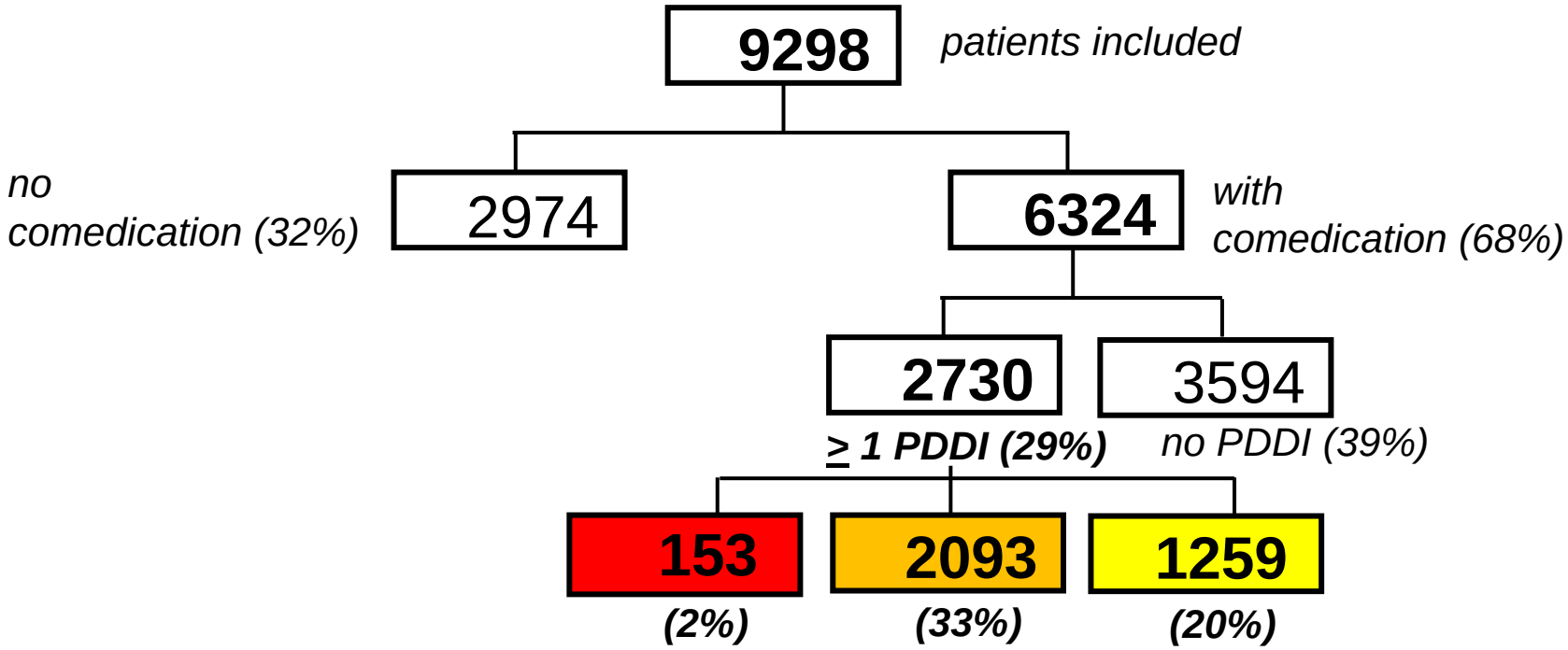
Prevalence of potential DDIs in 2018 compared to 2008



Prevalence DDIs	2008	2018
Red flag DDIs	↔	
Amber flag DDIs	↘ -16%	

ARV treatment	2008	2018
Patients on boosted ARVs	53%	30%
Patients on NNRTIs	43%	32%
Patients on unboosted INIs (without boosted ARVs or NNRTIs)	0%	**40%**

Deutschmann E et al. Clin Infect Dis 2020

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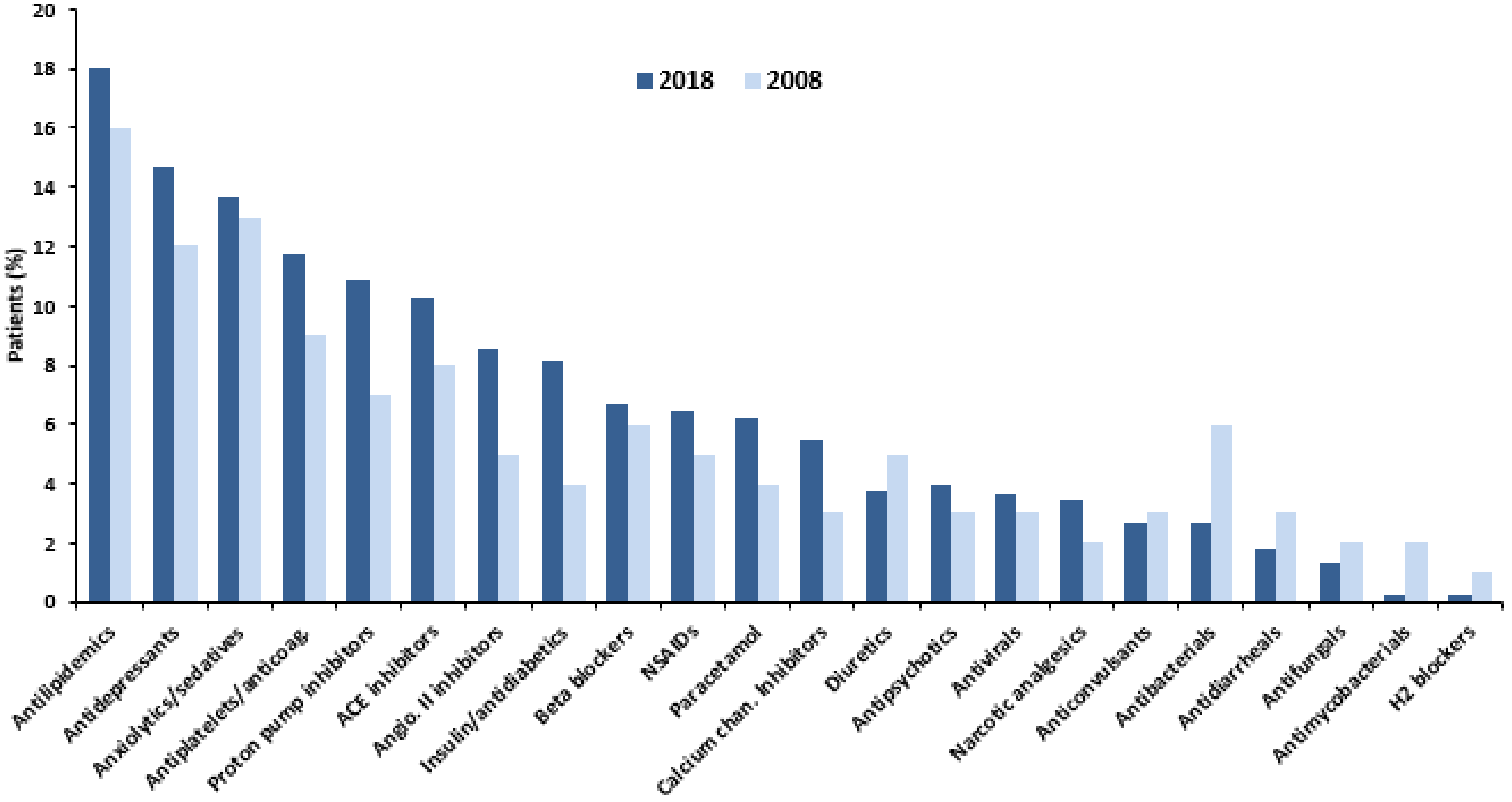
Comedication use in patients of SHCS in 2018 compared to 2018



Deutschmann E et al. Clin Infect Dis 2020

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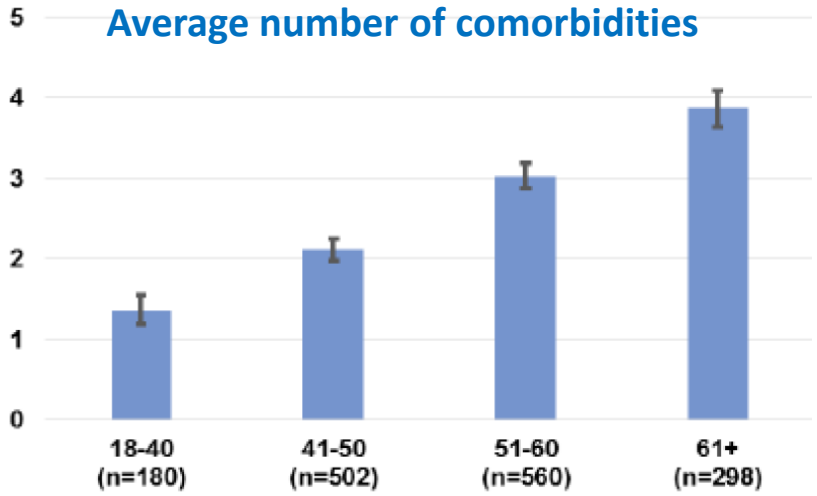
Number of comorbidities and polypharmacy increase with age

HOPS cohort

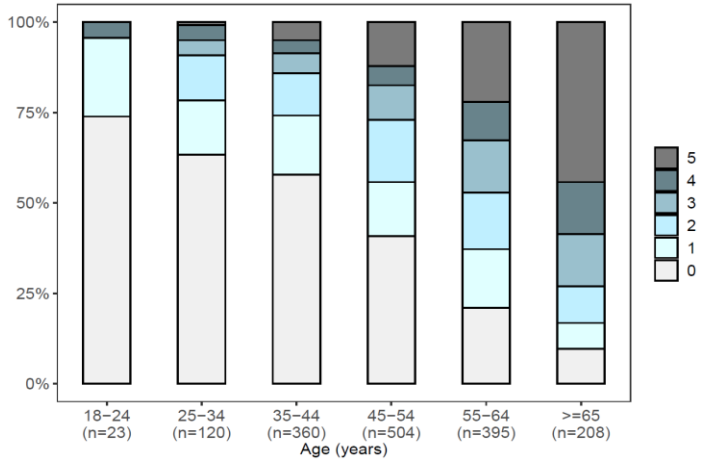
Swiss HIV Cohort

Average number of comorbidities

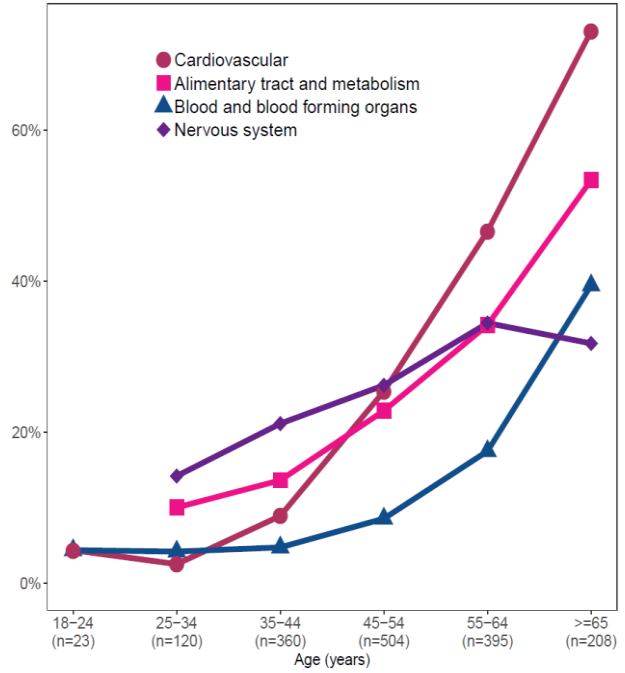


Palella FJ et al. AIDS 2019

Number of non- HIV medications



Prevalence of comedications use



Similar observations in European/Swiss cohort:

GEPPO cohort (Guaraldi G et al. BMC Geriatr 2018)
EuroSIDA cohort (Pelchen-Matthews A et al. AIDS 2018)
Dat'AIDS cohort (Allavena C et al. PLoS One 2018)
SHCS cohort (Hasse B et al. CID 2011)

Courlet P et al. Open Forum Infect Dis 2019

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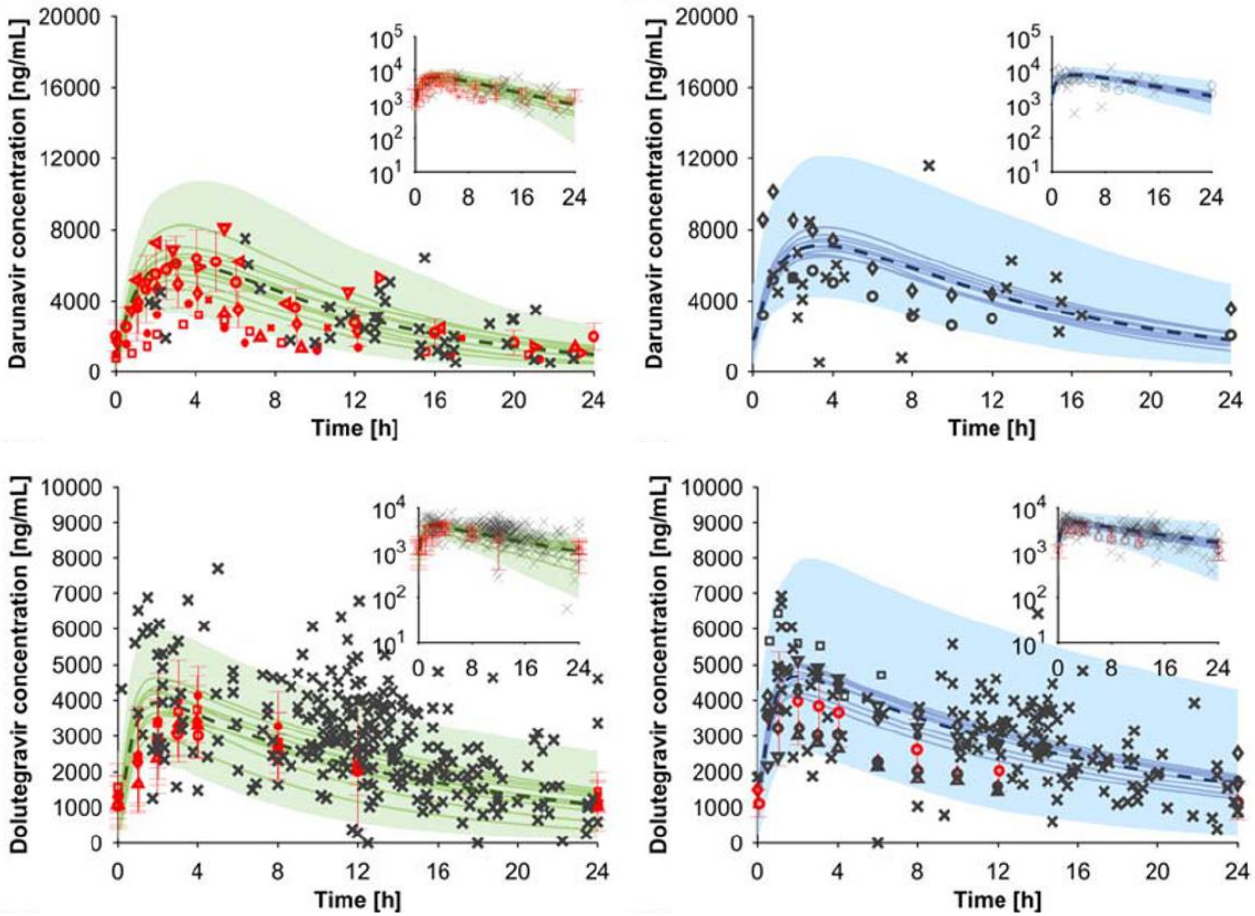
Effect of aging on antiretroviral drug pharmacokinetics

Young adults (20-50 years) **Elderly adults (55-85 years)**



Darunavir/r AUC elderly/young: **1.27** (observed)
1.33 (predicted)

Dolutegravir AUC elderly/young: **1.16** (observed)
1.31 (predicted)

Simulations combined with clinical data indicate that older age does not impact antiretroviral PK to a clinically significant extent. No a priori dose adjustment is needed in absence of severe comorbidities.

Stader F et al. Br J Clin Pharmacol 2020; Courlet P et al. AIDS 2019

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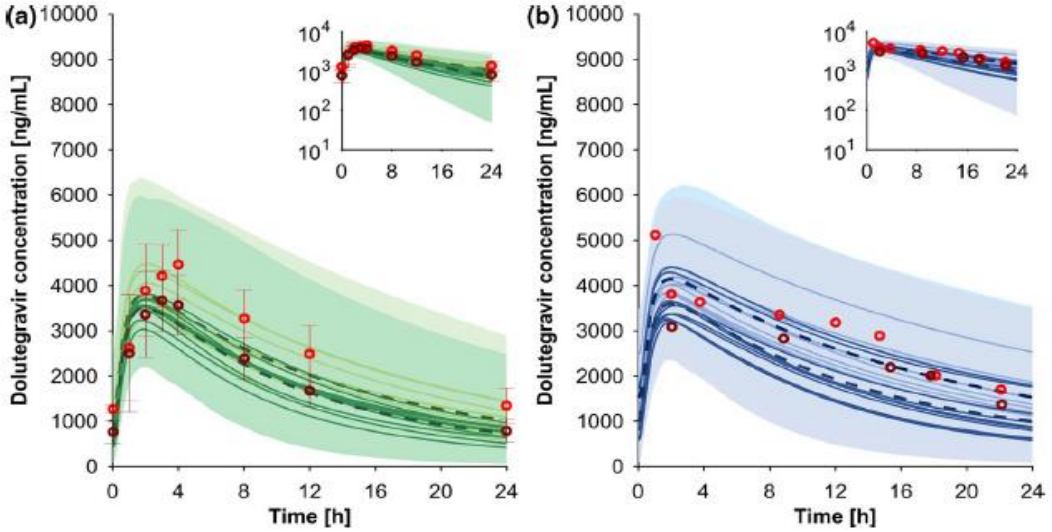
Effect of aging on magnitude of DDIs

	Young adults (20-50 years)	Elderly adults (55-85 years)
Dolutegravir + darunavir/r	AUC -**31%** (obs); **-21%** (pred)	AUC **-15**% (obs); **-28%** (pred)
Dolutegravir alone		



Some more examples of unchanged DDI magnitudes:

Amlodipine + darunavir/r	AUC **+111**% (obs); **+113**% (pred)	AUC **+110%** (obs); **+101%** (pred)
Amlodipine alone		
Rosuvastatin + darunavir/r	AUC **+50%** (obs); **+50%** (pred)	AUC **+60%** (obs); **+66%** (pred)
Rosuvastatin alone		

Simulations combined with clinical data indicate that magnitude of DDI is comparable in elderly and young adults.

Stader F et al. Clin Pharmacol Ther 2020; Stader F et al. AIDS 2019

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Common red flag DDIs in several cohort studies

Spanish HIV Cohort
Overall 3% of red flag DDIs

Boosted PI +

Comedication	
corticosteroids	57%
quetiapine, clozapine	14%
clopidogrel, ticagrelor	12%
domperidone	7%
simvastatin	6%
eplerenone	3%
amiodarone, ranolazine	2%

Lopez-Centeno B et al. Clin Infect Dis 2019

French HIV Cohort (elderly PLWH)
Overall 17% of red flag DDIs

Boosted PI +

Comedication	
corticosteroids	29%
PPI (with ATV, RPV)	27%
lercanidipine	11%
alfuzosin	9%
domperidone	5%
amiodarone	3%
simvastatin	3%
apixaban, rivaroxaban	3%

Desmessine L et al. Open Forum Infect Dis 2019

Swiss HIV Cohort
Overall 2% of red flag DDIs

Boosted PI +

Comedication	
corticosteroids	20%
quetiapine	20%
PPI (with ATV, RPV)	16%
clopidogrel	11%
domperidone	10%
alfuzosin, lecarnidipine	5%
simvastatin	3%
midazolam, triazolam	3%

Deutschmann et al. Clin Infect Dis 2020

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Be aware

- **avoid boosted antiretroviral drugs with budenoside, fluticasone, mometasone, triamcinolone** due to the risk of Cushing syndrome
- risk of Cushing syndrome is not limited to oral administration of corticosteroids and is not prevented by reducing the corticosteroid dose
- replace PI/r, PI/c, EVG/c by antiretroviral drugs with no inhibitory effects on CYP3A4 if possible
- if not possible, substitute corticosteroid with a more favorable one with periodic control of cortisol

www.hiv-druginteractions.org

Guidance for the Use of Non-oral Steroids with Strong CYP3A4 Inhibitors

		Preferred	Not Recommended	Do Not Coadminister	Follow Up
Drugs for HIV					
Any combination containing any of the following: • Atazanavir • Cobicistat • Darunavir • Fosamprenavir • Lopinavir • Ritonavir • Saquinavir	*Inhaled*	Beclometasone		Budesonide Fluticasone Mometasone	Periodic control of morning cortisol
	Nasal	Beclometasone		Budesonide Fluticasone Mometasone	
	Intra-articular or epidural	Methylprednisolone (30% dose reduction required)		Triamcinolone	
	Topical	Hydrocortisone	Clobetasol Betamethasone		

www.hiv-druginteractions.org, Elliot ER et al. Clin Med 2016

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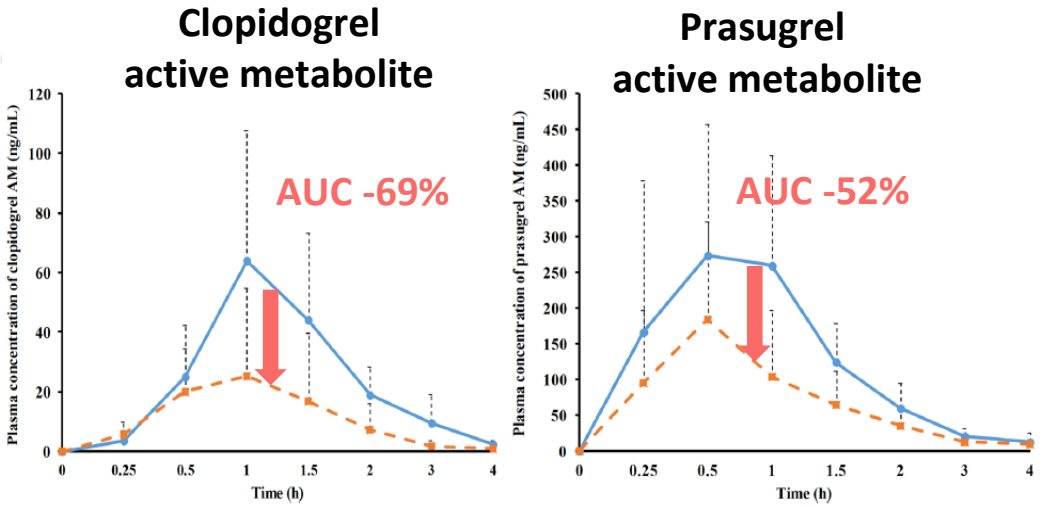
Be aware

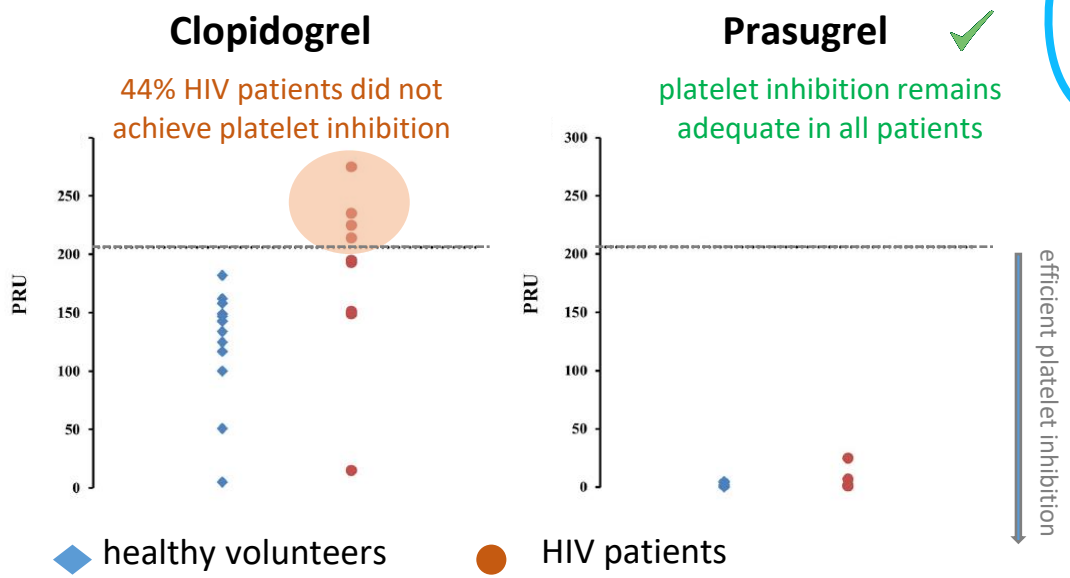
PK effect



antiplatelet drug alone

antiplatelet drug + RTV/Cobicistat boosted regimen

PD effect



Cases reports of the deleterious DDI between clopidogrel and boosted regimens start to emerge

- **avoid clopidogrel with boosted HIV regimens**
- use prasugrel unless patient has a clinical condition (e.g. history of stroke or transient ischaemic attack) which contraindicates its use in which case an alternative HIV regimen should be considered

Marsousi N et al. Clin Pharmacokinet 2018; Bravo I et al. BJCP 2018

Conclusions

- DDIs are still an issue we have to face with modern antiretroviral therapy particularly in the context of an aging population with polypharmacy.
- DDIs are mostly manageable.
- Potential for DDIs to be considered systematically when selecting an antiretroviral regimen or when adding new medications to an existing HIV treatment with particular attention to adjust dosage or perform clinical monitoring when needed.
- Searchable online drug interactions databases constitute valuable tools to recognise and manage unwanted DDIs in clinical practice.

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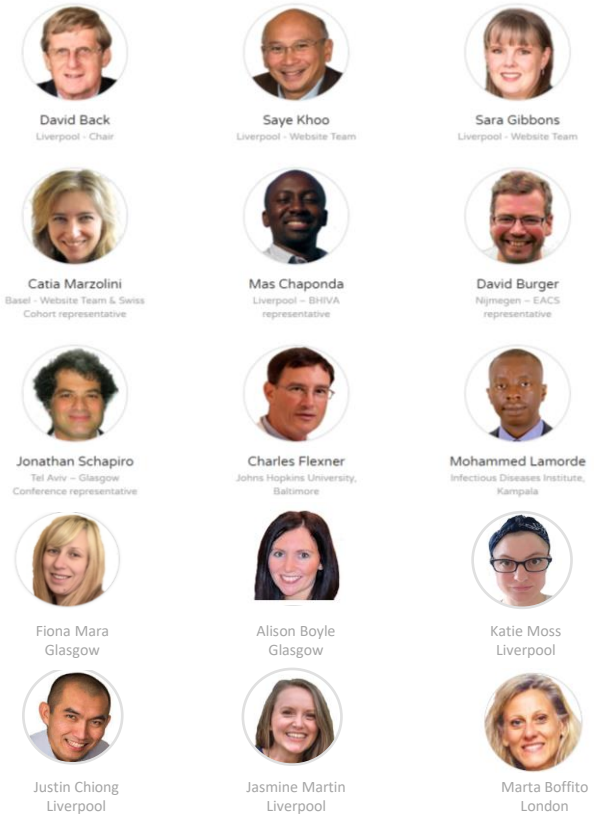

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