Psychotropic medications, recreational drugs and antiretrovirals

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HIV neuro psychiatry

Are clinicians concerned about DDI with psychotropic drugs?

The top 20 co-medications searches with darunavir as selected ARV in www.hiv-druginteractions.org for the past 12 months using MixPanel analytics

UK	Italy	Spain	Germany	France
1. Atorvastatin	1. Atorvastatin	1. Atorvastatin	1. Pantoprazole	1. Esomeprazole
2. Omeprazole	2. Rosuvastatin	2. Omeprazole	2. Atorvastatin	2. Atorvastatin
3. Sertraline	3. Pravastatin	**3. Lorazepam**	3. Pravastatin	3. Rosuvastatin
4. Lansoprazole	4. Pantoprazole	4. Paracetamol	4. Simvastatin	4. Omeprazole
5. Mirtazapine	5. Ramipril	5. Rosuvastatin	5. Ramipril	5. Rifabutin
6. Tenofovir	6. Fluvastatin	6. Methadone	6. Fluvastatin	6. Trimetho./sulfa.
7. Citalopram	7. Aspirin	**7. Alprazolam**	**7. Mirtazapine**	7. Dolutegravir
8. Amlodipine	8. Amlodipine	8. Pitavastatin	8. Amlodipine	**8. Venlafaxine**
9. Beclometasone	9. Clopidogrel	**9. Quetiapine**	9. Dolutegravir	9. Atovaquone
10. Emtricitabine	10. Bisoprolol	10. Pravastatin	10. Rivaroxaban	10. Pravastatin
11. Ramipril	11. Metformin	11. Trimetho./sulfa.	11. Ibuprofen	11. Clarithromycin
12. Paracetamol	12. Omeprazole	12. Simvastatin	12. Metoprolol	12. Fluconazole
13. Doxycycline	13. Simvastatin	**13. Mirtazapine**	**13. Citalopram**	13. Doxycycline
14. Amoxicillin	14. Dolutegravir	14. Aspirin	14. Bisoprolol	14. Bisoprolol
15. Trimetho./sulfa.	**15. Lorazepam**	15. Enalapril	15. Pregabalin	15. Tenofovir
16. Codeine	**16. Quetiapine**	16. Loratadine	16. Fluconazole	16. Ethambutol
17. Amitriptyline	17. Hydrochlorothia.	**17. Diazepam**	17. Aspirin	17. Metformin
18. Aspirin	18. Raltegravir	**18. Trazodone**	18. Clopidogrel	**18. Escitalopram**
19. Metformin	19. Valproate	19. Ibuprofen	19. Clarithromycin	19. Ethinylestradiol
20. Clarithromycin	**20. Alprazolam**	20. Cobicistat	20. Levetiracetam	20. Valproate

Case presentation

45 year old man with a history of schizophrenia, depression, sleep disorder and newly infected with HIV.

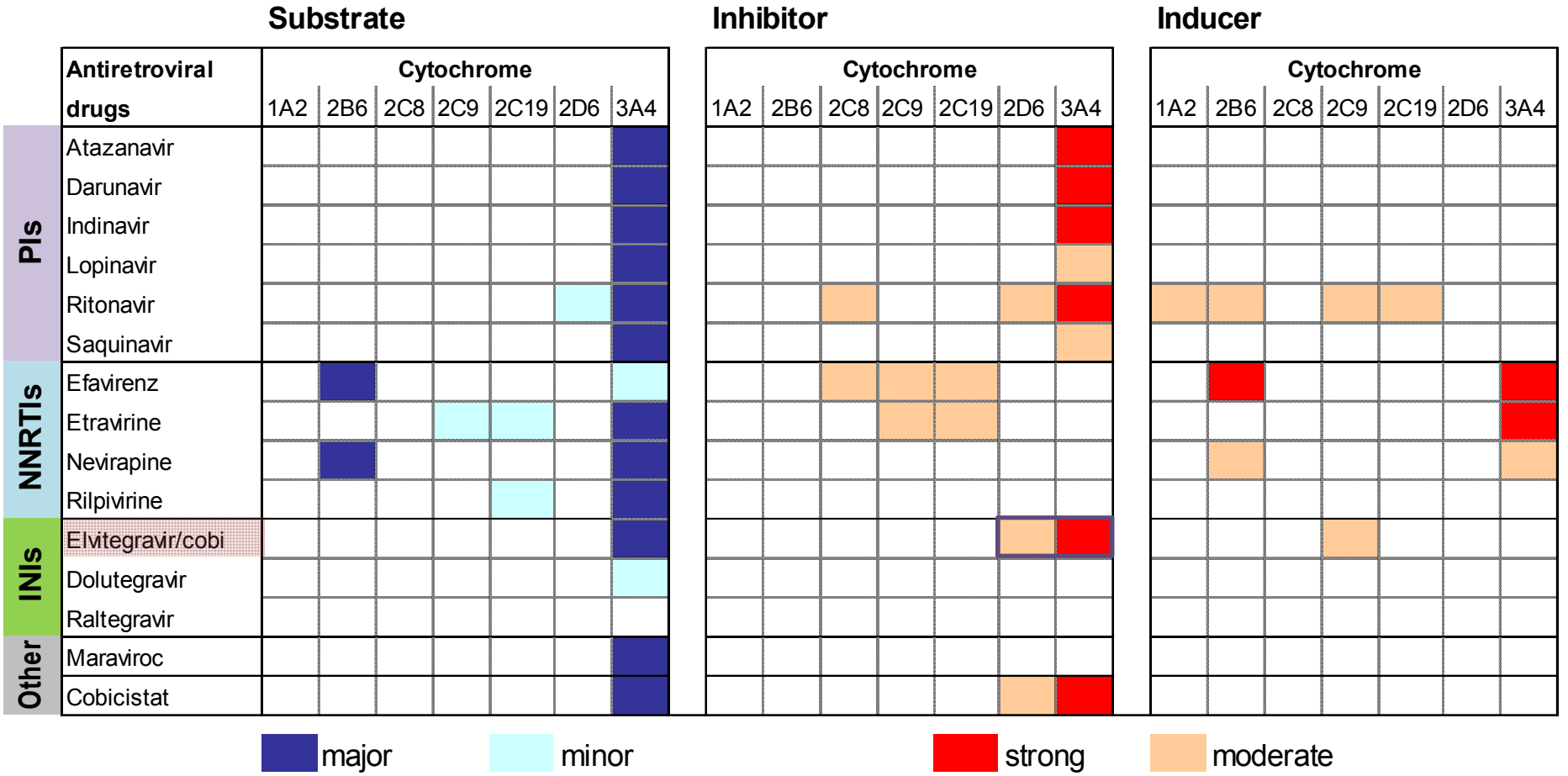
Current psychotropic medications:

escitalopram 20 mg QD
quetiapine 200 mg BID
zolpidem 10 mg QD

Patient is started on dolutegravir + tenofovir + emtricitabine but experiences recurrent headaches (possible side effect of dolutegravir).

Would you replace dolutegravir by raltegravir or by elvitegravir/cobicistat in this particular situation?

Metabolism of antiretroviral drugs



Raltegravir is metabolized by UGT1A1

Dolutegravir is mainly metabolized by UGT1A1 (CYP3A4 minor)

Elvitegravir is metabolized by UGT1A1> UGT1A3

NEW: bictegravir is equally metabolized by UGT1A1 and CYP3A4

Metabolism of antidepressants, anxiolytics and antipsychotics

Substrate

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

* lamotrigine is glucuronidated

Substrate

Anxiolytics/ Hypnotics	Cytochrome					
	1A2	2B6	2C9	2C19	2D6	3A4
alprazolam						major
bromazepam	major					minor
clorazepate						major
diazepam				major		major
lorazepam*						
oxazepam*						
chlordiazepoxide						major
estazolam						major
flunitrazepam				major		major
flurazepam						major
midazolam						major
temazepam*						
triazolam						major
zaleplon						minor
zolpidem	minor		minor		minor	major
zopiclone						major

major minor

* lorazepam, oxazepam, temazepam are glucuronidated

Substrate

Antipsychotics	Cytochrome					
	1A2	2B6	2C9	2C19	2D6	3A4
amisulpride*						
aripiprazole					major	major
asenapine	major				minor	minor
clozapine	major			minor	minor	major
olanzapine	major				minor	
paliperidone*						
quetiapine						major
risperidone					major	minor
chlorpromazine	major				major	
fluphenazine					major	
perphenazine					major	
pimozide						major
thioridazine					major	minor
haloperidol	minor				major	major
sulpiride*						

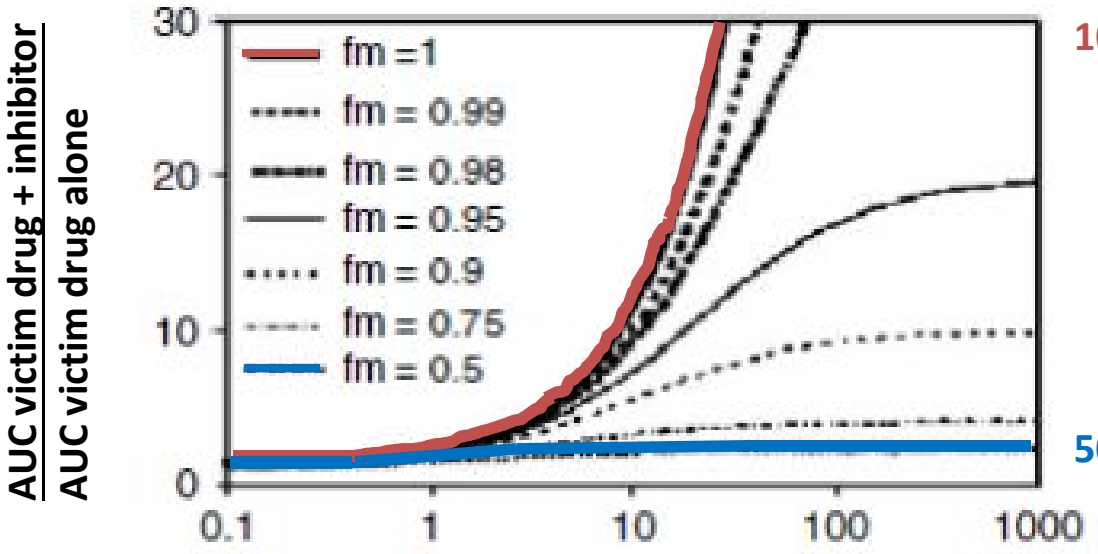
major minor

*amisulpride, paliperidone, sulpiride are mostly elim. unchanged

Spina E et al. Clinical Therapeutics 2008, individual product package labels

Multiple elimination pathways and magnitude of DDI

Effect of various extent of CYP2D6 metabolism on the magnitude of DDI



100% eliminated by CYP2D6

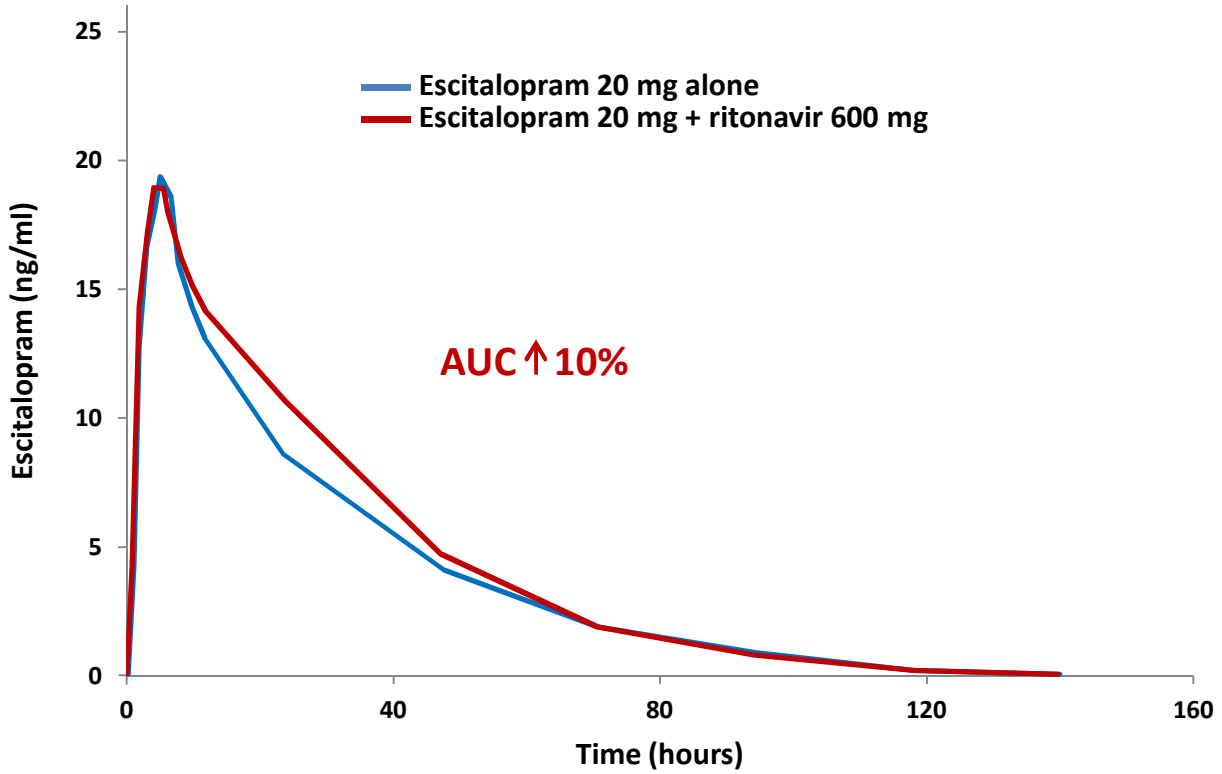
50% eliminated by CYP2D6

Drugs exclusively metabolized by CYP2D6 will be highly impacted by CYP2D6 inhibitors however the magnitude of DDI is mitigated for drugs eliminated by multiple pathways as metabolism can still occur through unaffected CYPs

Ito K et al. Drug Metab Dispos 2005

Interaction between ritonavir and escitalopram

Escitalopram is metabolized by CYP3A4, CYP2C19, CYP2D6

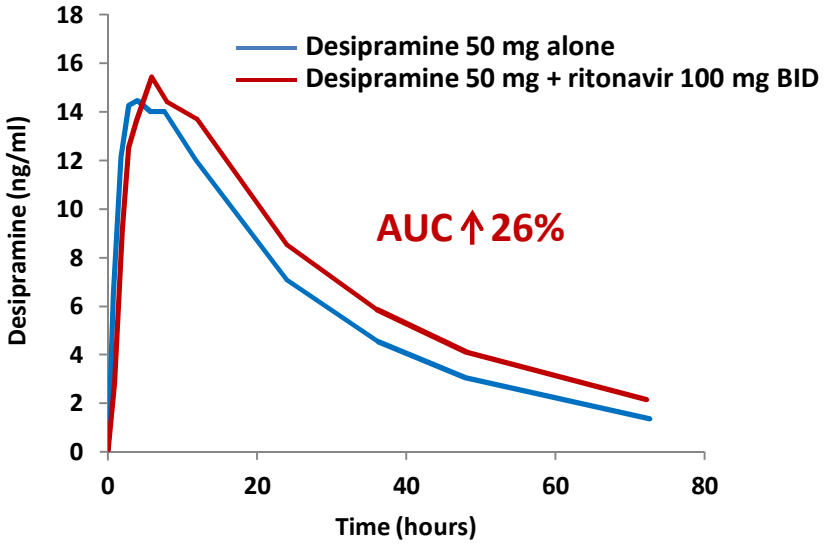


Ritonavir 600 mg does not significantly impact escitalopram exposure as multiple cytochromes contribute to metabolism (similar effect is expected with cobicistat).

Gutierrez MM et al. Clin Ther 2003

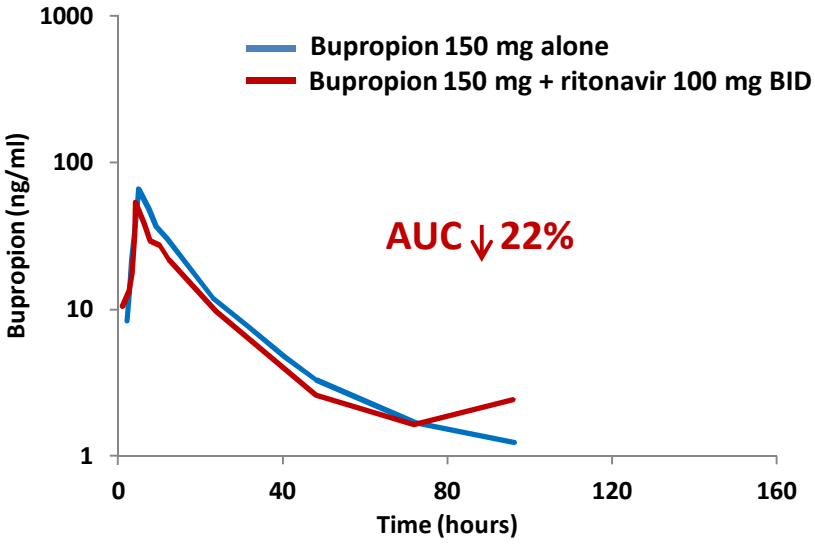
Ritonavir effect on CYP2D6 and CYP2B6 when used as booster

Desipramine is metabolized by CYP2D6



Ritonavir used as PK booster has a weak inhibitory effect on CYP2D6 (comparable CYP2D6 inhibitory effect with cobicistat)

Bupropion is metabolized by CYP2B6



Ritonavir used as PK booster has a weak inducing effect on CYP2B6

Aarnoutse RE et al. CPT 2005

Park J et al. J Clin Pharmacol 2010

Approach to quantify drug-drug interactions with ARVs

Magnitude of drug-drug interaction depends on:

- **Fraction of disposition pathway mediated by the enzyme of interest (DPI)**

Drug	DPI $_{CYP3A4}$
triazolam	0.96
quetiapine	0.90
zolpidem	0.26

almost exlusively metabolized by CYP3A4

CYP3A4 contributes to 26% of the overall metabolism

- **Inhibitor (InR) and inducer (IcR) strength**

Inhibitor $_{CYP3A4}$	InR $_{CYP3A4}$
ritonavir	1.0
cimetidine	0.21

strong inhibitor CYP3A4

weak inhibitor CYP3A4

Inducer $_{CYP3A4}$	IcR $_{CYP3A4}$
rifampicin	0.95
efavirenz	0.57

strong inducer CYP3A4

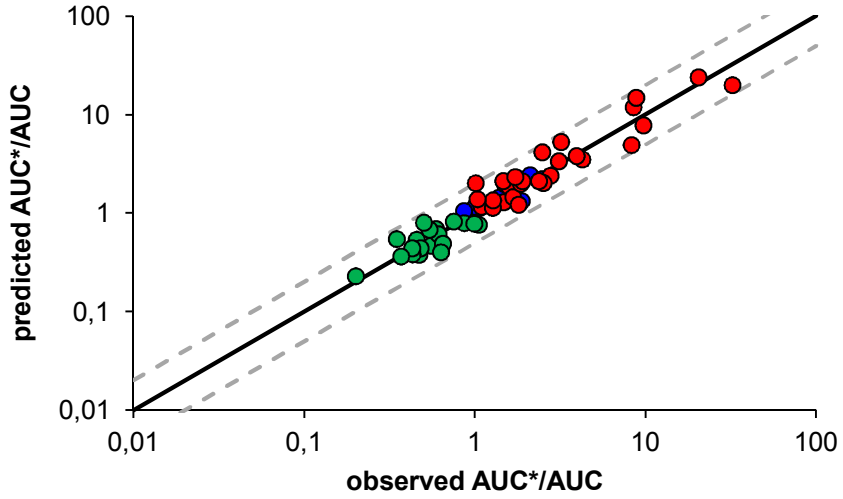
moderate inducer CYP3A4

➔ These parameters can be derived from available DDI studies involving similar drug combinations and reporting the magnitude of DDI

➔ These parameters can then be used to predict the magnitude of DDI for **uncharacterized drug combinations involving ARVs** to provide guidance on how to adjust dosage

Stader F et al. Antimicrob Agent Chemother 2018

Predictive performance and examples of DDI predictions



induction
competitive inhibition
mechanism based inhibition

98% predicted DDI magnitudes were within the 2 fold range of observed clinical data

Predicted DDI magnitudes for selected psychotropic drugs

Psychotropic drug	DPI	↑ AUC with RTV (InR = 1)		↓ AUC with EFV (IcR = 0.582)	
Triazolam	0.959	25.0 fold	strong	0.4 fold	moderate
Midazolam	0.940	12.4 fold		0.4 fold	
Quetiapine	0.896	8.0 fold		0.5 fold	
Clozapine	0.499	2.0 fold	moderate	0.6 fold	weak
Venlafaxine	0.205	1.3 fold	weak	0.8 fold	
Escitalopram	0.078	1.1 fold		0.9 fold	
Citalopram	0.054	1.1 fold		0.9 fold	

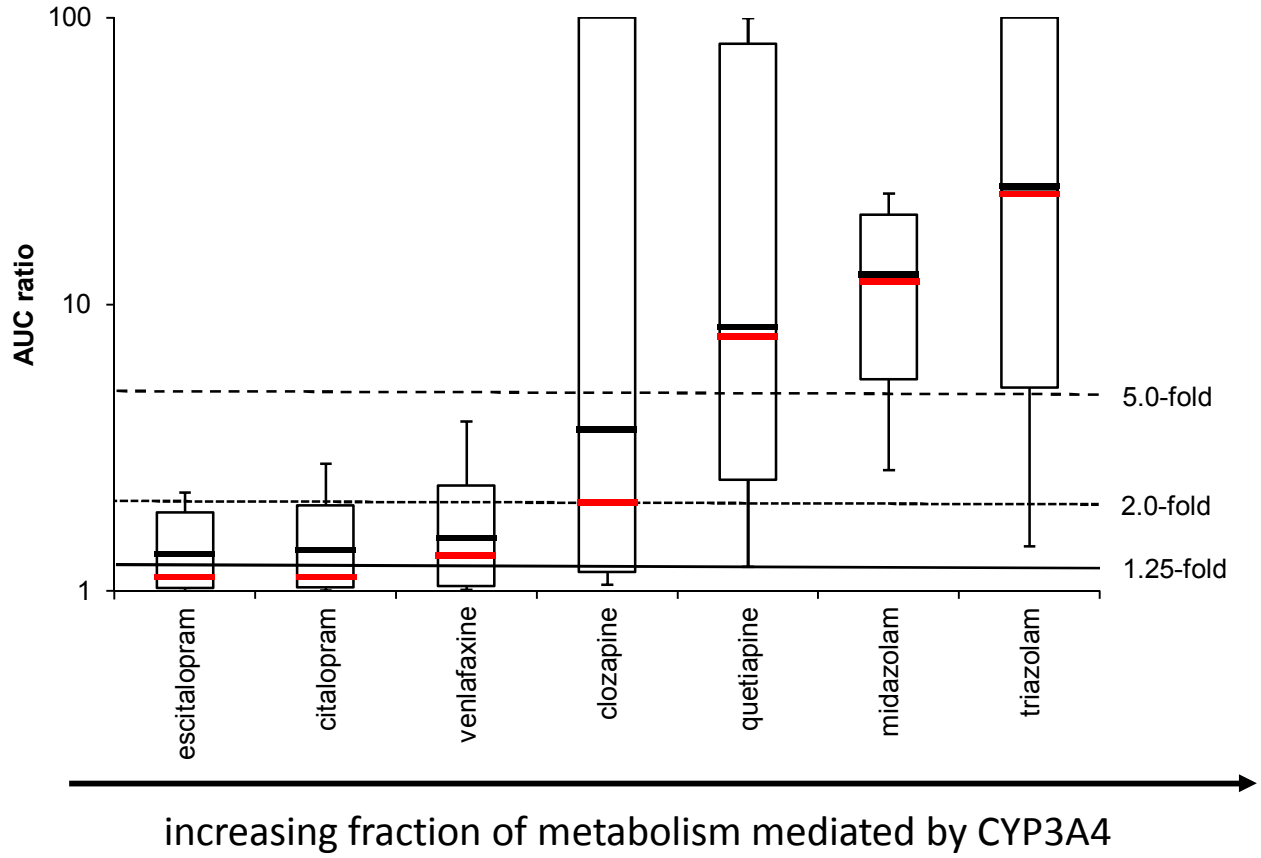
Stader F et al. Antimicrob Agent Chemother 2018

DDI magnitude depends on fraction metabolism via given CYP

Drug-drug interactions between ritonavir and various psychotropic drugs

Simulations using approach

Monte Carlo simulations capturing the observed variability in DDI studies (geometric mean + 95% CI)



Stader F et al. Antimicrob Agent Chemother 2018

Coming back to our case

45 year old man with a history of schizophrenia, depression, sleep disorder and newly infected with HIV.

Would you replace dolutegravir by raltegravir or by elvitegravir/cobicistat in this particular situation?

Psychotropic medications	**metabolism**	**Dolutegravir** no inhibitory effect	**Raltegravir** no inhibitory effect	**Elvitegravir/c** strong CYP3A4 inhibitor weak CYP2D6 inhibitor	**Predicted AUC**	**Management**
Escitalopram	CYP2C19, CYP3A4, CYP2D6	**no DDI**	**no DDI**	**weak DDI**	**+ 10%**	no action ⚠ **QT risk**
Zolpidem	CYP3A4, CYP2D6, CYP1A2, CYP2C9	**no DDI**	**no DDI**	**weak DDI**	**+ 35%**	no action
Quetiapine	CYP3A4	**no DDI**	**no DDI**	**strong DDI**	**+ 700%**	**avoid** ⚠ **QT risk**

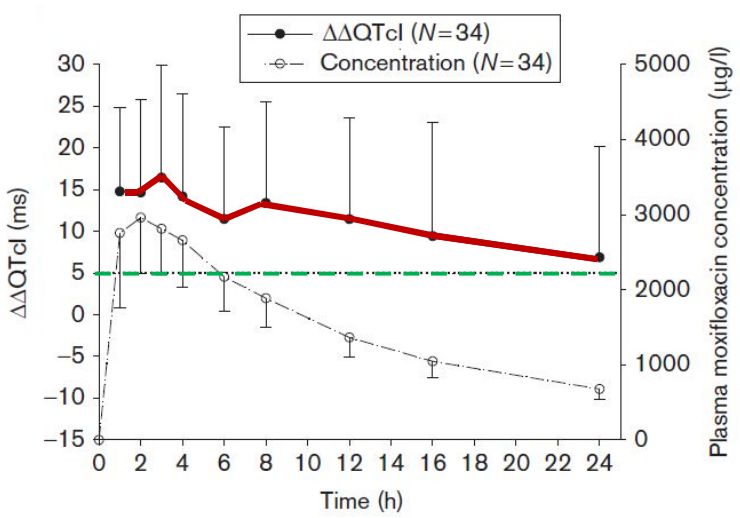
Overall, dolutegravir and raltegravir have a comparable favorable DDI profile
(main difference: dolutegravir inhibits the transporter OCT2 whereas raltegravir does not)

Novel integrase inhibitor BICTEGRAVIR has also a favorable DDI profile: no inhibitory/inducing effects on CYPs, UGTs. Inhibits transporter OCT2 but less than dolutegravir

- some psychotropic drugs have the potential to prolong QT interval
- excessive QT interval prolongation can be proarrhythmic and lead to fatal ventricular arrhythmia known as torsade de pointes (TdP)

QT prolongation potential of quetiapine and escitalopram

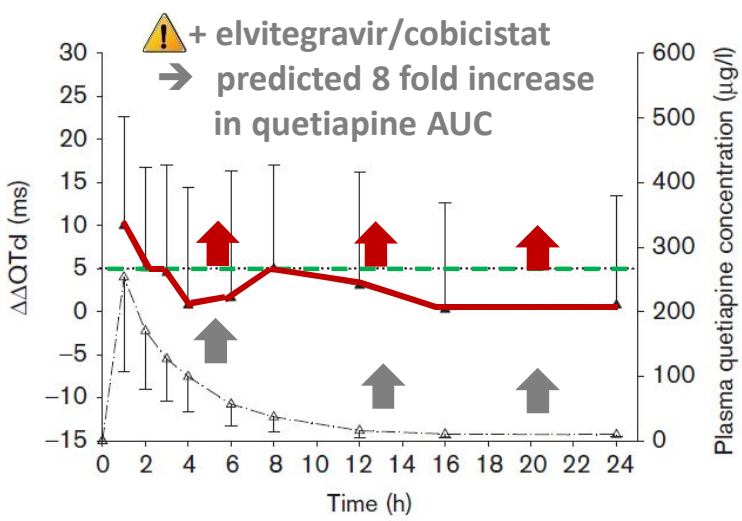
Moxifloxacin 400 mg (positive control)



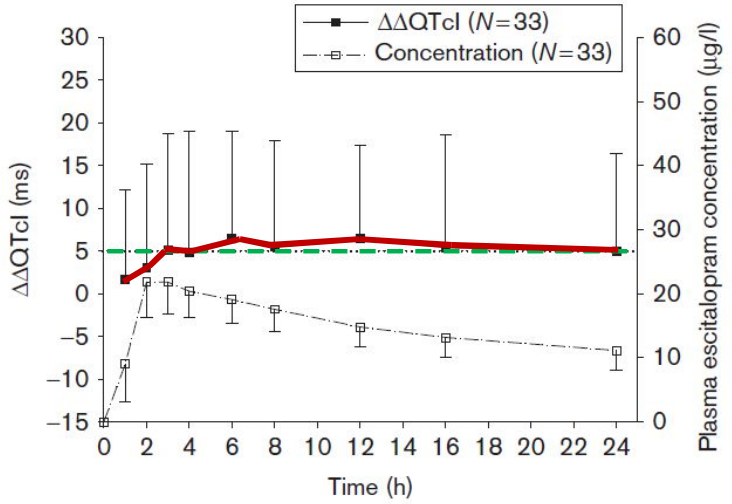
– – threshold of regulatory concern for the ability of drugs to prolong the QT interval

Quetiapine and escitalopram have the potential to prolong QT interval

Quetiapine 100 mg



Escitalopram 20 mg



Kim A et al. Clin Psychopharmacol 2016

Drug-drug interactions between antidepressants and ARVs

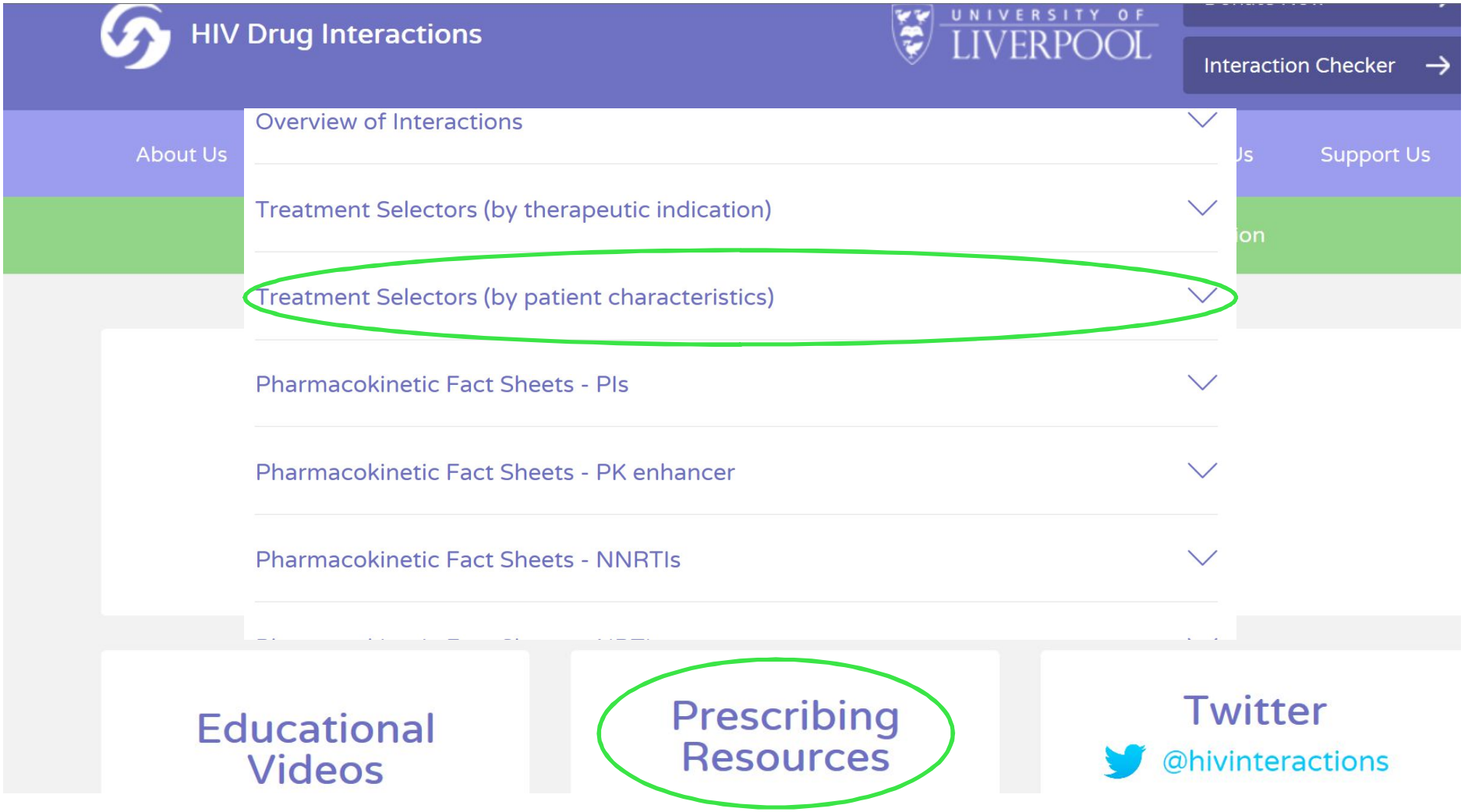
Antidepressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL
SSRI	citalopram	↑[a]	↑[a]	↑	↑	↑[a]	↓	↓	↓	↔[b]	↔	↔	↑	↔
	escitalopram	↑[a]	↑[a]	↑	↑	↑[a]	↓	↓	↓	↔[b]	↔	↔	↑	↔
	fluvoxamine	↑	↑	↑	↑	↑	↔	↔	E	↔	↔	↔	↑	↔
	fluoxetine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↔	↔	↔	↔	↑↓?	↔
	sertraline	↑	↓	↑	↓49%	↓	↓39%	↓	↓	↔	↔	↔	↓7%	↔
SNRI	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↑	↔
	venlafaxine	↑	↑	↑	↑	↑	↓	↓	↓	↔	D	↔	↑	↔
TCA	amitriptyline	↑[a]	↑[a]	↑	↑	↑[a]	↔	↔	↔	↔[b]	↔	↔	↑	↔
	clomipramine	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↓	↓	↓	↔[b]	↔	↔	↑[a]	↔
	desipramine	↑[a]	↑[a]	↑	↑	↑5%[a]	↔	↔	↔	↔[b]	↔	↔	↑	↔
	doxepin	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔
	imipramine	↑[a]	↑[a]	↑[a]	↑[a]	↑[a]	↓	↓	↓	↔[b]	↔	↔	↑[a]	↔
	nortriptyline	↑[a]	↑[a]	↑	↑	↑[a]	↔	↔	↔	↔[b]	↔	↔	↑	↔
	trimipramine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔
TeCA	maprotiline	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔
	mianserine	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
	mirtazapine	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
Oth-ers	bupropion	↔	↓	↔	↓	↓57%	↓55%	↔	↓	↔	↔	↔	↑?	↔
	lamotrigine	↔	↓32%	↔	↓	↓50%	↓	↔	↔	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↑	↓E	↓E	↓E	E	E	↔	↑	↔
	St John's wort	D	D	D	D	D	D	D	D	D	D	D[c]	D	D?
	trazodone	↑[a]	↑[a]	↑	↑	↑[a]	↓	↓	↓	↔[b]	↔	↔	↑	↔

Colour legend

- no clinically significant interaction expected
- these drugs should not be co-administered
- potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- potential interaction likely to be of weak intensity. Additional action/ monitoring or dosage adjustment is unlikely to be required

EACS guidelines 2017; www.hiv-druginteractions.org

www.hiv-druginteractions.org



Drug-drug interactions with anxiolytics/hypnotics

www.hiv-druginteractions.org

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Anxiolytic/Hypnotic Treament Selector

Charts reviewed October 2017. Full information available at www.hiv-druginteractions.org

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	RAL	ABC	FTC	3TC	TDF	ZDV	E/C/F/TAF	E/C/F/TDF
Anxiolytics	Alprazolam	↑[a]	↑[a]	↑[a]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Bromazepam	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Buspirone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Clorazepate	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Diazepam	↑	↑	↑	↓	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Hypnotics	Chlordiazepoxide	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Estazolam	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Flunitrazepam	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Flurazepam	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Lormetazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Midazolam (oral)	↑	↑	↑	↓[b]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Temazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Triazolam	↑	↑	↑	↓[b]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Valerian	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Zaleplon	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Zolpidem	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Zopiclone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑

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Drug-drug interactions with antipsychotics

www.hiv-druginteractions.org

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Antipsychotic Treament Selector

Charts reviewed October 2017. Full information available at www.hiv-druginteractions.org

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	RAL	ABC	FTC	3TC	TDF	ZDV	E/C/F/TAF	E/C/F/TDF
Atypical Antipsychotics	Amisulpride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Aripiprazole	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Asenapine	↓	↓	↓	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Clozapine	↑[a]	↑	↑[a]	↓	↓	↓	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
	Olanzapine	↓	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Paliperidone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Quetiapine	↑[b]	↑[b]	↑[b]	↓	↓	↓	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑[b]	↑[b]
	Risperidone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
Phenothiazines	Chlorpromazine	↑[a]	↑	↑[a]	↔	↔	↔	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
	Fluphenazine	↑[a]	↑	↑[a]	↔	↔	↔	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
	Perphenazine	↑[a]	↑	↑[a]	↔	↔	↔	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
	Pimozide	↑[a]	↑	↑[a]	↑	↓	↓	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Prochlorperazine	↑[a]	↑	↑[a]	↔	↔	↔	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
	Thioridazine	↑[a]	↑	↑[a]	↓	↓	↓	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔[d]	↑	↑
Others	Haloperidol	↑[a]	↑	↑[a]	↓	↓	↓	↔[c]	⇑	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Sulpiride	↔[a]	↔	↔[a]	↔	↔	↔	↔[c]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

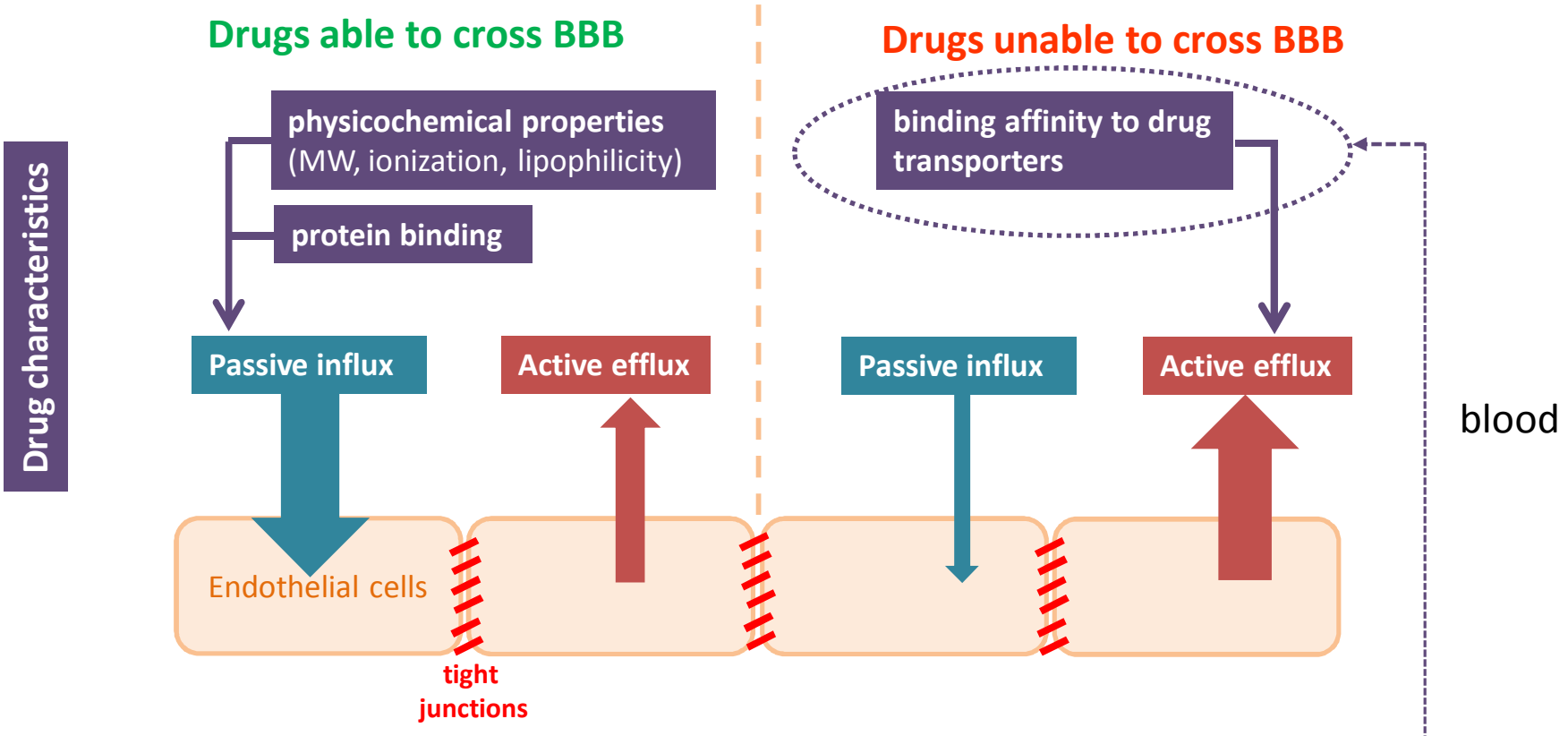
Cave: PK boosters impact differently cytochromes

when switching pharmacokinetic booster:
ritonavir and cobicistat: similar inhibition of CYP3A4 BUT
ritonavir induces CYP2C9, CYP2C19, CYP1A2 and UGTs whereas **cobicistat does not**

Therapeutic class	Drug	Metabolic pathway	Ritonavir	Cobicistat
Antidepressants	Agomelatine	CYP1A2	↓	↔
	Bupropion	CYP2B6	↓	↔
	Duloxetine	CYP2D6, CYP1A2	↑↓	↑
	Sertraline	CYP2B6>CYP2C9, CYP2C19, CYP2D6, CYP3A4	↓	↑
Antipsychotics	Asenapine	UGT1A4, UGT1A2, CYP3A4	↓	↑
	Olanzapine	CYP1A2, UGT1A4	↓	↔

Marzolini C et al. JAC 2016

Drug penetration across the blood-brain barrier



Differences in inhibition of transporters could impact the amount of drug that cross the blood-brain barrier.

Do cobicistat and ritonavir have a comparable inhibitory effect on drug transporters expressed at blood-brain barrier?

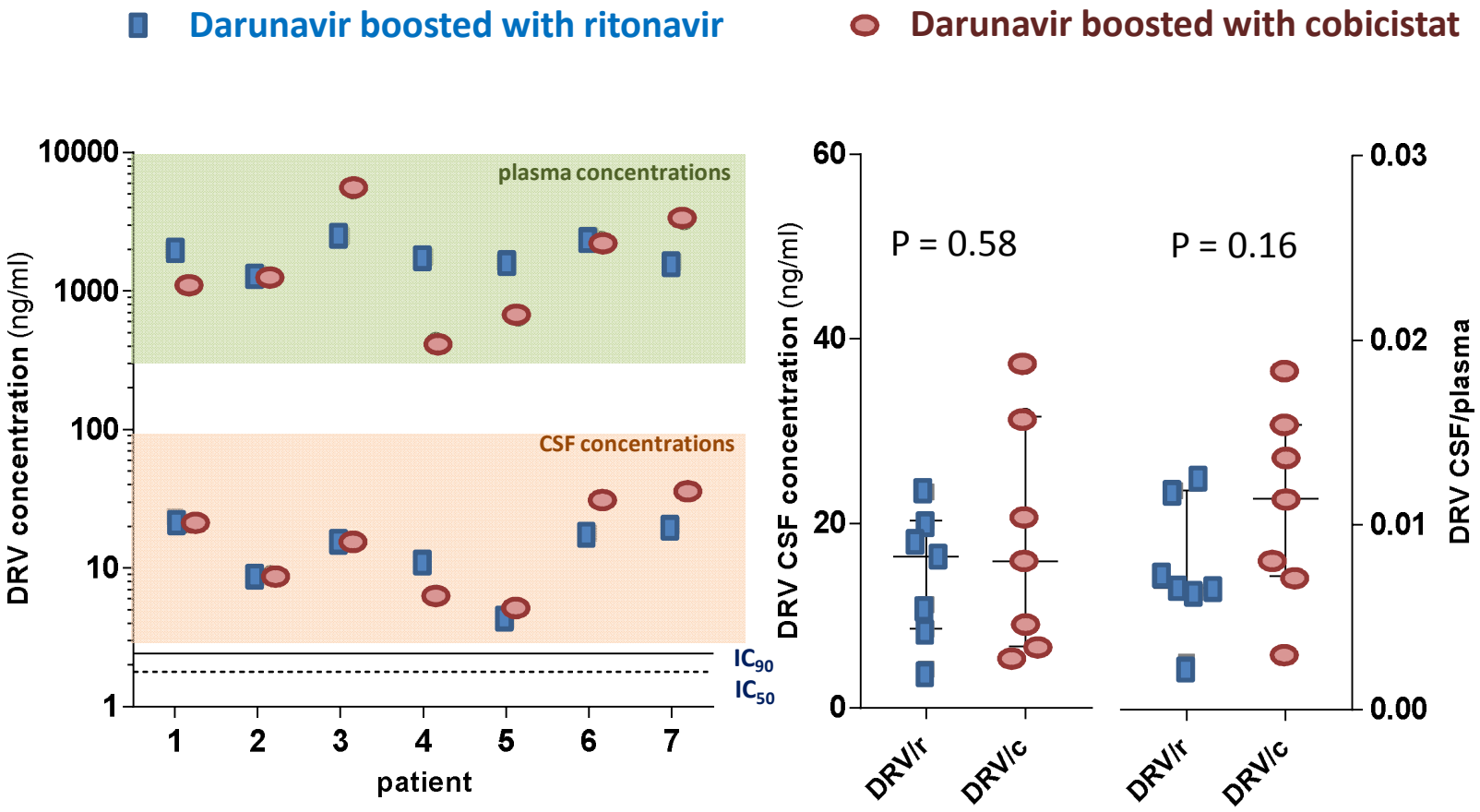
Clinical study design

Single-center, open, one-armed, sequential study

		Study period 1			Lumbar puncture	Study period 2			Lumbar puncture	
HIV patients with HAND requiring clinical investigation + treated or qualifying for DRV/r QD regimen		**Treatment at least 30 days with DRV/r (800/100mg) (Prezista/Norvir)**				**Treatment at least 30 days with DRV/c (800/150mg) (Prezista/Tybost)**				**Switch to DRV/r**
Assessments	**screening**	**treatment darunavir/ritonavir**				**treatment darunavir/cobicistat**				
		week				week				
		1	2	3	4	1	2	3	4	
Visit	1				2				3	
Informed consent	X									
In-/exclusion criteria	X									
Phys. examination	X				X				X	
Hematology	X				X				X	
Biochemistry	X				X				X	
Lumbar puncture					X				X	
Albumin, glucose, lactate, cell in CSF					X				X	
Initiation/maintain of darunavir/ritonavir	X	X	X	X	X					
initiation of darunavir/cobicistat						X	X	X	X	
HIV RNA viral load plasma					X				X	
HIV RNA viral load CSF					X				X	
Drug level					X				X	
Adherence evaluation	X				X				X	
Adverse effects					X				X	

Bartels H et al. JAC 2017

RTV and Cobi gives similar darunavir CSF concentrations



Boosting with cobicistat and ritonavir give comparable effective darunavir concentrations in CSF and therefore can be used interchangeably to boost once daily darunavir regimens

Bartels H et al. JAC 2017

Cave: pharmacogenetics can impact magnitude of DDI

Case report

Serotonin syndrome following initiation of **darunavir/r** (600/100 mg BID) and **esomeprazole** 40 mg QD in patient treated with **escitalopram** 10 mg BID.

Investigations showed that patient is a poor metabolizer of CYP2D6 and CYP2C19.

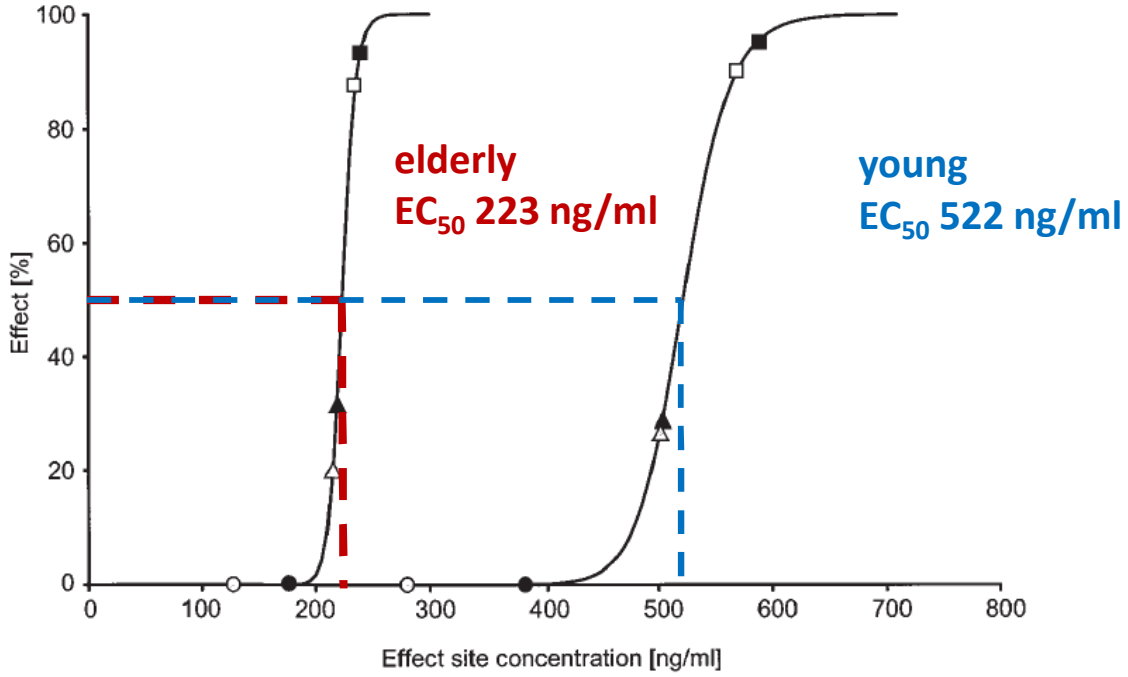
deficient CYP function + CYP inhibition by esomeprazole and darunavir/r

Lorenzini K et al. AIDS 2012

Cave: use of psychotropic drugs in elderly individuals

Age associated changes in pharmacodynamics: ➔ increase sensitivity to certain drugs

Effect of age on midazolam effect



- **Assessment of the concentration-hypnotic/sedative effect relationship of midazolam in young (24-28 y) and elderly (67-81 y)**
- **Total dose of midazolam needed to reach sedation in elderly is about half that needed in younger (age related changes in affinity of drugs to receptor sites or ↓ nb receptors)**

Albrecht S et al. Clin Pharmacol Ther 1999

Psychotropic drugs to avoid in elderly individuals

Psychotropic drug	Why avoid?	Recommendations
Benzodiazepines	• more sensitive to effect • **prolonged sedation → risk of falls** • paradoxical psychiatric reactions • **cognitive impairment** • depression • **drug dependency**	• very low-dose of short acting BZD for <u>short</u> duration
Tricyclic antidepressants	• peripheral anticholinergic side effects • **central anticholinergic side effects** (sedation, confusion, delirium) • **cognitive impairment → risk of falls**	• SSRI SNRI, mirtazapine • non-pharmacological treatment
Antipsychotics	• **anticholinergic/extrapyramidal symptoms** • **sedation → risk of falls** • association with increased risk of all-cause mortality in elderly patients with dementia	• atypical antipsychotics with favorable risk/benefit profile

Lemay G et al. Better prescribing in the elderly. Canadian Geriatrics Society 2012

Anticholinergic burden

Anticholinergic risk scale score

3 Points	2 Points	1 Point
Amitriptyline	Amantadine	Carbidopa-levodopa
Atropine/scopolamine	Baclofen	Entacapone
Benztropine	Cetirizine	Haloperidol
Chlorpromazine	Cimetidine	Methocarbamol
Clomipramine	Clozapine	Metoclopramide
Dicyclomine	Cyclobenzaprine	Mirtazapine
Diphenhydramine	Desipramine	Paroxetine
Doxepin	Loperamide	Pramipexole
Fluphenazine	Loratadine	Quetiapine
Flurazepam	Nortriptyline	Ranitidine
Hydroxyzine	Olanzapine	Risperidone
Hyoscyamine products	Prochlorperazine	Selegiline
Imipramine	Pseudoephedrine	Trazodone
Meperidine	Tiprolidine	Ziprasidone
Nitrazepam	Tolterodine	
Oxybutynin		
Perphenazine		
Solifenacin		
Trimipramine		

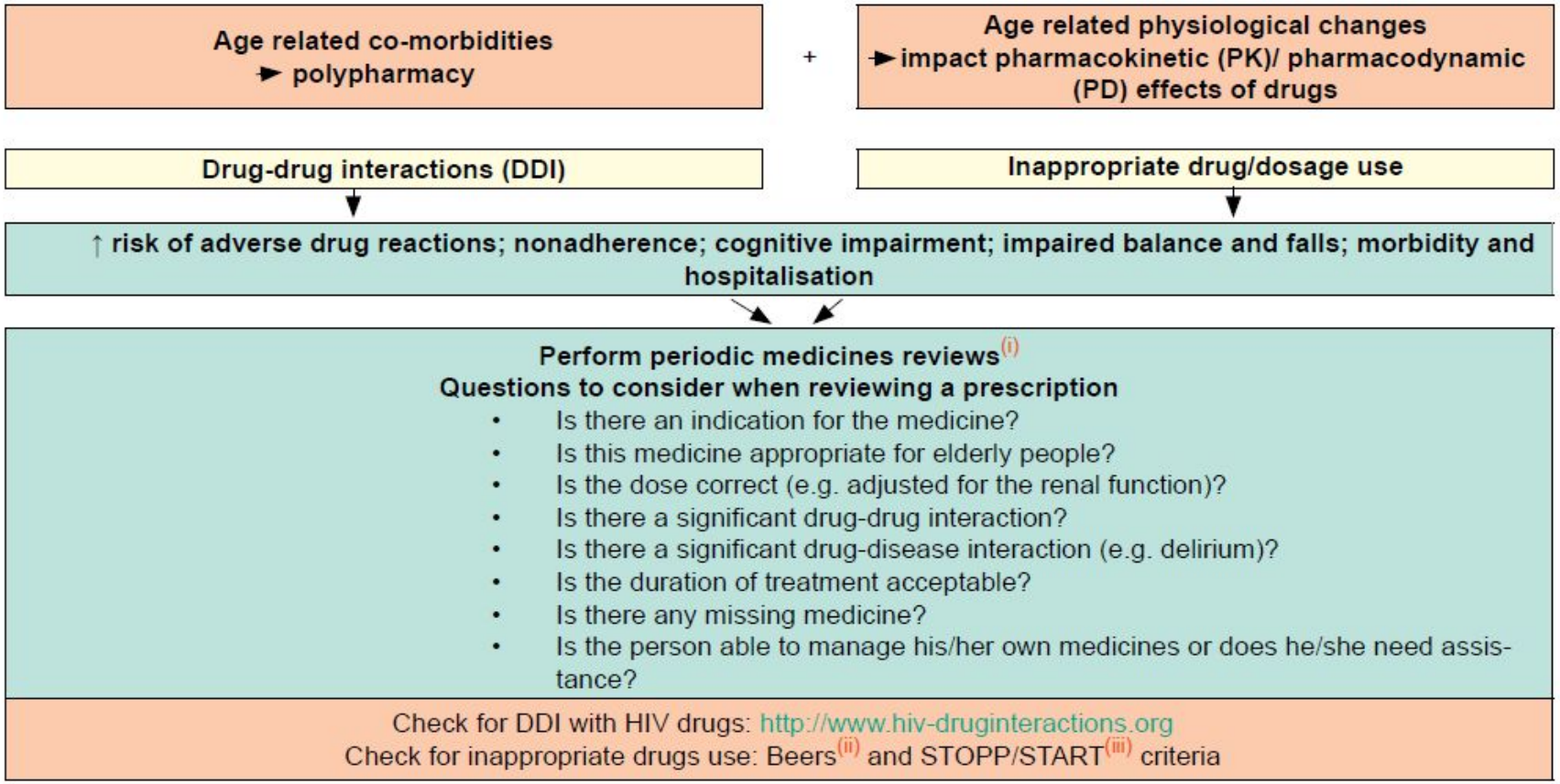
Elderly are more sensitive to adverse anticholinergic effects due to significant decrease in cholinergic receptors in the brain.

Drugs with anticholinergic properties can impair cognition (delirium, confusion) ➔ increase risk of falls, negative impact on adherence.

Total anticholinergic risk scale score of ≥3 is considered high.

Lemay G et al. Better prescribing in the elderly, Canadian Geriatrics Society 2012, Rudolph JL et al. Arch Intern Med 2008

Prescribing in elderly



The Beers and STOPP criteria are tools established by experts in geriatric pharmacotherapy to detect and reduce the burden of inappropriate prescribing in elderly. Inappropriate medicines include, for instance, those which in elderly persons with certain diseases can lead to drug-disease interactions, are associated with a higher risk of adverse drug reactions in the elderly, medicines that predictably increase the risk of falls in the elderly or those to be avoided in case of organ dysfunction. The START criteria consist of evidence-based indicators of potential prescribing omission in elderly with specific medical conditions.

EACS Guidelines 2017

Prevalence of recreational drug use in HIV infected individuals

Reference	Country	N	Year survey	Population	Prevalence (%) of drug use
Garin et al. BMJ 2017	Spain	208	2015	HIV positive (mostly MSM)	Cannabis 69 Nitrites 32 GHB 15 Ketamine 10 Cocaine 46 Ecstasy 20 Amphetamine 12 Mephedrone 4 Sildenafil 28 Crystal met 12
Pufall et al. CROI 2016	UK	526	2014	HIV positive MSM	GHB 20 Ketamine 11 Mephedrone 23 Crystal met 15
Allavena et al. J Int AIDS Soc 2014	France	1356	2012-2013	HIV positive	Cannabis 12 Cocaine 2
Daskalopoulou et al Lancet HIV 2014	UK	2248	2011-2012	HIV positive MSM	Cannabis 21 Nitrites 27 GHB 10 Ketamine 13 Cocaine 20 Ecstasy 12 Amphetamine 3 Mephedrone 7 Erectile dys. agents 21
De Ryck et al. AIDS Care 2013	Europe	1118	2007	HIV positive	Nitrites/GHB/Ecstasy 18 Erectile dys. agents 15
Dirks et al. HIV Med 2012	Germany	445	2009-2010	HIV positive MSM	Cannabis 19 Nitrites 26 GHB 3 Cocaine 3 Ecstasy 12 Erectile dys. agents 11
Peretti-Watel et al. Drug Alcohol Depend 2006	France	2484	2003	HIV positive	Cannabis 27 Nitrites 12 Cocaine/ Ecstasy /Amphetamine 6

Issues related to the use of recreational drugs

Use of recreational drugs raise concerns:

- **expansion of HIV and HCV epidemic and other STDs**
- **poor adherence**

Anonymous online survey on sexualized drug use (SDU) and sexual behavior among 742 HIV-positive MSM in Madrid

	No SDU (n=526)	SDU (n=16)	p
Age, median (IQR)	38 (32-46)	38 (33-44)	
On ART, n (%)	480 (95)	197 (97)	
Incomplete adherence to ART, n (%)	79 (17)	66 (34)	0.000
Stable partner, n (%)	272 (52)	91 (42)	0.019
≥ 20 sexual partners, n (%)	40 (8)	86 (44)	0.000
Unprotected anal intercourse, n (%)	226 (43)	189 (87)	0.000
Any STI, n (%)	282 (53)	183 (85)	0.000

- **drug-drug interactions with antiretrovirals**

Gonzalez-Baeza A et al. AIDS Patient Care STDS 2018

Deleterious DDI between ARVs and recreational drugs

Life-Threatening Interactions Between HIV-1 Protease Inhibitors and the Illicit Drugs MDMA and γ-Hydroxybutyrate

Arch Intern Med 1999

Robert D. Harrington, MD; Jane A. Woodward, PharmD; Thomas M. Hooton, MD; John R. Horn, PharmD

Patient ttt with boosted PI experienced a prolonged effect of ectasy and nearly fatal reaction from GHB

Fatal MDMA intoxication

De la Torre R et al. Lancet 1999

Sir—J A Henry and I R Hill (Nov 28, p 1751)[1] report a fatal interaction between ritonavir and 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). MDMA plasma

Esther Papaseit
Antonia Vázquez
Clara Pérez-Mañá
Mitona Pujadas
Rafael de la Torre
Magí Farré
Joan Nolla

Papaseit E et al. Intensive Care Med 2012

Surviving life-threatening MDMA (3,4-methylenedioxymethamphetamine, ecstasy) toxicity caused by ritonavir (RTV)

Possible fatal interaction between protease inhibitors and methamphetamine

Gillian Hales[1], Norm Roth[2] and Don Smith[1]*

Antiviral Ther 2000

DDI potential between ARVs and recreational drugs

Higher potential for DDI with **ritonavir** or **cobicistat** containing regimens
Low potential with bictegravir, raltegravir, dolutegravir, rilpivirine, maraviroc and NRTIs

Illicit drug	Metabolism, theoretical DDI with RTV/Cobi	Signs of toxicity	Recommendations
Methamphetamine **MDMA (ecstasy)**	CYP2D6: RTV/cobi as boosters limited CYP2D6 inhibition BUT small changes in PK could be relevant due to **non linear PK**. Cave: large variability in actual amount of drug and presence of other substances	Hypertension, seizure, hyperthermia, arrhythmia, tachycardia, teeth grinding	• Avoid combination if possible • If unavoidable, start with **1/4-1/2** of the usual amount and watch for signs of toxicity
Mephedrone	CYP2D6: RTV/cobi as boosters limited CYP2D6 inhibition	Tachycardia, agitation, tachycardia	• Use lower dose, inform users of signs of toxicity
GHB	GHB dehydrogenase, CYP? : Risk DDI unknown. Caution due to GHB **narrow therapeutic index**.	Seizure, bradycardia, respiratory depression	• Use with caution, use lower dose, inform users of signs of toxicity
Cocaine	CYP3A4 (minor): low-moderate risk of DDI	Tremor, paranoia, seizure, headache, hyperthermia	• Clinical relevance unknown, inform users of signs of toxicity
Ketamine	CYP3A4: **high potential for DDI**	Respiratory depression, hallucinations	• Avoid combination if possible • If unavoidable, start with **1/3-1/2** of the usual amount
Benzodiazepines	CYP3A4: **high potential for DDI**	Drowsiness, disorientation	• Avoid midazolam, triazolam • Caution with other BZD, use lower dose
Sildenafil, tadalafil, vardenafil	CYP3A4: **high potential for DDI**	Chest pain, nausea, irregular heart beat	• Lower dose: sildenafil **25mg/48h**, tadalafil: **10mg/72h**, vardenafil: **2.5 mg/72h**
Nitrites (poppers)	Non CYP mediated: no DDI	Dizziness, hypotension	

Urbina A et al. Recreational drugs and HIV, a guide for clinicians 2014, Antoniou T et al. Ann Pharmacother 2002, Bracchi M et al. AIDS 2015

Similar prevalence of recreational drugs use across ARV regimens

Recreational drug use drugs according to ARV regimen in 1167 MSM HIV infected individuals included in the ASTRA study:

Illicit drug use	PI boosted regimens	EFV or NVP regimens	Non interacting ARV regimens
Polydrug use	27%	27%	20%
Chemsex drug use	17%	15%	5%
Crystal met	10%	9%	5%
GHB	11%	10%	5%
Mephedrone	7%	6%	5%
Ketamine	11%	13%	30%
EDA	24%	20%	25%
Cocaine	22%	22%	25%
MDMA (ecstasy)	11%	11%	20%

Recreational drug use was comparable among treatment groups regardless on whether the patient was on a boosted PI regimen

- ➔ **underrecognition by healthcare providers of illicit drug use in patients**
- ➔ **unawareness of the risk of DDI with ARV**

Daskalopoulou M et al. AIDS 2016

In clinical practice

Take a full history of drug use

+

Discuss health risks associated with recreational drug use

+

Warn about risk of DDI and inform about toxicity signs

If patient does not want to stop using recreational drugs

↓

Switch to ARV regimen with low DDI potential if possible

If not possible

↓

Provide drug use recommendations to limit risk of toxicity

Drug-drug interactions with recreational drugs

www.hiv-druginteractions.org

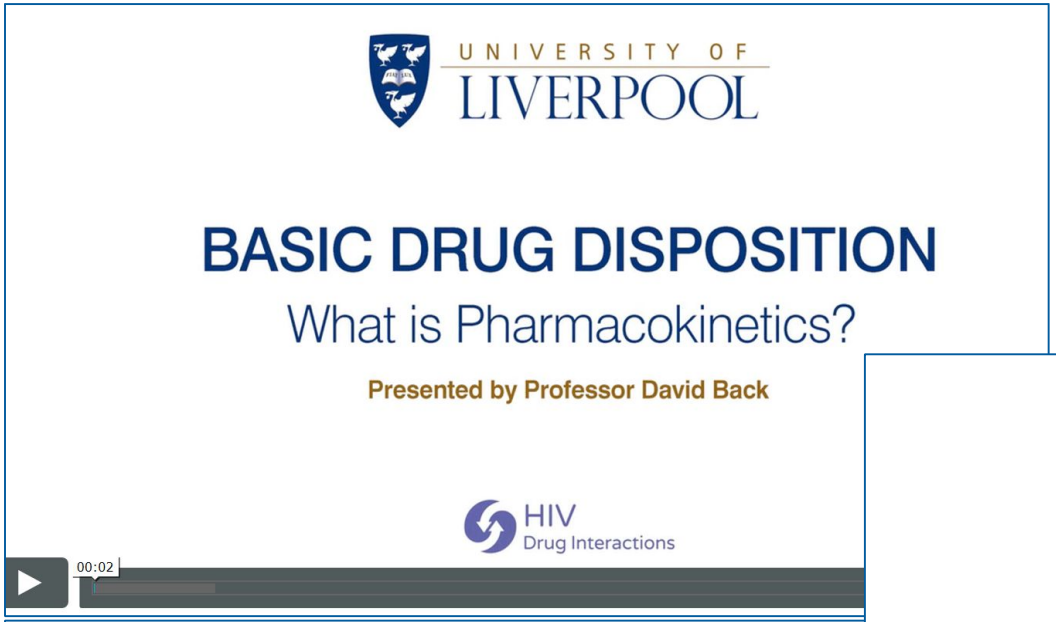
UNIVERSITY OF LIVERPOOL

Antiretrovirals and Recreational Drugs

Charts reviewed October 2017. Full information available at www.hiv-druginteractions.org

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	RAL	ABC	FTC	3TC	TDF	ZDV	E/C/F/TAF	E/C/F/TDF
Stimulants	Amyl nitrate (Poppers)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Cocaine	↑[ab]	↑[a]	↑[ab]	↑[c]	↑[c]	↑[c]	↔[b]	↔	↔	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]
	Ecstasy (MDMA)	↑[d]	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[d]	↑[d]
	Mephedrone	↑[e]	↑[e]	↑[e]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[e]	↑[e]
	Methamphetamine	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
Depressants	Alcohol	↔	↔	↔[f]	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Alprazolam	↑[g]	↑[g]	↑[g]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Codeine	↑[i]	↑[i]	↑[i]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[i]	↑[i]
	Diazepam	↑	↑	↑	↓	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	GHB (gamma hydroxybutyrate)	↑[j]	↑[j]	↑[j]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[j]	↑[j]
	Heroin (Diamorphine)	↓[k]	↓[k]	↓[k]	↑	↔[k]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[k]	↔[k]
	Hydrocodone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Hydromorphone	↓	↓	↓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Ketamine	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Pethidine (Meperidine)	↓[l]	↓[l]	↓[l]	↓[l]	↓[l]	↓[l]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Methadone	↓[b]	↓16%	↓53%[b]	↓52%	↑6%	↓~50%	↓16%[b]	↔	↔	↔	↓	↔	↔	↔	⇑	↑7%	↑7%
	Midazolam (oral)	↑[m]	↑[m]	↑[m]	↓[h]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[m]	↑[m]
	Morphine	↓[n]	↓[n]	↓[n]	↑	↔[n]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[n]	↔[n]
	Oxycodone	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↑
	Temazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Triazolam	↑[m]	↑[m]	↑[m]	↓[h]	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[m]	↑[m]
Hallucinogens	Cannabis	↑[o]⇓	↑[o]	↑[o]	↑[p]	↑[p]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[o]	↑[o]
	Lysergic acid diethylamide (LSD)	↑[q]	↑[q]	↑[q]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[q]	↑[q]
	Phencyclidine (PCP, angel dust)	↑[r]	↑[r]	↑[r]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑[r]	↑[r]

Educational videos



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