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Drug-drug interactions & other prescribing issues in PLWH

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for the EACS Drug-Drug interactions Guidelines panel

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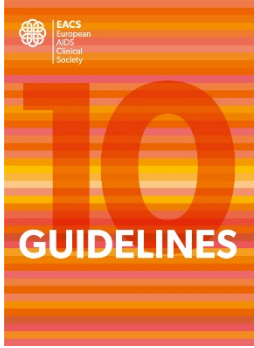

Part III

Drug-drug interactions and other prescribing issues in PLWH

- Drug-drug interactions between **ARVs** and **non-ARVs**
- Drug-drug interactions between **Antidepressants** and ARVs
- Drug-drug interactions between **Antihypertensives** and ARVs
- Drug-drug interactions between **Analgesics** and ARVs
- Drug-drug interactions between **Anticoagulants/antiplatelets agents** and ARVs
- Drug-drug interactions between **Bronchodilatators (for COPD)** and ARVs
- Drug-drug interactions between **Contraceptives** and ARVs
- Drug-drug interactions between **Corticosteroids** and ARVs
- Drug-drug interactions between **Antimalarial drugs** and ARVs
- Drug-drug interactions between **Pulmonary Antihypertensives** and ARVs
- Drug-drug interactions between **Immunosuppressants (for SOT)** and ARVs
- Drug-drug interactions between **DAAs** and ARVs
- Administration of ARVs in PLWH with **Swallowing difficulties**
- Dose adjustment of ARVs for **Impaired hepatic function**
- Dose adjustment of ARVs for **Impaired renal function**
- **Selected non-ARV drugs requiring dosing dosage adjustment in renal insufficiency** **NEW**
- **Prescribing in elderly** PLWH
- **Selected top 10 drug classes to avoid in elderly PLWH** **NEW**
- **Dosage recommendations for hormone therapy when used for gender transitioning** **NEW**

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Major updates to DDIs tables

+ **BICTEGRAVIR** : metabolism by CYP3A4 and UGT1A1
no inhibitory or inducing effects on CYPs or UGTs
inhibition of OCT2, MATE1

➔ **bictegravir does mostly not impact comedications**
exception: **metformin**

➔ **strong inhibitors CYP3A4: no clinically relevant increase in bictegravir exposure**

➔ **strong dual inhibitors CYP3A4 + UGT1A1: contraindicated**

➔ **strong inducers: contraindicated as substantial reduction in bictegravir levels**

➔ **divalent cations: similarly to other INSTIs, bictegravir is subject to chelation**

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DDI between ARVs and non-ARVs

Non-ARV drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL
Cardiovascular drugs	atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↑4% D10%	↔	↔	↔	↑	↔
	fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔	↑	↔
	pravastatin	↑	↑	↑	↑81%	↔	↔	↓44%	↓	↔	↔	↔	↔	↔	↑	↔
	rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑108%	↔	↔	↔	↔	↔	↔	↔	↔	↑38%	↔
	simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↔	↔	↔	↑	↔
	amlodipine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	diltiazem	↑a	↑a	↑	↑	↑a	E	↓69%	↓E	↓	E	E	E	↔	↑	↔
	metoprolol	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔
	verapamil	↑a	↑a	↑	↑	↑a	E	↓	↓E	↓	E	E	E	↔	↑	↔
	warfarin	↑	↑ or ↓	↑	↓	↓	↔	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↔	↓	↔
CNS drugs	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↑?	↔
	carbamazepine	↑D	↑D	↑D	↑	↑D b	D	↓27% D36%	D	↓D	D	D	D	D49%	↑ D	D b
	citalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔c	↔	↔	↔	↑	↔
	diazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	lamotrigine	↔	↓32%d	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↓1%
	midazolam (oral)	↑	↑	↑	↑	↑	↓18%	↓	↓	↓	↔	↑18%	↑15%	↔	↑	↓8%
	mirtazapine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↑↓?	↔
	phenytoin	D	↓D	D	↓D	↓D b	D	↓D	D	D	D	D	D	D	D	D b
	pimozide	↑	↑	↑	↑	↑	↔	↑	↓	↓	↔c	↔	↔	↔	↑	↔
	sertraline	↑	↓	↑	↓49%	↓	↔	↓39%	↓	↓	↔	↔	↔	↔	↓7%	↔
	triazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
Anti-infectives	clarithromycin	↑Ea	↑Ea	↑E	↑	↑a	↑	↓39%	↓39% E42%	↓31% E26%	E c	E	E	↔	↑E	↔
	fluconazole	↑?	↔	↑?	↔	↔	↑	↔	E86%	E100%	E	↔	↔	↔	↑?	↔
	itraconazole	↑E	↑E	↑E	↑E	↑E	↑	↓39%	↓E	↓61%	E	E	E	↔	↑E	↔
	rifabutin	↑D	↑	↑D	↑E50%	↑	D50%	↓38%	↓17% D37%	↑17%	D42%	e	D38%	↔	↑D	E19%
	rifampicin	D	D72%	D	D57%	D75%	D82%	D26%	D	D58%	D80%	D	D75%	D54%g	D	D40%b
	voriconazole	↑↓ E	↑↓ D	↑E	↓	↑↓ E	↑	↓E	↑14% E36%	↓E	E	E	E61%	↔	↑E	↔
	antacids	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	D	D	D	D h
	PPIs	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E
	H2 blockers	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E

Major updates to DDIs tables

+ **DORAVIRINE**: metabolism by CYP3A4
no inhibitory or inducing effects on CYPs, UGTs or drug transporters

➔ **doravirine does not impact comedications**

➔ **strong inhibitors: no clinically relevant increase in doravirine exposure**

➔ **strong inducers: contraindicated as substantial reduction in doravirine levels**

➔ **moderate inducers: DDI can be managed by increasing doravirine dose to 100 mg BID**

DDI between ARVs and non-ARVs

	Non-ARV drugs	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL
Cardiovascular drugs	atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↑4% D10%	↔	↔	↔	↑	↔
	fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔	↑	↔
	pravastatin	↑	↑	↑	↑81%	↔	↔	↓44%	↓	↔	↔	↔	↔	↔	↑	↔
	rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑108%	↔	↔	↔	↔	↔	↔	↔	↔	↑38%	↔
	simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↔	↔	↔	↑	↔
	amlodipine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	diltiazem	↑a	↑a	↑	↑	↑a	E	↓69%	↓E	↓	E	E	E	↔	↑	↔
	metoprolol	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔
	verapamil	↑a	↑a	↑	↑	↑a	E	↓	↓E	↓	E	E	E	↔	↑	↔
	warfarin	↑	↑ or ↓	↑	↓	↓	↔	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↔	↓	↔
CNS drugs	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↑?	↔
	carbamaze-pine	↑D	↑D	↑D	↑	↑D b	D	↓27% D36%	D	↓D	D	D	D	D49%	↑ D	D b
	citalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔c	↔	↔	↔	↑	↔
	diazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	lamotrigine	↔	↓32%d	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↓1%
	midazolam (oral)	↑	↑	↑	↑	↑	↓18%	↓	↓	↓	↔	↑18%	↑15%	↔	↑	↓8%
	mirtazapine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↑↓?	↔
	phenytoin	D	↓D	D	↓D	↓D b	D	↓D	D	D	D	D	D	D	D	D b
	pimozide	↑	↑	↑	↑	↑	↔	↑	↓	↓	↔c	↔	↔	↔	↑	↔
	sertraline	↑	↓	↑	↓49%	↓	↔	↓39%	↓	↓	↔	↔	↔	↔	↓7%	↔
	triazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
Anti-infectives	clarithromy-cin	↑Ea	↑Ea	↑E	↑	↑a	↑	↓39%	↓39% E42%	↓31% E26%	E c	E	E	↔	↑E	↔
	fluconazole	↑?	↔	↑?	↔	↔	↑	↔	E86%	E100%	E	↔	↔	↔	↑?	↔
	itraconazole	↑E	↑E	↑E	↑E	↑E	↑	↓39%	↓E	↓61%	E	E	E	↔	↑E	↔
	rifabutin	↑D	↑	↑D	↑E50%	↑	D50%	↓38%	↓17% D37%	↑17%	D42%	e	D38%	↔	↑D	E19%
	rifampicin	D	D72%	D	D57%	D75%	D82%	D26%	D	D58%	D80%	D	D75%	D54%g	D	D40%b
	voriconazole	↑↓ E	↑↓ D	↑E	↓	↑↓ E	↑	↓E	↑14% E36%	↓E	E	E	E61%	↔	↑E	↔
	antacids	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	D	D	D	D h
	PPIs	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E
	H2 blockers	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E

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Major updates to DDIs tables

boosted ARVs alter clopidogrel efficacy ➔ avoid

alternative: prasugrel

www.hiv-druginteractions.org,
Marsousi N et al. Clin Pharmacokinet 2018;
Itkonen MK et al. Clin Pharmacol Ther 2018

DDIs with anticoagulants

Anticoagulants & Antiplatelets		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL
Anticoagulants	acenocoumarol	↔	↓	↔	↓	↓	↔	↑or↓	↑	↓	↔	↔	↔	↔	↓	↔
	apixaban	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔	↔	↔	↔	↑a	↔
	argatroban	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	dabigatran	↑	↑	↑	↑	↑?	↔	↔	↑	↔	↑?	↔	↔	↔	↑	↔
	dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	edoxaban	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔
	enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenprocoumon	↑	↑or↓b	↑	↑or↓	↑or↓	↔	↓	↑or↓	↓	↔	↔	↔	↔	↑or↓	↔
	rivaroxaban	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔
	warfarin	↑	↑or↓b	↑	↓	↓	↔	↑or↓	↑	↑or↓	↔	↔	↔	↔	↓	↔
Antiplatelet agents	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	clopidogrel	↓c	↓c	↓c	↓c	↓c	↔	↓c	↓c	↑d E	↔	↔	↔	↔	↓c	↔
	dipyridamole	↑	↓f	↔	↓	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔
	prasugrel	↓g	↓g	↓g	↓g	↓g	↔	↔	↔	↔	↔	↔	↔	↔	↓g	↔
	ticagrelor	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔

EACS tables are linked to DDIs websites and have been revised to include all updates made to the websites in the past year

HIV Drug Interactions

www.hiv-druginteractions.org

HEP Drug Interactions

www.hep-druginteractions.org

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Selected Top 10 Drug Classes To Avoid in Elderly PLWH

Drug class	Problems/alternatives
First generation antihistamines e.g., clemastine, diphenhydramine, doxylamine, hydroxyzine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: cetirizine, desloratadine, loratadine
Tricyclic antidepressants e.g., amitryptiline, clomipramine, doxepin, imipramine, trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: citalopram, escitalopram, mirtazapine, venlafaxine
Benzodiazepines Long and short acting benzodiazepines e.g., clonazepam, diazepam, midazolam Non-benzodiazepines hypnotics e.g., zolpidem, zopiclone	Elderly are more sensitive to their effect, risk of falls, fractures, delirium, cognitive impairment, drug dependency. Use with caution, at the lowest dose and for a short duration. Alternatives: non-pharmacological treatment of sleep disturbance/sleep hygiene.
Atypical antipsychotics e.g., clozapine, olanzapine, quetiapine	Anticholinergic adverse reactions, increased risk of stroke and mortality (all antipsychotics). Alternatives: aripiprazole, ziprasidone
Urological spasmolytic agents e.g., oxybutynin, solifenacin, tolterodine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: non-pharmacological treatment (pelvic floor exercises).
Stimulant laxatives e.g., senna, bisacodyl	Long-term use may cause bowel dysfunction. Alternatives: fibres, hydration, osmotic laxatives
NSAIDs e.g., diclofenac, indomethacin, ketorolac, naproxen	Avoid regular, long-term use of NSAIDs due to risk of gastrointestinal bleeding, renal failure, worsening of heart failure. Alternatives: paracetamol, weak opioids
Digoxin Dosage > 0.125 mg/day	Avoid doses higher than 0.125 mg/day due to risk of toxicity. Alternatives for atrial fibrillation: beta-blockers
Long acting sulfonylureas e.g., glyburide, chlorpropamide	Can cause severe prolonged hypoglycemia. Alternatives: metformin or other antidiabetic classes
Cold medications Most of these products contain antihistamines (e.g., diphenhy-	First generation antihistamines can cause central and peripheral anticholinergic adverse reactions as described above. Oral decongestants can increase blood pressure

Dosage recommendations for hormone therapy used for gender transitioning

a ARVs with no predicted effect:
DOR, RPV, MVC, BIC, DTG, RAL, NRTI

b ARVs inhibiting estrogen metabolism:
ATV, ATV/c, DRV/c, DRV/c

c ARVs inducing estrogen metabolism:
ATV/r, DRV/r, LPV/r, EFV, ETV, NVP

d ARVs inhibiting androgen metabolism:
ATV, ATV/c, ATV/r, DRV/c, DRV/r, EVG/c, LPV/r

e ARVs inducing androgen metabolism:
EFV, ETV, NVP

		HIV Drugs	Starting Dose	Average Dose	Maximum Dose
Estrogens	Estradiol oral	No predicted effect a	2 mg/day	4 mg/day	8 mg/day
		Inhibits metabolism b	1 mg/day	2 mg/day	4 mg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Estradiol gel (preferred for >40 y and/or smokers)	No predicted effect a	0.75 mg bid	0.75 mg tid	1.5 mg tid
		Inhibits metabolism b	0.5 mg bid	0.5 mg tid	1 mg tid
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Estradiol patch (preferred for >40 y and/or smokers)	No predicted effect a	25 µg/day	50-100 µg/day	150 µg/day
		Inhibits metabolism b	25 µg/day*	37.5-75 µg/day	100 µg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Conjugated estrogen†	No predicted effect a	1.25-2.5 mg/day	5 mg/day	10 mg/day
		Inhibits metabolism b	0.625-1.25 mg/day	2.5 mg/day	5 mg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Ethinylestradiol	No predicted effect a	No interaction expected, but not recommended due to thrombotic risks		
		Inhibits metabolism b	Not recommended		
		Induces metabolism c	Not recommended		
Androgen Blockers ‡	Spironolactone	No predicted effect a	50 mg/day	150 mg/day	400 mg/day
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
	Finasteride	No predicted effect a	2.5 mg/day	2.5 mg/day	5 mg/day
		Inhibits metabolism d	Finasteride has a large safety margin. No dose adjustment required.		
		Induces metabolism e	Increase finasteride dosage as needed based on clinical effects and monitored hormone levels.		
	Cyproterone acetate	No predicted effect a	50 mg/day	150 mg/day	150 mg/day
		No predicted effect a	25 mg/day	75 mg/day	75 mg/day
		Induces metabolism e	Increase cyproterone dosage as needed based on clinical effects and monitored hormone levels.		
	Goserelin	No predicted effect a	3.6 mg/month	3.6 mg/month	3.6 mg/month
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
	Leuprorelin acetate	No predicted effect a	3.75 mg/month	3.75 mg/month	3.75 mg/month
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		

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10 GUIDELINES

Acknowledgements

EACS panel members

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Drug-drug Interactions

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