Update on DDIs of Antiretroviral Drugs

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FUNDACIÓ LLUITA CONTRA LA SIDA

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Overview

1. Scenarios for DDIs
2. Interaction Potential of a Drug
3. Main ARV Interactions of Concern
4. DDIs of new ARVs

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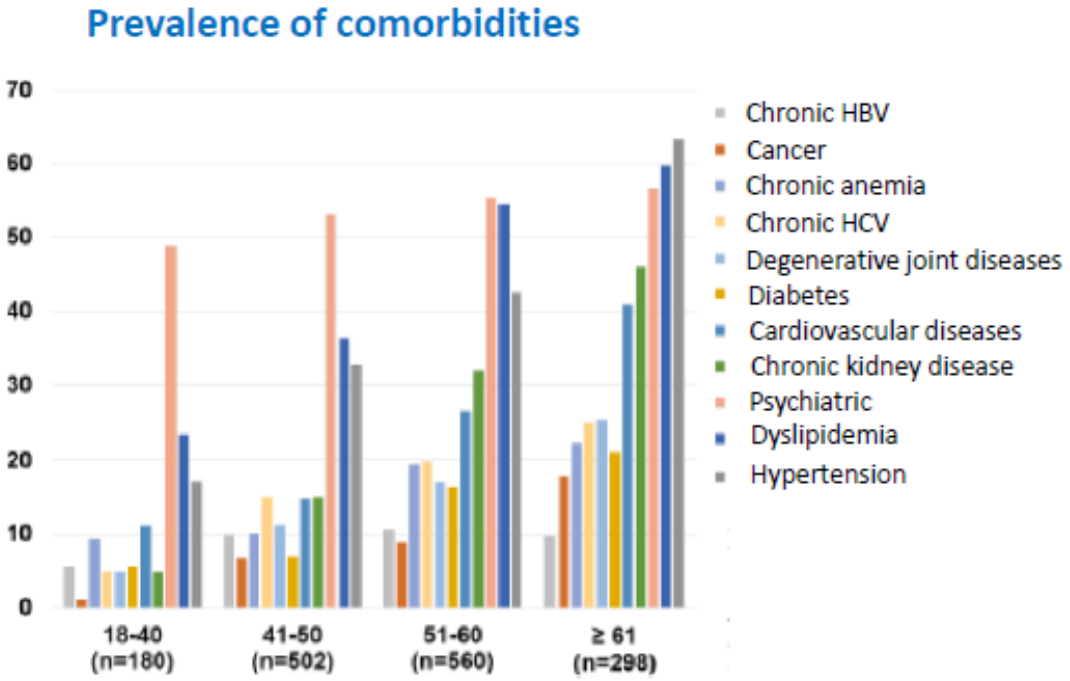
Scenarios for DDIs

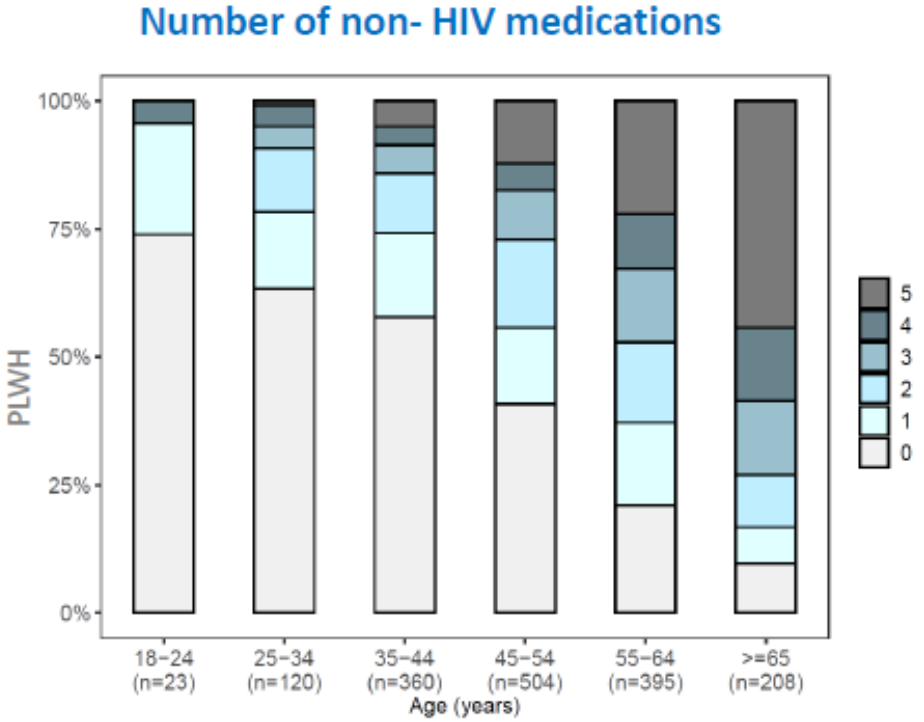
Comorbidities and polypharmacy (≥ 5 co-meds increase with age)

US HIV HOPS cohort



Palella FJ et al. AIDS 2019

Swiss HIV Cohort



Courlet P et al. Open Forum Infect Dis 2020

Similar observations in other HIV cohorts:

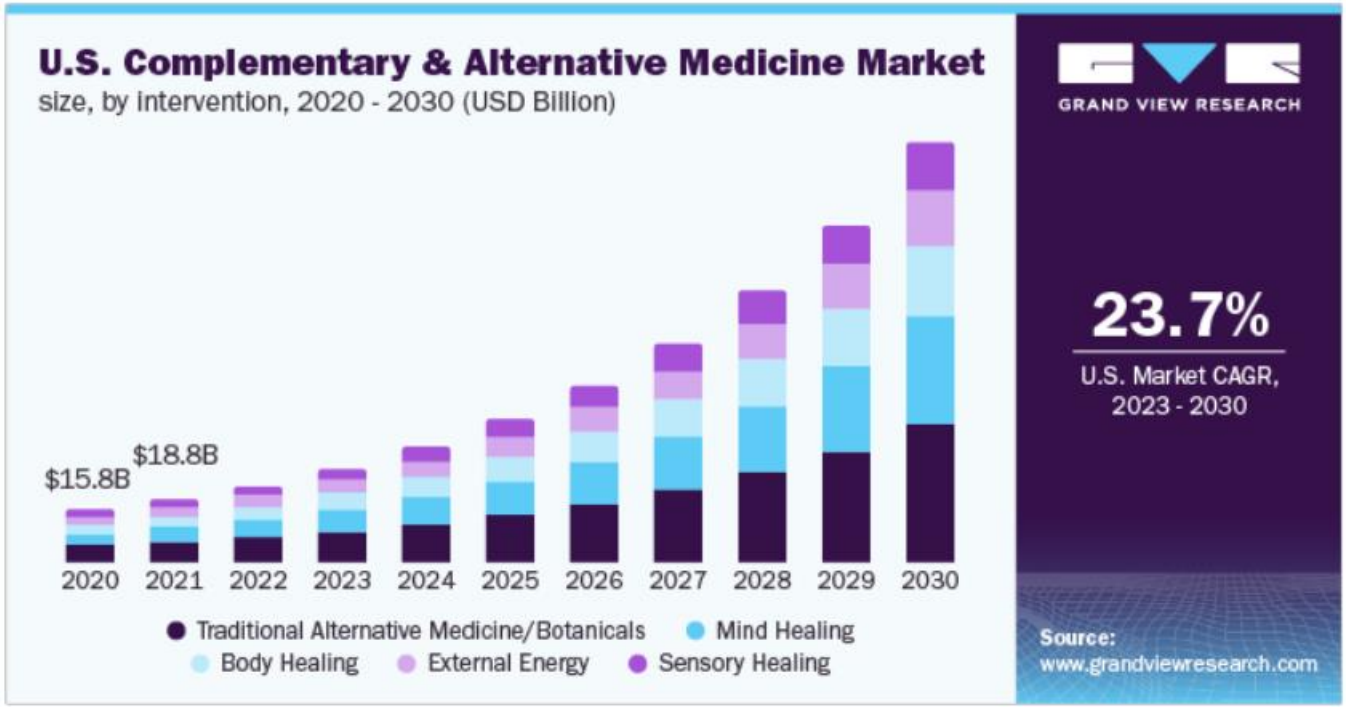
GEPPO (Guaraldi. BMC Geriatr 2018)
EuroSIDA (Pelchen-Matthews. AIDS 2018)
Dat'AIDS (Allavena. PlosOne 2018)
Swiss HIV cohort (Hasse. AIDS 2011)

Scenarios for DDIs

PDF

Market Analysis Report

Complementary And Alternative Medicine Market Size, Share & Trends Analysis Report By Intervention (Botanicals, Mind Healing, Body Healing, External Energy, Sensory Healing), By Distribution Method, By Region, And Segment Forecasts, 2023 - 2030



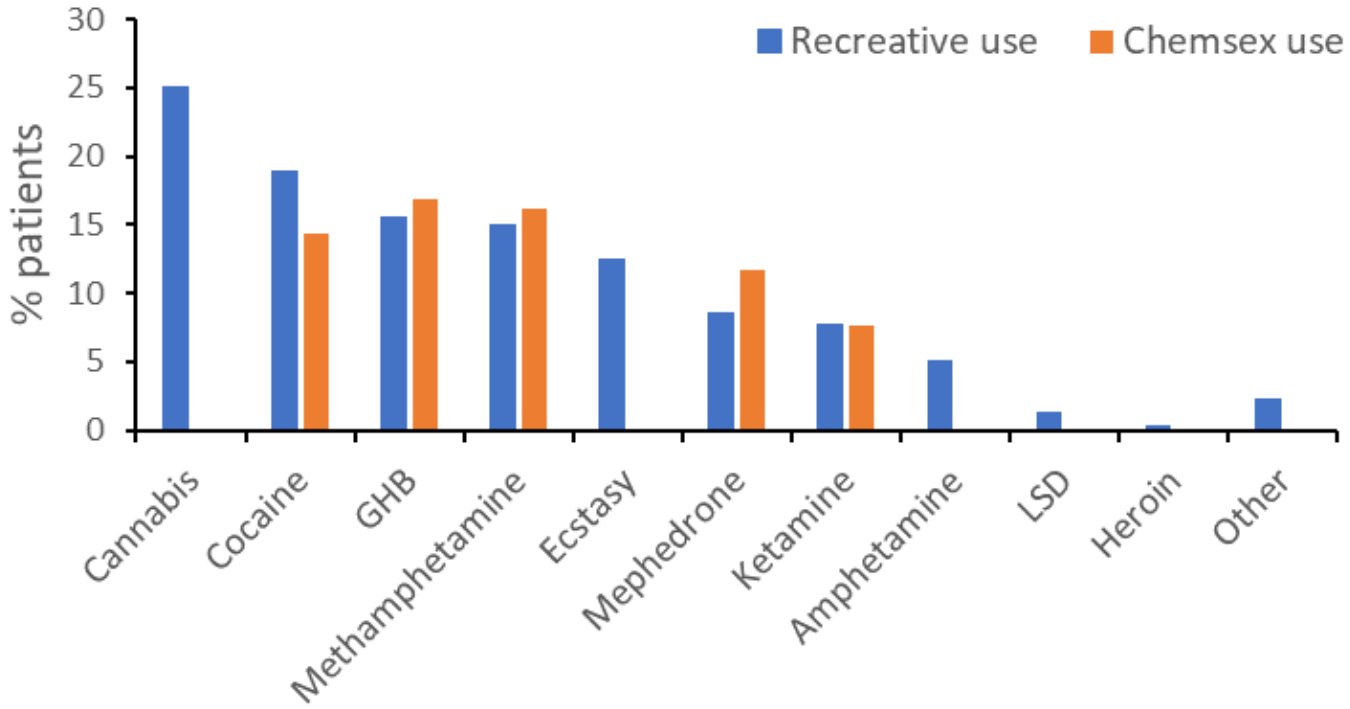
The global complementary and alternative medicine market size was valued at USD 117,210.3 million in 2022 and is expected to expand at a compound annual growth rate (CAGR) of 25.1% from 2023 to 2030.

Scenarios for DDIs

Chems4EU: chemsex use and its impacts across four European countries in HIV-positive men who have sex with men attending HIV services

In the previous 12 months

- 44.6% had used any recreational drugs
- 24.0% reported chemsex
- 6.5% reported slamsex



HIV Medicine. 2021;22:944–957.

Scenarios for DDIs

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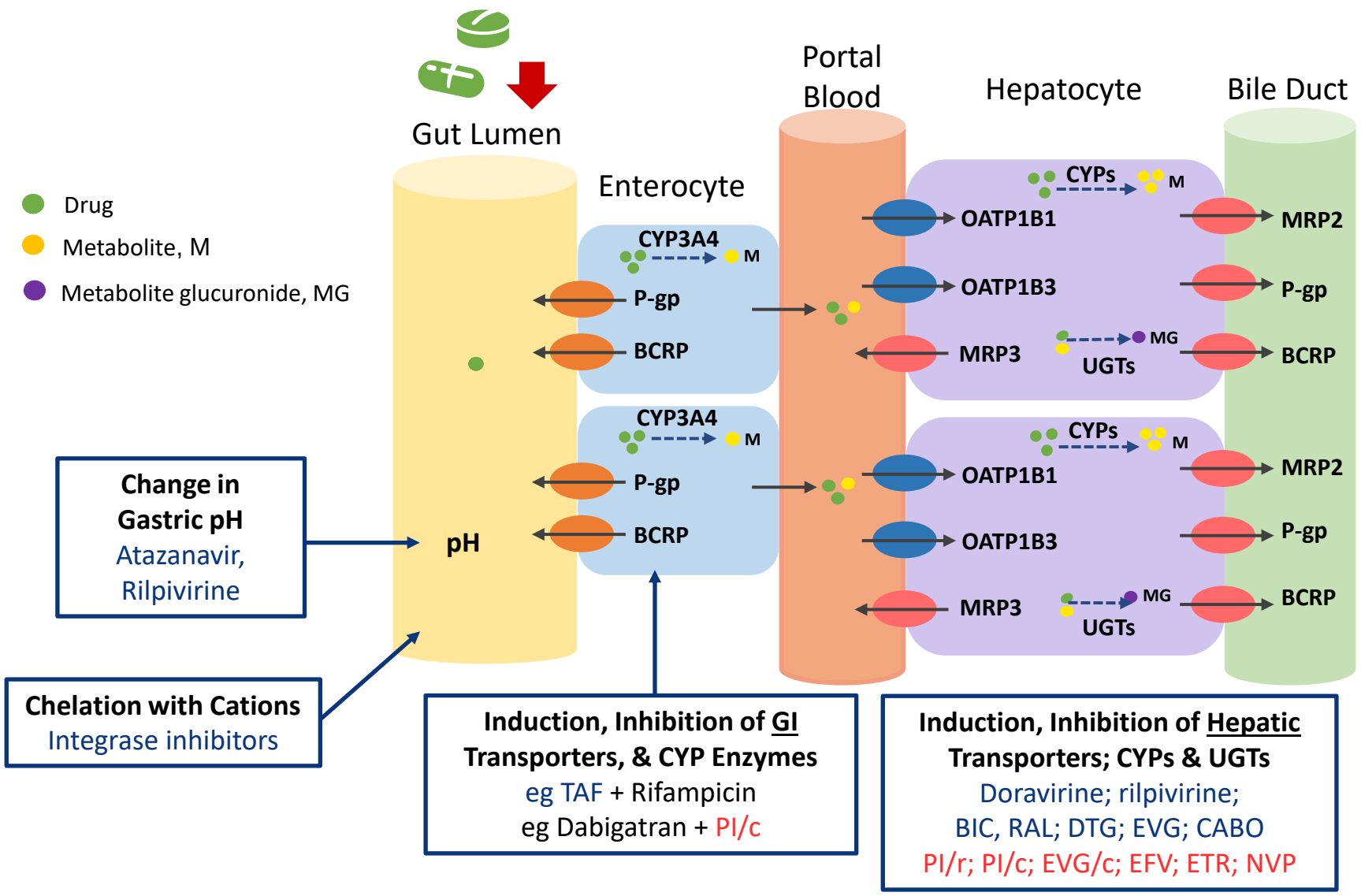
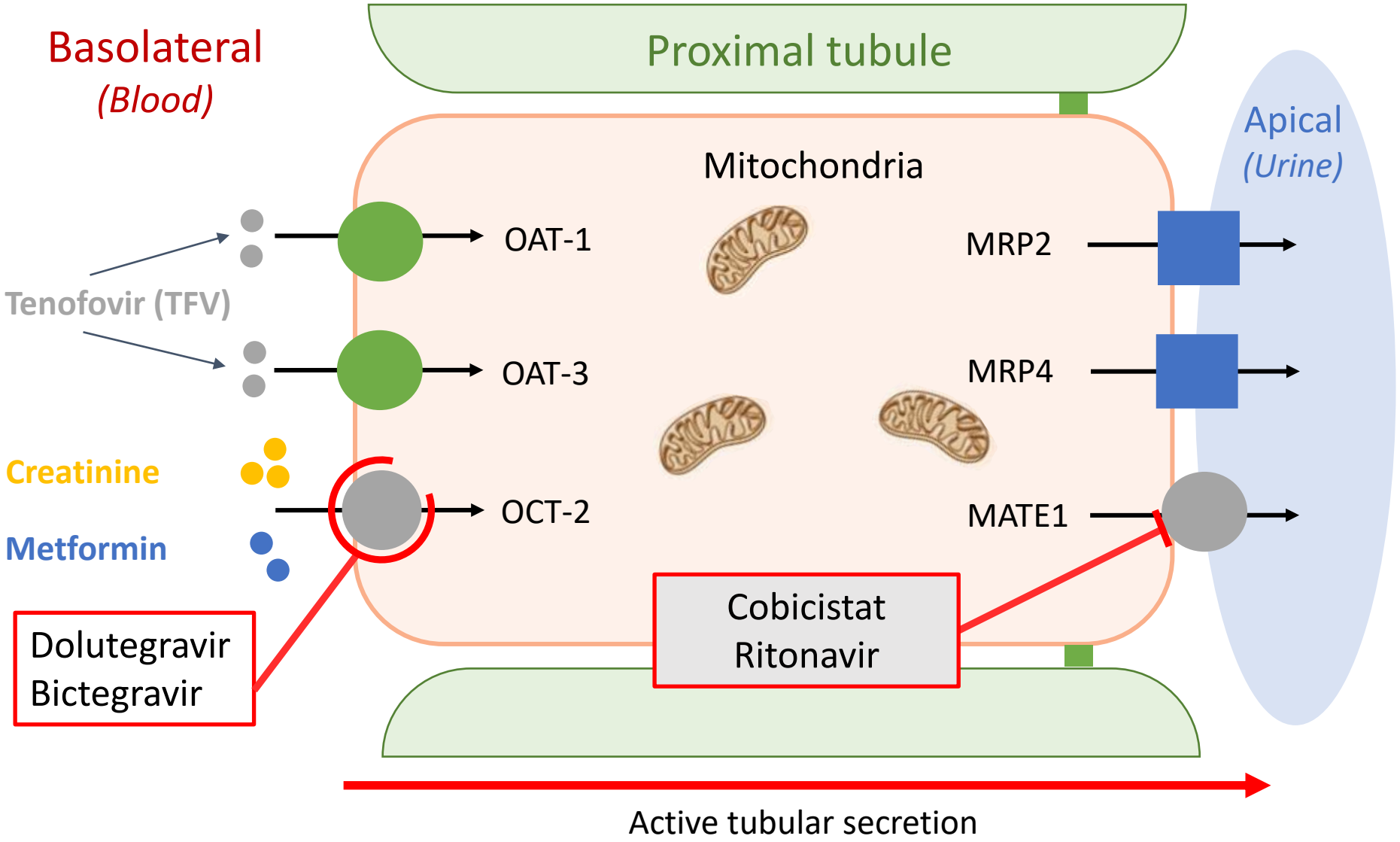
Interaction Potential of a Drug: Disposition and Mechanisms of DDIs



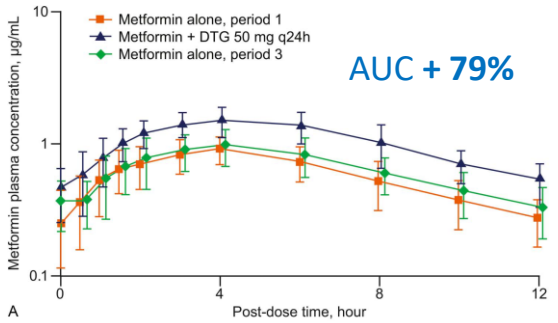
Enzyme = Catalyst
Transporter = Pump
Victim drugs
Perpetrator drugs

GI, gastrointestinal; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; OAT, organic anion transporter; MRP, multidrug resistance-associated protein; UGT, UDP-glucuronosyltransferase; PI, protease inhibitor; /r, ritonavir; /c, cobicistat.

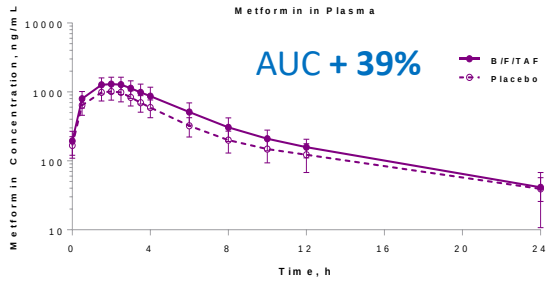
Some DDIs can Occur in the Kidney



Dolutegravir on Metformin



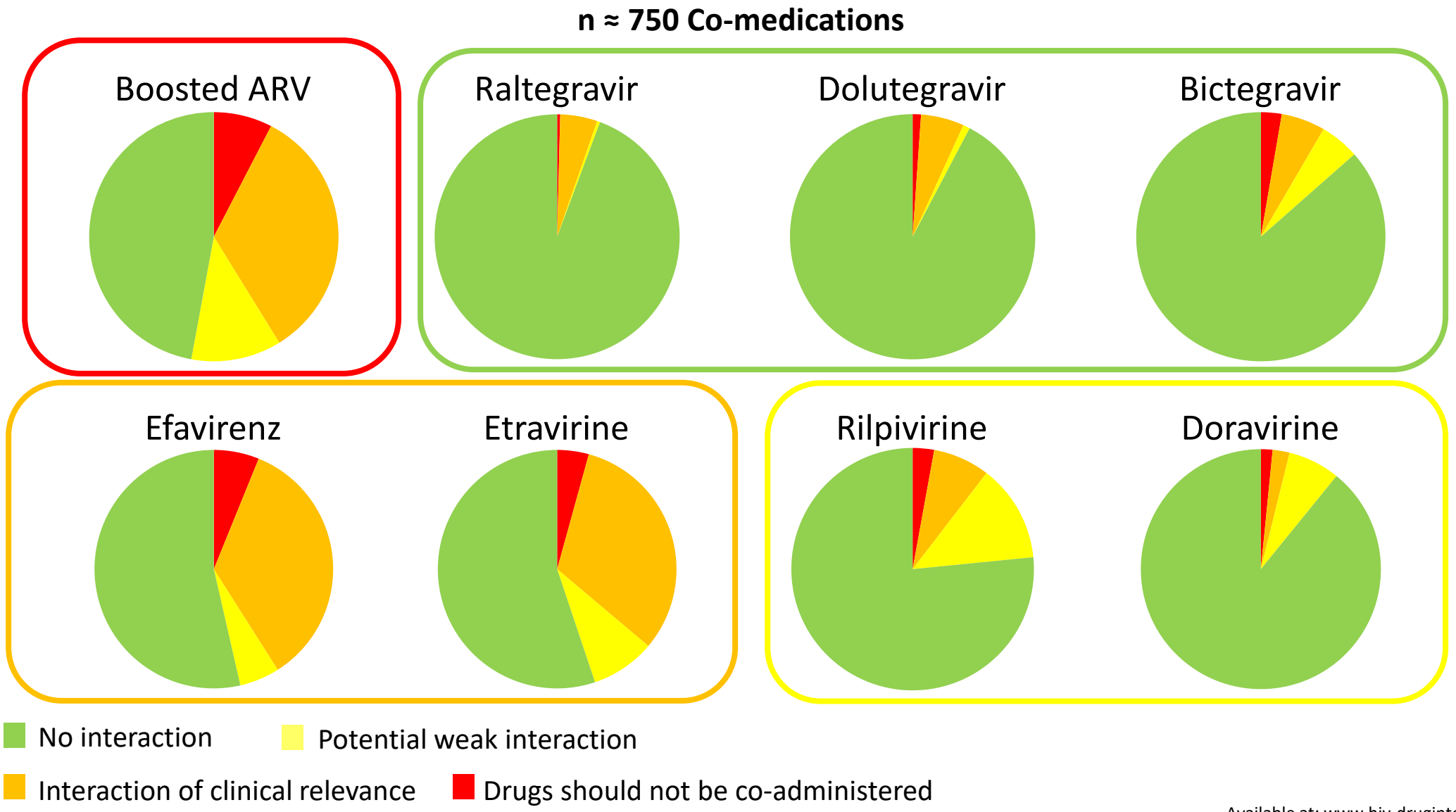
Bictegravir on Metformin



OAT, organic anion transporter; OCT, organic cation transporter;
MRP, multidrug resistance-associated protein;
MATE, multidrug and toxin extrusion protein.

Song IH, *et al. J Acquir Immune Defic Syndr* 2016; **72**(4):400–407;
Custodio J, *et al. Open Forum Infect Dis* 2017; **4**(Suppl1):S249.

DDI Profile of Antiretroviral Drugs: www.hiv-druginteractions.org



Available at: www.hiv-druginteractions.org.

Overview

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Patient #1

57 yo male.
Multi-R HIV. ART: **DRV/r bid + ETR + DTG**
COPD frequent worsenings.
GP wants to prescribe **inhaled CE**

Which is your referred option for this patient?

1) Fluticasone / salmeterol
2) Beclometasone / formoterol
3) Budesonide + salbutamol
4) Any after stopping DRV/r

Drug interactions & pharmacokinetics

Interaction between antiretroviral boosters and corticosteroids can lead to development of Cushing's syndrome

Hypothalamic–pituitary–adrenal axis suppression by inhaled or nasal corticosteroids in HIV-infected patients

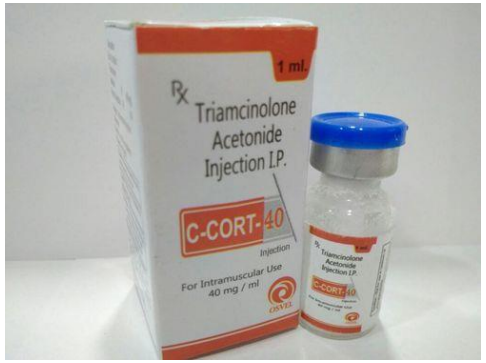
International Journal of Clinical Pharmacy (2020) 42:347–350

Ritonavir/Cobicistat-Induced Cushing Syndrome in HIV Patients Treated With Non-Oral Corticosteroids: A Call for Action?

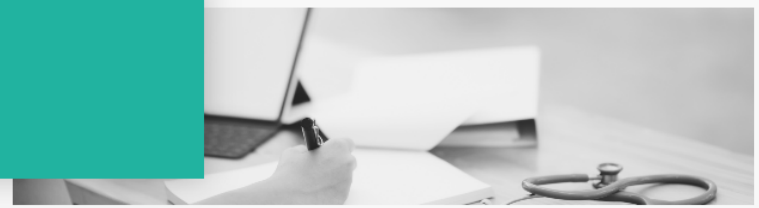
Am J Med Sci. 2021 Jan;361(1):137-139

Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management

HIV Medicine (2013), 14, 519–529



Clinical cases including **ARVs** and **Fluticasone**

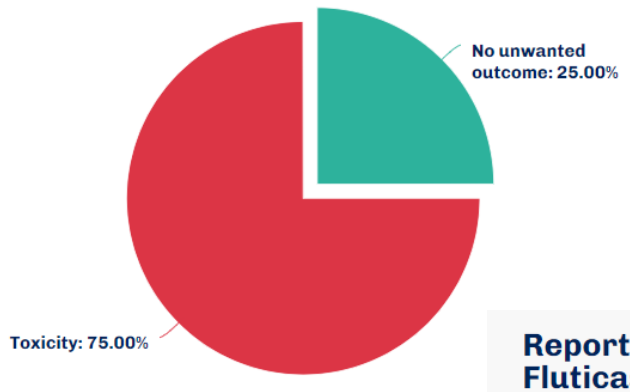


There are 4 clinical cases including any of the components of and **Fluticasone** in our database.

Out of these, the clinical outcome was as follows:

- No unwanted outcome in 1 (25.0 %) cases
- Toxicity in 3 (75.0 %) cases

Outcomes



Reported clinical cases involving ARVs and Fluticasone

Visited Case

P = Perpetrator V = Victim

View	ARV involved	Comedication	Outcome↑ (A-Z)/↓ (Z-A)
	Cobicistat (P)	**Fluticasone** (V)	Toxicity
	Cobicistat (P)	**Fluticasone** (V)	No unwanted outcome
	Ritonavir (P)	**Fluticasone** (V)	Toxicity
	Ritonavir (P)	**Fluticasone** (V)	Toxicity

Corticosteroids (risk for DDIs)

High risk	Intermediate risk	Low risk
Fluticasone **Budesonide** **Momethasone** **Triamcinolone** **Dexamethasone***	**Metylprednisolone** (intraarticular, epidural, reduce dose 30%)	**Beclomethasone** (inhaled, nasal) **Hydrocortisone** (topic)

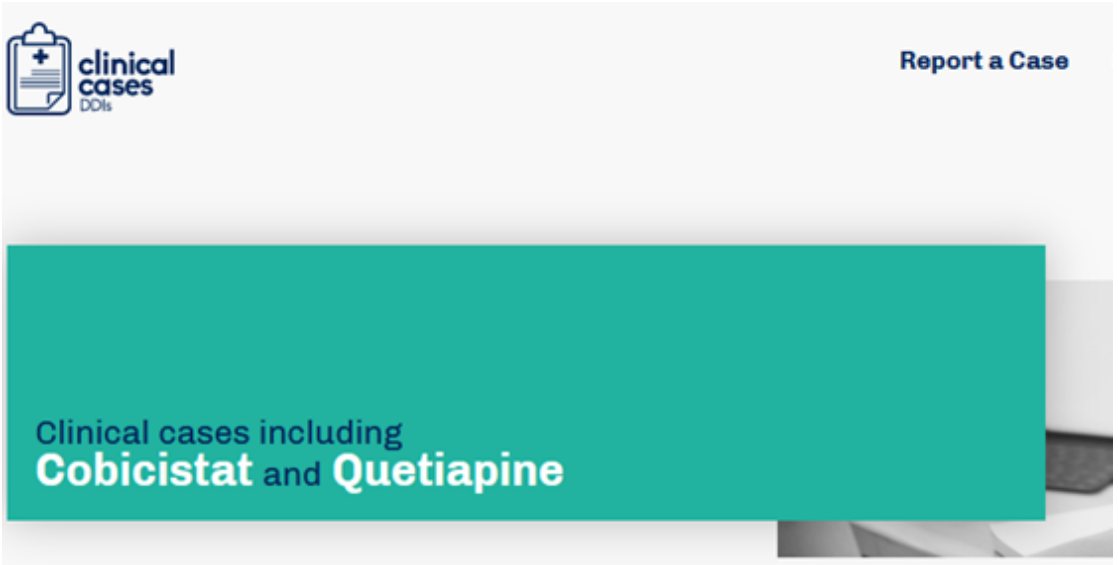
Use the minimmun effective dose for the shortest time period
Close monitoring. Consider monitoring cortisol levels
*Victima & prepetrator (miltiple dosing)

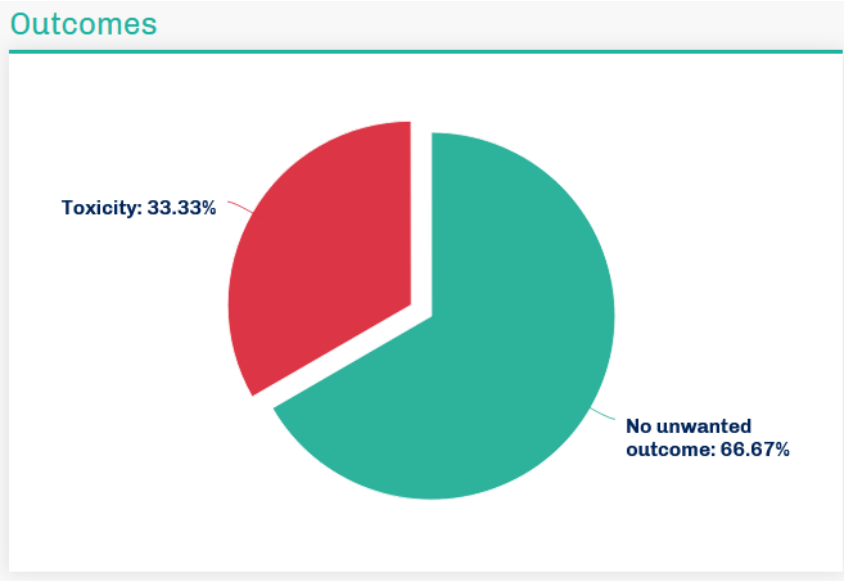
Patient #2

29 yo male.
ART: **DRV/c/FTC/TAF**
Schizophrenia
Prescribed with **quetiapine**

Which is your attitude with this patient?

1) Change ART
2) Change anti-psychotic (alternatives?)
3) Start with initial dose of quetiapine 100 mg bid (target dose 300 mg/day)
4) Start with full dose of quetiapine 300 mg/day and monitor adverse events





European SPC COBI is contraindicated with quetiapine due to the known inhibition of CYP3A4 metabolism by cobicistat and therefore potential increase in quetiapine exposure.

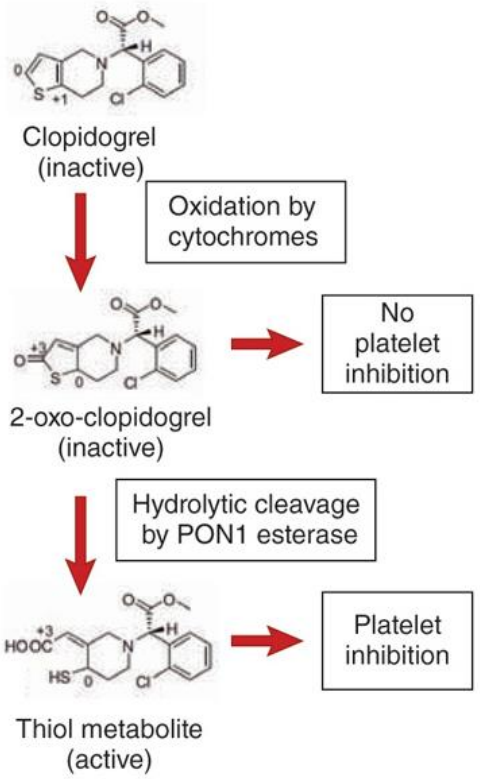
In the US prescribing information the recommendation is to dose reduce the quetiapine to 1/6th of the dose.

Patient #3

45 yo male
ART: **DRV/c + RPV**
Coronary syndrome – AMI with coronary stent
Prescribed with **AAS + clopidogrel, simvastatin 40 mg qd, valsartan 50 mg qd, carvedilol 6.25 mg qd, omeprazole 20 mg qd**

Which is your expected outcome?

1) Nothing remarkable
2) Lack of efficacy of ART
3) Lack of efficacy of co-medication
4) Potential toxicity of co-medication



Do Not Coadminister
Darunavir/Cobicistat/ Emtricitabine/Tenofovir alafenamide (DRV/c/FTC/TAF)
Clopidogrel

Coadministration of clopidogrel and ritonavir (100 mg twice daily) decreased the AUC and Cmax of clopidogrel's active metabolite by 51% and 48%.

The decrease in clopidogrel's active metabolite leads to insufficient inhibition of platelet aggregation in 44% of the patients.

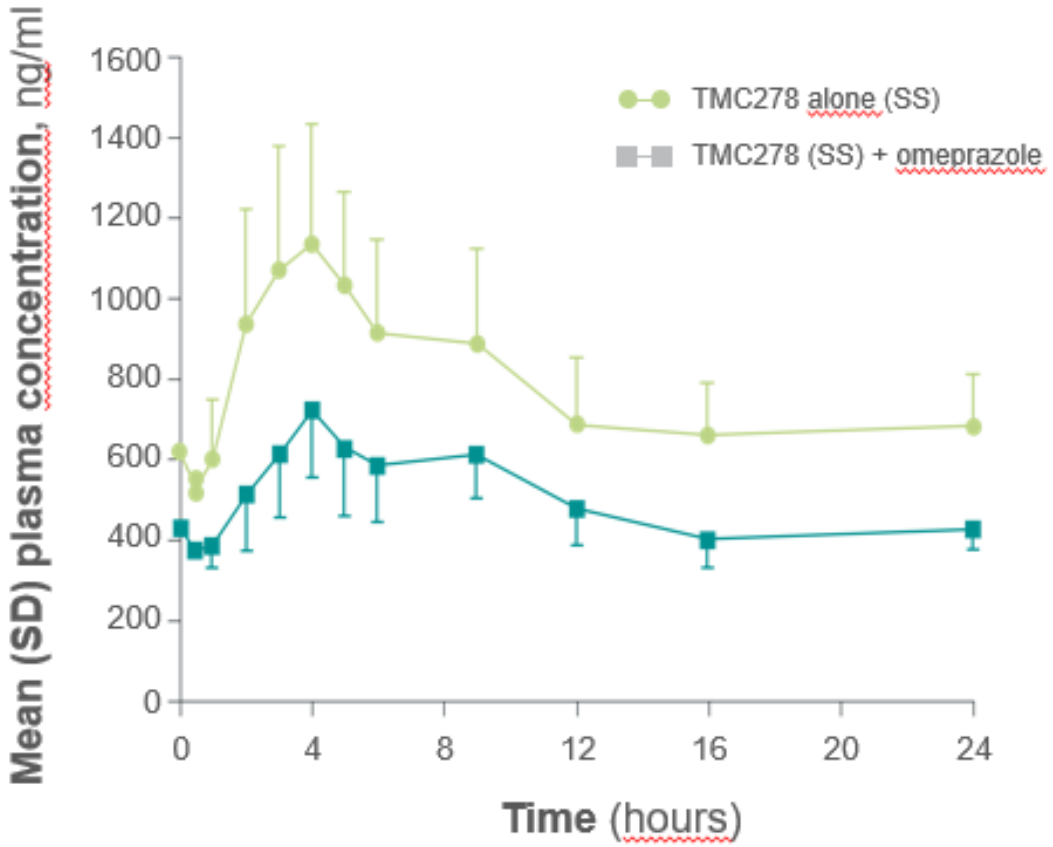
British Journal of Clinical Pharmacology

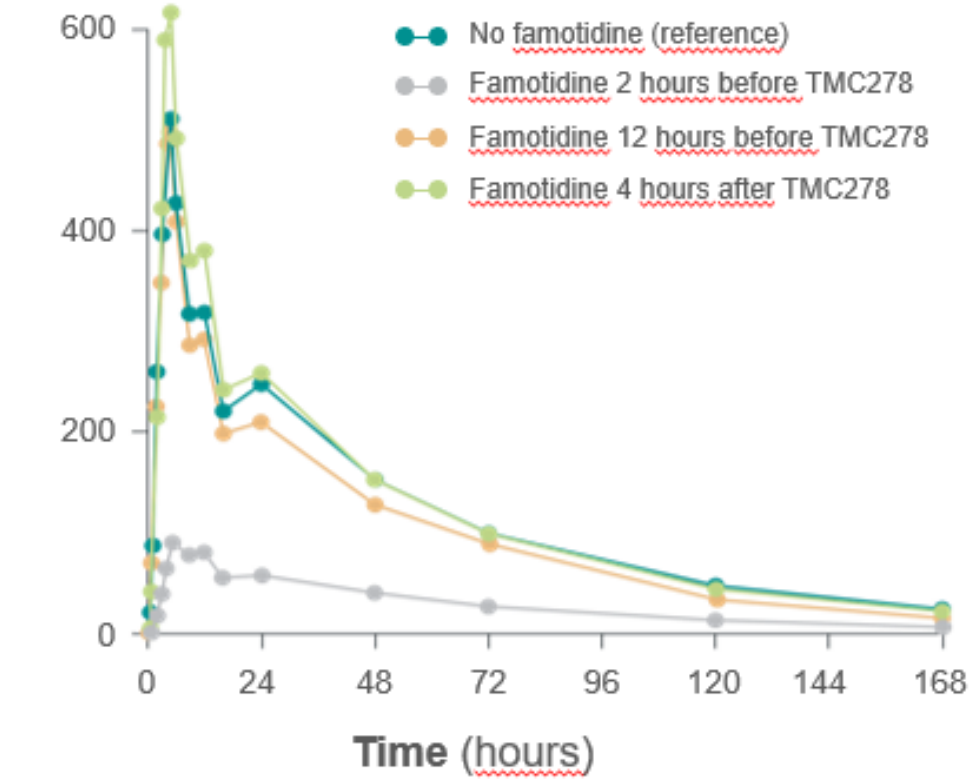
Bravo I, Álvarez H, Mariño A, Clotet B, Moltó J.
Br J Clin Pharmacol. 2018 Jul;84(7):1617-1619.

CASE REPORT

Recurrent coronary disease in HIV-infected patients: role of drug–drug interactions

Rilpivirine & Gastric pH





Crauwels H, et al. AIDS Rev 2013;15:87-101.

CAT | CAST

fármacos

ASÍ NOS MEDICAMOS LOS CATALANES

Estos son los 20 medicamentos **más consumidos** durante el 2021:

	FÁRMACO	GRUP	% ENVASES	ENVASES
1	**Paracetamol**	ANALGÉSICOS	5,82%	8.081.671
2	**Omeprazol**	IBP	4,73%	6.560.759
3	**Simvastatina**	ESTATINAS (COLESTEROL)	3,33%	4.622.067
4	**Ácido acetilsalicílico**	ANTIAGREGANTE	2,65%	3.675.843
5	**Enalapril**	ANTIHIPERTENSIVOS	2,18%	3.023.194
6	**Bisoprolol**	BETABLOQUEANTE (PARA EL CORAZÓN)	2,03%	2.822.373
7	**Metformina**	DIABETES	1,98%	2.741.610
8	**Lorazepam**	ANSIOLÍTICOS	1,95%	2.703.231
9	**Atorvastatina**	ESTATINAS (COLESTEROL)	1,85%	2.573.839
10	**Metamizol de sodio**	ANALGÉSICOS	1,85%	2.570.485

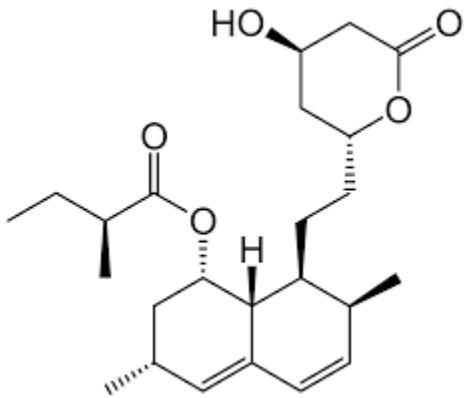
www.hiv-druginteractions.org

Lipid-Lowering Treatment Selector

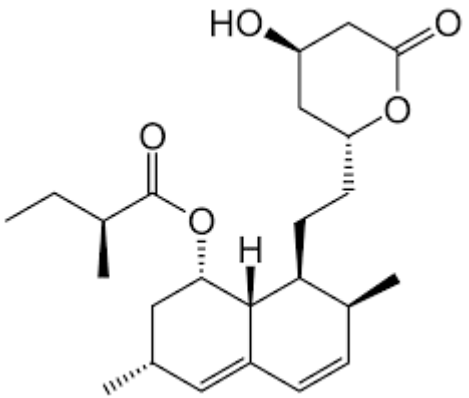
	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC/ F/TAF	DTG	EVG/c/ F/TAF	EVG/c/ F/TDF	RAL	FTC or 3TC	F/TAF	TDF	ZDV
Statins																				
Atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔
Fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔
Lovastatin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔
Pitavastatin	↑	↑ [a]	↑	↓26%	↓20%	↔	↓11%	↔	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔
Pravastatin	↑	↑	↑	↑81%	↔	↔	↓44%	↓	↔	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔
Rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↔	↔	↑38%	↑38%	↔	↔	↔	↔	↔
Simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔

www.hiv-druginteractions.com

Prezcobix US Prescribing Information, Janssen Pharmaceuticals Inc, June 2018.



Monacolina



Lovastatina

Patient #4

23 yo male
ART: **DTG/3TC**
Regular use of **protein supplemments (gym) + anabolic steroids 1/yr**

Any concern regarding DDIs?

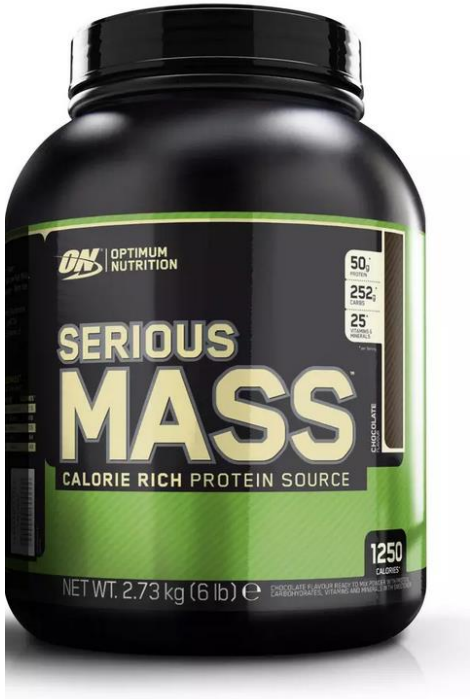
1) None
2) Lack of efficacy of ART
3) Lack of efficacy of co-medication
4) Potential toxicity of co-medication

Drug interactions between INSTI and cations

Carbonato cálcico 267 mg

OH Al 200 mg
OH Mg 200 mg

Magnesio 126 mg



Calcio 167 mg
Magnesio 15.3 mg
Hierro 1.3 mg
Zinc 080 mg, Cu, Mn, Se, Cr…

~ 199 mg

Magnesio 247 mg

DDIs between INSTI & +2 cations

		Mg/Al	Ca	Fe	Multivitaminas
RAL	AUC	↓ 49%	↓ 55%		
	Cmax	↓ 44%	↓ 52%		
	Cmin	↓ 63%	↓ 32%		
EVG	AUC	↓ 45%			
	Cmax	↓ 41%			
	Cmin	↓ 47%			
DTG	AUC	↓ 74%	↓ 39%	↓ 54%	↓ 33%
	Cmax	↓ 72%	↓ 37%	↓ 57%	↓ 35%
	Cmin		↓ 39%	↓ 56%	↓ 32%
BIC	AUC	↓ 79%			
	Cmax	↓ 80%			
	Cmin				

Isentress, Genvoya, Tivicay, Biktarvy PI

HIV-1 Virologic Rebound Due to Coadministration of Divalent Cations and Bictegravir

Alex E. Rock · Patricia L. DeMarais · Pamala T. Vergara-Rodriguez · Blake E. Max

Infectious Diseases and Therapy

Infect Dis Ther. 2020 Sep; 9(3): 691–696.

Use of dietary supplements containing polyvalent cations and antacids among people living with HIV and its impact on viral suppression

AIDS. 2021 .

Real-life experiences on the clinical management of Drug-Drug Interactions (DDIs) in the provision of HIV healthcare

ARV involved	Comedication	Outcome↑ (A-Z)/↓ (Z-A)
Dolutegravir (V)	**Mineral Supplements** (P)	No unwanted outcome
Raltegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Raltegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Raltegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Raltegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Dolutegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Bictegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Dolutegravir (V)	**Mineral Supplements** (P)	Loss of efficacy
Bictegravir (V)	**Mineral Supplements** (P)	Loss of efficacy

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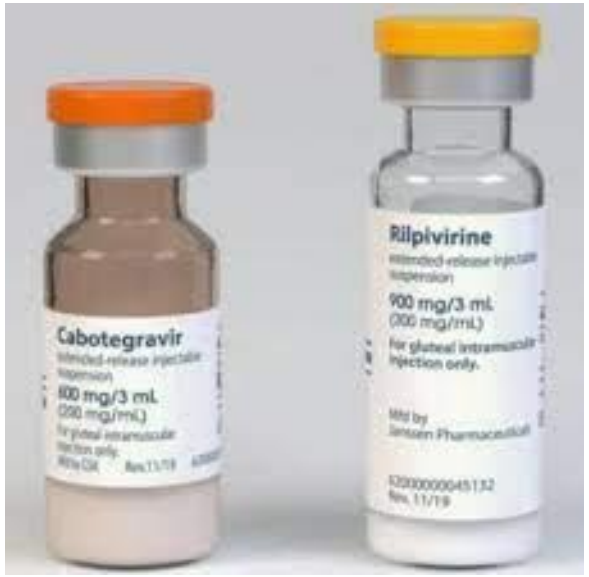
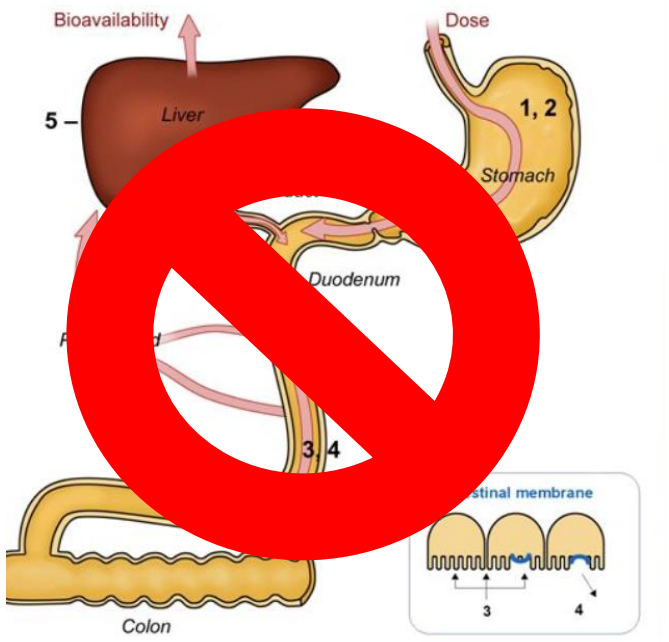
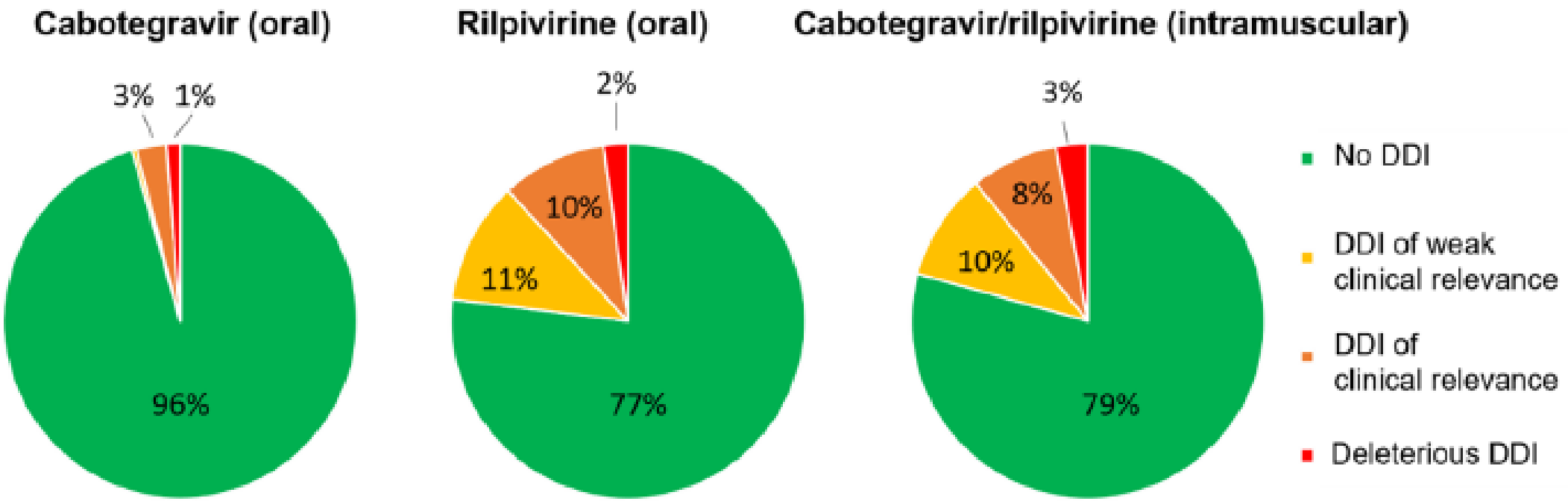
pH dependent absorption
Drug chelation
First pass metabolism
GI transporters





Lack of DDIs?

Pharmacokinetics and Drug–Drug Interactions of Long-Acting Intramuscular Cabotegravir and Rilpivirine



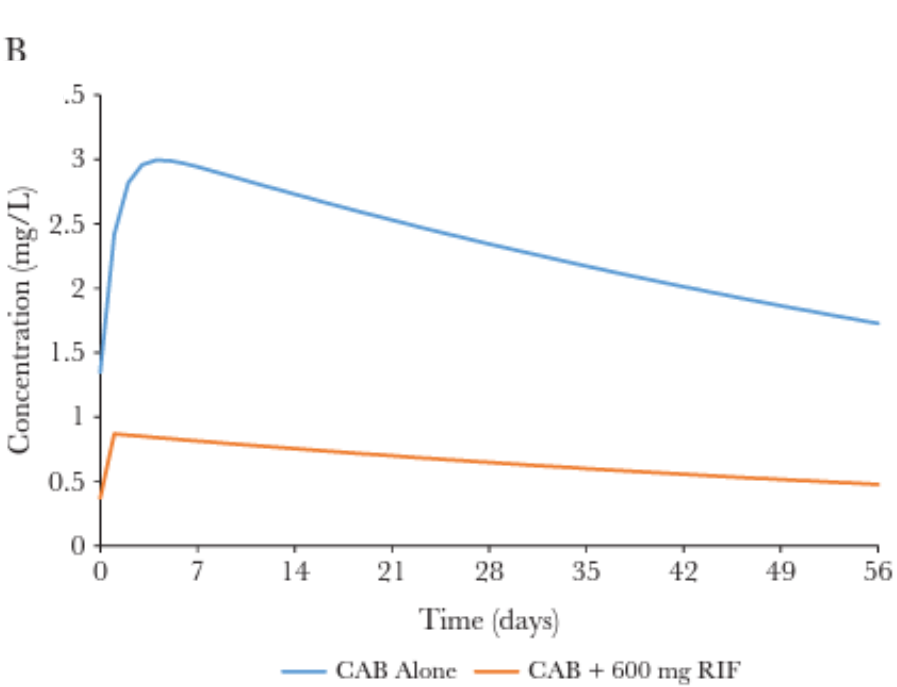
Hodge Clin Pharmacokinet 2021

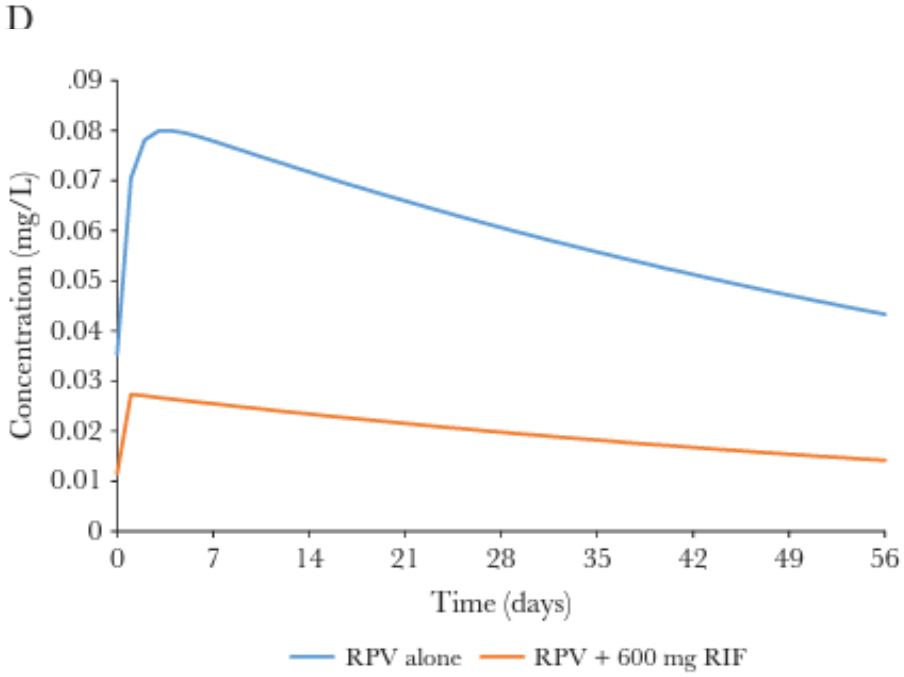
The Journal of Infectious Diseases

MAJOR ARTICLE

Predicting Drug–Drug Interactions Between Rifampicin and Long-Acting Cabotegravir and Rilpivirine Using Physiologically Based Pharmacokinetic Modeling

Rajith K. R. Rajoli,[1] Paul Curley,[1] Justin Chiong,[1] David Back,[1] Charles Flexner,[2] Andrew Owen,[1] and Marco Siccardi[1]



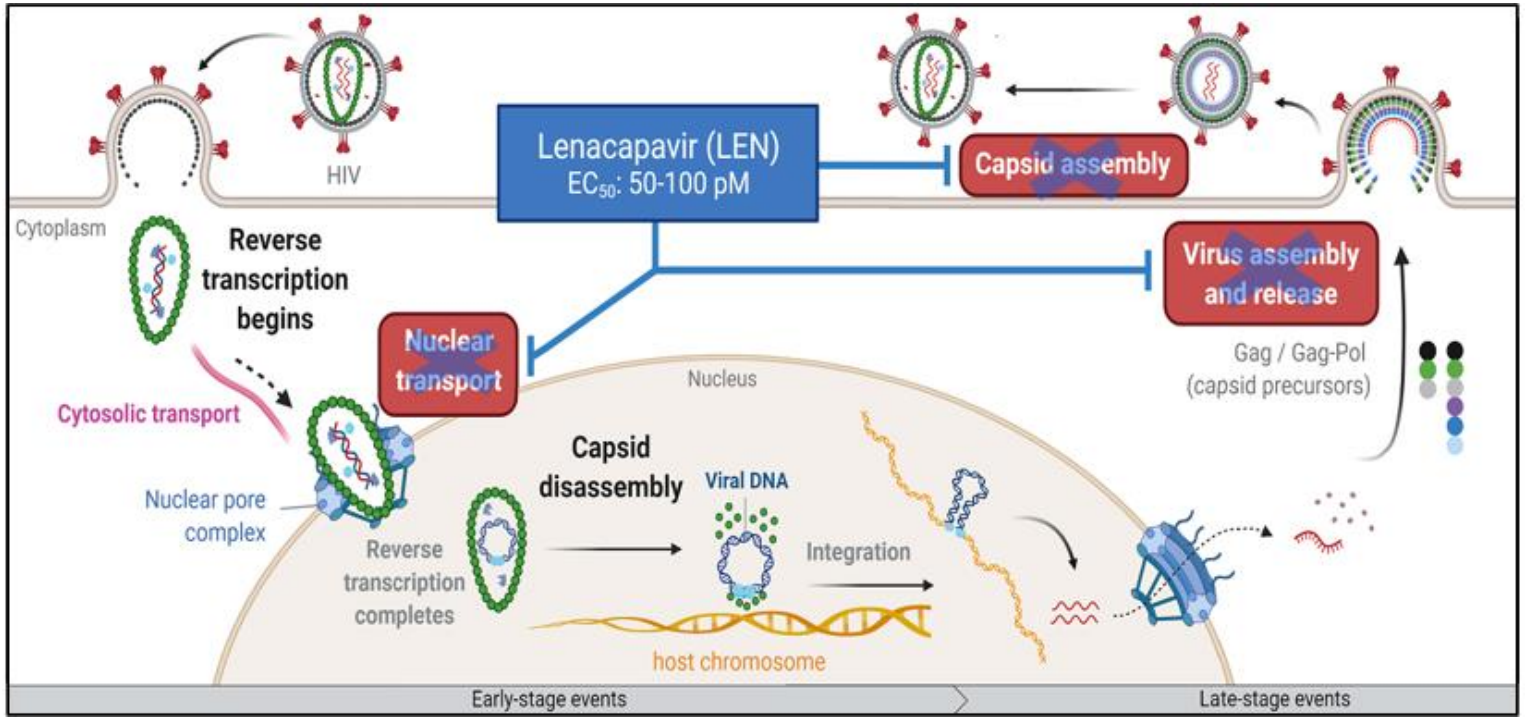


Lenacapavir

LEN Targets Multiple Stages of the HIV Replication Cycle

LEN binding directly between capsid protein subunits and inhibits 3 essential steps of the viral lifecycle:

1. Capsid-mediated nuclear uptake of HIV proviral DNA
2. Virus assembly and release
3. Capsid core formation

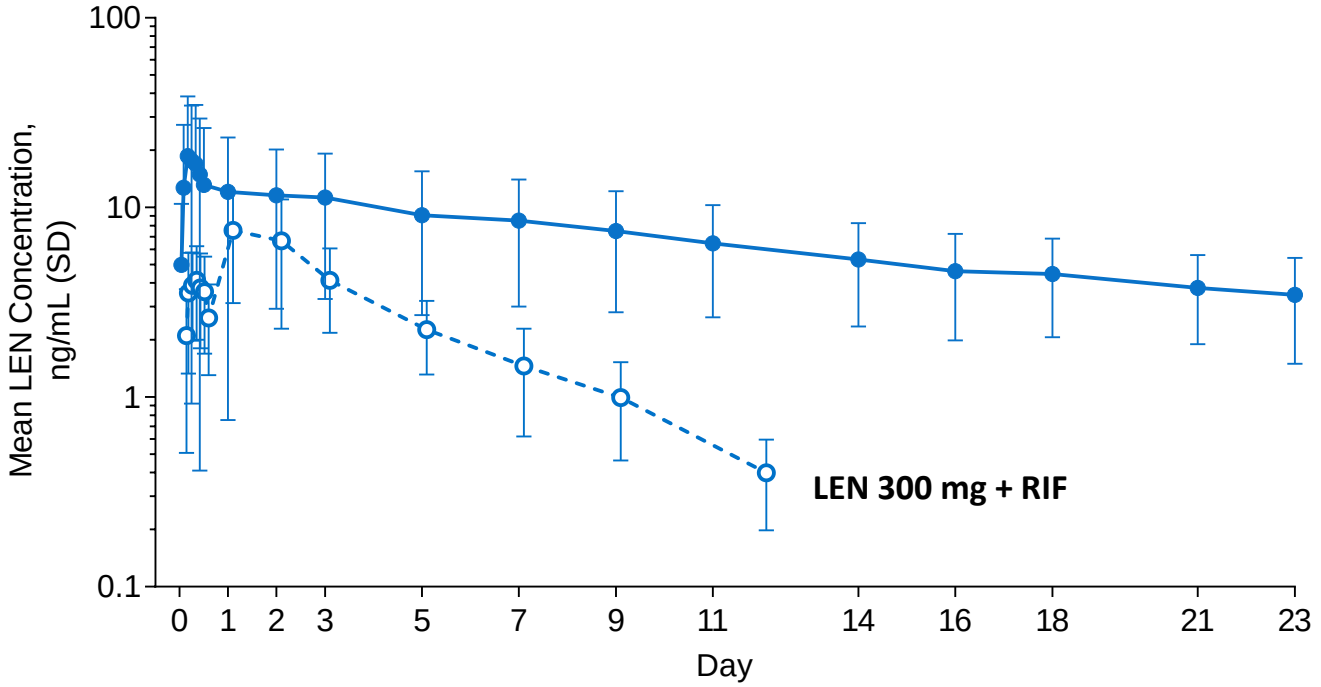


LEN modulates the stability and/or transport of capsid complexes, leading to inhibition of multiple processes in the HIV lifecycle

Date of issue of marketing authorisation valid throughout the European Union	17/08/2022

Lenacapavir as victim for DDIs

Lenacapavir is a substrate of CYP3A, P-gp and UGT1A1.



85% Decrease in LEN AUC

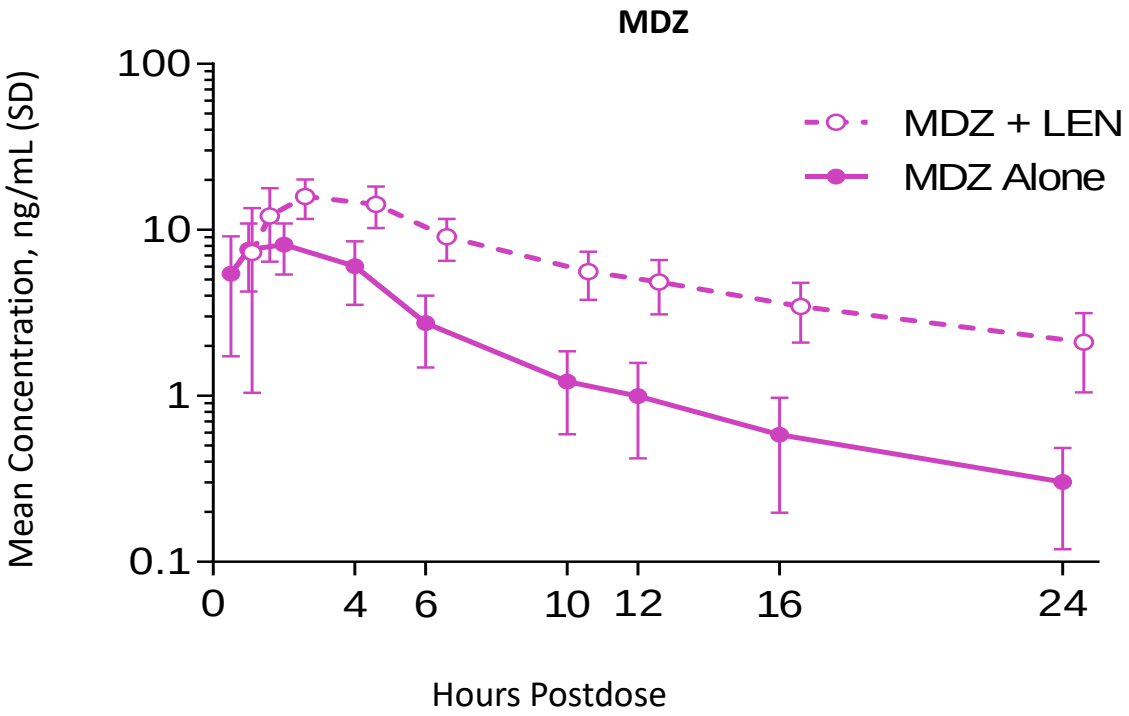
LEN + RIF coadministration contraindicated

RFB, EFV, ETR, anticonvulsants… contraindicated/not recommended

Begley R. CROI 2021.

Lenacapavir as perpetrator for DDIs

LEN is a moderate inhibitor of CYP3A

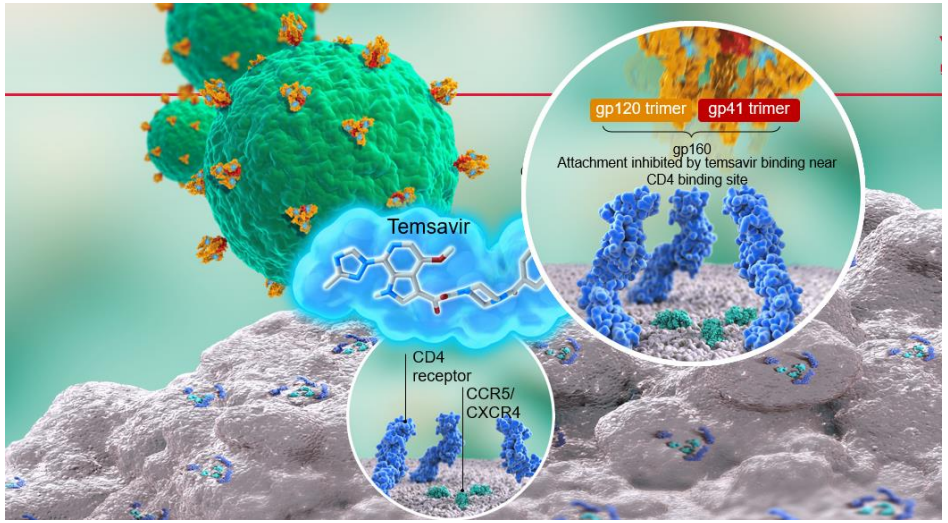


3.3x (3.1–3.6x) Increase in MDZ AUC

Caution with LEN coadministration with sensitive CYP3A substrates

Fostemsavir

- Prodrug metabolized to temsavir (TMR), a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T cell[1,2]
- Unique resistance profile with no *in vitro* cross-resistance to other antiretroviral (ARV) classes[3,4] and activity regardless of HIV-1 tropism[3-6]



Date of issue of marketing authorisation valid throughout the European Union

04/02/2021

1. Brown et al. *J Pharm Sci.* 2013;102:1742-1751. **2.** Langley et al. *Proteins.* 2015;83:331-350. **3.** Nowicka-Sans et al. *Antimicrob Agents Chemother.* 2012;56:3498-3507. **4.** Li et al. *Antimicrob Agents Chemother.* 2013;57:4172-4180. **5.** Ray et al. *J Acquir Immune Defic Syndr.* 2013;64:7-15. **6.** Zhou et al. *J Antimicrob Chemother.* 2014;69:573-581.

Temsavir is a substrate of P-gp, BCRP and CYP3A4

Concomitant Drug Class: Drug Name	Effect on Concentration of Temsavir and/or Concomitant Drug	Clinical Comment
Androgen receptor inhibitor: Enzalutamide	↓ **Temsavir**	Coadministration is contraindicated due to potential for loss of therapeutic effect to RUKOBIA.
Anticonvulsants: Carbamazepine Phenytoin	↓ **Temsavir**	
Antimycobacterial: Rifampin	↓ **Temsavir**	
Antineoplastic: Mitotane	↓ **Temsavir**	
Herbal product: St John's wort *(Hypericum perforatum)*	↓ **Temsavir**	

Temsavir inhibits OATP1B1/3 and BCRP

Concomitant Drug Class: Drug Name	Effect on Concentration of Temsavir and/or Concomitant Drug	Clinical Comment
Hepatitis C virus direct-acting antivirals: Grazoprevir Voxilaprevir	↑ **Grazoprevir** ↑ **Voxilaprevir**	Coadministration may increase exposures of grazoprevir or voxilaprevir; however, the magnitude of increase in exposure is unknown. Increased exposures of grazoprevir may increase the risk of ALT elevations. Use an alternative HCV regimen if possible.
Oral contraceptive: Ethinyl estradiol	↑ **Ethinyl estradiol**	**Ethinyl estradiol daily dose should not exceed 30 mcg.** Caution is advised particularly in patients with additional risk factors for thromboembolic events.
Statins:		
Rosuvastatin	↑ **Rosuvastatin**	Use the lowest possible starting dose for statins and monitor for statin-associated adverse events.
Atorvastatin	↑ **Atorvastatin**	
Fluvastatin	↑ **Fluvastatin**	
Pitavastatin	↑ **Pitavastatin**	
Simvastatin	↑ **Simvastatin**	

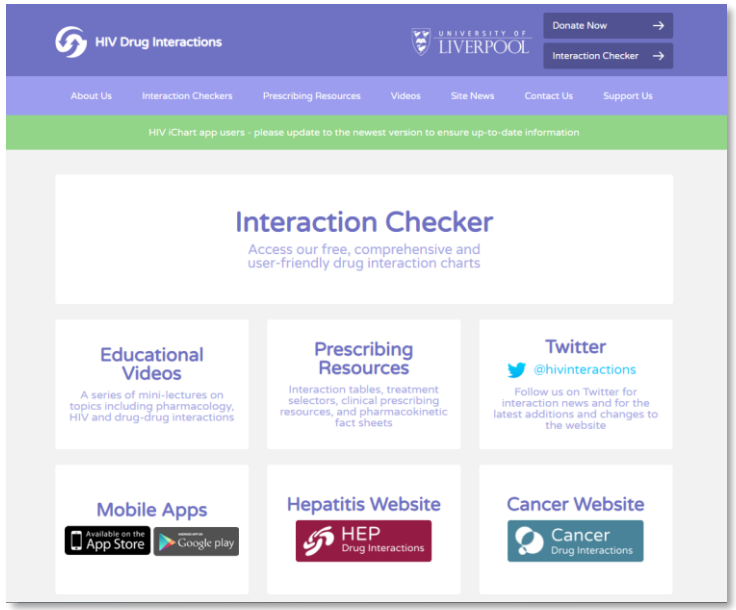
A stepwise approach to DDI management

Note all co-medications (prescribed, OTC and herbal products)

Consult pharmacist and online resources

Consider the nature of any interaction and whether an alternative to an ‘interacting drug’ is possible.

Some interactions can be managed by dose adjustment with careful monitoring



http://www.interaccionesvih.com/

http://www.clinicalcasesddis.com/

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Thank you!