Relevant Drug-Drug Interactions in 2018

Impact on ART Choice

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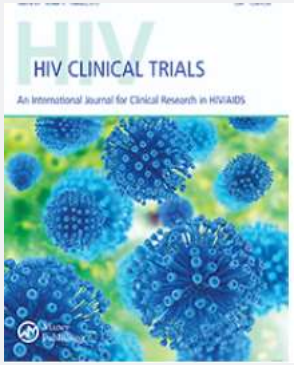
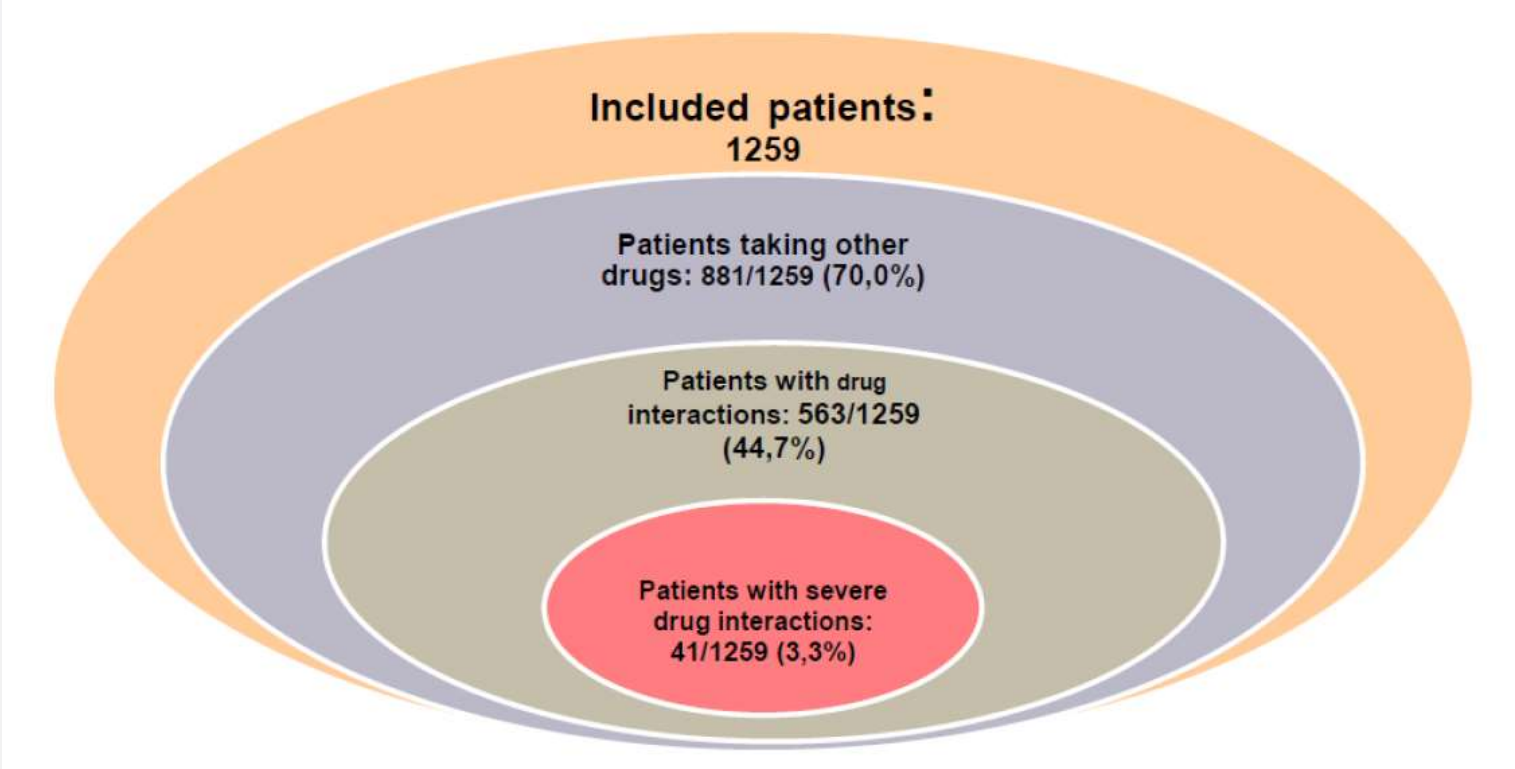
Frequency and severity of potential drug interactions in a cohort of HIV-infected patients Identified through a Multidisciplinary team





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Molas E, et al. HIV Clin Trials 2018;19:1-7

Scenarios for DDIs in Clinical Practice

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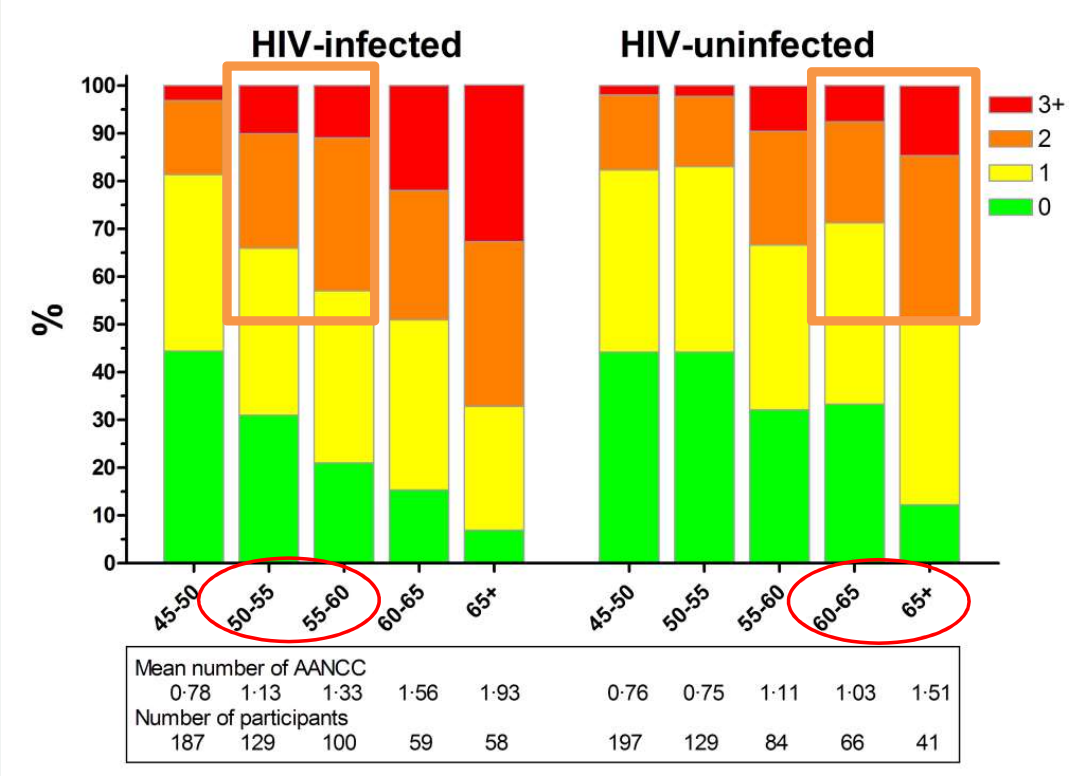
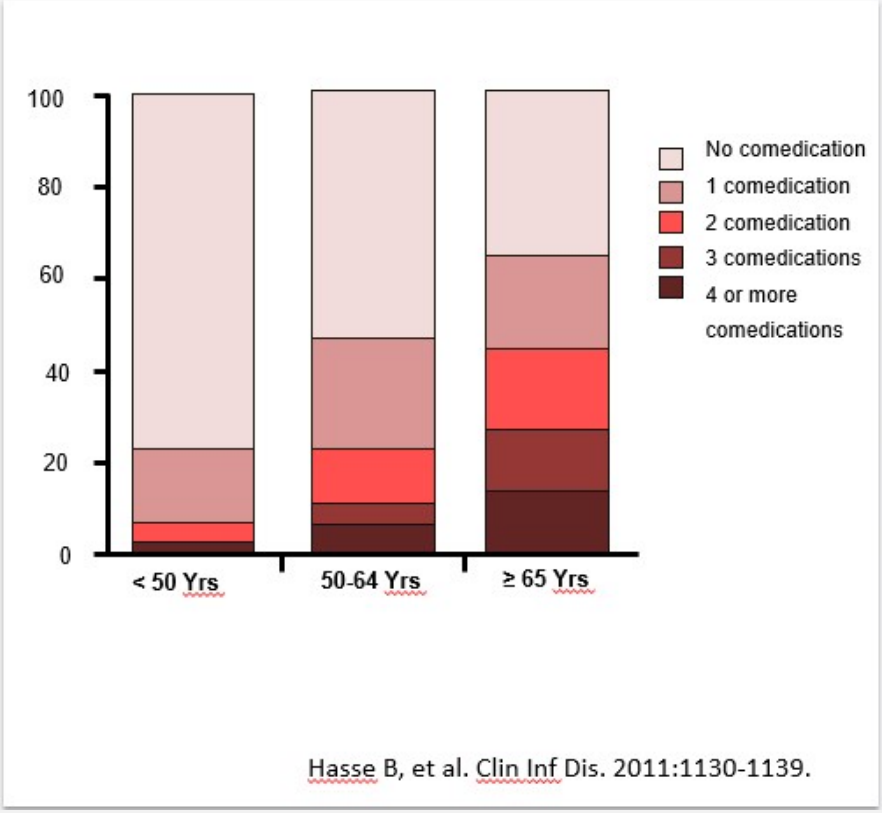
Aging, polypharmacy & DDIs



Schouten J, et al. Clin Infect Dis. 2014;59:1787–97



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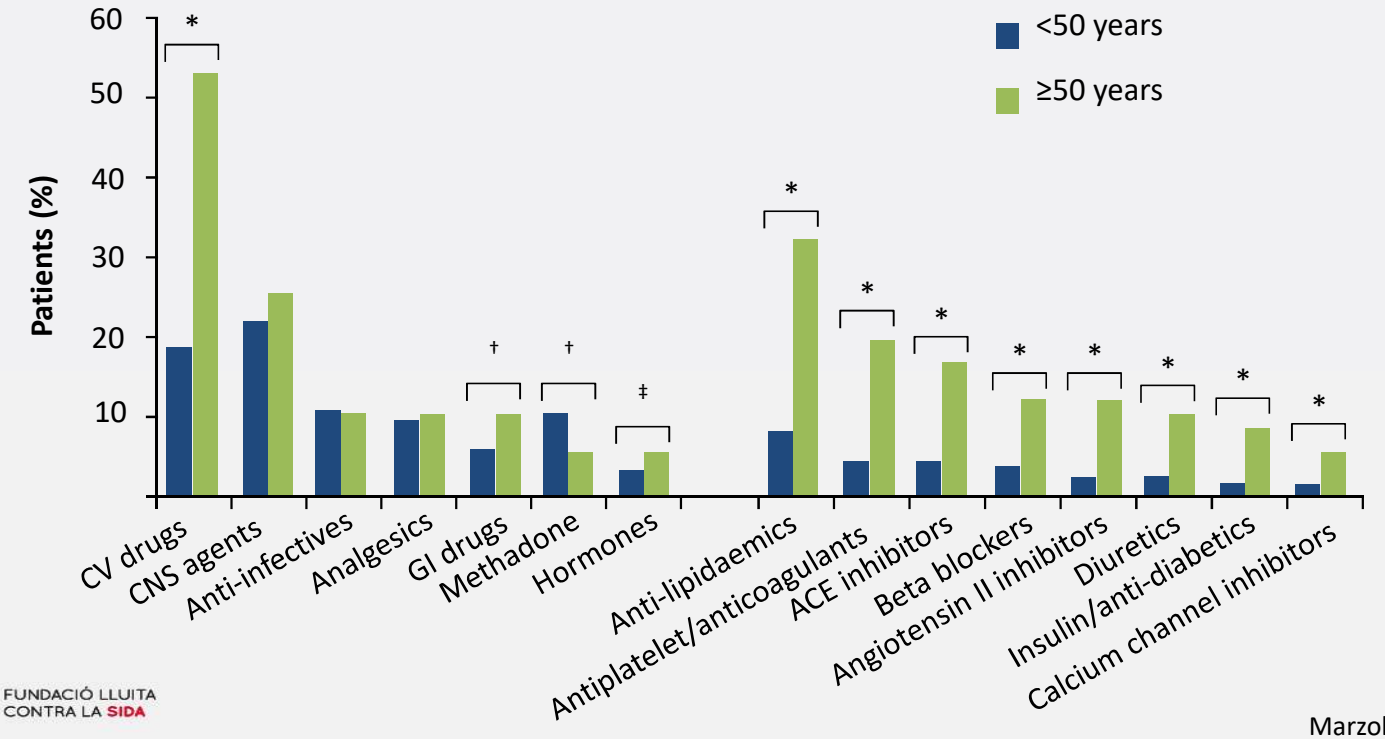
Co-medications in the Swiss Cohort Study

Prospective study of 1,497 PLWHIV scheduled for a SHCS follow up visit once from 2008–2009, to compare the use of co-medication according to age <50 versus ≥50 years

Therapeutic drug classes used in PLWHIV aged <50 versus ≥50 years[2]



Potential DDIs

35% pts <50 years

51% pts >50 years

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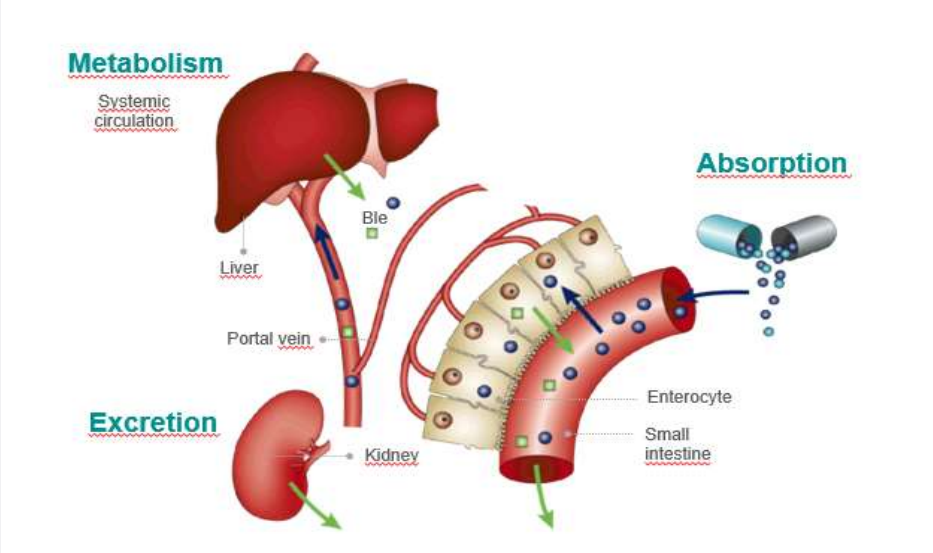
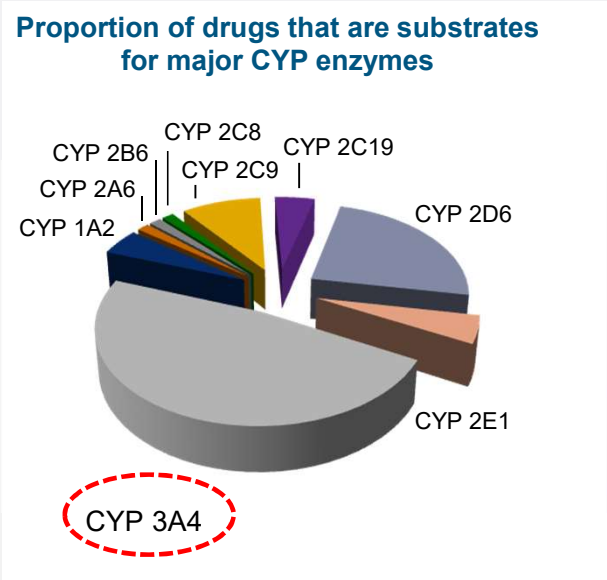
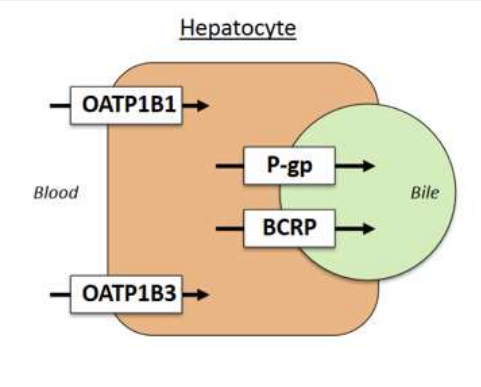
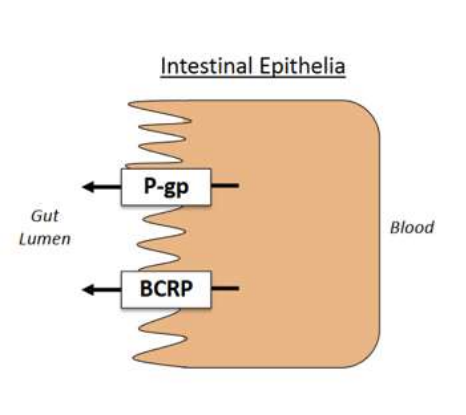
Marzolini C et al. J Antimicrob Chemother 2011;66:2107–2111









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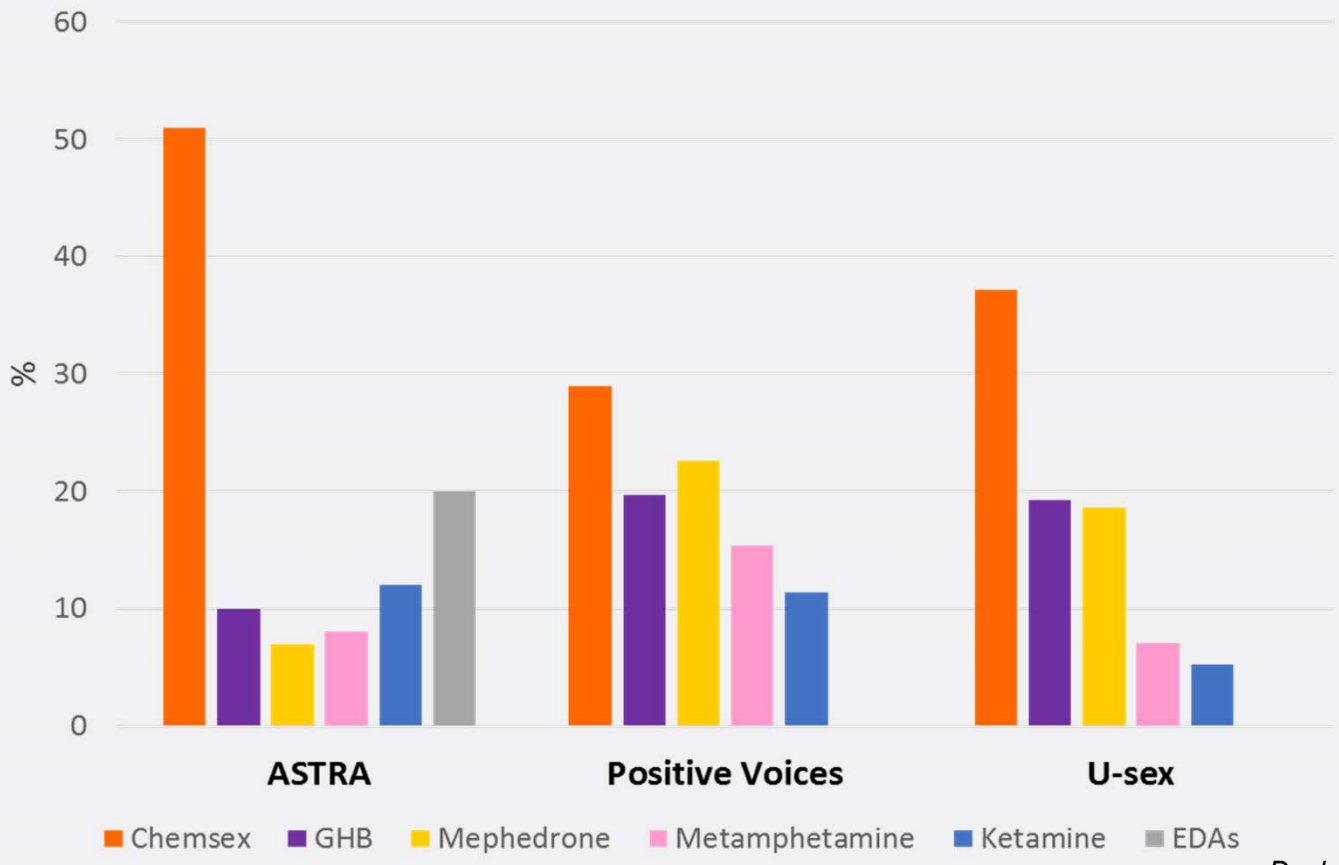
Scenarios for DDIs in Clinical Practice

Chemsex in MSM; HIV+



Daskaopaoulou M, et al. Lancet 2014
Pufall EL, et al. CROI 2016
Ryan P, et al, GESIDA 2016

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Pufall EL, et al. CROI 2016
Ryan P, et al. GESIDA 2016

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Recreational drugs. Metabolic pathways

Drug	Mephedrone	Methamphe - tamine	GHB	MDMA	Cocaine	Erectile dysfunction agents	Ketamine
Metabolic pathway	CYP2D6	CYP2D6	CYP2D6	CYP2D6	Esterases 10% CYP3A4	CYP3A4	CYP3A4

CYP450 enzyme IC_{50}(μM)	1A2	2B6	2C8	2C9	2C19	2D6	3A
COBI	>25	2.8	30	>25	>25	9.2	0.2
RTV	>25	2.9	5.5	4.4	>25	2.8	0.2

$C_{max} \approx 2.2$ μM

$C_{max} \approx 1.2$ μM

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German et al. 12th IWCPHT 2011

Management of DDIs in the Clinic

- **Proactive attitude**
- **Identify all drugs taken by the patient**

  Centralized medication history
- **Review the therapeutic regimen**

  Promote interdisciplinary communication
- **Skills on electronic resources to identify DDIs**

  Electronic prescribing systems / databases on DDIs

Co-meds and potential for DDIs

Highest potential	Moderate potential	Low potential
Simvastatin	Atorvastatin, Rosuvastatin	Pitavastatin
Quetiapine Midazolam, Triazolam Hypericum	Risperidone Diazepam, Zolpidem Trazodone, Mirtazapine	Olanzapine Lorazepam, Temazepam Escitalopram, Venlafaxine
Fluticasone, Budesonide Triamcinolone	Beclometasone	
Alfuzosine	Tamsulosine	Finasteride

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ART and potential for DDIs

Highest potential	Moderate potential	Low potential
Boosted PI Perpetrators – enzyme & transporters inhibition Victims – absorption (ATV); induction	**Rilpivirine** Victim of enzymatic induction/inhibition. Absorption	**Raltegravir** Victim of few induction & absorption interactions
EVG/cobi Perpetrator – enzyme & transporters inhibition Victim – absorption (ATV); induction	***Maraviroc*** Victim of enzymatic induction/inhibition ←	**NRTIs** Victims of few transporter-mediated interactions **TAF vs TDF**
Efavirenz, *Nevirapine, Etravirine* Perpetrators – enzyme & transporters induction	**Dolutegravir** Victim of few induction & absorption interactions Perpetrator of few interactions (transporter inhibition)	

www.hiv-druginteractions.org

Spanish ART guidelines Jan 2018

3er Fármaco	Pauta†	Comentarios‡
Preferentes. Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.		
INI	DTG/ABC/3TC	ABC está contraindicado en pacientes con HLA-B*5701 positivo
	DTG+FTC/TAF	
	RAL+FTC/TAF	RAL puede administrarse indistintamente como 1 comprimido de 400 mg cada 12 horas, o 2 comprimidos de 600 mg (nueva formulación) cada 24 horas*.
Alternativas. Pautas eficaces, pero que no se consideran preferentes bien porque su eficacia ha resultado inferior a las pautas preferentes en ensayos clínicos o porque tienen desventajas potenciales o restricciones en su indicación. Pueden ser, sin embargo, de elección en subgrupos de pacientes o en casos especiales		
INI	EVG/c/FTC/TAF	Mayor potencial de interacciones que otras pautas basadas en INI
IP potenciado	DRV/c/FTC/TAF* o	Puede considerarse de elección cuando se requiera de una pauta con elevada barrera genética (pacientes con problemas de adherencia)
	DRV/p+FTC/TAF**	Es imprescindible evaluar posibles interacciones
ITINN	RPV/FTC/TAF*	No indicado en pacientes con CVP >100.000 copias/mL Puede considerarse de elección en pacientes con CVP <100.000 copias/mL Realizar previamente un estudio genotípico que descarte mutaciones de resistencia a ITINN Contraindicado si se utilizan inhibidores de la bomba de protones Se debe tomar siempre con una comida

Scenarios for DDIs in Clinical Practice

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Self-prescribed / OTC

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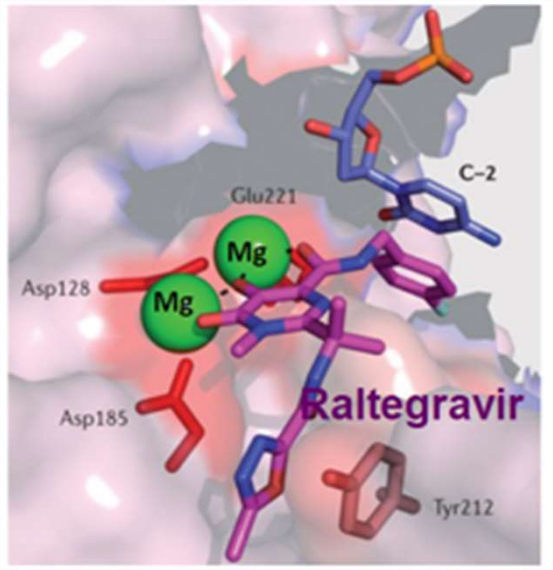
Integrase inhibitors quelation

Binding of integrase inhibitor

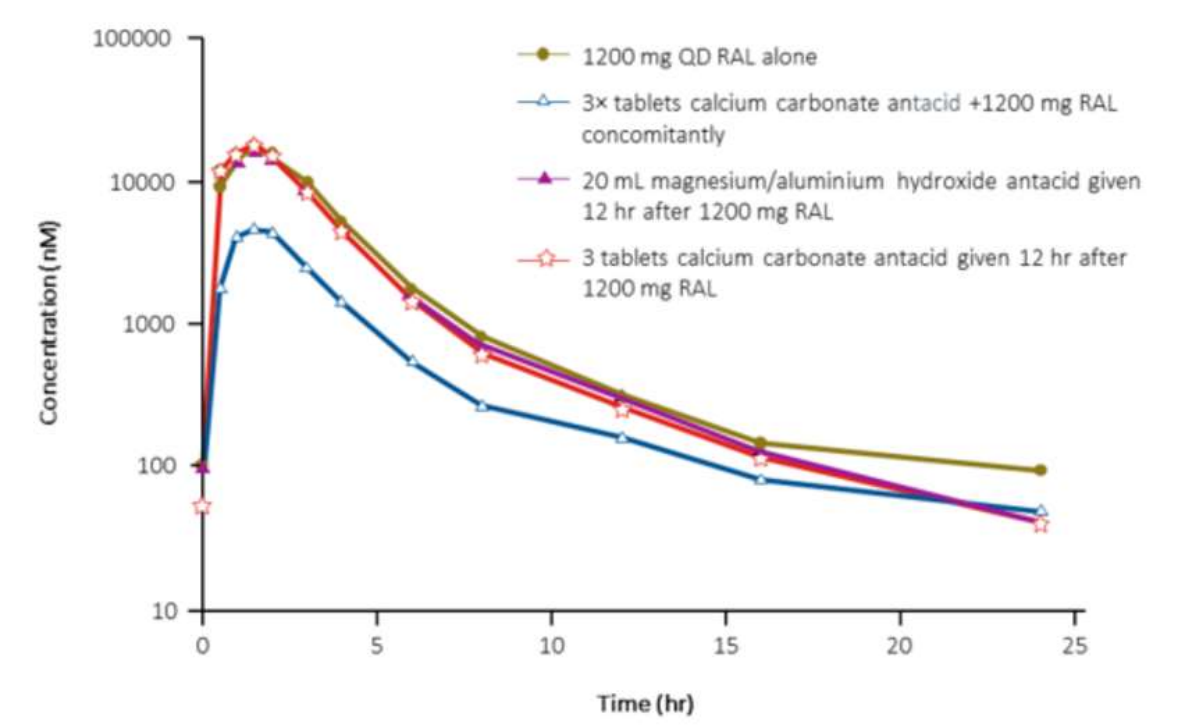


		Mg / Al	Ca	Fe	Multivitaminas
DTG	AUC	↓ 74%	↓ 39%	↓ 54%	↓ 33%
	Cmax	↓ 72%	↓ 37%	↓ 57%	↓ 35%
	Cmin		↓ 39%	↓ 56%	↓ 32%
EVG	AUC	↓ 45%			
	Cmax	↓ 41%			
	Cmin	↓ 47%			
RAL	AUC	↓ 49%	↓ 55%		
	Cmax	↓ 44%	↓ 52%		
	Cmin	↓ 63%	↓ 32%		

Effect of metal-cation antacids on the pharmacokinetics of 1200 mg raltegravir

Krishna R et al. J Pharm Pharmacol 2016;68:1359-65.

JPP
Journal of Pharmacy
And Pharmacology



	GMR		
	Calcium carbonate concomitantly	Calcium carbonate 12h after RAL	Mg/Al antacid 12h after RAL
C_{max}	0.26	0.98	0.86
AUC_{0-24}	0.28	0.90	0.86
C_{24}	0.52	0.43	0.42

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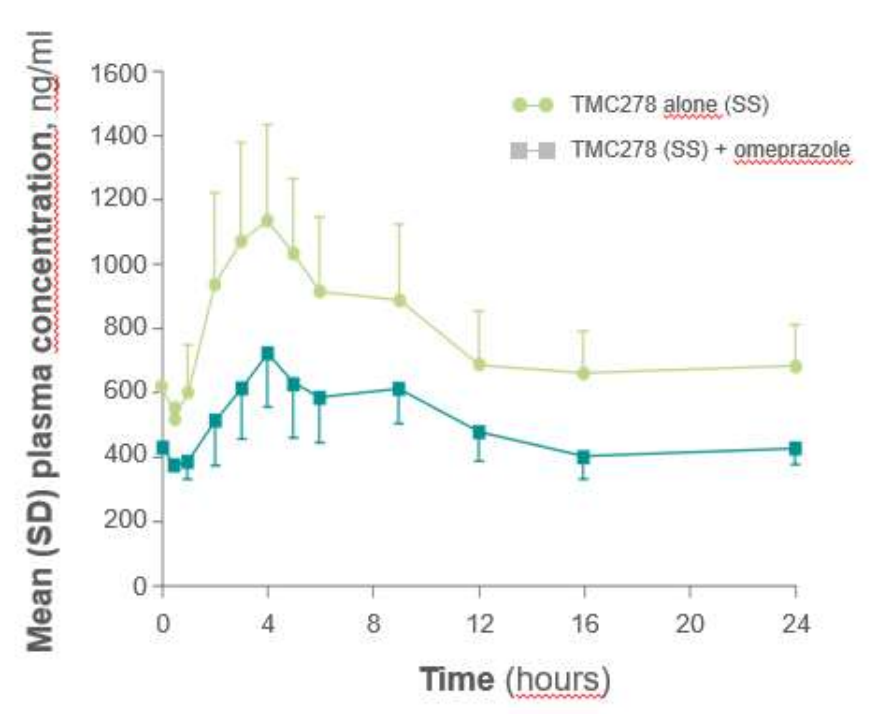
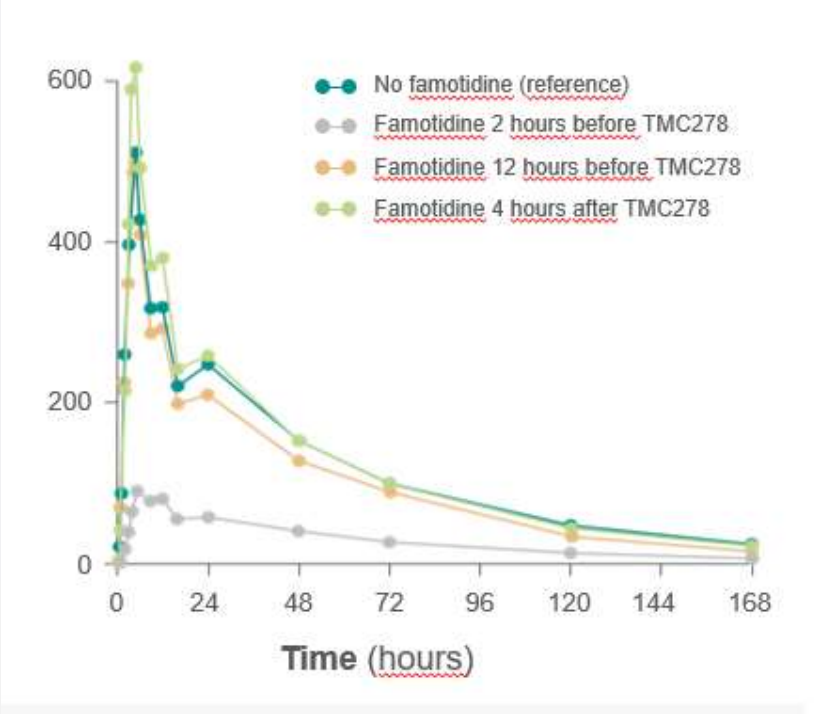
Rilpivirine & Gastric pH





Omeprazole was the most prescribed drug in 2016 in Catalonia

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

Summary / Considerations

→ **Drug interactions with ART are frequent in clinical practice…..**

… but not all them are equally relevant

→ **It is important to consider the DDI potential (and relevance) of each drug**

… antiretrovirals and co-meds

… influence in ART choice

→ **The DDI potential may vary among different scenarios**

… one recommendation may not fit all situations

Thank you