Polipatología, polifarmacia e interacciones relevantes de las pautas preferentes en las guías de TARV.

José Moltó, MD PhD

Fundació Lluita contra la Sida, Badalona, Spain.

Servicio Enfermedades Infecciosas, Hospital Universitari Germans Trias i Pujol,

Universitat Autònoma de Barcelona (UAB), Barcelona, Spain.

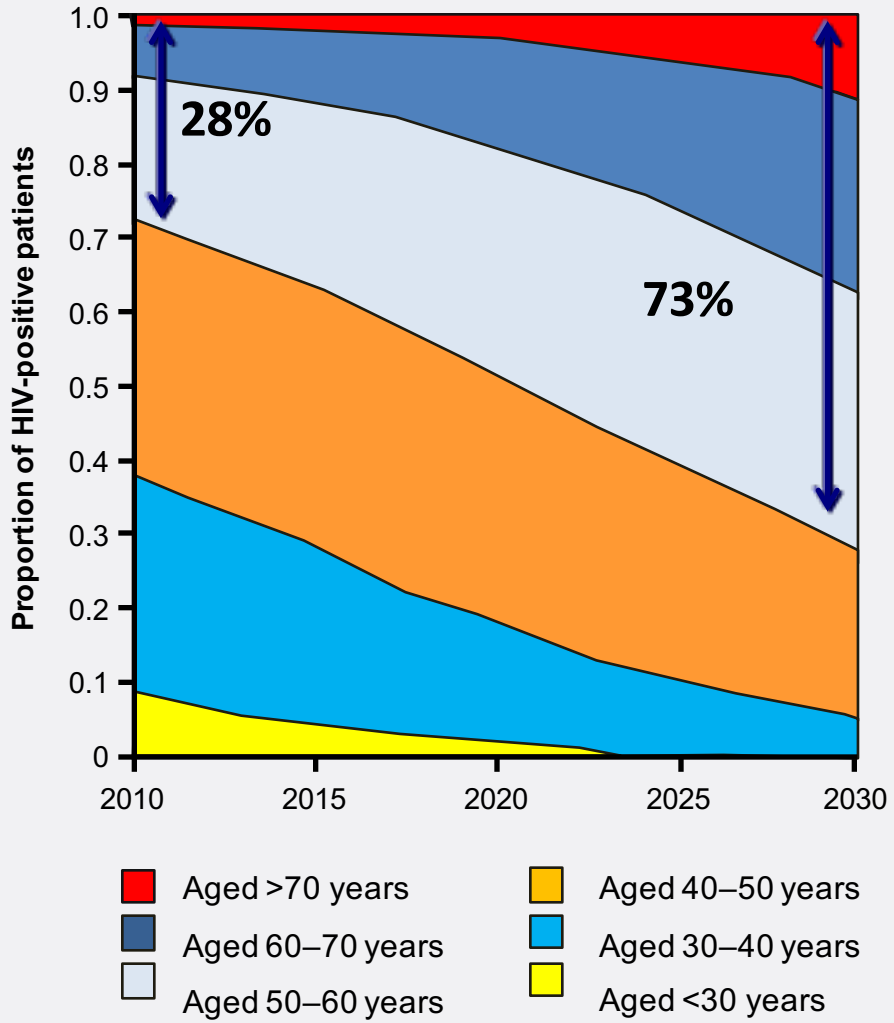
Tractament Antiretroviral i Pràctica Clínica.
Barcelona 20 Junio 2017

FUNDACIÓ LLUITA CONTRA LA SIDA

La población de pacientes añosos crece cada vez más

- ATHENA: Observational cohort of 10,278 HIV-positive pts in the Netherlands

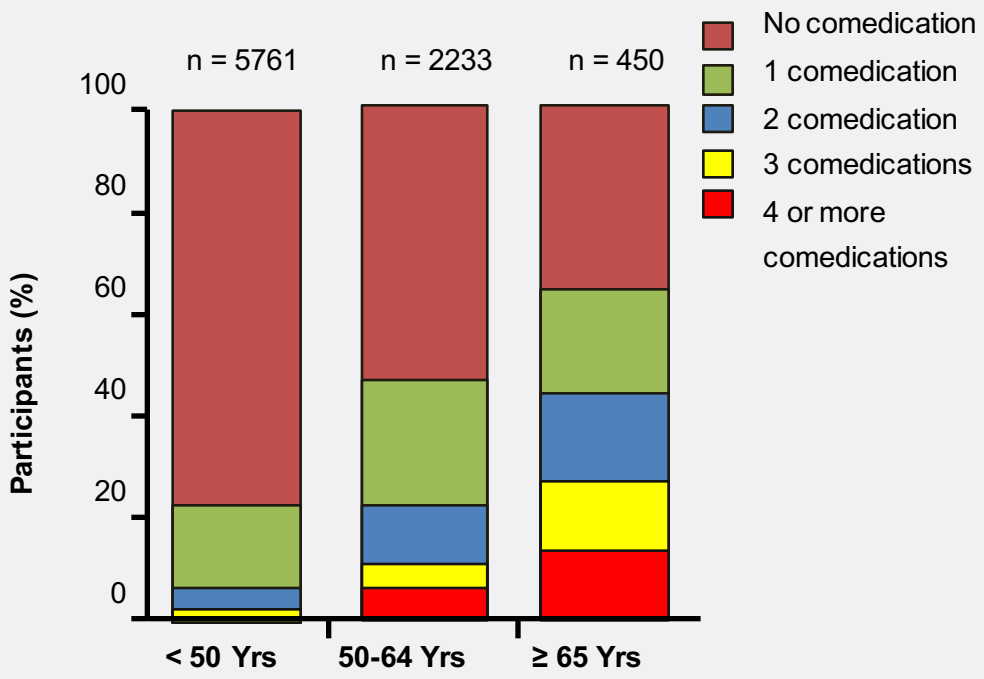
- **Modeling study projections:**
  - Proportion of HIV-positive pts ≥ 50 yrs of age to increase from 28% in 2010 to 73% in 2030
  - Median age of HIV-positive pts on combination ART to increase from 43.9 yrs in 2010 to 56.6 yrs in 2030



Smit M, et al. Lancet Infect Dis 2015;15:810–8

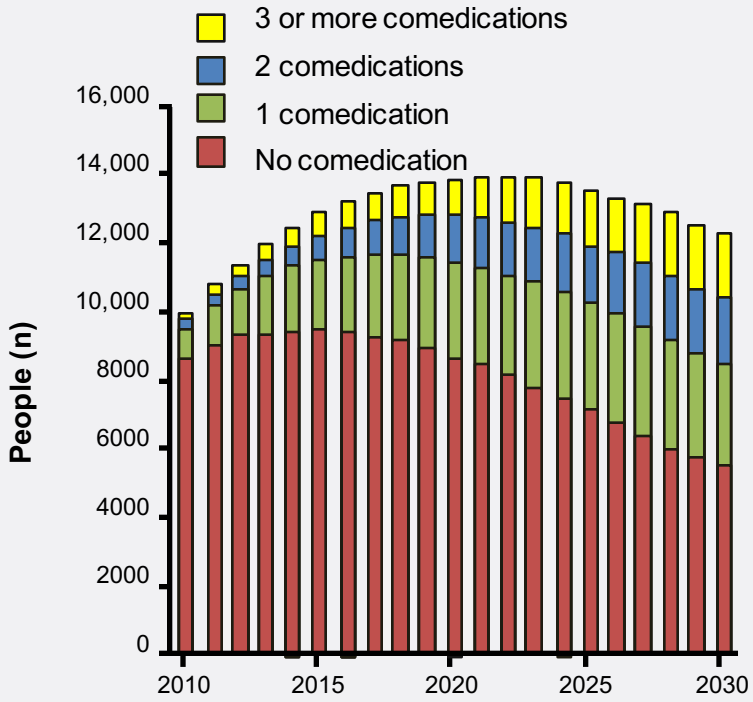
La polifarmacia cada vez es/será más frecuente

Swiss HIV Cohort Study (N = 8444)
Prospective Observational study



115 (5.2%) of 2233 participants 50-64 yrs of age and 64 (14.2%) of 450 participants ≥ 65 yrs of age received ≥ 4 meds other than ART

ATHENA Modeling Study



Predicts that 20% of pts will be taking ≥ 3 meds other than ART in 2030

Hasse B, et al. Clin Inf Dis. 2011:1130-1139.
Smit M, et al. Lancet Infect Dis. 2015;15:810-818.

Los pacientes >50 años presentan interacciones medicamentosas con mayor frecuencia (Swiss Cohort Study)

1497 pacientes
(1020 <50; 477 ≥50 años)

Interacciones potencialmente relevantes

- 51% pts >50 años *vs.* 35% pts <50 años

Fármacos implicados

- **Agentes cardiovasculares** (hipolipemiantes, antiagregantes/anticoagulants, antihipertensivos, antidiabéticos)
- **Sistema nervioso central** (ansiolíticos hipnóticos, antidepresivos, antipsicóticos, antiepilépticos)
- **Antirretrovirales** (IP, ITINAN)

FUNDACIÓ LLUITA CONTRA LA SIDA

Marzolini C. JAC 2011;66:2107-2111.

Envejecimiento / polifarmacia en pacientes VIH. HUGTIP

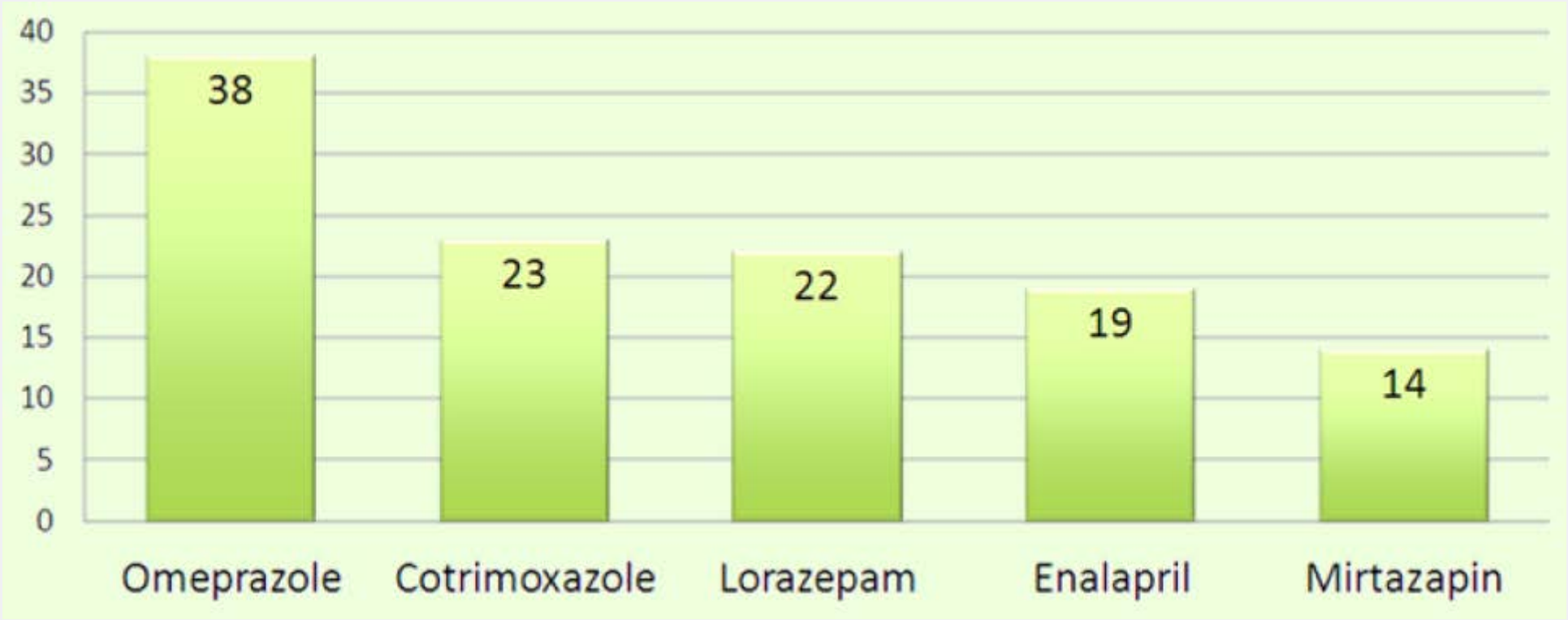
	Group A (<35 years old)	Group B (35-50 years old)	Group C (51-64 years old)	Group D (From 65 years old)
Patients (%)	68 (21.9)	149 (47.9)	80 (25.7)	14 (4.5)
Patients with CO (% of each group)	27 (39%)	80 (53%)	60 (75%)	12 (85%)
Co-medication mean score	3.09	4.66	5.53	7.29
ATC families (%)	NS: 9 patients (13%) AI: 5 patients (7.3%) MS: 4 patients (5.8%)	NS: 45 patients (30.2%) ATM: 28 patients (18%) CV: 21 patients (14%) BH: 21 patients (14%)	NS: 36 patients (45%) CV: 27 patients (33.7%) ATM: 26 patients (32.5%)	CV: 9 patients (64%) ATM: 8 patients (57%) BH: 7 patients (50%)

NS	Nervous system	**ATM**	Alimentary tract and metabolism
AI	Anti-infectives	**CV**	Cardiovascular
MS	Musculoskeletal	**BH**	Blood and Hematopoietic drugs

FUNDACIÓ LLUITA CONTRA LA SIDA

Andreu A. 15th EACS. 2015

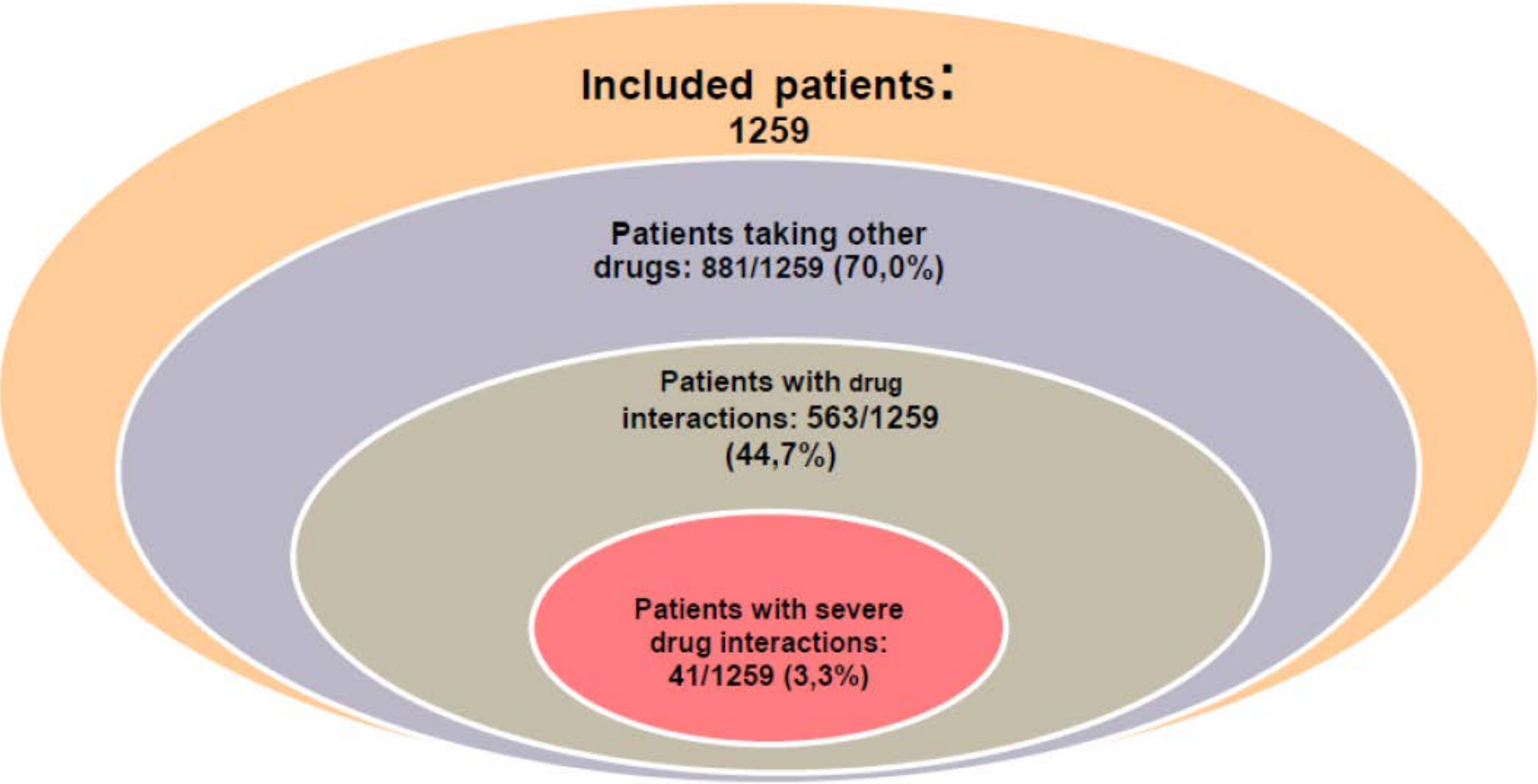
Envejecimiento / polifarmacia en pacientes VIH. HUGTIP



Most prescribed drugs

Andreu A. 15th EACS. 2015

Interacciones medicamentosas en el área metropolitana de Barcelona. H Mar



Knobel H. PE 10/12. 15th EACS 2015

Traffic light summary of DDIs

	Liverpool Website Definition:	GRADE Equivalent *Is it safe to administer both drugs ?*
◆	No clinically significant interaction, or interaction unlikely	YES
44.7% ■	Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration	Probably **YES** if ▪Benefit outweighs risk, or ▪Interaction safely managed Probably **NO** if ▪Risk outweighs benefit ▪Interaction not safely managed
3.3% ●	Interaction likely, do not use or use with caution	NO
∇	No clear data, actual or theoretical	DONT KNOW

FUNDACIÓ LLUITA CONTRA LA SIDA

Adapted from http://www.hiv-druginteractions.org/

Drug interaction (DI) between ART and non-ART by class of ART

NRTIs.

NRTI	Patients N	Patients with DI
FTC	676	22 (3,3%)
3TC	329	15 (4,6%)
TDF	704	57 (8,1%)
ABC	302	27 (8,9%)

NNRTIs.

NNRTI	Patients N	Patients with DI
RPV	180	19 (10,6%)
EFV	240	72 (30,0%)
ETV	80	39 (48,8%)
NVP	163	80 (49,1%)

PI/r.

PI/r	Patients N	Patients with DI
LPV/r	99	43 (43,4%)
ATV/r	71	38 (53,5%)
DRV/r	313	173 (55,3%)

INSTI.

INSTI	Patients N	Patients with DI
RAL	146	13 (8,9%)
DTG	14	2 (14,3%)
EVG/COBI	21	7 (33,3%)

- Among contraindicated interactions: 35 (85.4%) involve a PI and 6 (14.6%) a NNRTI. Represents 7.2% of PI/r exposed and 0.9% of NNRTIs exposed. ($p < 0.0001$)

List of severe or contraindicated drug-drug interactions

ART drug	Other drug	Patients (41)
PI/r		
PI/r	Quetiapine	19 (46,3%)
PI/r	Simvastatin	5 (12,2%)
ATV/r	Omeprazole	3 (7,3%)
PI/r	Ivabradine	2 (4,9%)
PI/r	Midazolam	2 (4,9%)
PI/r	Phenytoin	1 (2,4%)
PI/r	Trazodone	1 (2,4%)
PI/r	Eplerenona	1 (2,4%)
ATV/r	NVP	1 (2,4%)
NNRTI		
RPV	Omeprazole	4 (9,8%)
NVP	Silodosin	1 (2,4%)
RPV	Dexamethasone	1 (2,4%)

Knobel H. PE 10/12. 15th EACS 2015

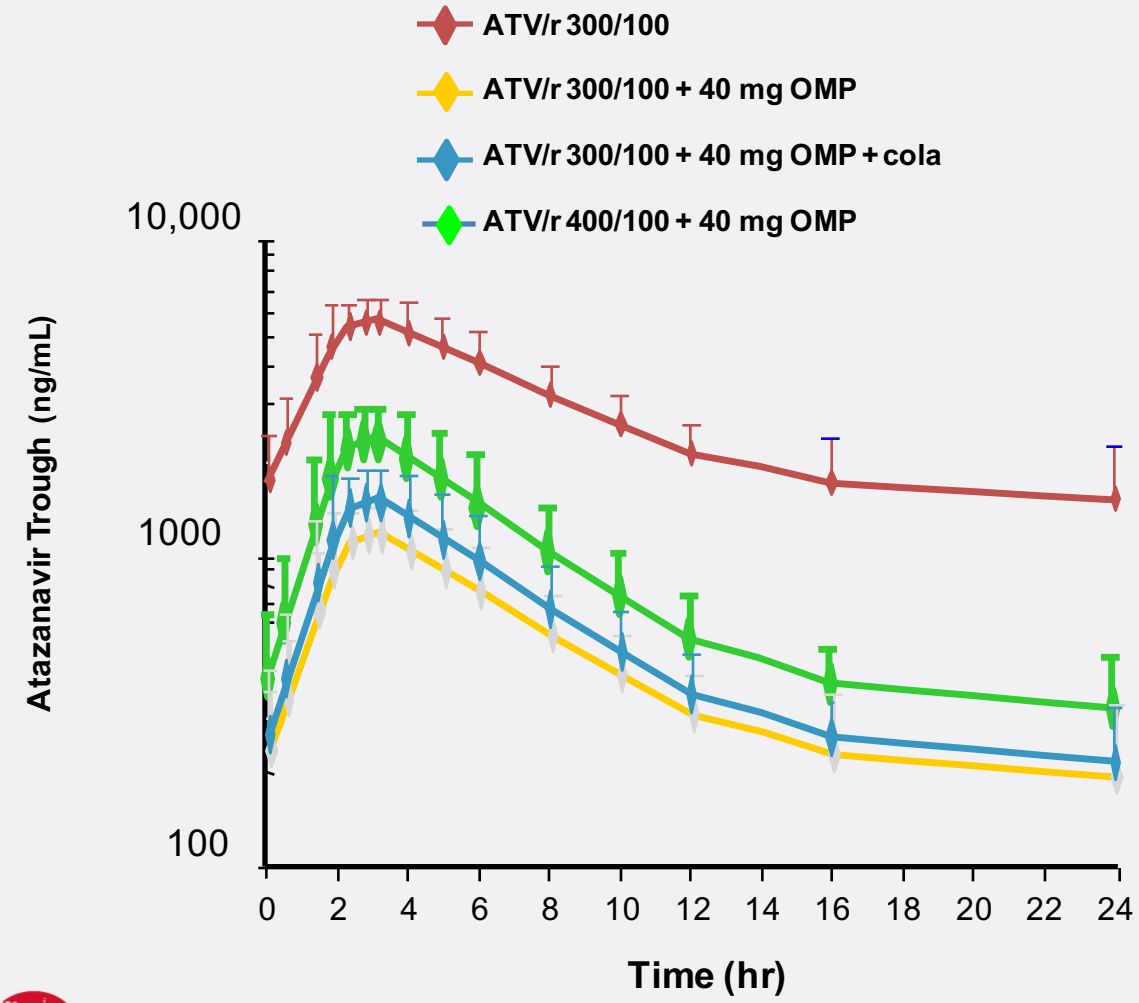
Pautas preferentesTARV (Gesida Enero 2017)

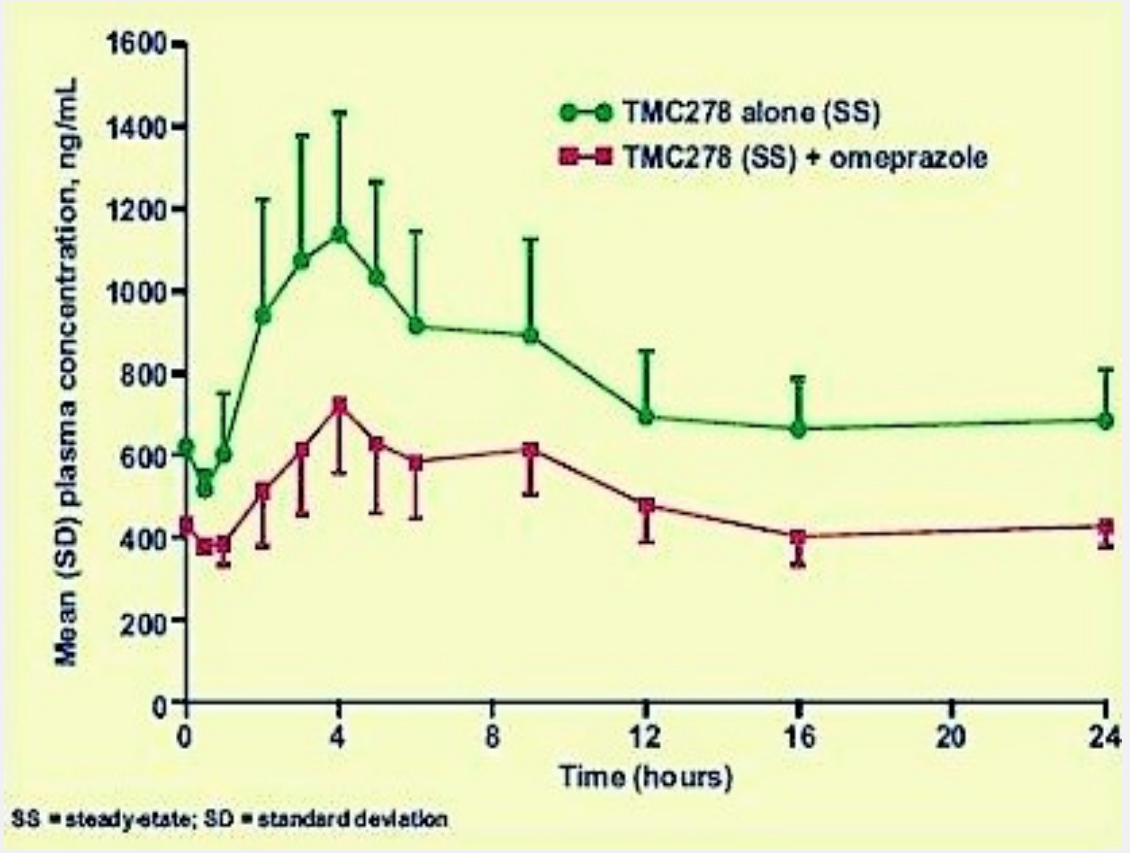
3er Fármaco	Pauta†	Comentarios‡
Preferentes. *Pautas aplicables a la mayoría de los pacientes y que en ensayos clínicos aleatorizados han mostrado una eficacia superior frente a otras o mostrando no-inferioridad presentan ventajas adicionales en tolerancia, toxicidad o un bajo riesgo de interacciones farmacológicas.*		
INI	ABC/3TC/DTG	- ABC está contraindicado en pacientes con HLA-B*5701 positivo; cuando se prescriba se deben tomar las medidas necesarias para tratar de minimizar todos los FRCV modificables - Información escasa en pacientes con CD4+ <200 células/µL
	TFV*/FTC+DTG	- Información escasa en pacientes con CD4+ <200 células/µL
	TFV*/FTC+RAL	
	TAF/FTC/EVG/COBI*	- Información escasa en pacientes con CD4+ < 200 células/µL - Mayor potencial de interacciones que otras pautas basadas en INI

Hipolipemiantes

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	DTG	RAL	E/C/F/TAF	E/C/F/TDF
Statins	Atorvastatin	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↑
	Fluvastatin	↔	↔	↔	↑	↑	↔	↔	↔	↔	↑	↑
	Lovastatin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↑
	Pravastatin	↔	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↑
	Rosuvastatin	↑213%	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑ 38%	↑ 38%
	Simvastatin	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↑
Fibrates	Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑⇑
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Gemfibrozil	↓	↓	↓41%	↔	↔	↔	↔	⇑	⇑	↔	↔
	Ezetimibe	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

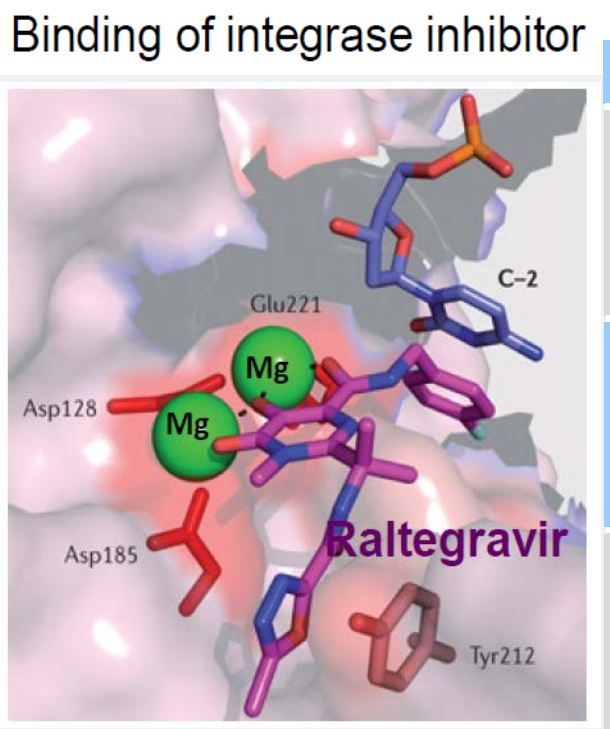
Agentes GI





Agarwala S., et al. CROI 2005, poster 658
Crauwels HM, et al. 9th ICDTHI 2008; Glasgow [P239]

Inhibidores de la integrasa. Quelación por cationes



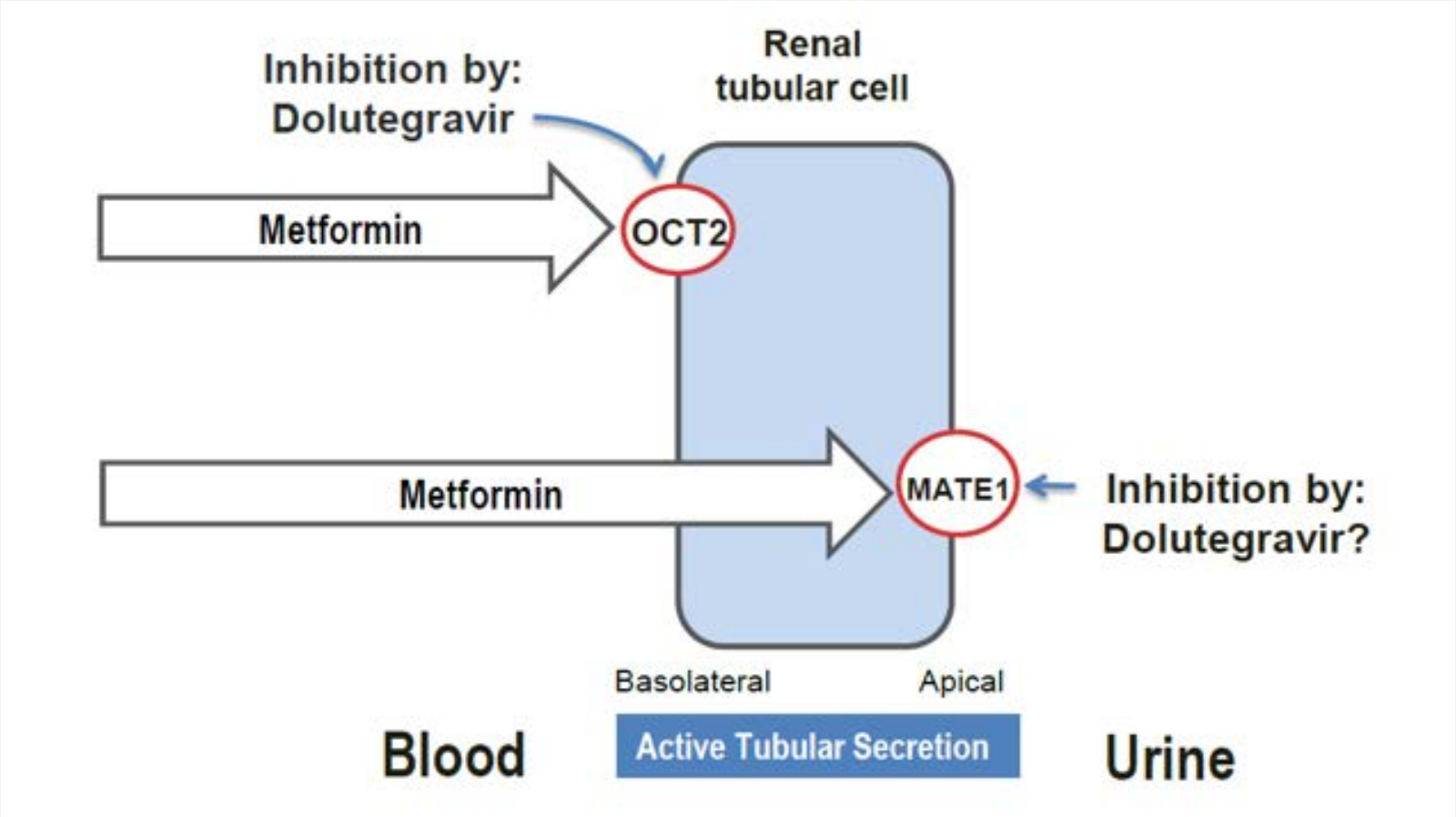
		Mg / Al	Ca	Fe	Multivitaminas
DTG	AUC	↓74%	↓39%	↓54%	↓33%
	Cmax	↓72%	↓37%	↓57%	↓35%
	Cmin		↓39%	↓56%	↓32%
EVG	AUC	↓45%			
	Cmax	↓41%			
	Cmin	↓47%			
RAL	AUC	↓49%	↓55%		
	Cmax	↓44%	↓52%		
	Cmin	↓63%	↓32%		

FT Isentress®
FT Stribild®
FT Tivicay®

Agentes GI. Tabla resumen

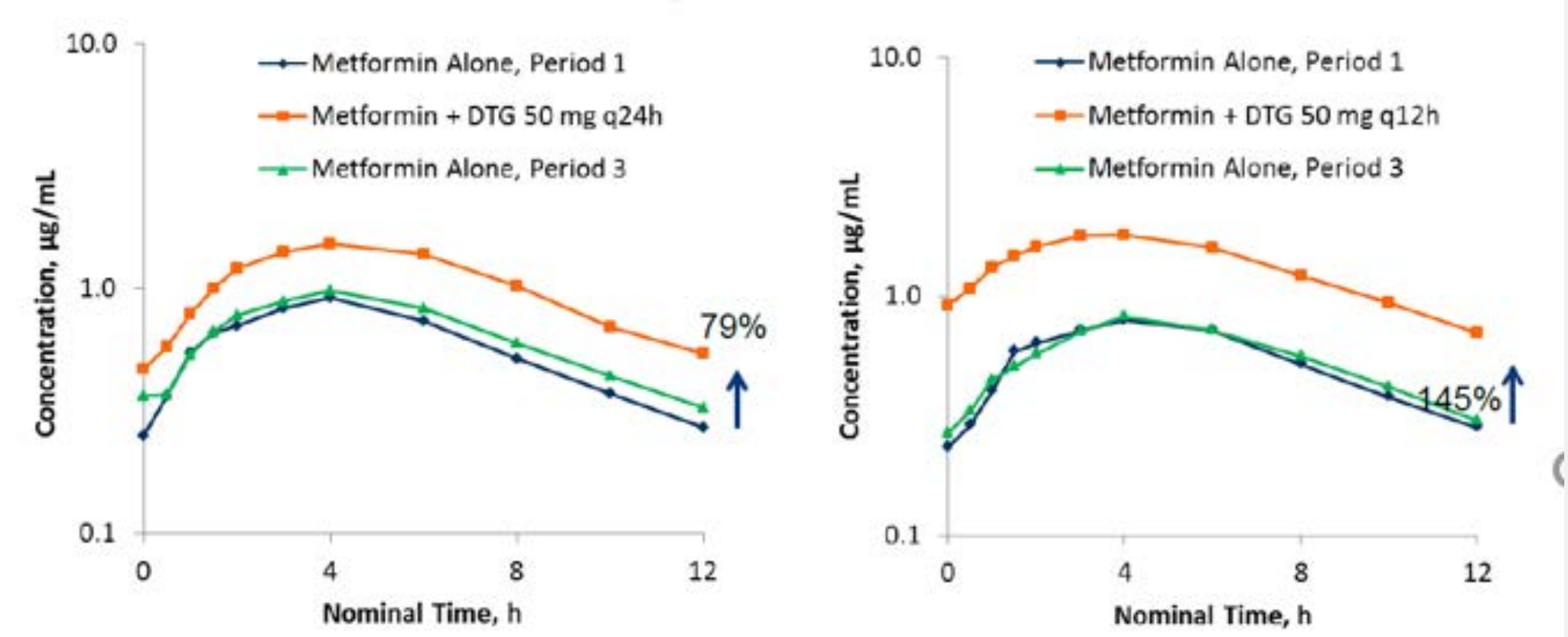
	Antiácidos	Anti-H1	IBP
Darunavir			
Atazanavir			
Rilpivirina			
Raltegravir			
Dolutegravir			
Elvitegravir			

Metformina



Song IH, et al. JAIDS 2016; 72:400-407.

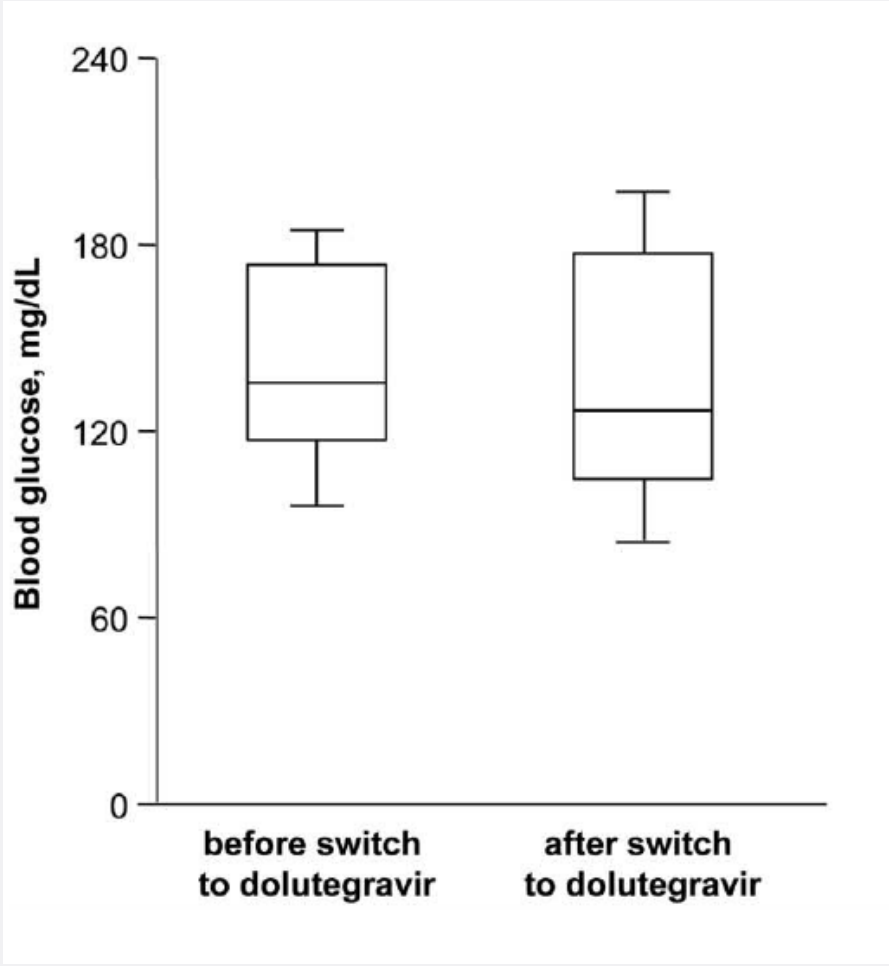
Metformina



Song IH, et al. JAIDS 2016; 72:400-407.

Metformina

How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life?



Therapeutic range 0.13 – 90 mg/L
No clear PK/PD relationship
No increased AEs with other OCT2 inhib or polymorphisms

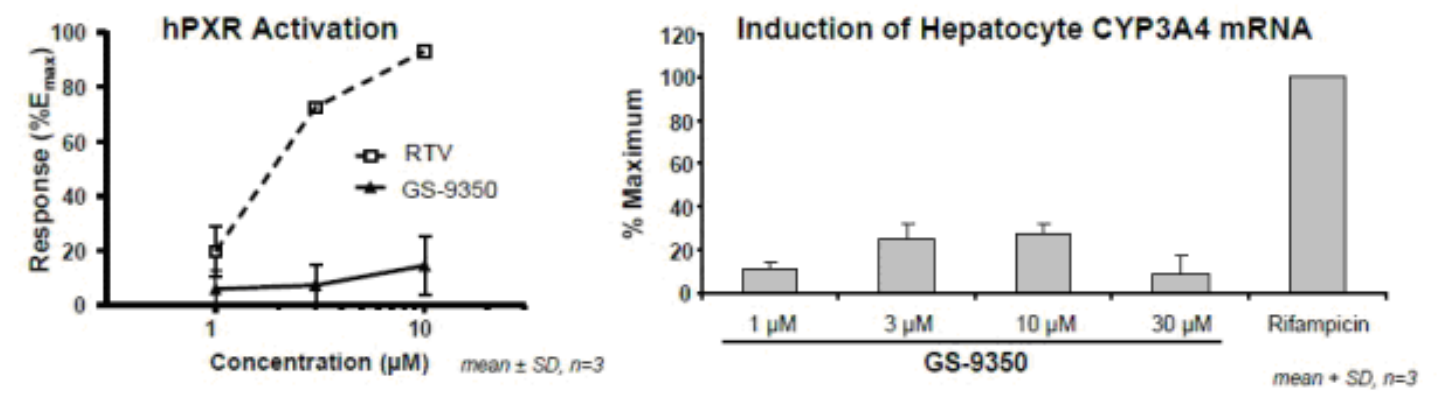
Gervasoni C, et al. JAIDS 2017

Fármacos potenciadores.
Cobicistat vs. Ritonavir in vitro

- Mayor especificidad

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**

- Menor inducción enzimas/transportadores



Xu L, et al. ACS Med Chem Lett. 2010;1:209-13.

Interacciones medicamentosas. Cobicistat vs. Ritonavir

Drug Class	Drug Name
Alpha 1 adrenoceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone, Quinine
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoin
Antimycobacterial	Rifampicin
Ergot derivatives	Dihydroergotamine, Ergometrine, Ergotamine
GI motility agent	Cisapride
Herbal products	St John's wort (*Hypericum perforatum)*
HMG CoA reductase Inhibitors	Lovastatin, Simvastatin
Neuroleptic	Pimozide
PDE 5 Inhibitor	Sildenafil (for pulmonary arterial hypertension)
Sedative/hypnotics	Triazolam, oral midazolam

Marzolini C, et al. JAC 2016;71:1755-8

Case report

Acute leg ischaemia in an HIV-infected patient receiving antiretroviral treatment

Jordi Navarro[1,2†], Adrian Curran[1,2†], Joaquin Burgos[1,2], Ariadna Torrella[2], Inma Ocaña[1], Vicenç Falcó[1,2], Manuel Crespo[1,2], Esteban Ribera[1,2]*

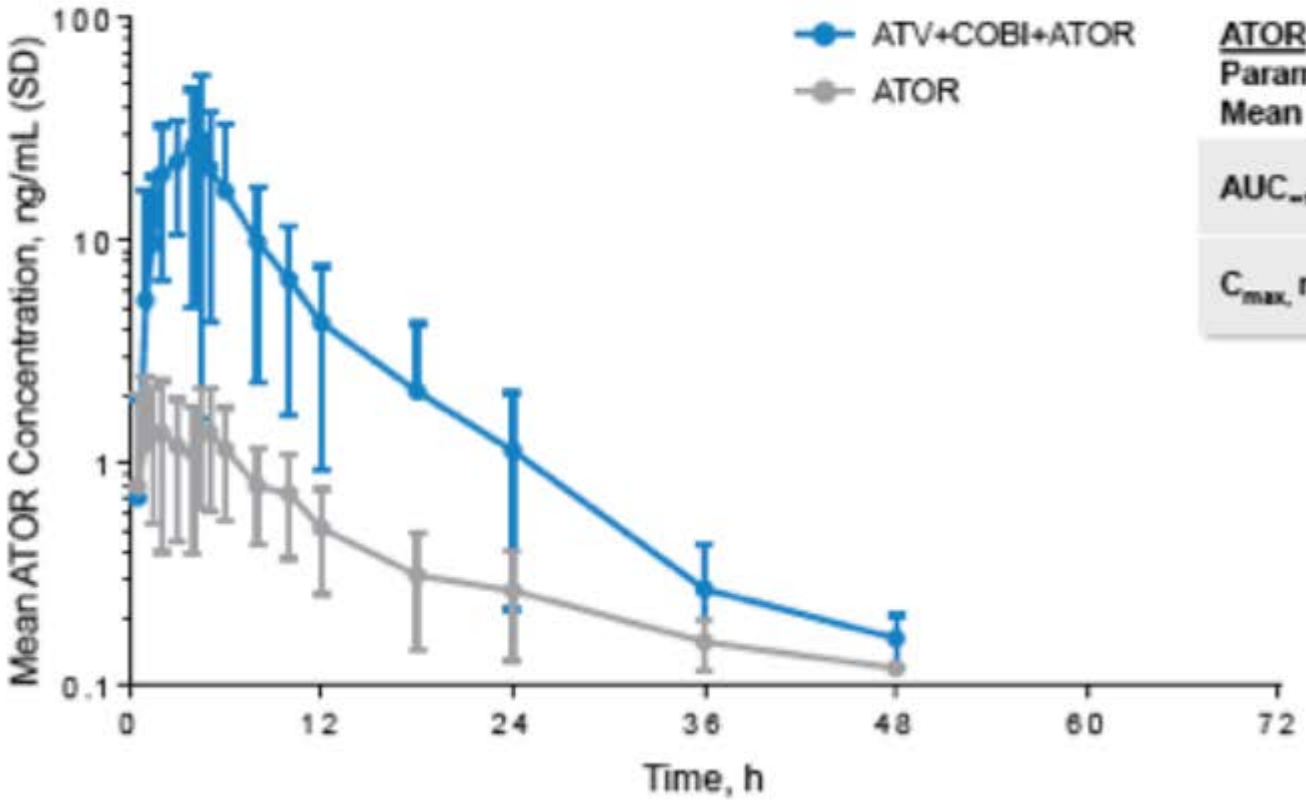
An HIV-infected patient treated with tenofovir disoproxil fumarate/emtricitabine/elvitegravir/cobicistat developed severe acute ischaemia of both legs during a migraine episode. After being interrogated he admitted taking an ergotamine-containing preparation. Ergotism due to interaction between ergotics and cobicistat was diagnosed. We describe the first reported case of this interaction.

Antiviral Therapy 2017; **22**:89–90

Hipolipemiantes

		ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	DTG	RAL	E/C/F/TAF	E/C/F/TDF
Statins	Atorvastatin	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↑
	Fluvastatin	↔	↔	↔	↑	↑	↔	↔	↔	↔	↑	↑
	Lovastatin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↑
	Pravastatin	↔	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↑
	Rosuvastatin	↑213%	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑ 38%	↑ 38%
	Simvastatin	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↑
Fibrates	Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑⇑
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Gemfibrozil	↓	↓	↓41%	↔	↔	↔	↔	⇑	⇑	↔	↔
	Ezetimibe	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

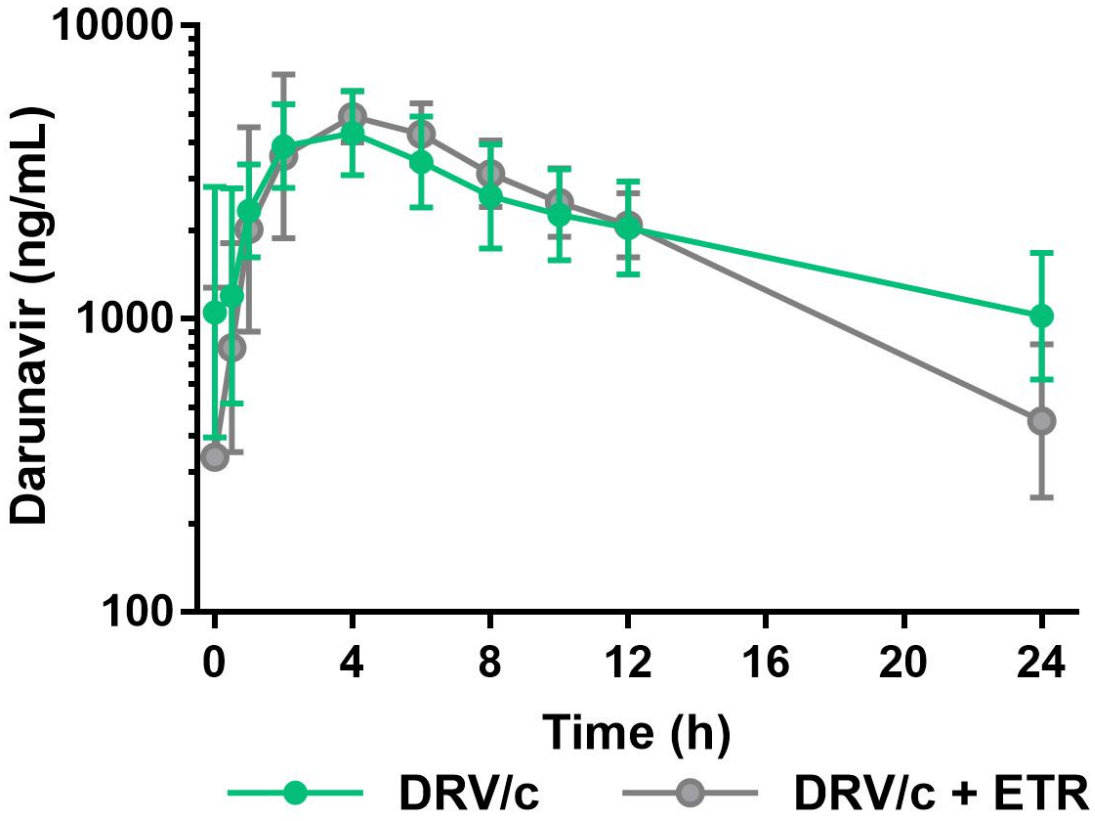
Effect of ATV+COBI on ATOR PK



ATOR PK Parameter Mean (%CV)	ATV + COBI + ATOR N=16	ATOR N=16	GMR % (90% CI)
AUC_{∞}, h·ng/mL	193.4 (65)	20.3 (49)	922 (758, 1120)
C_{max}, ng/mL	36.0 (73)	1.8 (66)	1890 (1350, 2630)

Custodio et al. 18th Antiviral PK. 2017

Effect of ETR in DRVc pharmacokinetics



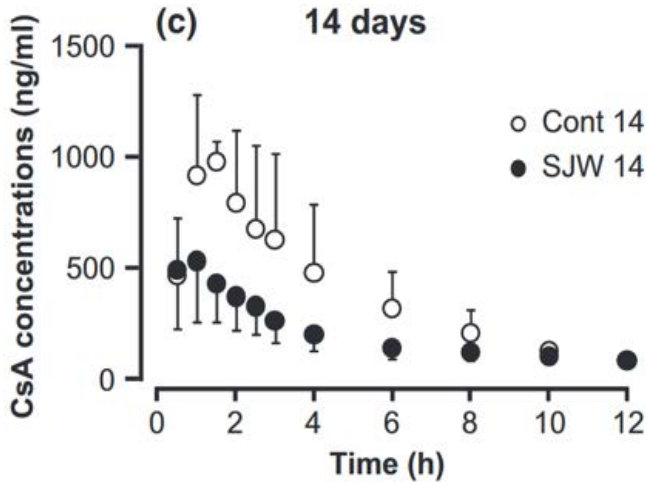
	Day 0 (n=15)	Day 14 (n=15)	LSM ratio (90% CI)
C_{max} (ng/mL)	4885.3 ± 1420.2	5329.3 ± 1158.2	1.11 (0.99 – 1.24)
AUC_{0-24} (ng.h/mL)	57173.6 ± 18925.6	54848.0 ± 9953.7	0.99 (0.86 – 1.13)
C_{24} (ng/mL)	1145.9 ± 567.7	539.3 ± 380.0	0.44 (0.33 – 0.58)
$t_{1/2}$ (h)	16.8 ± 12.0	7.6 ± 7.3	-

FUNDACIÓ LLUITA CONTRA LA SIDA

Molto et al. 18th Antiviral PK. 2017

Otras interacciones

Interacciones entre medicamentos y plantas medicinales
Efecto del hipérico en la exposición a la ciclosporina



Fukunaga K, et al. J Vet Pharmacol Ther 2012;35:446-51

Transplantation. 2002 Oct 27;74(8):1200-1.

Rhabdomyolysis due to red yeast rice (Monascus purpureus) in a renal transplant recipient.

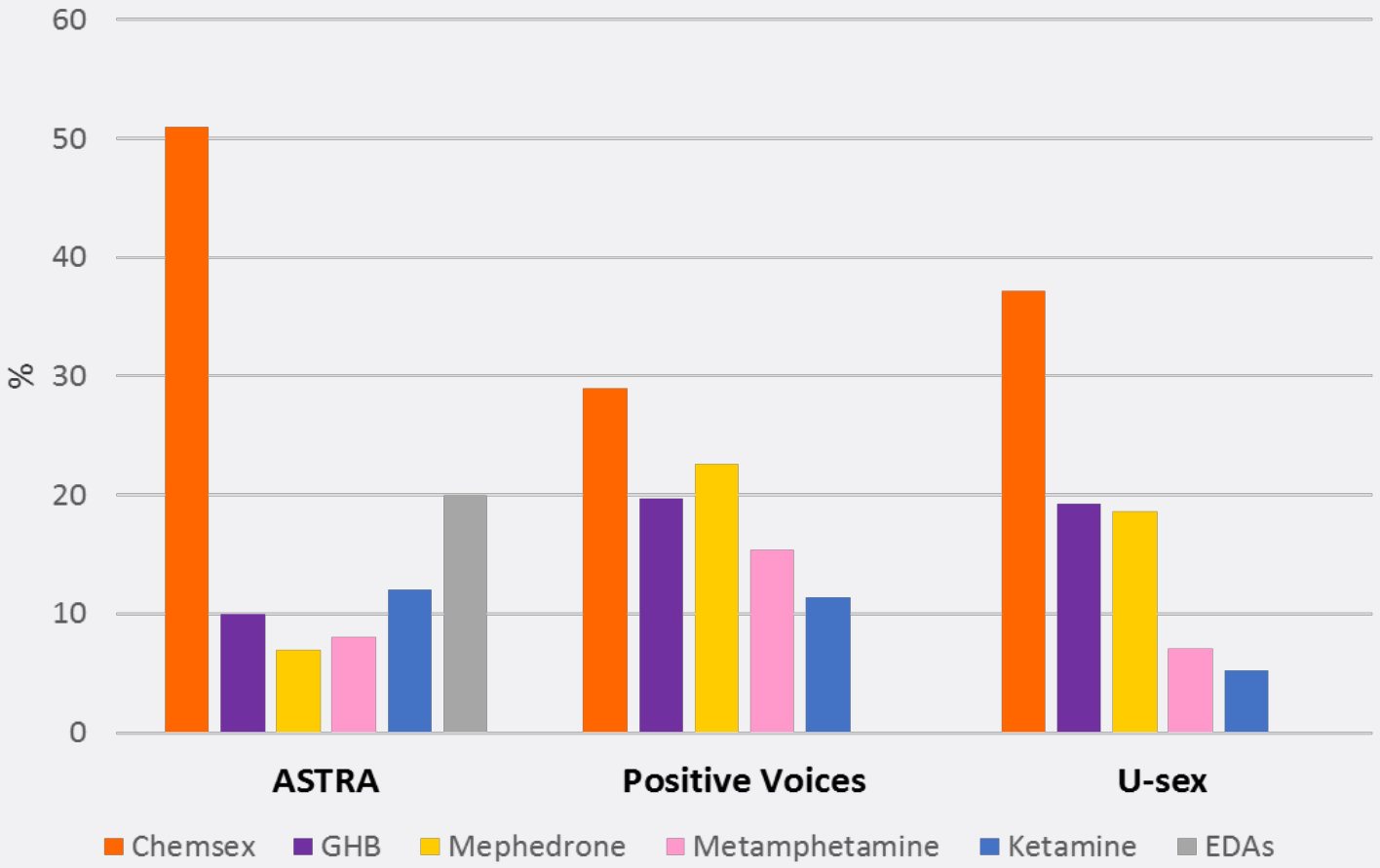
Prasad GV[1], Wong T, Meliton G, Bhaloo S.

Ned Tijdschr Geneeskd. 2016;160(0):D99.

['Red yeast rice' as a cholesterol-lowering substance?Caution is warranted].

Brouwers JR[1], Roeters van Lennep JE, Maas AH.

Otras interacciones



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

Conclusiones

- La polifarmacia y las interacciones medicamentosas son un problema clínico en aumento
  - Envejecimiento/pluripatología
  - Pautas preferentes sin potenciación…
- Revisión detallada de la medicación concomitante
- Consulta bases de datos específicas
- Diferenciar entre significación estadística (PK) y relevancia clínica (PD)
- Dar pautas claras al paciente
  - Anticiparse a las consecuencias

Gracias