Interacciones de los nuevos IPs en el tratamiento del VHC

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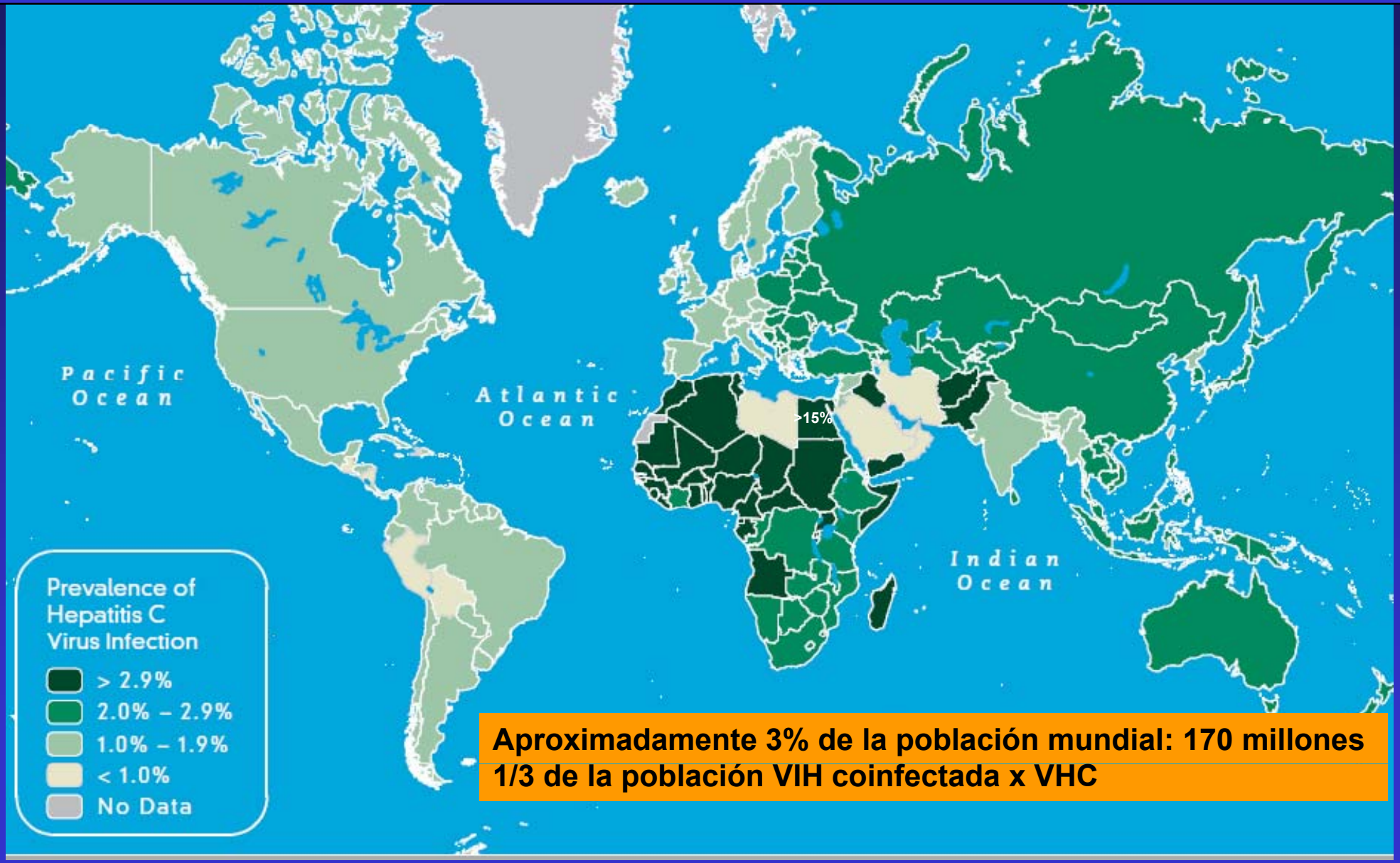
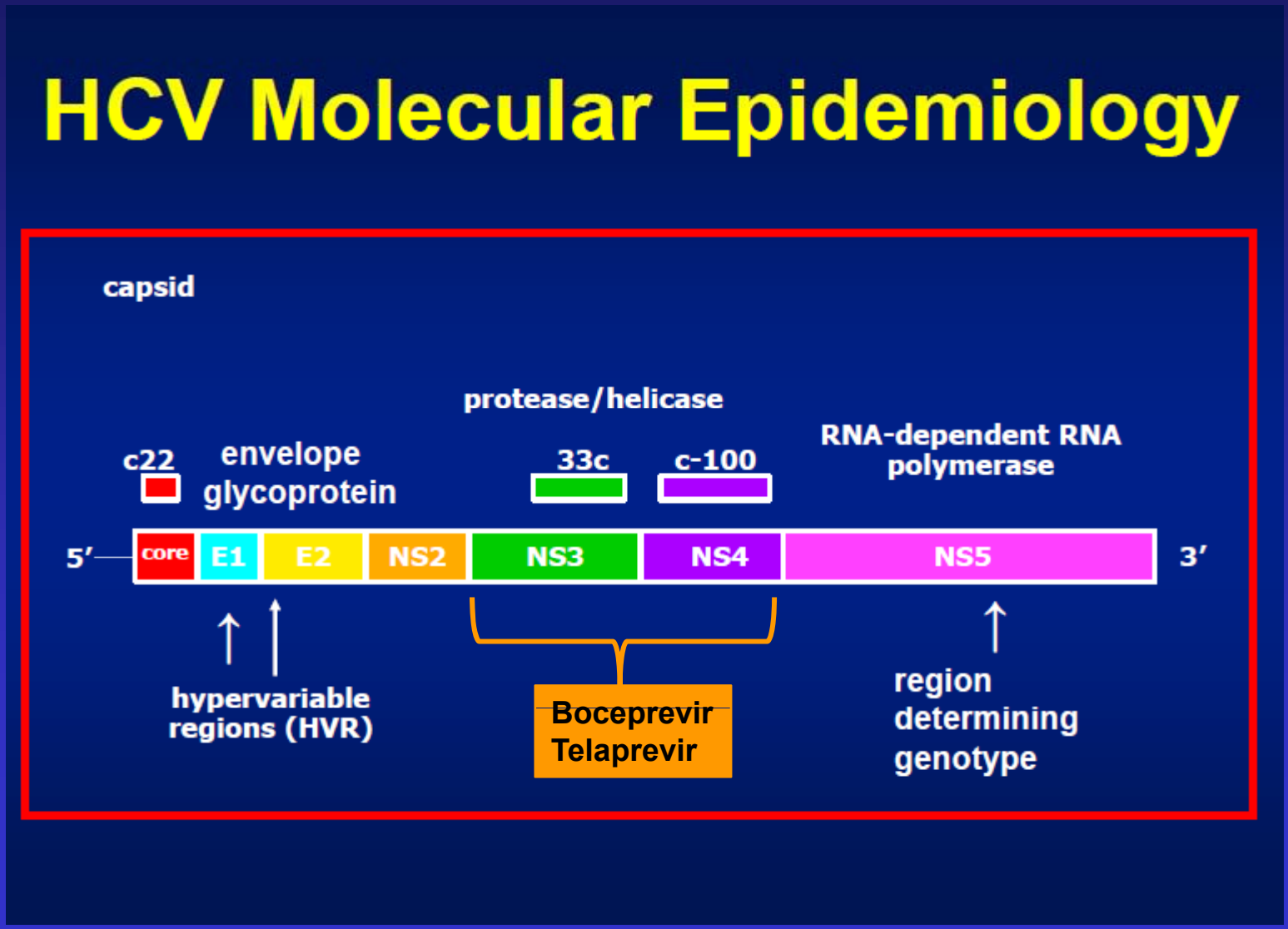
Prevalencia Global de la infección por VHC



Aproximadamente 3% de la población mundial: 170 millones
1/3 de la población VIH coinfectada x VHC

http://www.cdc.gov/hepatitis/Resources/MtgsConf/HCVSymposium2011-PDFs/21_Holmberg.pdf

Inhibidores de la proteasa del VHC

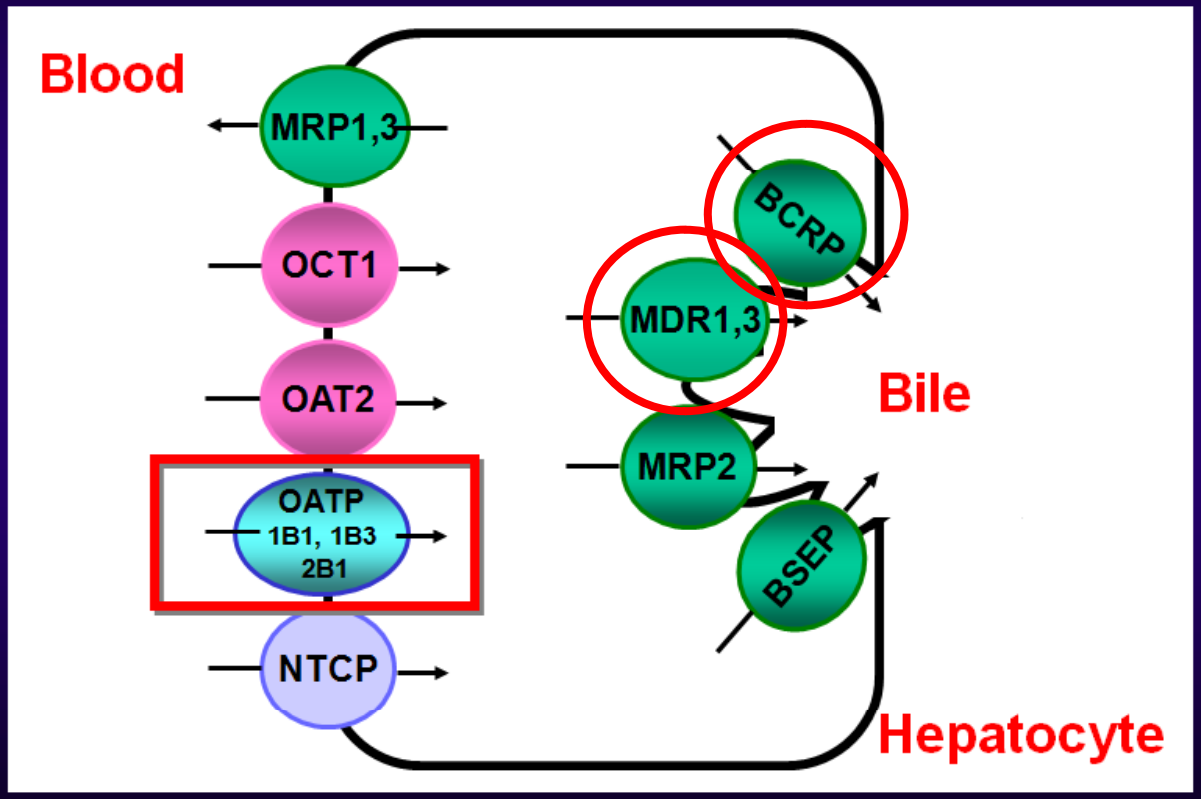


http://www.cdc.gov/hepatitis/Resources/MtgsConf/HCVSymposium2011-PDFs/21_Holmberg.pdf

	BOCEPREVIR (BOC) VICTRELIS ®	TELAPREVIR (TPV) INCIVO ®
Posología	800 mg/8h (12 comp/día) Con alimentos	750 mg/8h (6 comp/día) Con alimentos (min 20g grasa)
Metabolismo	Aldoketoreductasa 1C2 +1C3>CYP3A4[1]	CYP3A4[2]
Efecto inhibidor potente	CYP3A4*[1]	CYP3A4*
Efecto inductor	No (CYP1A2, 2B6, 2C8, 2C9, 2C19,3A)	Bajo potencial (CYP2C, 3A, 1A)
Transportadores	*In vitro*: sustrato Pgp[1] e ¿inhibidor? Sustrato de BRCP[1] No sustrato pero inh de OATP1B1	Sustrato[2] e inhibidor de Pgp[2]
Unión a prot plasmáticas	68-75%	59-76%
SIN EMBARGO…. ?????	**Los inhibidores de la aldoketoreductasa diflunisal e ibuprofeno no aumentaron AUC BOC Ritonavir no aumentó AUC BOC**	**Ritonavir no aumentó AUC TVR**

* Probablemente el efecto inhibidor sobre el CYP3A4 de telaprevir es mayor. [1]Victrelis ® EMA 2012. [2]Incivek ® EMA 2012.

Transporters in the Liver

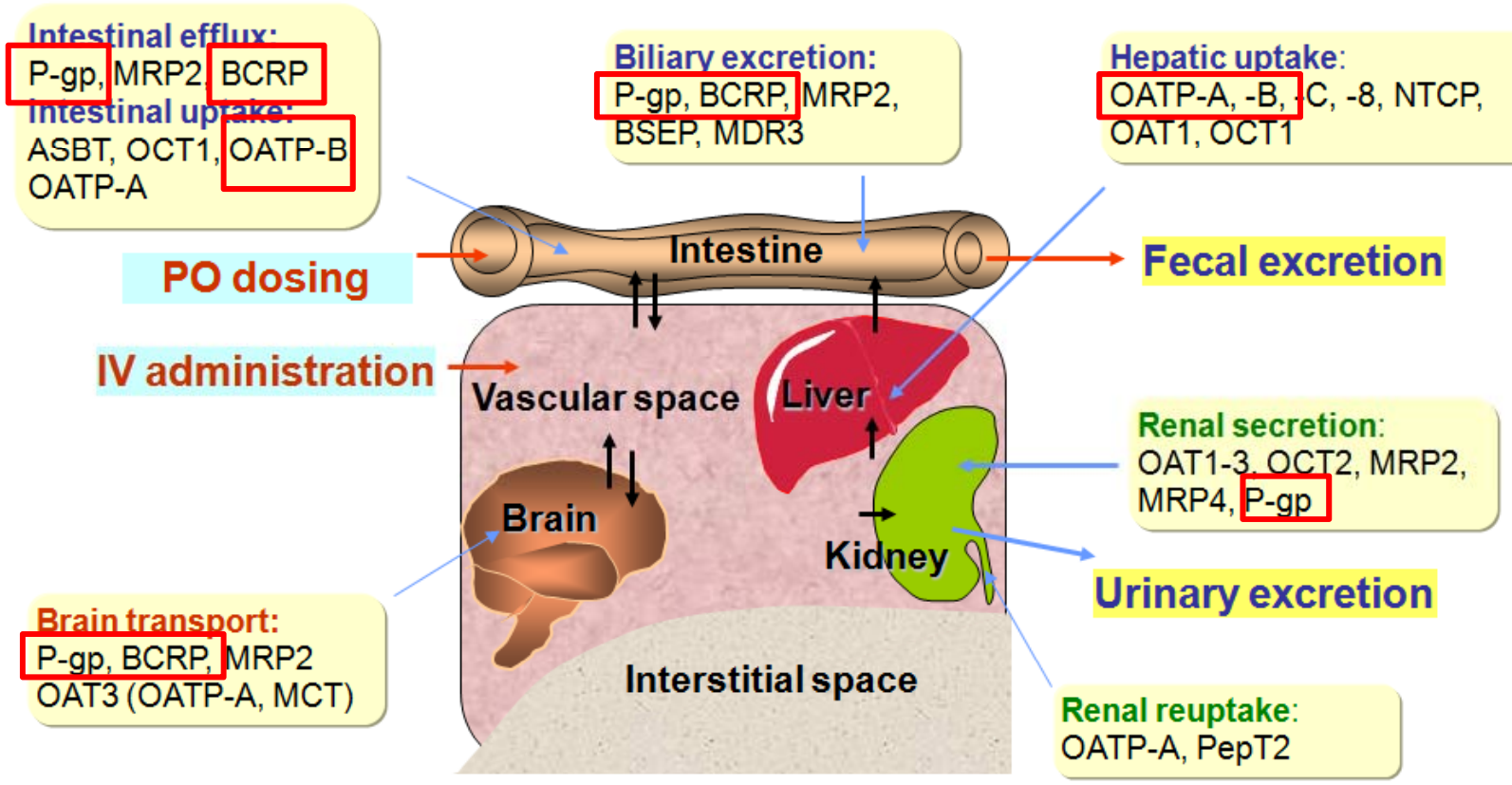


OATP1B1:
benzylpenicillin, atorvastatin,cerivastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin

Kathy Giacomini. UCSF. Transporters: Focus on OATP1B1 and Selected Renal Transporters. FDA. 2006

Drug Transporters: Overview

Boehringer Ingelheim

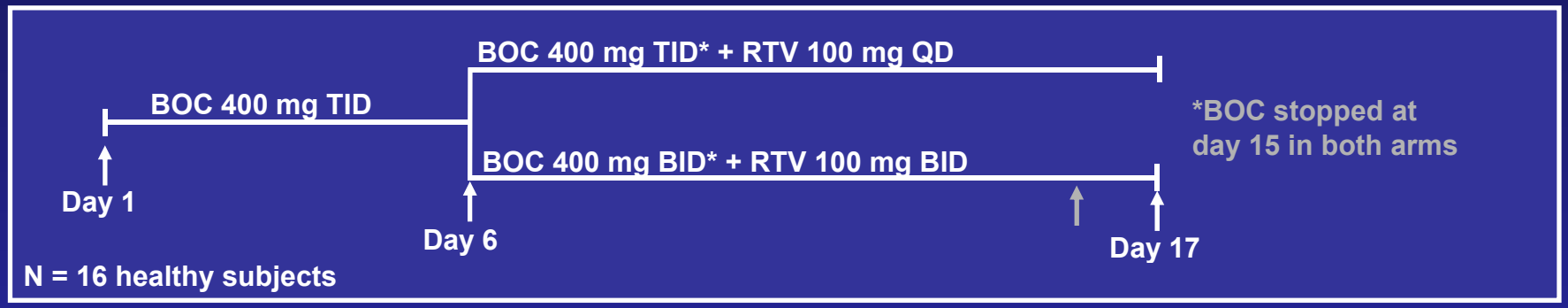


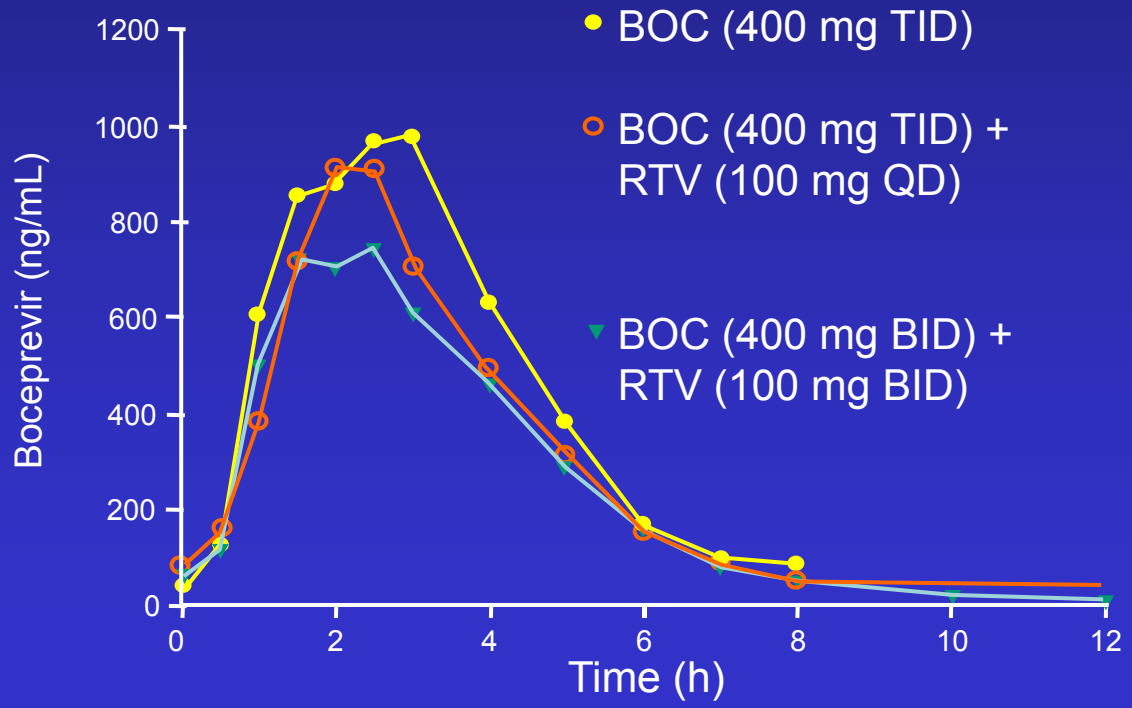
- Transporters contribute to the absorption, distribution and elimination of drugs, metabolites, various endogenous molecules, vitamins, and nutrients
- Tissue entry of drugs can be either facilitated or hindered by transporters

Mitchell E. Taub BI Experience/Opinion: Transporter Based Drug Interactions Clinical Pharmacology Subcommittee of Advisory Committee Meeting for Pharmaceutical Science (ACPS).FDA.2006

Ritonavir no potencia boceprevir ni telaprevir

Ritonavir no potencia boceprevir





BOC + RTV (100 mg QD) vs BOC
$AUC_{(T)}$ ratio estimate
81% (90% CI: 73–91)
C_{max} R.E.
73% (90% CI: 57–93)

BOC + RTV (100 mg BID) vs BOC
$AUC_{(T)}$ ratio estimate
82% (90% CI: 75–88)
C_{max} R.E.
x% (90% CI: y–z)

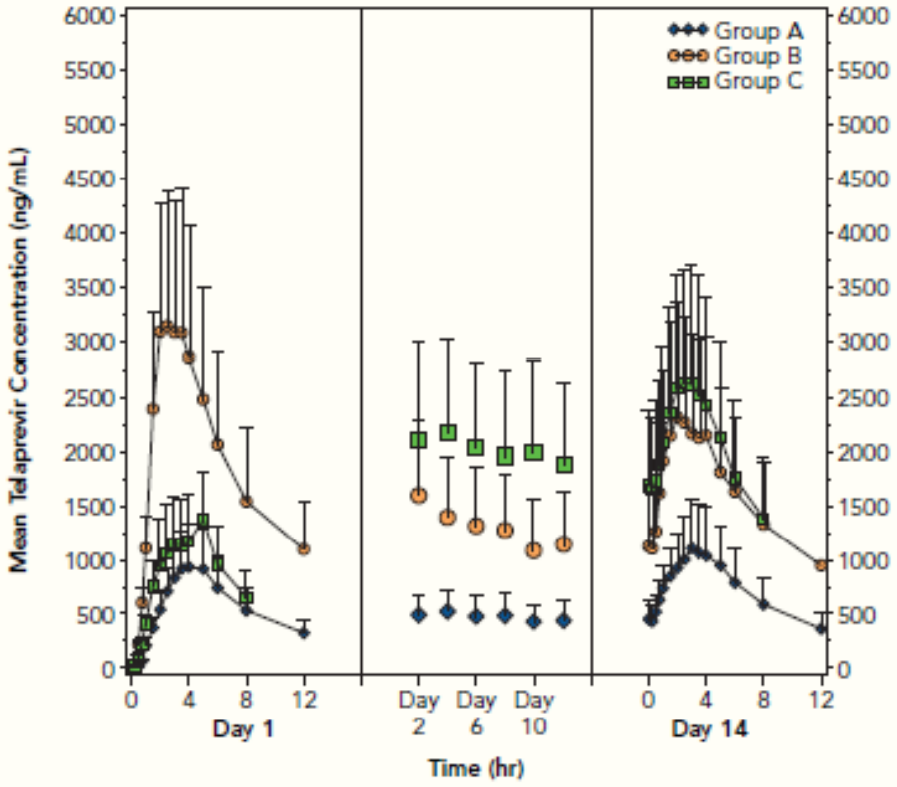
$AUC_{(T)}$, area under the plasma concentration versus time curve from time 0 dosing interval; BID, two time a day; BOC, boceprevir; CI, confidence interval; RTV, ritonavir; TID, three times a day.

Kasserra C. Abstr #118. 18th CROI 2011.

Ritonavir no potencia telaprevir

- Telaprevir (TVR)-RTV. Estudio abierto aleatorizado, voluntarios sanos.

Figure 1: Mean (SE) Plasma Concentration – Time Profile (Day 1 and Day 14) or Pre-dose Concentrations (Days 2–12) of TVR



Garg V. Abstr #629. 18th CROI 2011.

Table 1: Dose Regimens in the Different Treatment Groups (N=6/Group)

Treatment Group	TVR Regimen	RTV Regimen
A	250 mg q12h	100 mg q12h
B	750 mg q12h	100 mg q12h
C	750 mg q8h	none

	Group A: TVR/RTV 250/100mg Q12H	Group B: TVR/RTV 750/100mg Q12H
Cmax	↓59%	↓15%
Cavg	↓67%	↓24%
Cmin	↓75%	↓32%

La ausencia de potenciación de RTV podría explicarse por:

-TVR inhibe su propio metabolismo (…por lo que RTV no ejerceria inhibición adicional)

-desplazam. prot plasmáticas de TVR por RTV.

Interacciones con los antirretrovirales no esperadas

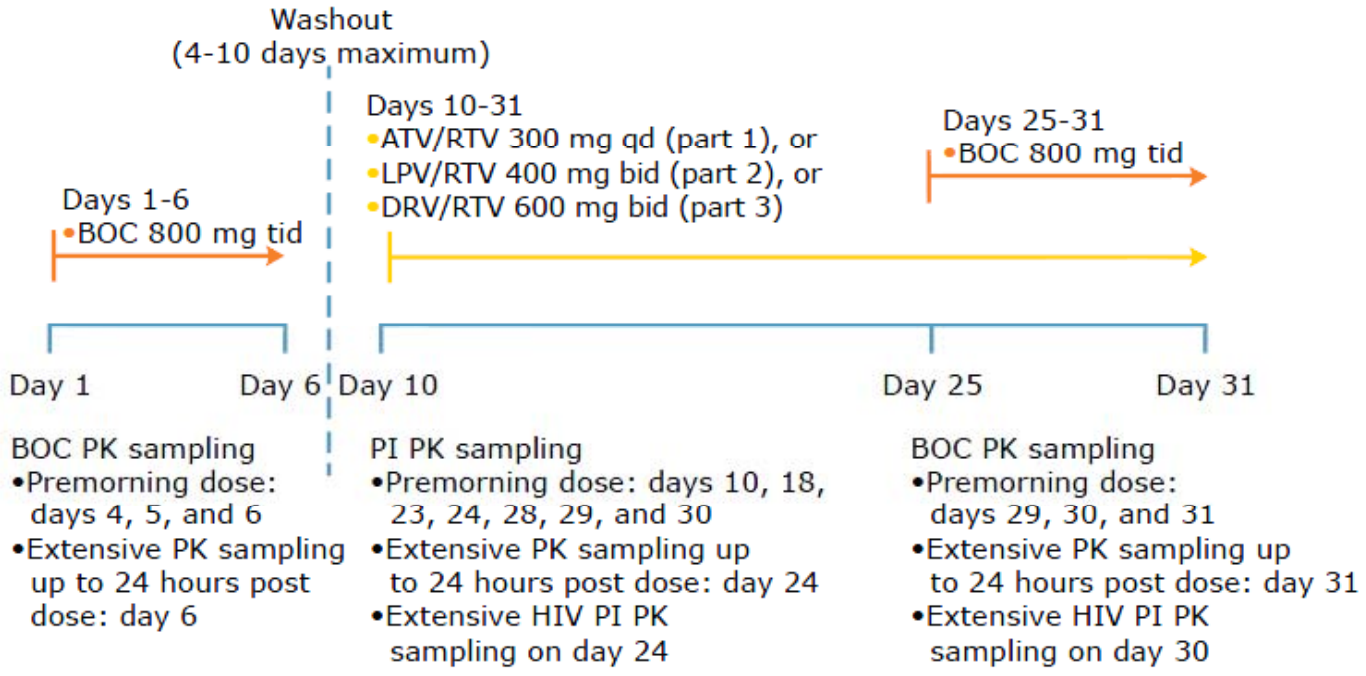
Boceprevir (BOC) – ATV/r, DRV/r, LPV/r

Subjects and Methods

Study Design

- Single-center, 3-part open-label, DDI trial (**Figure 1**)

Figure 1. Study design.



ATV, atazanavir; bid, twice daily; BOC, boceprevir; DRV, darunavir; LPV, lopinavir; PI, protease inhibitor; PK, pharmacokinetic; qd, once daily; RTV, ritonavir; tid, 3 times daily.

Voluntarios sanos

Seguridad:
la mayoria de efectos adversos (EA)fueron leves y se produjeron a nivel digestivo.
Ningún EA grave

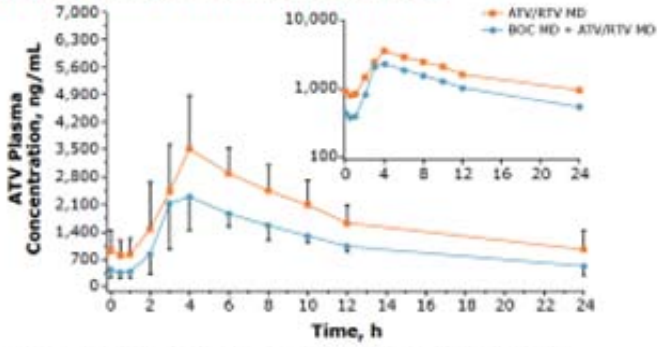
Hulskotte. Abstr #771LB. 19th CROI 2012.

Boceprevir (BOC) –IP/r (volunt. Sanos)

ATV/BOC PK

- Mean ATV concentrations were lower at all time points with BOC + ATV/RTV compared with ATV/RTV alone (**Figure 2**)

Figure 2. Mean (SD) plasma concentration-time profiles for ATV/RTV alone and in combination with BOC.

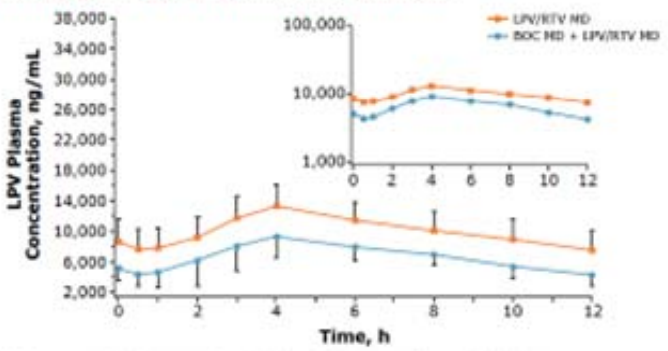


ATV, atazanavir; BOC, boceprevir; MD, multiple dose; RTV, ritonavir; SD, standard deviation.

LPV/BOC PK

- Mean LPV concentrations were lower at all time points with BOC + LPV/RTV compared with LPV/RTV (**Figure 3**)

Figure 3. Mean (SD) plasma concentration-time profiles for LPV/RTV alone and in combination with BOC.

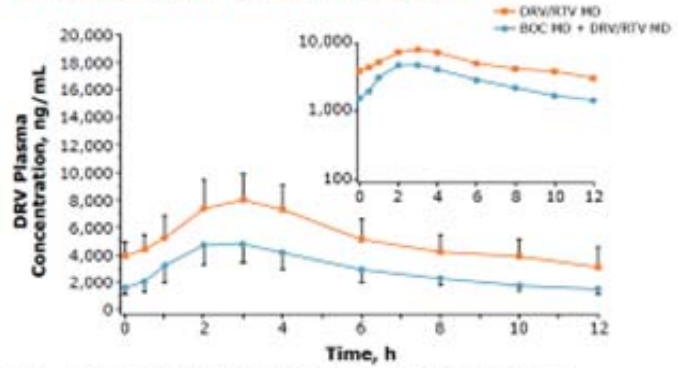


BOC, boceprevir; LPV, lopinavir; MD, multiple dose; RTV, ritonavir; SD, standard deviation.

DRV/BOC PK

- Mean DRV concentrations were lower at all time points in the BOC + DRV/RTV treatment vs DRV/RTV alone (**Figure 4**)

Figure 4. Mean (SD) plasma concentration-time profiles for DRV/RTV alone and in combination with BOC.



BOC, boceprevir; DRV, darunavir; MD, multiple dose; RTV, ritonavir; SD, standard deviation.

	ATV/r	BOC
AUC	↓35%	↔
Cmin	↓49%	↓18%

	LPV/r	BOC
AUC	↓34%	↓45%
Cmin	↓43%	↓57%

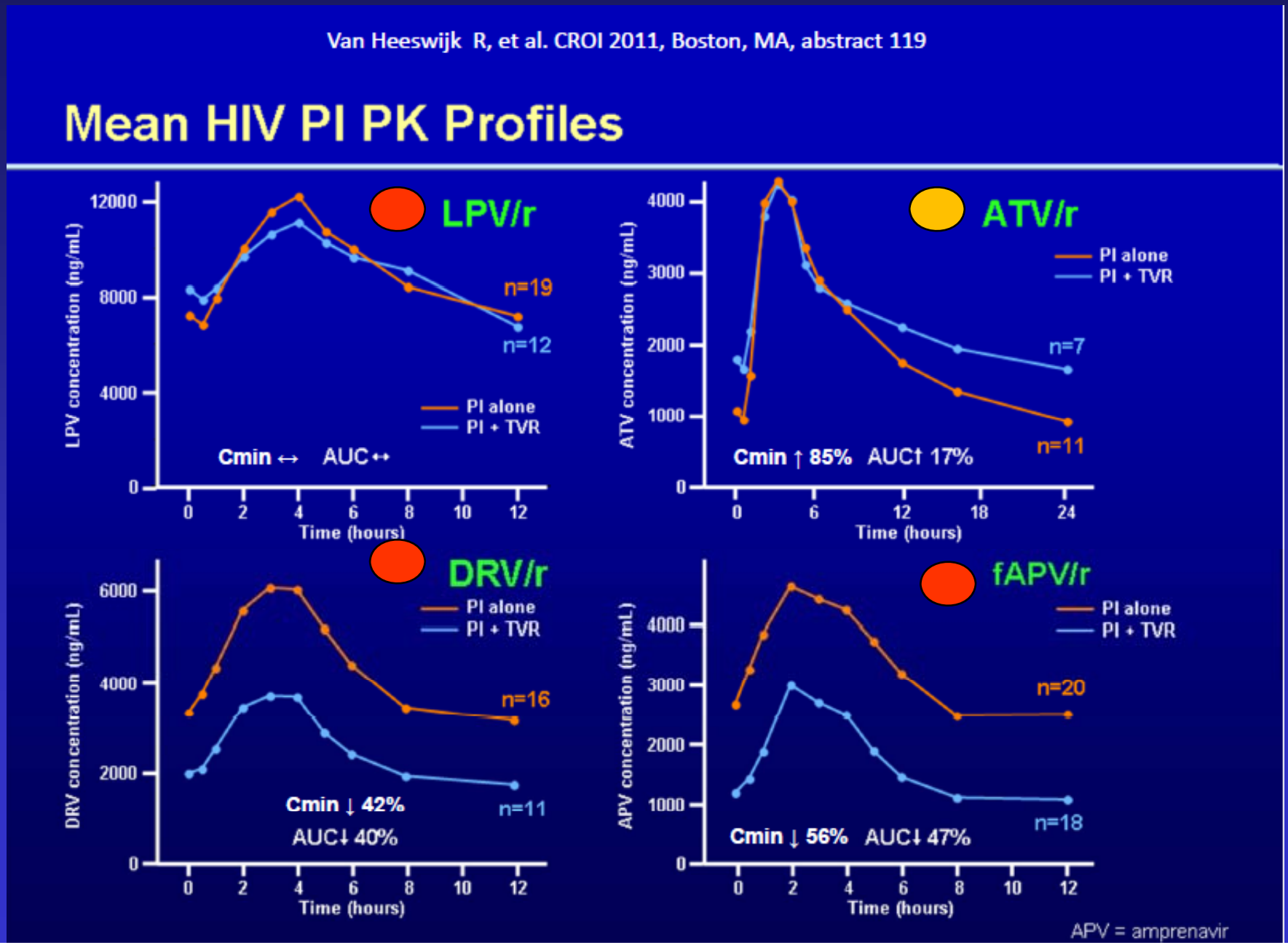
	DRV/r	BOC
AUC	↓44%	↓32%
Cmin	↓59%	↓35%

Valorar sólo si CV VIH <50 c/mL y ausencia de resistencias

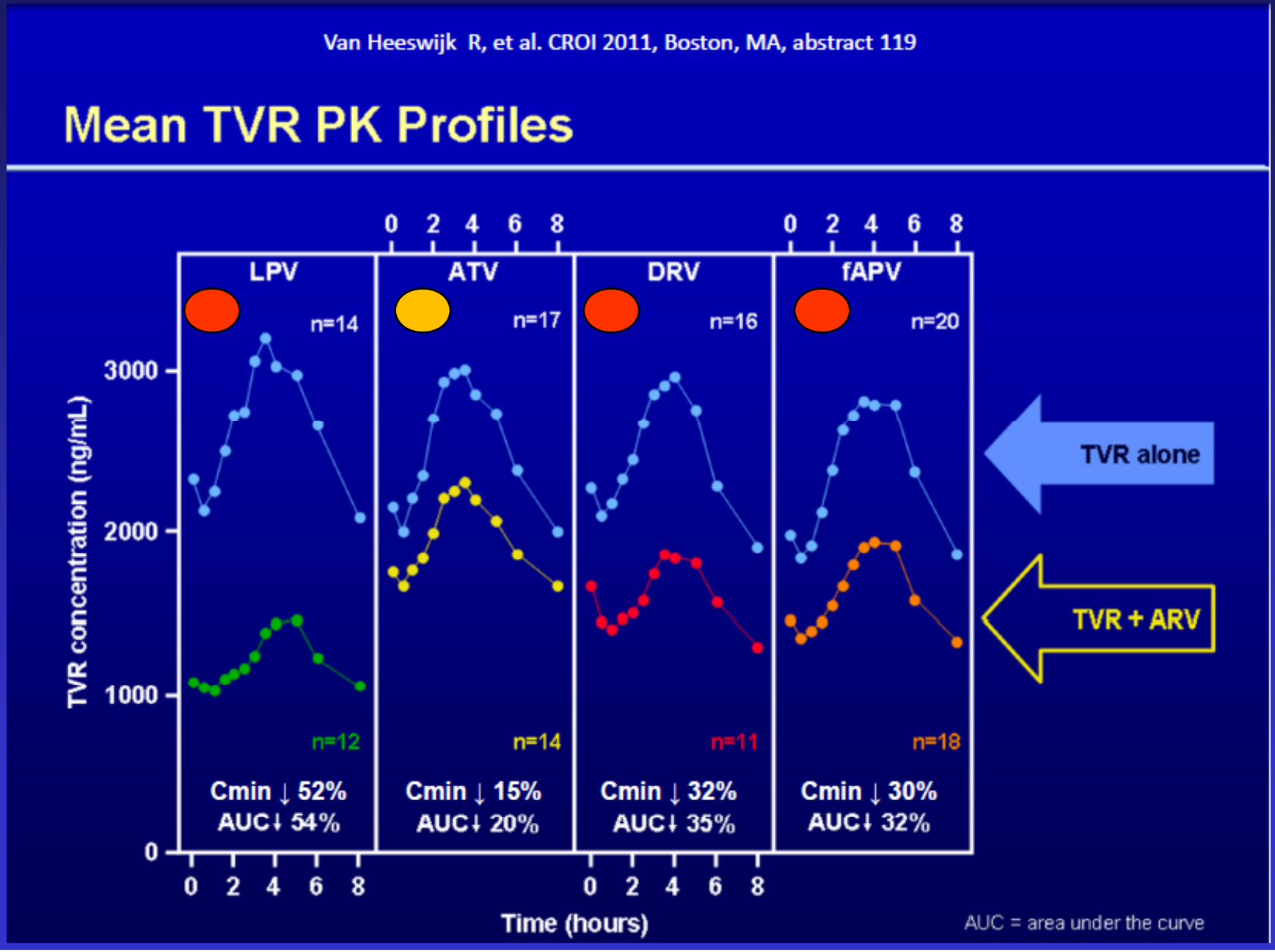
No deben administrarse conjuntamente

Hulskotte. Abstr #771LB. 19th CROI 2012.
Victrelis. Nota informativa AEMPS 17 Feb 2012

Telaprevir – ATV/r, DRV/r, fAPV/r, LPV/r (v sanos)



Telaprevir – ATV/r, DRV/r, fAPV/r, LPV/r (v sanos)



Boceprevir (BOC) –Raltegravir

Estudio fase 1 abierto, aleatorizado, cruzado, en voluntarios sanos (N=22)

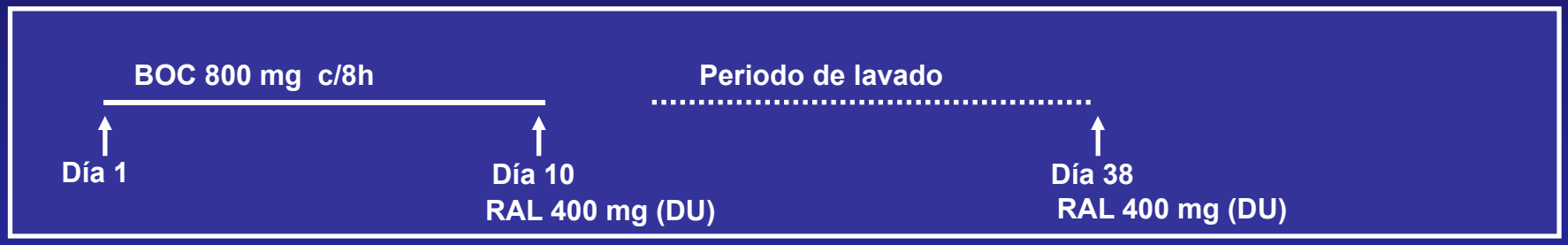
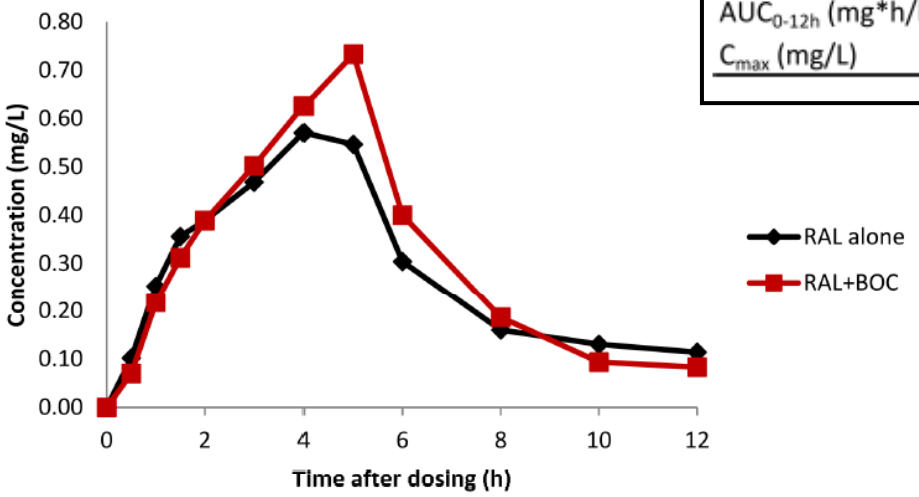


Figure 1: RAL plasma concentration vs. time curves



	RAL + BOC	RAL	GMR (90% CI)		paired sample t-test
$AUC_{0\text{-}12h}$ (mg*h/L)	4.27 (3.22-5.66)	4.22 (3.19-5.59)	1.01	(0.85-1.20)	0.664
C_{max} (mg/L)	1.06 (0.76-1.49)	0.98 (0.73-1.31)	1.09	(0.89-1.33)	0.471

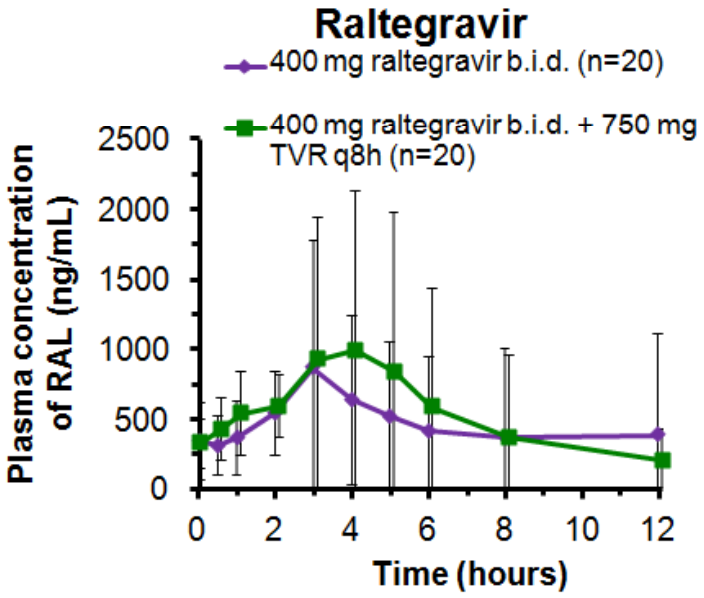
Parámetros PK de boceprevir comparables a datos históricos

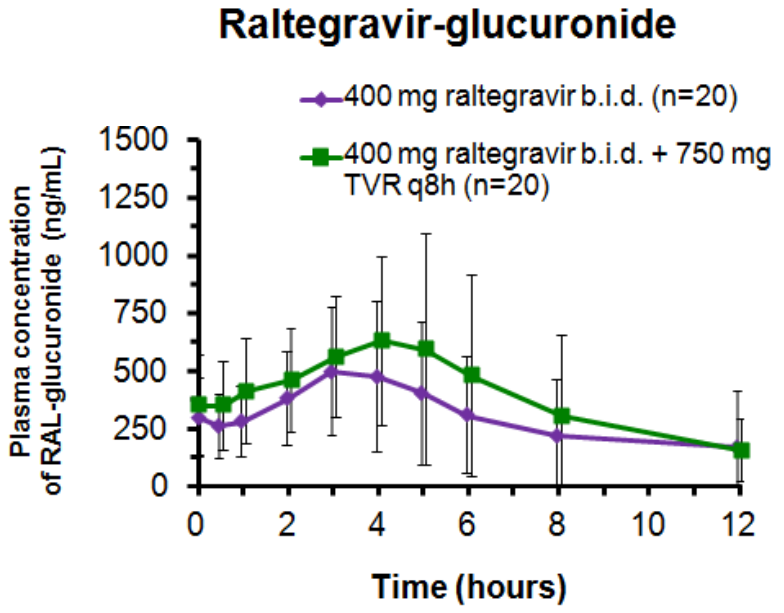
Ausencia de interacción PK entre BOC y RAL

de Kanter. Abstr #772LB. 19th CROI 2012.

Telaprevir (TPV)–Raltegravir

Telaprevir + raltegravir drug interaction study: Mean (SD) PK Profiles of RAL and RAL-glucuronide





Parameter	LSmeans ratio, %	90% CI
C_{min}, ng/mL	1.78	1.26–2.53
C_{max}, ng/mL	1.26	0.97–1.62
AUC_{12h}, ng.h/mL	1.31	1.03–1.67

Parameter	LSmeans ratio, %	90% CI
C_{min}, ng/mL	1.96	1.44–2.67
C_{max}, ng/mL	1.25	0.99–1.57
AUC_{12h}, ng.h/mL	1.37	1.11–1.70

Co-administration of telaprevir increased exposure to raltegravir by 31%. Exposure to the raltegravir-glucuronide metabolite increased similarly, by 37%. The effect of telaprevir on raltegravir was not considered to be clinically relevant.

No dose adjustment of either drug will be necessary.

van Heeswijk R, et al. 51st ICAAC 2011. Abstract A1-1738a

↑ RAL y ↑ RAL-glucurónido sugiere no interacción en UDPGT

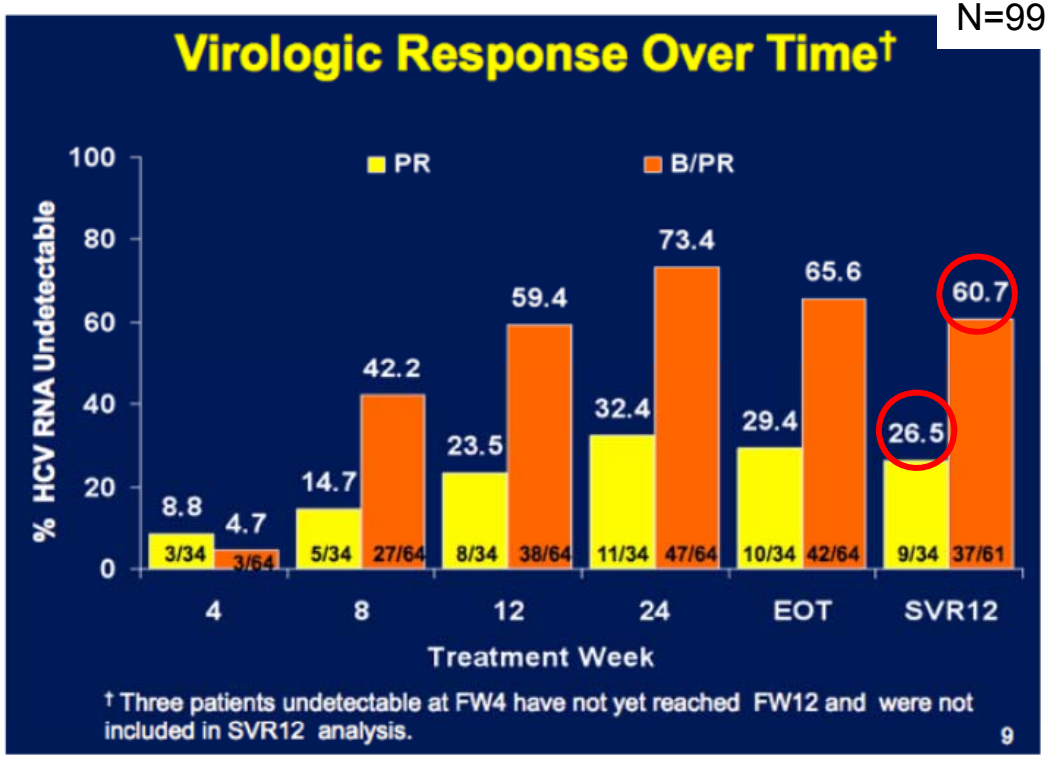
¿Bloqueo Pgp xTPV?

	RAL	TVR
AUC	↑31%	↑7%
Cmin	↑78%	↑14%

Boceprevir (BOC)

VHC/VIH en TARV con IP/r ó RAL permitido. Criterio exclusion: no nucleósidos

N=99



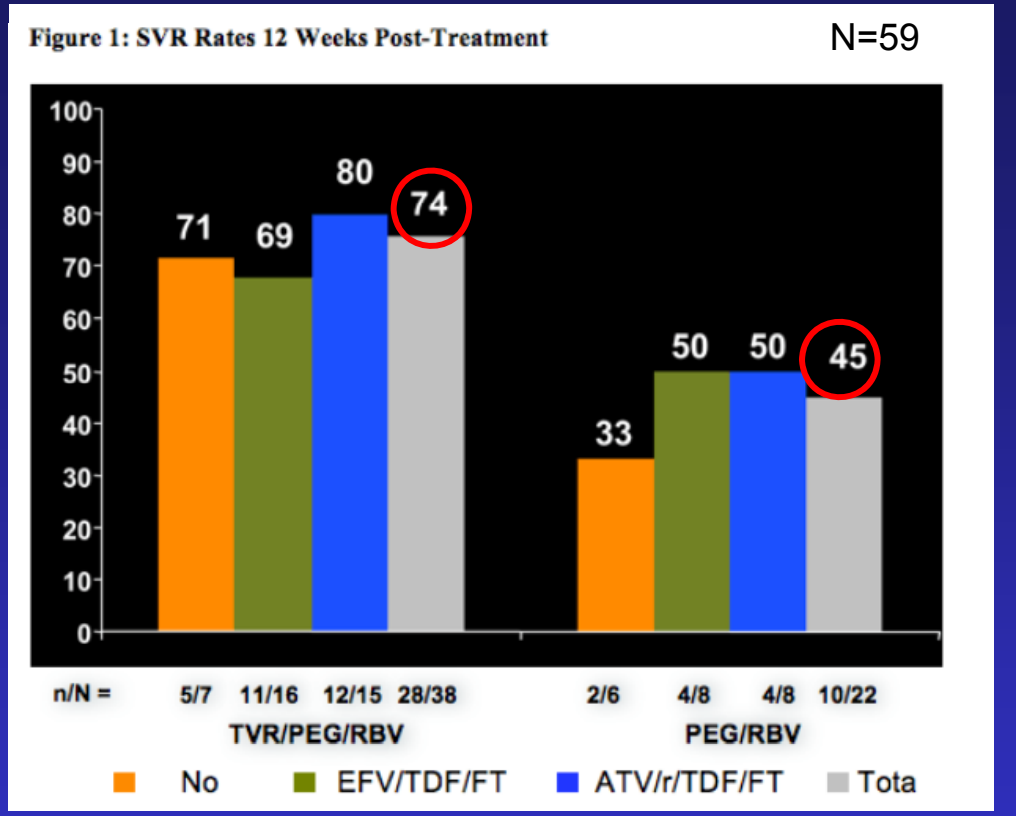
	PR (N=34)	B/PR (N=61)
Atazanavir/r	8/13 (62%)	12/18† (67%)
Lopinavir/r	0/10 (0%)	10/15†† (67%)
Darunavir/r	0/5 (0%)	8/12 (67%)
Other PI/r*	0/3 (0%)	4/7 (57%)
Raltegravir**	1/3 (33%)	3/7 (43%)
Other¶	0	0/2 (0%)

†Excludes 2 patients not yet at FW12 but undetectable at FW4 and †† 1 not yet at FW12 but undetectable at FW4.
*Includes saquinavir, fosamprenavir and tipranavir
**Raltegravir without concurrent HIV PI/r

Telaprevir (TVR)

VHC/VIH sin TARV (n=13), con TDF/FTC + EFV (n=24) ó ATV/r (n=22)

N=59



Repercusión clínica?

Dieterich DT. Telaprevir. Abstr #46. 19th CROI 2012

Sulkowski M. Boseprevir. Abstr #47. 19th CROI 2012

Mallolas J. Abst 366. 47th Annual Meeting EASL 2012

Interacciones de los ARV con IP del VHC

	ATV/r	Boceprevir
AUC	↓35%	↔
Cmin	↓49%	↓18%

	DRV/r	Boceprevir
AUC	↓44%	↓32%
Cmin	↓59%	↓35%

	LPV/r	Boceprevir
AUC	↓34%	↓45%
Cmin	↓43%	↓57%

Hulskotte. Abstr #771LB. 19th CROI 2012

- Interacciones complejas e impredecibles
- Mecanismo poco claro ¿Desplazamiento de la unión a proteínas plasmáticas?
- Repercusión clínica no claramente establecida

	ATV/r	Telaprevir
AUC	↑17%	↓20%
Cmin	↑85%	↓15%

	DRV/r	Telaprevir
AUC	↓40%	↓35%
Cmin	↓42%	↓32%

	LPV/r	Telaprevir
AUC	↑6%	↓54%
Cmin	↑14%	↓52%

	FPV/r	Telaprevir
AUC	↓47%	↓32%
Cmin	↓56%	↓30%

van Heeswijk. Abstr #119. 18th CROI 2011.

	EFV	Boceprevir
AUC	↑20%	↓19%
Cmin	--	↓44%

Kasserra C. Abstr #118. 18th CROI 2011

	Etravirina	Boceprevir
AUC	↓23%	↑10%
Cmin	↓29%	↓12%

Hammond K. Abstr #O-15. 13th IWCPHT 2012

	TDF	Boceprevir
AUC	↔	↔
Cmax	↑32%	

Kasserra C. Abstr #118. 18th CROI 2011

	RAL	Boceprevir
AUC	↔	N.D.
Cmax	↔	

de Kanter. Abstr #772LB. 19th CROI 2012.

	EFV	Telaprevir ↑1125 mg/8h
AUC	↓18%	↓18%
Cmin	↓10%	↓25%

van Heeswijk. Abstr #119. 18th CROI 2011.

	Etravirina	Telaprevir
AUC	↔	↓16%
Cmin	↔	↓25%

Kakuda T. Abstr #O-18. 13th IWCPHT 2012

	TDF	Telaprevir
AUC	↑30%	↔
Cmin	↑41%	↑3%

Van Heeswijk R. Abstract A-966. 48th ICAAC 2008.

	RAL	Telaprevir
AUC	↑31%	↑7%
Cmin	↑78%	↑14%

Van Heeswijk R. Abstract A1-1738a. 51st ICAAC 2011.

http://www.hivclinic.ca/main/drugs_interact.html

Antiretroviral Treatment Options for Patients on Boceprevir or Telaprevir

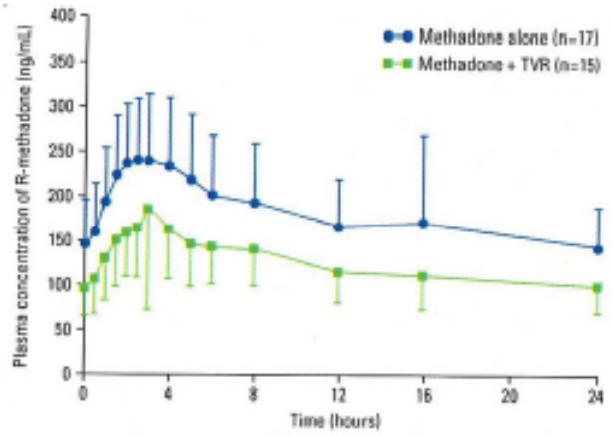
	Boceprevir (Victrelis®) 800 mg q8h with food	Telaprevir (Incivek®) 750 mg po q8h with food
PIs	Avoid with PIr[1]	Avoid DRVr, FPVr, LPVr[2, 3]
	Possible ATVr????	ATVr OK[2]
NNRTIs	Avoid Efavirenz[4, 5]	Dose ↑ to 1125 mg q8h with Efavirenz[2, 6]
	Etravirine (?)[7]	Etravirine OK[8]
		Rilpivirine OK[8]
InSTIs	Raltegravir OK[9, 10]	
Maraviroc	No data *potential ↓/↑ MVC; potential benefit on fibrosis?*	
NRTIs	Tenofovir OK[4, 11]	
	Avoid AZT (anemia)	

Key: = avoid combination = caution/dose adjustment = combination OK

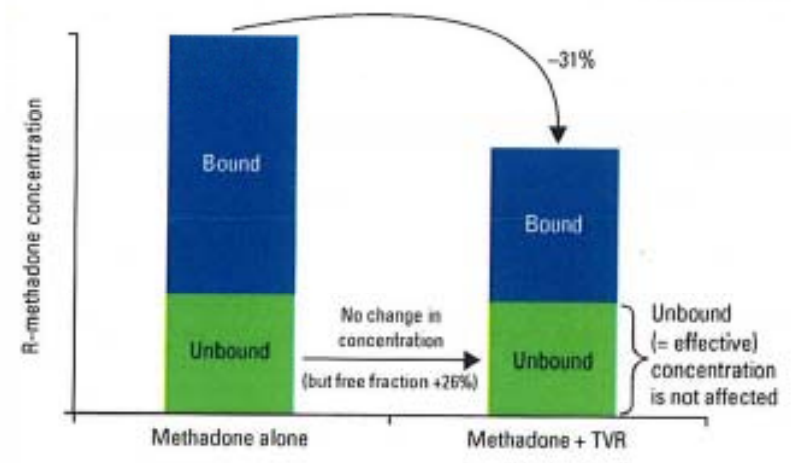
Interacciones con otros grupos de fármacos

Telaprevir-Metadona

Individualized dose of methadone QD + TVR 750 mg q8 h x 7D



- Methadone R-isomer responsible for opioid effects
- Methadone R AUC ↓29% and C_{min} ↓ 31%
- No withdrawal symptoms
- No methadone dose adjustment necessary with TVR



IP del VHC …. ¿Interacciones por desplazamiento de la unión a proteínas plasmáticas?

- Boceprevir UPP 68-75%

- Telaprevir UPP 50-76%

Van Heeswijk R, et al. IWCP Hepatitis Therapy, Cambridge MA, June 2011, Abstract PK_18

Con permiso: Dra J Kiser 13th IWCPHT 2012

Boceprevir-ketoconazol

N = 12 healthy subjects

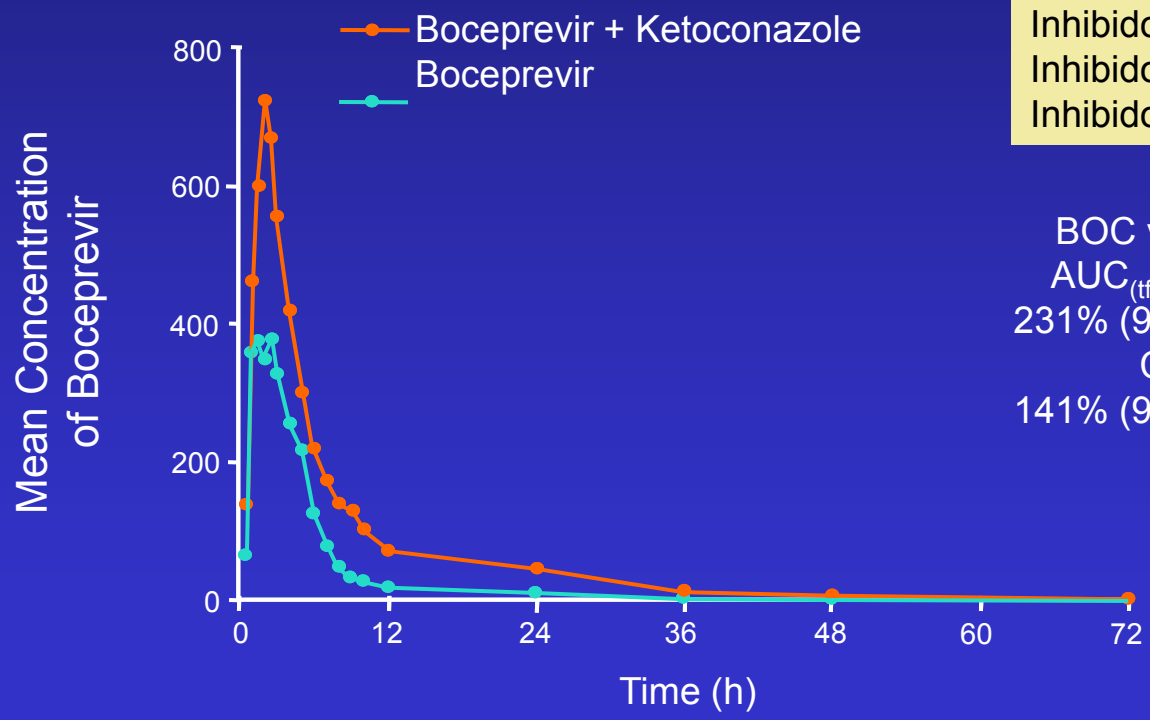
Day:

BOC 400-mg single dose on day 1

1 — 4

KET 400 mg BID days 1–6 + BOC 400-mg single dose on day 4

1 — 4 — 6



Ketoconazol:
Inhibidor potente: 1A2, 2C9, 3A4
Inhibidor moderado: 2A6, 2C19, 2D6
Inhibidor debil: 2B6, 2C8.
Inhibidor de la glicoproteína-P, otros?

BOC vs BOC + KET
$AUC_{(tf)}$ ratio estimate
231% (90% CI: 200–267)
C_{max} R.E.
141% (90% CI: 100–199)

Mecanismo ¿?

Bloqueo CY3A4?
Bloqueo transportadores?

$AUC_{(tf)}$, area under the plasma concentration versus time curve to the final measurable sampling time; BID, two times a day; BOC, boceprevir; CI, confidence interval; KET, ketoconazole; TID, three times a day.

Kasserra C. Abstr #118. 18th CROI 2011.

Interacciones IP VHC – inmunosupresores

Ciclosporina (Sustrato 3A4 y Pgp, Inh 3A4 y Pgp)

Boceprevir 800 mg/8h
CyA: DU 100 mg

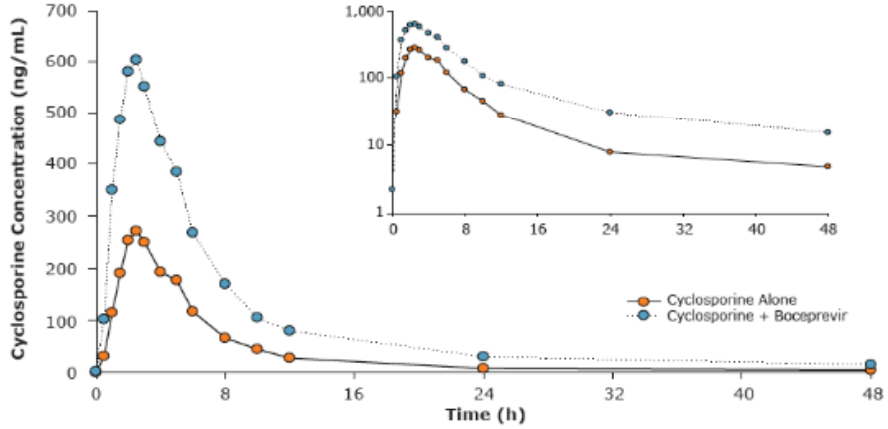


Table 1. Mean (CV%) Pharmacokinetic Parameters for Cyclosporine

Treatment	T_{max},[a] h	C_{max}, ng/mL	AUC_{last}, ng·h/mL	AUC_{inf}, ng·h/mL	$t_{1/2}$, h	CL/F, L/h
Cyclosporine alone (day 1, n = 10)	2.50 (1.00–5.00)	388 (48)	1775 (24)	1800[b] (26)	11.3[b] (36)	58.8[b] (26)
Cyclosporine + boceprevir (day 11, n = 10)	2.50 (1.00–5.00)	737 (27)	4545 (13)	4870[b] (16)	15.7[b] (23)	21.0[b] (16)

AUC_{last}, area under the concentration-time curve from time 0 to last measurable time point; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CL/F, apparent clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; $t_{1/2}$, apparent terminal half-life; T_{max}, time of maximum observed concentration.
[a]Median (range).
[b]n = 9.

	Cy A	Boceprevir
AUC	↑ x 2,7 veces	↔
Cmax	↑ x 2 veces	↔

Telaprevir 750 mg/8h
CyA: DU 10 mg, normalizada a 100 mg

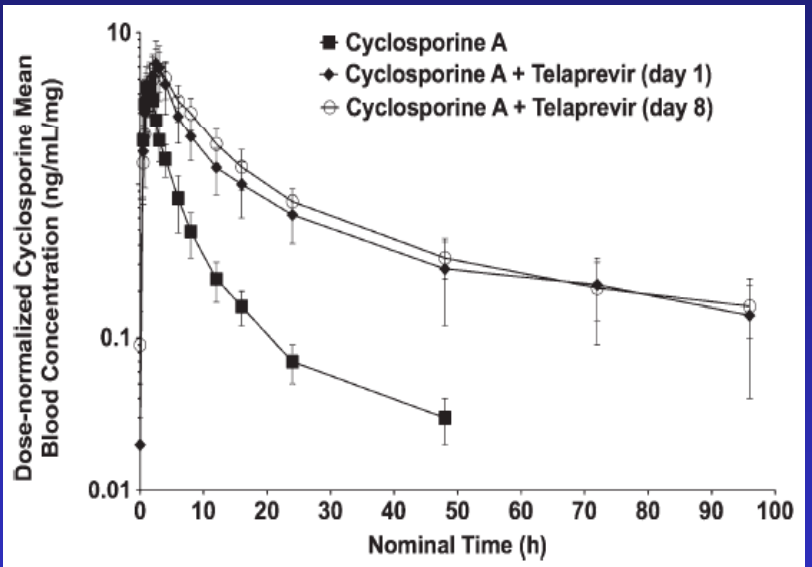


Fig. 1. Dose-normalized mean (SD) blood concentration-time profiles of cyclosporine following administration of cyclosporine alone and with telaprevir (log-linear scale).

	Cy A	Telaprevir
AUC	↑ x 4,64 veces	↔ (historico)
Cmax	↑ 32%	↔ (historico)

Interacciones IP VHC – inmunosupresores

Tacrolimus (Sustrato 3A4 y Pgp, Inh 3A4 y Pgp)

Boceprevir 800 mg/8h
Tacrolimus : DU 0,5 mg

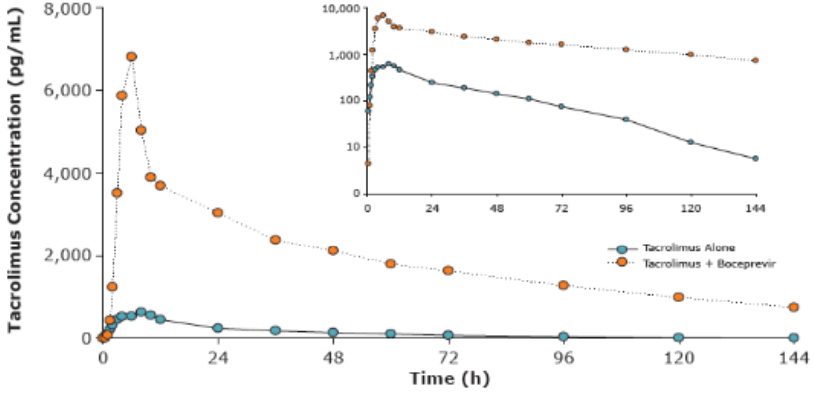


Table 4. Mean (CV%) Pharmacokinetic Parameters of Tacrolimus

Treatment	T_{max}, [a] h	C_{max}, ng/mL	AUC_{last}, ng·h/mL	AUC_{inf}, ng·h/mL	$t_{1/2}$, h	CL/F, L/h
Tacrolimus alone (day 1, n = 12)	5.00 (2.00–12.0)	0.808 (36)	18.3 (59)	21.8 (53)	36.7 (22)	29.6 (57)
Tacrolimus + boceprevir (day 13, n = 12)	6.00 (4.00–24.0)	7.80 (25)	275 (27)	345 (32)	61.3 (18)	1.60 (32)

AUC_{last}, area under the concentration-time curve from time 0 to last measurable time point; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CL/F, apparent clearance; C_{max}, maximum observed concentration; CV, coefficient of variation; $t_{1/2}$, apparent terminal half-life; T_{max}, time of maximum observed concentration.
[a]Median (range).

	Tacrolimus	Boceprevir
AUC	↑ x 17 veces!!	↔
Cmax	↑ x 10 veces	↔

Telaprevir 750 mg/8h
Tacrolimus : DU 0,5 mg, normalizada a 2 mg

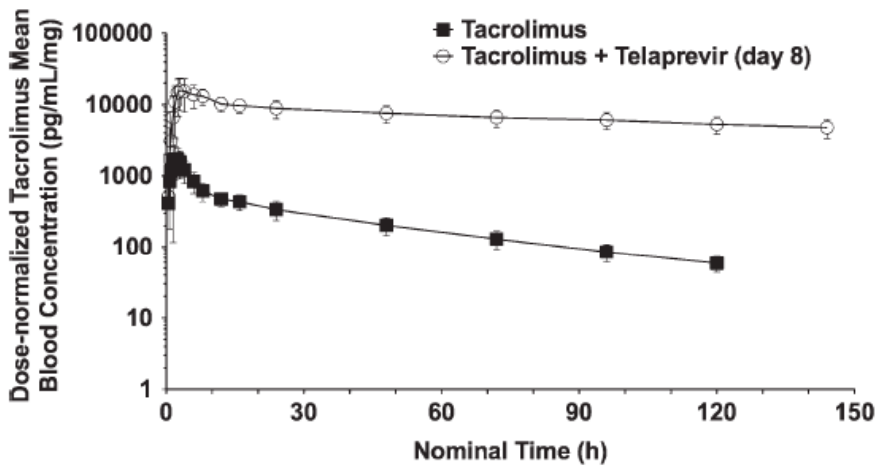


Fig. 2. Dose-normalized mean (SD) blood concentration-time profiles of tacrolimus following administration of tacrolimus alone and with telaprevir (log-linear scale).

	Tacrolimus	Telaprevir
AUC	↑ x 70 veces!!	↔ (historico)
Cmax	↑ x 9,3 veces	↔ (historico)

Telaprevir- amlodipino/atorvastatina
En voluntarios sanos

DU 5 mg amlodipino + 20 mg atorvastatina antes y despues de TVR dosis multiples

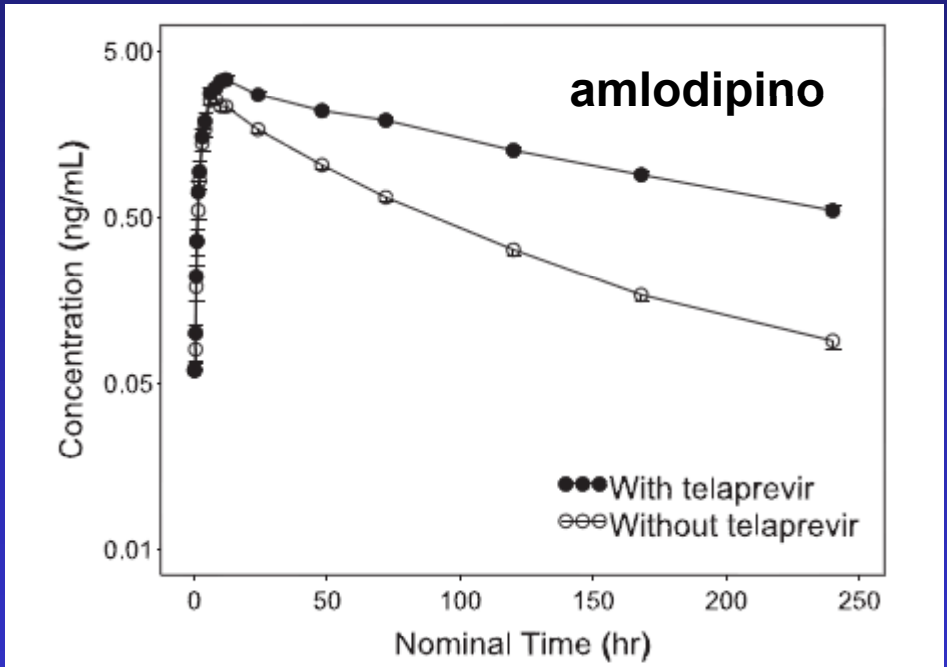


FIG. 1. Mean plasma concentration-time profile of amlodipine following oral administration with and without telaprevir. Error bars represent the standard error of the mean.

	Amlodipino	TVR
AUC	↑x 2,8 veces	↔ (hist)
Cmax	↑27%	↔

Lee JE Antimicrob Agents Chemother 2011;55(10):4569

Telaprevir- amlodipino/atorvastatina
En voluntarios sanos

DU 5 mg amlodipino + 20 mg atorvastatina antes y despues de TVR dosis multiples

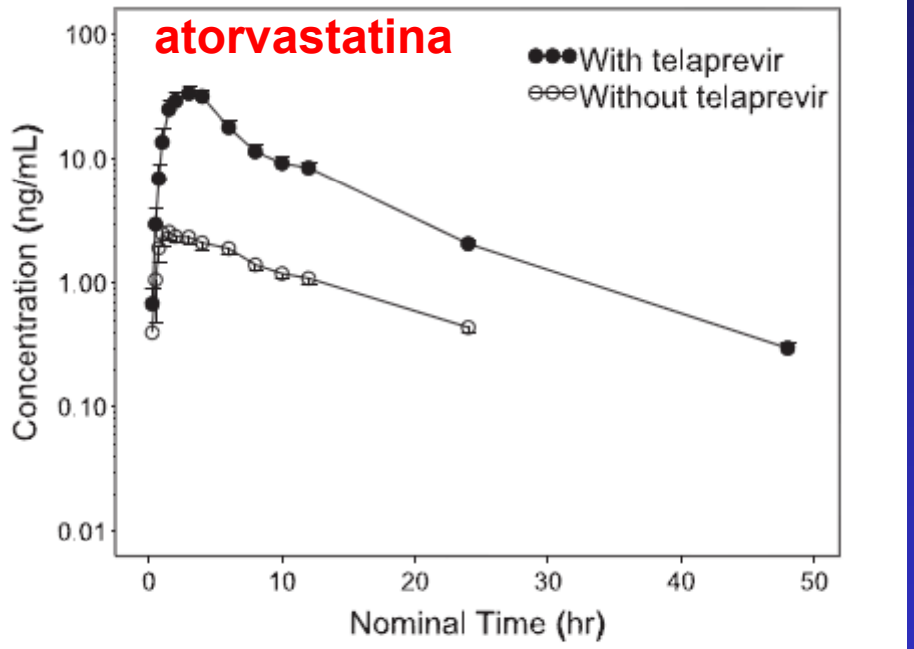


FIG. 2. Mean plasma concentration-time profile of atorvastatin following oral administration with and without telaprevir. Error bars represent the standard error of the mean.

Atorvastatina *CYP3A4* → *O*-OH-Ator, *p*-OH-Ator, *Lactonas inactivas* (*70% activ total*)

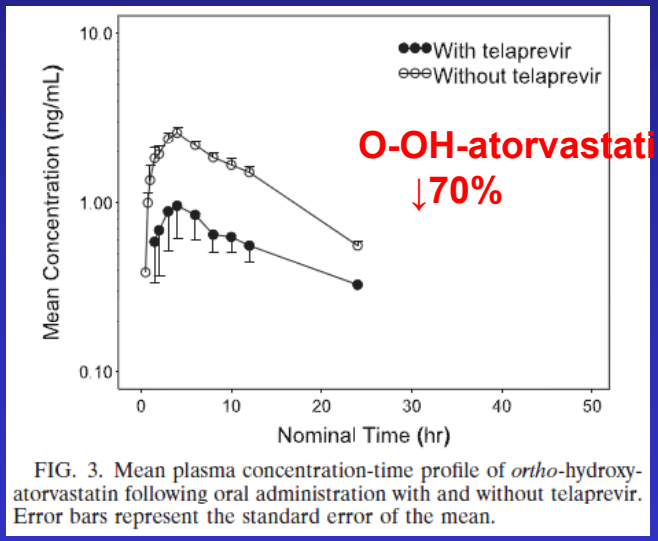


FIG. 3. Mean plasma concentration-time profile of *ortho*-hydroxy-atorvastatin following oral administration with and without telaprevir. Error bars represent the standard error of the mean.

↑ *p*-OH-atorvastatina

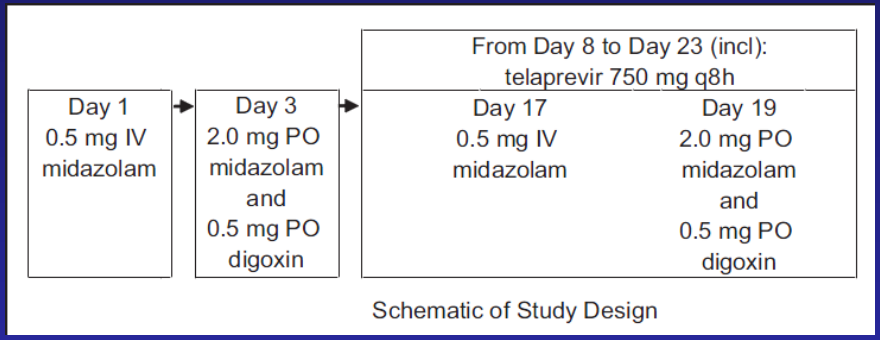
¿vías alternativas de formación: 2C8?

	Atorvastatina	TVR
AUC	↑x 7,9 veces!!	↔ (hist)
Cmax	↑x10,6 veces!!	↔

- **BD ator 14%→ bloqueo CYP3A4 intestinal ó bloqueo Pgp. (poco efecto CYP3A4 hepatico t1/2 sin cambio significativo)**
- **Bloqueo de OATP1B1 x TVR ¿? → dism elimin hepat**

Lee JE Antimicrob Agents Chemother 2011;55(10):4569

Telaprevir- digoxina
En voluntarios sanos



Schematic of Study Design

	Digoxina
AUC	↑85%
Cmax	↑50%

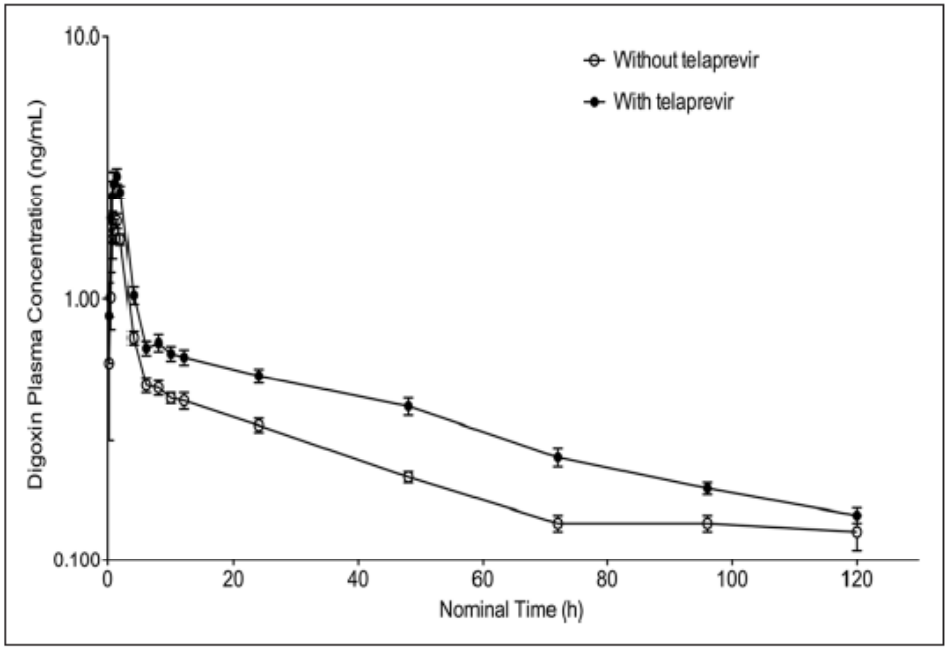


Figure 3. Mean plasma concentration versus time profile of digoxin.

- **No se modificó el aclaramiento renal de digoxina------→ no efecto el Pgp renal**
- **Probable inhibición Pgp intestinal xTVR o saturación Pgp x TVR (sustrato de Pgp)**
- **Es poco probable que TVR bloquee Pgp a otros niveles**

Garg V. J Clin Pharmacol 2012 Jan 26 [Epub ahead of print]

Telaprevir- midazolam En voluntarios sanos

TVR es un inhibidor potente del CY3A4 intestinal>hepatico

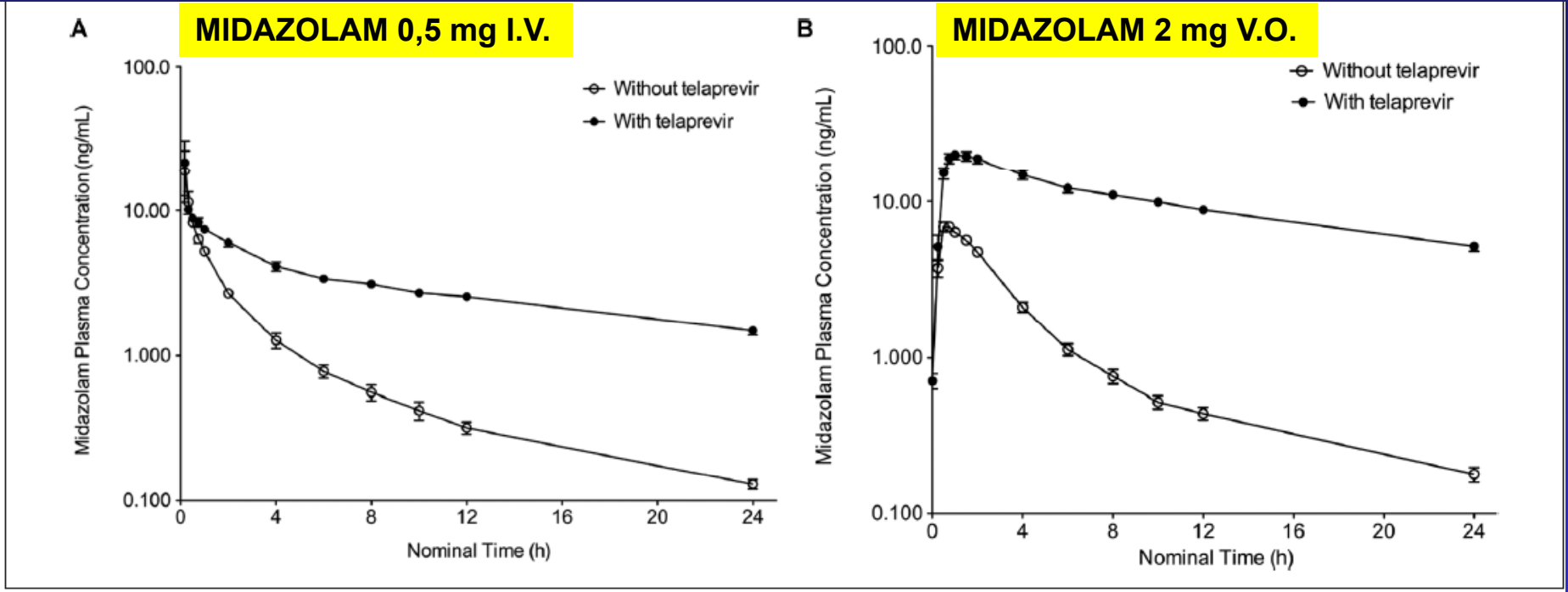


Figure 2. Mean plasma concentration versus time profile of midazolam. Error bars represent standard error of the mean. A, Intravenous midazolam. B, Oral midazolam.

	Midazolam i.v.	Midazolam v.o.
AUC	↑x 3,4 veces	↑x 9 veces
Cmax	≈	↑x2,9 veces

Asociación no recomendada

Garg V. J Clin Pharmacol 2012 Jan 26 [Epub ahead of print]

Secreción tubular activa de tenofovir en túbulos renales proximales

Renal drug-drug interactions: what we have learned and where we are going

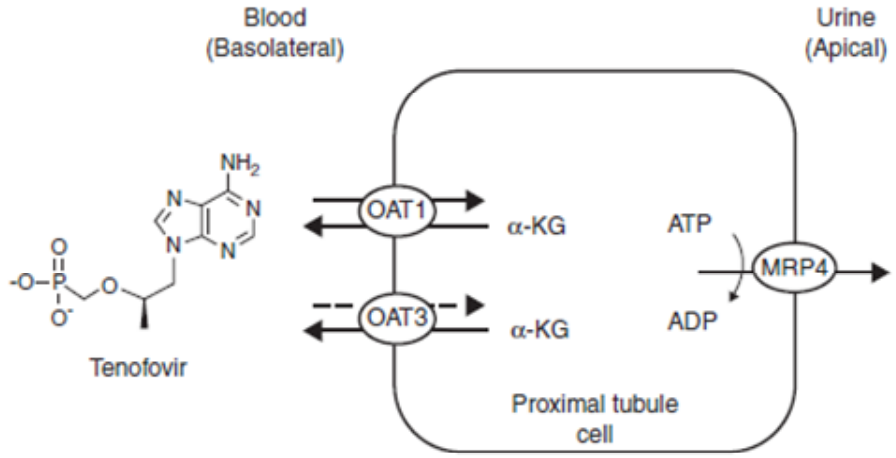
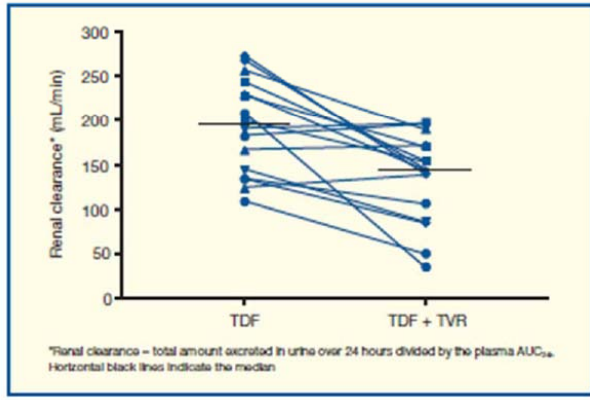


Figure 2. Mechanism of active tubular secretion of tenofovir. Tenofovir undergoes active tubular secretion through an anionic transport pathway facilitated by exchange for intracellular alpha-ketoglutarate (α-KG) at the basolateral membrane of proximal tubule cells by the organic anion transporters 1 and 3 (OAT1 and -3) and ATP-dependent efflux into the urine at the apical membrane by the multidrug resistance protein 4 (MRP4). Dashed line represents relatively less efficient tenofovir transport mediated by OAT3 [82]. Tenofovir has been shown not to be a substrate for the apical efflux pumps Pgp, BCRP and MRP2 [71,72].

Adapted from [72] with permission of the American Society of Microbiology.

TFV Renal Clearance (CL_R) ↓36% with TVR:



	TDF	TVR
AUC	↑30%	↔
Cmin	↑41%	↑3%

	TDF	BOC
AUC	↔	↔
Cmax	↑32%	

Lepist EI, Ray A. Renal drug--drug interactions: what we have learned and where we are going Expert Opin. Drug Metab. Toxicol. 2012, 8 (4);433-448: 433-448.

Table 5. Summary of Drugs to Avoid and Drugs to Use With Caution in Combination With BOC and TPV

	Avoid	Use With Caution	
		↑ Concentration of Concomitant Med or HCV PI	↓ Concentration of Concomitant Med or HCV PI
Alpha-1 adrenoreceptor antagonist	Alfuzosin	Doxazosin, terazosin, tamsulosin, silodosin	
Anticonvulsants	Carbamazepime, phenobarbital, phenytoin		
Antifungals		Ketoconazole, itraconazole, posaconazole, voriconazole	
Antimicrobials		Clarithromycin, erythromycin	
Antimycobacterials	Rifampin, rifapentine	Rifabutin	
Antiretroviral drugs	Lopinavir , darunavir fosamprenavir (TPV), efavirez (BOC)		Efavirenz (TPV)*
Benzodiazepines and sleep aids	Flurazepam, quazepam, triazolam, oral midazolam	Alprazolam, trazodone	
Cardiovascular	Amiodarone, bosentan, dofetilide, flecainide, lidocaine, propafenone, quinidine, sildenafil, and tadalafil for pulmonary arterial hypertension	Calcium-channel blockers, digoxin, carvedilol, nabivolol, irbesartan, losartan	
Ergot derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine		
Herbal products	St. John's wort		
HMG-CoA reductase inhibitors	Lovastatin, simvastatin, atorvastatin (TPV)	Atorvastatin (BOC), pravastatin, rosuvastatin	
Immunosuppressants	Tacrolimus, sirolimus	Cyclosporine	
Oral contraceptives		Drosperinone (BOC)	Ethinyl estradiol
Respiratory		Fluticasone, salmeterol	
Second-generation antipsychotics	Quetiapine	Iloperidone, aripiprazole	

Interactions unique to one of the HCV protease inhibitors are indicated in parentheses (e.g., TPV or BOC).
Abbreviations: Med, medication; PI, protease inhibitor; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A.
*A higher dose of TPV (1,125 mg every 8 hours) has been studied with efavirenz with promising preliminary rates of SVR.

Kiser J. Review and management of drug interactions with boceprevir and telaprevir. Hepatology 2012;55(5):1620-1628.

Nuevos fármacos para el VHC

TMC 435 (IP-VHC) – antirretrovirales

TMC 435 sustrato del CYP3A4
Inhibidor leve CYP1A2 y 3A4 intestinal
Inhibidor de OATP1B1 y MRP2

Sekar V, 45th EASL 2010.
Huisman MT, 61st AASLD 2010

	Efavirenz	TMC435
AUC	↓10%	↓71%
Cmin	↓13%	↓91%

	Rilpivirina	TMC435
AUC	↑12%	↑6%
Cmin	↑25%	↓4%

	Raltegravir	TMC435
AUC	↑8%	↓11%
Cmin	↑14%	↓14%

	Tenofovir	TMC435
AUC	↑18%	↓14%
Cmin	↑24%	↓7%

Ouwerkerk-Mahadevan S. Abstr #49. 19th CROI 2012.

Daclatasvir (inh complejo replicación NS5A)

Daclatasvir sustrato del CYP3A4
Sustrato e inhibidor de la Pgp

	Efavirenz	Daclatasvir ↑90 mg/dia
AUC	↓10%	↔
Cmin	↓13%	↓38%

↑ daclatasvir a 90 mg/24h

	Atazanavir	Daclatasvir ↓ 30 mg/24h
AUC	↔	↔
Cmin	↔	↑83%

~~↓ daclatasvir a 30 mg/24h~~

	Tenofovir	Daclatasvir
AUC	↔	↔
Cmin	↔	↑15%

Daclatasvir = 60 mg/día

Bifano M. Abstr #618. 19th CROI 2012.

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Case Report - Possible interaction with ribavirin and oseltamivir.

Review - Optimising antiretroviral regimens in HIV/HCV co-infected patients.

Guidelines - UK guidelines for boceprevir and telaprevir.

Meeting Report - 19th CROI, Seattle.

Review - Interactions with boceprevir and telaprevir.

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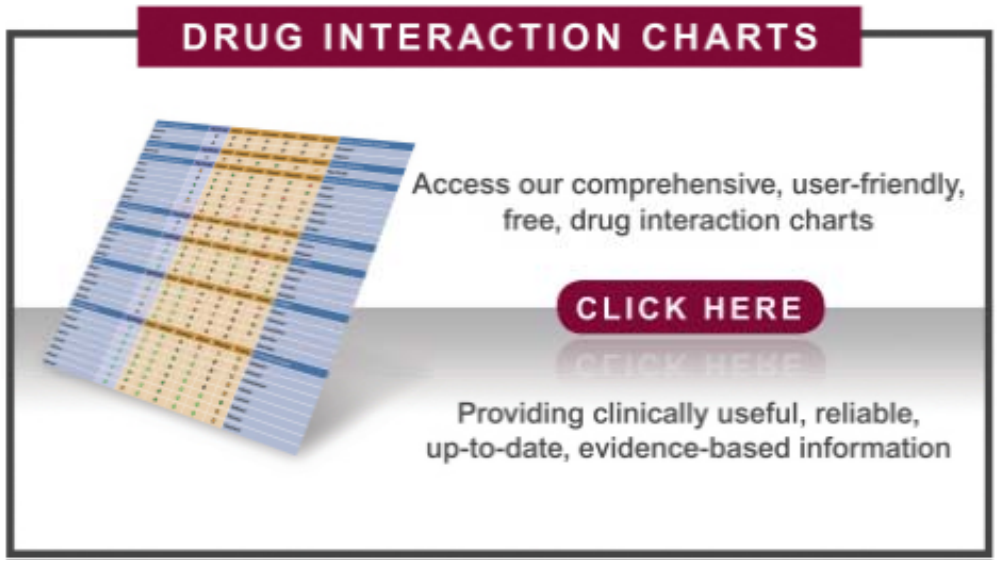
Updated printable charts
The printable charts have been updated to include all the recent additions to the list of



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UNIVERSITY OF LIVERPOOL

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www.hiv-druginteractions.org
A comprehensive HIV drug-drug interaction resource, freely available to healthcare workers, patients and researchers.

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Conclusiones

- Interacciones complejas, impredecibles y mecanismo por establecer…..
  ¿Desplazamiento proteínas?
- Precaución por el efecto inhibidor de boceprevir y telaprevir sobre el CYP3A4 (probablemente TPV>BOC)
- Como farmacéuticos, papel muy importante en la revisión de tratamientos concomitantes con BOC/TPV para evitar toxicidad/ineficacia

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- Dr J Mallolas
  - Diapositivas Boceprevir EASL
- Dra Jennifer Kiser
  - Diapositivas interacciones VHC. 13th IWCPHT 2012

¡Gracias por vuestra atención!