Il paziente infetto HIV/HCV

Le interazioni con i farmaci antiretrovirali

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Worldwide prevalence of HCV infection in HIV-infected individuals

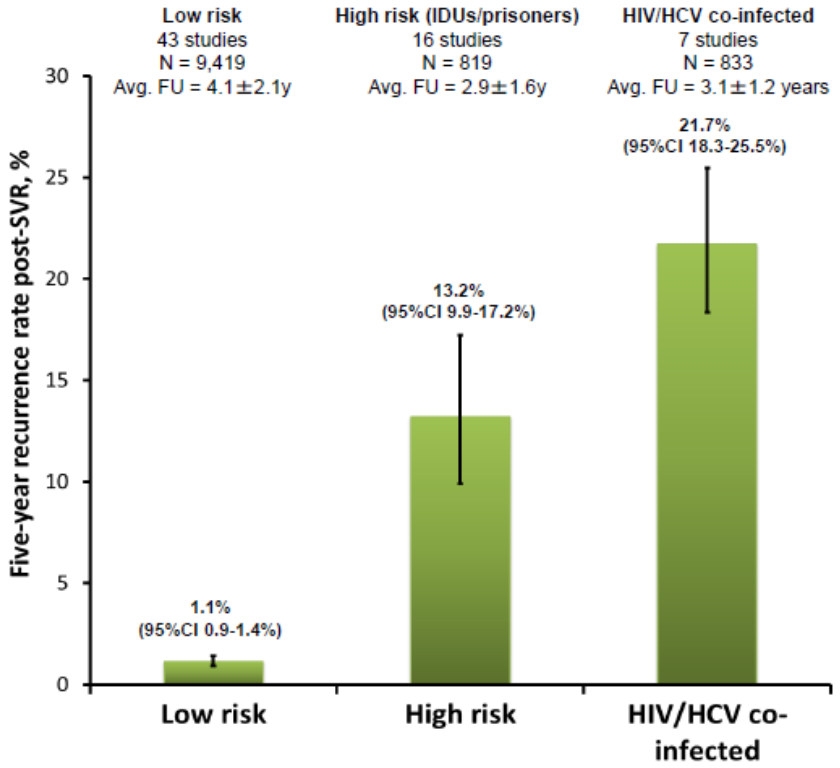
US: ~300,000[1]

	Prevalence
HCV/HIV co-infection	4–74% (overall)[4–8] 50–90% (IDUs)[9,10] 2–7% (MSM)[9,10]

1. http://www.cdc.gov/hiv/pdf/library_factsheets_HIV_and_viral_Hepatitis.pdf Accessed July 2015;
2. Soriano V et al. AIDS 2002;16:813–826; 3. Chanbancherd P et al. Southeast Asian J Trop Med Public Health 2003;34(3):580–582;
4. Speers S et al. Public Health Rep 2011; 126(3):344–348; 5. Hennessey KA et al. J Urban Health 2009; 86(1):93–105;
6. Turner J et al. J Viral Hepat 2010; 17(8):569–577; 7. Fischer MJ et al. J Acquir Immune Defic Syndr 2010; 53(2):222–226;

Risk of late relapse or re-infection with hepatitis C after SVR[1]

Meta-analysis of 66 studies in 11,071 patients, the 5-year rate of HCV recurrence (late relapse/re-infection) post-SVR



- In this analysis, the 5-year rate of HCV recurrence (late relapse /re-infection) post-SVR was: 1.14% in HCV mono-infected "low risk" patients, 13.22% in HCV mono-infected IDUs/prisoners, and 21.72% in HIV/HCV co-infected patients
- The large differences in event rates by risk group suggest that re-infection is significantly more common than late relapse


Le Interazioni farmacologiche dei DAAs hanno e avranno un’importanza clinica?

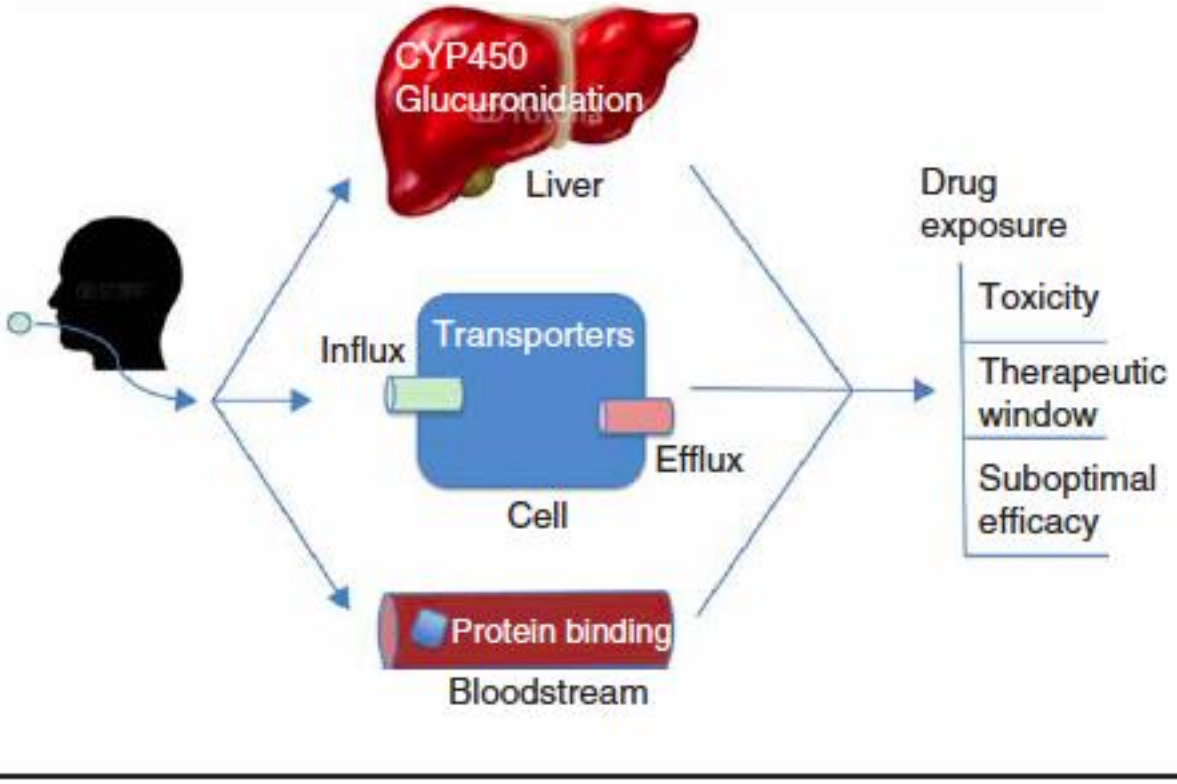
	Mechanism	Dosage	Absorption	Half-life	Elimination
SOF	NS5B POLYM	400 mg q.d.	Bioav ?	<1 h 007 27 h	Urine 80%
SIM	NS3/4A PROT	150 mg q.d. with food	**Bioav incr 60% food**	**10-13 h HVs 41 h in HCV+**	Biliary 91%
LED	NS5A	90 mg q.d.	**Bioav 30-50% pH-depend**	50 h	Feces 70%
DAC	NS5A	60 mg	Bioav ?	12-15 h	Feces 88%
3D	P NS3/4A O NS5A D NS5B	2x 75/50/12.5 e 250 mg b.i.d.	Bioav ? D 70%	P/O 5.5/23 h D 6 h	Feces >86%

Burgess, et al. Annals of Pharmacother 2015

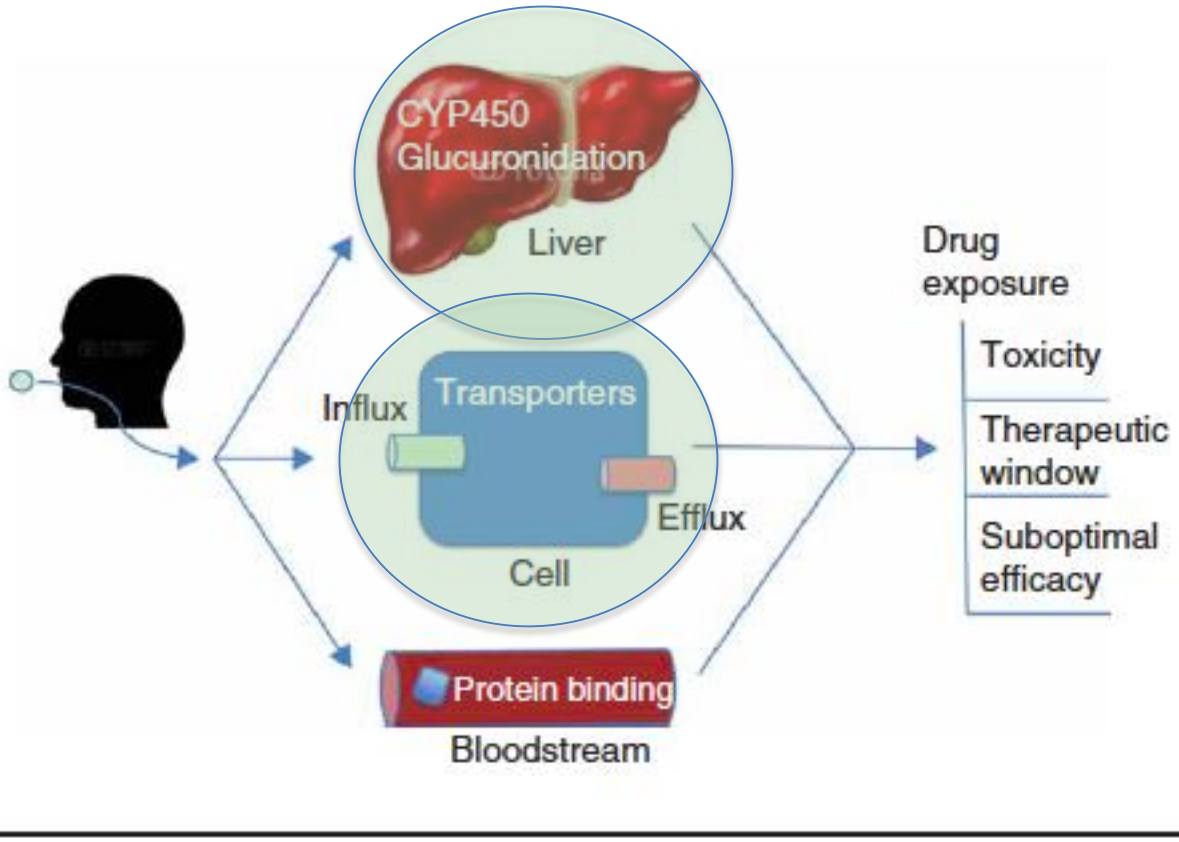
	SIM	SOF	DAC	2D/r	3D/r	SOF/LED
ATV/r	No data	No data	DCV ↑	No data	ATV ↔; OBV ↔ ; PTV ↑; DSV ↔	ATV ↔ **LDV ↑** SOF ↔
DRV/r	SIM ↑ (x7!) DRV ↔	SOF ↑; DRV ↔	No data	No data	DRV ↔; OBV ↓; PTV ↓; DSV ↓	DRV ↔ **LDV ↑**
LPV/r	No data	No data	No data	LPV ↔; OBV ↑; PTV ↑	LPV ↔; OBV ↔; PTV ↑; DSV ↔	No data
TPV/r	No data	No data	No data	No data	No data	No data
MVC	No data	No data	No data	No data	No data	No data

	SIM	SOF	DAC	2D/r	3D/r	SOF/LED
EFV	SIM ↓ (-70%) EFV ↔	SOF ↔ EFV ↔	DCV ↓	ALT elevations	ALT elevations	EFV ↔; FTC ↔; TDF ↑; LDV ↓; SOF ↔
NVP	No data	No data	No data	No data	No data	No data
RPV	SIM ↔ RPV ↔	SOF ↔ EFV ↔	No data	No data	RPV ↑; OBV ↔; PTV ↑; DSV ↔	FTC ↔; RPV ↔; TDF ↑; LDV ↔; SOF ↔
ETV	No data	No data	No data	No data	No data	No data
RAL	SIM ↔ RAL ↔	SOF ↔ EFV ↔	No data	RAL ↑	RAL ↑	RAL ↔ LDV ↔
ELV/COBI	No data	No data	No data	No data	No data	No data
DLG	No data	No data	No data	No data	No data	No data
TDF	SIM ↔ TFV ↔	SOF ↔ EFV ↔	DCV ↔ TFV ↔	No data	No data	No data
E/C/F/TAF	No data	No data	No data	No data	No data	LDV ↑ SOF ↑

Mechanisms of drug-drug interactions involving DAAs

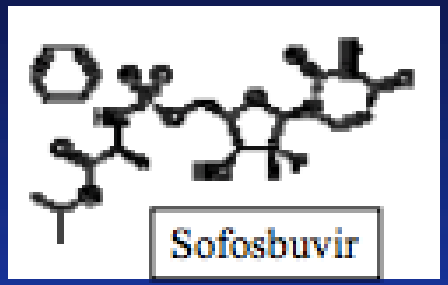


Mechanisms of drug-drug interactions involving DAAs



SOFOSBUVIR

Sofosbuvir metabolism



Sofosbuvir

First-pass metabolism

Portal vein

007-MP

007-DP

007-TP

Active metabolite

GS-007

Nucleoside

Systemic circulation

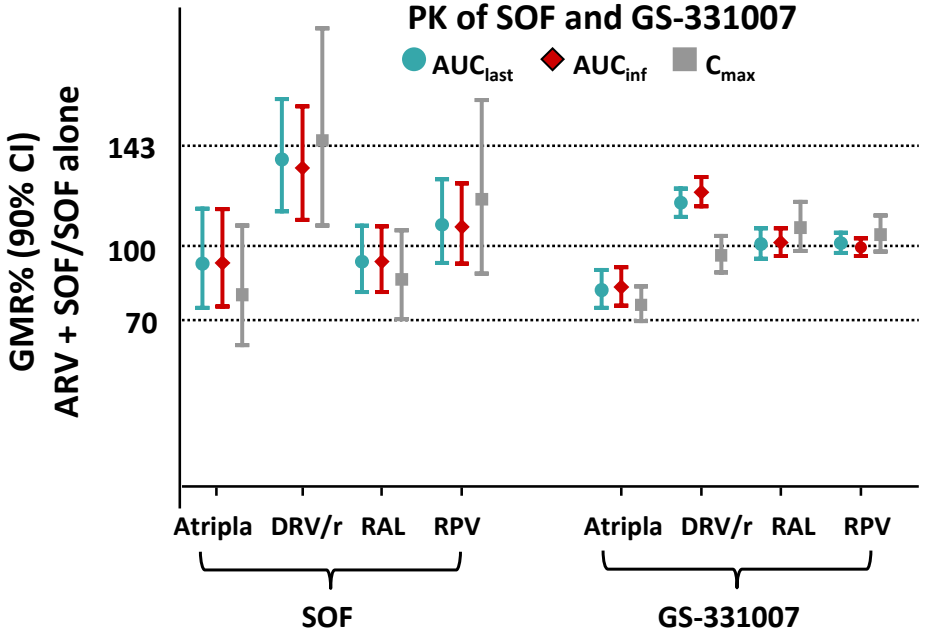
DAA	Substrate	Effect	Clinical DDI extent	Comments
Simeprevir	CYP3A4 P-gp	Inhibits OATP1B1 and multi-drug resistant protein 2 Inhibits gut CYP3A4 and P-gp	Moderate	Bile elimination
Paritaprevir/r	CYP3A4 P-gp and OATP1B1/3	Inhibits liver CYP3A4 Inhibits gut P-gp, BCRP Inhibits OATP1B1/3	Significant	Efavirenz and rilpivirine contraindicated Hyperbilirubinemia
Sofosbuvir	Cathepsin A, esterases and kinases P-gp and BCRP	Inhibits gut P-gp	Low	Urine elimination (80%) and bile (14%)
Dasabuvir	CYP2C8, 3A4 and 2D6 P-gp and BCRP	Inhibits UGT1A1 Inhibits OATP1B1	Significant	
Daclatasvir	CYP3A4 and P-gp	Inhibits OATP1B1/3 and P-gp	Moderate	Increases statin exposure Darunavir/r increases daclatasvir exposure
Ledipasvir	P-gp and BCRP	Inhibits gut P-gp and BCRP Inhibits OATP1B1/3	Low	Increases statin exposure
Ombitasvir	CYP3A4 P-gp and BCRP	Inhibits CYP2C8 and UGT1A1	Significant	

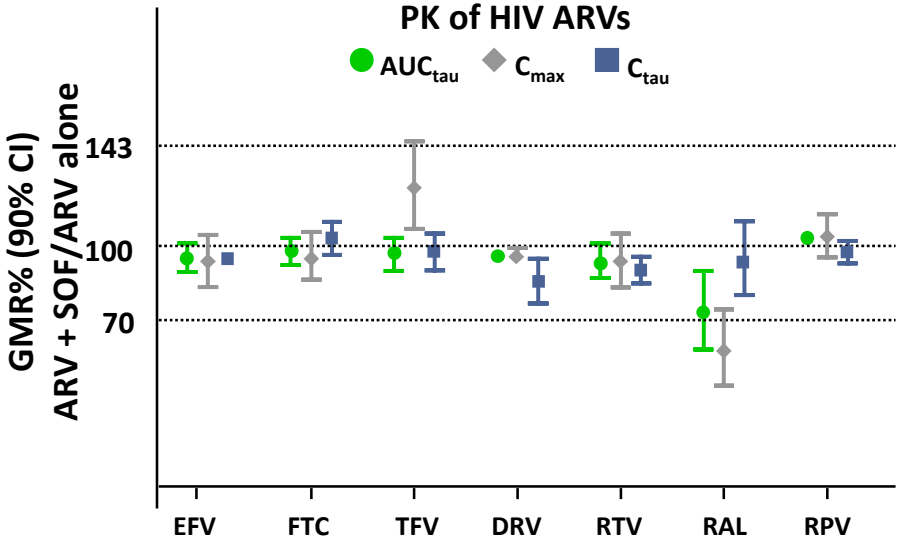
BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

ARV drug interaction data with SOF

PK supports use of SOF with common ARV regimens





- No clinically significant DDIs were observed between SOF and EFV, RPV, DRV + RTV, RAL, or the NRTI backbone of FTC/TDF[1]
- These data support use of SOF 400 mg with common ARV regimens in the HCV/HIV co-infected population[1]
- SOF co-administration with <u>tipranavir is not recommended</u> since expect SOF exposures to be decreased due to P-glycoprotein (P-gp) induction[2]

GMR, geometric mean ratio; DRV/r, darunavir/ritonavir; RAL, raltegravir; RPV, rilpivirine; EFV, efavirenz; FTC, emtricitabine; TFV, tenofovir; TDF, tenofovir disoproxil fumarate; SOF-sofosbuvir, DDI- drug–drug interactions

1. Kirby B et al. AASLD 2012. Boston, MA. #1877
2. Sovaldi (sofosbuvir) Summary of Product Characteristics. August 2015

Effect of ARVs on Sofosbuvir: *Victim*

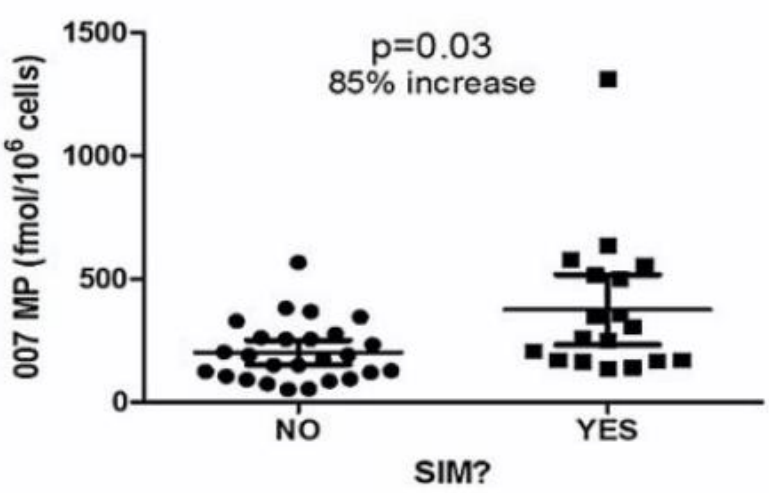
Drug	Effect on Sofosbuvir and GS-331007 AUC (exposure)	Recommendation
Darunavir/r	SOF increased 34%; GS-331007 – no effect	No dose adjustment
Rilpivirine	No effect on SOF or GS-331007	No dose adjustment
Efavirenz	No effect on SOF or GS-331007	No dose adjustment
Raltegravir	No effect on SOF or GS-331007: RAL decreased 27%	No dose adjustment
Tenofovir	No effect on SOF or GS-331007	No dose adjustment

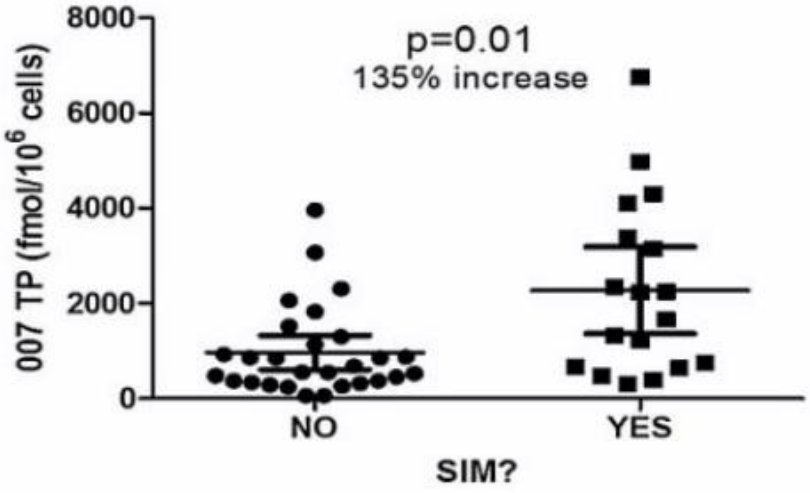
Mathias A 14th Int Workshop on Clin Pharm of HIV Ther Session 5; Kirby B et al 63rd AASLD 2012; Abs 1877. ; Sofosbuvir USPI 2013

Effect of Other Co-administered Drugs on Sofosbuvir: *Victim*

Drug	Effect on Sofosbuvir and GS-331007 AUC (exposure)	Recommendation
Methadone *(multiple dose)*	SOF increased 30%; no effect on GS-331007	No dose adjustment
Cyclosporine	SOF increased 4-fold but no effect on GS-331007	No dose adjustment
Tacrolimus	No effect on SOF or GS-331007	No dose adjustment
Rifampicin	Rifampicin is a potent P-gp inducer*	Not recommended

Results





Plots are mean (95% CI)

- Increased 007 MP (85%) and TP (135%) levels observed in subjects also receiving simeprevir.
- This interaction remained after controlling for fibrosis score and liver decompensation.
- No significant ribavirin associations.

LEDIPASVIR
LEDIPASVIR/SOFOSBUVIR

Drug	CYP Activity	Transporters	Interaction Potential
Ledipasvir	▪ Little metabolism ▪ Not Inhibitor of CYP or UGT ▪ Not Inducer of CYP or UGT	▪ P-gp substrate (likely) ▪ Inhibition of intestinal P-gp (weak) ▪ Inhibition of OATP1B1/3 (weak)	▪ **Weak**

Eley T et al, 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-13; Eley T et al, 2011, 62nd AASLD Abs 381; Eley T et al 2012, 7th Int Workshop on Clin Pharm of Hep Ther; Abs O-4; Kirby B et al 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-20; Mathias A, 14th Int Workshop on Clin Pharm of HIV Ther, Session 5

German, AASLD 2014

Effect of P-gp Inducers on LDV/SOF[2]

Object	Perpetrator	AUC	C_{max}
SOF	Rifampin	↓ 72%	↓ 77%
GS-331007		↔	↔
LDV		↓ 59%	↓ 35%

- P-gp inducers (eg, rifampin, St. John's wort) should not be used with LDV/SOF
- Use of other P-gp inducers (eg, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine, and oxcarbazepine) with LDV/SOF is not recommended

Effect of LDV/SOF on OATP Substrates[4]

Object	Perpetrator	AUC	C_{max}
Pravastatin	LDV*	↑ 168%	↑ 166%
Rosuvastatin		↑ 699%	↑ 1670%

*LDV administered in combination with VDV and TGV.

- VDV is a potent OATP inhibitor; LDV is a weak OATP inhibitor
- SOF and GS-331007 are not OATP inhibitors
- LDV/SOF may be administered with OATP substrates

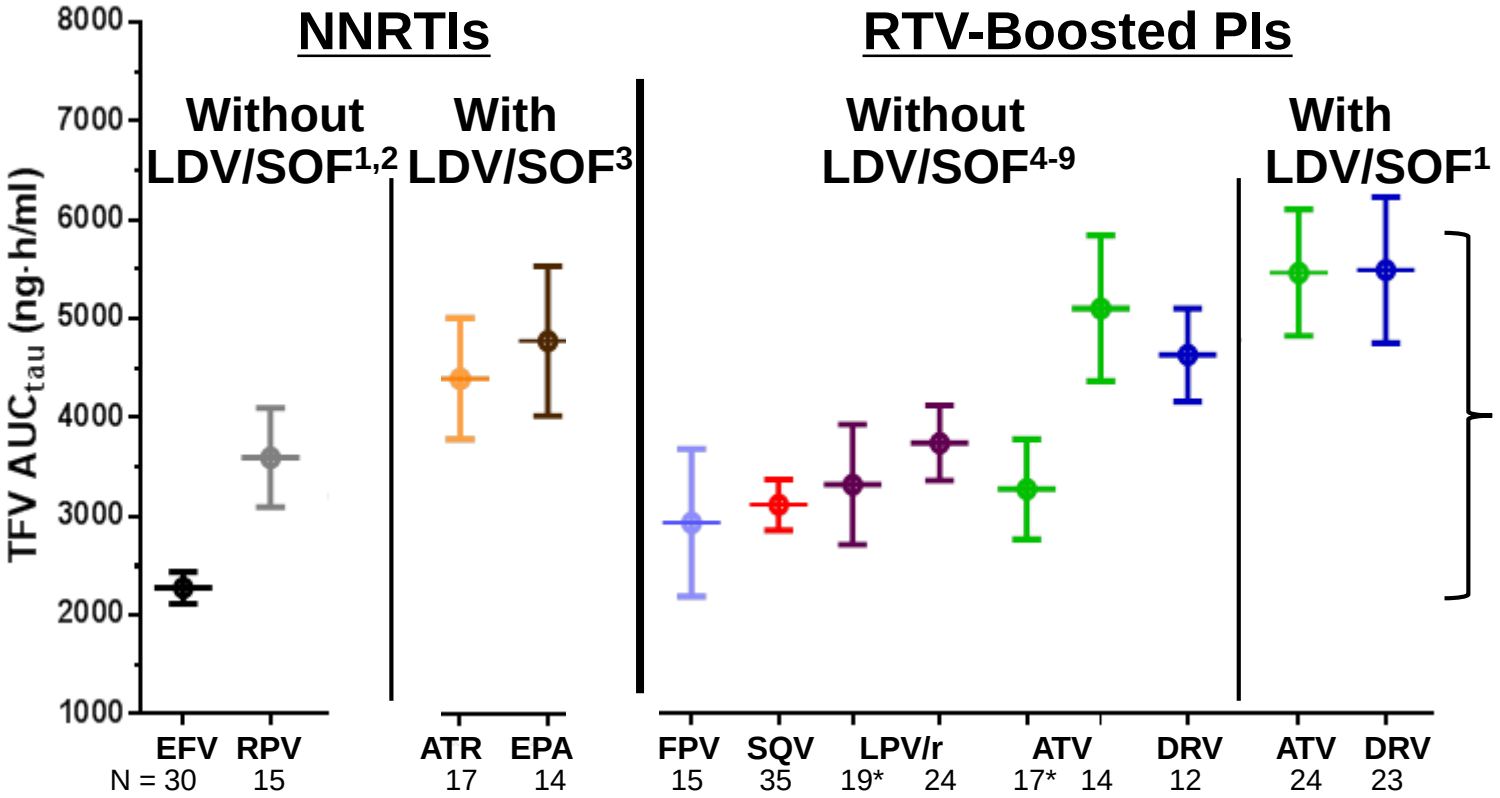
- Overall incidence of statin-related adverse events (eg, myopathy, fatigue, asthenia) in the pooled Phase 2/3 population was similar in HCV-infected patients who did and did not receive statins
- Clinically relevant interactions are not expected with LDV/SOF and most statins (eg, pravastatin); the use of rosuvastatin is not recommended

Effect of ARVs on LED/SOF

Perpetrator*	Object	AUC	C_{max}	C_{tau}
ATV/RTV+FTC/TDF	SOF	↔	↔	NA
	GS-331007	↔	↔	↑42%
	LDV	↑96%	↑68%	↑118%
DRV/RTV+FTC/TDF	SOF	↓ 27%	↓ 37%	NA
	GS-331007	↔	↔	↔
	LDV	↔	↔	↔

*Similar results when LDV/SOF and ATV/RTV+FTC/TDF or DRV/RTV+FTC/TDF were administered simultaneously or following a 12-hour stagger.

Tenofovir (TFV) Exposures when Coadministered with Various ARVs with or without LDV/SOF



- **TFV exposures are higher when TDF is coadministered with LDV/SOF compared to without LDV/SOF**
- **Compared to the range of TFV exposures with available safety data**
  - For EFV or RPV: TFV exposures fall within the range[1]
  - For RTV-boosted PIs: TFV exposures partially exceed the range[2]

1, Data on File, Gilead Sciences.
2. Hoetelmans RMW, et al. 6th IWCPHT 2005. Quebec City, Canada. Poster #2.11
3. German P, et al. ICPHHT 2014. #O6
4. Luber AD, et al. *HIV Medicine*. 2010;11:193-9 (FPV+RTV)
5. Chittick GE, et al. *AAC*. 2006; 50(4):1304-10 (SQV+RTV)
6. Zhu. 9th IWCPHT. 2008. #023 (ATV+RTV & LPV/r)
7. Kearney B, et al. *JAIDS*. 2006;43(3):278-83 (LPV/r)
8. Agarwala S, et al. 6th IWCPHT 2005. #16. (ATV+RTV)
9.. Hoetelmans RMW, et al. *BJCP*. 2007;64(5):655-61 (DRV+RTV)

* HIV-infected subjects in CASTLE study

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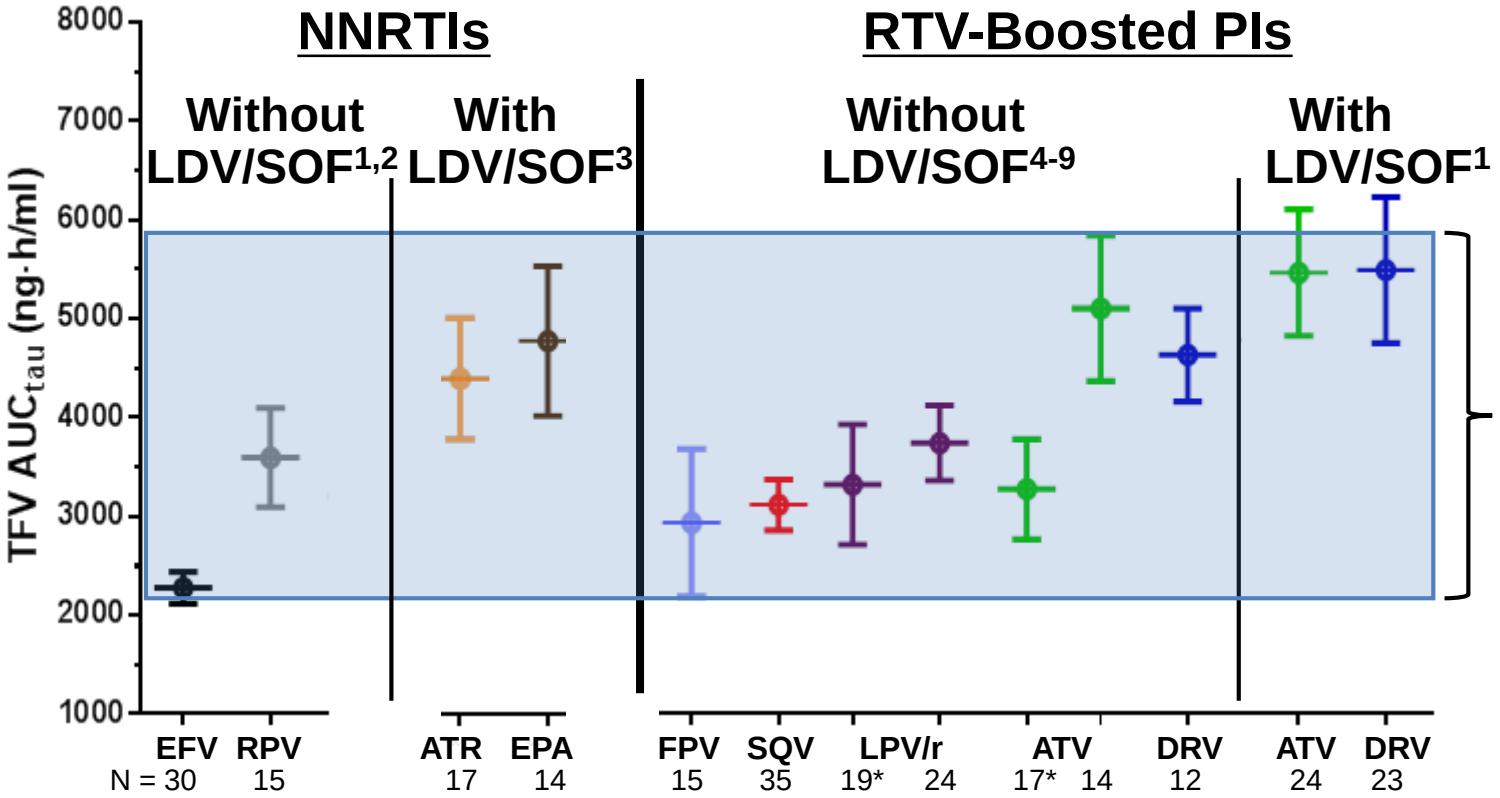

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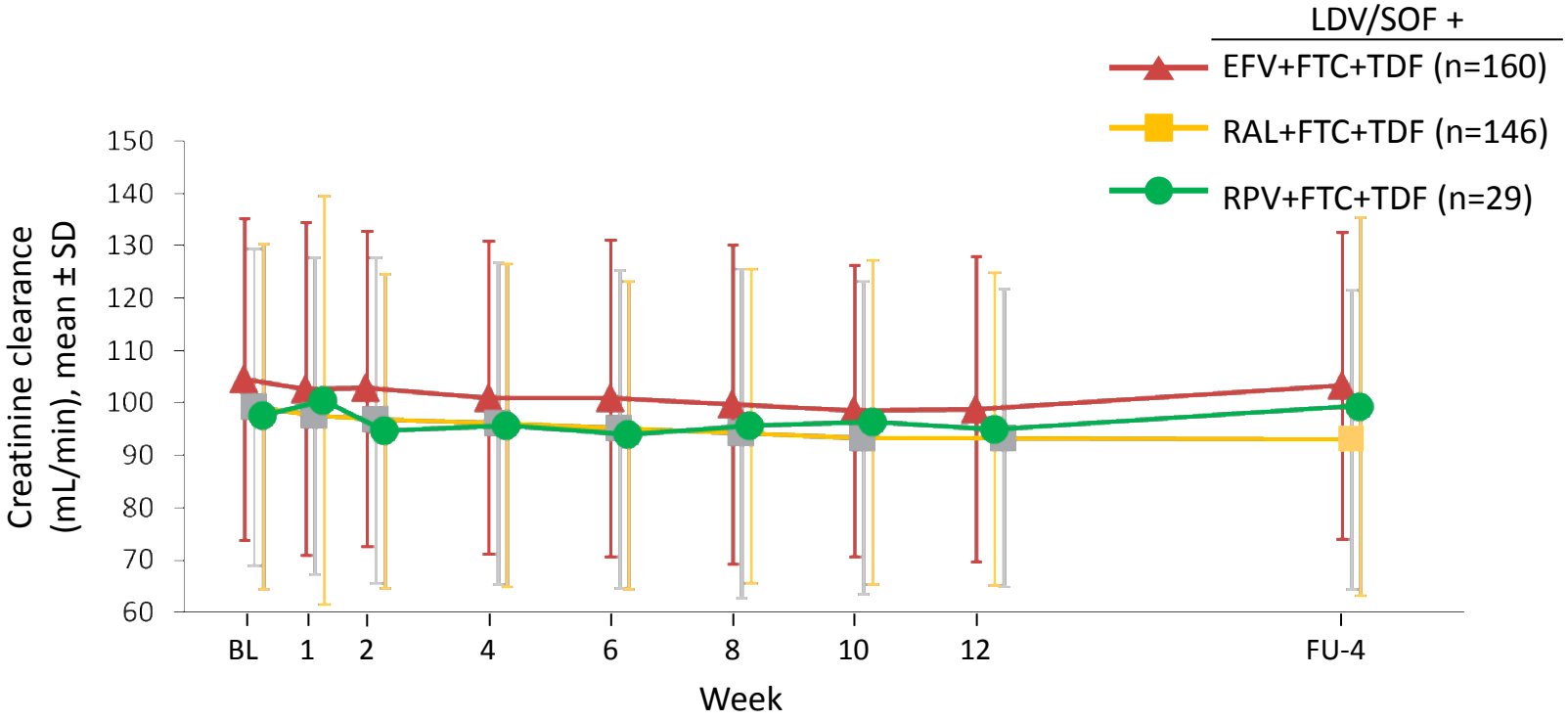
* HIV-infected subjects in CASTLE study

ION-4: LDV/SOF in HIV/HCV

Renal function[1]

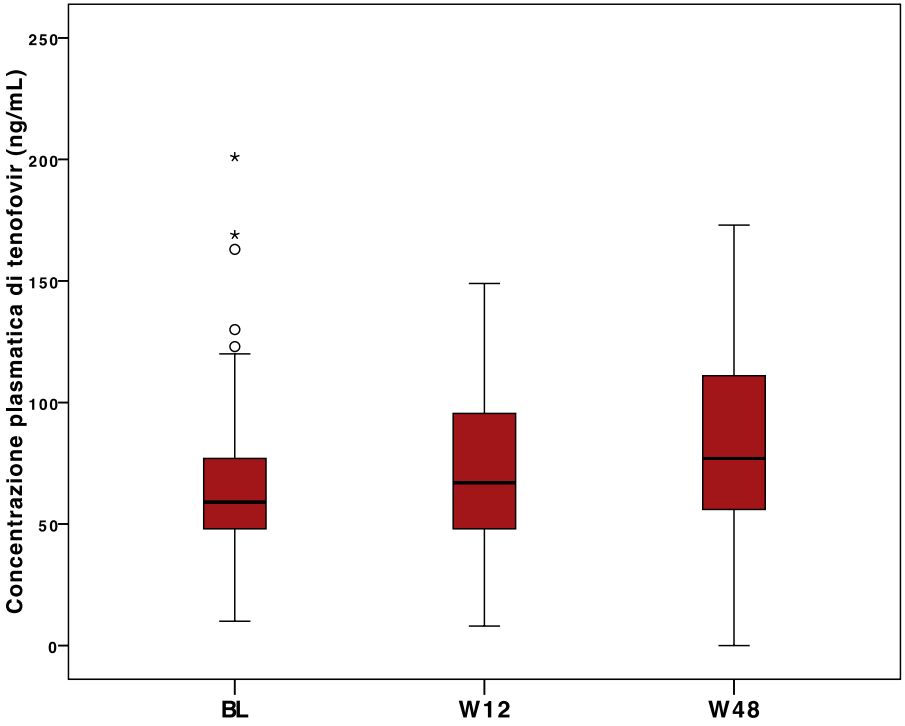


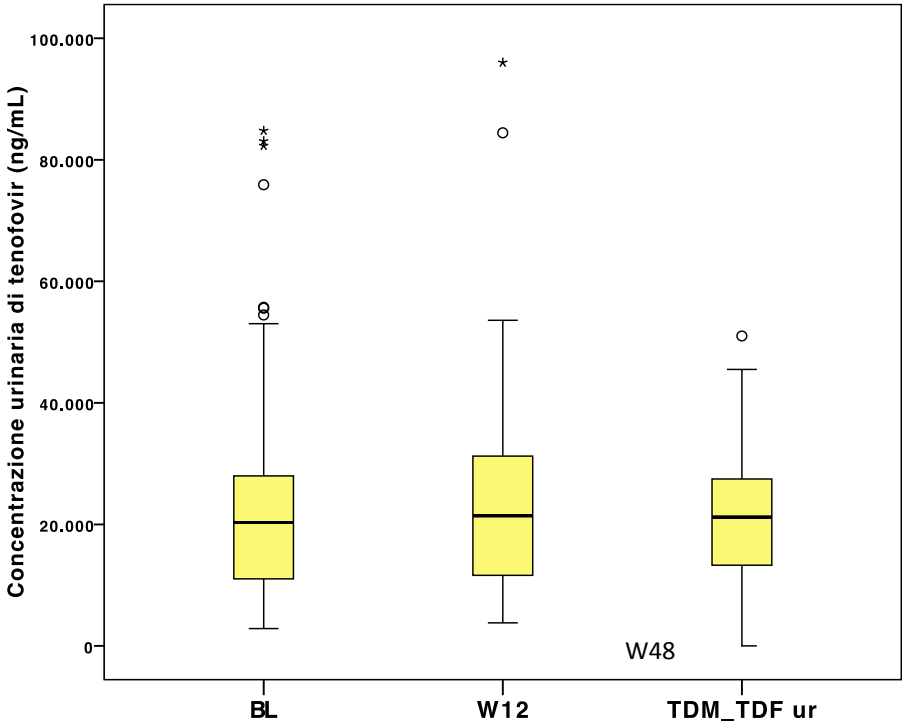
- **No grade 3 or 4 creatinine abnormalities nor any grade 3 or 4 AEs in the renal or urinary disorder occurred in study[2]**
- [illegible]
  - 2 completed treatment with no ART change
  - 1 discontinued TDF, 1 had dose reduction of TDF

*equivalent to 0.4 mg/dL

1. Adapted from Naggie S et al. CROI 2015. Seattle, WA. #LB-152; 2. Naggie S et al. NEJM 2015

TFV PK nello switch a EVP





Marinaro L, et al. Submitted

Impatto delle puliriterapie
Tenofovir e Diclofenac

Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration

M Bickel,[1] P Khaykin,[1] C Stephan,[1] K Schmidt,[1] M Buettner,[2] K Amann,[2] T Lutz,[3] P Gute,[3] A Haberl,[1] H Geiger,[4] HR Brodt[1] and O Jung[4]

[1]Department of Infectious Disease, Goethe University, Frankfurt/Main, Germany, [2]Department of Nephropathology, Institute of Pathology, Friedrich Alexander University, Erlangen, Germany, [3]Infektiologikum, Frankfurt/Main, Germany and [4]Department of Nephrology, Goethe University, Frankfurt/Main, Germany

89 patients with diclofenac use: 61 patients (68.5%) TDF+ & 28 patients (31.5%) TDF-

1. Thirteen patients **(14.6%) developed acute kidney injury (AKI)** shortly after initiating diclofenac treatment. ONLY IN TDF recipients
2. All cases were accompanied by new onset of at least two parameters indicating **proximal tubular damage**, such as normoglycaemic-glucosuria and hypophosphataemia.
3. TFV-associated nephrotoxicity was demonstrated by renal biopsy in four cases.
4. Additionally, **11.5% of patients on TDF treatment developed new-onset proximal tubular damage, while having a preserved glomerular filtration rate**. In contrast, diclofenac did not affect renal function in patients with TDF-sparing cART, as only one case of isolated hypophataemia was observed in these patients.

In univariate analysis, risk factors for AKI were TDF-containing cART (P = 0.0076) and pre-existing hypophosphataemia (P = 0.0086).

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[1]Department of Infectious Disease, Goethe University, Frankfurt/Main, Germany, [2]Depart
Institute of Pathology, Friedrich Alexander University, Erlangen, Germany, [3]Infektiologikum, Frankfurt/Main, Germany
and

89 p

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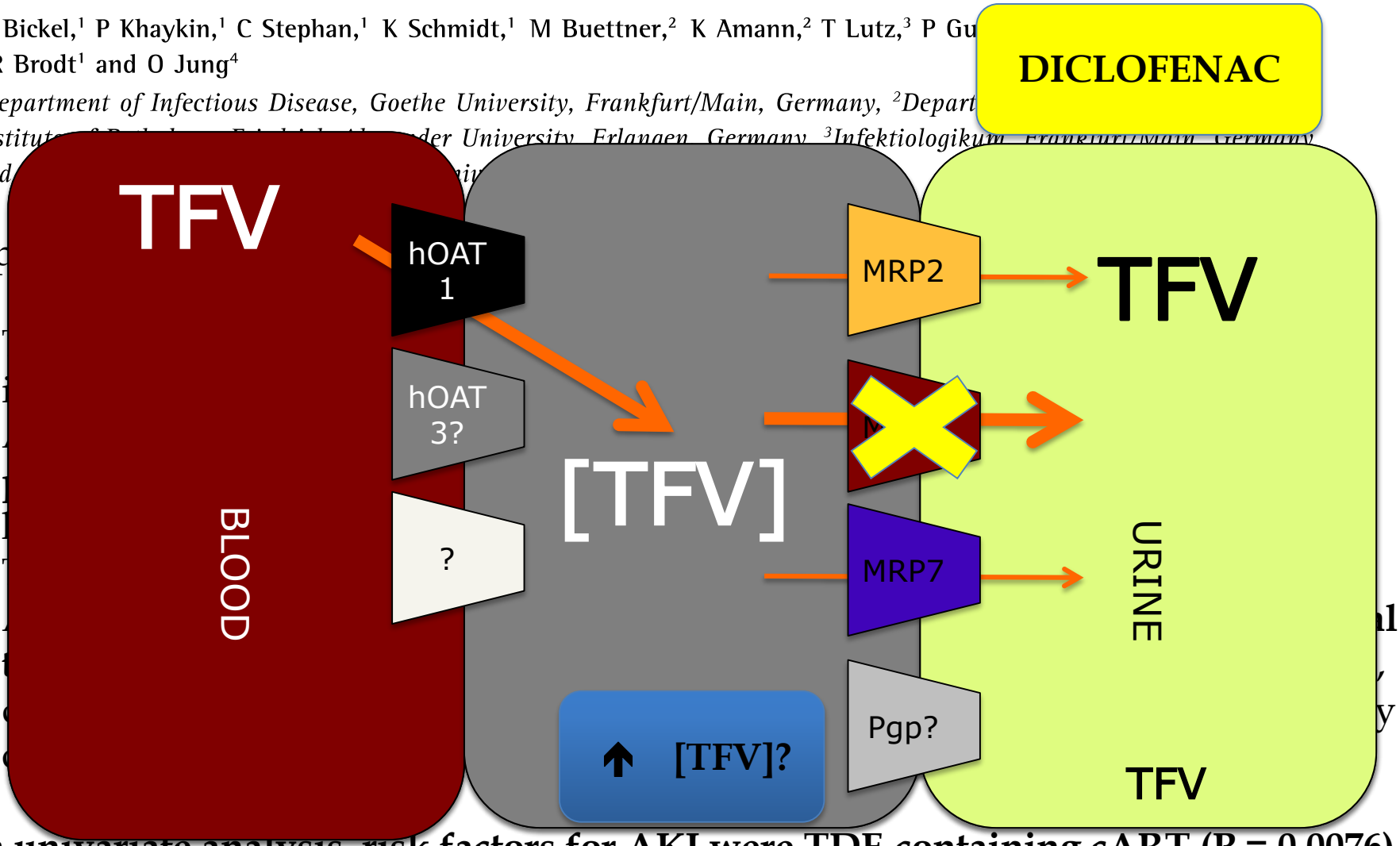

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Effect of LDV/SOF on HIV ARVs

Integrase-Containing Regimens

Perpetrator	Object	AUC	C_{max}	C_{tau}
LDV	RAL	↓ 15%	↓ 18%	↑15%
SOF		↓ 27%	↓ 43%	↔
LDV/SOF	DTG	↔	↔	↔
	FTC	↔	↔	↔
	TFV	↑65%	↑61%	↑115%
LDV/SOF	EVG	↔	↔	↑46%
	COBI	↑53%	↔	↑225%
	FTC	↔	↔	↔
	TAF	↔	↔	NA
	TFV	↔	↔	↔

- TFV, administered as TDF and not TAF, increases with LDV/SOF

Kirby et al, AASLD 2012; German et al, IWCPHHT 2014; Garrison et al, IWCPHHT 2015

SIMEPREVIR

DAA	Substrate	Effect	Clinical DDI extent	Comments
Simeprevir	CYP3A4 P-gp	Inhibits OATP1B1 and multi-drug resistant protein 2 Inhibits gut CYP3A4 and P-gp	Moderate	Bile elimination
Paritaprevir/r	CYP3A4 P-gp and OATP1B1/3	Inhibits liver CYP3A4 Inhibits gut P-gp, BCRP Inhibits OATP1B1/3	Significant	Efavirenz and rilpivirine contraindicated Hyperbilirubinemia
Sofosbuvir	Cathepsin A, esterases and kinases P-gp and BCRP	Inhibits gut P-gp	Low	Urine elimination (80%) and bile (14%)
Dasabuvir	CYP2C8, 3A4 and 2D6 P-gp and BCRP	Inhibits UGT1A1 Inhibits OATP1B1	Significant	
Daclatasvir	CYP3A4 and P-gp	Inhibits OATP1B1/3 and P-gp	Moderate	Increases statin exposure Darunavir/r increases daclatasvir exposure
Ledipasvir	P-gp and BCRP	Inhibits gut P-gp and BCRP Inhibits OATP1B1/3	Low	Increases statin exposure
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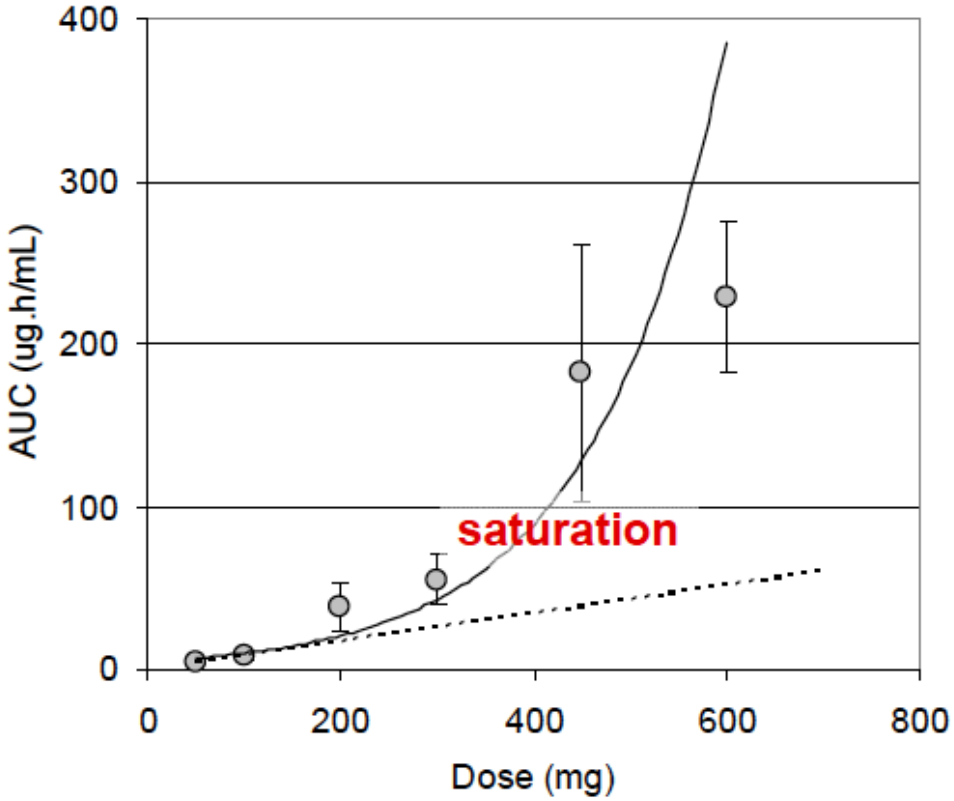
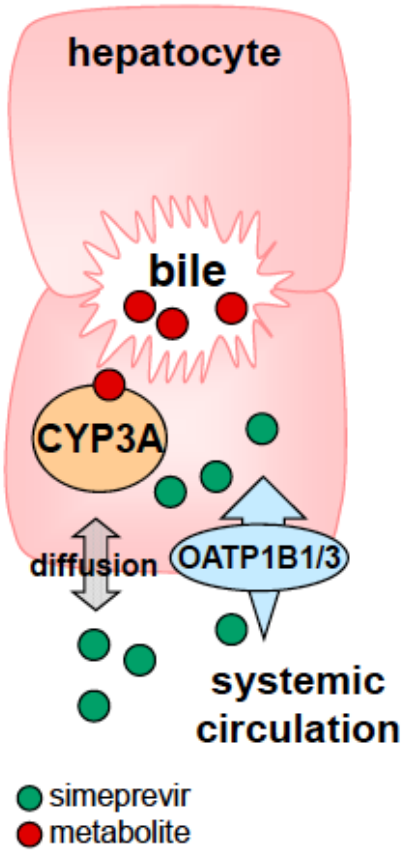
BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

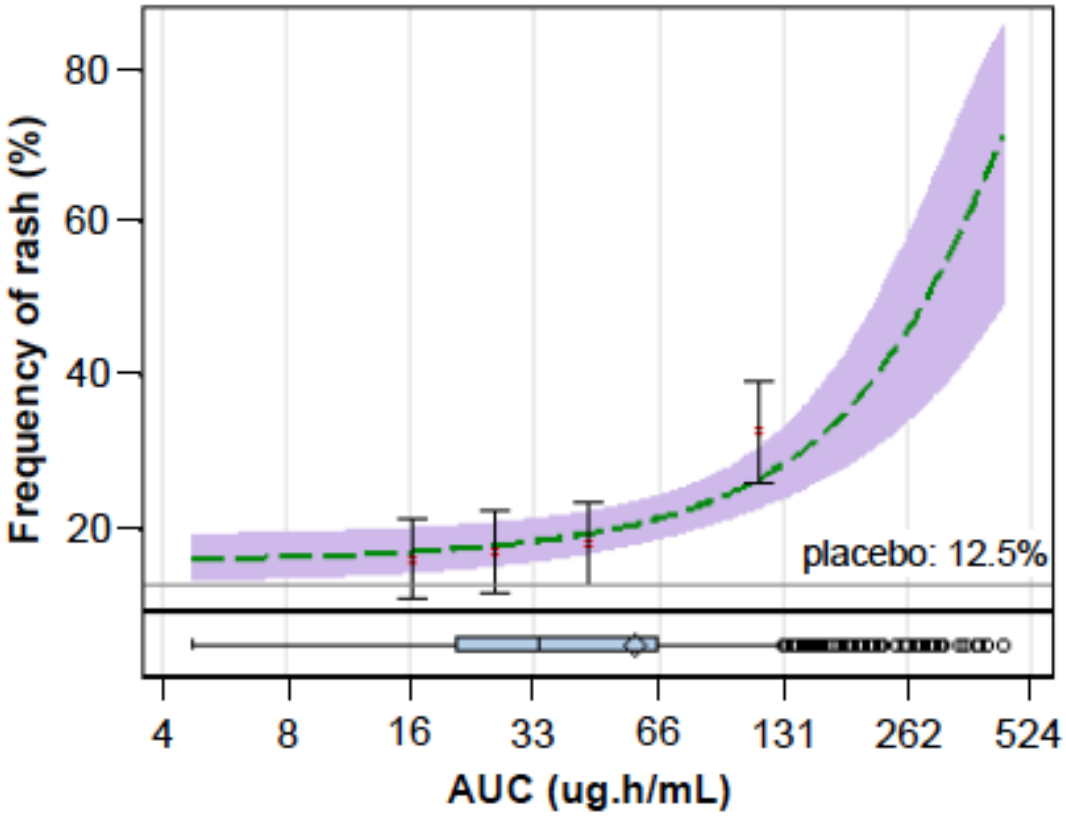
Simeprevir Exhibits Non-Linear Pharmacokinetics





Trial C101 (healthy subjects)

An Increased Incidence of Rash was Associated with Higher Exposures in Phase 3



Similar relationships between exposures and:

- photosensitivity
- pruritus
- dyspnea
- increased bilirubin

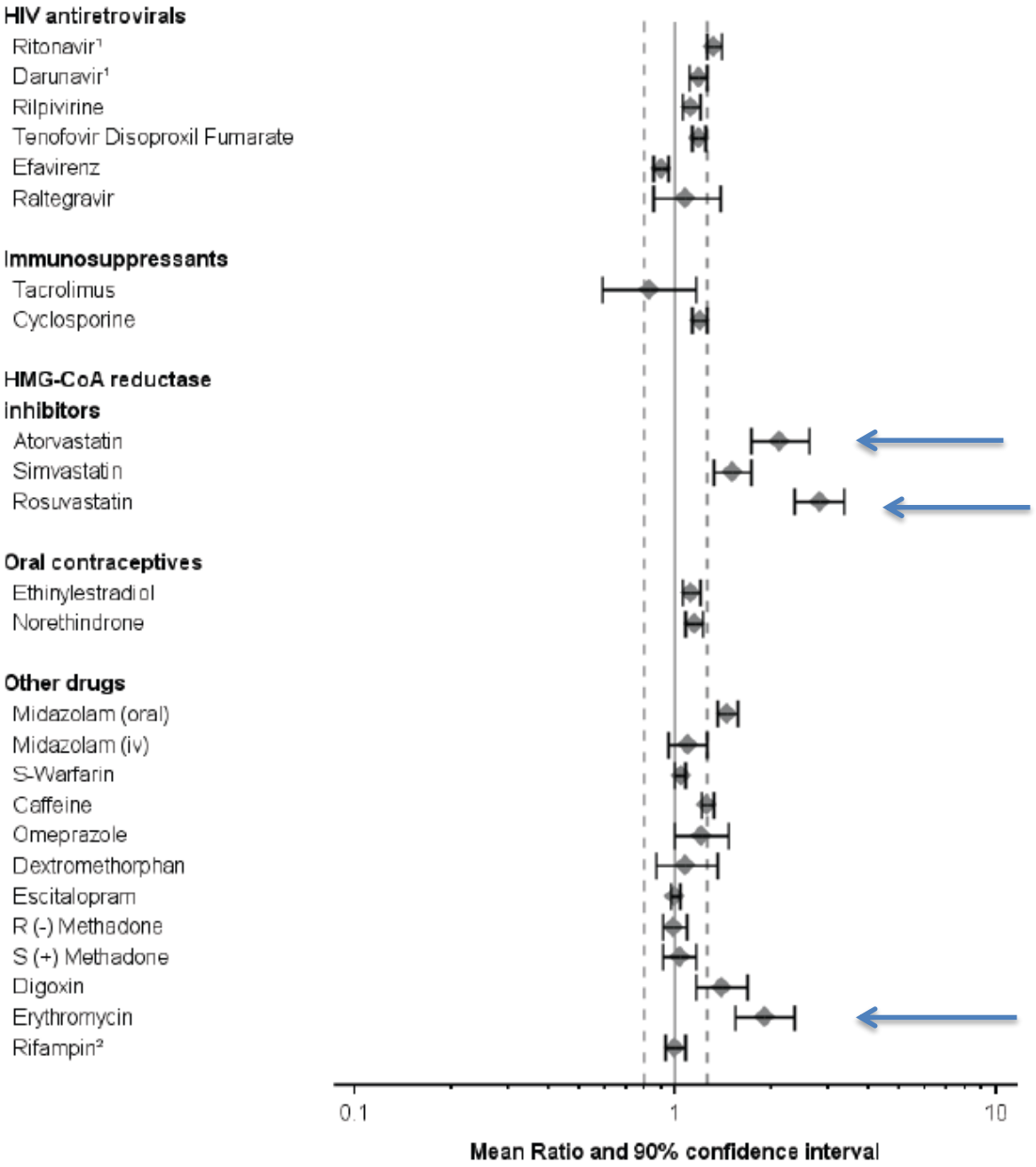
Phase 3 trials (C208, C216, HPC3007)

Effect of ARVs on Simeprevir: *Victim*

Drug	Effect on Simeprevir AUC (exposure)	Mechanism/ *Recommendation*
Darunavir/r	2.6-fold increase (DRV increased 18%)	RTV Inhibits CYP3A4 *Not recommended*
Rilpivirine	No effect	*No dose adjustment*
Efavirenz	70% decrease	EFV induces CYP3A4 *Not recommended*
Raltegravir	11% decrease	*No dose adjustment*
Tenofovir	14% decrease (TFV increased 18%)	Intestine or renal transport *No dose adjustment*

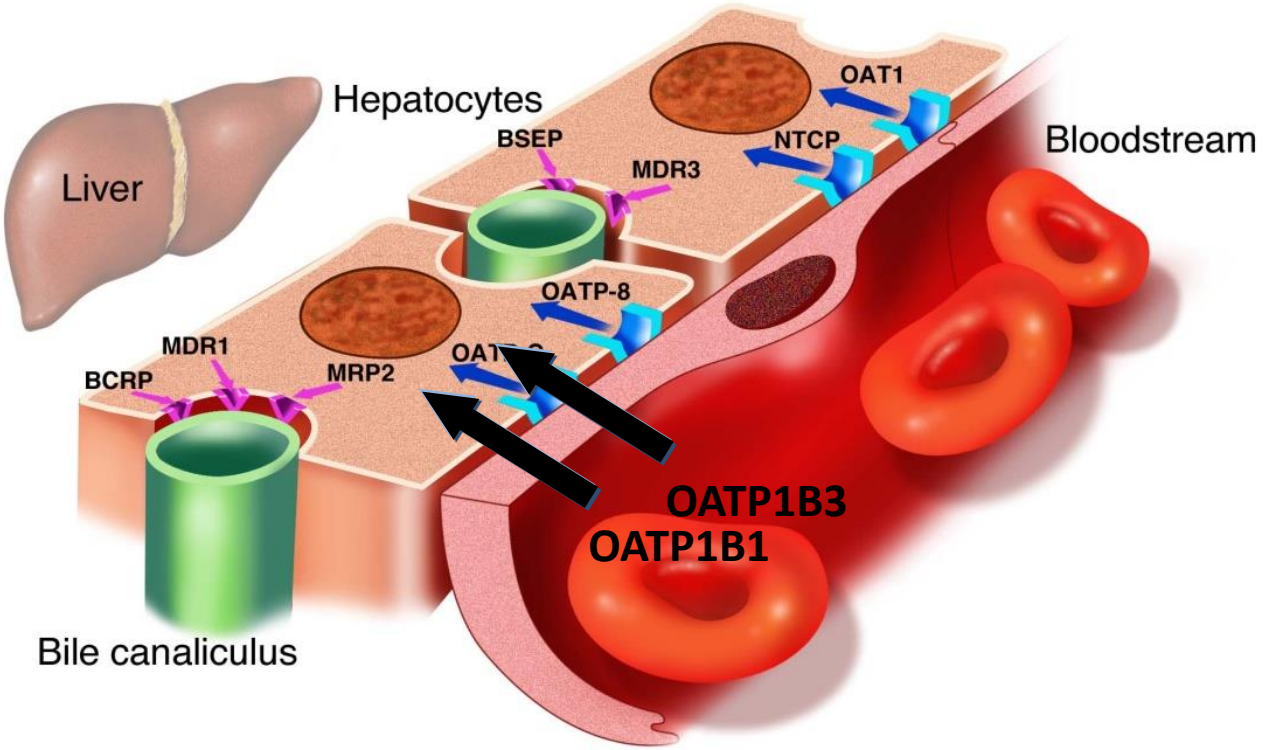
Ouwerkerk-Mahadevan S et al, IDSA 2012; Abs 1618; Ouwerkerk-Mahadevan S et al, CROI 2012; Abs 49 ; Simeprevir (Olysio) USPI

Figure 6: Effect of SMV Administration at 150 mg Once Daily on Exposure of Coadministered Drugs



Simeprevir, FDA Advisory Commitee Briefing Document

Drug-drug interactions involving both cytochromes and drug transporters can have profound effects



1) Dingemasse J et al. Antiviral Ther 2010, 2) Treiber A et al. DMD 2007, 3) Hartkoorn RC et al. Pharmacogenetics & Genomics 2010, 4) Annaert P. et al. Xenobiotica 2010

DACLATASVIR

DAA	Substrate	Effect	Clinical DDI extent	Comments
Simeprevir	CYP3A4 P-gp	Inhibits OATP1B1 and multi-drug resistant protein 2 Inhibits gut CYP3A4 and P-gp	Moderate	Bile elimination
Paritaprevir/r	CYP3A4 P-gp and OATP1B1/3	Inhibits liver CYP3A4 Inhibits gut P-gp, BCRP Inhibits OATP1B1/3	Significant	Efavirenz and rilpivirine contraindicated Hyperbilirubinemia
Sofosbuvir	Cathepsin A, esterases and kinases P-gp and BCRP	Inhibits gut P-gp	Low	Urine elimination (80%) and bile (14%)
Dasabuvir	CYP2C8, 3A4 and 2D6 P-gp and BCRP	Inhibits UGT1A1 Inhibits OATP1B1	Significant	
Daclatasvir	CYP3A4 and P-gp	Inhibits OATP1B1/3 and P-gp	Moderate	Increases statin exposure Darunavir/r increases daclatasvir exposure
Ledipasvir	P-gp and BCRP	Inhibits gut P-gp and BCRP Inhibits OATP1B1/3	Low	Increases statin exposure
Ombitasvir	CYP3A4 P-gp and BCRP	Inhibits CYP2C8 and UGT1A1	Significant	

BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

Daclatasvir DDIs - *victim*

CYP3A4 and/or Pgp INDUCERS - anti-HIV	EFV	Increase to 90 mg/day
CYP3A4 and/or Pgp INDUCERS - other than EFV	*Etravirine*, Carbamazepine, oxacarbazepine, phenobarbital, dexame St John's wort	Not recommended
CYP3A4 and/or Pgp INHIBITORS Anti-HIV	ATV/RTV **DRV/r and LPV/R**	Decrease to 30 mg/day **Standard dose***
CYP3A4 and/or Pgp INHIBITORS other than anti-HIV	charithromycin, itraconazole, quinidine, ranolazine	Caution or decrease to 30 mg/day

*** Daclatasvir AUC increase by 40% (DRV/r) and 15% (LPV/R)- HEP DART meeting Dec 2014**

Daclatasvir DDIs - *perpetrator*

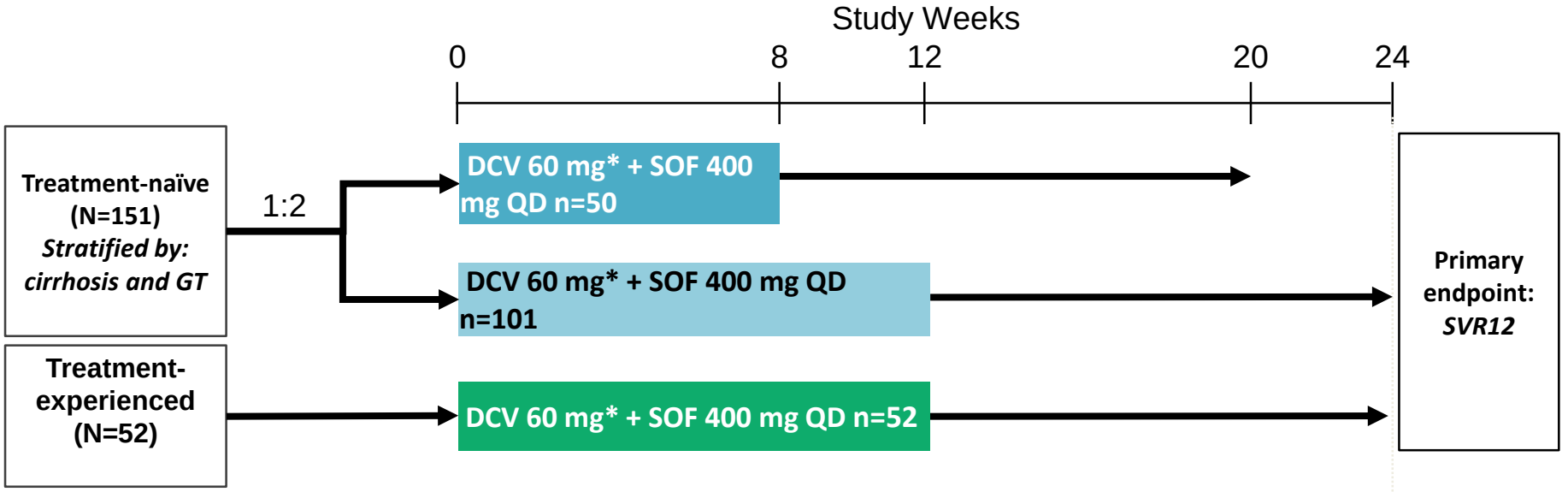
- ✓ No effect of gastric acid modifiers, midazolam or oral contraceptives
- ✓ Caution with rosuvastatin (increase of AUC by 58%%)

Bifano M et al, 2013, 8th Int Workshop on Clin Pharm of Hep Ther, Abs O-15; Bifano M et al AVT 2014; In Press; Bifano M et al 2013; EASL; Abs 794.

‡

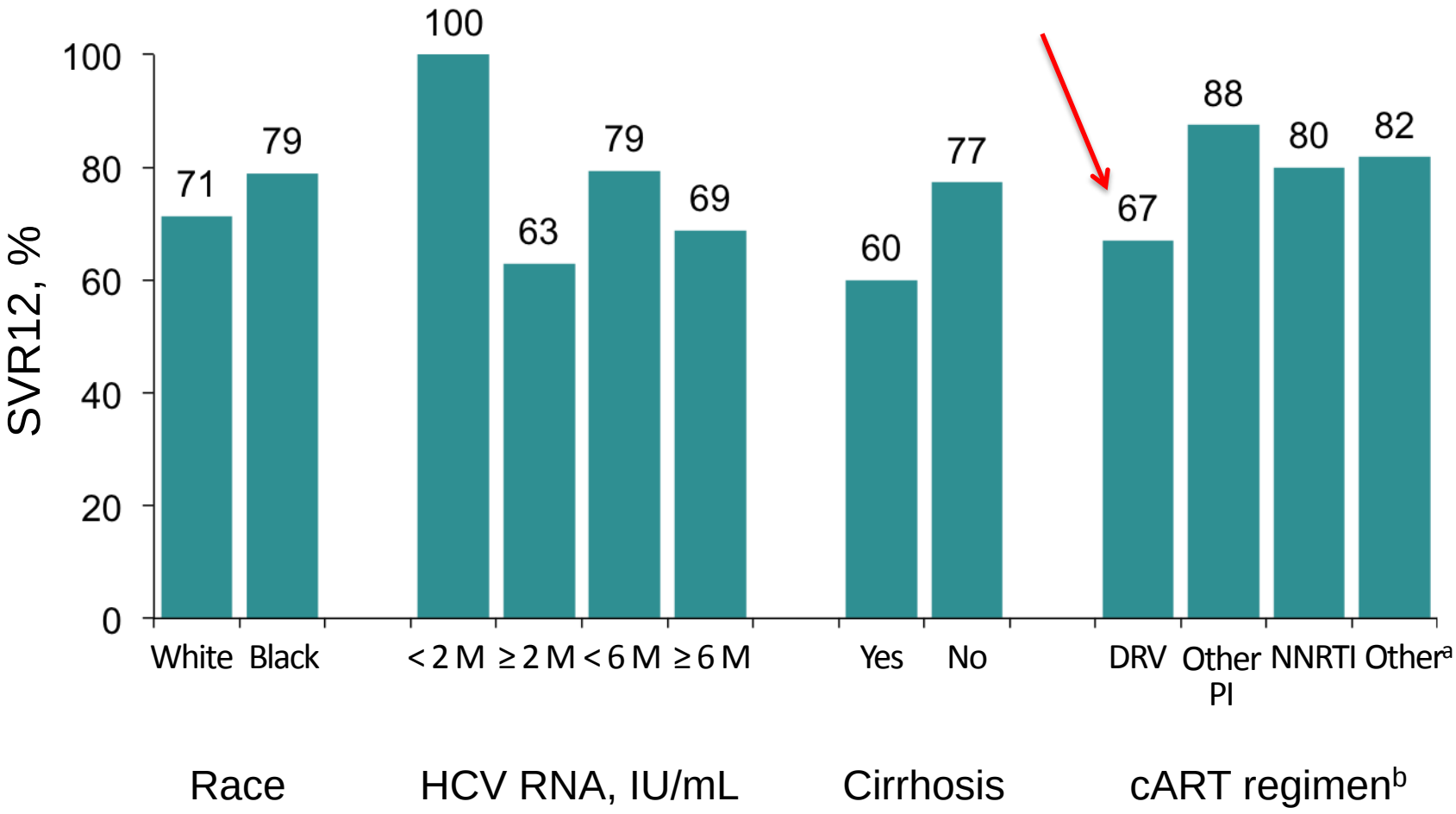
All-Oral 12-Week Combination Treatment with DCV+SOF in HIV/HCV co-infected Patients

- Phase 3, randomised, open label study of daclatasvir (DCV) + SOF for 8 or 12 weeks in HIV/HCV co-infected, TN or TE, GT1-4 patients, including cirrhotics



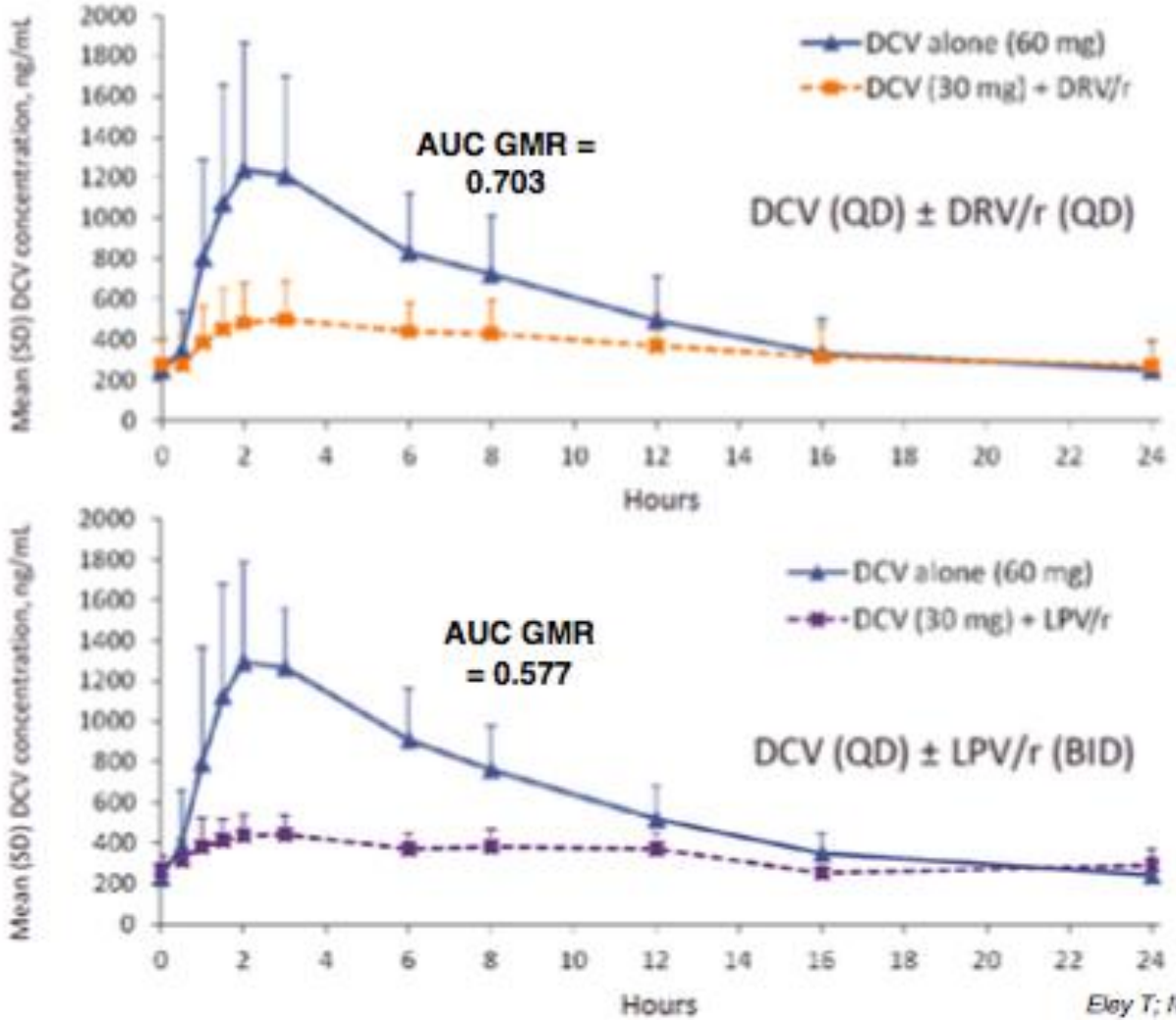
***Dose-adjusted for concomitant antiretrovirals: 30mg with ritonavir-boosted PIs, 90mg with NNRTIs except rilpivirine.**

SVR12 by Baseline Factors: 8-Week Group



[a]RAL, n=8; DTG, n=1; no cART, n=2. [b]DCV dose was reduced to 30 mg/day with ritonavir-boosed PI regimens in ALLY-2; based on recent data, DCV 60mg/day is recommended when used with DRV/r or LPV/r regimens [Eley et al. HIVDART 2014; Poster 63]

DRV/r and LPV/r → DAC



Eley T; IWCPHHT May 2015

Effect of Daclatasvir on Co-meds: *Perpetrator*

Drug	Effect of Daclatasvir on co-med	Recommendation
Sofosbuvir	SOF AUC increased 35%; GS-331007 – no effect	No dose adjustment
Midazolam	MDZ AUC decreased 13%	No dose adjustment
Cyclosporine	No effect on CsA	No dose adjustment
Tacrolimus	No effect on TAC	No dose adjustment
Oral Contraceptive	No effect on EE; Norgestrel AUC increased 12%	No dose adjustment

OMBITASVIR/PARITAPREVIR/R
DASABUVIR

Abbvie 3D (ABT-450/r; ABT-267; ABT-333)

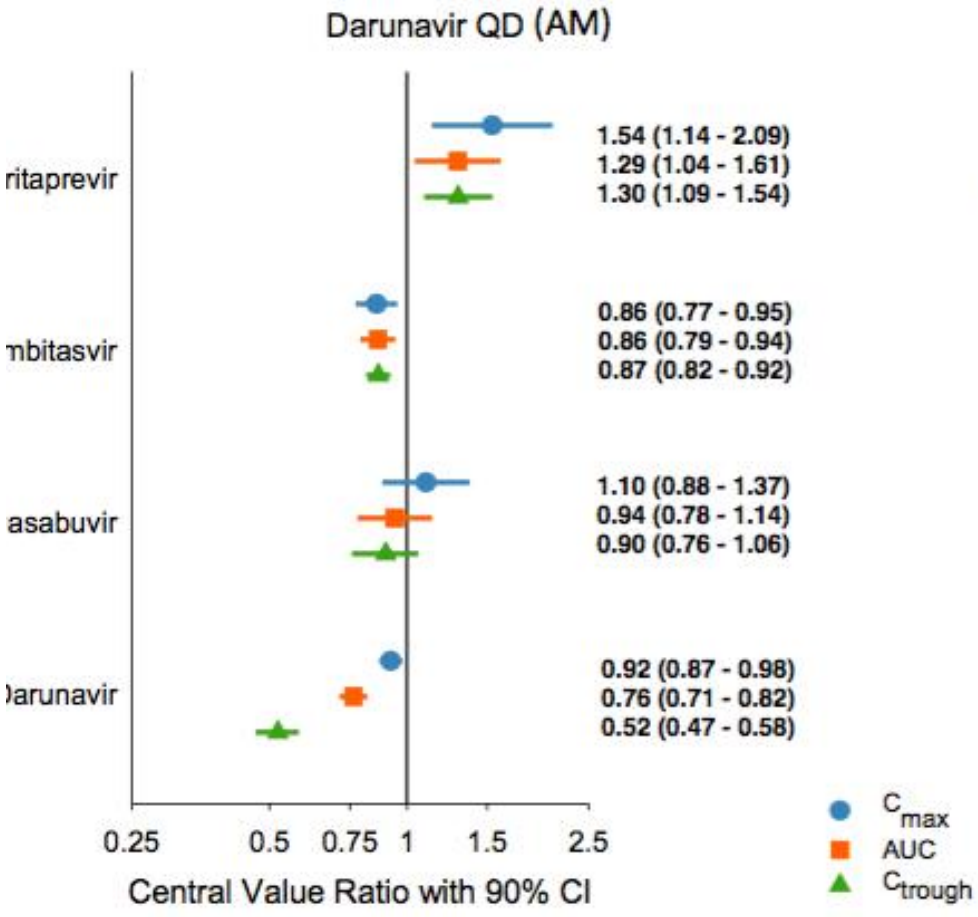
Drug	CYP/enzyme Activity	Transporters	Interaction Potential
ABT-450	▪ Metabolised by **CYP3A4** ▪ Inhibits **CYP2C8** ▪ Inhibits **UGT1A1**	▪ Transported by **P-gp, OATP1B1** ▪ Inhibits **OATP1B1 and OATP1B3**	▪ **High**
ABT-267	▪ Metabolised by **CYP3A4** ▪ Inhibits **CYP2C8** ▪ Inhibits **UGT1A1**	▪ Transported by **P-gp**	▪ **Moderate**
ABT-333	▪ Metabolised by **CYP2C8 > CYP3A4 > CYP2D6** ▪ Inhibits **UGT1A1**	▪ Transported by **P-gp** ▪ Inhibits **OATP1B1**	▪ **Moderate**

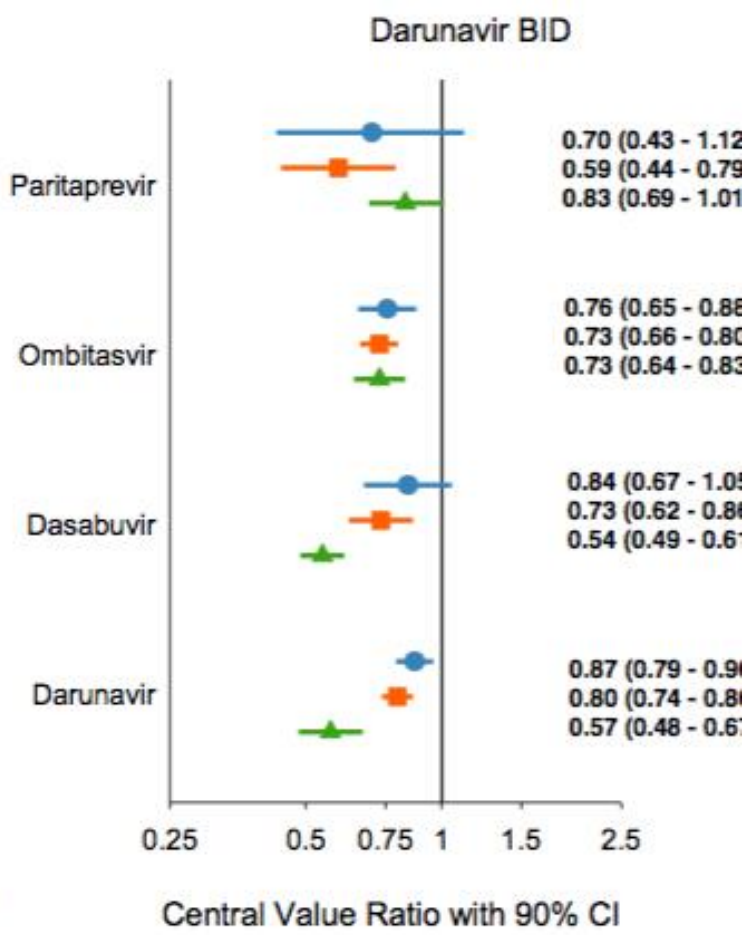
3Ds and ARVs

	Regimen evaluated	Recommendation
Nucleoside Reverse Transcriptase Inhibitor	Emtricitabine/Tenofovir Abacavir/lamivudine	No dose adjustment required No dose adjustment required
Integrase Inhibitors	Raltegravir Dolutegravir Elvitegravir/cobicistat	No dose adjustment required No dose adjustment required Not evaluated
Protease Inhibitors	Atazanavir Darunavir Lopinavir	No dose adjustment required* No dose adjustment required* Not recommended/Contraindicated**
Non-Nucleoside Reverse Transcriptase Inhibitor	Efavirenz/Emtricitabine/Tenofovir Rilpivirine	Contraindicated Not recommended***

*Dose PI at the same time as OBV/PTV/RTV without additional RTV
** Not recommended (USPI) or contraindicated.(EU SPC). Coadministration of the 3D or 2D was tolerated in over 100 subjects for 14 days.
***EU SPC: Rilpivirine should be used cautiously, in the setting of repeated ECG monitoring. Please refer to the SPC for additional details.

3Ds and DRV

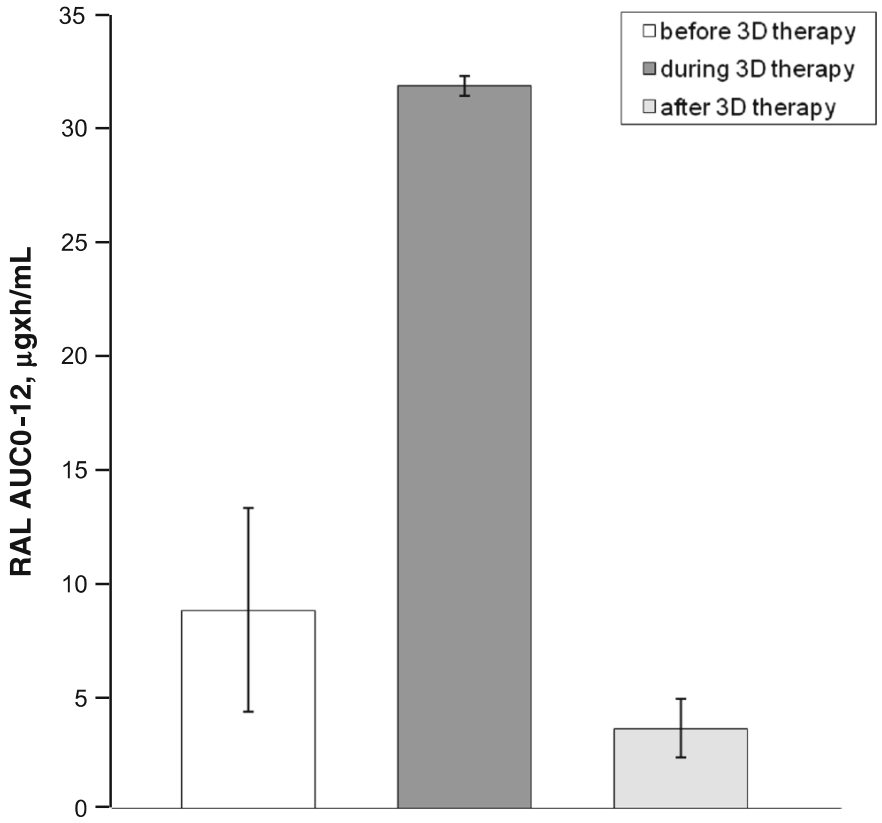

Darunavir QD (AM)
ritaprevir
mbitasvir
asabuvir
Darunavir
1.54 (1.14 - 2.09)
1.29 (1.04 - 1.61)
1.30 (1.09 - 1.54)
0.86 (0.77 - 0.95)
0.86 (0.79 - 0.94)
0.87 (0.82 - 0.92)
1.10 (0.88 - 1.37)
0.94 (0.78 - 1.14)
0.90 (0.76 - 1.06)
0.92 (0.87 - 0.98)
0.76 (0.71 - 0.82)
0.52 (0.47 - 0.58)
0.25
0.5
0.75
1
1.5
2.5
Central Value Ratio with 90% CI
Cmax
AUC
Ctrough


Darunavir BID
Paritaprevir
Ombitasvir
Dasabuvir
Darunavir
0.70 (0.43 - 1.12
0.59 (0.44 - 0.79
0.83 (0.69 - 1.01
0.76 (0.65 - 0.88
0.73 (0.66 - 0.80
0.73 (0.64 - 0.83
0.84 (0.67 - 1.05
0.73 (0.62 - 0.86
0.54 (0.49 - 0.61
0.87 (0.79 - 0.9
0.80 (0.74 - 0.8
0.57 (0.48 - 0.6
0.25
0.5
0.75
1
1.5
2.5
Central Value Ratio with 90% CI

Drugs contraindicated with Ritonavir for CYP3A4-based interactions

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

3Ds + Raltegravir



- Child-Pugh B8
- cyclosporine ↓20 mg qd and ↑30 mg bid on the basis of TDM

Cattaneo D, et al. Eur J Clin Pharm 2015

BCRP interactions (and pH)
Omeprazole 20/40mg

	DAA AUC	OMEPRAZOLE AUC
LEDIPASVIR/SOFOSBUVIR	SOF e 007 invariati **LED AUC ridotta 42-48% se OME 2 h prima** **LED AUC ridotta 4-8% se contemporaneo (20 mg)**	N.A.
3Ds	Ombitasvir 1.05 (0.98-1.12) Dasabuvir 1.08 (0.98-1.20) **Paritaprevir 1.18 (1.03-1.37)**	**0.62 (0.51-0.75)**

GRAZOPREVIR/ELBASVIR

MK-5172 (grazoprevir) e MK-8742 (elbasvir)

DRUG INTERACTIONS WITH MK-5172 AND MK-8742

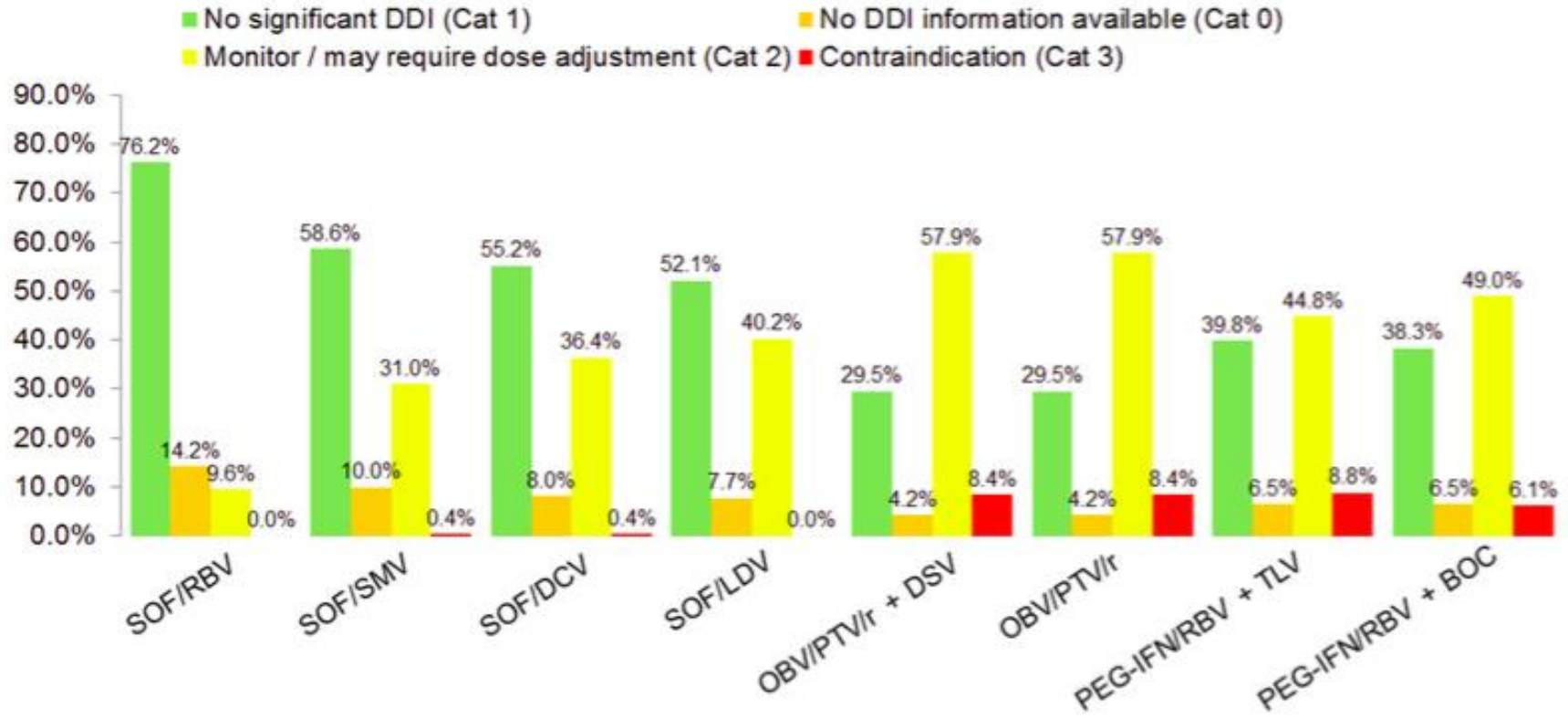
	MK-5172 (Merck)	**MK-8742 (Merck)**
Pharmacology	NS3/4A protease inhibitor	NS5A inhibitor
Adult Dose	*Investigational*: 100 mg once daily	*Investigational:* 50 mg once daily
Kinetic Characteristics	Substrate of CYP3A4, P-gp and OATP1B1.[1] Inhibitor of CYP2C8, 3A4 (weak), UGT1A1 (weak) and possibly BCRP.	Substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. No age effect observed in young (22-45 yrs) vs elderly (65-78 yrs) males; ~33% higher AUC in elderly female vs male subjects after adjusting for body weight.[2]

Alice Tseng, Pharm.D., FCSHP, AAHIVP, Toronto General Hospital and Pierre Giguere, M.Sc.Phm., The Ottawa Hospital www.hcvdruginfo.ca

HIV ARV	Effect on GZR AUC	Effect on EBR AUC	Effect on Interacting Drug AUC	Recommendation
tenofovir disoproxil fumarate	↔ 0.9x	↔ 0.9x	↑1.2x with GZR ↑1.3x with EBR	No adjustment
raltegravir	↔ 0.9x	↔ 1.0x	↑1.4x with GZR ↔1.0x with EBR	No adjustment
dolutegravir	↔ 1.0x	↔ 1.0x	↑1.2x with GZR+EBR	No adjustment
rilpivirine	↔ 0.9x	↔ 1.1x	↔ 1.1x with GZR+EBR	No adjustment
efavirenz	↓ 0.2x	↓ 0.5x	↔ 1.0x with GZR ↓0.8x with EBR	Not recommended
darunavir/ritonavir	↑ 7.5x	↑ 1.7x	↔1.1x with GZR ↔1.0x with EBR	Not recommended
atazanavir/ritonavir	↑ 10.6x	↑ 4.8x	↑1.4x with GZR ↔1.1x with EBR	Not recommended
lopinavir/ritonavir	↑ 12.9x	↑ 3.7x	↔1.0x with GZR ↔1.0x with EBR	Not recommended

ALTRI FARMACI

Clinical significance of drug-drug interactions during therapy with novel DAAs against HCV



Hoener Zu Siederdissen C, *et al* EASL-ILC 2015; Poster presentation P0754

DDIs with immune suppressive agents

	SIM	SOF	LED	DAC	3Ds
Cyclosporine	↑SIM e CSA	OK?	OK?	OK?	↑CSA Reduce 20% Monitor CSA
Tacrolimus	Monitor TCA	OK?	OK?	OK?	↑TAC 0.5 mg/w Monitor TAC
Sirolimus	No Data Monitor SIR	OK?	OK?	OK?	No Data Monitor SIR
Micofenolato Azatiprina Metilprednisone	OK?	OK?	OK?	OK?	↑steroids Monitor clinically

Table 4C. Drug-drug interactions between HCV DAAs and lipid lowering drugs.

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

SIM, simeprevir; DCV, daclatasvir; SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir.

Colour legend. Green: No clinically significant interaction expected. Amber: Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring. Red: These drugs should not be co-administered.

- Some drugs may require dose modifications dependent on hepatic function. Please refer to the product label for individual drugs for dosing advice.
- The symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hep-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Table 4E. Drug-drug interactions between HCV DAAs and cardiovascular drugs.

		SIM	DCV	SOF	SOF/ LDV	3D
Antiarrythmics	Amiodarone	•	•	•	•	•
	Digoxin	•	•	•	•	•
	Flecainide	•	•	•	•	•
	Vernakalant	•	•	•	•	•
Antiplatelet and anticoagulants	Clopidogrel	•	•	•	•	•
	Dabigatran	•	•	•	•	•
	Warfarin	•	•	•	•	•
Beta blockers	Atenolol	•	•	•	•	•
	Bisoprolol	•	•	•	•	•
	Propranolol	•	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•	•
	Diltiazem	•	•	•	•	•
	Nifedipine	•	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•	•
	Candesartan	•	•	•	•	•
	Doxazosin	•	•	•	•	•
	Enalapril	•	•	•	•	•

Serious Bradycardia Risk With Amiodarone Plus Hep-C Antivirals, FDA Cautions

Deborah Brauser | Disclosures

March 23, 2015

SILVER SPRING, MD — The US Food and Drug Administration (FDA) is updating labeling information for the hepatitis C antivirals ledipasvir/sofosbuvir (*Harvoni*, Gilead Sciences) and sofosbuvir (*Sovaldi*, Gilead Sciences) after their manufacturer reported bradycardia, pacemaker intervention, and even death in patients who took the medications along with the antiarrhythmic agent amiodarone[1].

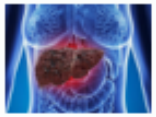
Gilead Sciences reported these serious treatment-related adverse events for nine patients. All were taking amiodarone, with three also taking ledipasvir/sofosbuvir, five also taking sofosbuvir and daclatasiver (*Daklinza*, Briston-Myers Squibb), and one also taking sofosbuvir and simeprevir (*Olysio*, Johnson & Johnson). Seven were also taking a beta-blocker.

All of the patients developed symptomatic bradycardia after taking the combinations, with six developing the condition 24 hours after use. In addition, one patient died from cardiac arrest after treatment and three others underwent pacemaker implantation.

There have been no cases of bradycardia reported for patients taking sofosbuvir plus ribavirin alone or with pegylated interferon.

RELATED LINKS

HCV Drugs Cost-effective, but Who Should Get Them?



Ledipasvir Sofosbuvir Combination Cuts Cirrhotic Hepatitis C

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DRUG & REFERENCE INFORMATION

Pediatric Pacemaker Implantation

Syncope

Pediatric Long QT Syndrome

Meccanismo?

1. GI transporter – with increase in amiodarone exposure
2. Local effect on cardiomyocyte – accumulation of amiodarone in the heart.
3. Protein binding displacement

VOLONTARI SANI VS. PAZIENTI

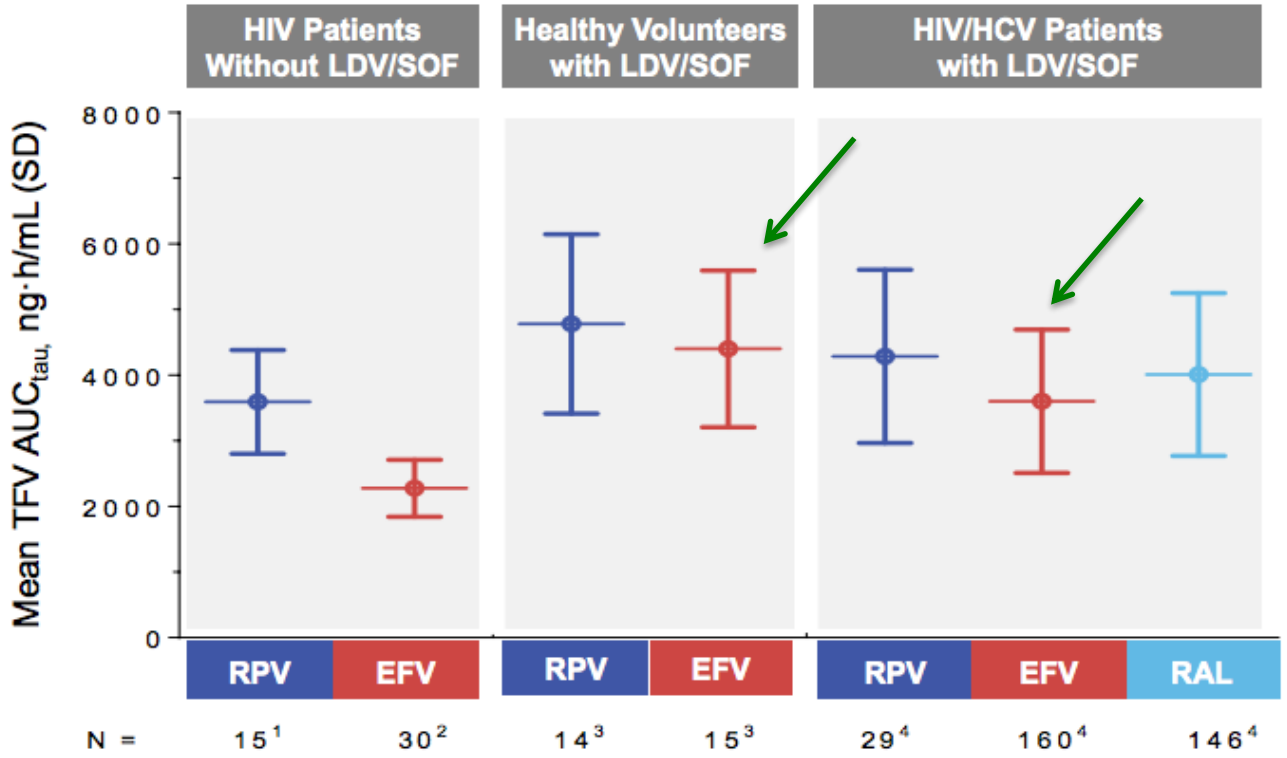
Most DDI studies are in Healthy Subjects: Physiological Changes in Patients

Parameter	HCV-infected
Albumin	↓*[1]
α1-acid glycoprotein	↑↓[3]
Gastric pH	↑[4]
Cytokines	↑[6]
CYP450's expression or function	↓[5]
Transporter expression or function	?

* Magnitude of effect dependent on stage of liver involvement

† Also **hemodynamic** changes (portal systemic shunting) and renal changes with hepatic impairment

Tenofovir (TFV) PK With ARV Regimens With or Without LDV/SOF



- Lack of marked changes in TFV renal clearance in healthy volunteers

1. Hoetelmans et al, IAS 2005; 2. Gilead Study GS-US-236-0120; 3. German et al, IWCPHT 2014; 4. Gilead Study GS-US-337-0115 (ION-4).

Combinazioni “difficili”

- Non è possibile modificare la HAART:
  - Multi-fallito con terapia di salvataggio
    - Non dati su etravirina
    - Pochi dati su Dolutegravir (DAC OK)
    - Spesso PI/r based
- Non è possibile modificare i farmaci concomitanti
  - Epilessia: fenobarbital, carbamazepina, valproato?
  - Cardiovascolari: statine, antiaritmici, nuovi anticoagulanti

Pazienti “difficili” (2)

- Insufficienza renale/dialisi
- Trapianto
- Cirrosi compensata/scompensata

Insufficienza renale

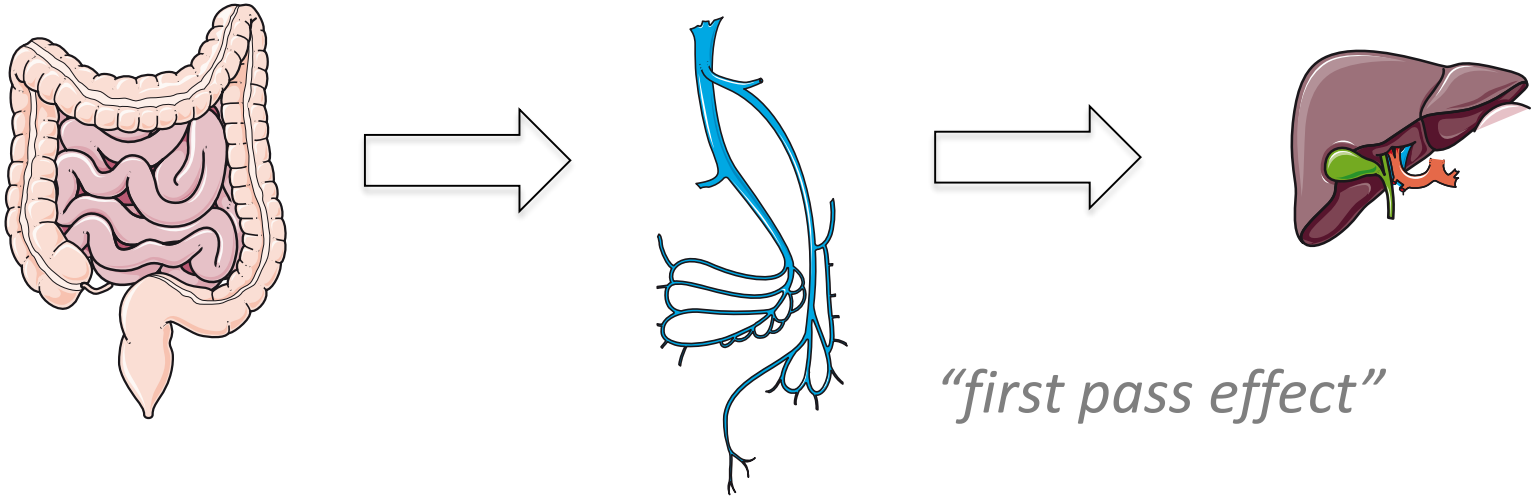
ml/min	RBV	SOF	SIM	LED	DAC	3Ds
50-80	Standard	Standard	Standard	Standard	Standard	Standard
30-50	200 or 400 EOD	Standard	Standard	Standard	Standard	Standard
<30	200 mg	Standard or 200 mg?	Standard dose??	Not available	Standard dose??	Standard dose??
Dyalisis	200 mg	Standard or 200 mg?	Standard dose??	Not available	Standard dose??	Standard dose??

Insufficienza renale

ml/min		SOF AUC	007 AUC	3Ds
50-80	50-80	+61%	+55%	Standard
30-50	30-50	+107%	+88%	Standard
<30	<30	+171%	+451%	Standard dose??
Dyalisis	Dyalisis	+28% 1h before +60% 1h after	+1280% 1h before +2070% 1h after	Standard dose??

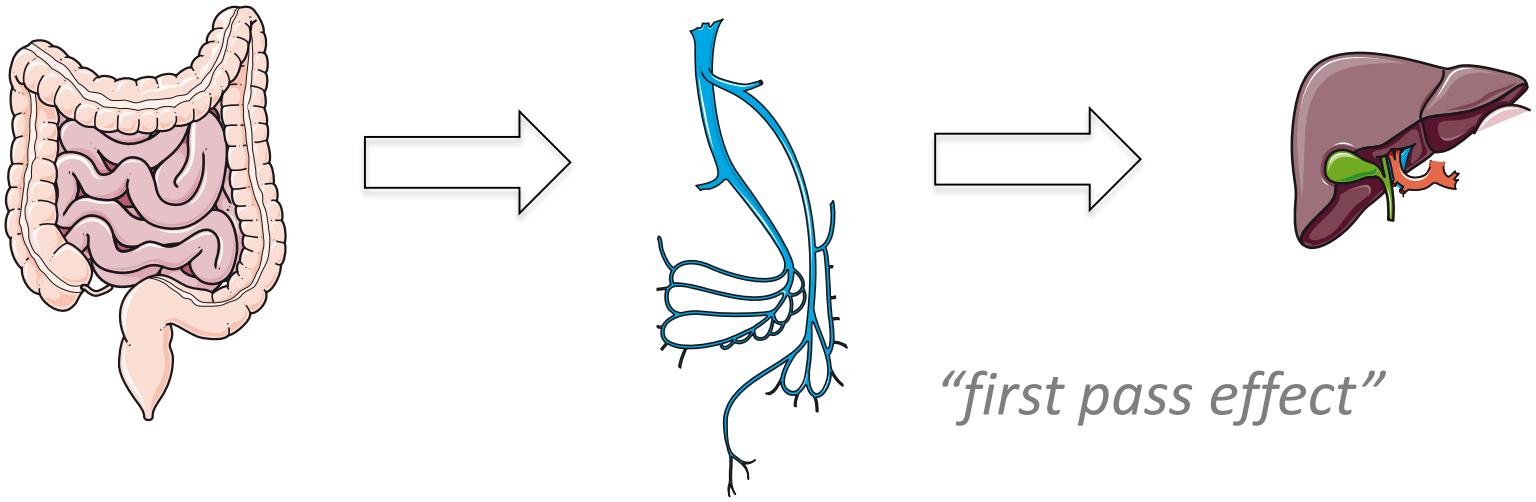
Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation

Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation



“first pass effect”

Drugs absorbed from the gastrointestinal tract are exposed to the metabolizing enzymes and bile excretory transport systems of the liver before reaching the systemic circulation



"first pass effect"

The effect of chronic liver disease on the bioavailability of orally administered drugs is mainly the result of reduced pre-systemic hepatic metabolism

PK Changes with Advancing Liver Disease

	Liver Impairment			Notes
	mild	*moderate*	*severe compensated*	
Teleprevir	↓0.85	↓0.54		*SS, HCV-*
Boceprevir	↔	1.32	1.45	
Simeprevir		↑2.44	↑5.22	*SS, HCV-*
Sofosbuvir		↑1.26	↑1.43	*Parent (SS, HCV+)*
		(↑1.18**)	(↔1.09**)	*GS 331007 metabolite*
Ledipasvir	no adjustment	no adjustment		*SS, HCV-*
ABT 450r	↓0.71	↑1.62	↑10.23	*Single dose, HCV-*
Ombitasvir (ABT-267)	0.92	0.70	0.45	
Dasabuvir (ABT-333)	1.17	0.84	4.19	
Faldeprevir		↔	↔	*No change in cirrhosis*
Asunaprevir	↓0.79	↑ 9.8	↑ 32	*SS, HCV-, concentrates in liver, ↑PK in >60 years*
Daclatasvir	↓0.57	↓0.62	↓0.64	*Single dose, HCV-*
		unbound ↔	unbound ↔	
MK5172	↑1.62	↑4.88		*SS, 100mg/200mg (HCV-)*
MK8742	↔	↔		*Single dose*

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1. **Hepatic decompensation** with sofosbuvir plus **simeprevir** in a patient with Child-Pugh B compensated cirrhosis.
Soriano V, Barreiro P, de Mendoza C, Peña JM.
Antivir Ther. 2015 Jun 4. doi: 10.3851/IMP2969. [Epub ahead of print]
PMID: 26042495
Similar articles

2. **Hepatic decompensation** likely attributable to **simeprevir** in patients with advanced cirrhosis.
Stine JG, Intagliata N, Shah NL, Argo CK, Caldwell SH, Lewis JH, Northup PG.
Dig Dis Sci. 2015 Apr;60(4):1031-5. doi: 10.1007/s10620-014-3422-x. Epub 2014 Nov 6.
PMID: 25373453
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cases of fulminant hepatitis or hepatic failure have been reported in patients treated with abiraterone acetate in Japan.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the addition of the description on the risk of fulminant hepatitis and hepatic failure to the information on hepatic function disorder in the section of "Important precaution" and to the subsection of the "Clinically significant adverse reactions" in the section of "Adverse reactions" in the package insert.

Reference:
Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Revision of Precautions, MHLW/PMDA, 7 July 2015 (*www.pmda.go.jp/english/*)

Anagliptin

Risk of intestinal obstruction

Japan. The MHLW and the PMDA have announced the revision of the package insert for anagliptin (Suiny®) to include risk of intestinal obstruction.

Anagliptin is indicated for type 2 diabetes mellitus.

The MHLW/PMDA stated that cases associated with intestinal obstruction have been reported in patients treated with anagliptin in Japan.

Based on expert advice and available evidence, the

Asunaprevir and daclatasvir hydrochloride

Risk of hepatic failure

Japan. The MHLW and the PMDA have announced the revision of the package inserts for asunaprevir (Sunvepra®) and daclatasvir hydrochloride (Daklinza®) to include risk of hepatic failure.

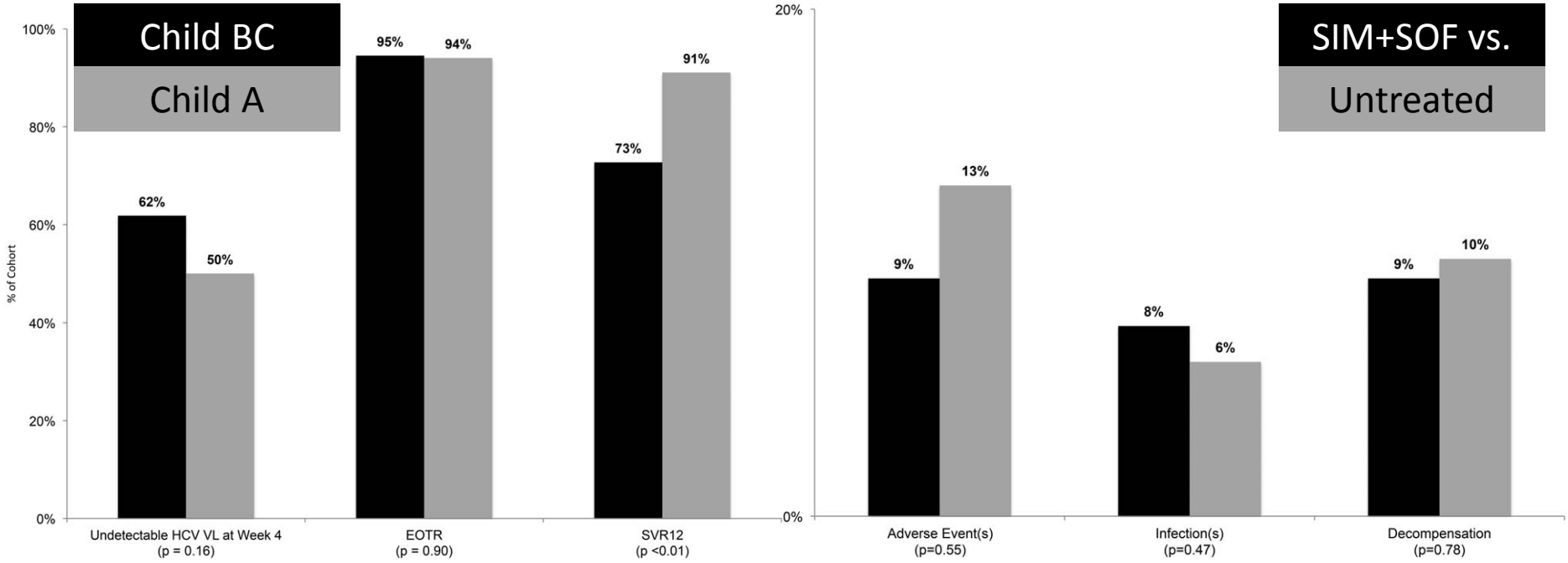
Asunaprevir and daclatasvir hydrochloride are used for improvement of viraemia in patients with serogroup 1 (genotype I) chronic hepatitis C or compensated cirrhosis type C.

The MHLW/PMDA stated that cases of decreased hepatic residual function such as decreased albumin level, prolonged prothrombin time, ascites, hepatic

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Safety and Efficacy of Simeprevir/Sofosbuvir in Hepatitis C–Infected Patients With Compensated and Decompensated Cirrhosis

Varun Saxena,[1] Lisa Nyberg,[2] Marypat Pauly,[3] Aditi Dasgupta,[1] Anders Nyberg,[2] Barbara Piasecki,[4] Bradley Winston,[5] Jacquelyn Redd,[5] Joanna Ready,[3] and Norah A. Terrault[1]



Conclusioni

- Il profilo di interazioni dei DAAs varia in funzione dei composti (> per RTV)
- Dati PK vs. real life (healthy volunteers vs paziente, cirrosi) e impatto clinico
- Necessità di dati di sicurezza e di PK nella real life (fase IV) e monitoraggio dei farmaci concomitanti (molti non testati!)
- PK per ridurre la durata della terapia?

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LATEST ARTICLES

Review - Drug interactions with new HCV DAAs

Webcasts - HIV2014, Glasgow

Meeting Report - 65th AASLD (The Liver Meeting)

Meeting Report - HIV2014, Glasgow.

Drug Interactions – Boceprevir or telaprevir and eltrombopag

Meeting Report - 54th ICAAC, Washington.

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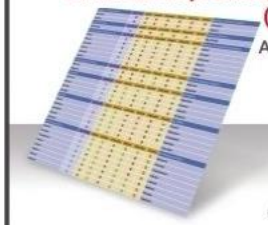
Ombitasvir/Paritaprevir/r alone or + Dasabuvir (OBV/PTV/r ± DSV) now added



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Providing clinically useful, reliable, up-to-date, evidence-based information

INTERACTION CHARTS FOR PHONES AND TABLETS

HEP iChart – NEW VERSION AVAILABLE

A new version of the interaction app for mobile devices is now available. The new app includes tablet support for Android devices and is fully compatible with the latest versions of iOS.

Please delete the existing app from your device and download the new version from the App Store or Google Play (search for HEP iChart).

This is an "offline" app that is downloaded to your device. An internet connection is not required to use the app, but is needed for downloading updates.

INTERACTION QUERY SERVICES

Telaprevir & Simeprevir Interaction Query Services

Services for healthcare professional for queries relating to drug-drug interactions with telaprevir or simeprevir which the hospital

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25-27 September 2015, Glasgow, UK.

ASSOCIATED SITES

www.hiv-druginteractions.org

A comprehensive HIV drug-drug interaction resource, freely available to healthcare workers, patients and researchers. The site is also available in a low graphics version - www.hiv-druginteractionslite.org.

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German Liver Foundation

Deutschen Leberstiftung

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