DAA e interazioni farmacologiche nel coinfetto: quale gestione clinica?

Stefano Bonora
Università di Torino

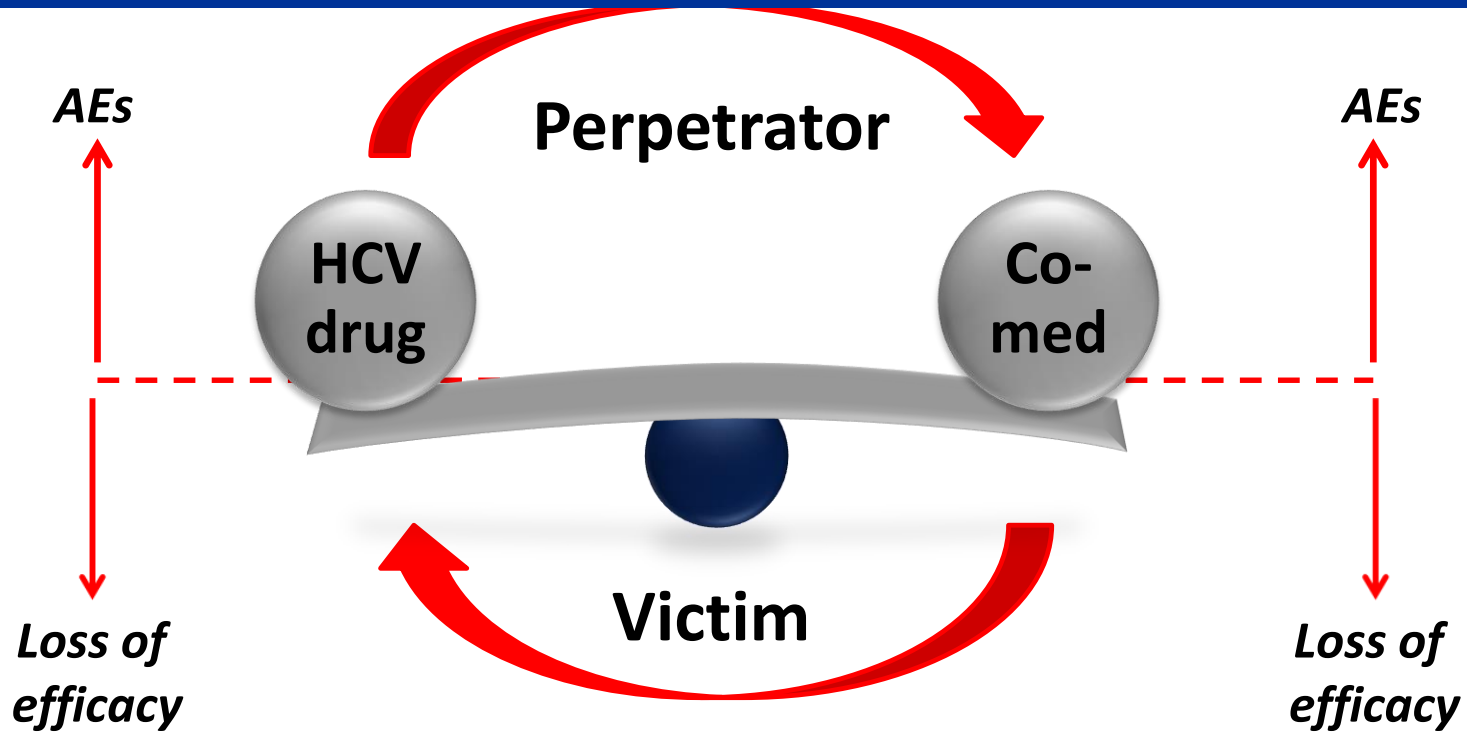
CISAI*, Perugia, 30-31 marzo 2017*

Outline

- Mechanisms
- Problem
- Solution (?)
- New drugs

Mechanisms

Drug–drug interactions

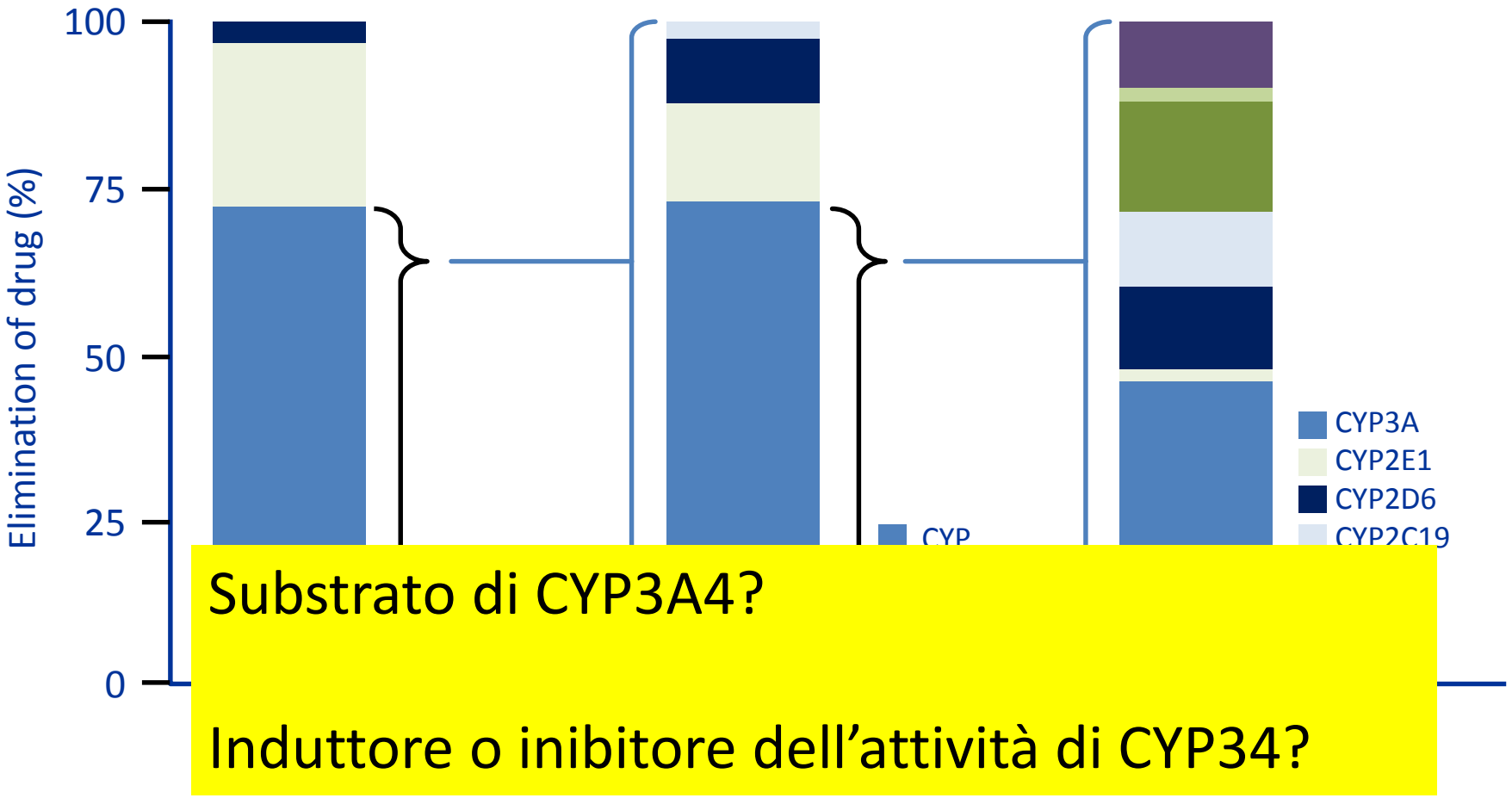


Need to understand:

- The disposition or handling of each drug
- The therapeutic window of each drug
- Exposure – Response and Exposure – Adverse Response relationship to interpret pharmacokinetic (PK) data

Personal Communication: Professor D J Back

Routes of Elimination of the Top Most Prescribed Drugs

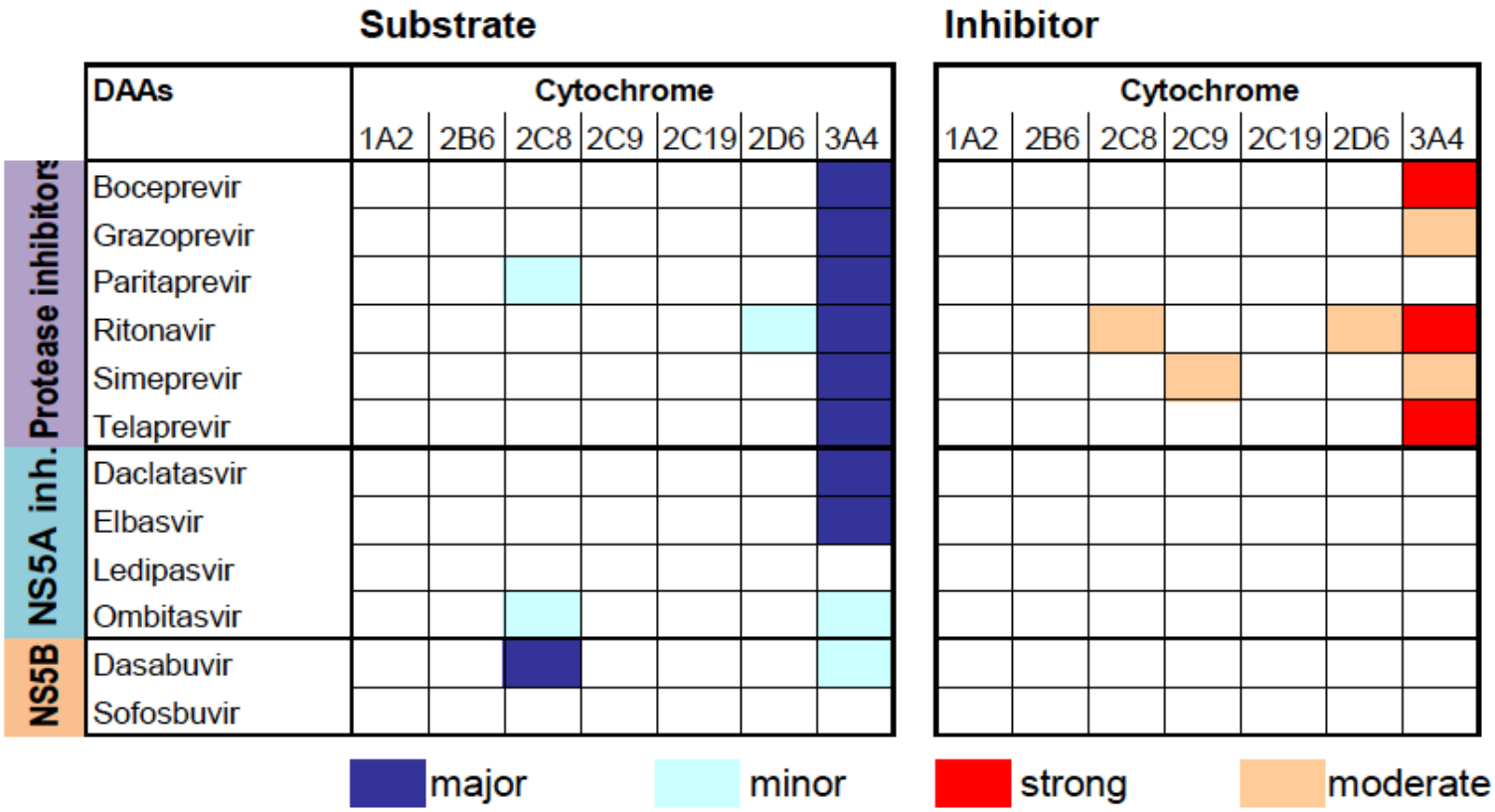


Substrato di CYP3A4?

Induttore o inibitore dell'attività di CYP34?

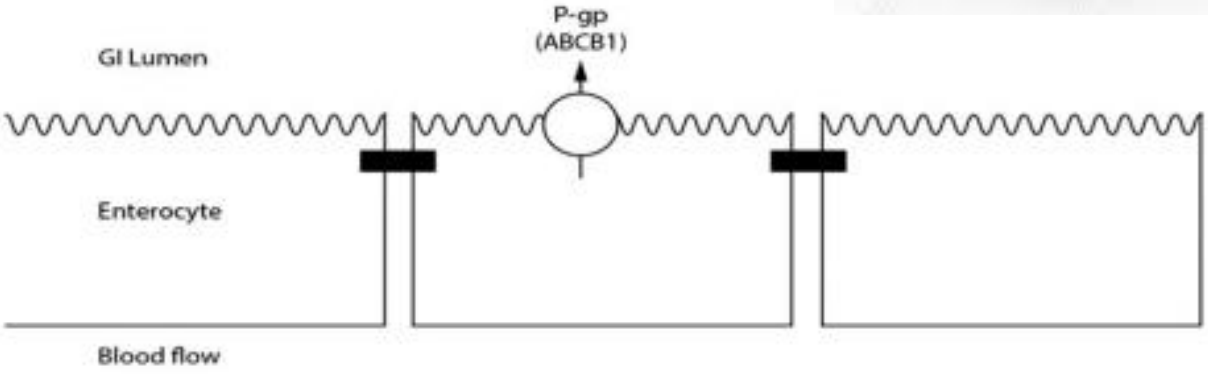
Wienkers LC et al. Nat Rev Drug Discov 2005

HCV drugs and cytochromes

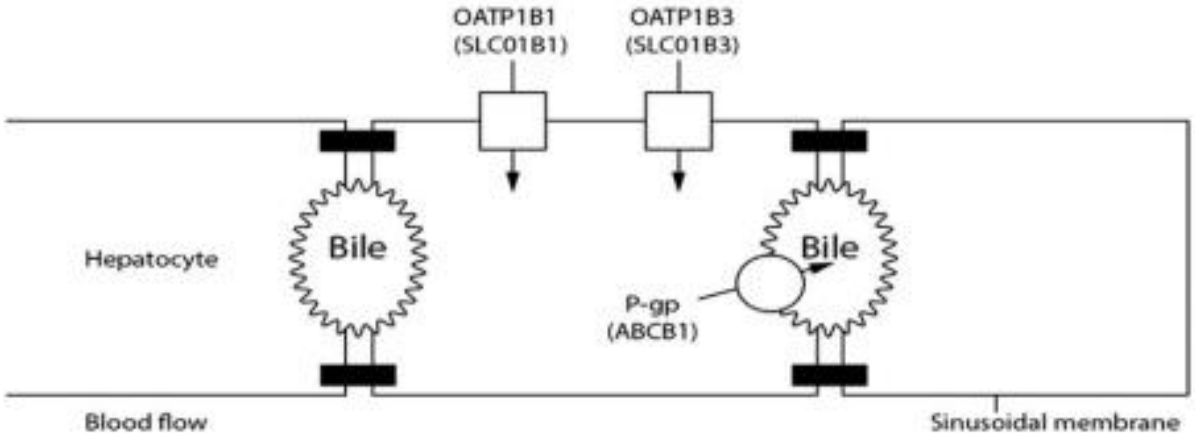


By courtesy of C. Marzolini

P-gp


P-gp
(ABCB1)
GI Lumen
Enterocyte
Blood flow

OATP…


OATP1B1
(SLC01B1)
OATP1B3
(SLC01B3)
Hepatocyte
Bile
Bile
P-gp
(ABCB1)
Blood flow
Sinusoidal membrane

HCV drugs and interaction with drug transporters

	DAAs	OATP1B1	OATP1B3	OCT1	OCT2	P-gp	BCRP	MRP2
Protease inh.	Boceprevir							
	Grazoprevir						X	
	Paritaprevir	X	X			X	X	
	Ritonavir	X	X			X	X	
	Simeprevir	X				x		X
	Telaprevir	X	X		X	X		
NS5A inh.	Daclatasvir	x	x	X		x	x	
	Elbasvir					x	X	
	Ledipasvir	x	x			x	x	
	Ombitasvir							
NS5B	Dasabuvir					X	X	
	Sofosbuvir					x	x	

substrate X inhibitor x weak inhibitor

By courtesy of C. Marzolini

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

Mechanisms of Drug Interactions of DAAs

DAA	Victim of DDI	Perpetrator of DDI	DDI Potential
Ombitasvir/paritaprevir/r + dasabuvir (3D)	Substrate for CYP3A4, CYP2C8, OATP1B1/3, P-gp, BCRP	Inhibits CYP3A4, OATP1B1/3, OCT1, BCRP, P-gp, UGT1A1, CYP2C8, CYP2C19.	High
Simeprevir	Substrate for CYP3A4, P-gp & OATP1B1	Inhibits gut CYP3A4, CYP1A2, OATP1B1 & P-gp	Moderate
Grazoprevir/elbasvir	Substrate for CYP3A4, P-gp & OATP1B1	Inhibits P-gp & BCRP	Moderate
Daclatasvir	Substrate for CYP3A4, P-gp	Inhibits OATP1B1, P-gp & BCRP.	Moderate
Ledipasvir/sofosbuvir	Substrate for P-gp & BCRP Gut pH	Inhibits P-gp & BCRP	Moderate/ Low
Velpatasvir/sofosbuvir	Substrate for P-gp & BCRP Gut pH	Inhibits P-gp & BCRP	Moderate/ Low
Sofosbuvir	Substrate for P-gp & BCRP		Low

Available at www.hep-druginteractions.org and relevant SmPCs ie Incivo (telaprevir), updated 27th July 2015; Victrelis (boceprevir), updated 5th March 2015; Viekirax (2D), updated 2nd Oct 2015; Exviera (dasabuvir) updated 2nd Oct 2015; Olysio (Simeprevir), updated 25th Aug 2015; Daklinza (daclatasvir), updated 30th Sept 2015; Sovaldi (sofosbuvir), updated 27th Aug 2015; Harvoni (LDV/SOF), updated 27th Nov 2015

Problem

The efficacy and safety of direct acting antiviral treatment and clinical significance of drug–drug interactions in elderly patients with chronic hepatitis C virus infection

J. Vermehren, K.-H. Peiffer, C. Welsch, G. Grammatikos, M.-W. Welker, N. Weiler, S. Zeuzem, T. M. Welzel &

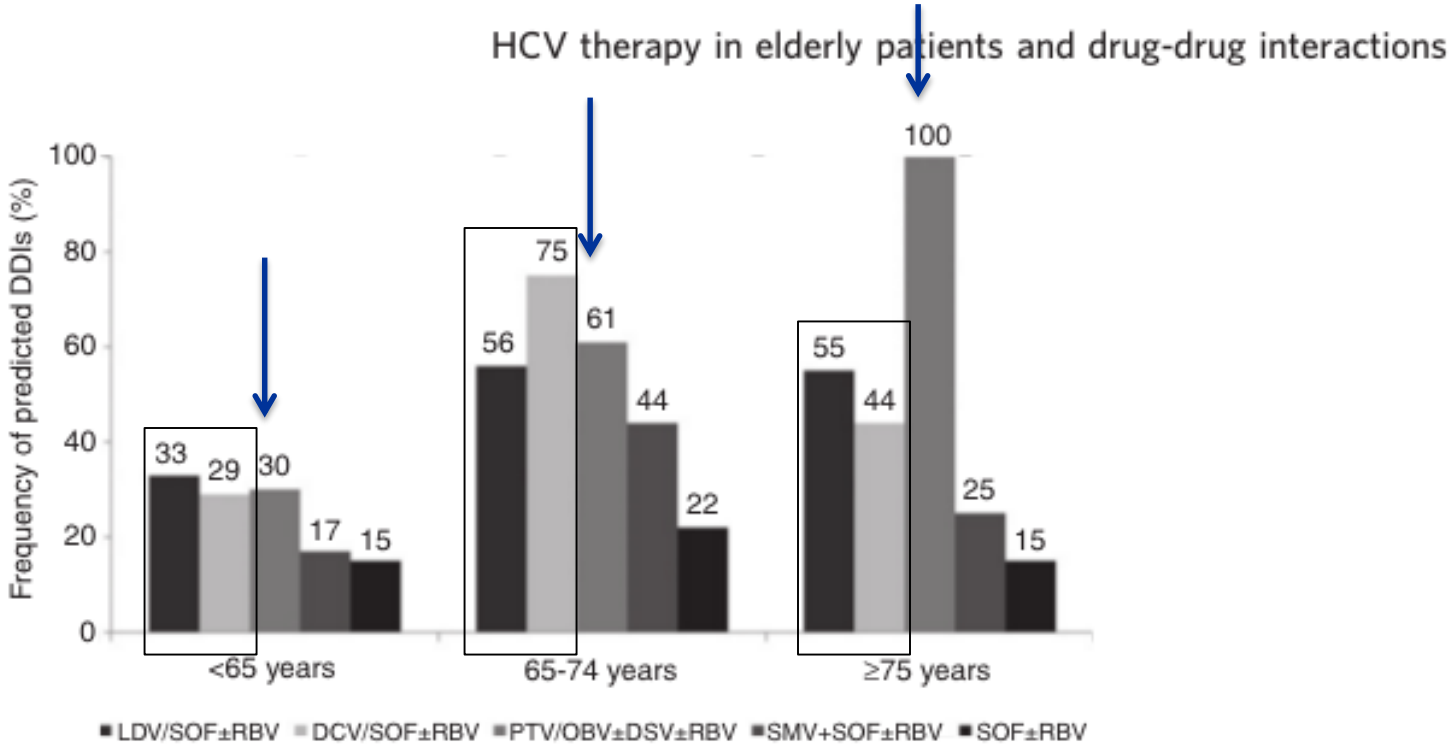


Figure 3 | Frequencies of predicted clinically significant drug–drug interactions (defined as category 2/3 interactions according to the hep-druginteractions.org database) between concomitant medications and antiviral therapy according to treatment regimen and age groups (n = 541). All listed patients had ≥1 drug of concomitant medications predicted to cause DDIs.

DOI: 10.1111/hiv.12471
HIV Medicine (2016)

ORIGINAL RESEARCH

High frequency of potential interactions between direct-acting antivirals and concomitant therapy in HIV/hepatitis C virus-coinfected patients in clinical practice

J Macías,[1,2] P Monge,[1] M Mancebo,[1] N Merchante,[1,2] K Neukam,[1,2] LM Real[1,2] and JA Pineda[1]
[1]*Infectious Diseases and Microbiology Unit, Hospital Universitario de Valme, Seville, Spain and* [2]*Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain*

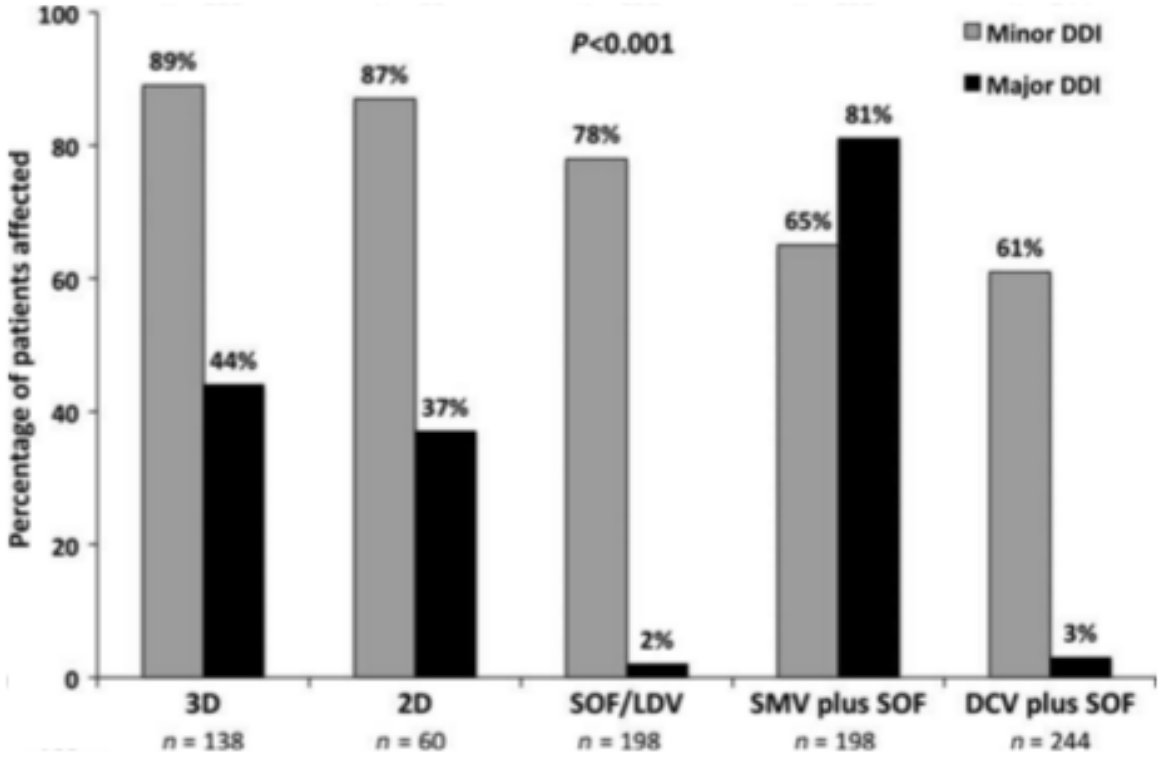
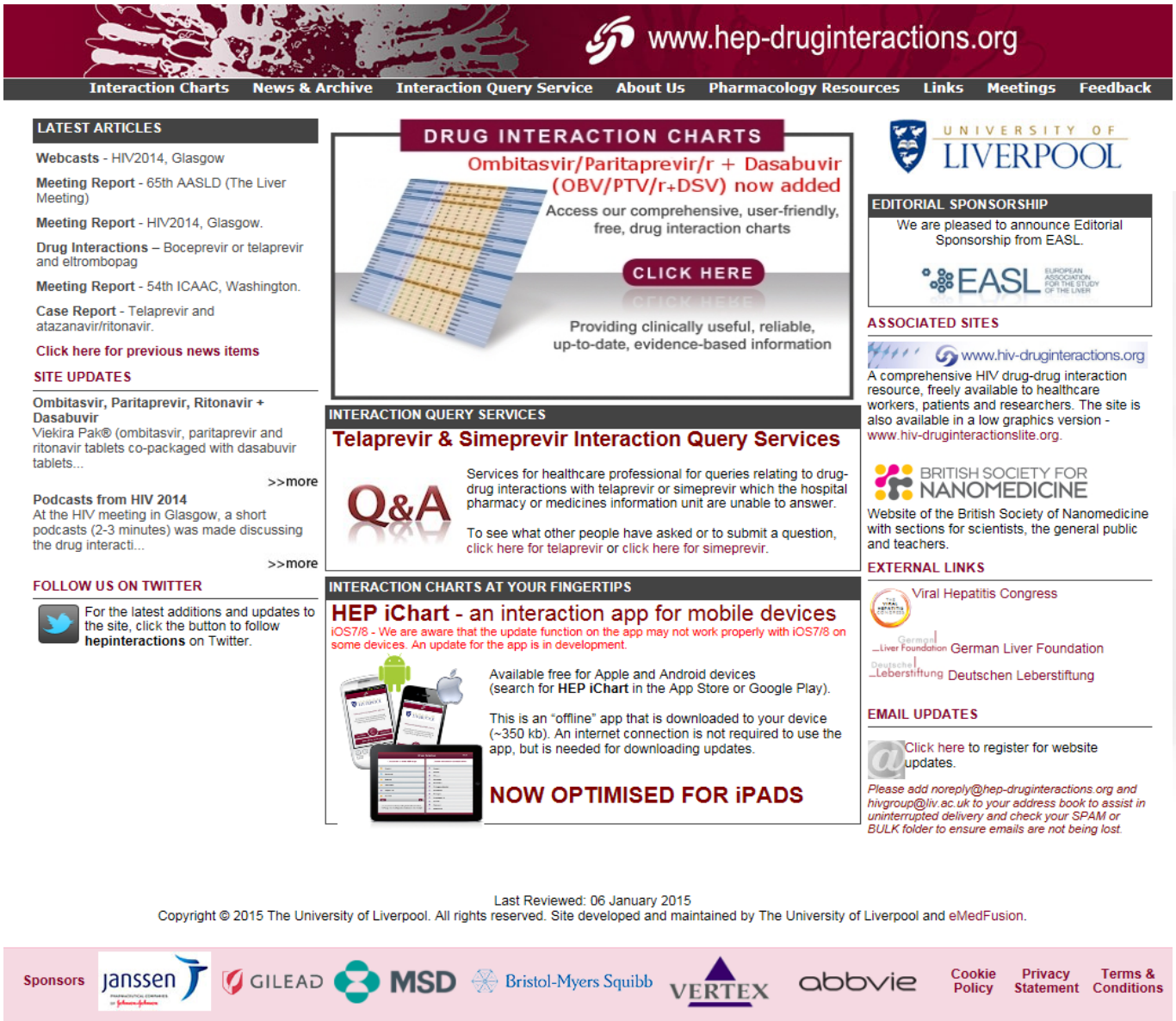


Fig. 1 Frequency of minor and major drug–drug interactions (DDIs) by direct-acting antiviral (DAA) regimen. Minor DDI: drugs may require close monitoring, alteration of drug dosage or alteration of the timing of administration. Major DDI: drugs should not be co-administered. 2D, paritaprevir-r/ombitasvir; 3D, paritaprevir-r/ombitasvir plus dasabuvir; DCV, daclatasvir; LDV, ledipasvir; SMV, simeprevir; SOF, sofosbuvir.

Solution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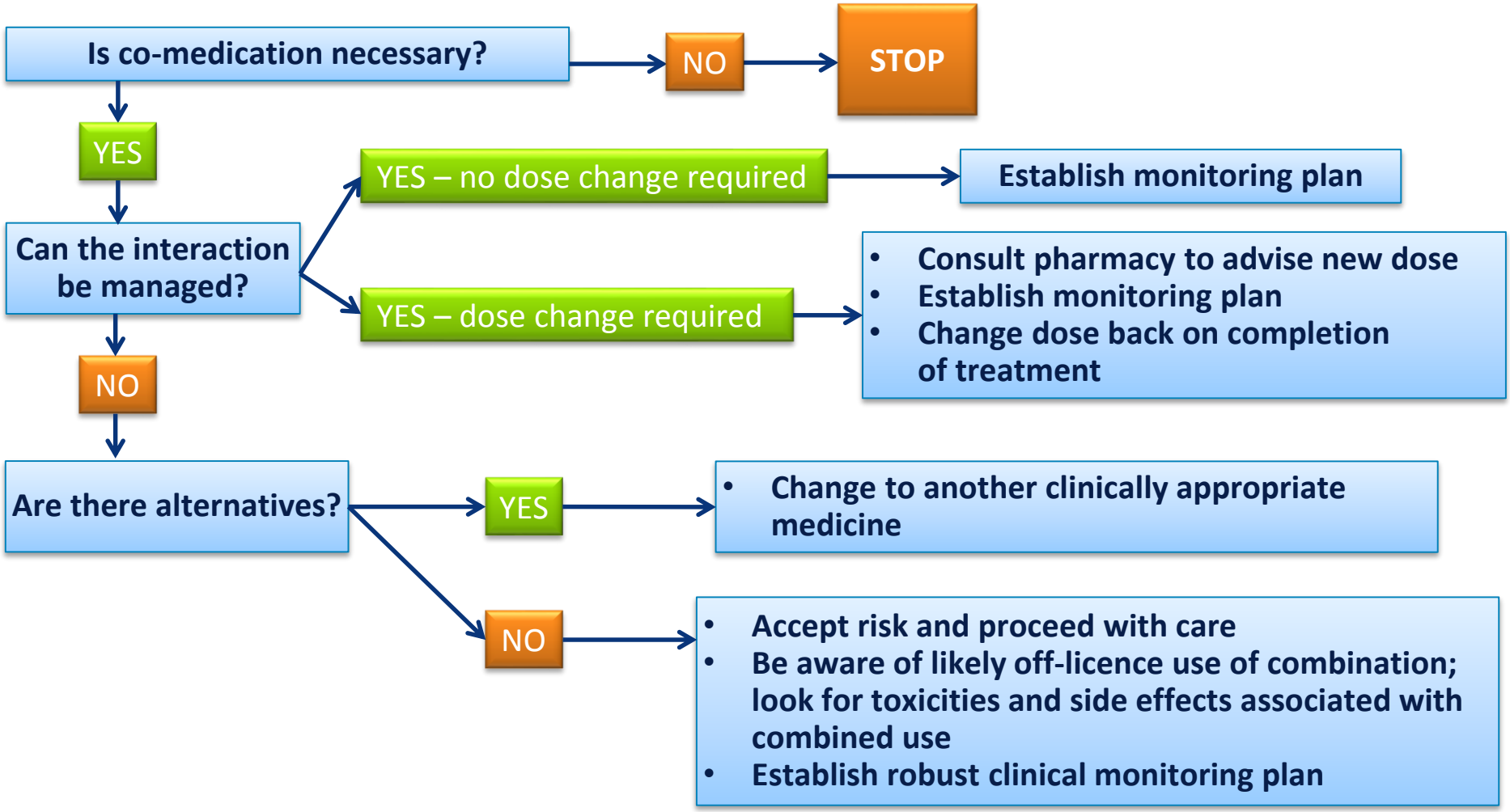
Use a stepwise approach to DDI management



Back D. VHC 2015; Oral presentation O113.

- ✓ Aumento o diminuzione di concentrazioni evidenziata in studio PK ma di incerto significato clinico
- ✓ Nessun dato, possibile interazione di entità non prevedibile

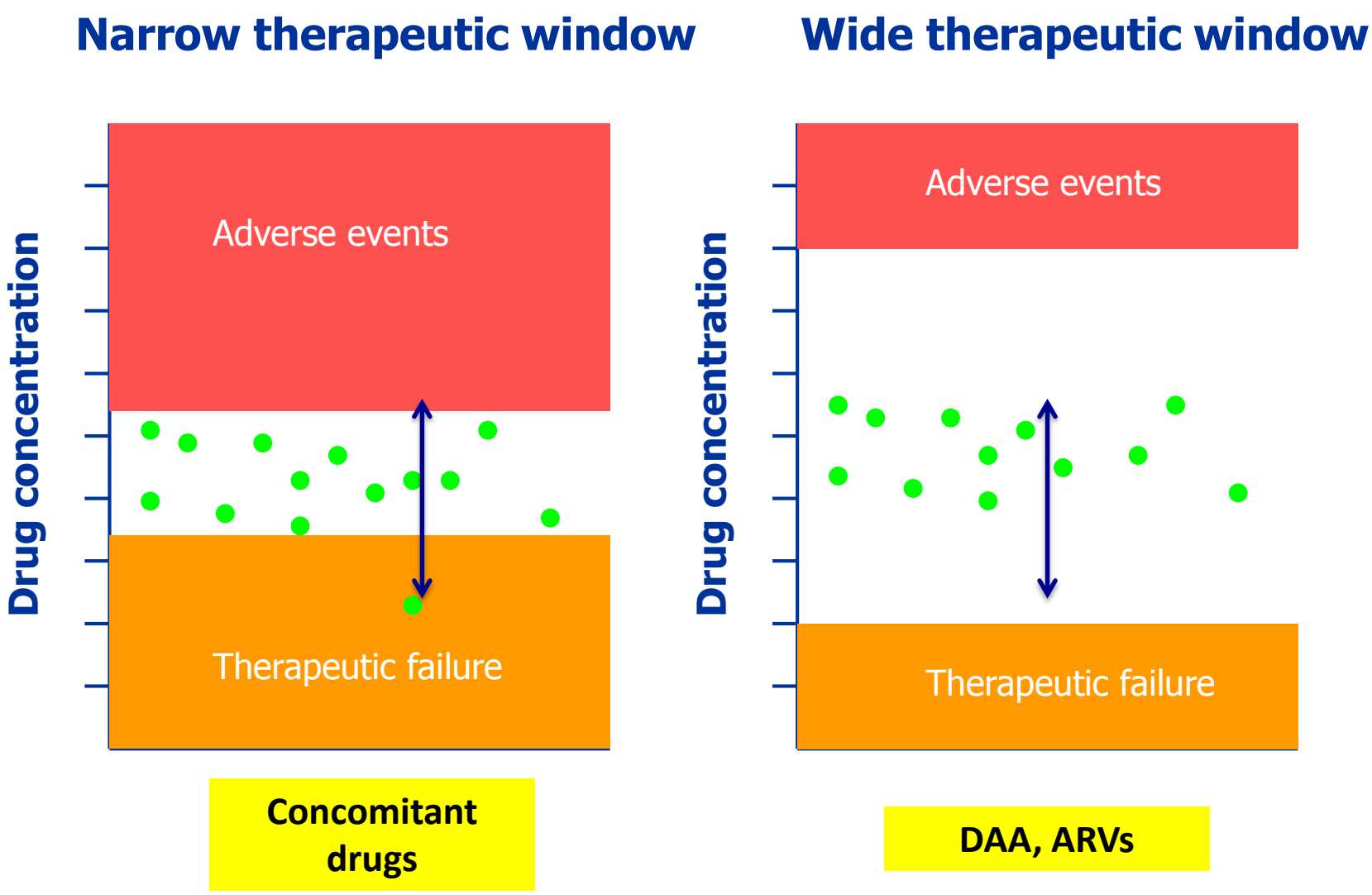
Altri farmaci

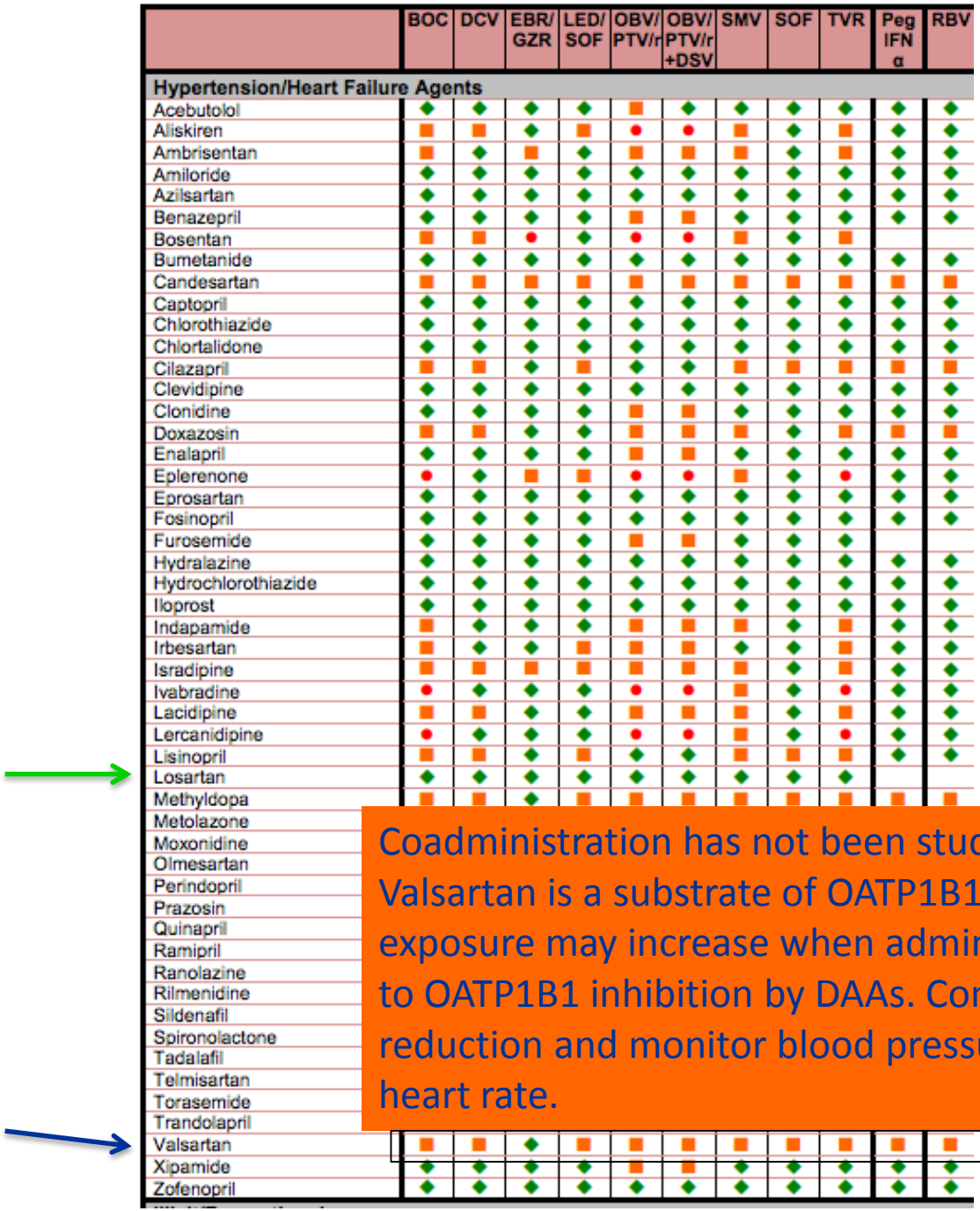
Tossicità

Cirrosi

Comorbidità/fragilità

Therapeutic window





Coadministration has not been studied. Valsartan is a substrate of OATP1B1. Valsartan exposure may increase when administered due to OATP1B1 inhibition by DAAs. Consider dose reduction and monitor blood pressure and heart rate.

Hindawi Publishing Corporation
Case Reports in Medicine
Volume 2016, Article ID 3191089, 3 pages
http://dx.doi.org/10.1155/2016/3191089

Case Report

An Unexpected Interaction between Sofosbuvir/Ledipasvir and Atorvastatin and Colchicine Causing Rhabdomyolysis in a Patient with Impaired Renal Function

Shyam Patel,[1] Jennifer Andres,[2] and Kamran Qureshi[3]

- ✓ IRC
- ✓ IMA
- ✓ Colchicine
- ✓ Atorva 80 mg

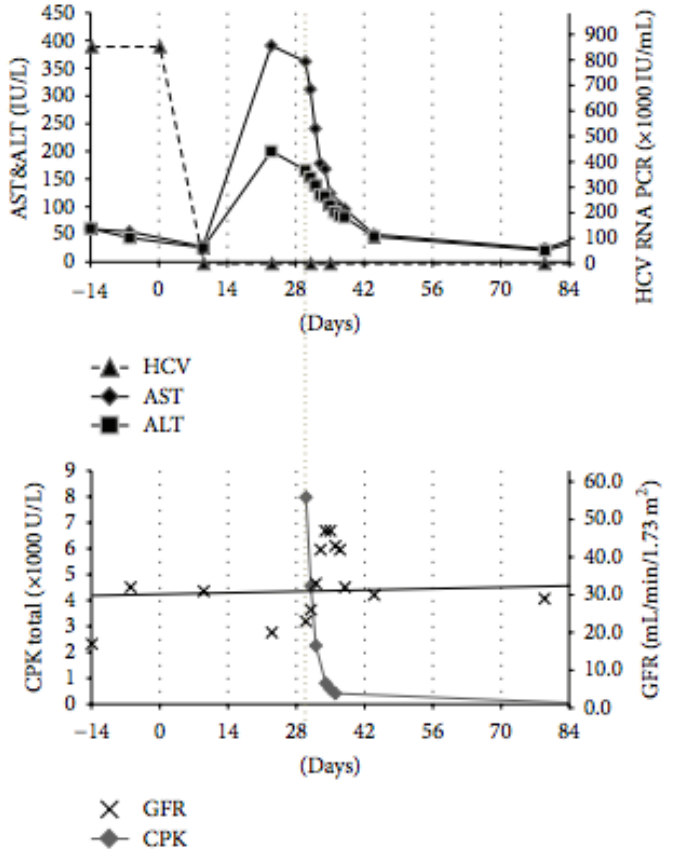
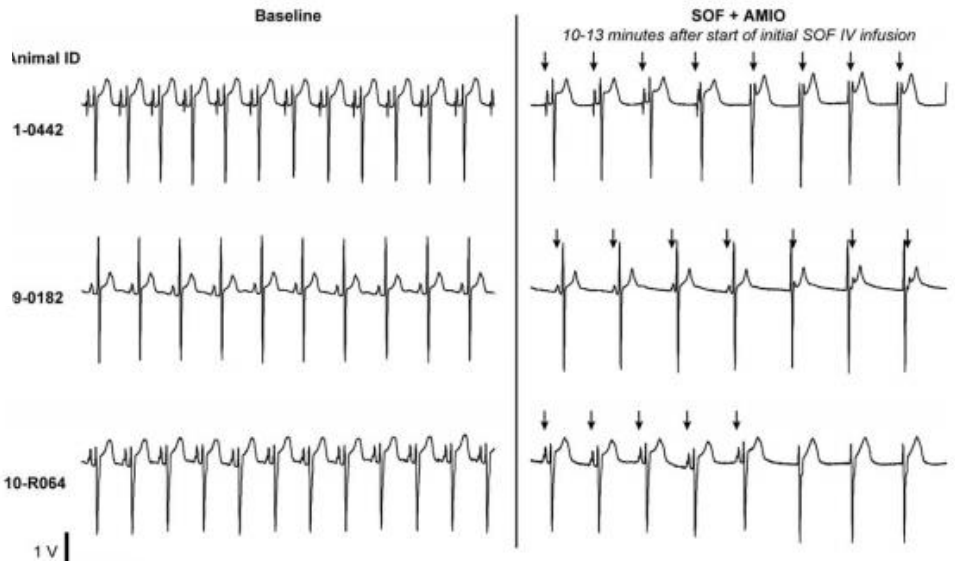


FIGURE 1: Timeline of laboratory changes. Interrupted line denotes hospital admission day.

RAPID COMMUNICATION | HEPATOLOGY, VOL. 64, NO. 5, 2016

Assessment of the Clinical Cardiac Drug-Drug Interaction Associated With the Combination of Hepatitis C Virus Nucleotide Inhibitors and Amiodarone in Guinea Pigs and Rhesus Monkeys

Christopher P. Regan,[1] Pierre Morissette,[1] Hillary K. Regan,[1] Jeffery J. Travis,[1] Pamela Gerenser,[1] Jianzhong Wen,[2] Kevin Fitzgerald,[1] Shaun Gruver,[1] Joseph J. DeGeorge,[3] and Frederick J. Sannajust[1]



Data highlight that the cardiac effect is attributed to a primary effect at the SA node level, with involvement of the AV node at later time points

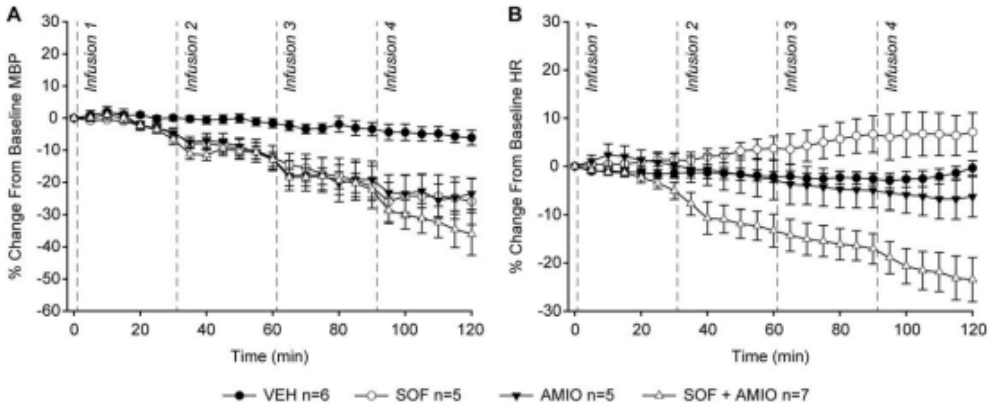


Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■+	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■+	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir; /r, ritonavir.

Daclatasvir dosing

ATV/COBI

Table 1. Daclatasvir Dosing With Concomitant CYP3A4 Inhibitors and Inducers

Drugs That Strongly Inhibit CYP3A (Decrease Daclatasvir Dose to 30 mg)	Drugs That Moderately Inhibit CYP3A (Standard Daclatasvir Dose of 60 mg)	Drugs That Strongly Induce CYP3A (Daclatasvir Contraindicated)	Drugs That Moderately Induce CYP3A (Increase Daclatasvir Dose to 90 mg)
– Ritonavir-boosted atazanavir – Clarithromycin – Itraconazole – Ketoconazole – Nefazodone – Nelfinavir – Posaconazole – Telithromycin – Voriconazole	– Ritonavir-boosted darunavir	– Rifamycins	– Bosentan – ethasone – nz – ne – nil – n – tine

Abbreviations: C

Rilpivirine?

Etravirine (without PI/r)?

ATV unboosted?

Darunavir/COBI?

ELV/COBI/FTC/TDF or TAF?

Daclatasvir (DCV) pharmacokinetics in HCV/HIV co-infected patients co-administered with rilpivirine and other antiretroviral drugs.

A. Barco[1], L. Marinaro[1], M. Merli[2], C. Alcantarini[1], C. Montrucchio[1], G. Vendemiati[1], M. Milesi[1], F. Patti[1], F. Favata[1], A. Ariaudo[1], H. Hasson[2], A. D'Avolio[1], C. Uberti-Foppa[2], G. Di Perri[1], S. Bonora[1]

1 Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

2 Infectious Diseases Clinic, IRCCS, San Raffaele Hospital, Milan, Italy

This is the first report on DCV exposures in HIV/HCV patients co-administered with RPV. Results show that standard DCV dose of 60 mg provides adequate DCV levels, comparable to those reported with other regimens.

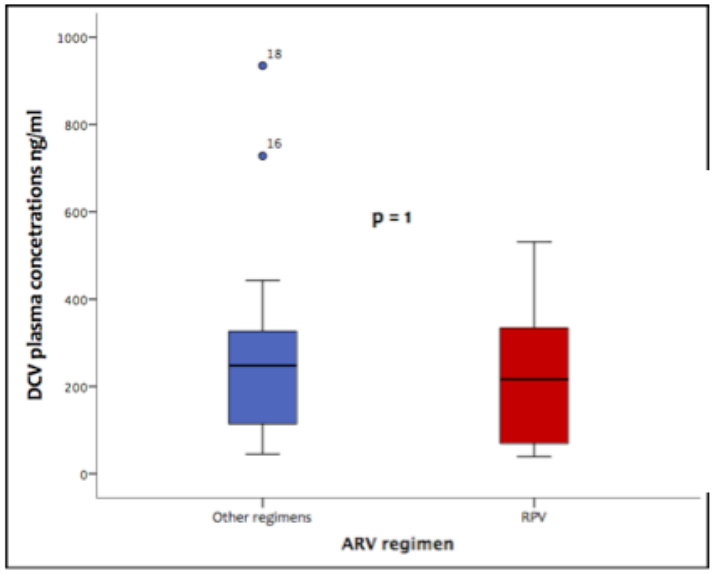
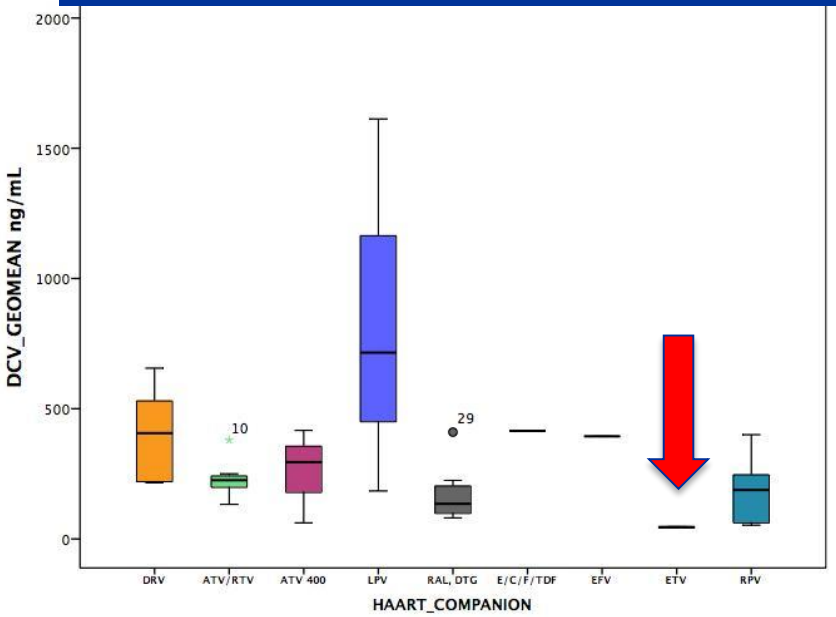
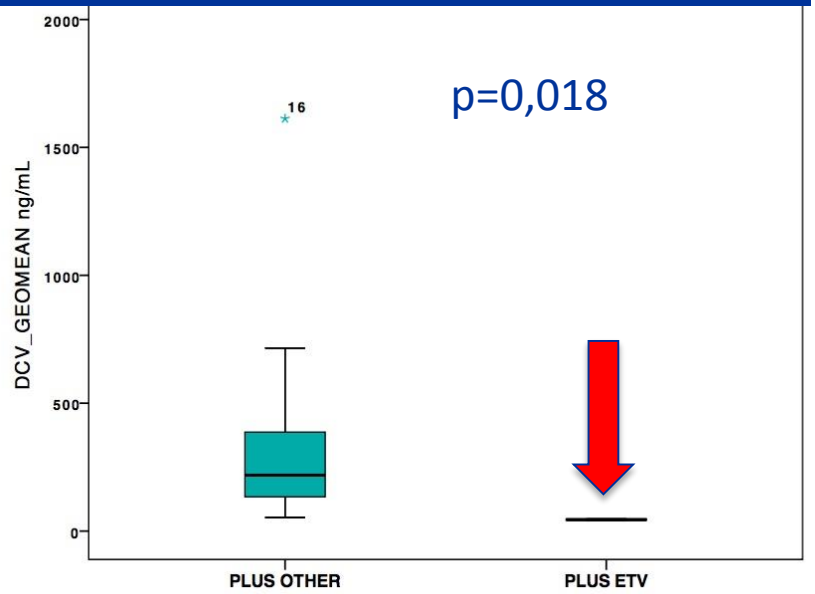


Figure 1. Median plasmatic DCV concentrations in patients on RPV vs other regimens.

DCV 60 mg plus ETV? 90 mg better…





DCV C_{trough} was significantly lower, 45 ng/mL (42;45) if coadministrated 60 mg with ETV when compared to DCV C_{trough} with other antiretrovirals.

Daclatasvir (DCV) pharmacokinetics in HCV/HIV co-infected patients co-administered with rilpivirine and other antiretroviral drugs.

A. Barco[1], L. Marinaro[1], M. Merli[2], C. Alcantarini[1], C. Montrucchio[1], G. Vendemiati[1], M. Milesi[1], F. Patti[1], F. Favata[1], A. Ariaudo[1], H. Hasson[2], A. D'Avolio[1], C. Uberti-Foppa[2], G. Di Perri[1], S. Bonora[1]

1 Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino, Italy

2 Infectious Diseases Clinic, IRCCS, San Raffaele Hospital, Milan, Italy

Appropriateness of reduced DCV dose of 30 mg both in individuals treated with ATV/r and in patients receiving unboosted ATV.

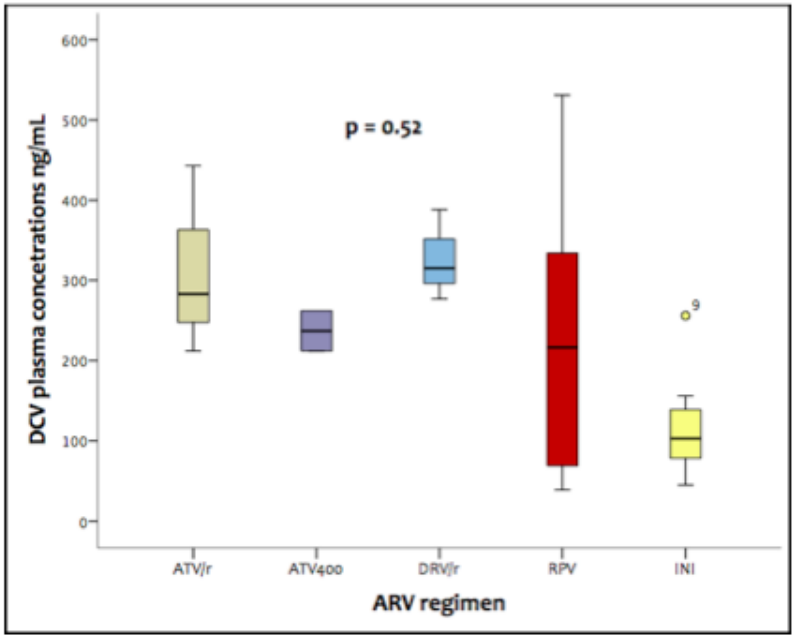
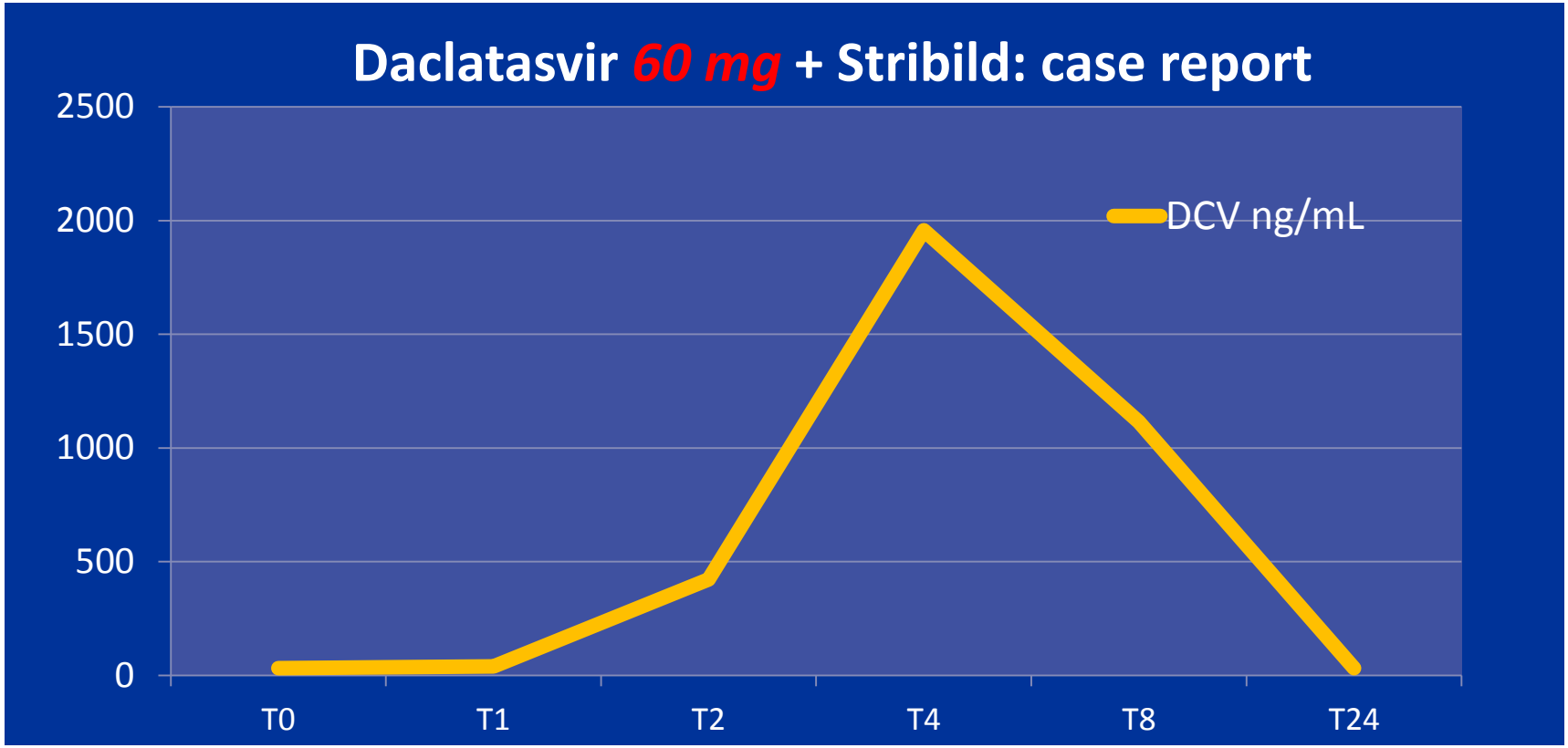


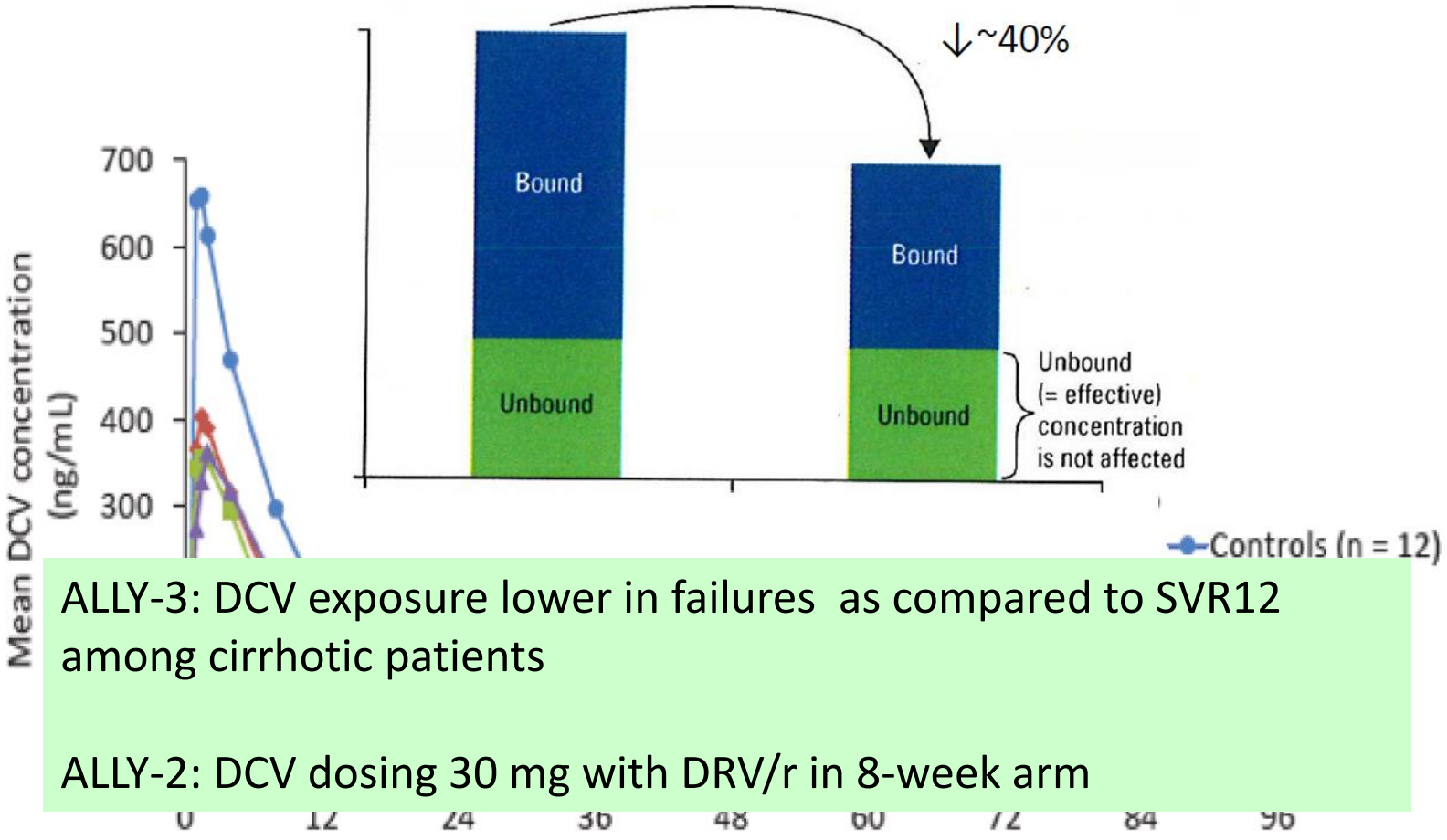
Figure 2. Median plasmatic DCV concentrations according to main ARV component.



	DCV	Reference [1,2]
Cmin ng/mL	32	212 (103 – 299)
Cmax ng/mL	1957	1534
AUCss ngh/mL	13513	14122

[1]Barco A. et Al. International Congress of Drug Therapy in HIV Infection 23-26 October 2016, Glasgow, UK
[2]Daklinza® Summary of Product Characteristics, Bristol-MyersSquibb.

Daclatasvir decreased with Hepatic Impairment – but unbound unchanged



ALLY-3: DCV exposure lower in failures as compared to SVR12 among cirrhotic patients

ALLY-2: DCV dosing 30 mg with DRV/r in 8-week arm

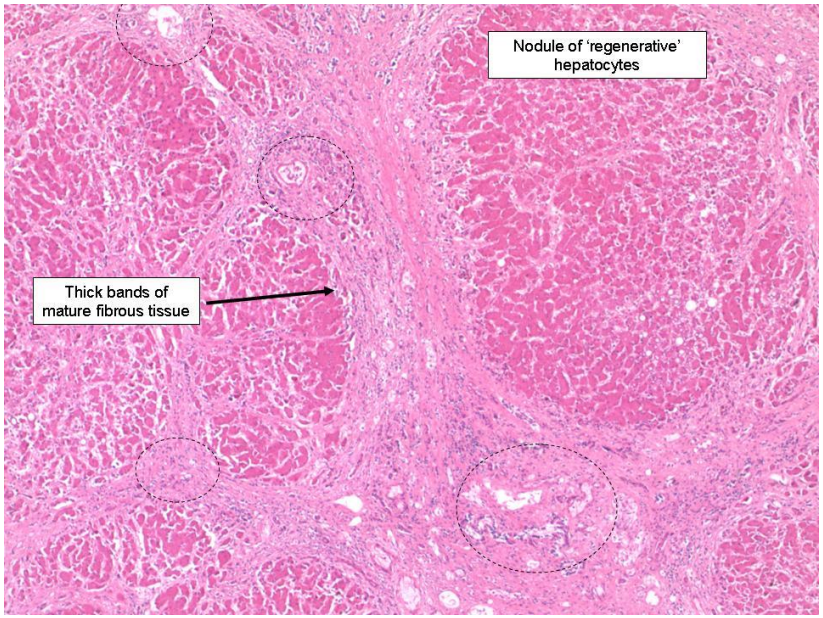
Total concentrations appear lower, but free amount is unchanged.

Bifano, M. 62nd AASLD 2011

CIRRHOSIS results in several pathophysiologic changes in the liver that may influence pharmacokinetics

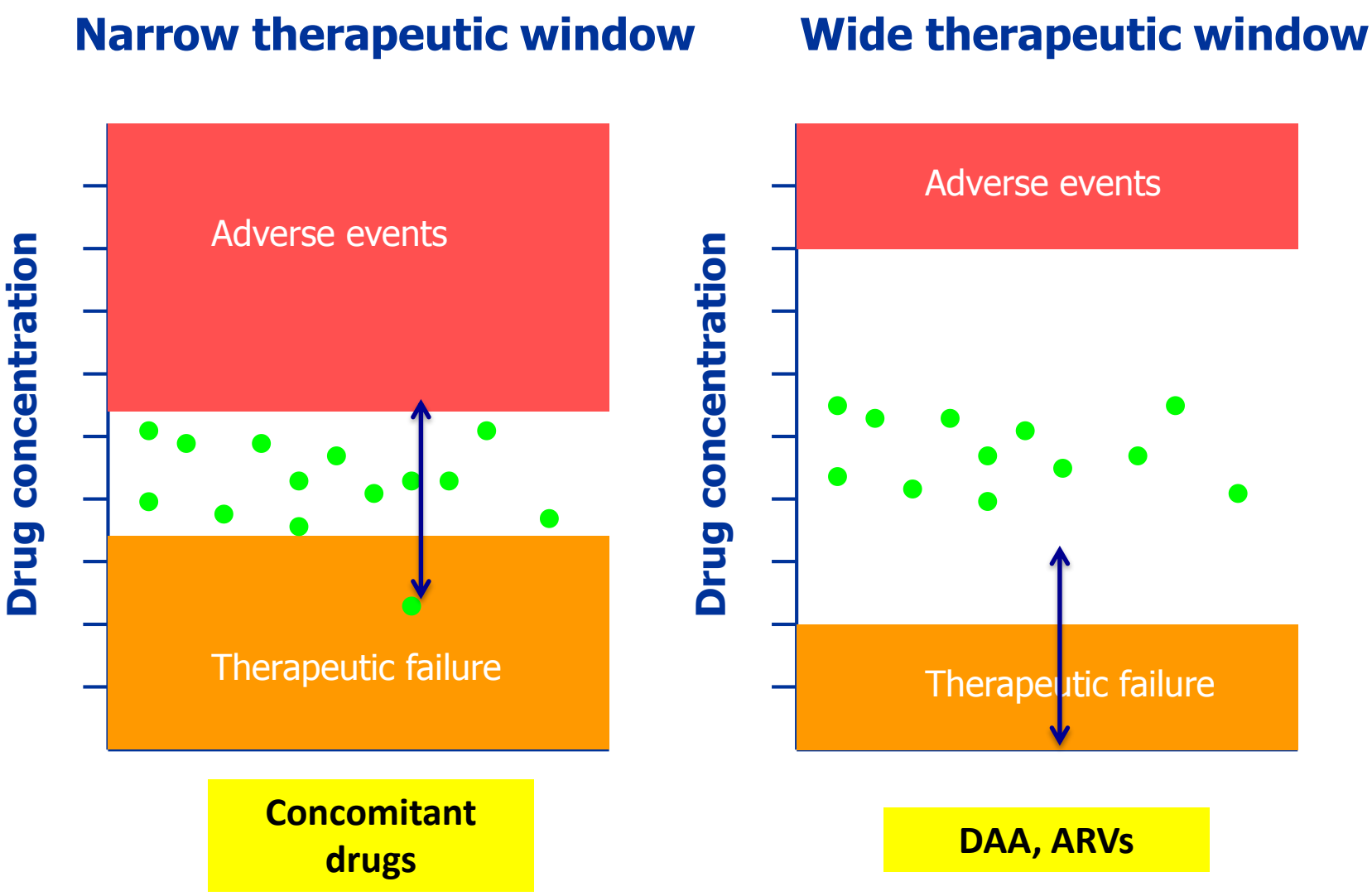
Histologically it consists of a diffuse process characterized by fibrosis and a conversion of normal organ architecture into structurally abnormal nodules

1. Reduction in liver blood flow
2. Intra- and extra-hepatic portal-systemic shunting
3. Reduction in the number and function of hepatocytes
4. Capillarization of the sinusoids



Loss of fenestration, thickening of the cytoplasm, and development of an organized basement membrane is called capillarization.

Therapeutic window



Pharmacokinetics, Efficacy, and Safety of Hepatitis C Virus Drugs in Patients with Liver and/or Renal Impairment

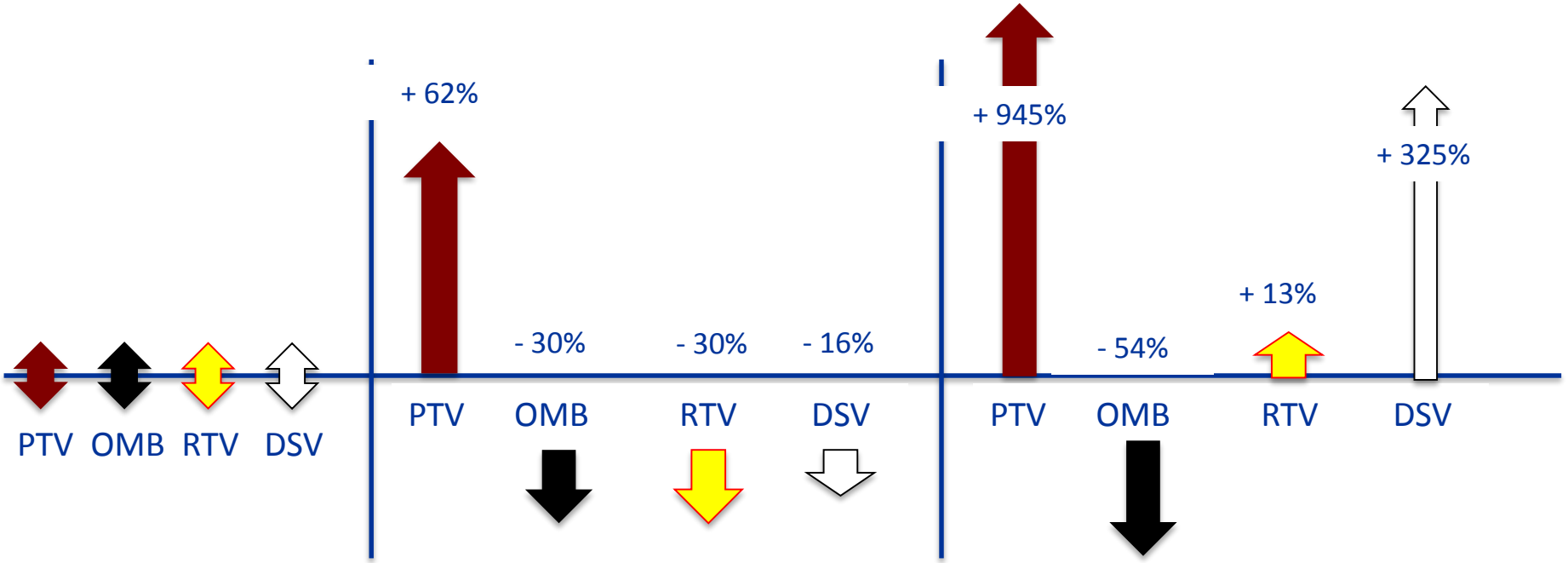
Smolders EJ, et al. Drug Saf. 2016; 39: 589–611.

		Child-Pugh score A	Child-Pugh score B	Child-Pugh score C
SMV	150 mg od [11]	150 mg od [11]	Contraindicated [11, 65] [a]	Contraindicated [11, 65][a]
ASV	100 mg bid [14, 15]	100 mg bid [14, 15]	Contraindicated[14, 15]	Contraindicated [14, 15]
DCV	60 mg od [18]	60 mg od [18]	60 mg od [18]	60 mg od [18]
SOF	400 mg od [23]	400 mg od [23]	40 0mg od [23]	400 mg od [23]
LDV/SOF	90 mg od/400 mg od [21]	90 mg od/400 mg od [21]	90 mg od/400 mg od [21]	90 mg od/400 mg od [21]
VEL/SOF	100 mg od/ 400 mg od [37]	100 mg od/ 400 mg od [37, 77]	100 mg od/ 400 mg od [37, 77]	Unknown
GZV/ELB	100 mg od/50 mg od [93, 94]	100 mg od/50 mg od [93, 94]	Contraindicated [50]	Contraindicated [50]
OMB/PTV/RTV	25 mg od/150 mg od/100 mg od [51, 52]	25 mg od/150 mg od/100 mg od [51, 52]	Contraindicated [54, 55] [c]	Contraindicated [51]
DAS	250 mg bid [52, 53]	250 mg bid [52, 53]	Contraindicated [54, 55] [c]	Contraindicated [53]
RBV	<75kg = 500 mg bid≥75kg = 600 mg bid [56]	<75kg = 500 mg bid≥75kg = 600 mg bid [56]	<75kg = 500 mg bid≥75kg = 600 mg bid [56]	<75kg = 500 mg bid≥75kg = 600 mg bid [56]

Protease Inhibitors and Dasabuvir * contraindicated in case of CHILD > A

* Due to the elevated AUC of dasabuvir (and M1) in CP-C patients, dasabuvir is contraindicated in these patients.

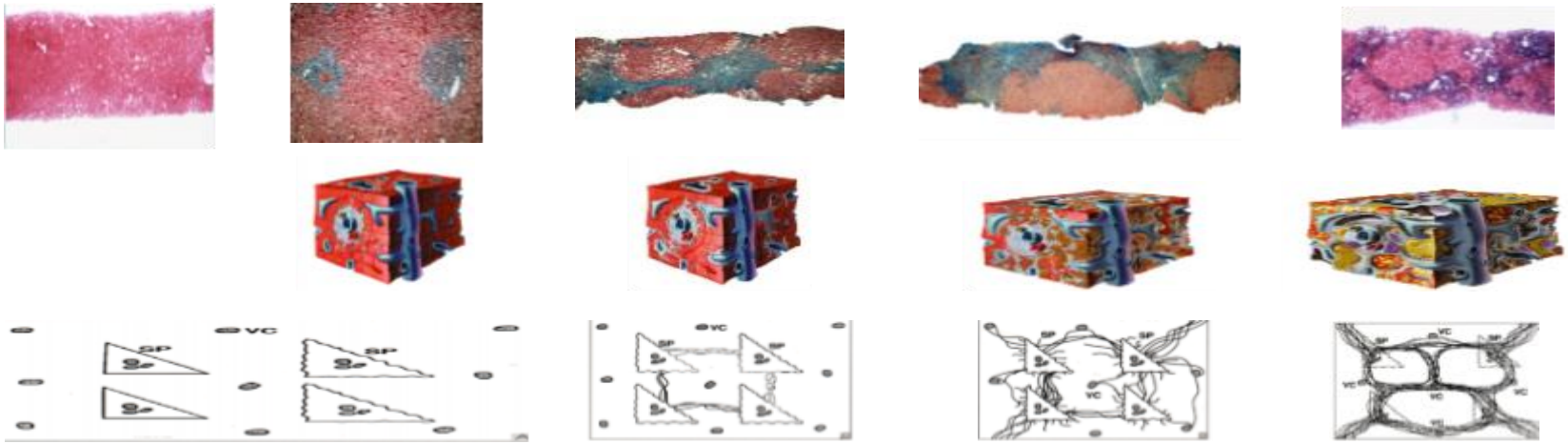
PARITAPREVIR – OMBITASVIR – RITONAVIR - DASABUVIR



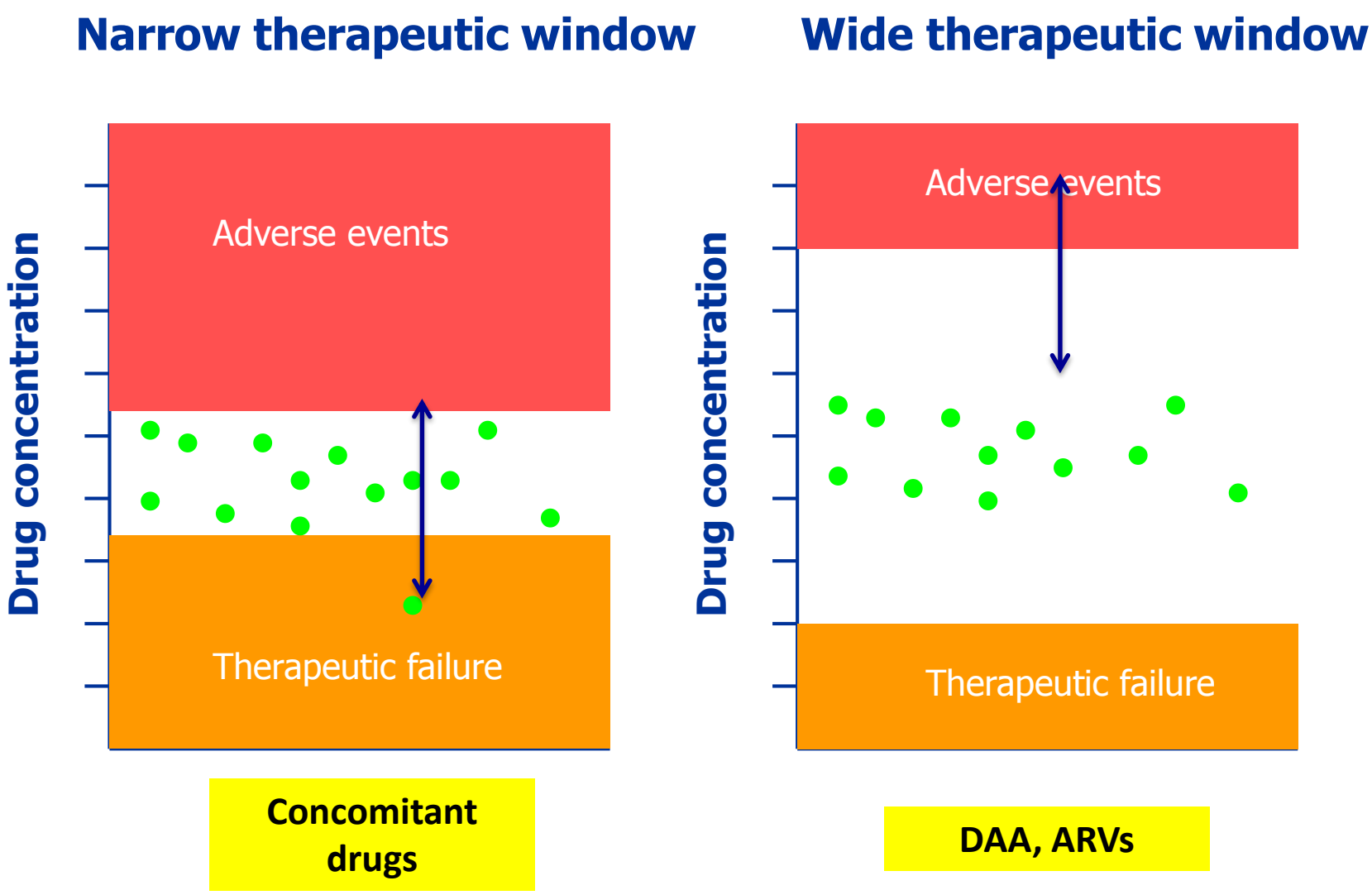
Normal

Moderate (Child A/B)

Severe (Child C)

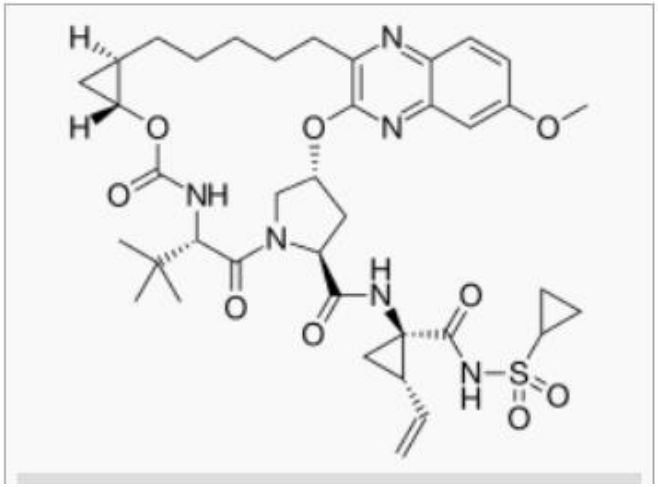


Therapeutic window



New drugs

Grazoprevir

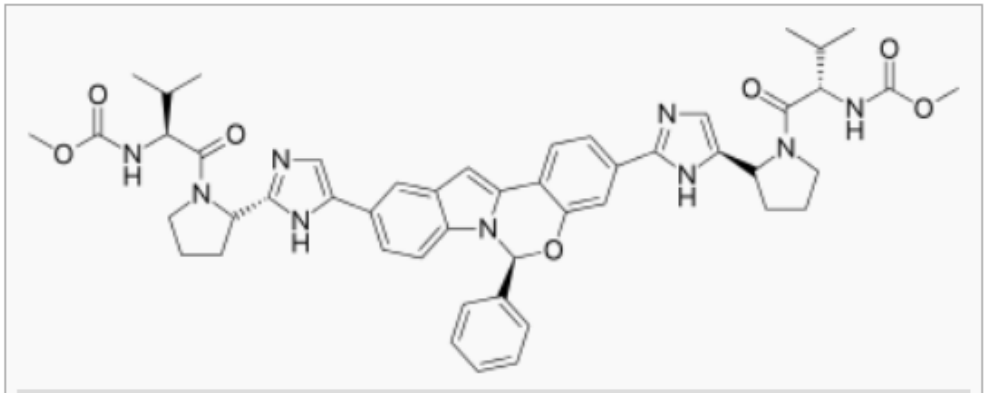


Drug-Drug Interaction Potential

Victim: Metabolised by **CYP3A4**
Transported by **P-gp & OATP1B1/3**

Perpetrator: Inducer of -
Inhibitor of **BCRP**
Weak Inhibitor of **CYP3A4**

Elbasvir



Drug-Drug Interaction Potential

Victim: Metabolised by **CYP3A4**
Transported by **P-gp**

Perpetrator: Inducer of -
Inhibitor of **BCRP**
Minimal inhibitor of P-gp

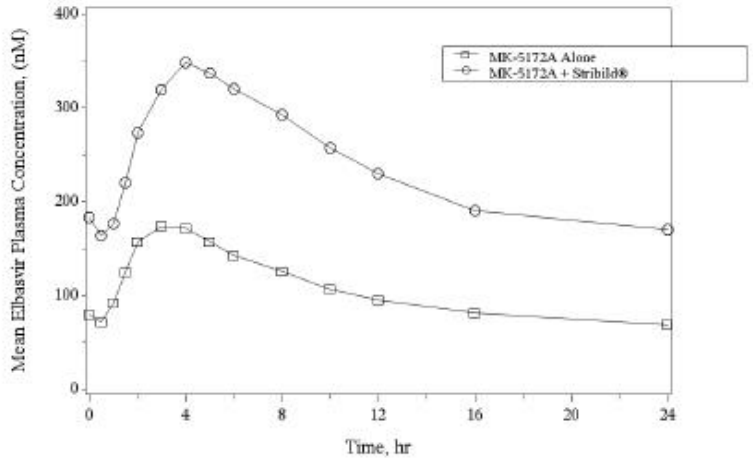
HIV ARV	Effect on GZR AUC	Effect on EBR AUC	Effect on Interacting Drug AUC	Recommendation
tenofovir disoproxil fumarate	↔ 0.9x	↔ 0.9x	↑1.2x with GZR ↑1.3x with EBR	No adjustment
raltegravir	↔ 0.9x	↔ 1.0x	↑1.4x with GZR ↔1.0x with EBR	No adjustment
dolutegravir	↔ 1.0x	↔ 1.0x	↑1.2x with GZR+EBR	No adjustment
#63 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

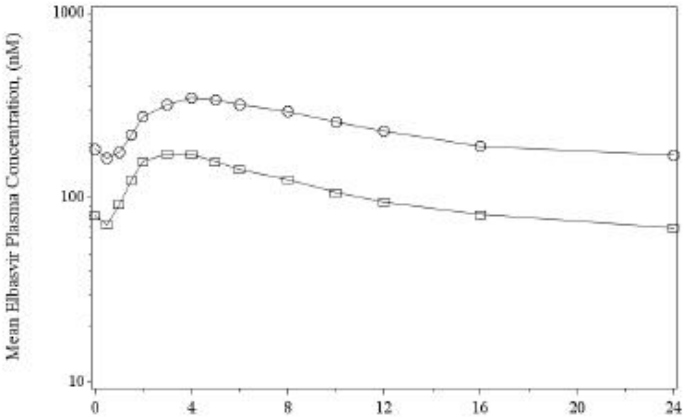
Talaty et al., AASLD 2013; Caro et al., AASLD 2013; Yeh et al., CROI 2014 ; Yeh et al., CROI 2014; Yeh et al., CROI 2015; Yeh et al., IWCPHHT 2015

MERCK

PK RESULTS: ELBASVIR

Grazoprevir (100 mg) Elbasvir (50 mg)





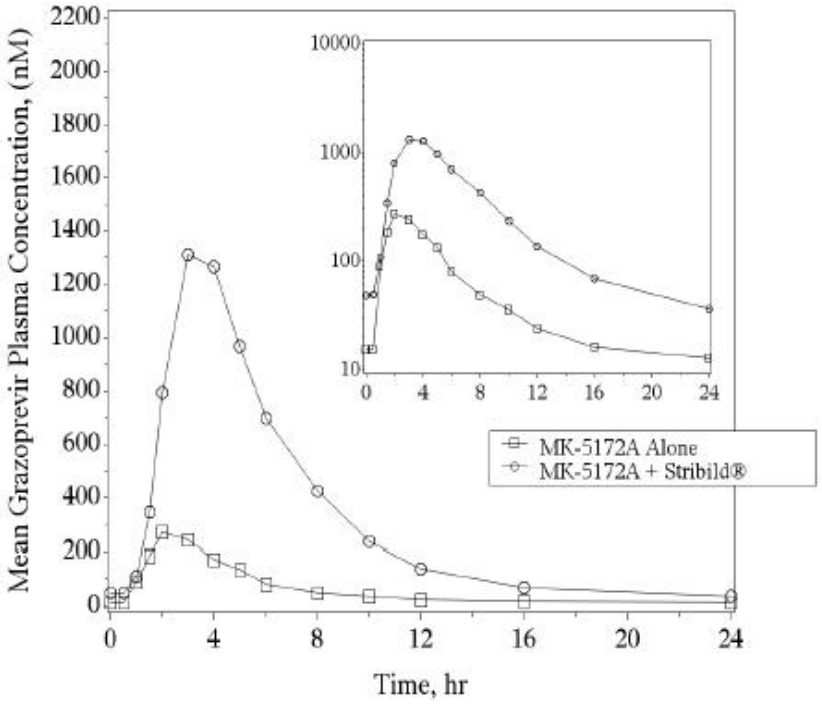
Elbasvir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Zepatier™ Alone	
	GMR	90% CI
AUC_{0-24} ‡	2.18	(2.02, 2.35)
C_{max} ‡	1.91	(1.77, 2.05)
C_{24} ‡	2.38	(2.19, 2.60)

‡Back-transformed least-squares geometric mean ratio and confidence interval from mixed-effects model performed on natural log-transformed values.

- Zepatier™ and Stribild® co-administration increases steady state elbasvir exposure via CYP3A inhibition

PK RESULTS: GRAZOPREVIR

Grazoprevir (100 mg) Elbasvir (50 mg)



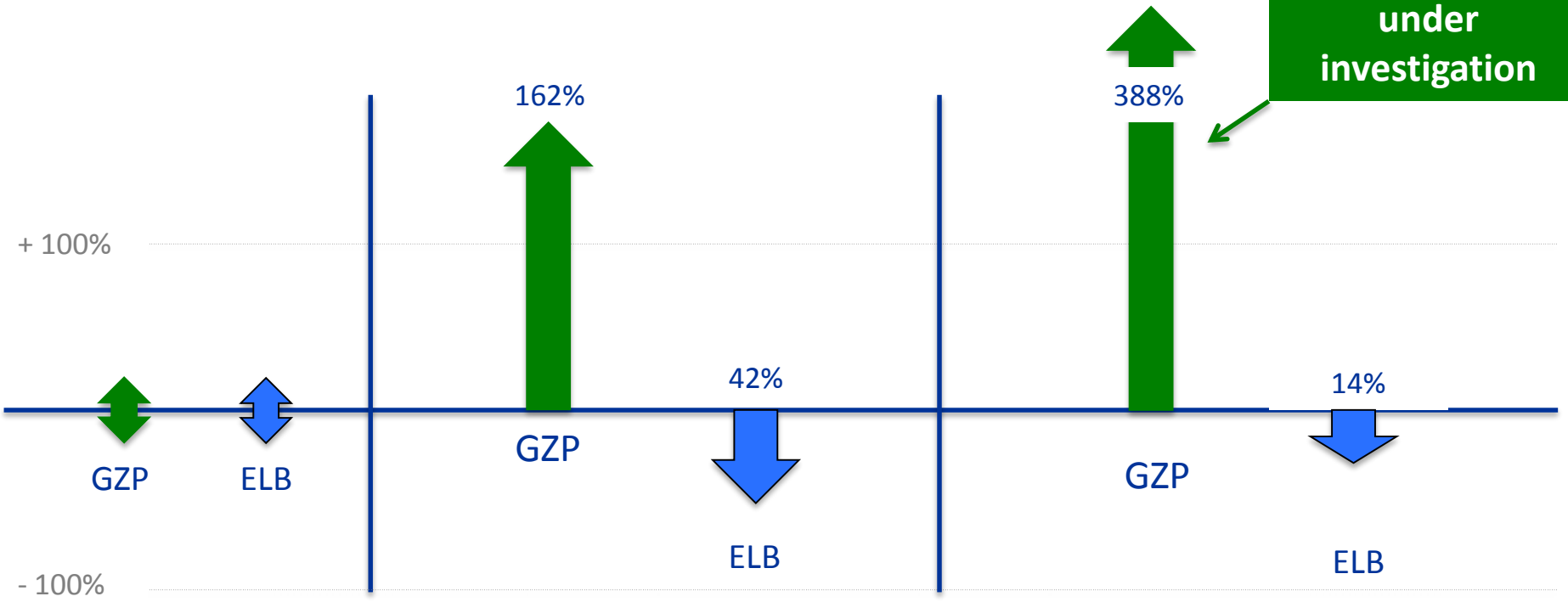
Grazoprevir Pharmacokinetic Parameter	Zepatier™ + Stribild®/ Zepatier™ Alone	
	GMR	90% CI
AUC_{0-24} ‡	5.36	(4.48, 6.43)
C_{max} ‡	4.59	(3.70, 5.69)
C_{24} ‡	2.78	(2.48, 3.11)

‡Back-transformed least-squares geometric mean ratio and confidence interval from linear mixed-effects model performed on natural log-transformed values.

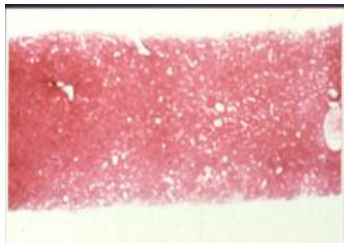
- Zepatier™ and Stribild® co-administration increases steady state grazoprevir exposure via a combination of CYP3A and OATP1B1 inhibition

GRAZOPREVIR – ELBASVIR

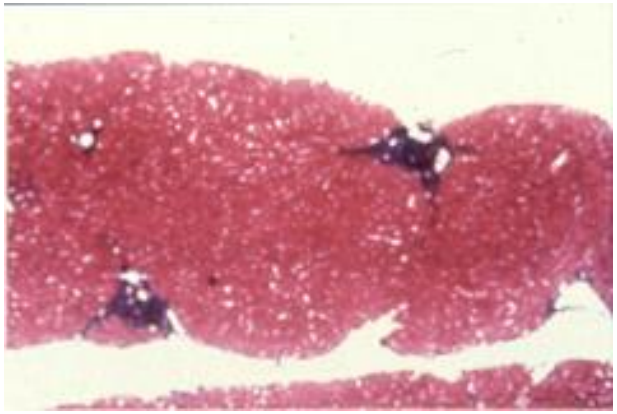
50 mg dose was under investigation



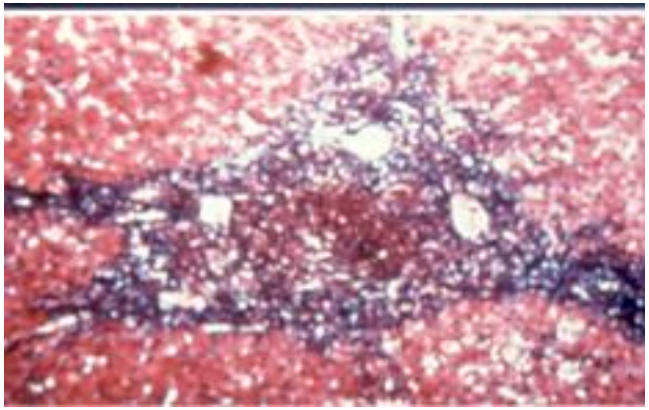
Normal



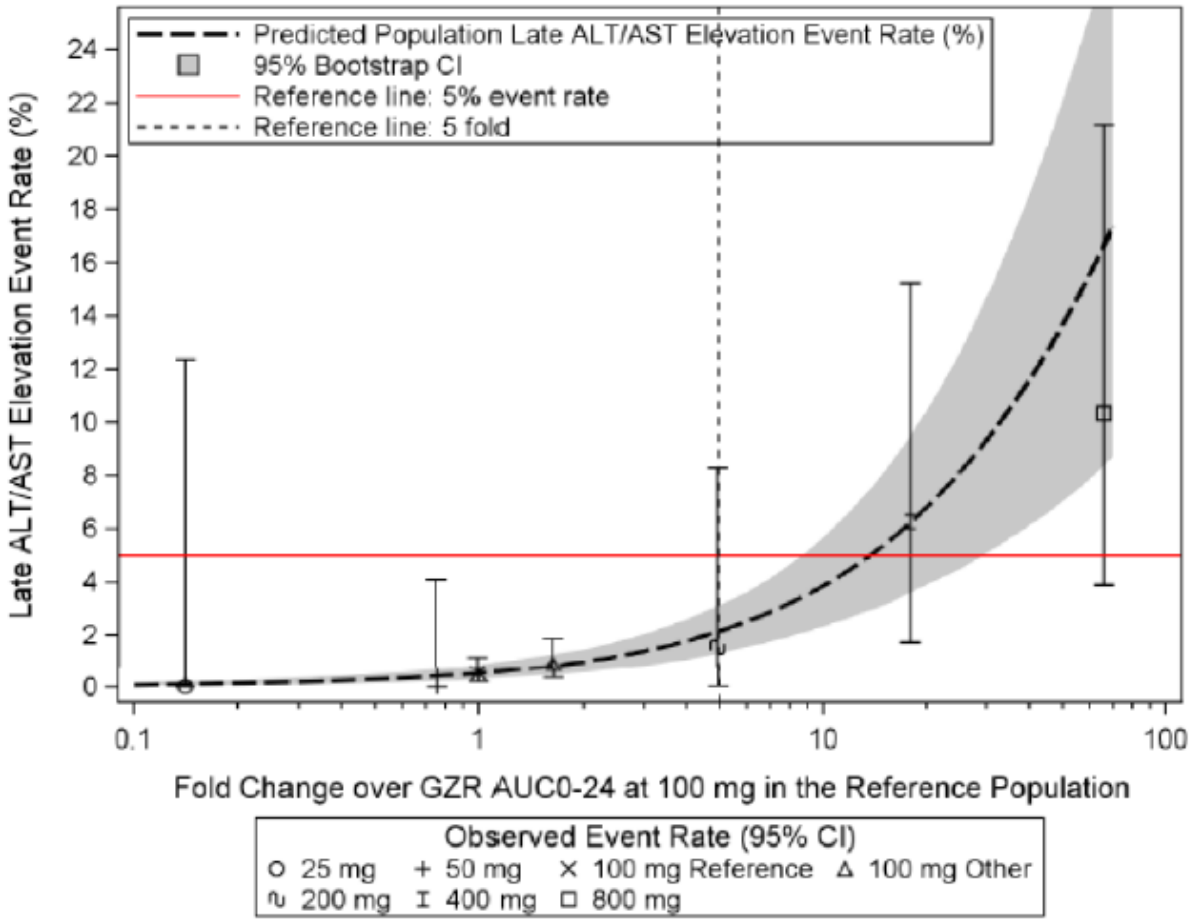
Mild (Child A)



Moderate (Child B)



PK/PD basis for interpretation of DDI data



Zepatier®, FDA Clin Pharm review, p16

Radboudumc

Velpatasvir

Drug-Drug Interaction Potential

Victim: Metabolised by: CYP3A4; CYP2C8; CYP2B6
Transported by: P-gp; BCRP; OATP

Perpetrator: Inducer of: -
Inhibitor of: P-gp; BCRP; OATP

Table 4A. Drug-drug interactions between HCV DAAs and HIV antiretrovirals.

		SOF	SOF/LDV	SOF/VEL	3D	GZR/EBR	DCV	SIM
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆*	◆*	■	◆	◆	◆
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆*	◆*	■+	●	■	●
	Darunavir/r; darunavir/cobicistat	◆	◆*	◆*	■+	●	◆	●
	Lopinavir/r	◆	◆*	◆*	●	●	◆	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■	●
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

SOF, sofosbuvir; SOF/LDV, sofosbuvir plus ledipasvir; SOF/VEL, sofosbuvir plus velpatasvir; 3D, ritonavir-boosted paritaprevir, plus ombitasvir and dasabuvir; GZR/EBR, grazoprevir plus elbasvir; DCV, daclatasvir; SIM, simeprevir; /r, ritonavir.

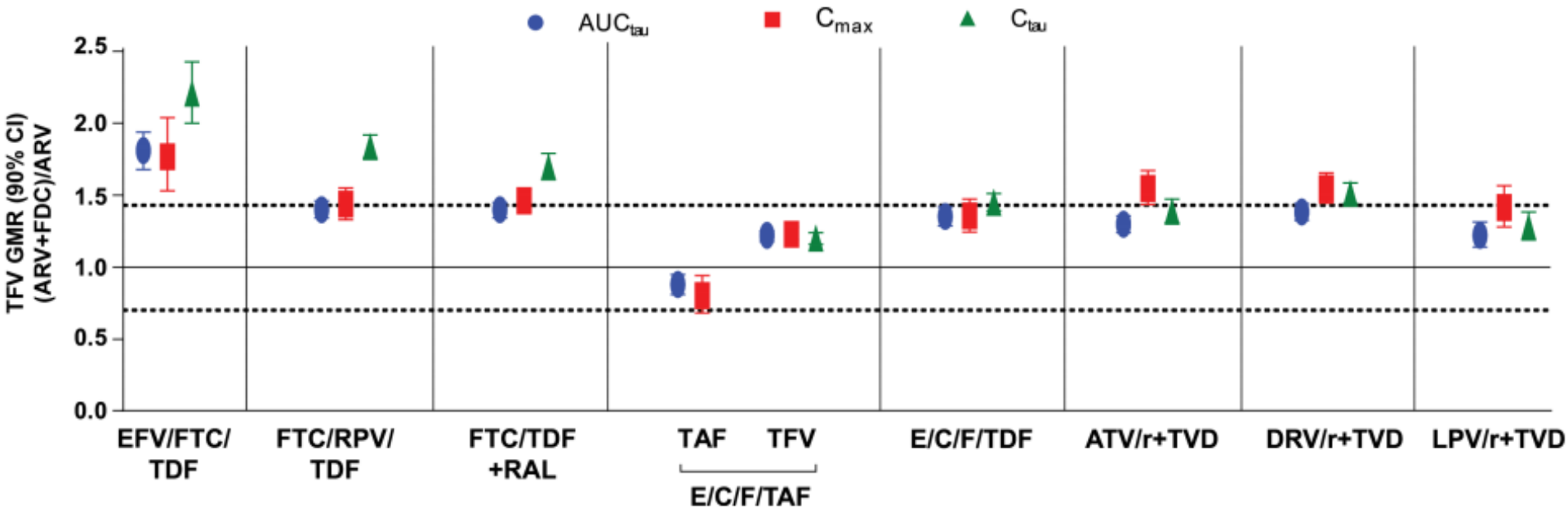
Drug-Drug Interaction Profile of SOF/VEL

Characterization of SOF/VEL drug-drug interaction profile using *in vitro* data, Phase 1 clinical data, and population PK data from Phase 2/3 studies

SOF/VEL Effect on Drug		No Change	Effect of Drug on SOF/VEL	
Tenofovir	↑ AUC 40–81%	Anticoagulants Atazanavir/r Calcium Channel Blockers Cobicistat Cyclosporine Darunavir/r Diuretics Dolutegravir Efavirenz Elvitegravir Emtricitabine Famotidine Lopinavir/r Metadone Raltegravir Rifaximin Rilpivirine Sofosbuvir or GS-331007 (primary SOF metabolite) SSRIs Tacrolimus Tenofovir alafenamide	Efavirenz	↓ VEL AUC 53%
Ethinyl estradiol	↑ Cmax 39%, ↓ in Ctau 17%, no change in AUC		ATV/r	↑ VEL AUC 142%
Norgestrel	↑ AUC 19% and Ctau 23%		Omeprazole (depending on dose and fed/fasted)	↓ VEL AUC 26-57%
Pravastatin	↑ AUC 35%		Rifampin	↓ VEL 82% and SOF 72%
Rosuvastatin	↑ AUC 169%			
Digoxin	↑ AUC 34%			

Mogalian, EASL 2016, Poster FRI-168

Effect of SOF/VEL on TFV*



- Co-administration of SOF/VEL with TDF-containing ARVs increased TFV exposure ~20-81%
- No significant impact of SOF/VEL on TAF or TFV derived from TAF

*Dotted lines depict no-PK-alteration boundary.

Chaponda, BHIVA, 2016, Presentation # P6

Drug-Drug Interaction Profile of SOF/VEL

Characterization of SOF/VEL drug-drug interaction profile using *in vitro* data, Phase 1 clinical data, and population PK data from Phase 2/3 studies

SOF/VEL Effect on Drug		No Change	Effect of Drug on SOF/VEL	
Tenofovir	↑ AUC 40–81%	Anticoagulants Atazanavir/r Calcium Channel Blockers Cobicistat Cyclosporine Darunavir/r Diuretics Dolutegravir Efavirenz Elvitegravir Emtricitabine Famotidine Lopinavir/r Metadone Raltegravir Rifaximin Rilpivirine Sofosbuvir or GS-331007 (primary SOF metabolite) SSRIs Tacrolimus Tenofovir alafenamide	Efavirenz	↓ VEL AUC 53%
Ethinyl estradiol	↑ Cmax 39%, ↓ in Ctau 17%, no change in AUC		ATV/r	↑ VEL AUC 142%
Norgestrel	↑ AUC 19% and Ctau 23%		Omeprazole (depending on dose and fed/fasted)	↓ VEL AUC 26-57%
Pravastatin	↑ AUC 35%		Rifampin	↓ VEL 82% and SOF 72%
Rosuvastatin	↑ AUC 169%			
Digoxin	↑ AUC 34%			

Mogalian, EASL 2016, Poster FRI-168

pH-Based Interactions: Acid-Reducing Agents[13]

Perpetrator*	Object	AUC, %	C_{max}, %
SOF/VEL (fasted) simultaneous with **FAM 40 mg**	SOF	↔	↔
	GS-331007	↔	↔
	VEL	↔	↔
SOF/VEL (fasted) 12 h after **FAM 40 mg**	SOF	↔	↓23
	GS-331007	↔	↔
	VEL	↔	↔
SOF/VEL (fasted) simultaneous with **OME 20 mg**	SOF	↓29	↓34
	GS-331007	↔	↔
	VEL	↓37	↓37
SOF/VEL (fasted) 12 h after **OME 20 mg**	SOF	↓44	↓45
	GS-331007	↔	↔
	VEL	↓56	↓57
SOF/VEL (fed) 2 h after **OME 20 mg**	SOF	↔	↓16
	GS-331007	↔	↔
	VEL	↓38	↓48
SOF/VEL (fed) 4 h before **OME 20 mg**	SOF	↔	↓21
	GS-331007	↔	↔
	VEL	↓26	↓33
SOF/VEL (fed) 4 h before **OME 40 mg**	SOF	↔	↓30
	GS-331007	↔	↔
	VEL	↓53	↓56

*Agents in *bold* denote perpetrator. FAM, famotidine; OME, omeprazole

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