14th Residential Course on Clinical Pharmacology of Antiretrovirals

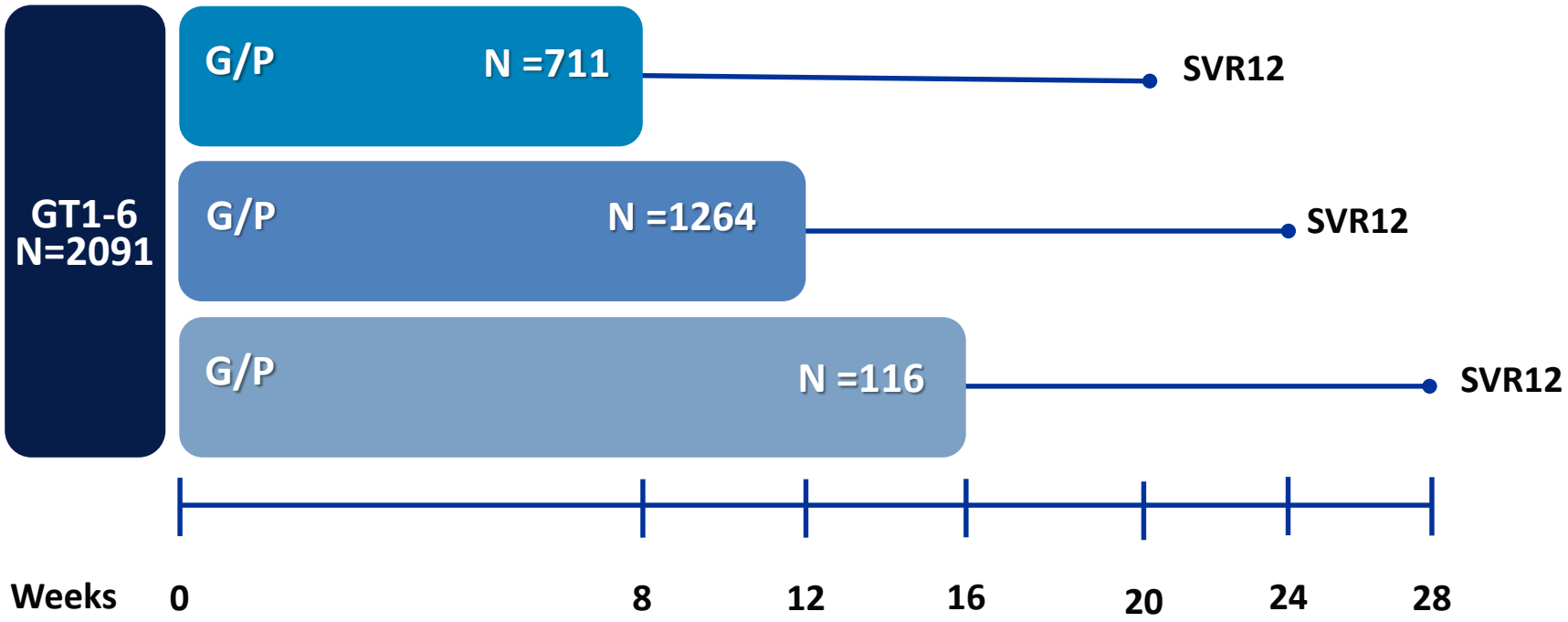
Which drug-drug interactions are still a concern in HCV treatment?

Letizia Marinaro

Torino , 16-18 January

Adherence to Pangenotypic Glecaprevir/Pibrentasvir Treatment and SVR12 in HCV-infected Patients: An Integrated Analysis of the Phase 2/3 Clinical Trial Program

Objective: Assess the factors associated with non-adherence to G/P and the impact on SVR12 rates in patients with HCV infection enrolled in 8 phase 3 clinical studies*



*Patients pooled from ENDURANCE-1, ENDURANCE-2, ENDURANCE-3, ENDURANCE-4, EXPEDITION-1, EXPEDITION-4, SURVEYOR-II, and MAGELLAN-1 phase 3 studies, and enrolled in Australia, Austria, Belgium, Canada, Chile, France, Germany, Greece, Hungary, Israel, Italy, Korea, Lithuania, Mexico, New Zealand, Poland, Portugal, Puerto Rico, Romania, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom, and United States

Baseline Demographics and Clinical Characteristics

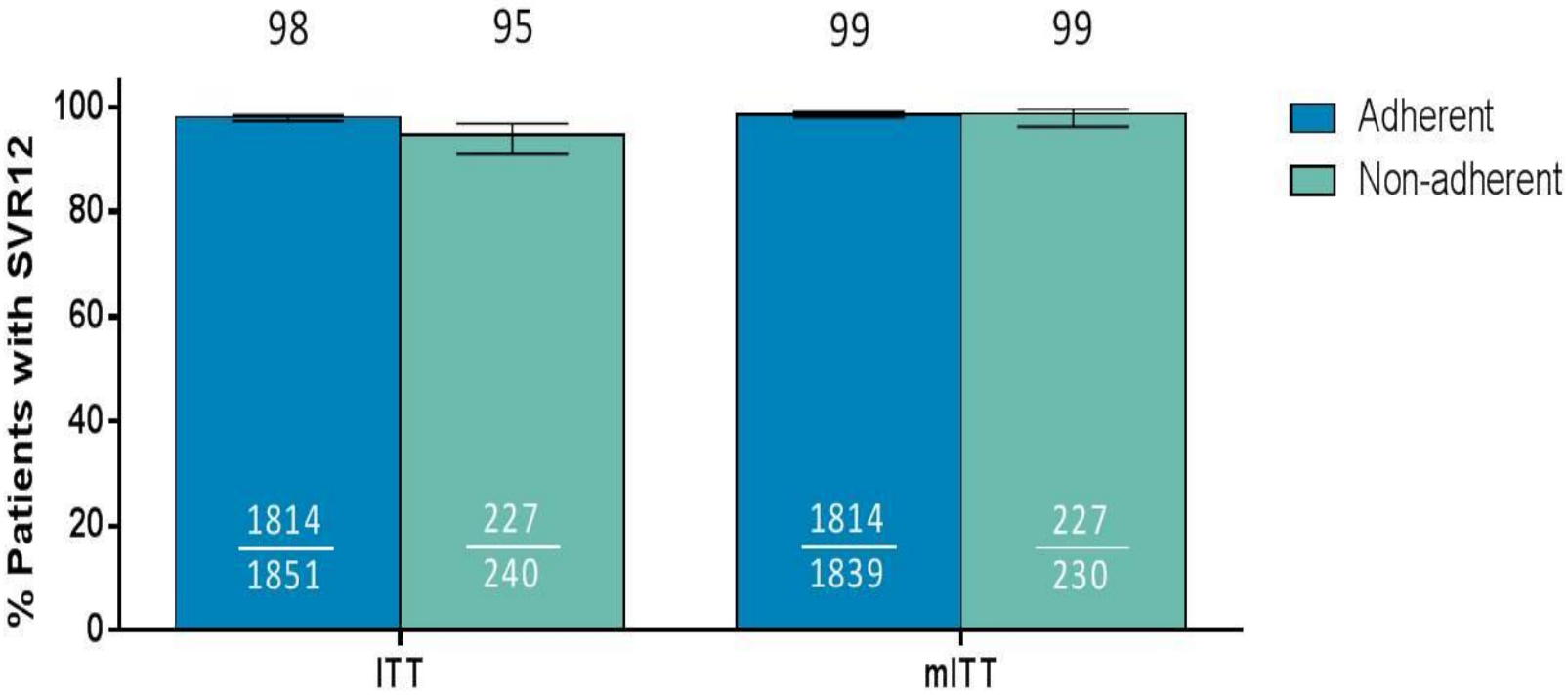
Characteristic	Adherent N = 1851	Non-adherent N = 240
Male, n (%)	992 (54)	158 (66)
White race, n (%)	1462 (79)	197 (82)
Age, median years (range)	54 (19–84)	53 (20–88)
BMI, median kg/m^2 (range)	25.8 (17.3–65.7)	25.9 (17.9–49.0)
HCV genotype, n (%)		
1	863 (47)	78 (33)
2	359 (19)	29 (12)
3	427 (23)	105 (44)
4/5/6	144 (8) / 27 (1) / 31 (2)	18 (8) /4 (2) / 6 (3)
<80% adherence	NA	235 (98)
>120% adherence	NA	5 (2)*

BMI, body mass index.

*4/5 only had >120% adherence between the first two treatment visits

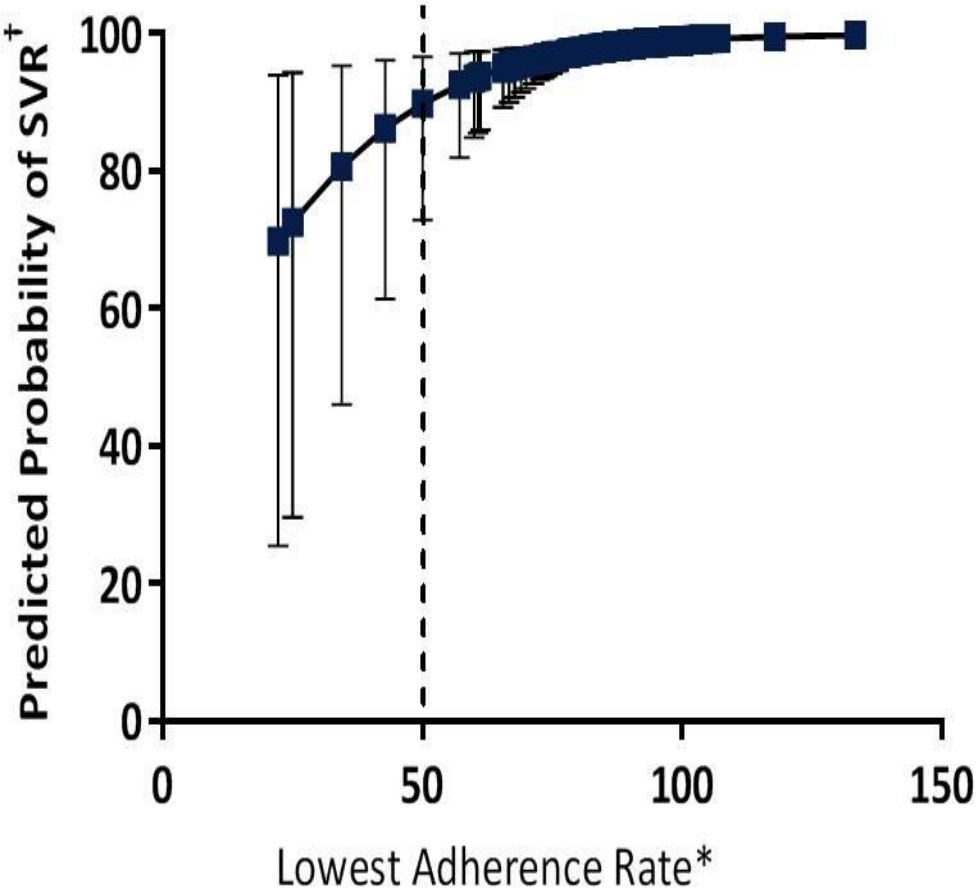
Overall, 89% (1851/2091) of patients were adherent to G/P at all consecutive treatment intervals

SVR12



Reason for Non-response, n (%)	Adherent	Non-adherent
On-treatment virologic failure	7 (0.4)	2 (0.8)
Relapse	18 (1)	1 (0.4)
Missing Data	9 (0.5)	4 (1.6)
Early Discontinuation	3 (0.2)	6 (2.5)

Impact of Adherence on Predicted SVR12



Adherence rates as low as 50% correlate with predicted chance for SVR12 of at least 90%

*Lowest adherence observed in any of the 4-week intervals

†Predicted probability of SVR was derived from a logistic regression using lowest adherence rate as the predictor and SVR12 as the outcome

Forgiveness?

GLE is rapidly absorbed with Tmax 5 h and with a half–life of 6.6h in humans.

PIB is slowly absorbed with Tmax of 3.7-9h and with a half–life of 14.9h in humans.

BUT

GLE was widely distributed in most tissues with peak levels at 0.5-2 hours, and radioactivity declined to below the limit of quantification at 24h, **except in liver (highly distributed: ratio tissue / blood up to 269, and persist up to 96h post dose)**

PIB was widely distributed in most tissues with a peak levels at 4-8 hours. Highest concentrations are in bile, adrenal gland, **liver** and small intestine. **Radioactivity declined to below the limit of quantification at 24h**

EMA Assesment Report 2017)

Sofosbuvir and Ribavirin Liver Pharmacokinetics in Patients Infected with Hepatitis C Virus

Darius Babusis,[a] Michael P. Curry,[b] Brian Kirby,[a] Yeojin Park,[a] Eisuke Murakami,[a] Ting Wang,[a] Anita Mathias,[a] Nezam Afdhal,[b] John G. McHutchison,[a] Adrian S. Ray[a]

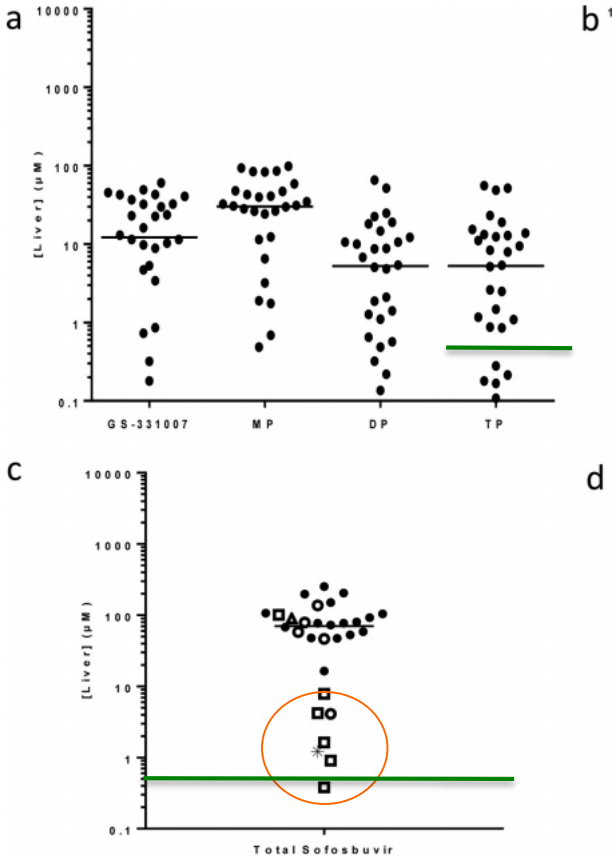
[a]Gilead Sciences, Inc., Foster City, California, USA

[b]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

AAC, May 2018

Comparison of maximal plasma nucleoside levels with total levels in the liver, sofosbuvir results in an estimated liver/plasma ratio of **approximately 30-fold**

The five patients with the lowest levels of sofosbuvir-related metabolites stopped **therapy at least 3 weeks** before transplantation.



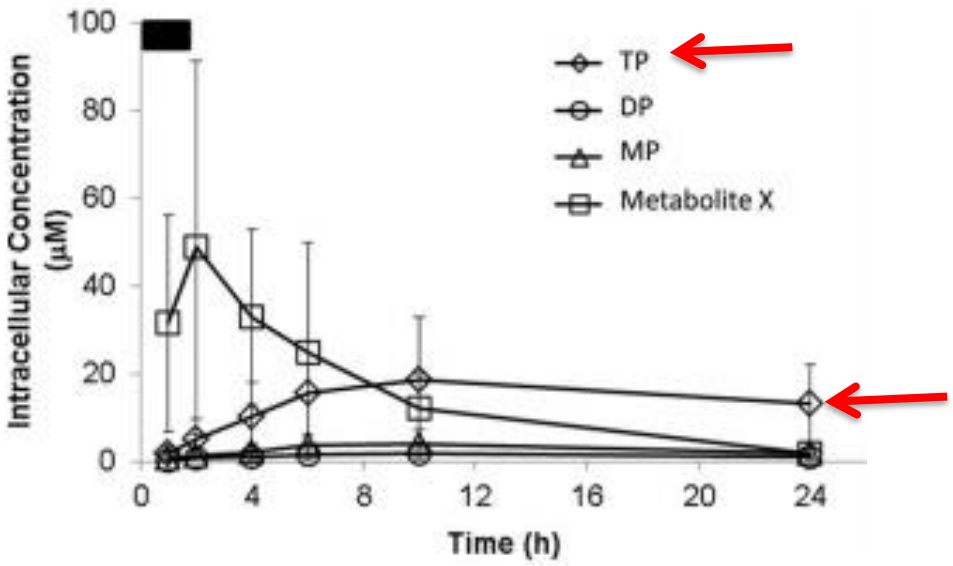
Sofosbuvir and Ribavirin Liver Pharmacokinetics in Patients Infected with Hepatitis C Virus

Darius Babusis,[a] Michael P. Curry,[b] Brian Kirby,[a] Yeojin Park,[a] Eisuke Murakami,[a] Ting Wang,[a] Anita Mathias,[a] Nezam Afdhal,[b] John G. McHutchison,[a] Adrian S. Ray[a]

[a]Gilead Sciences, Inc., Foster City, California, USA

[b]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

AAC, May 2018



TP metabolite has an half-life of >24 hours

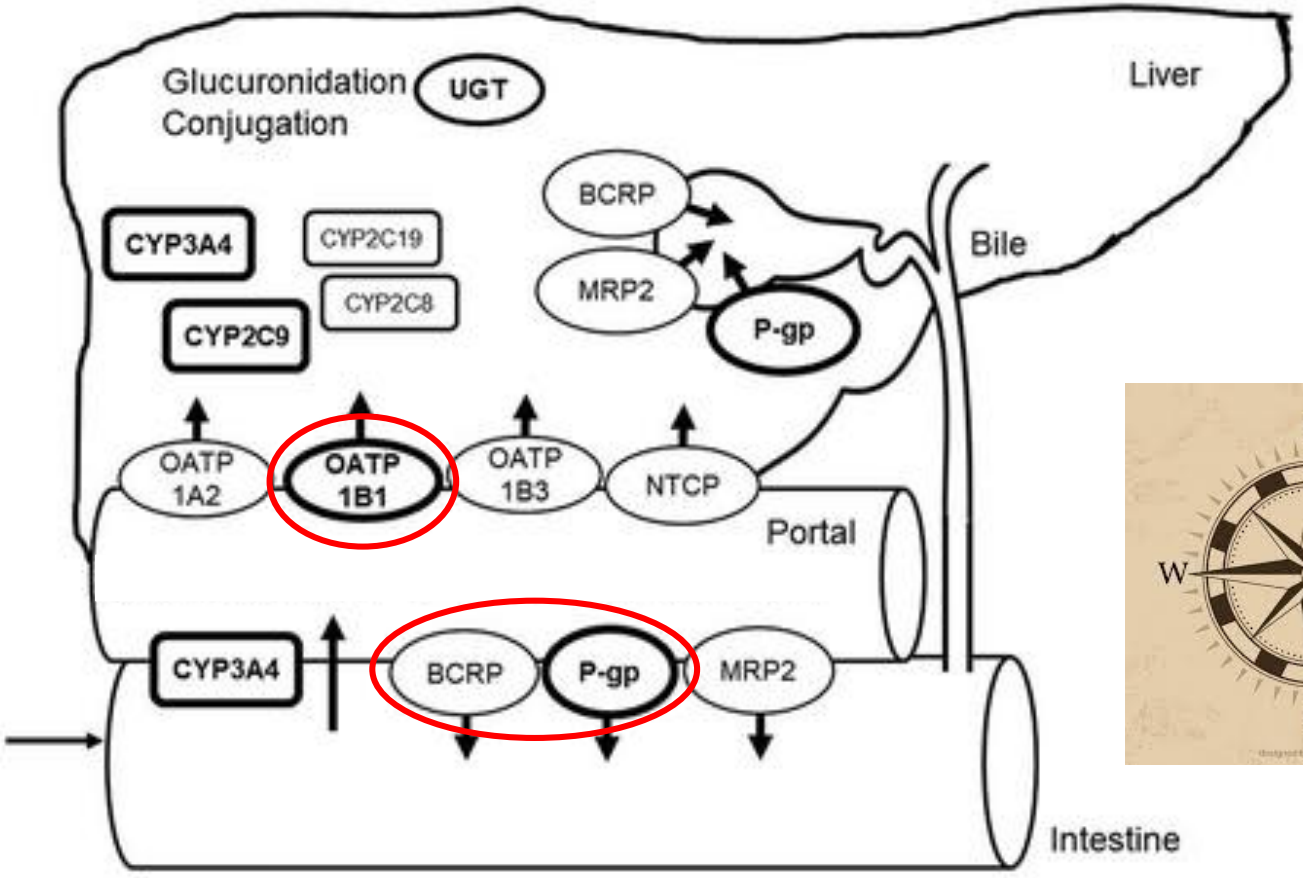
Sticking points in management patients to be treated with DAA treatment

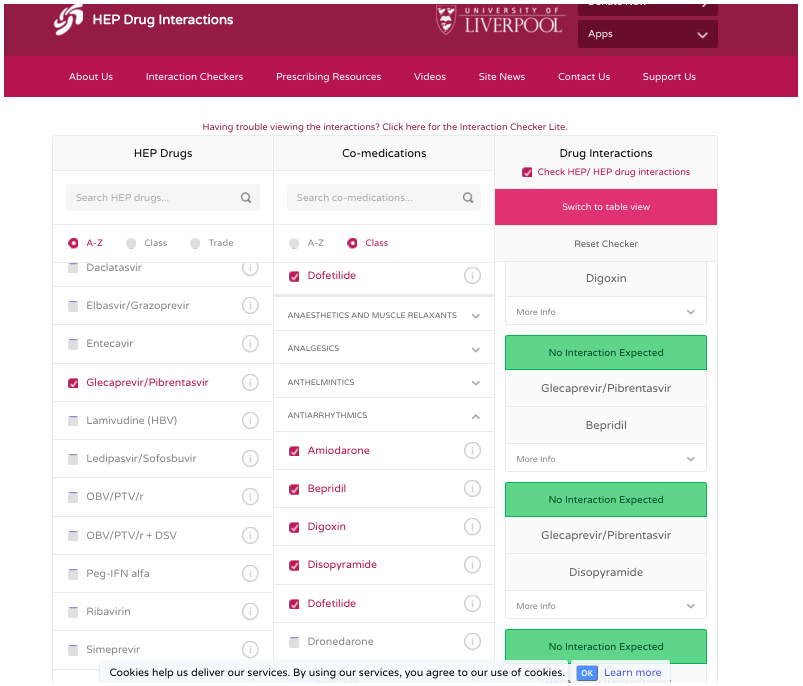
Elegibility	
Regimen choice	
Interactions analysis	
Counselling	
Efficacy Monitoring	
Toxicity monitoring	

Mechanisms of Drug Interactions of DAAs

DAA	Victim of DDI	Perpetrator of DDI	DDI Potential
Grazoprevir/elbasvir	Substrate for CYP3A4, P-gp & OATP1B1	Inhibits P-gp & BCRP	Moderate
Velpatasvir/sofosbuvir	Substrate for P-gp & BCRP Gut pH	Inhibits P-gp & BCRP	Moderate/ Low
Glecapravir/pibrentasvir	Substrate for P-gp & BCRP	Inhibits P-gp & BCRP	Moderate/ Low

Transporters of DAAs: orienteering map for clinicians



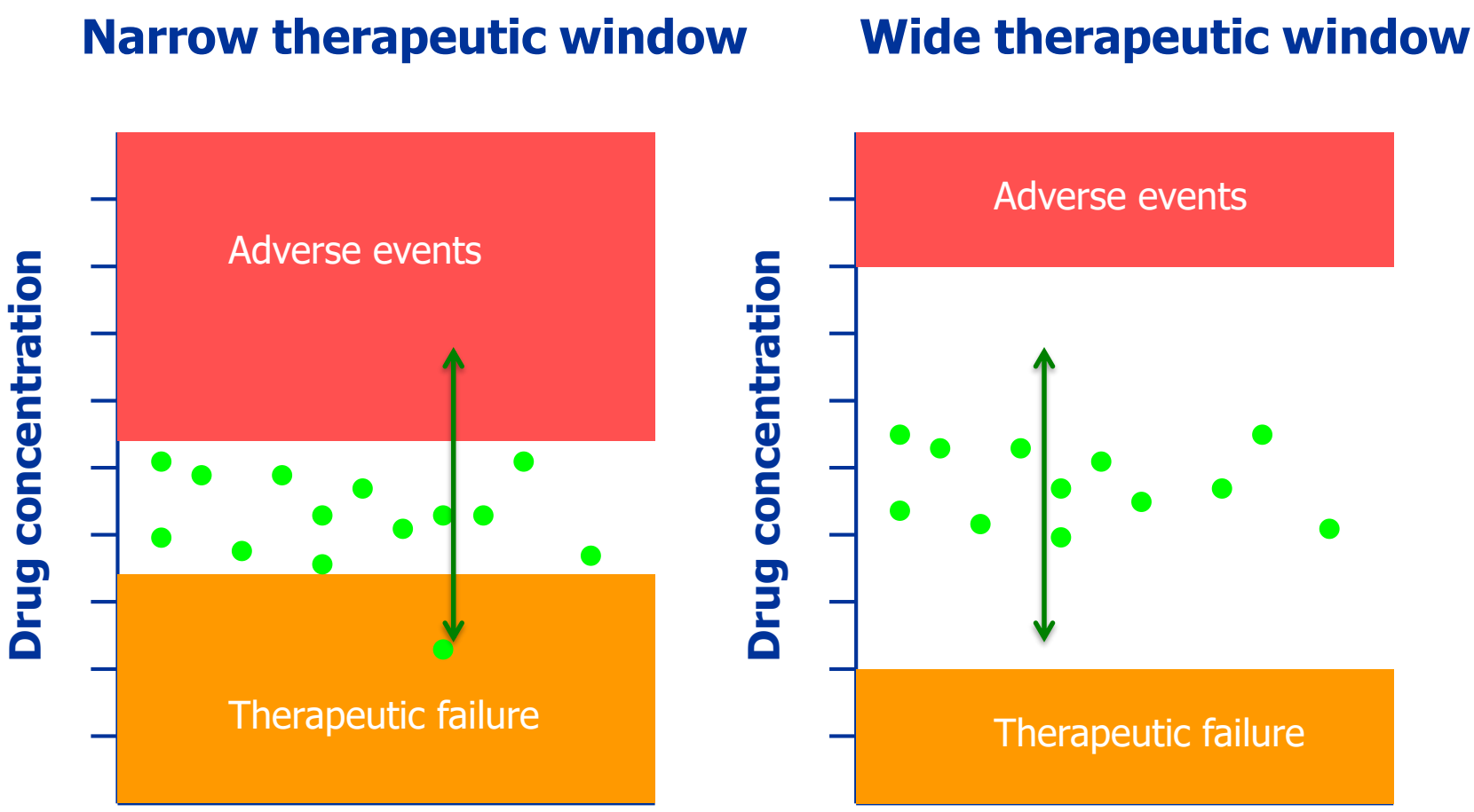

HEP Drug Interactions
UNIVERSITY OF LIVERPOOL
Apps
About Us
Interaction Checkers
Prescribing Resources
Videos
Site News
Contact Us
Support Us
Having trouble viewing the interactions? Click here for the Interaction Checker Lite.
HEP Drugs
Co-medications
Drug Interactions
Check HEP/ HEP drug interactions
Switch to table view
Reset Checker
Search HEP drugs...
Search co-medications...
A-Z
Class
Trade
Daclatasvir
Elbasvir/Grazoprevir
Entecavir
Glecaprevir/Pibrentasvir
Lamivudine (HBV)
Ledipasvir/Sofosbuvir
OBV/PTV/r
OBV/PTV/r + DSV
Peg-IFN alfa
Ribavirin
Simeprevir
Dofetilide
ANAESTHETICS AND MUSCLE RELAXANTS
ANALGESICS
ANTHELMINTICS
ANTIARRHYTHMICS
Amiodarone
Bepridil
Digoxin
Disopyramide
Dofetilide
Dronedarone
Digoxin
More Info
No Interaction Expected
Glecaprevir/Pibrentasvir
Bepridil
More Info
No Interaction Expected
Glecaprevir/Pibrentasvir
Disopyramide
More Info
No Interaction Expected
Cookies help us deliver our services. By using our services, you agree to our use of cookies.
OK
Learn more


dreamstime.com

DRIVERS OF CLINICAL SIGNIFICANCY IN DDI

$$\left[\frac{\text{PK Variation}}{\text{Therapeutic Range}}\right] \times$$

Therapeutic window



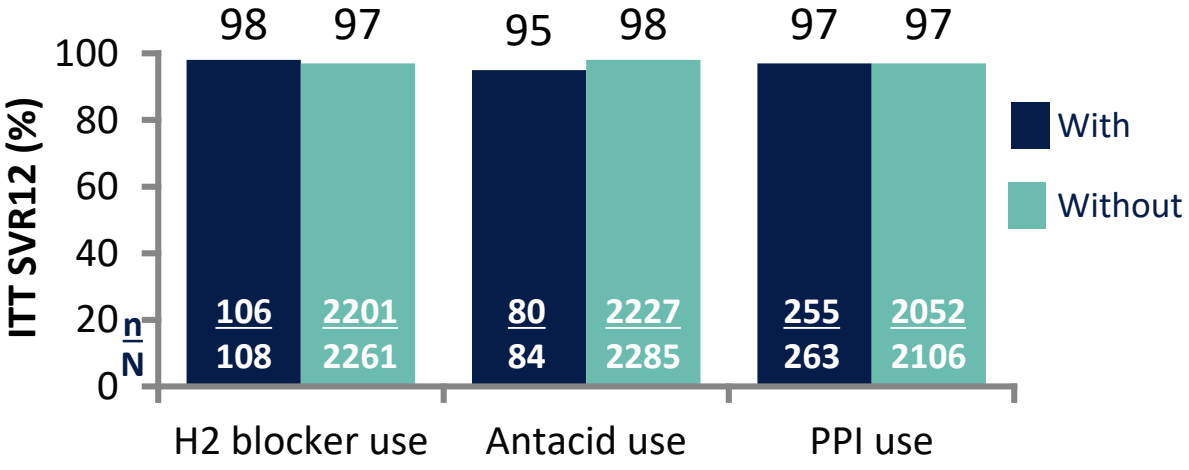
DRIVERS OF CLINICAL SIGNIFICANCY IN DDI

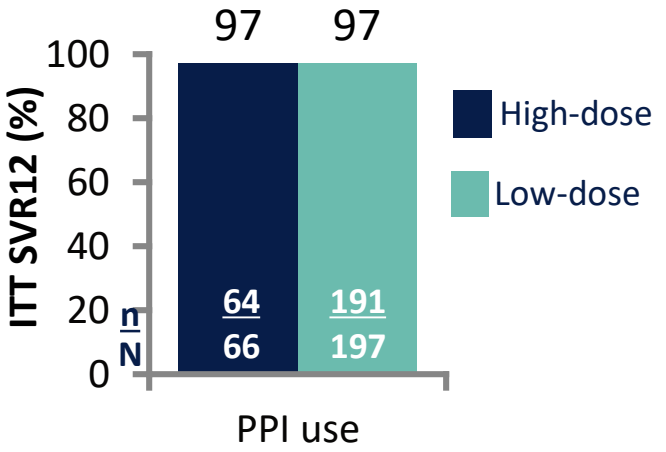
$$\left[\frac{\text{PK Variation}}{\text{Therapeutic Range}}\right] \times \left[\text{Clinical impact}\right]$$

G/P in Patients Taking PPIs and Other Acid-Reducing Drugs: Integrated Analysis of Nine Phase 2/3 Studies

Pooled clinical trial data of G/P for 8/12/16 weeks in HCV GT1–6 infected patients was used to evaluate the efficacy and safety of G/P in patients receiving PPIs, H2 blockers, or antacids

Characteristic, n (%)	Overall n=2369	Concomitant H2 Blocker Use n=108	Concomitant Antacid Use n=84	Concomitant PPI Use n=263
Treatment-naive	1640 (69)	70 (65)	54 (64)	178 (68)
Fibrosis stage				
F0 – F1	1651 (70)	61 (56)	54 (64)	142 (54)
F2	165 (7)	9 (8)	3 (4)	24 (9)
F3	245 (10)	13 (12)	14 (17)	39 (15)
F4	303 (13)	25 (23)	13 (15)	58 (22)
Missing	5	0	0	0





Flamm S, *et al*. ACG 2017 (poster presentation).

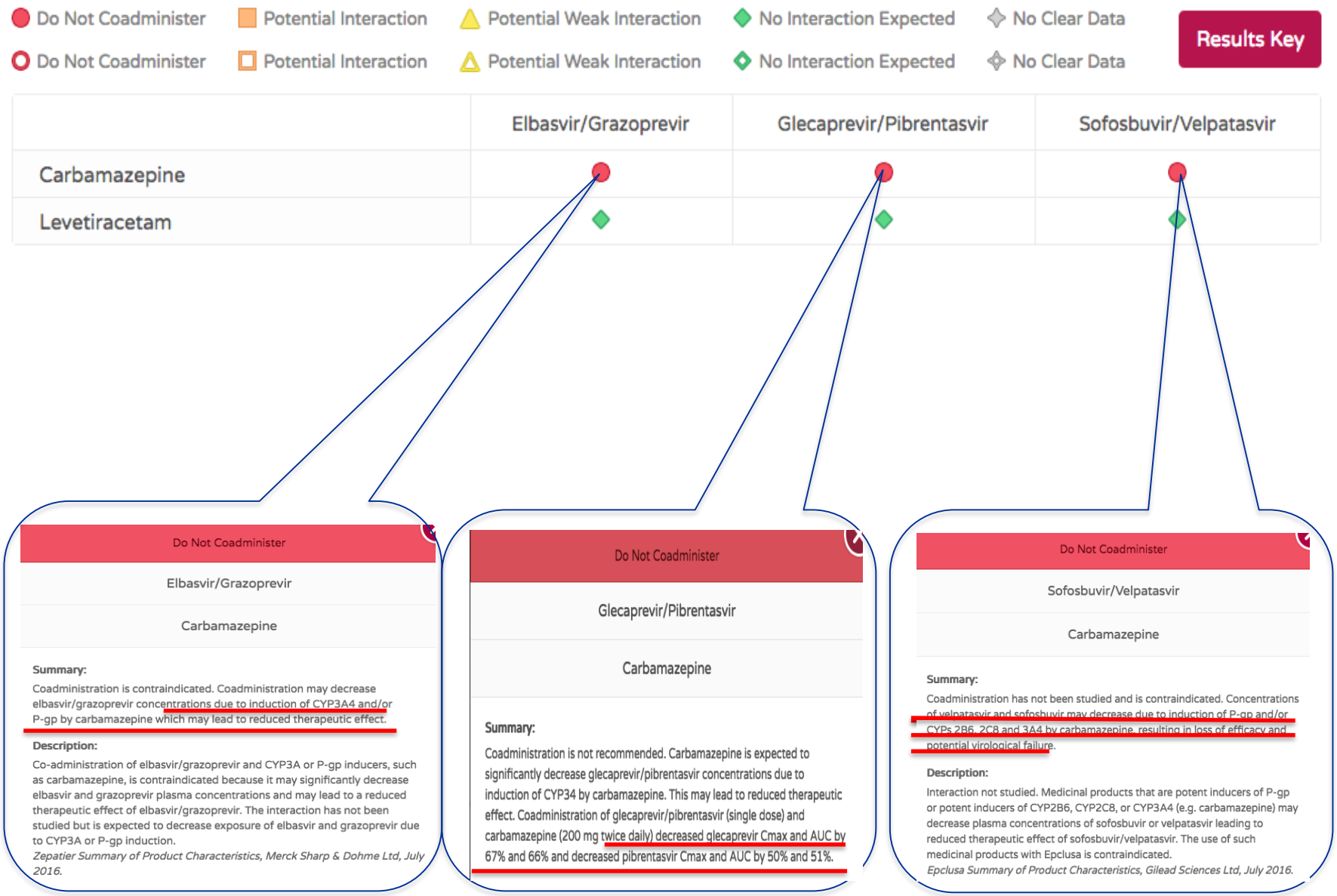
DRIVERS OF CLINICAL SIGNIFICANCY IN DDI

$$\left[\frac{\text{PK Variation}}{\text{Therapeutic Range}} \times \text{Clinical impact}\right] \times \text{Interaction Lenght}$$

Pasquale, 52 ys

- **HCV** Gen. 4;
- Metavir score F0 (2017);
- HCV-RNA 2.599.952 UI/mL, Wild Type;
- 1999 head trauma with cerebral haemorrhage.
- CARBAMAZEPINE ½ CP twice daily, TDF/FCT + RAL.
- November 2017 discontinued carbamazepina from 1 month: subsequent seizure.
- Carbamazepine reintroduction

Anticonvulsants and DAAs



Pasquale, 52 ys

Switch from carbamazepine to levetiracetam:

- week 1: carbamazepine 400 mg morning; carbamazepine 200 mg + levetiracetam 500 mg evening;
- week 2: carbamazepine 200 mg + levetiracetam 500 mg morning: carbamazepine 200 mg + evetiracetam 500 mg evening;
- week 3: carbamazepine 200 mg + levetiracetam 500 mg morning; levetiracetam 1000 mg evening;
- week 4: stop carbamazepine; levetiracetam 1000 mg morning, 1000 mg evening.

Switch back from levetiracetam to carbamazepin after completion of DAA treatment (waiting 2-4 weeks at least).

HIV/HCV Drug–Drug Interactions

ARV(s)	GLE/PIB	GZR/EBR	SOF/LDV	SOF/VEL	SOF/VEL/VOX
ATV + (RTV or COBI)	X	X	✓*	✓*	X
DRV + (RTV or COBI)	X	X	✓*	✓*	✓*†‡
LPV + RTV	X	X	✓*	✓*	X
EFV	X	X	✓*	X	X
RPV	✓	✓	✓*	✓	✓
BIC	–§	–§	✓†	✓†	✓†
DTG	✓	✓	✓*	✓	✓
RAL	✓	✓	✓	✓	✓
EVG/COBI/FTC/TDF	✓*†	X	X	✓*	✓*†
EVG/COBI/FTC/TAF	✓†	X	✓	✓	✓†
3TC/ABC	✓	✓	✓	✓	✓
TAF or TDF	✓	✓	✓*	✓*	✓*

*Monitor for tenofovir toxicity if used with TDF. †No clinically significant drug interaction per prescribing information. ‡Guidelines recommend monitoring liver enzymes owing to lack of clinical safety data. §No information in prescribing information.

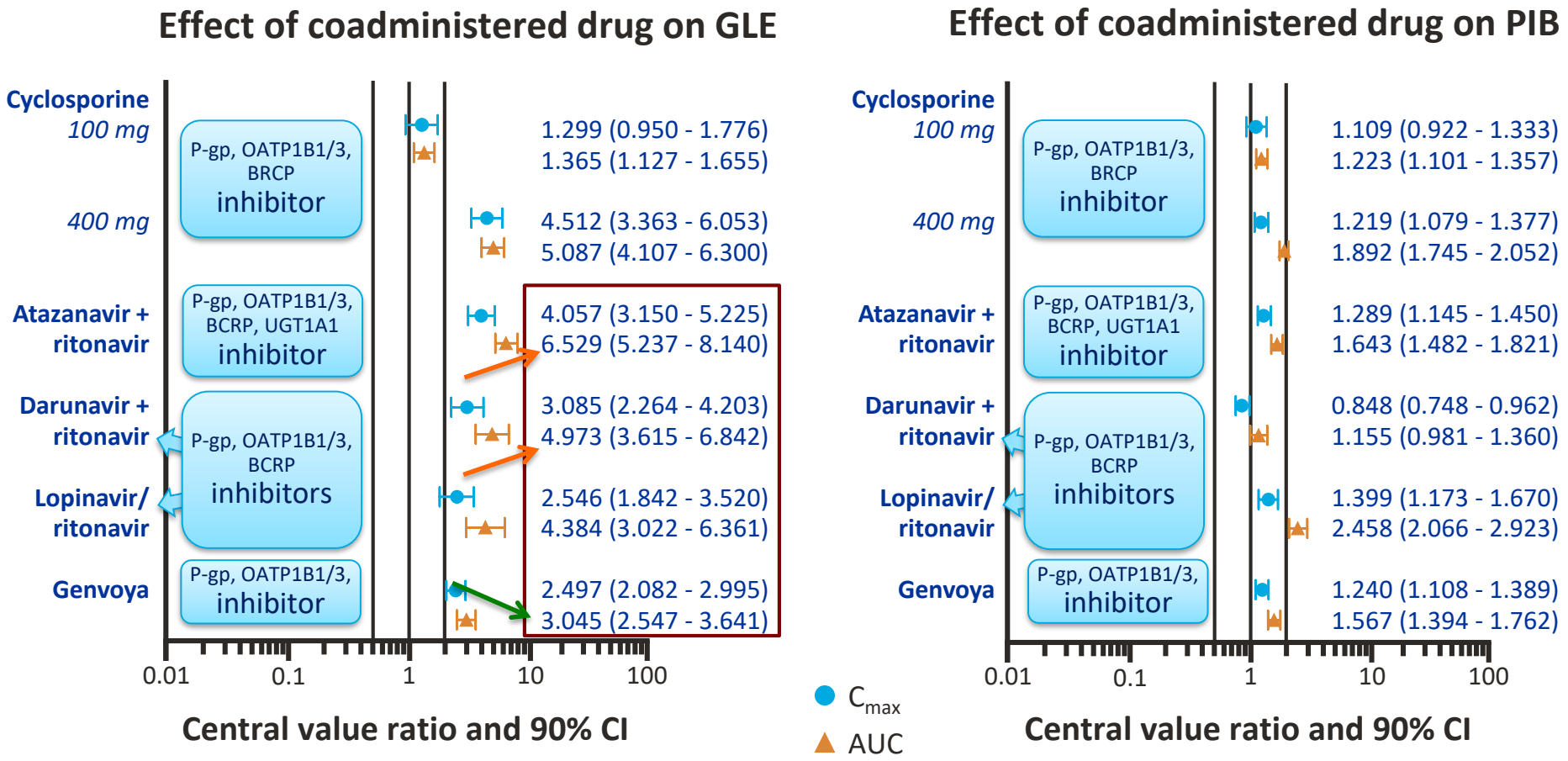
DHHS Guidelines. 2018.

PK thresholds orienteering tool for DDI evaluation

	GLE	PIB
efficacy	-	<50%
toxicity	< 3-fold (cirrhotic) < 6-fold (non- cirrhotic)	-

According to Assessment Report EMA 2017

Effect of Inhibitors and Inducers on GLE and PIB Exposures

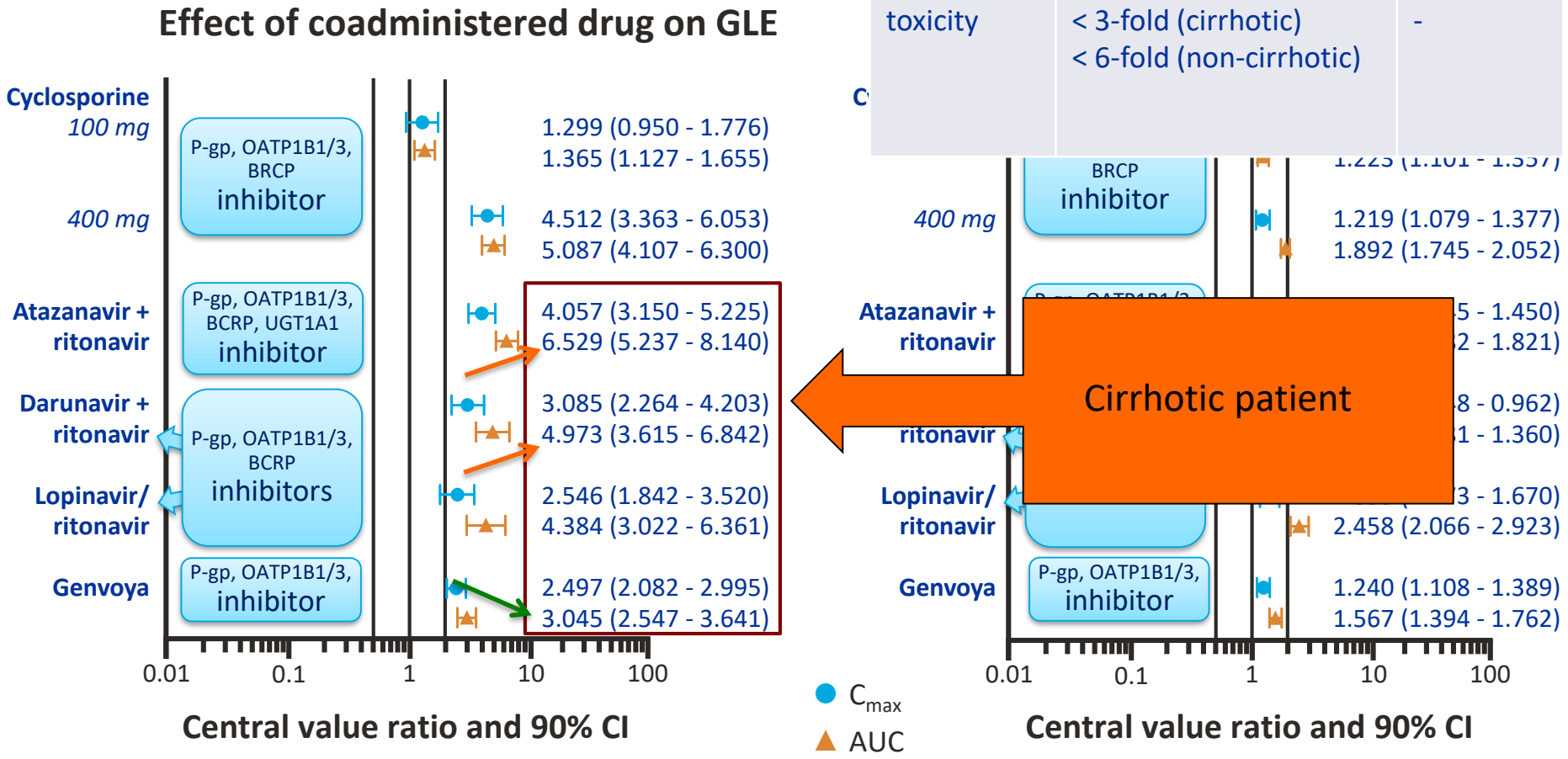


Except for strong OATP inhibitors or P-gp/CYP3A inducers, G/P exposures were minimally affected by other enzyme or transporter modulators

Genvoya = elvitegravir/cobicistat/emtricitabine/tenofovir AF.
Dashed vertical lines represent a 50% reduction and 200% increase; values outside this interval may be expected to lead to reduced efficacy (decreased exposures) or increased adverse events (increased exposures).

Effect of Inhibitors and Inducers on GLE

	GLE	PIB
efficacy	-	<50%
toxicity	< 3-fold (cirrhotic) < 6-fold (non-cirrhotic)	-

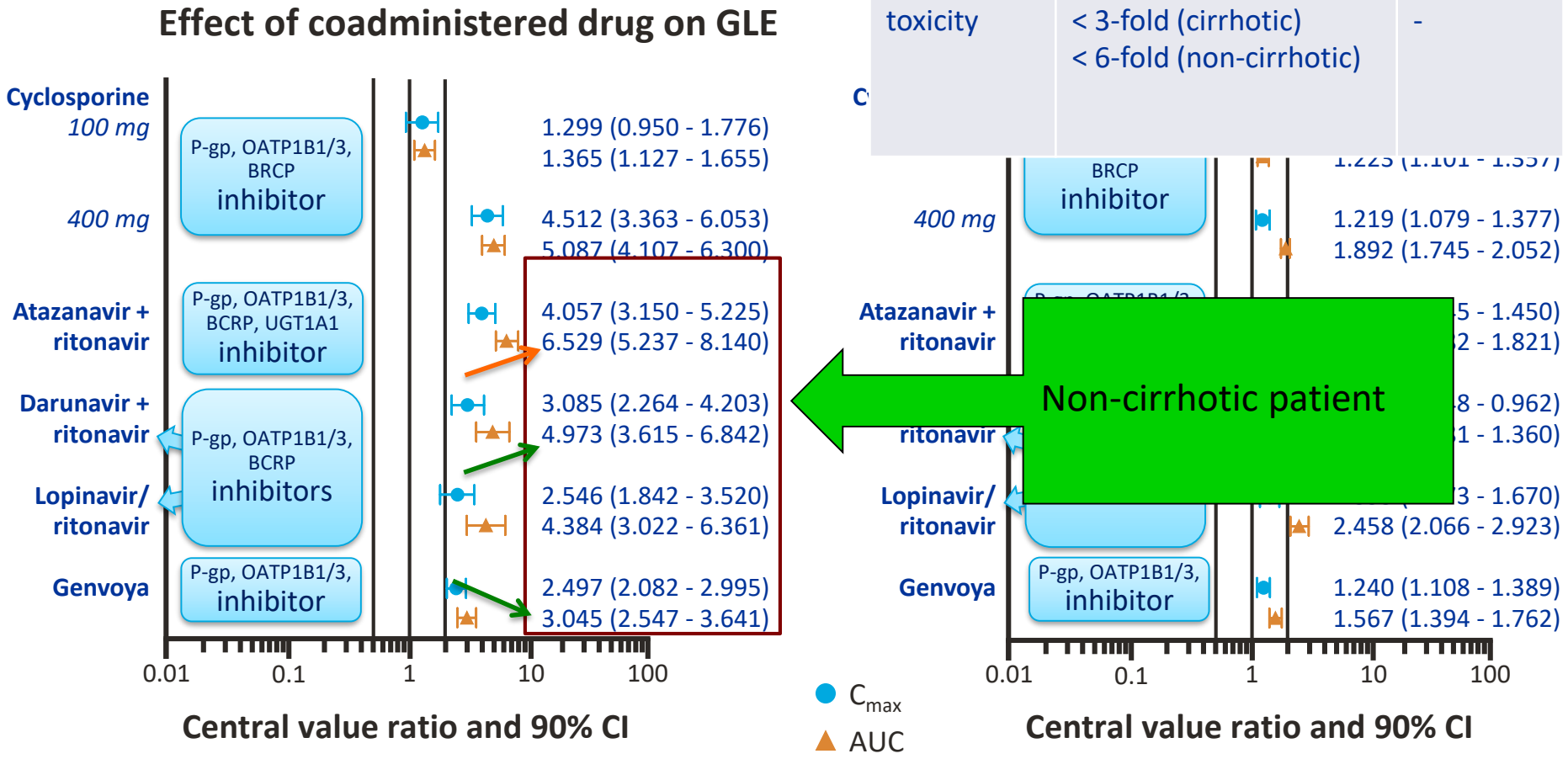


Except for strong OATP inhibitors or P-gp/CYP3A inducers, G/P exposures were minimally affected by other enzyme or transporter modulators

Genvoya = elvitegravir/cobicistat/emtricitabine/tenofovir AF.
Dashed vertical lines represent a 50% reduction and 200% increase; values outside this interval may be expected to lead to reduced efficacy (decreased exposures) or increased adverse events (increased exposures).

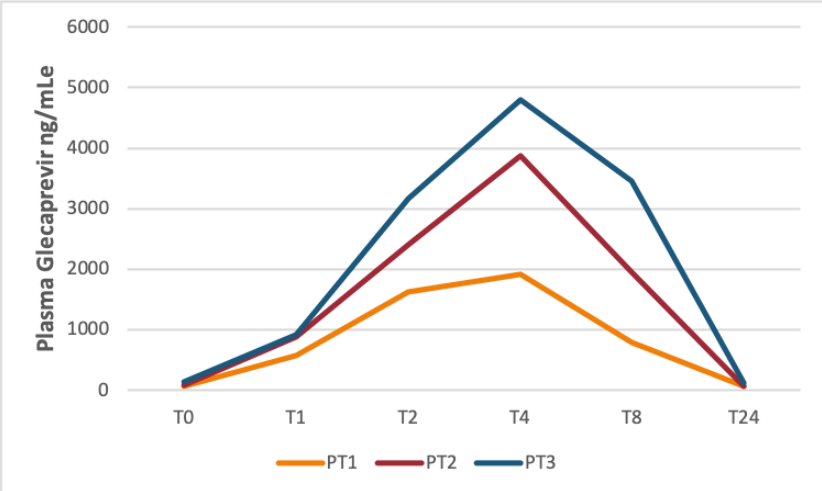
Effect of Inhibitors and Inducers on GLE

	GLE	PIB
efficacy	-	<50%
toxicity	< 3-fold (cirrhotic) < 6-fold (non-cirrhotic)	-



Except for strong OATP inhibitors or P-gp/CYP3A inducers, G/P exposures were minimally affected by other enzyme or transporter modulators

Genvoya = elvitegravir/cobicistat/emtricitabine/tenofovir AF.
Dashed vertical lines represent a 50% reduction and 200% increase; values outside this interval may be expected to lead to reduced efficacy (decreased exposures) or increased adverse events (increased exposures).



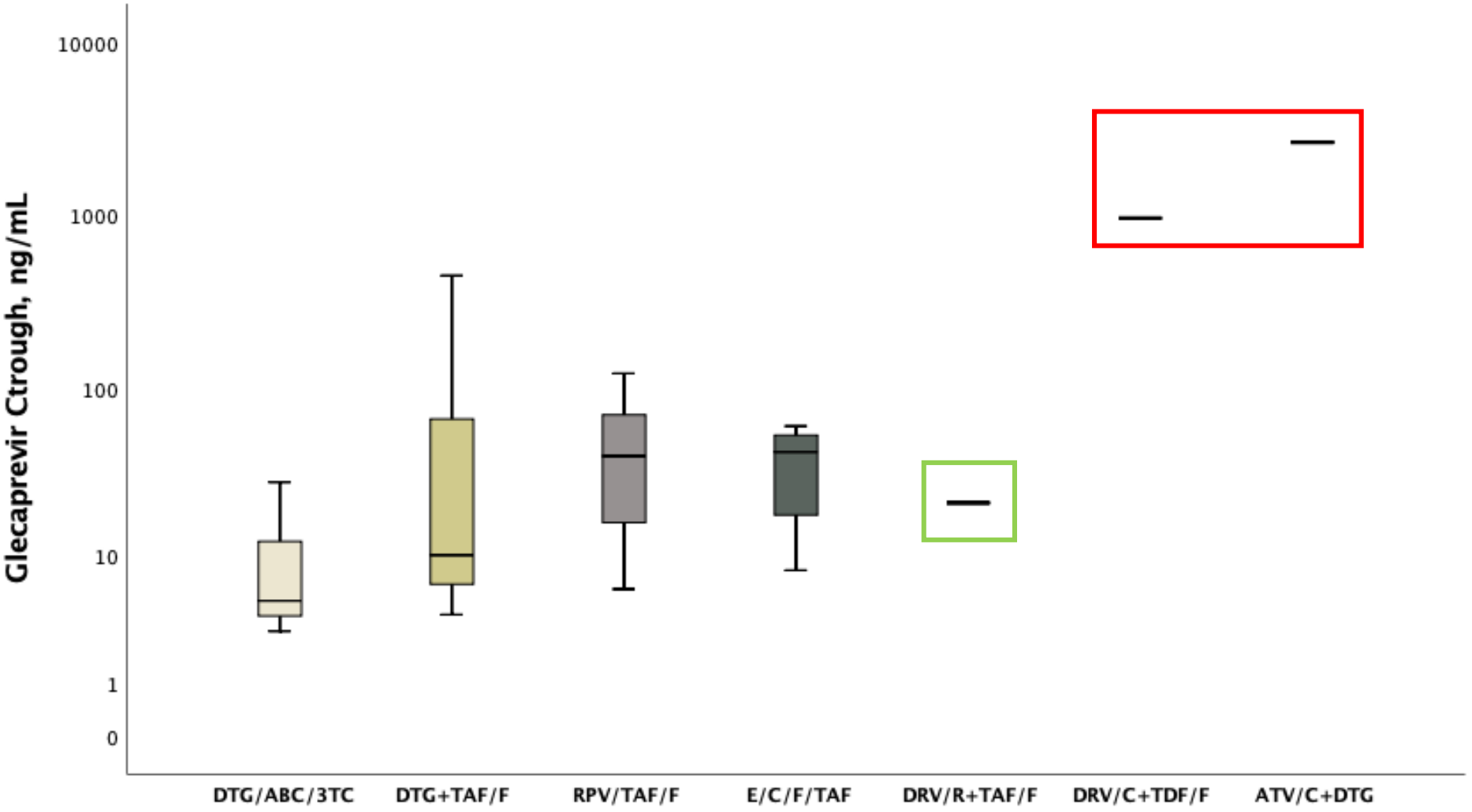
Glecaprevir AUC increase remained < 3 times reference exposure

N subject , concomitant ARV			AUC_{SS}	ratio	Cmax	ratio	Cmin	Tmax
P1, E/C/F/TAF	F1	GLE	14773	3,07	1913	3,2	62	4
		PIB	2189	1,5	326	2,9	20	4
P2, E/C/F/TAF	F1	GLE	13242	2,75	1971	3,3	7	4
		PIB	1309	0,9	133	1,2	8	4
P3, DRV/C+MVC+DTG	F0	GLE	13772	2,8	1502	2,5	42	8
		PIB	899	0,6	75	0,6	8	8
*Reference		GLE	4800	-	597	-	#	5
		PIB	1430	-	110	-	#	5

Ref Ctrough in healthy subjects.
GLE 400 mg, geomean (mean, CV%): 4,98 (7,88, 130%).
PIB 180 mg, geomean (mean, CV%): 9,97 (12,9, 84%).

* Maviret-epar-public-assessment report EMA/449689/2017-reference value for HCV infected subjects without cirrosis.

Tot 20 patients		**Glecaprevir Ctrough ng/mL, 42 determinations**	***P***	**Pibrentasvir Ctrough ng/mL, 42 determinations**	***P***
Sex, Male Female	 13 (65) 7 (35)	 18 (6;50) 47 (10;967)	*0,122*	 13 (8;22) 26 (13;74)	*0,088*
Age, ys	50 (44;55)				
Metavir F0 F1 F2 F3	 3 (15) 10 (50) 4 (20) 3 (15)				
ARV TAF/F+DTG E/C/F/TAF RPV/F/TAF DTG/ABC/3TC TAF/F+DRV/R TDF/F+DRV/C DTG+ ATV/C	 7 (35) 4 (20) 3 (15) 3 (15) 1 (5) 1 (5) 1 (5)	 10 (6;236) 42 (16;57) 40 (6;40) 5 (3;5) 21 967 2643	*0,247*	 11 (6;33) 24 (17;33) 5 (14;5) 10 (13;10) 10 29 164	*0,258*


Glecaprevir Ctrough, ng/mL
10000
1000
100
10
1
0
DTG/ABC/3TC
DTG+TAF/F
RPV/TAF/F
E/C/F/TAF
DRV/R+TAF/F
DRV/C+TDF/F
ATV/C+DTG

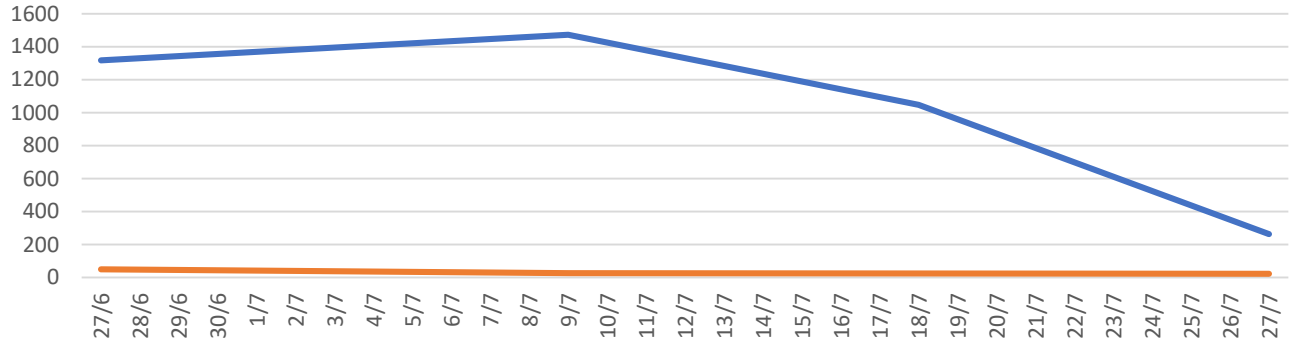
R.V. female 45 ys

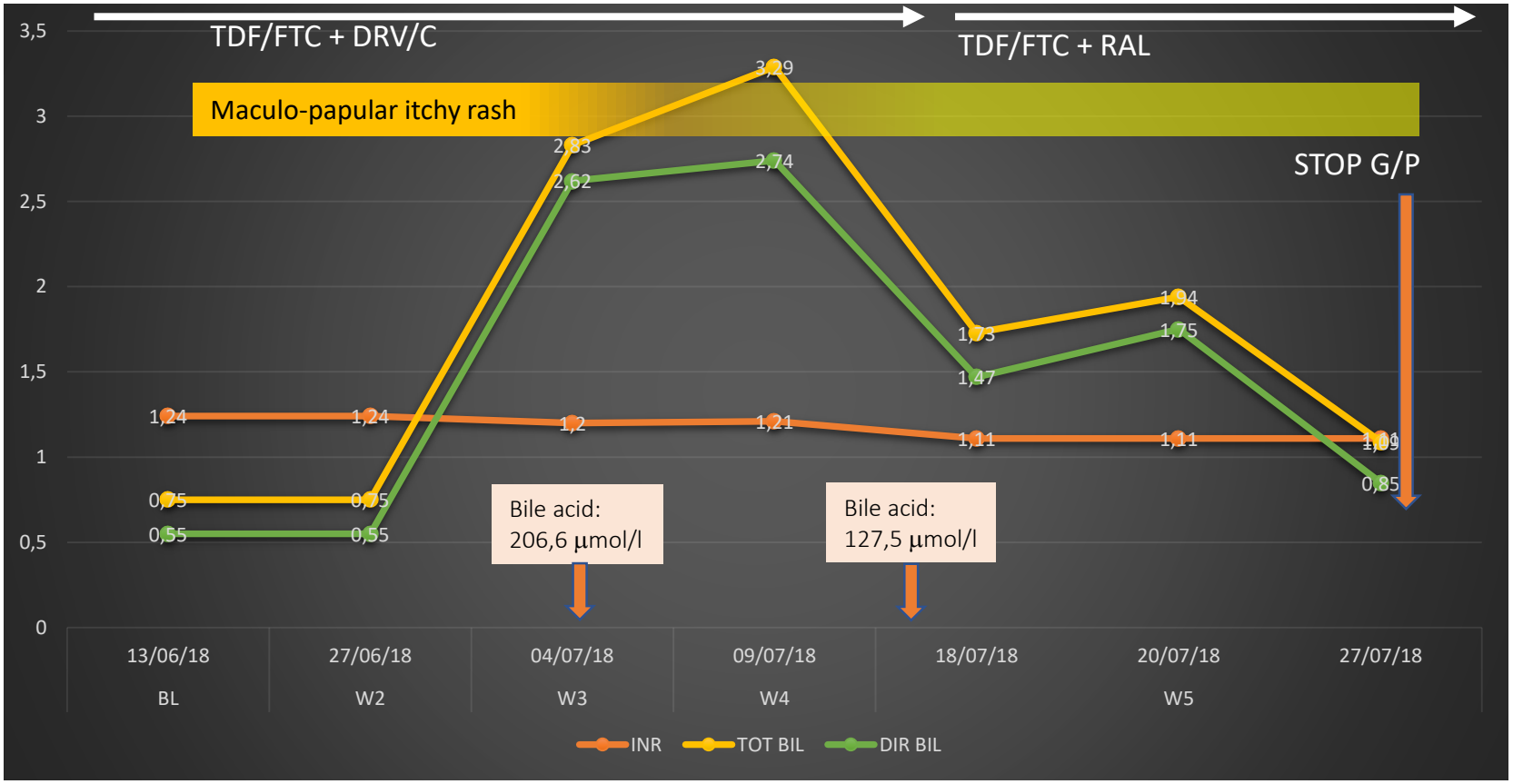
- Genotype 4 WT
- HCV RNA 1961272 UI/mL
- Stiffness: 7,7 Kpa, F2
- TDF/FTC + DRV/COBI
- Rash with TAF/FTC
- Rheumatoid factor: 69 UI/mL (rv 0-14)
- Anti CCP3: negative

BL EXAMS	13/6/2018
PTL mm^3	135000
Albumin mg/dl	39
INR	1,24
PTT sec	36,4
Crioglobulinemia %	assenti
Creatinine mg/dl	0,8
HBV DNA UI/ml	Anti HBc pos/DNA 0
AST U/l	131
ALT U/I	93
GGT U/I	305
Bilirubina tot/dir mg/dl	0,75/0,5
Alfa fetoprotein UI/ml	7

* Ctrough, ng/mL

	27/06	09/07	18/07	27/07
GLE	1317	1472	1048	264
PIB	50	28	25	23





CV miscellaneous

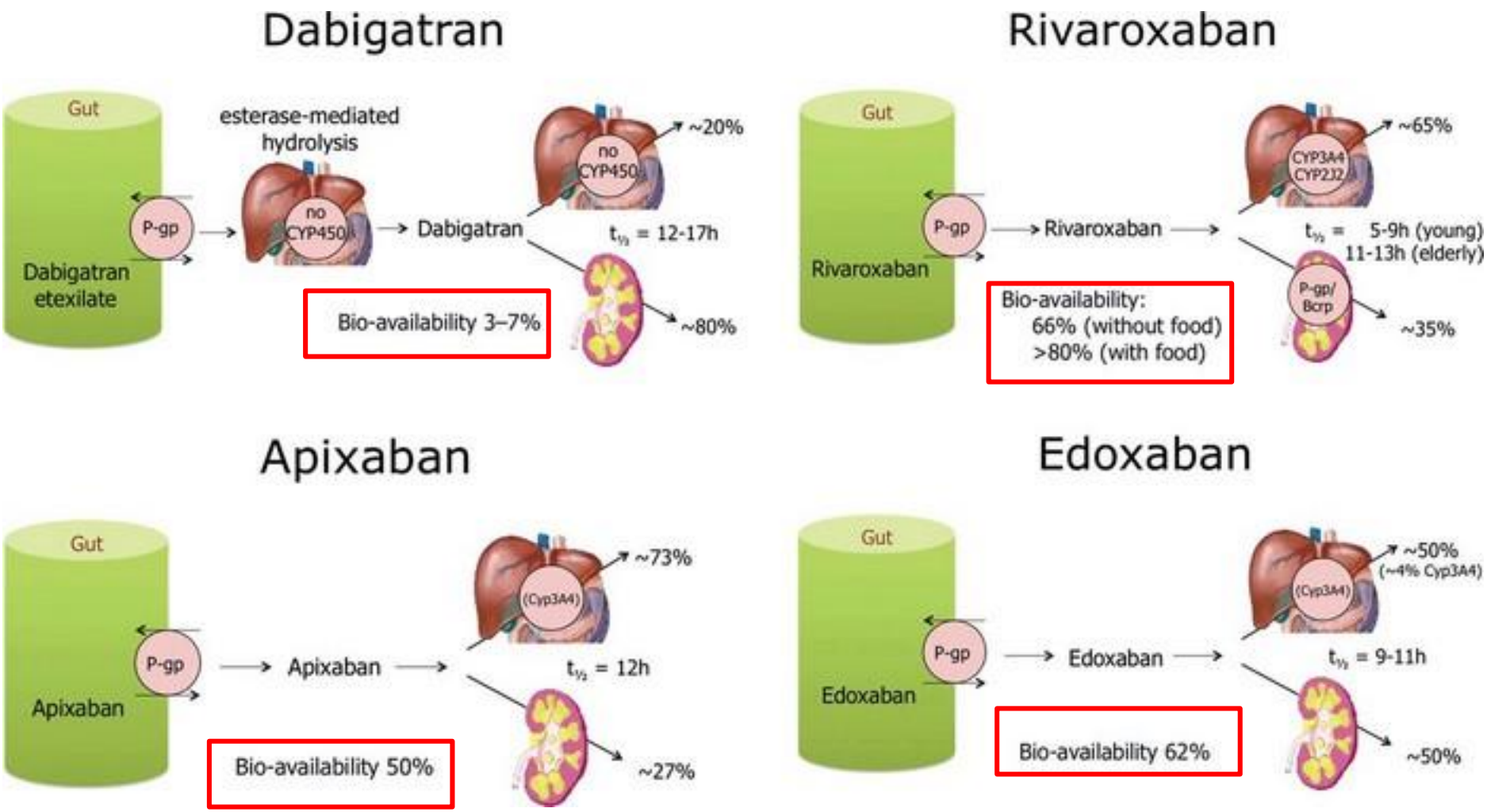
Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Results Key

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
Amiodarone	▢	▢	●
Amlodipine	◆	◆	◆
Apixaban	▢	▢	▢
Clopidogrel	◆	◆	◆
Dabigatran	▢	●	▢
Digoxin	◆	▢	▢
Edoxaban	▢	▢	▢
Flecainide	◆	◆	◆
Nicardipine	◆	◆	◆
Prasugrel	◆	◆	◆
Rivaroxaban	▢	▢	▢
Ticagrelor	▢	▢	▢
Ticlopidine	◆	◆	◆

GLE and PIB increase dabigatran AUC and Cmax about 2.4-fold and 2-fold, resp.


Dabigatran
Gut
Dabigatran etexilate
P-gp
esterase-mediated hydrolysis
no CYP450
Dabigatran
no CYP450
~20%
$t_{½}$ = 12-17h
~80%
Bio-availability 3–7%
Rivaroxaban
Gut
Rivaroxaban
P-gp
Rivaroxaban
CYP3A4 CYP2J2
~65%
$t_{½}$ = 5-9h (young) 11-13h (elderly)
P-gp/ Bcrp
~35%
Bio-availability:
66% (without food)
>80% (with food)
Apixaban
Gut
Apixaban
P-gp
Apixaban
(Cyp3A4)
~73%
$t_{½}$ = 12h
~27%
Bio-availability 50%
Edoxaban
Gut
Edoxaban
P-gp
Edoxaban
(Cyp3A4)
~50%
(~4% Cyp3A4)
$t_{½}$ = 9-11h
~50%
Bio-availability 62%

CNS miscellaneous

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Results Key

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
Amitriptyline	◆	◆	◆
Aripiprazole	■	■	◆
Buprenorphine	◆	◆	▲
Bupropion	◆	◆	◆
Chlorpromazine	◆		◆
Citalopram	◆		◆
Escitalopram	◆		◆
Etoricoxib	◆		◆
Fluoxetine	◆		◆
	◆		
	◆		
	◆		
	◆		
	◆		
	◆		
	■		
Risperidone	◆		
Sertraline	◆	◆	◆
Tramadol	◆	◆	◆
Venlafaxine	◆	◆	◆

Potential Interaction
Elbasvir/Grazoprevir
Aripiprazole

Summary:

Coadministration has not been studied. Concentrations of aripiprazole may increase as it is metabolised by CYP3A4 and grazoprevir is a weak inhibitor of CYP3A4 in vitro. As aripiprazole has a narrow therapeutic index and unpredictable therapeutic levels, monitor patients closely for signs and symptoms of toxicity.

Potential Interaction
Glecaprevir/Pibrentasvir
Aripiprazole

Summary:

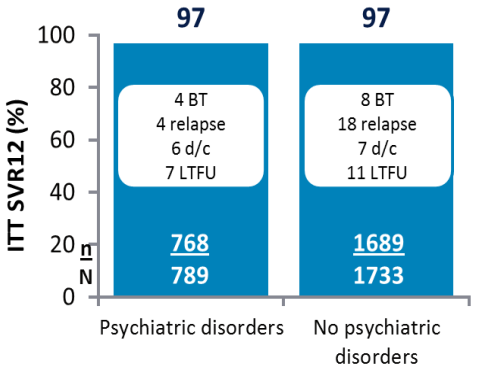
Coadministration has not been studied. Aripiprazole is metabolised by CYP3A4 and concentrations may increase due to weak inhibition of CYP3A4 by glecaprevir/pibrentasvir. As aripiprazole has a narrow therapeutic index and unpredictable therapeutic levels, monitor patients closely for signs and symptoms of toxicity.

Integrated Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with Psychiatric Disorders

Integrated efficacy and safety analysis of G/P for 8–16 weeks in treatment-naive or -experienced HCV GT1–6 infected patients with a psychiatric disorder* across 10 phase 2/3 clinical trials

Baseline characteristics	Psychiatric disorders N = 789	No psychiatric disorders N = 1733
Median age, years (range)	53 (21–82)	54 (19–88)
Treatment-naive, n (%)	568 (72)	1197 (69)
Genotype, n (%)		
1	331 (42)	764 (44)
2	144 (18)	332 (19)
3	251 (32)	418 (24)
4–6	63 (8)	219 (13)
History of IDU, n (%)	439 (56)	595 (34)

Safety, n (%)	Psychiatric disorders N = 789	No psychiatric disorders N = 1733
DAA-related SAE	0	1 (<1)†
AE leading to d/c	5 (<1)	8 (<1)



SVR12 rates were 97–100% across psychiatric disorders or use of CNS medications

Characteristic, % (n/N)	G/P treatment compliance‡
Psychiatric disorders	87 (687/789)
No psychiatric disorders	90 (1560/1733)

BT, breakthrough; CNS, central nervous system; d/c, discontinuation; EOT, end of treatment; IDU, injection drug use; ITT, intent-to-treat; LTFU, lost to follow-up.
* Medical history of psychiatric or neurological disorder or concomitant medication use of antidepressants or antipsychotics. † Grade 3 ALT at EOT in a patient with multiple gallstones.
‡ Compliance defined as taking ≥80% and ≤120% of the total number of tablets expected to be taken during G/P treatment.

Back, EASL 2018

N.F. female, 40 YS

HCV +

Stiffness 10 kPa

HAART: TAF/FTC + RAL

Co-medications: aripiprazole,methadone, lorazepam

Starts glecaprevir/pibrentasvir

	Symptoms	Action
BL		Aripiprazole dosed 15 mg
W2	Agitation, aggressiveness	Aripiprazole dosed 22,5 mg
W4	transient improvement	

N.F. female, 40 YS

HCV +

Stiffness 10 kPa

HAART: TAF/FTC + RAL

Co-medications: methadone, aripiprazole, lorazepam

Starts glecaprevir/pibrentasvir

	Symptoms	Action	*Aripiprazole Ctrough ng/mL
BL		Aripiprazole dosed 15 mg	
W2	Agitation, aggressiveness	Aripiprazole dosed 22,5 mg	878
W4	transient improvement		1154
W8	Agitation and loss to follow-up		*Ref 150-500 (Hiemke 2011)

R.F. male, 46 YS

HCV +

Stiffness 7 kPa

HAART: E/C/F/TAF

Co-medications: aripiprazole,methadone, sertraline, lorazepam.

Starts sofosbuvir/velpatasvir

	Symptoms	Action	Aripiprazole Ctrough ng/mL
BL	Good tolerance	Aripiprazole dosed 15 mg	464
W4	Good tolerance		
W8	Good tolerance		
W12	Good tolerance		475

*Ref 150-500 (Hiemke 2011)

SVR 12

Conclusions

- DAA lastly available reach SVR rates close to 100% with treatment lenght of 8 weeks at shortest.
- Efficacy close to 100% maintained even with suboptimal adherence. Possible role of pharmacological persistence and of therapeutic "forgiveness".
- DDI management based on clinical impact prediction taking into account not only the effect magnitude but also specific consequences on a determined clinical scenario ("beyond Liverpool site…".)
- DAA therapy duration could represent per se an important element in managing drug interactions.

A special thanks to all the Staff of the Infectious Diseases Unit and of the Clical Pharmacological Laboratory ,
University of Turin,
Ospedale Amedeo Di Savoia.

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

TDM
Therapeutic Drug Monitoring