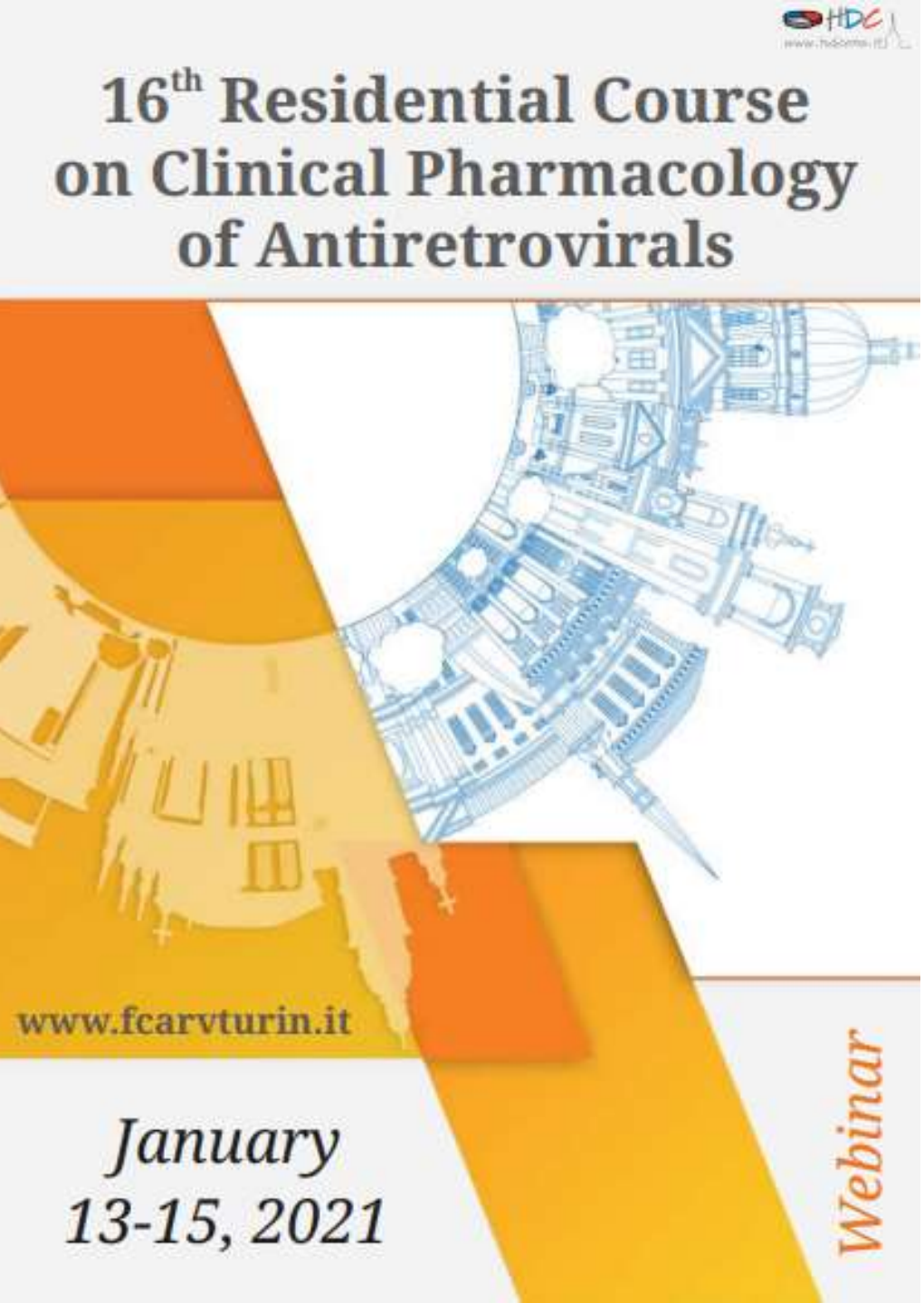


MANAGEMENT OF POLYPHARMACY AND DDIs

Clinical experiences

Chiara Alcantarini

Clinica di Malattie Infettive

Università degli Studi di Torino

Ospedale Amedeo di Savoia

In the age of polypharmacy…

- In DAAs era, DDIs remain a concern in the clinical scenario.
- Nowadays, one of the few “difficult-to-treat” populations are HCV+ subjects administered with anticonvulsants.
- Due to a substantial lack of PK and clinical data, these patients have to be managed on case-by-case basis.

Clinical case

R. D.

- 61 yo Caucasian female born in 1959
- History of previous IVDA
- Heavy smoker (28 Pack-years)
- History of epilepsy since 1989

  → oxcarbazepine 150 mg x 2 + phenobarbital 100 mg + pregabalin 150 mg x 2
- Depression and anxiety disorders treated with venlafaxine
- Periodic use of PPIs
- HIV/HCV+ since 1990

HIV history

- Followed by another Unit until 2013

  HIV-RNA: 113536 cp/ml, CD4+: 181 cell/µl ,16%, ratio 0.2
- Resistance test: No mutations for NNRTI, PI, NRTI, INSTI
- HLA-B5701: negative but allergy to abacavir
- Previous ARV regimen: AZT+3TC→ AZT/3TC/ABC

Clinical case

R. D.

HAART:

- 2014: **ATV 300** mg **/RTV 100** mg **+ TDF/FTC**
- Jun 2019: **RAL 400** mg BID + **TDF/FTC**
- Oct 2019: **DTG 50** mg BID + **TDF/FTC**
- Aug 2020: **DTG 50** mg BID + **TAF/FTC**

HIV-RNA: undetectable

HIV–RNA: <20 cp/ml
CD4+: 871 cell/µl, 36.7% and ratio 0.7

Clinical case

R. D.

HCV:

- Aug 2020: HCV-RNA:21200000 UI/ml

  genotype 3a
- Wild type for NS3, NS5B, NS5A sequences
- Treatment naïve
- Transient elastography (FibroScan):

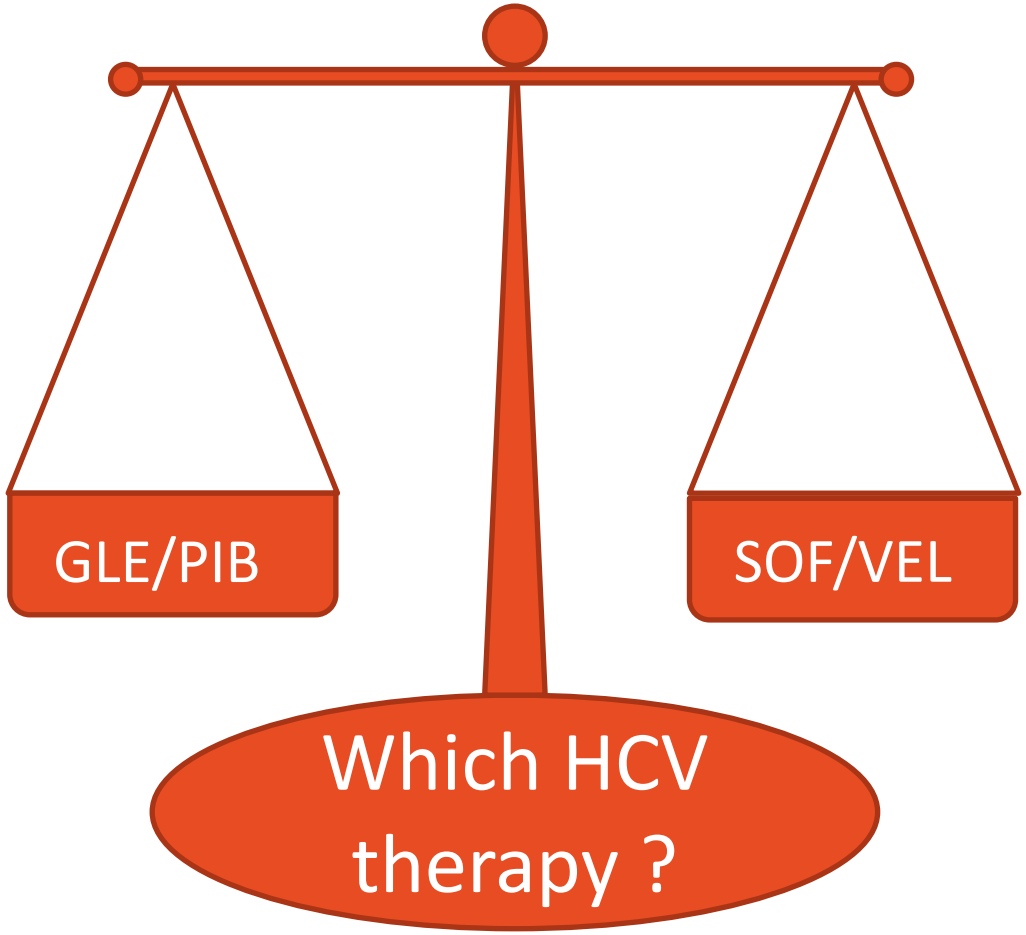
  Stiffness: 6.5 KPa CAP 208 dB/m
- Fibrosis F1 (Metavir)

Which HCV therapy ?

Clinical case

R. D.

HCV:



Which HCV therapy ?

Clinical case

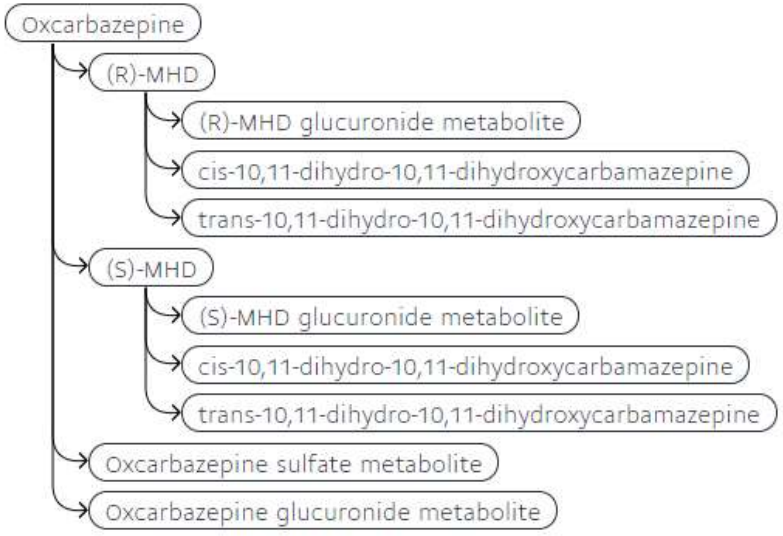
R. D.

Some concerns:

1. DDIs with oxcarbazepine/phenobarbital and DAAs
2. Fixed duration and association of HCV drugs
3. HCV Genotype 3
4. SARS-CoV-2 pandemic

1. DDIs with oxcarbazepine

- Oxcarbazepine is a structural derivative of carbamazepine and exerts a majority of its activity via a pharmacologically active metabolite, MHD (monohydroxy derivative).
- Oxcarbazepine is a substrate of P-gp but its induction is not demonstrated (unlike carbamazepine).



DRUGBANK

Compared to other anti-epileptic drugs, which are generally metabolized via the cytochrome P450 system, oxcarbazepine has a reduced propensity for involvement in drug-drug interactions owing to its primarily reductive metabolism.

1. DDIs with oxcarbazepine

- The interaction potential of oxcarbazepine is relatively low and dose- dependent.

Phenytoin, phenobarbital or carbamazepine can reduce slightly the concentrations of MHD.

Verapamil may moderately decrease MHD without clinical relevance.

- The influence of oxcarbazepine on other antiepileptic drugs is not clinically relevant in most cases.

However, oxcarbazepine appears to **increase concentrations of phenytoin** (by inhibition of CYP2C19) and to **decrease** trough concentrations of **lamotrigine** and **topiramate**.

Oxcarbazepine lowers concentrations of ethinylestradiol and levonorgestrel (by induction of P450 CYP3A4 e CYP3A5), and women treated with oxcarbazepine should consider additional contraceptive measures.

May, Theodor W., Elisabeth Korn-Merker, and Bernhard Rambeck. "Clinical pharmacokinetics of oxcarbazepine." *Clinical pharmacokinetics* 42.12 (2003): 1023-1042.

Drug-Drug Interactions Between Antiretrovirals and Carbamazepine/Oxcarbazepine: A Real-Life Investigation

Dario Cattaneo, PhD,† Sara Baldelli, ChemD,† Valeria Cozzi, BiolSciD,† Marta Fusi, PharmD,† Chiara Atzori, MD,‡ Valeria Micheli, BiolSciD,§ Carlo Filice, MD,¶ and Cristina Gervasoni, MD*‡*

Ther Drug Monit • Volume 42, Number 2, April 2020

- 11 HIV+ patients prescribed carbamazepine (n=7) or oxcarbazepine (n=4).
- HIV-infected patients not treated with antiepileptic drugs were controls.
- TDM results of DRV were comparable in both groups.
- **ATV and DTG C trough were significantly low** when compared with values of HIV-infected pts not treated with antiepileptic drugs (190 ± 91 vs 546 ± 380 ng/ mL; -65%, P < 0.001; 191 ± 78 vs 1096 ± 510 ng/mL; -83%, P < 0.001, respectively)

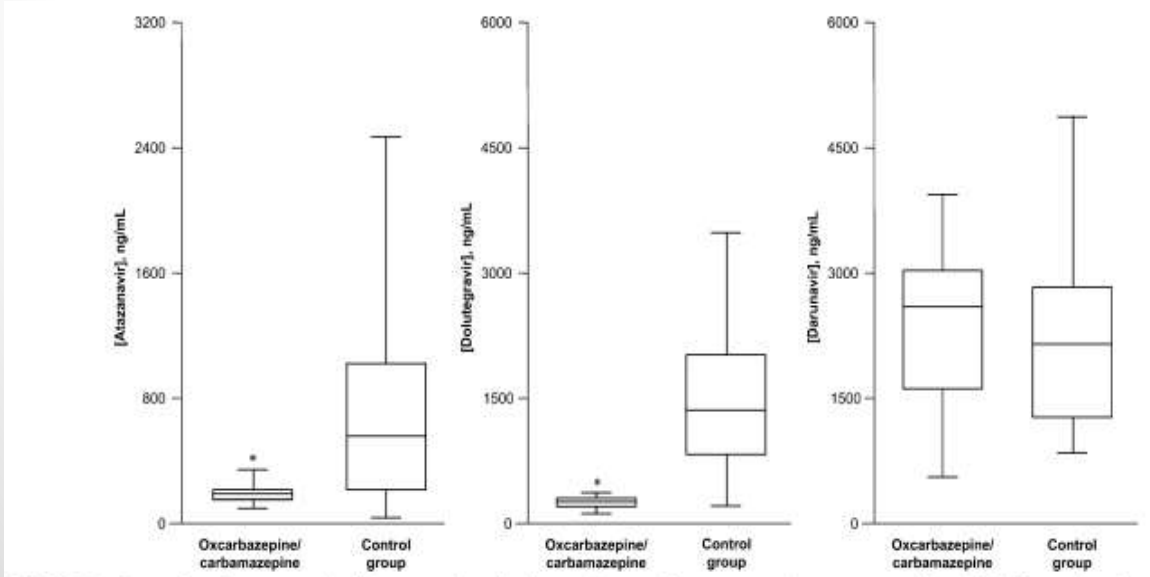
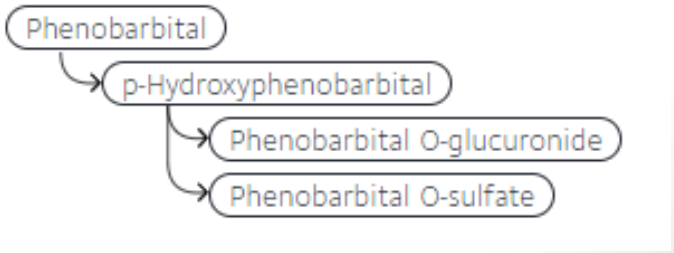


FIGURE 1. Box-plot of atazanavir, dolutegravir and darunavir trough concentrations measured in HIV-infected patients treated with carbamazepine/oxcarbazepine versus controls. *$P < 0.001$ versus controls.

- **Co-administration of carbamazepine or oxcarbazepine with ATV or DTG should be avoided** owing to the potential risk of virological failure; the adoption of TDM is strongly advisable, eventually combining with increased antiretroviral doses.

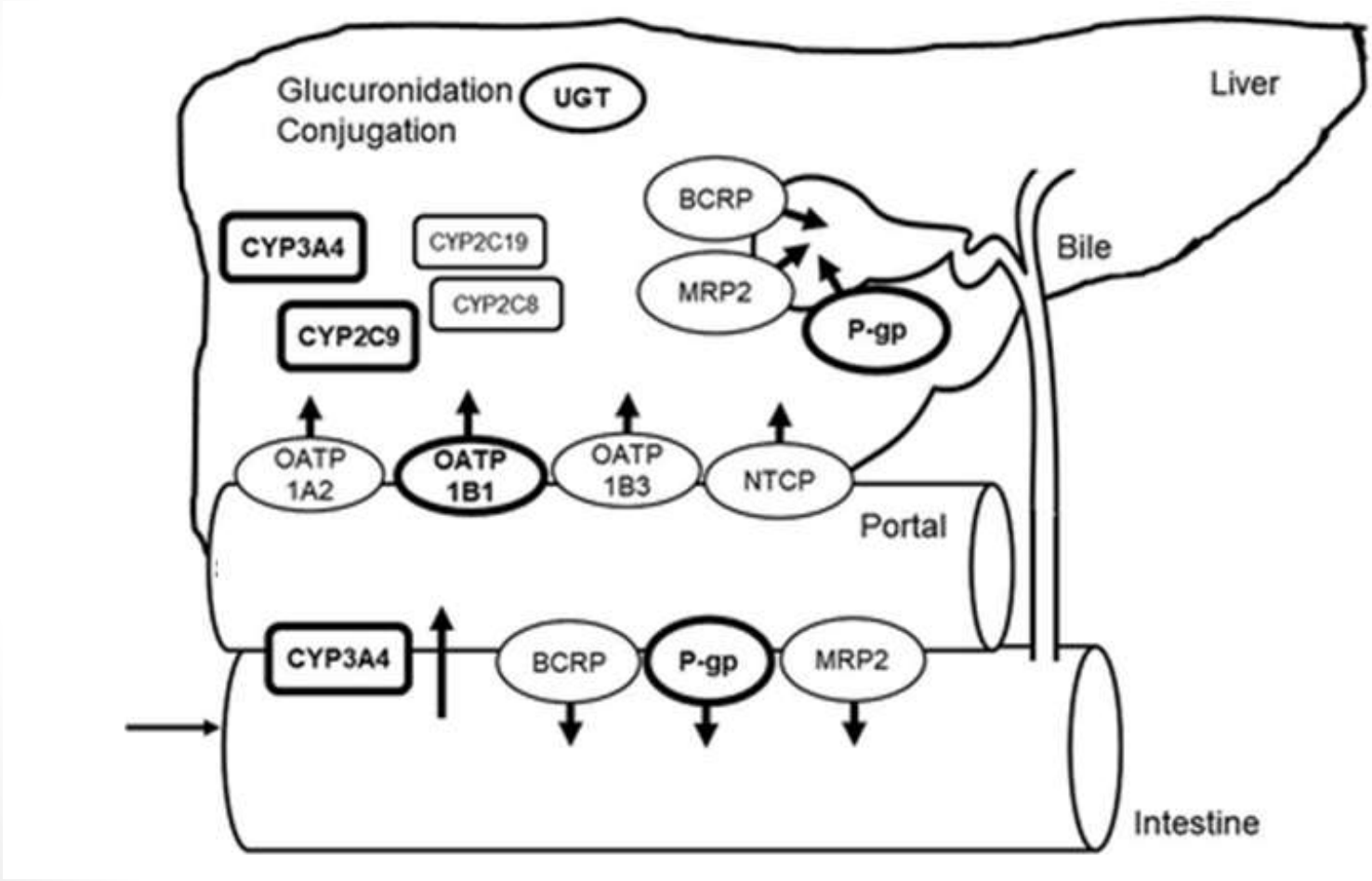
1. DDIs with phenobarbital

- Phenobarbital is an anti epileptic drug with a oral bioavailability of about 90%. C_{max} are reached 8 to 12 hours after oral administration.
- It is one of the longest-acting barbiturates available : half-life of 2 to 7 days and has very low protein binding (20 to 45%).
- Phenobarbital is metabolized by the liver, mainly through hydroxylation and glucuronidation, and induces many isozymes of the cytochrome P450 system: 2B6, 2C19, 2C9, 2E1, 2B6, 2C8, 3A4, 1A2, 3A5, 1A1, 2C18, 3A7, 4B1, 2A6
- It induces UDPGT 1-1 and 2B7.
- It is a substrate and inducer of P-gp, it induces OATP 1 and 2, bile salt export pump, multidrug resistance-associated protein 1, SLCO2A1.



DRUGBANK

Transporters of DAAs: orienteering map for clinicians



HEP Drug Interactions

UNIVERSITY OF LIVERPOOL

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

Results Key

	G/P	SOF/VEL
Oxcarbazepine	●	●
Phenobarbital	●	●

Oxcarbazepine + G/P→ reduced G/P plasma concentrations due to moderate induction of CYP3A4

Oxcarbazepine + SOF/VEL→ reduced SOF/VEL plasma concentrations due to moderate induction of CYPs 2B6, 2C8 and 3A4

Phenobarbital + G/P→ reduced G/P plasma concentrations due to alteration of drug absorption, metabolism and biliary excretion mediated by strong induction of CYP3A, P-gp and OATP

Phenobarbital + SOF/VEL→ reduced SOF/VEL plasma concentrations due to strong induction of CYPs 2B6, 2C8 and 3A4 and P-gp .

RISK OF VIROLOGICAL FAILURE !

	DCV	ELB/ GZR	G/P	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF	SOF/ VEL	SOF/ VEL/ VOX	RBV
Anticonvulsants											
Carbamazepine	●	●	●	●	●	●	●	●	●	●	◆
Clonazepam	◆	◆	◆	◆	■	■	■	◆	◆	◆	◆
Eslicarbazepine	●	●	●	◆	●	●	●	◆	●	●	◆
Ethosuximide	◆	◆	◆	◆	■	■	■	◆	◆	◆	◆
Gabapentin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Lacosamide	◆	◆	◆	◆	■	■	■	◆	◆	◆	◆
Lamotrigine	◆	◆	◆	◆	■	■	◆	◆	◆	◆	◆
Levetiracetam	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Oxcarbazepine	●	●	●	●	●	●	●	●	●	●	◆
Perampanel	△	◆	◆	◆	■	■	■	◆	◆	◆	◆
Phenobarbital	●	●	●	●	●	●	●	●	●	●	◆
Phenytoin	●	●	●	●	●	●	●	●	●	●	◆
Pregabalin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Primidone	●	●	●	●	●	●	●	●	●	●	◆
Retigabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Rufinamide	■	■	■	■	■	■	■	■	■	■	◆
Sultiame	◆	◆	◆	◆	■	■	■	◆	◆	◆	◆
Tiagabine	◆	◆	◆	◆	■	■	■	◆	◆	◆	◆
Topiramate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Valproate (Divalproex)	◆	◆	◆	◆	■	■	◆	◆	◆	◆	◆
Vigabatrin	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Zonisamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

1. DDIs with oxcarbazepine/phenobarbital

Clinical case

R. D.

- We consult the neurologist for a possible switch from oxcarbazepine and phenobarbital to another agent:

It's not safe!

The patient has a severe and resistant form of epilepsy, the only drug that can be discontinued is oxacarbazepine with a gradual tapering of dosage

We stop oxcarbazepine, maintaining phenobarbital…

Treatment recommendations for TN or TE patients with CHC without cirrhosis

Criterio 3,4,7,8,9

Genotipo	Regimi Pangenotipici		Regimi Genotipo dipendenti
	SOF/VEL	GLE/PIB	GZR/EBR
Genotipo 1a	12 settimane	8 settimane	12 settimane se HCVRNA <800.000 IU/Ml e no RAS significative in NS5a
Genotipo 1b	12 settimane	8 settimane	12 settimane
Genotipo 2	12 settimane	8 settimane	No
Genotipo 3	12 settimane	8-16 settimane	No
Genotipo 4	12 settimane	8 settimane	12 settimane se HCV RNA <800.000 IU/Ml
Genotipo 5	12 settimane	8 settimane	No
Genotipo 6	12 settimane	8 settimane	No

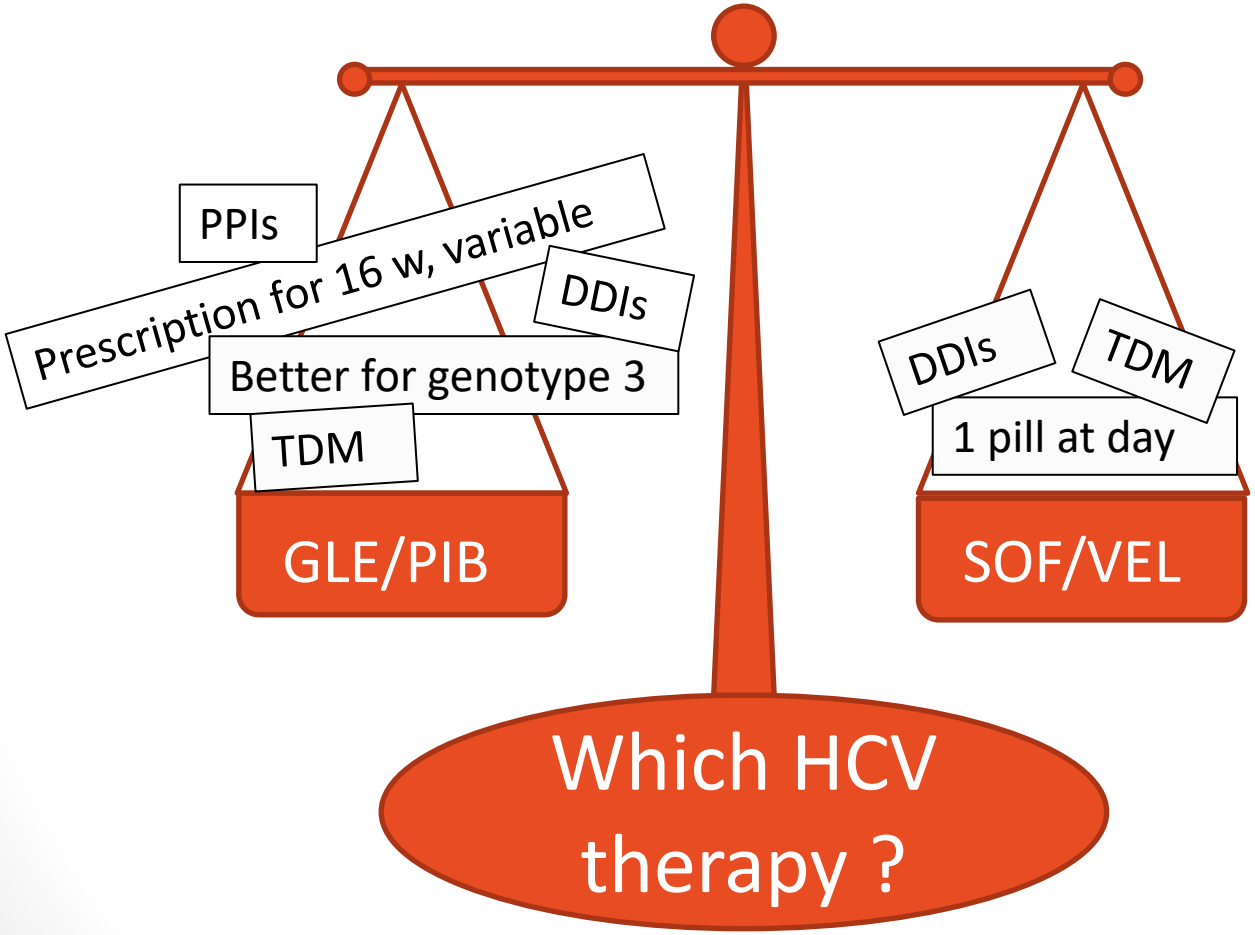
http://www.webaisf.org/pubblicazioni/documento-aisf-hcv-2018.aspx

8 weeks for Treatment Naïve, 16 weeks for Treatment Experienced

Clinical case

R. D.

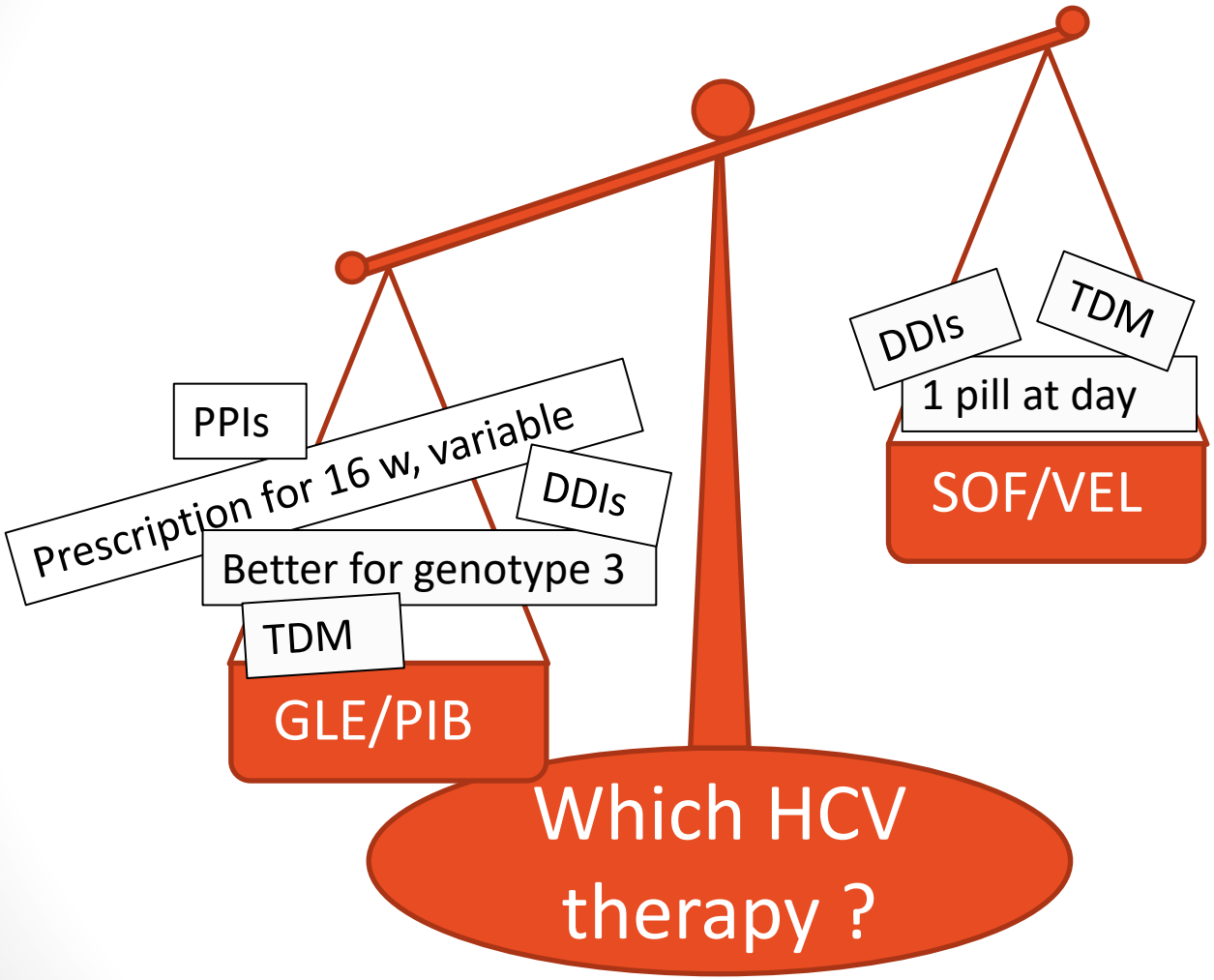
HCV:



Clinical case

R. D.

HCV:



A possible solution:

Clinical case

R. D.

Prescription of glecaprevir / pibrentasvir for 16 weeks monitoring G/P concentrations and HCV-RNA in order to modulate the duration of HCV therapy according to the virological response and TDM

22 Sep 2020: she started GLE/PIB

Clinical case

R. D.

	BL	W2	W4	W8
	22 Sep	6 Oct	20 Oct	17 Nov
HCV-RNA	21200000	38	NEG	NEG
AST	49	29	26	16
ALT	49	25	22	12
GGT	73	72	57	53
Tot Bil	0,24	0,21	0,31	0,32
HIV-RNA	<20	neg	<20	<20

TDM W2
GLE C_{trough}:60 ng/ml
PIB C_{trough}: 36 ng/ml

TDM W4
GLE C_{20}:200 ng/ml
PIB C_{20} : 33 ng/ml

Unexpected high drug concentrations !

TDM W2
GLE C_{trough}:60 ng/ml
PIB C_{trough}: 36 ng/ml

TDM W4
GLE C_{20}:200 ng/ml
PIB C_{20}: 33 ng/ml

High drug concentrations !

Unable to perform AUC due to COVID-19 pandemic and problems with patient

Glecaprevir PK Fact Sheet

Summary of Key Pharmacokinetic Parameters	
Cmax	597 (114) ng/mL (geometric mean, %CV), in non-cirrhotic HCV-infected subjects
C24	3.07 (54), 5.50 (46), 3.72 (71) ng/mL (geometric mean, %CV), in healthy White, Han Chinese and Japanese adults, respectively [2]
AUC	4800 (122) ng·h/mL (geometric mean, %CV), in non-cirrhotic HCV-infected subjects

Pibrentasvir PK Fact Sheet

Summary of Key Pharmacokinetic Parameters	
Cmax	110 (49) ng/mL (geometric mean, %CV), in non-cirrhotic HCV-infected subjects
C24	9.94 (75), 5.33 (48), 6.68 (60) ng/mL (geometric mean, %CV), in healthy White, Han Chinese and Japanese adults, respectively [2]
AUC	1430 (57) ng·h/mL (geometric mean, %CV), in non-cirrhotic HCV-infected subjects

ICAR Italian Conference on AIDS and Antiviral Research — n. 274

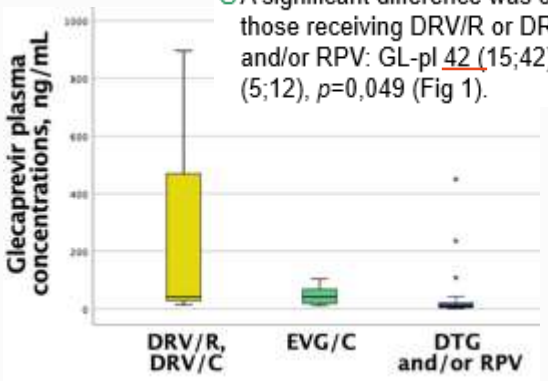
Glecaprevir/pibrentasvir pharmacokinetics when co-administered with antiretroviral drugs in a cohort of HCV/HIV patients.

V. Pirriatore [1], L. Marinaro [1], R. Angilletta [1], A. Palazzo [1], A. Barco [1], C. Alcantarini [1], N. Forni [1], C. Montrucchio [2], M. Ferrara [1], A. Lazzaro[1], M. Tettoni [1], A. De Nicolò [3], A. D'Avolio [3], A. Calcagno [1], G. Di Perri [1] and S. Bonora [1]

62 determinations from 30 patients

Patients characteristics	N (%), median (IQR)
Gender (male)	21 (70)
Age (years)	51 (45;55)
BMI (kg/m2)	22 (20;24)
Metavir score	
0-2	25 (83,3)
3	4 (13,3)
4	1 (3,3)
Stiffness (kPa)	6,3 (5,6;8)
CAP (dB/m)	207 (179;229)
ARV:	
DRV/r	1 (3,3)
DRV/C	2 (6,6)
EVG/C	6 (20)
DTG and/or RPV	21 (70)

- Median GI-pl and Pib-pl were 16 ng/ml (7,2;43,5) and 11 ng/mL (7,75;22,2) respectively.
- A significant difference was observed between those receiving DRV/R or DRV/C, EVG/C, DTG and/or RPV: GL-pl 42 (15;42), 42 (17,2;77), 10 (5;12), p=0,049 (Fig 1).



Factors that could explain high G/P concentrations

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assesment Report 2017

Table 11 Impact of covariates on GLE and PIB pharmacokinetic exposures

DAA	Covariate	Covariate Effect on $AUC_{24,ss}$
GLE	Bodyweight, BMI and BSA:	No significant impact.
	Age:	32% higher exposures for 10-year increase in age (65 years versus 55 years).
	Sex:	39% higher exposures in females.
	Race:	No significant impact.
	Cirrhosis status:	2.2-fold exposure in subjects with cirrhosis.
	Renal function:	55% higher exposure in moderate or severe renal impairment, and 86% higher exposure in end stage renal disease. Dialysis has no impact on GLE pharmacokinetics.
	Co-medications:	5% lower exposure in subjects who took high dose PPIs (omeprazole 40 mg QD equivalent or higher). 16% higher exposure in subjects who took opioid medications.
PIB	Bodyweight, BMI and BSA:	3% decreased exposures for 10-kg increase in bodyweight (90 kg versus 80 kg).
	Age:	13% higher exposures for 10-year increase in age (65 years versus 55 years).
	Sex:	37% higher exposures in females.
	Race:	26% higher exposures in Asians.
	Cirrhosis status:	7% higher exposure in subjects with cirrhosis.
	Renal function:	13% higher exposure with moderate or severe renal impairment, and 54% higher exposure with end stage renal disease. Dialysis has no impact on PIB pharmacokinetics.
	Co-medications:	27% higher exposure in subjects who took BCRP inhibitors.

CYP450 polymorphism? Poor/ Intermediate metabolizer?

- Perfect adherence
- Very rapid HCV viral load decay
- High G/P concentrations

Clinical case

R. D.

STOP G/P at 12 weeks

	BL	W2	W4	W8	W12
	22 Sep	6 Oct	20 Oct	17 Nov	15 Dec
HCV-RNA	21200000	38	NEG	NEG	NEG
AST	49	29	26	16	18
ALT	49	25	22	12	14
GGT	73	72	57	53	55
Tot Bil	0,24	0,21	0,31	0,32	0,34
HIV-RNA	<20	neg	<20	<20	neg

09/March: we are waiting for SVR 12

Conclusions

- DDIs between anticonvulsants and DAAs are one of the most difficult scenario to manage in HCV treatment, due to the lack of clinical data.
- In our case, despite transient de-escalation of a complex anticonvulsant regimen according to neurologist's guidance, potential DDI of unknown clinical significance between phenobarbital and DAAs remained as a concern.
- EOT virological response to 12 weeks of GLE/PIB without safety and tolerability issues was observed.
- TDM showed unexpected high exposure to GLE/PIB, supporting the treatment choice and underscoring the unpredictability of DDIs in the clinical setting.

Acknowledgements

Unit of Infectious Diseases

Prof. Giovanni Di Perri
Prof. Stefano Bonora
Prof. Andrea Calcagno
Letizia Marinaro
Mariacristina Tettoni
Laura Trentini
Filippo Lipani
Ilaria Motta
Mattia Trunfio
Sabrina Audagnotto
Walter Rugge
Stefano Torresan
Micol Ferrara
Alessandro Lazzaro

Clin. Pharm. Lab.

Prof. Antonio D'Avolio
Mauro Sciandra
Amedeo De Nicolò
Jessica Cusato
Valeria Avataneo
Miriam Antonucci
Alice Ianniello

Mol. Biol. Lab.

Valeria Ghisetti
Tiziano Allice
Elisa Burdino
Maria Grazia Milia