British HIV Association
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Professor David Back

University of Liverpool

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
David Back	Acts in a Consultancy capacity for Merck, Janssen and as a speaker at company sponsored events for Merck, Janssen, Bristol Myers Squibb and Gilead. He has also received educational grants from Merck, Janssen, Bristol Myers Squibb, Gilead, ViiV Healthcare, Boehringer Ingelheim and Roche.
Date	**22 September 2012**

Drug-Drug Interactions with new HCV Drugs

David Back

University of Liverpool

October 2012

UNIVERSITY OF LIVERPOOL

LIVERPOOL HIV PHARMACOLOGY GROUP
LHPG

Disclosures

Speakers Bureau: *Janssen, Merck, BMS, Boehringer Ingelheim.*

Grant Support: *Janssen, Merck, BMS, Boehringer Ingelheim, Roche, Vertex, Gilead.*

❑ Interactions with the new HepC DAAs are challenging!

- *Number of known interactions*
- *Number of potential interactions (based on metabolic profile)*
- *Magnitude of the interactions*
- *Applying data from Healthy Volunteer studies to HCV patients*

Drug Interactions pre-DAAs

- ie involving pegylated interferon/ribavirin were limited.
- Ribavirin – Abacavir (efficacy) and ribavirin – zidovudine (toxicity) caused some concern in co-infected patients

Ribavirin and Abacavir drug interaction in HIV-HCV coinfected patients: fact or fiction?

AIDS 2012, Vol 00 No 00

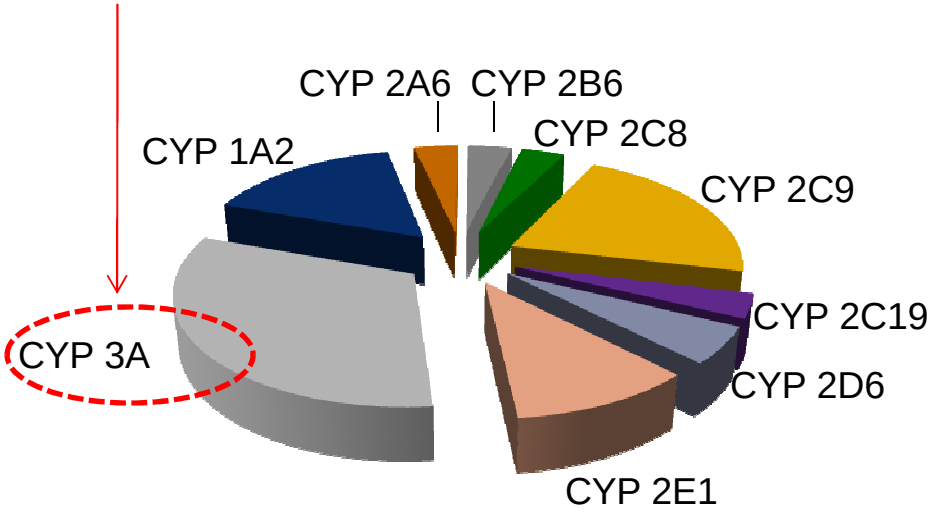
Caroline Solas[a,b], Elodie Pambrun[c,d], Maria Winnock[c,d], Dominique Salmon[e], Isabelle Poizot-Martin[f], Stéphanie Dominguez[g], Firouzé Bani-Sadr[h], Jacques Izopet[i], Rodolphe Garraffo[j] and Gilles Peytavin[k] for The ANRS CO-13 HEPAVIH Study Group

- However the **DAAs** have increased potential for **DDIs**
- The focus is **CYP3A4-**mediated interactions – but this is **not** the only mechanism

DDI: drug–drug interaction; HCV: hepatitis C virus

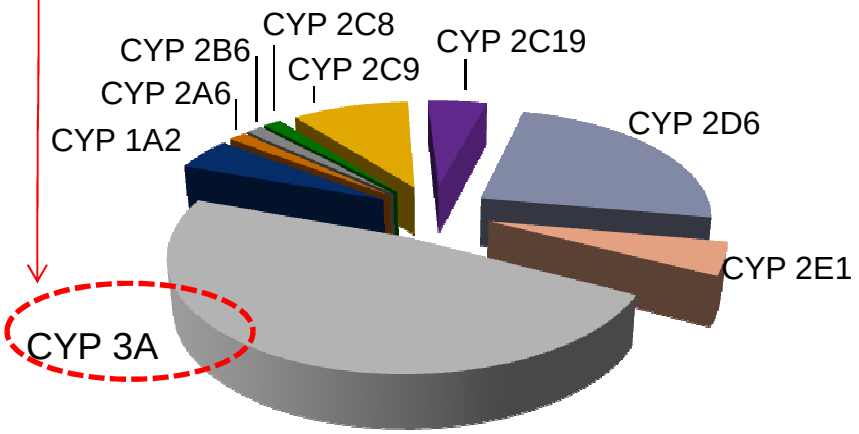
Telaprevir and Boceprevir are *metabolised by* and *strongly inhibit* CYP3A4

CYP 3A isozymes are the most abundant in the liver



Proportion of total CYP enzymes present in human liver

CYP 3A isozymes involved in the metabolism of majority of drugs



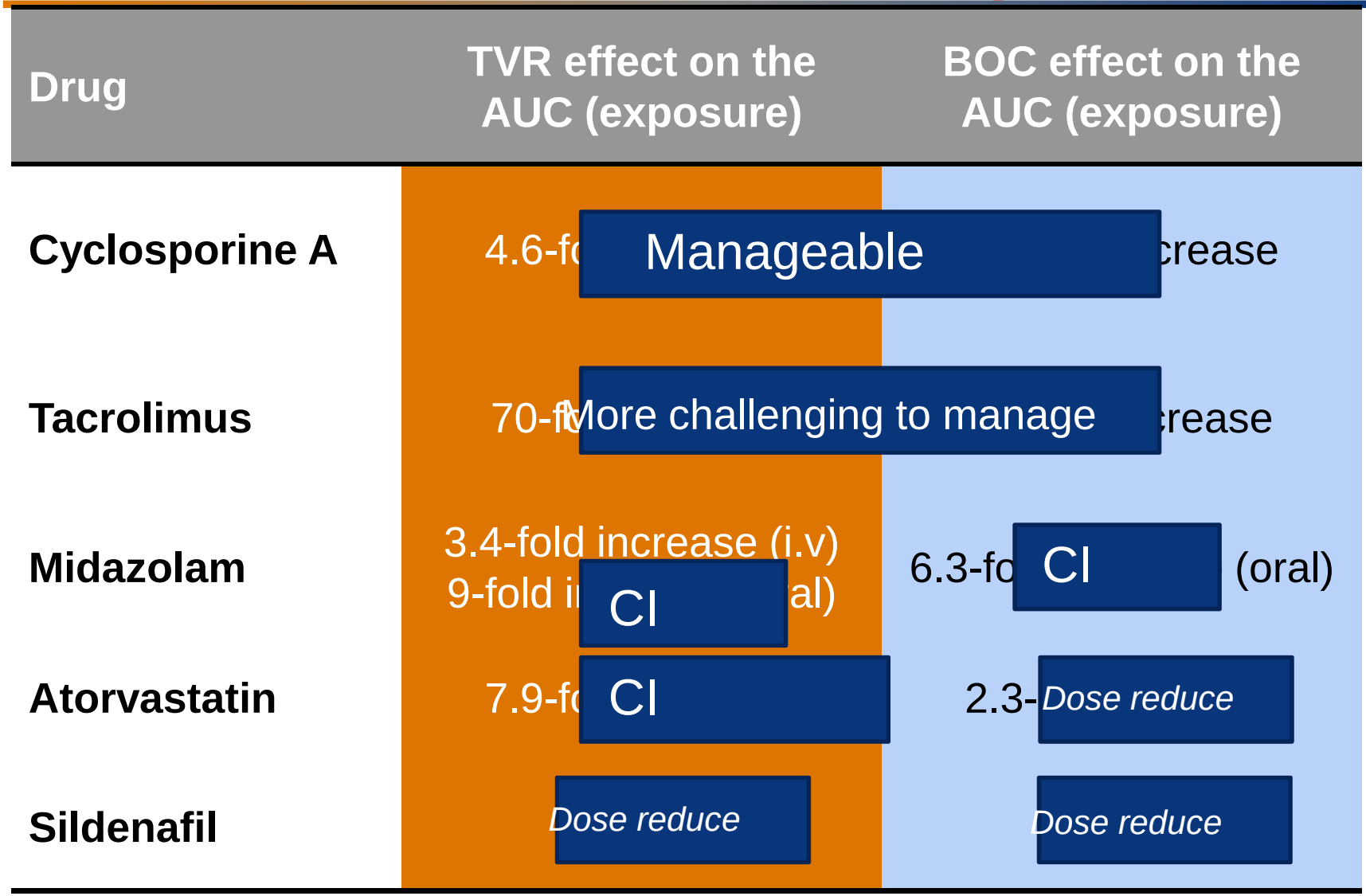
Proportion of drugs that are substrates for major CYP enzymes

- **Boceprevir also metabolised by Aldo-Keto Reductase (AKR)**

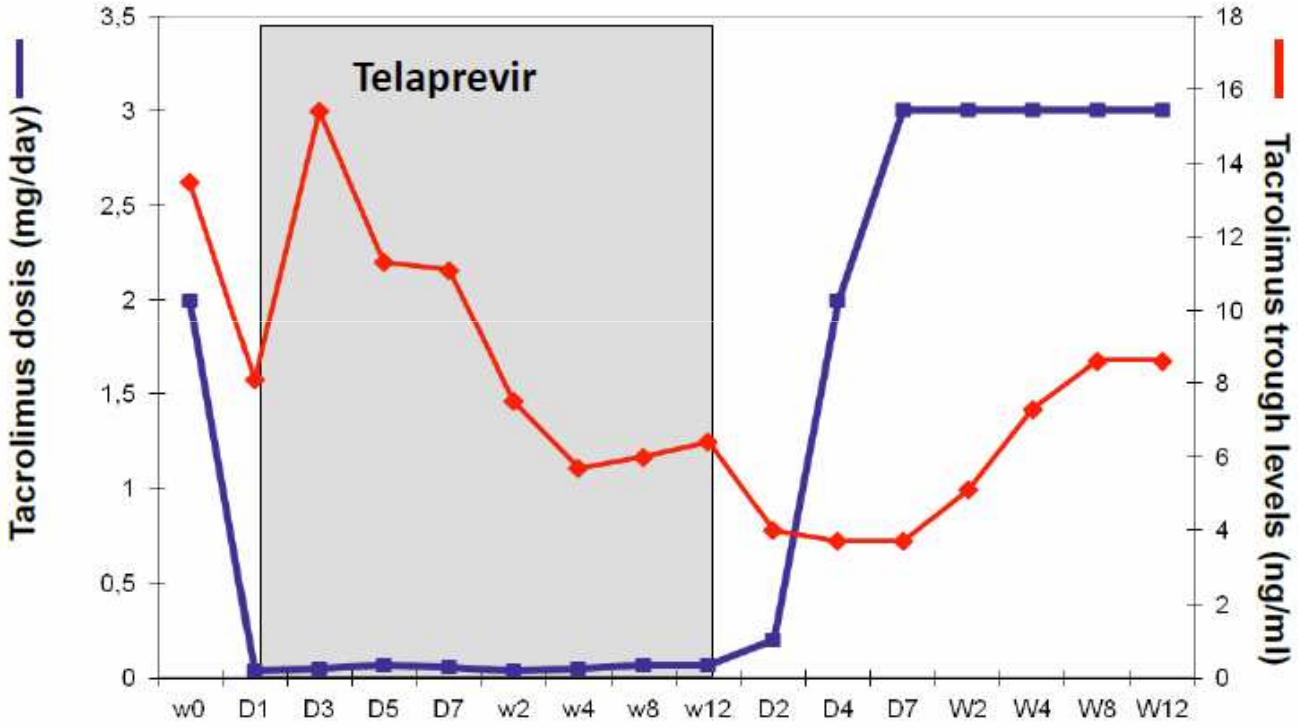
CYP: cytochrome P450
All percentages are approximate. For illustrative purposes, hepatic CYP enzymes present at <5% are all represented as 3.3%

Hacker MP, et al. Pharmacology: Principles and Practice. Academic Press 2009

Telaprevir & Boceprevir increase exposure to CYP3A substrates: *Perpetrator*



Garg V, et al. Heptatology 2011:54:20–27; Garg V, et al. J Clin Pharmacol 2012 ; Lee JE, et al. Antimicrob Agents Chemother 2011;55:4569–74; Telaprevir EU SmPC; Hulskotte EGJ et al HEPDart 2011; Abs 122 and Abs 123; Kessara C et al, CROI 2011, Abs 118; Boceprevir EU SmPC



- Suggested starting dose of TAC would be 0.2-0.5 mg/d every 2-3 days and close monitoring
- Immediately after stopping TPV TAC should be started at least same pre-treatment dose

Xavier Forns

- In most cases there are no DDI data so we need to understand metabolic profiles of drugs in the regimen to understand the potential for interaction

Interaction of Anxiolytics with TVR & BOC

Drug	Major Clearance Pathway	Effect of TVR	Effect of BOC
Midazolam	CYP3A4	D	D
Triazolam	CYP3A4		
Alprazolam	CYP3A4	D	
Diazepam	CYP2C19; CYP3A4		
Estazolam	CYP3A4		
Flurazepam	CYP mediated		
Zolpidem	CYP3A4>2C9,1A2,2D6	D	
Zoplicone	CYP3A4>>2C8		
Lorazepam	Glucuronidation		
Oxazepam	Glucuronidation		

D = Data from study

From www.hep-druginteractions.org or individual SPCs

Interaction of Lipid Lowering Agents with TVR & BOC

Drug	Major Clearance Pathway	Effect of TVR	Effect of BOC
Atorvastatin	**CYP3A4, OATP1B1**	D	D
Lovastatin	**CYP3A4**		
Simvastatin	**CYP3A4**		
Pravastatin	**OATP1B1/3**		D
Rosuvastatin	CYP2C9 (minor); **OATP1B1**		

Interaction of the antiviral drug telaprevir with renal and hepatic drug transporters

Annett Kunze [a], Jörg Huwyler [b], Gian Camenisch [a], Heike Gutmann [a,*]

[a] Division of Drug Metabolism and Pharmacokinetics, Drug–Drug Interactions Section, Novartis Institutes for BioMedical Research, CH-4056 Basel, Switzerland
[b] Department of Pharmaceutical Sciences, Division of Pharmaceutical Technology, University of Basel, CH-4056 Basel, Switzerland

Biochemical Pharmacology 84 (2012) 1096–1102

From www.hep-druginteractions.org or individual SPCs

Interaction of Lipid Lowering Agents with TVR & BOC

Drug	Major Clearance Pathway	Effect of TVR	Effect of BOC
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Lovastatin	**CYP3A4**		
Simvastatin	**CYP3A4**		
Pravastatin	**OATP1B1/3**		D
Rosuvastatin	CYP2C9 (minor); **OATP1B1**		
Fluvastatin	**CYPs(Multiple); OATP1B1/ 2B1**		
Pitavastatin (US)	CYP2C9 (minor) **UGT1A3; OATP1A2/1B3**		
Gemfibrozil	Enzymes unknown		

D = Data from study

Contraindication or Caution when co-administering statins with CYP3A4 mediated metabolism…<u>but can you avoid using a statin during DAA treatment?</u>

From www.hep-druginteractions.org or individual SPCs

- If Metabolism involves just CYP3A4 – co-med levels will *increase.*
- But if other additional metabolic pathways – co-med levels *could decrease.*
- Also note *other interaction mechanisms.*

Telaprevir & Boceprevir decrease exposure of other CYP-metabolised drugs:

Perpetrator

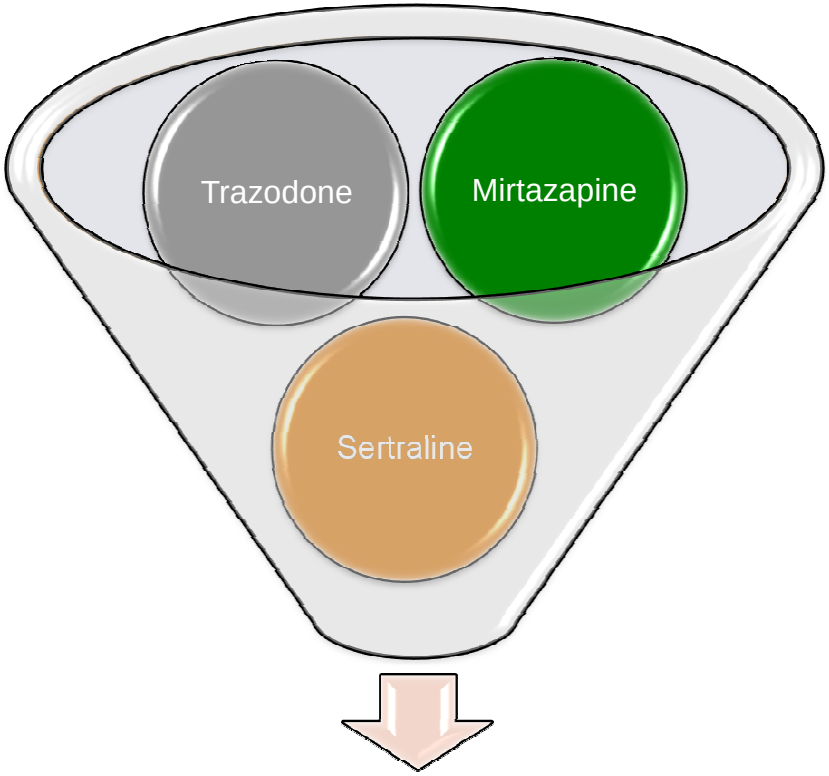
Co-medication	TVR effect	BOC effect
	AUC	AUC
Escitalopram (SSRI) *Metabolised by CYP2C19 & CYP3A4*	↓ **35%**	↓ **21%**

- Mechanism: Not clearly determined but INDUCTION of CYP2C19?
- Doses may need to be increased when combined with telaprevir
- Dose adjustment not anticipated with boceprevir.

van Heeswijk R, et al. IWCPHT 2010. Abstract 12; Telaprevir EU SmPC; Hulskotte EGJ et al HEP Dart 2011; Abs 121; Boceprevir EU SmPC.

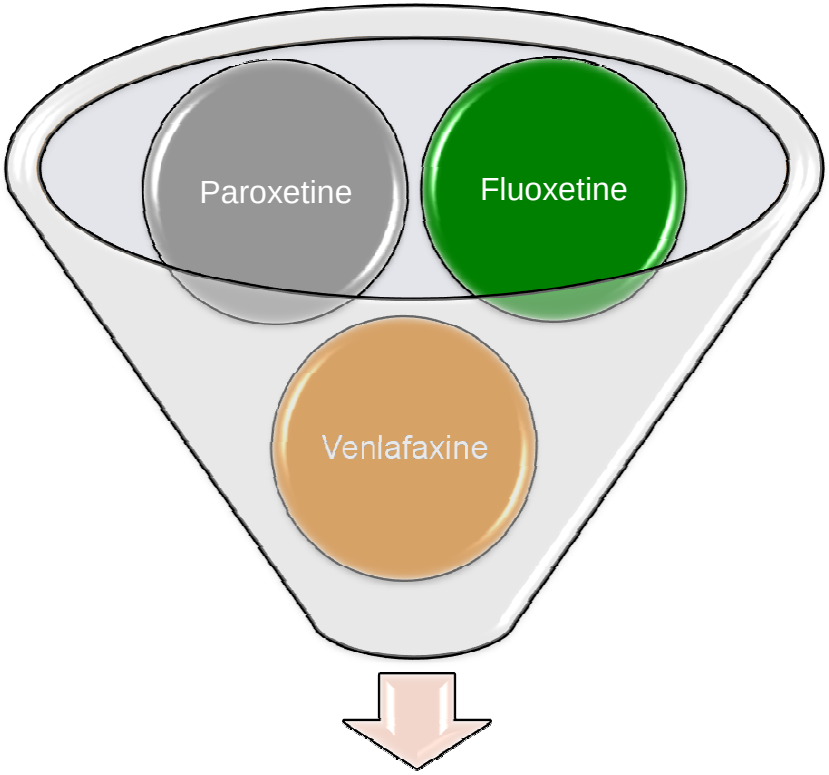
Other antidepressants that have not been studied with telaprevir

Antidepressants metabolized by CYP 3A4



Interaction is likely, caution is advised

Antidepressants metabolized primarily by non CYP 3A4



Interaction is unlikely

❑ HIV-HCV co-infection

Telaprevir & Boceprevir decrease exposure of HIV protease inhibitors *Perpetrator*

Boosted PI	% Change in AUC of Boosted PI by BOC	% Change in AUC of Boosted PI by TVR
Atazanavir/r	↓ 35%	↑ 17%
Lopinavir/r	↓ 34%	↔
Darunavir/r	↓ 44%	↓ 32%

Mechanism?

- CYP3A4 is inhibited by ritonavir; induction of another pathway
- Displacement from protein binding and increased clearance

Van Heeswijk R et al CROI 2011; Abs 119; Telaprevir EU SmPC

Hulskotte E et al; CROI 2012 Abs 771LB

Telaprevir and boceprevir are also *Victims* of drug interactions: HIV drugs

Co-medication	Effect on Boceprevir AUC	Effect on Telaprevir AUC
Efavirenz (600 mg qd)	↓ 19% (C_{min} 44%)	↓ 26%
Atazanavir/r	↔	↓ 20%
Darunavir/r	↓ 32%	↓ 35%
Lopinavir/r	↓ 45%	↓ 54%

Telaprevir EU SmPC; van Heeswijk R et al, CROI 2011; Abstract 119. Modified from Kassera C, et al. CROI 2011. Abstract 118 Boceprevir EU SmPC

Potential protein displacement interaction with darunavir and telaprevir

- Summation of *in vivo* and *in vitro* data consistent with plasma protein displacement between TVR and DRV but clinical confirmation necessary

Compound	Parameter	Alone	Combination	Trend
Telaprevir	C_{min} (ng/mL)	1835	1237	↓ Total concentration
Darunavir	C_{min} (ng/mL)	2964	1794	
Telaprevir	% Unbound	12.2	15.6	↑Free fraction
Darunavir	% Unbound	9.25	15.2	
Telaprevir	Free C_p (ng/mL)	224	193	~ Free concentration
Darunavir	Free C_p (ng/mL)	274.2	272.7	

Bertelsen Data on file

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Bertelsen Data on file

Telaprevir: Summary of DDIs with HIV antiretrovirals

HIV antiretroviral	Recommendation
Studies completed	
Atazanavir/r	Clinical and laboratory monitoring for hyperbilirubinemia is recommended
Darunavir/r Fosamprenavir/r Lopinavir/r	Not recommended
Efavirenz	TVR dose increase necessary (1125 mg q8h)
Etravirine and rilpivirine	No dose adjustment required
Raltegravir	No dose adjustment required
Tenofovir	Increased clinical and laboratory monitoring is warranted
Studies not completed	
Abacavir/zidovudine	An effect of telaprevir on UDP-glucuronyltransferases cannot be ruled out and may affect the plasma concentrations of abacavir or zidovudine (not studied)

Kakuda TN, et al. International Workshop on Clinical Pharmacology of HIV Therapy 2012. Abstract O-18
Telaprevir EU SmPC

UDP-glucuronosyltransferase: uridine 5'-diphospho-glucuronosyltransferase

Boceprevir: Summary of DDIs with HIV antiretrovirals

HIV antiretroviral	Recommendation
Studies completed	
Atazanavir/r Darunavir/r Lopinavir/r	Not recommended
Efavirenz	Reduction in boceprevir levels; clinical outcome not directly assessed
Etravirine	No dose adjustment required*
Raltegravir (non CYP)	No dose adjustment required**
Tenofovir	No change in TFV AUC but Cmax increased by 32%. No dose adjustment but clinical/laboratory monitoring warranted

- ***All the PK Interaction studies are in HEALTHY VOLUNTEERS***

*De Kanter C, et al. CROI 2012. Abstract 772LB; **Hammond K et al, IWCPHT 2012; Abs O-15 Abs Victrlelis SmPC

So.....

- The interactions with HIV PIs (in healthy volunteers) are: ***unexpected, and difficult to explain.***
- Although total concentrations are reduced the ‘free’ concentrations may be less affected – need more data!
- Is the magnitude of the interaction different in HCV patients?

Most DDI studies are in Healthy Subjects: Physiological Changes (*vs.* healthy volunteers)

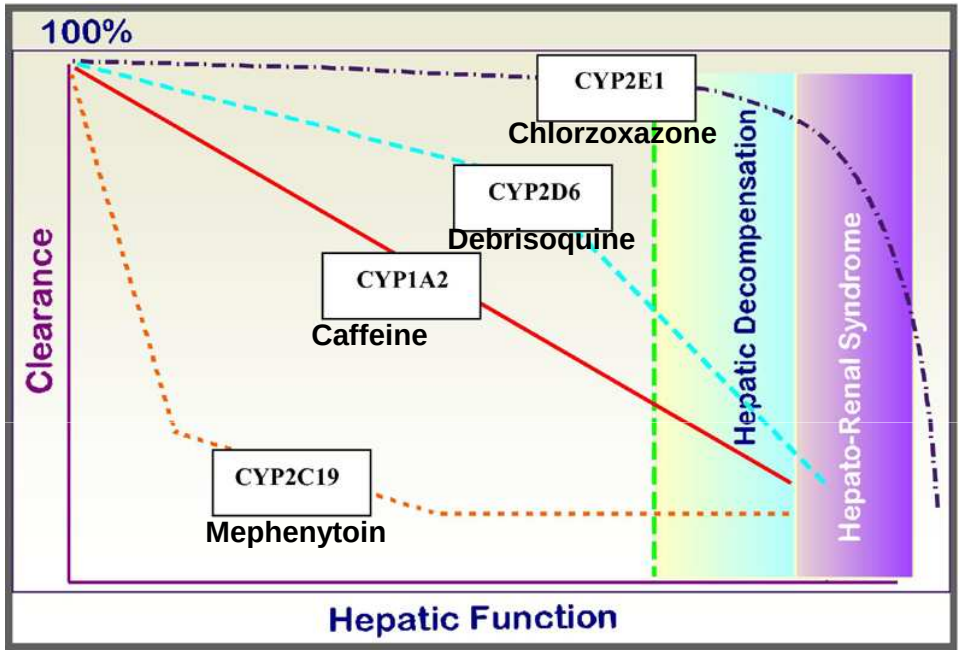
Parameter	HCV-infected
Albumin	↓*[1]
α1-acid glycoprotein	↑↓[3]
Gastric pH	↑[4]
Cytokines	↑[6]
Cytochrome P450's	↓[5]

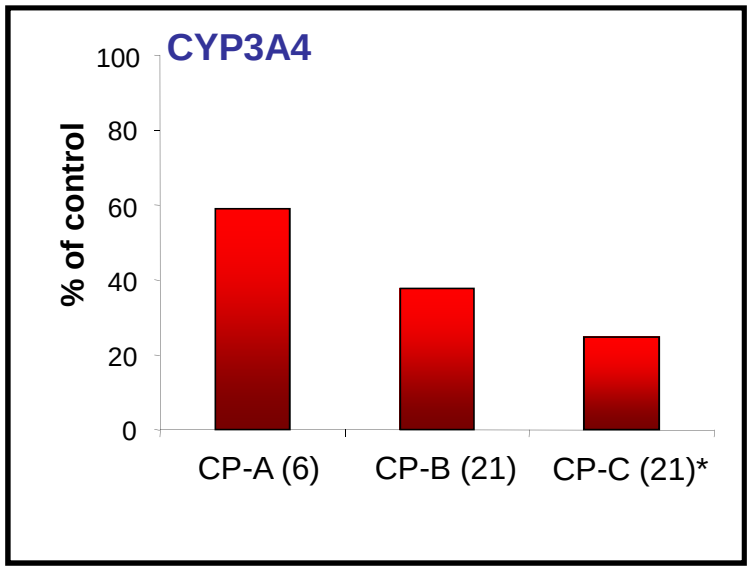
* Magnitude of effect dependent on stage of liver involvement

† Also **hemodynamic** changes with hepatic impairment

[1] Nagao Y & Sata M. *Virology Journal* 2010; **7**: 375; [2] Monga HK *et al*. *Clin Infect Dis* 2001; **33**: 240-7; [3] Ozeki T *et al*. *Br J Exp Path* 1988; **69**: 589-95; [4] Nam YJ *et al*. *Korean J Hepatol* 2004; **10**: 216-22; [5] Frye RF *et al*. *Clinical Pharmacol Ther* 2006; **80**: 235-45; [6]Huang et al *Clin Pharmacol Ther* 2010; 87: 32-36

Differences in CYP enzymes in patients with hepatic impairment





Model of hepatic dysfunction and implications for clearance of drugs predominantly metabolized by CYP pathway in liver. Study in healthy volunteers and patients with liver disease

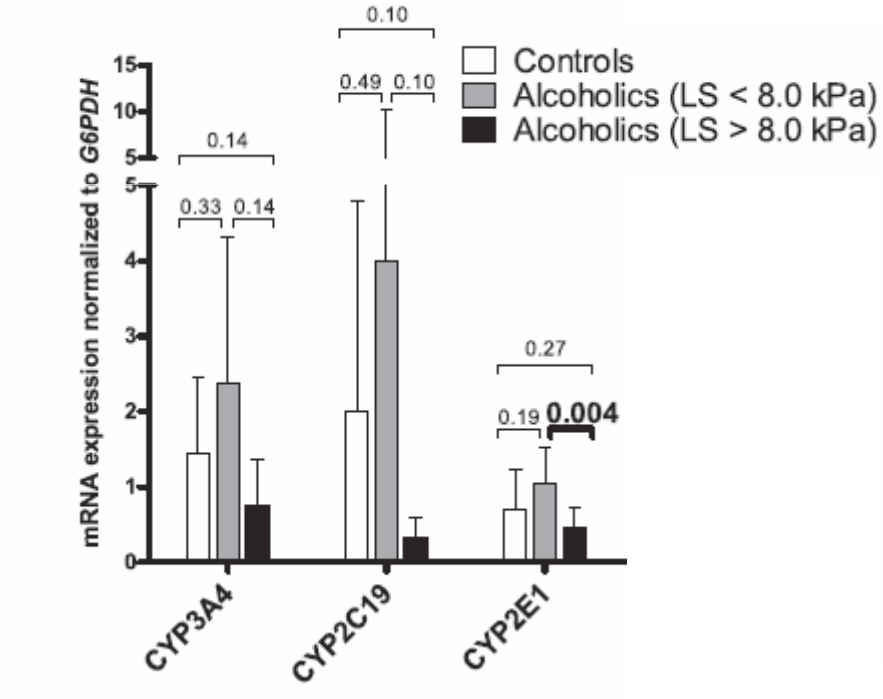
Frye RF *et al*. *Clinical Pharmacol Ther* 2006; **80**: 235-45 Johnson TN *et al*. *Clinical Pharmacokin* 2010; **49**: 189-206

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. **, No. *
** 2012

Association of Liver Stiffness with Hepatic Expression of Pharmacokinetically Important Genes in Alcoholic Liver Disease

Dirk Theile, Walter Emil Haefeli, Helmut Karl Seitz, Gunda Millonig, Johanna Weiss, and Sebastian Mueller



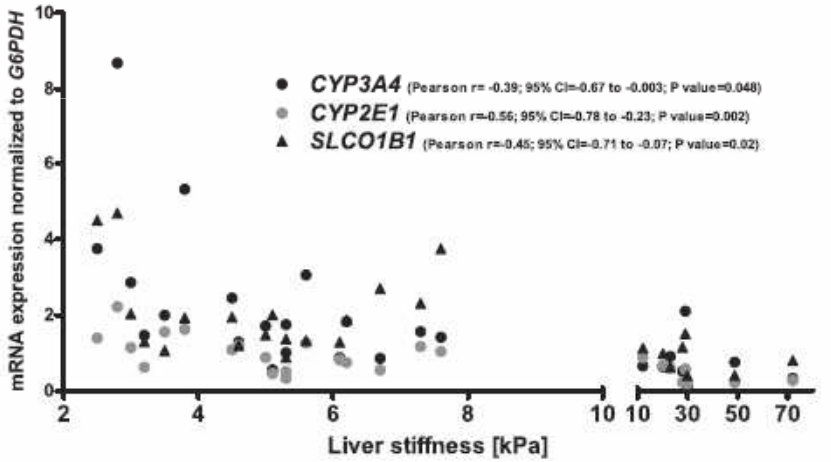


Fig. 2. Correlation of liver stiffness evaluated by transient elastography with hepatic mRNA expression of *CYP3A4* (black circles), *CYP2E1* (gray circles), and *SLCO1B1* (black triangles) among all alcoholics evaluated.

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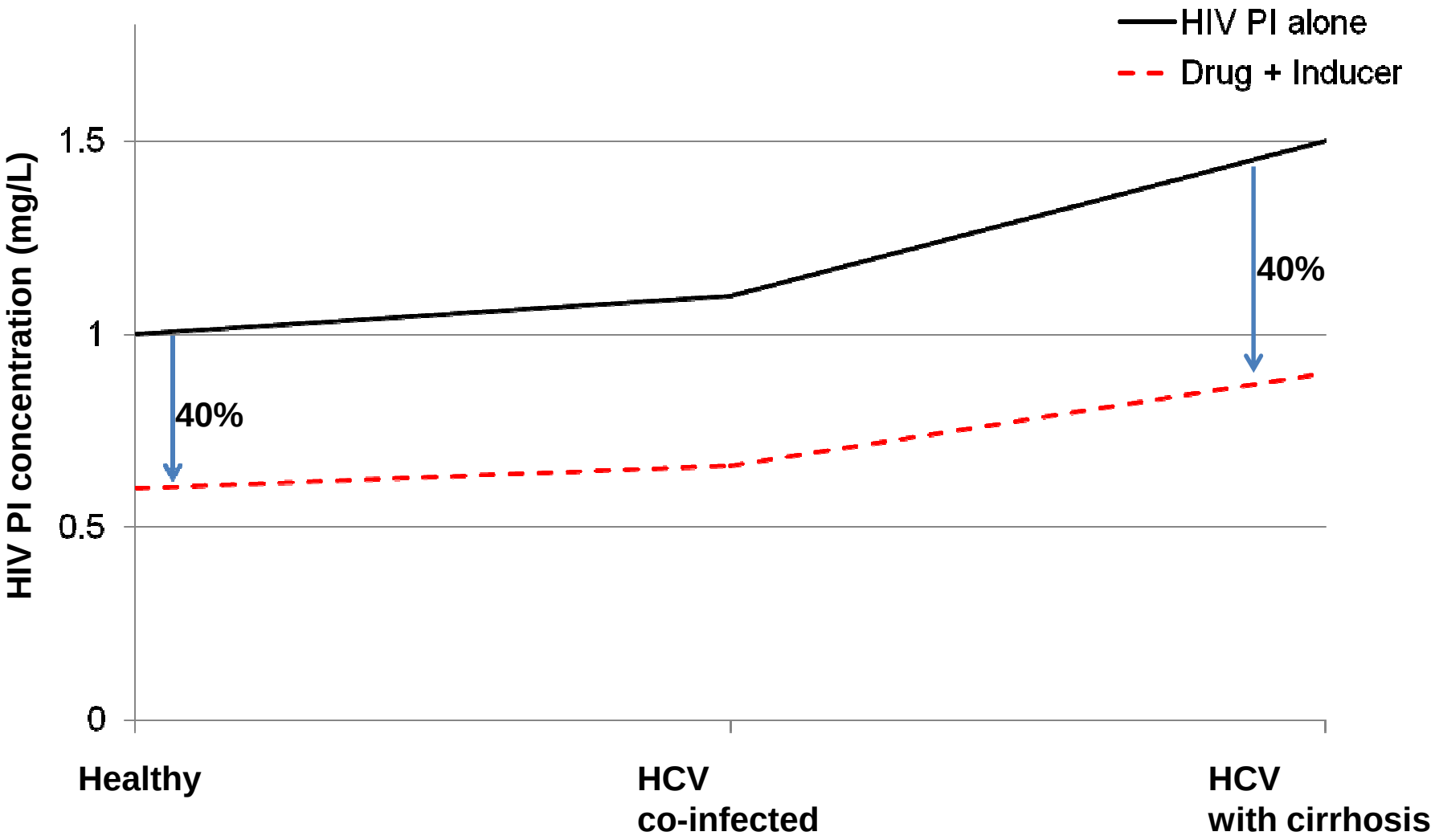
Potential Impact of a drug-drug interaction on healthy volunteers and HCV patients



Correspondence

AIDS 2012, **26**:1845–1850

HIV protease inhibitors in combination with boceprevir: are drug–drug interactions the same for all patients?

Patient 1.

- On darunavir/r 800/100 mg QD monotherapy
- Liver cirrhosis (liver stiffness 34kPa)
- DRV concentration at wk 5 of HCV therapy with BOC – 3777 ng/ml (normal range)

Patient 2.

- On fos-amprenavir/r 700/100 mg BID containing regimen
- Liver cirrhosis (liver stiffness 32kPa)
- FPV concentration at wk 8 of HCV therapy with BOC – 1699 ng/ml (normal range)

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Carolynne Schwarze-Zander and Jürgen K. Rockstroh,
Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany.

LIVERPOOL HIV PHARMACOLOGY GROUP
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- What about the second generation of drugs?

Drug Interactions with TMC435 (Simeprevir)

Drug	Effect of TMC435	Effect of Drug on TMC435
Methadone *(CYP3A4 & CYP2B6)*	No effect	na
Escitalopram *(CYP2C19)*	No effect	na
Efavirenz *(CYP2B6)*	na	↓ 70%
Rilpivirine *(CYP3A4)*	↓ 12%	No effect
Raltegravir *(UGTs)*	No effect	↓ 11%

Na = not assessed

Overall weaker inhibitory effect on CYP enzymes

Simmen K et al Int Liver Congress Hong Kong 2008; Abs 507. Beumont-Mauviel M et al AASLD 2011; Abs 1353 & 1354

Drug Interactions with BI201355 (Faldaprevir)

Drug	Effect of BI201335 AUC GMR
Oral Midazolam *(CYP3A4)*	2.92
Omeprazole *(CYP2C19)*	1.58
Efavirenz *(CYP2B6)*	1.16
S-Warfarin *(CYP2C9)*	1.29

- Study in healthy volunteers (n=14-24); 240 mg BID BI201335.

Sabo JP et al ICAAC 2012 Abs A-1248

❑ What about herbals, drugs of abuse and legal highs?

- *Heroin, dihydrocodeine, oxycodone*
- *Cannabis and synthetic cannabinoids*
- *Cocaine, crack cocaine*
- *Amphetamine, ecstasy, methamphetamine, GHB and GBL*
- *LSD, ketamine, phencyclidine,*
- *Mephedrone, BZP (piperazines), MDPV, 2 DPMP, benzo fury*
- *Butane, nitrites*
- *Anabolic steroids*

DDI management: a stepwise approach

- ✓ **Be vigilant for DDIs** when starting PI-based therapy
- ✓ **Check all patient's concomitant drugs** (prescribed/OTC) and herbal products
- ✓ **Consult the SmPCs** of PIs
- ✓ **Consult on-line resources and a pharmacist/ pharmacologist** to seek guidance

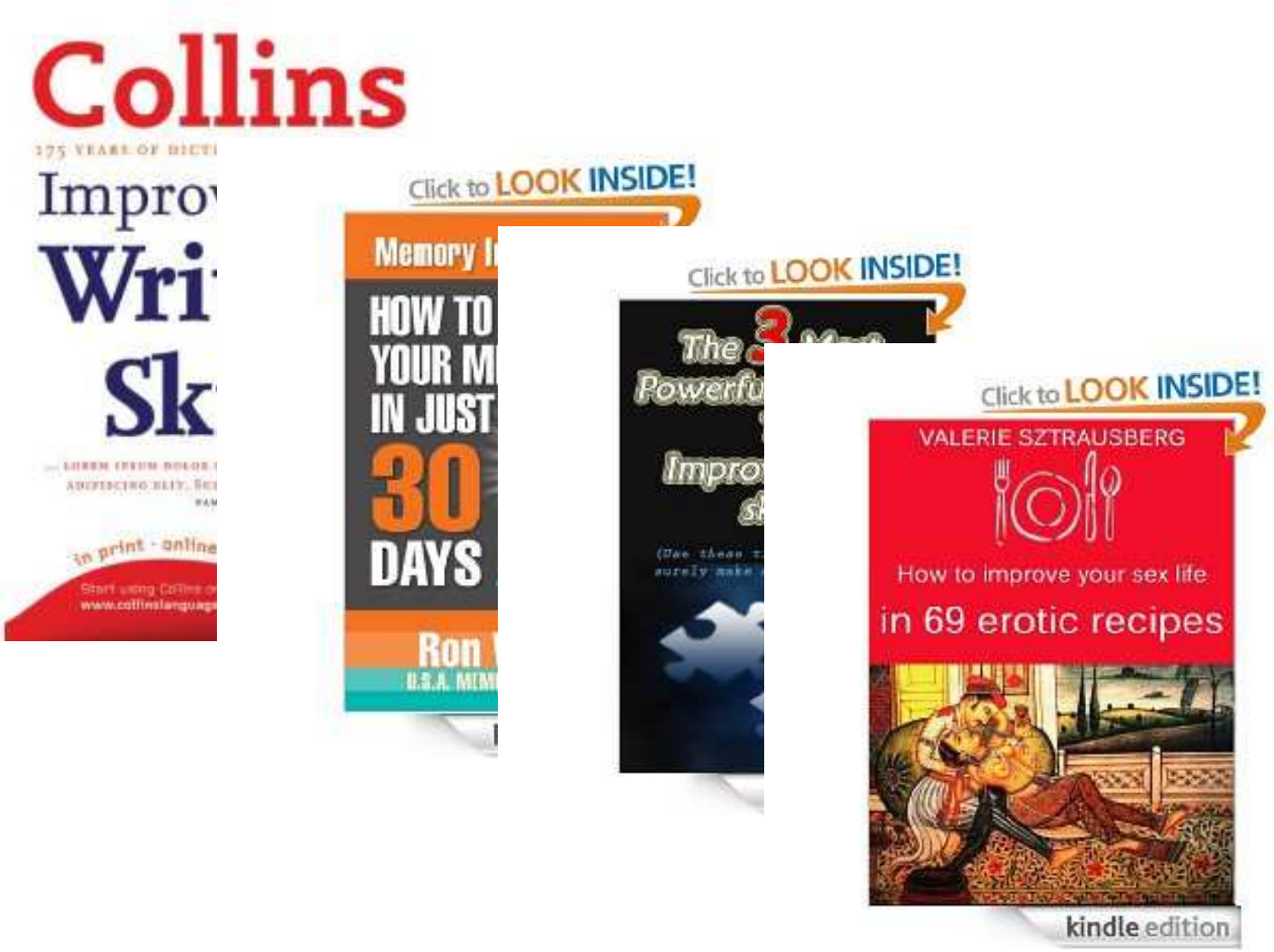
DDI: drug-drug interaction; OTC: over-the-counter; PI: protease inhibitor; SmPC: summary of product characteristics

Awareness

Resources

Management

There is always room for improvement



www.hep-druginteractions.org

LATEST ARTICLES

Review - New drugs for HCV in HIV/HCV co-infection.

Review - HCV treatment and mental health.

Drug Interactions - Peginterferon and Cytochrome P450.

Drug Interactions - Telaprevir and ketoconazole, rifampicin or efavirenz.

Meeting Report - 7th Hepatitis Pharmacology Workshop. Cambridge, USA.

Drug Interactions - Boceprevir and ciclosporin or tacrolimus.

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SITE UPDATES

New comedications added to Analagesics, Antidepressants & Anxiolytics/Hypnotics/Sedatives. Three comedication classes have been expanded to include 11 additional drugs – details are giv...

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Further additions to the comedication list
The latest additions to the comedication list have recently been uploaded to the database and all ve...

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This is an "offline" app that is downloaded to your device (~350 kb). An internet connection is not required to use the app, but is needed for downloading updates.

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ASSOCIATED SITES

www.hiv-druginteractions.org

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

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Viral Hepatitis Congress

German Liver Foundation

Deutschen Leberstiftung

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Click here to register for website updates.

Please add noreply@hep-druginteractions.org and hivgroup@liv.ac.uk to your address book to assist in uninterrupted delivery and check your SPAM or BULK folder to ensure emails are not being lost.

Sponsors: Janssen, MSD, Roche, VERTEX

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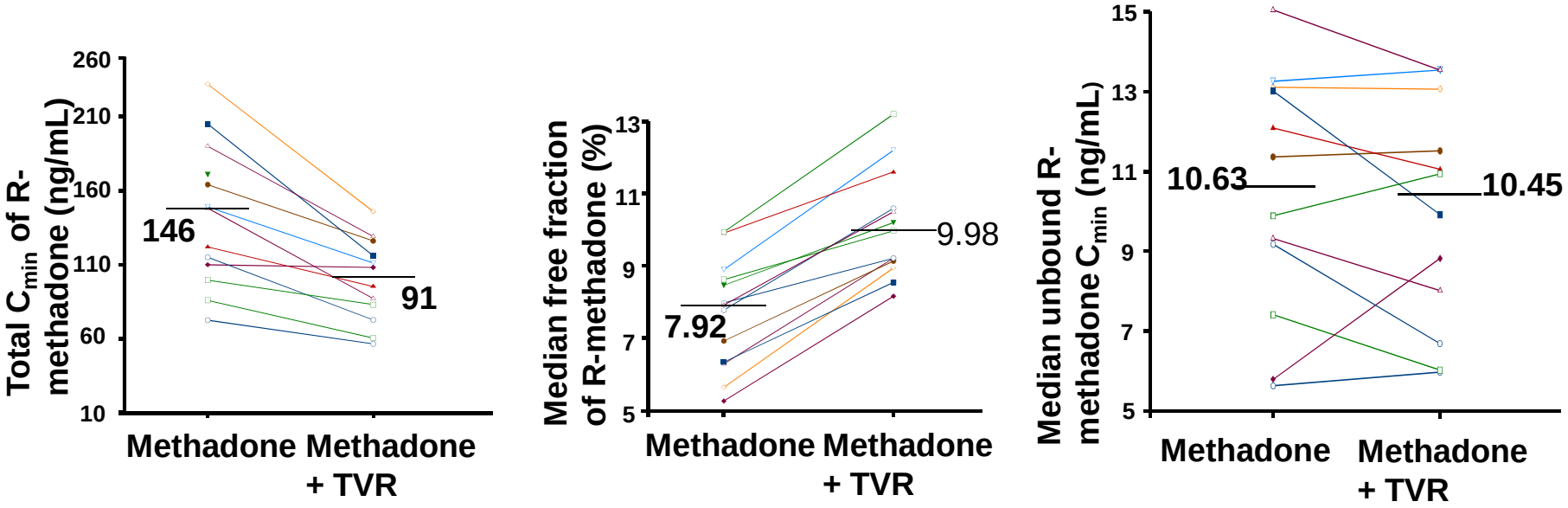
THANK YOU!

Interaction with Methadone (metabolised by CYP3A4, CYP2B6) : a further complication:

- During telaprevir co-administration vs methadone alone:
  - Total C_{min} of R-methadone **reduced** by 31%
  - Free fraction of R-methadone **increased** by 26%
  - **No change** in the unbound (effective) concentration of R-methadone



Protein Binding Displacement

van Heeswijk R, et al. J Hepatol 2011;54(Suppl. 1):S491

Interaction of Antidepressants with TVR & BOC

Antidepressant	Major Clearance Pathway	Effect of TVR	Effect of BOC
SSRI			
Escitalopram	CYP2C19, 3A4, 2D6; weak inhibitor CYP2D6	↓ 35%	↓ 21%
Citalopram	CYP2C19, 3A4, 2D6; weak inhibitor CYP2D6	↓ ? QT	↓ ? QT
Fluvoxamine	CYP2D6>other CYPs; FLUV inhibits CYP1A2; 2C; 3A4 (moderate).	↔ ? ↑ TVR	↔ ? ↑ BOC
Fluoxetine	CYP2D6, 2C9 > 3A4; FLU inhibits CYP2D6	↔	↔
Paroxetine	CYP2D6 and other CYPs; PAR inhibits CYP2D6, P-gp	↔ ? ↑ TVR	↔ ? ↑ BOC
Sertraline	CYP2B6>2C9, 2C19, 2D6, 3A4; SER inhibits CYP2D6, P-gp	↓/↑ ? ↑ TVR	↓/↑ ? ↑ BOC
SNRI			
Duloxetine	CYP2D6, 1A2, weak inhibitor CYP2D6	↔	↔
Venlafaxine	CYP2D6>3A4; VEN a weak inhibitor of CYP2D6	↔/↑	↔/↑
TeCA			
Mirtazapine	CYP3A4 , 2D6 > CYP1A2	↑	↑
Others			
Bupropion	CYP2B6>> 2C19. BUP inhibits 2D6 (moderate)	↔	↔
Trazodone	CYP3A4	↑	↑

From www.hep-druginteractions.org & SPcs of individual drugs

Interaction of Analgesics with TVR & BOC

	Major Clearance Pathway	Effect of TVR	Effect of BOC
Alfentanil	CYP3A4	● ↑	● ↑
Buprenorphine	CYP3A4> glucuronidation Bup inhibits 3A4 & 2D6	● ↔ AUC	● ↑ 20%
Codeine	Glucuronidation> CYP2D6 (to morphine) & CYP3A4 (to norcodeine)	● ↔	● ↔
Diamorphine	Deacetylation to morphine; then glucuronidation	● ↔	● ↔
Fentanyl	CYP3A4	● ↑	● ↑
Methadone	CYP3A4 & CYP2B6 > 2D6, 2C19	↓ 31% (Total) ● ↔ Free)	↓ 16% (Total) ●
Morphine	Glucuronidation >>CYP3A4 (to normorphine) > 2C8	● ↔	● ↔
Pethidine	CYP2B6>3A4	● ↔	● ↔
Tramadol	CYP3A4, CYP2B6 > 2D6	● ↑ ?	● ↑ ?

From www.hep-druginteractions.org & SPcs of individual drugs