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LIVERPOOL MASTERCLASS IN ANTIVIRAL PHARMACOLOGY

Hepatic Impairment and Renal Impairment: Implications for DDIs

Fiona Marra

56 year old female

- **HIV (VL <40, CD4 258)**
  - - Diagnosed 1996
  - - M184V resistance
  - - Switched off PI 6 months previously over concerns with drug use and liver disease to **RPV/TAF/FTC + DTG**
- **HCV Genotype 3**
  - - Fibroscan 28.4kPa.
  - - Childs Pugh B cirrhosis (raised bilirubin, low albumin)
  - - Recently started **Sofosbuvir/Velpatasvir**
- **PWID**
- **New diagnosis Breast Cancer** (at week 4 of HCV treatment)
- **eGFR 39mls/min-** stable for 3 years

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Questions

Dosing of RPV/F/TAF + DTG in CPB patient - any concerns?

Dosing of SOF/VEL in CPB pt - any concerns?

Dosing of RPV/F/TAF + DTG in patient with eGFR <50?

Dosing of SOF/VEL in patient with eGFR < 50?

DDIs with breast cancer treatment with ARVs and DAAs?

DDIs with other drugs used (PWID) etc?

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Liver disease in HIV

cART

Drug and alcohol abuse

Hepatitis Viruses

Co-morbidity treatment

HIV

NAFLD

Guaraldi G *et al ClinInfect Dis 2008 47(2): 250-257*

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ARVs dose adjustment in liver disease

NRTI

NNRTI

Integrase

NRTI	Childs Pugh A	Childs Pugh B	Childs Pugh C
Abacavir	200mg BD	contraindicated	contraindicated
Zidovudine	normal	normal	↓ dose by 50% or increase interval
All others	normal	normal	normal
NNRTI	**Childs Pugh A**	**Childs Pugh B**	**Childs Pugh C**
Efavirenz	caution	caution	caution
Etravirine	normal	normal	No data
Nevirapine	normal	contraindicated	contraindicated
Rilpivirine	normal	normal	No data
Doravirine	normal	normal	No data
Integrase	**Childs Pugh A**	**Childs Pugh B**	**Childs Pugh C**
Raltegravir	normal	normal	normal
Dolutegravir	normal	normal	No data
Elvitegravir	normal	normal	No data
Bictegravir	normal	normal	No data, not recommended

EACS Guidelines, Accessed Oct 2020

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ARVs dose adjustment in liver disease

PI

PI	Childs Pugh A	Childs Pugh B	Childs Pugh C
Atazanavir	normal	300 mg qd (unboosted)	Not recommended
Atazanavir/c	normal	Not recommended	Not recommended
Darunavir	normal	normal	Not recommended
Darunavir/c	normal	normal	Not recommended
Lopinavir/r	caution	caution	caution

Other

Other	Childs Pugh A	Childs Pugh B	Childs Pugh C
Enfurivitide	normal	normal	normal
Maraviroc	Increased concentrations likely	Increased concentrations likely	Increased concentrations likely
Ibalizumab	normal	normal	normal

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Impact of Hepatic Impairment on PK of DAAs

DAA class	DAA	$AUC_{24h\ or\ inf}$ (fold increase vs healthy subjects)		
		CTP A	CTP B	CTP C
NS3 PIs	Simeprevir[1]	–	2.44-fold	5.22-fold
	Paritaprevir[2]	0.7	1.6	10.2
	Grazoprevir[3]	1.6	4.5	12[5]
	Glecaprevir[5]	1.3	2.0	11.1
	Voxilaprevir[6]	–	4.0	6.0
NS5A inhibitors	Daclatasvir[7]	0.60	0.98	0.95
	Ledipasvir[8]	–	1.0	1.1
	Ombitasvir[2]	0.9	0.7	0.5
	Elbasvir[9]	0.8	0.9	N/A
	Velpatasvir[10]	–	0.8	1.1
	Pibrentasvir[5]	0.8	1.3	2.1
NS5B non-nucleoside inhibitor	Dasabuvir[2]	1.2	0.8	4.2
NS5B nucleoside inhibitor	Sofosbuvir[11]	–	1.2	1.1

1. Ouwerkerk-Mahadevan S, *et al. Rev Antivir Ther & Infect Dis* 2013; **6**:O-04_PK; 2. Khatri A, *et al. Hepatology* 2012; **56**: 555A–556A; 3. Yeh WW, et al. *Rev Antivir Ther & Infect Dis* 2014; **4**:P_37; 4. Zepatier SmPC (accessed July 2017); 5. Kosloski M, *et al J Hepatol* 2016; **64**:S406; 6. Lawitz E, *et al J Hepatol* 2016; **64**: S613; 7. Bifano M, *et al. Hepatology* 2011; **54**:1004A; 8. German P, *et al Hepatology* 2013; **58**:432A; 9. Marshall W, *et al. Rev Antivir Ther & Infect Dis* 2014; **4**:P_41; 10. Mogalian E, *et al Hepatology* 2014; **60**:S317; 11. Lawitz E, *et al. J Hepatol* 2012; **56**:S445–S446.

Dose adjustment of ARVs for Impaired Renal Function

	eGFR[i] (mL/min)				Haemodialysis[iii]
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC[iii]	300 mg q12h or 600 mg q24h	No dose adjustment required			
FTC[v]	200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h[v]
3TC[v]	300 mg q24h	150 mg q24h	100 mg q24h[vi]	50-25 mg q24h[vi]	50-25 mg q24h[iv, vi]
TDF[vii]	300[viii] mg q24h	300[viii] mg q48h	Not recommended (300[viii] mg q72-96h, if no alternative	Not recommended (300[viii] mg q7d, if no alternative)	300[viii] mg q7d[iv]
TAF[ix,x]	25[xi] mg q24h			no data	limited data
ZDV	300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h[iv]
Combinations					
ABC[iii]**/3TC**[v]	600/300 mg q24h	Use individual drugs			
ZDV/3TC	300/150 mg q12h				
ABC/3TC/ZDV	300/150/300 mg q12h				
TAF[ix]**/FTC**[v]	25[xi]/200 mg q24h		Use individual drugs[xv]		
TDF[viii]**/FTC**[v]	300[viii]/200 mg q24h	300[viii]/200 mg q48h	Use individual drugs		
NNRTIs					
EFV	600 mg q24h	No dose adjustment required			
ETV	200 mg q12h				
NVP	200 mg q12h				
RPV	25 mg q24h				
TAF[ix]**/FTC**[v]**/RPV**	25[xi]/200/25 mg q24h		Use individual drugs[xv]		
TDF[viii]**/FTC**[v]**/RPV**	300[viii]/200/25 mg q24h	Use individual drugs			
DOR	100 mg q24h	No dose adjustment required; < 10: no PK data			
TDF[viii]**/3TC**[v]**/DOR**	300[viii]/300/100 mg q24h	Use individual drugs			

PIs[vii]		
ATV/c	300/150 mg q24h	No dose adjustment required[xiii]
ATV/r	300/100 mg q24h	No dose adjustment required[xiii]
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[xiii]
DRV/c	800/150 mg q24h	No dose adjustment required[xiii]
TAF[ix]**/FTC**[v]**/DRV/c**	10/200/800/150 mg q24h	Use individual drugs
LPV/r	400/100 mg q12h	No dose adjustment required[xiii]
Other ART		
RAL	1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required[xiii]
DTG	50 mg q24h	No dose adjustment required[xiii]
3TC[v]**/DTG**	300/50 mg q24h	Use individual drugs
ABC[iii]**/3TC**[v]**/DTG**	600/300/50 mg q24h	Use individual drugs[xvi]

EACS Guidelines, Version 10. Nov 2019

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Sofosbuvir/Velpatasvir in renal impairment

License Update 2020: No dose adjustment is required for patients with mild or moderate renal impairment. Safety data are limited in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and ESRD requiring haemodialysis.

Epclusa can be used in these patients with no dose adjustment when no other relevant treatment options are available

	HCV-Negative Subjects					HCV-Infected Subjects	
	Mild RI (eGFR ≥50 and <80 mL/min/1.73m^2)	Moderate RI (eGFR ≥30 and <50 mL/min/1.73m^2)	Severe RI (eGFR <30 mL/min/1.73m^2)	ESRD Requiring Dialysis		Severe RI (eGFR <30 mL/min/1.73m^2)	ESRD Requiring Dialysis
				Dosed 1 hr Before Dialysis	Dosed 1 hr After Dialysis		
Sofosbuvir	1.6-fold↑	2.1-fold↑	2.7-fold↑	1.3-fold↑	1.6-fold↑	~2-fold↑	1.8-fold↑
GS-331007	1.6-fold↑	1.9-fold↑	5.5-fold↑	≥10-fold↑	≥20-fold↑	~7-fold↑	18-fold↑
Velpatasvir	-	-	1.5-fold↑	-	-	-	1.4-fold↑

Epclusa SmPC, Gilead. Accessed Oct 2020

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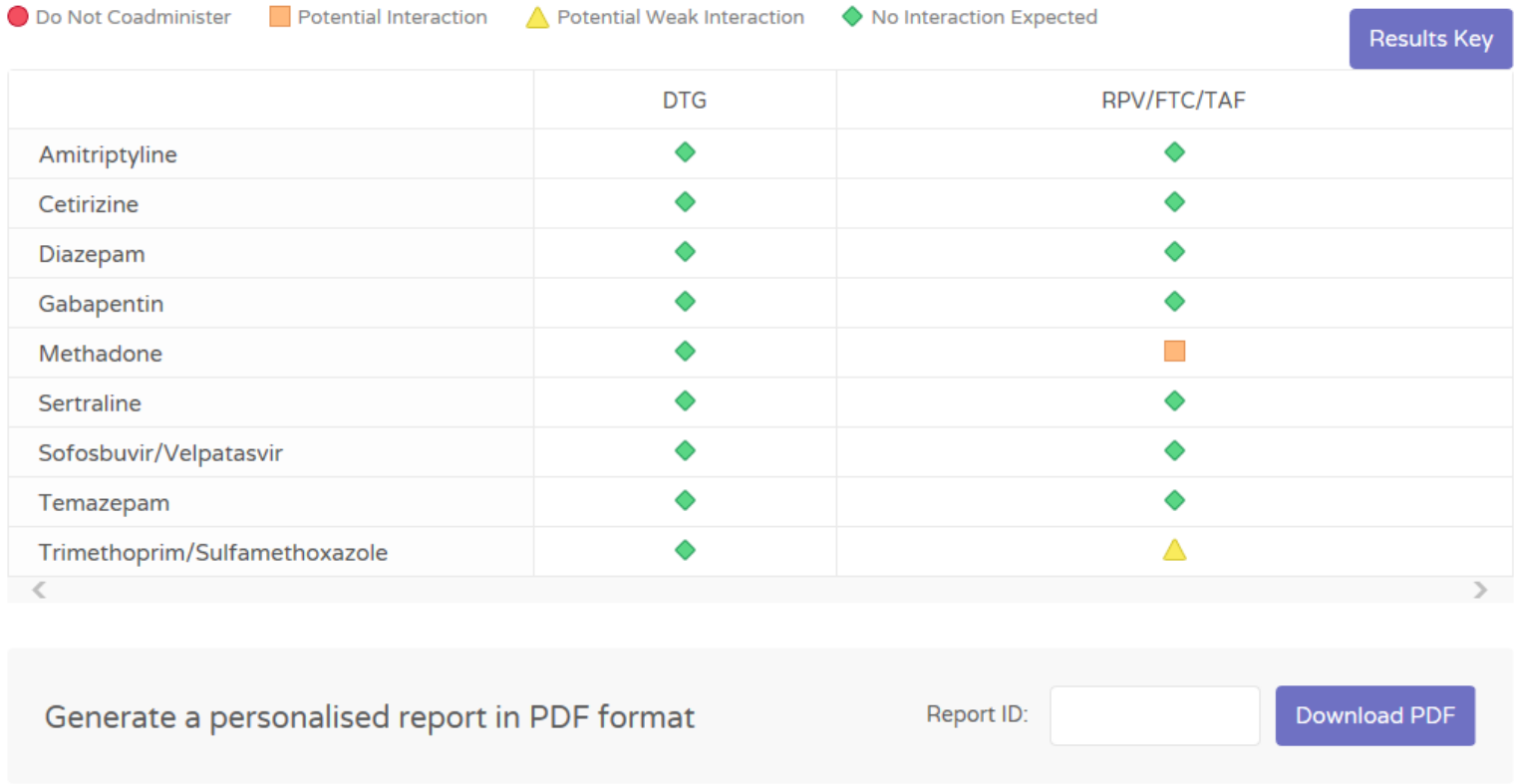
Drug History pre Breast Cancer

- methadone
- diazepam
- temazepam
- sertraline
- cetirizine
- co-trimoxazole
- gabapentin
- amitriptyline



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Suggested new medication

Oncology medications	Liver disease dose adjustment (Childs Pugh B)	Renal disease dose adjustment (eGFR 39mls/min)
Epirubicin	Dose reduction based on Bilirubin	Normal dose
Cyclophosphamide	Normal dose	Normal dose
Paclitaxel	20% dose reduction	Normal dose
Herceptin	Normal dose	Normal dose
Zolendronic acid	Normal dose	Normal dose
Dexamethasone	Normal dose	Normal dose
Metoclopramide	caution	Reduce dose by 50%
Ondansetron	maximum 8mg	Normal dose
Chlorphenamine	Normal dose	Normal dose
Filgrastim	Normal dose	Normal dose
Aprepitant	caution	Normal dose
Omeprazole	Normal dose	Normal dose
Fluconazole	caution	Reduce dose by 50%
Aciclovir	Normal dose	caution

Drug Interactions

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

Results Key

	DTG	RPV/FTC/TAF
Aciclovir (Acyclovir)	◆	◆
Aprepitant	◆	▲
Chlorphenamine	◆	◆
Cyclophosphamide	◆	◆
Dexamethasone	◆	●
Epirubicin	◆	▲
Filgrastim	◆	◆
Fluconazole	◆	▲
Metoclopramide	◆	◆
Omeprazole	◆	●
Ondansetron	◆	■
Paclitaxel	■	■
Trastuzumab	◆	◆
Zoledronic acid	◆	◆

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Do Not Coadminister

Rilpivirine/ Emtricitabine/Tenofovir alafenamide (RPV/FTC/TAF)

Dexamethasone

Quality of evidence: Very Low

Summary:

Coadministration is contraindicated with systemic dexamethasone (except as a single dose) as significant decreases in rilpivirine plasma concentrations may occur. Emtricitabine and tenofovir alafenamide are unlikely to interact with dexamethasone.

Potential Interaction

Rilpivirine/ Emtricitabine/Tenofovir alafenamide (RPV/FTC/TAF)

Paclitaxel

Quality of evidence: Very Low

Summary:

Coadministration has not been studied. Paclitaxel is primarily metabolized by CYP2C8 and to a lesser extent by CYP3A4. In vitro data suggest that paclitaxel induces CYP3A4 via PXR mediated activation and therefore could potentially decrease rilpivirine concentrations. Monitor response to antiretroviral therapy. Emtricitabine and tenofovir alafenamide are unlikely to interact with paclitaxel metabolic pathway.

Dexamethasone and possibly paclitaxel ↓ Rilpivirine levels

Fluconazole and aprepitant may ↑

Options:

- Switch to Doravarine ?
- Leave current regimen as DTG + TAF alone may hold the regimen?
- Double up Rilpivirine? ☑

- Data available with RPV and rifabutin
- Well tolerated

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Omeprazole interactions

Do Not Coadminister

Rilpivirine (RPV)

Omeprazole

Quality of evidence: Low

Summary:

Coadministration is contraindicated as significant decreases in rilpivirine plasma concentrations may occur. When rilpivirine (150 mg once daily) and omeprazole (20 mg once daily) were coadministered, rilpivirine exposure decreased by ~40% and omeprazole exposure decreased by ~14%. [Note: this interaction study has been performed with a dose higher than the licensed dose for rilpivirine assessing the maximal effect on the co-administered drug. The recommendation is applicable to the licensed dose of rilpivirine 25 mg once daily.]

Potential Interaction

Sofosbuvir/Velpatasvir

Omeprazole

Summary:

Coadministration of omeprazole is not recommended. If it is considered medically necessary to coadminister, sofosbuvir/velpatasvir should be administered with food and taken 4 hours before omeprazole 20 mg. Coadministration of sofosbuvir/velpatasvir with food 4 hours before omeprazole (20 mg once daily) decreased sofosbuvir Cmax by 21% but increased AUC by 5%; velpatasvir Cmax and AUC decreased by 33% and 26%.

Proton pump inhibitors			
Omeprazole (20 mg once daily)/ sofosbuvir/ velpatasvir (400/ 100 mg single dose fasted)[c] Omeprazole dosed simultaneously with Epclusa[d]	Sofosbuvir	↓ 0.66 (0.55, 0.78)	↓ 0.71 (0.60, 0.83)
Lansoprazole[e] Rabeprazole[e] Pantoprazole[e] Esomeprazole[e] (Increase in gastric pH)	Velpatasvir	↓ 0.63 (0.50, 0.78)	↓ 0.64 (0.52, 0.79)

Omeprazole switched to H2

Epclusa SmPC, Gilead, 2020

Rilpivirine and QTc concerns?

Odefsey SmPC:

At supratherapeutic doses (75 mg) rilpivirine has been associated with prolongation of the QTc. Rilpivirine 25 mg is not associated with a clinically relevant effect on QTc. Odefsey should be used with caution with medicinal products with a known risk of Torsade de Pointes.

CREDIBLEMEDS®

? Possible Risk of TdP

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Other medications that may prolong QTc?

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Methadone	Known Risk of TdP
Fluconazole	Known Risk of TdP
Ondansetron	Known Risk of TdP
Metoclopramide	Conditional Risk of TdP
Epirubicin	Possible Risk of TdP

NB:

- **Is the drug required? Review**

- **Remember effect of hepatic impairment**

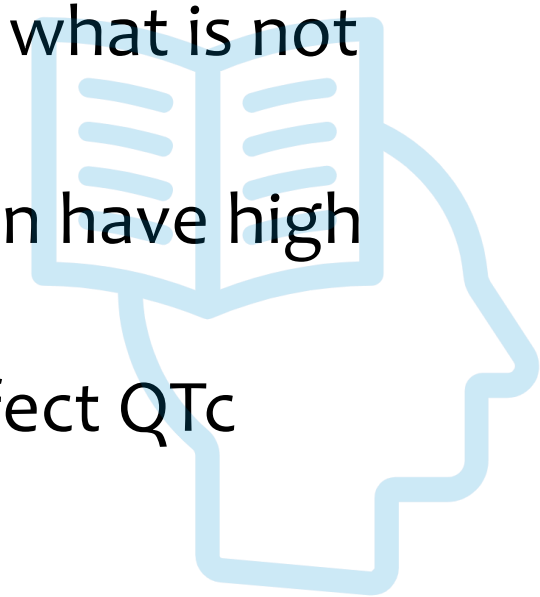
- **ECG monitoring**

Outcomes

- **HCV treatment completed**, SVR achieved
- HIV regimen tolerated well, no blips
- Anti-emetics switched, ECGs regularly
- Albumin improved, liver disease stable
- Paclitaxel discontinued at week 2 due to toxicities ? Liver disease related
- Patient is well and continues on chemotherapy

Learning points

- Drug interactions studies not performed in renal or hepatic impairment. Likely potentiated effect?
- Review all drug doses in cirrhosis and CKD and stop what is not required.
- Carry out regular drug histories. Herbal drugs etc can have high incidence of DILI
- Increased drug exposure in cirrhosis or CKD may affect QTc
- Minimise burden on the liver where possible:
  - Treat HCV, weight loss, avoid DILI



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