
# *Drug drug interaction of new HCV drugs*

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# Disposition of “old” DAAs

| Drug | Dosing regimen | CYP | P-glycoprotein | Non-CYP metabolism |
|---|---|---|---|---|
| **Telaprevir** | Q8h<br>No significant boosting by RTV | CYP 3A4:<br>▪ Substrate<br>▪ Inhibitor | ▪ Substrate<br>▪ Inhibitor | – |
| **Boceprevir** | tid<br>No significant boosting by RTV | CYP 3A4/5:<br>▪ Substrate<br>▪ Inhibitor | ▪ Substrate | AKR<br>▪ Substrate |

AKR: aldo-keto reductase; DAA: direct-acting antiviral
Q8h: every 8 hours; RTV: ritonavir; tid: three times daily

Telaprevir EU SmPC; Boceprevir EU SmPC
Kassera C, et al. CROI 2011. Abstract 118; Garg V, et al. CROI 2011. Abstract 629

| | VICTIM of DDI | PERPETRATOR of DDI | DDI potential |
|---|---|---|---|
| Teleprevir | Substrate for CYP 3A4, PgP | Inhibits CYP 3A4, PgP, OATP1B1/2<br>? Protein binding | Significant |
| Boceprevir | Substrate for aldoketoreductase, CYP 3A4, PgP, BCRP | Inhibits CYP 3A4, PgP, OCT 1&2 | Significant |
| Simeprevir | Substrate for CYP 3A4, PgP | Inhibits OATP1B1, MRP2<br>Mild inhibitor gut CYP 3A4, PgP | Moderate |
| Sofosbuvir | cathepsin A, esterases, kinases<br>PgP & BCRP substrate (parent) | Weak inhibitor of gut PgP & BCRP | Low |
| Ledipasvir | Primarily excreted unchanged (>98% faeces), PgP / BCRP substrate | Weak inhibitor of PgP/BCRP,<br>?OATP1B1/3 | ? |
| ABT450r | Substrate for CYP 3A4, PgP, OATP1B1/3 | Weak inhibitor PgP/BCRP (gut),<br>?OATP1B1/3 | |
| Ombitasvir (ABT-267) | Substrate for PgP, BCRP (CYP 3A4 ) | Weak inhibitor of UGT1A1 | Moderate to Significant (RTV) |
| Dasabuvir (ABT-333) | Substrate of CYP 2C8 > 3A4 > 2D6,<br>Substrate of PgP, BCRP | Weak inhibitor of UGT1A1 | |
| Daclatasvir | Substrate for CYP 3A4, PgP | Inhibits OATP1B1/3 & PgP | Moderate |
| Asuneprevir | Substrate for OATP1B1/2B1<br>CYP 3A4 | Inhibits CYP2D6 (mod) &<br>OATP1B1/3 (weak), ?BCRP,<br>Weak CYP3A4 inducer | ? |
| Faldeprevir | Substrate for CYP 3A4, PgP, OATP1B1 & MRP2 | Inhibitor of CYP 3A4, 2C9, UGT1A1,<br>Probably inhibits OATP1B1/3, MRP2 | Moderate |
| MK-5172 | Substrate for CYP 3A4, PgP, ?<br>OATP1B1 | Inhibits CYP 2C8, weak inhibitor of UGT1A1, ? BCRP | Moderate |
| MK-8742 | Substrate for CYP 3A4, PgP,<br>?OATP1B1 | weak inhibitor of UGT1A1 | Moderate |

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| Dasabuvir (ABT-333) | Substrate of CYP 2C8 > 3A4 > 2D6,<br>Substrate of PgP, BCRP | Weak inhibitor of UGT1A1 | |
| Daclatasvir | Substrate for CYP 3A4, PgP | Inhibits OATP1B1/3 & PgP | Moderate |
| Asuneprevir | Substrate for OATP1B1/2B1<br>CYP 3A4 | Inhibits CYP2D6 (mod) &<br>OATP1B1/3 (weak), ?BCRP,<br>Weak CYP3A4 inducer | ? |
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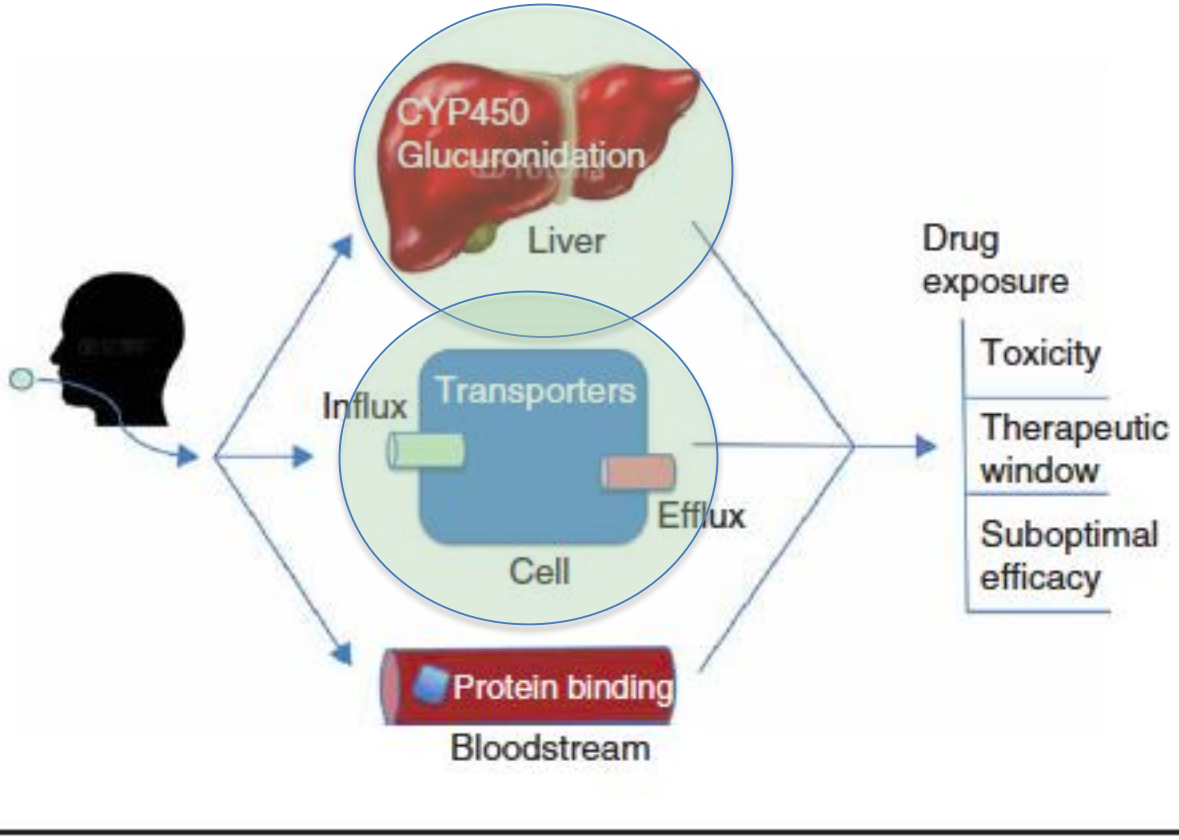
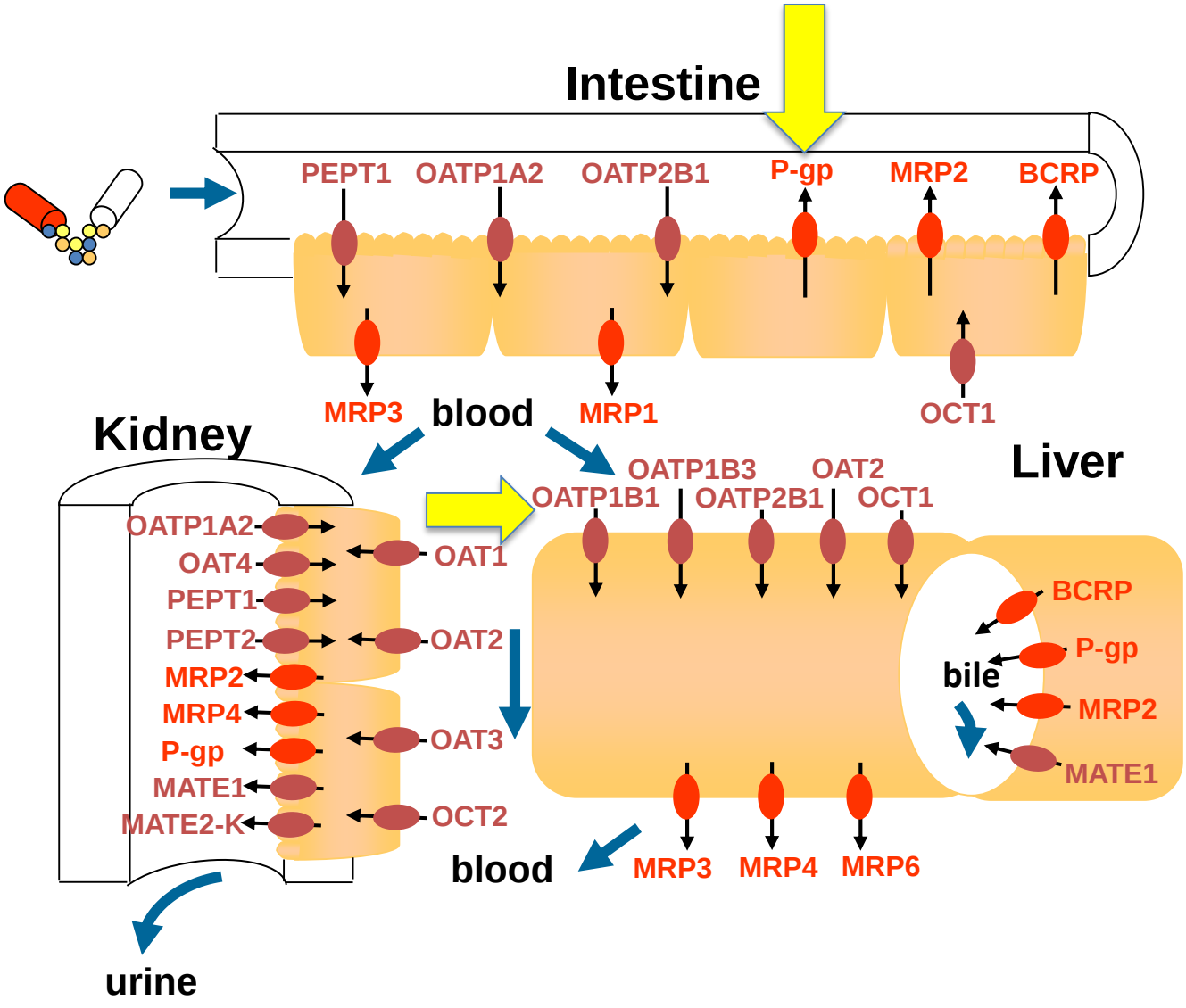
| MK-8742 | Substrate for CYP 3A4, PgP,<br>?OATP1B1 | weak inhibitor of UGT1A1 | Moderate |

# Mechanisms of drug-drug interactions involving DAAs



# Drug transporters




Marzolini C et al. In: Drug Interactions in Infectious Diseases 2011

By courtesy of Catia Marzolini

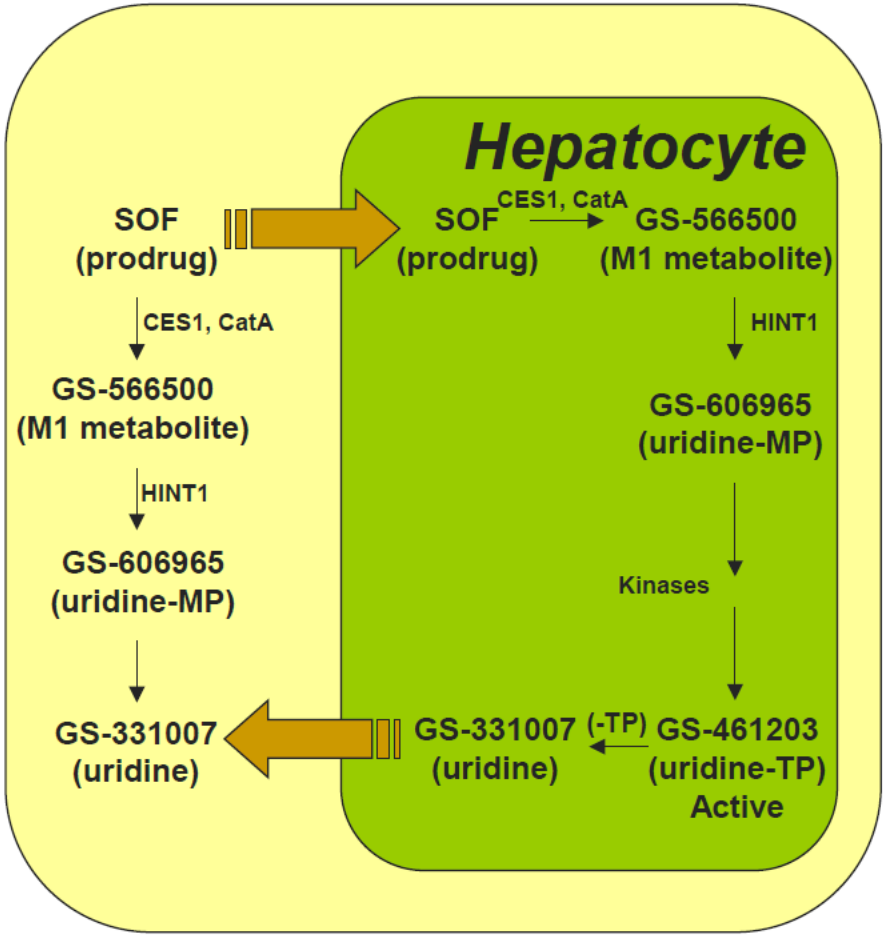
| DAA | Substrate | Effect | Clinical DDI extent | Comments |
|---|---|---|---|---|
| Simeprevir | CYP3A4<br>P-gp | Inhibits OATP1B1 and multi-drug resistant protein 2<br>Inhibits gut CYP3A4 and P-gp | Moderate | Bile elimination |
| Paritaprevir/r | CYP3A4<br>P-gp and OATP1B1/3 | Inhibits liver CYP3A4<br>Inhibits gut P-gp, BCRP<br>Inhibits OATP1B1/3 | Significant | Efavirenz and rilpivirine contraindicated<br>Hyperbilirubinemia |
| Sofosbuvir | Cathepsin A, esterases and kinases<br>P-gp and BCRP | Inhibits gut P-gp | Low | Urine elimination (80%) and bile (14%) |
| Dasabuvir | CYP2C8, 3A4 and 2D6<br>P-gp and BCRP | Inhibits UGT1A1<br>Inhibits OATP1B1 | Significant | |
| Daclatasvir | CYP3A4 and P-gp | Inhibits OATP1B1/3 and P-gp | Moderate | Increases statin exposure<br>Darunavir/r increases daclatasvir exposure |
| Ledipasvir | P-gp and BCRP | Inhibits gut P-gp and BCRP<br>Inhibits OATP1B1/3 | Low | Increases statin exposure |
| Ombitasvir | CYP3A4<br>P-gp and BCRP | Inhibits CYP2C8 and UGT1A1 | Significant | |

BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

# Sofosbuvir Intracellular Activation

- As nucleotide analog prodrug SOF is activated by sequential metabolic pathways including
  - Low affinity and high capacity hydrolases (CES1, CatA and HINT1)
  - Nucleotide phosphorylation (UMP-CMP kinase and NDP kinase)
- Only SOF can enter hepatocytes and be converted to active TP (GS-461203)
- SOF can also undergo extraheptic metabolism to form GS-331007 (predominant metabolite) principally eliminated in urine



# Effect of ARVs on Sofosbuvir: *Victim*

| Drug | Effect on Sofosbuvir and GS-331007 AUC (exposure) | Recommendation |
|---|---|---|
| Darunavir/r | SOF increased 34%; GS-331007 – no effect | No dose adjustment |
| Rilpivirine | No effect on SOF or GS-331007 | No dose adjustment |
| Efavirenz | No effect on SOF or GS-331007 | No dose adjustment |
| Raltegravir | No effect on SOF or GS-331007: RAL decreased 27% | No dose adjustment |
| Tenofovir | No effect on SOF or GS-331007 | No dose adjustment |

Mathias A 14th Int Workshop on Clin Pharm of HIV Ther Session 5; Kirby B et al 63rd AASLD 2012; Abs 1877. ; Sofosbuvir USPI 2013

**Table 15. Potentially Significant Drug Interaction**

| Concomitant Drug Class: Drug Name | Clinical Comment |
|---|---|
| **Anti-convulsants:**<br>Carbamazepine<br>Phenytoin<br>Phenobarbital<br>Oxcarbazepine | Co-administration of SOF with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended. |
| **Anti-mycobacterials:**<br>Rifampin<br>Rifabutin<br>Rifapentine | Co-administration of SOF with rifabutin or rifapentine is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended.<br><br>SOF should not be used with rifampin, a potent intestinal Pgp inducer. |
| **Anti-retrovirals:**<br>Tipranavir/ritonavir | Co-administration of SOF with ritonavir-boosted tipranavir is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended. |
| **Herbal Supplements:**<br>St John's Wort | SOF should not be used with St John's Wort, a potent intestinal Pgp inducer. |

↓ = decrease; Pgp = p-glycoprotein; SOF = sofosbuvir

Sofosbuvir, Briefing Document, FDA

# DAAs in Development

| Drug | CYP Activity | Transporters | Interaction Potential |
|---|---|---|---|
| **Ledipasvir** | ▪ Little metabolism<br>▪ Not Inhibitor of CYP or UGT<br>▪ Not Inducer of CYP or UGT | ▪ P-gp substrate (likely)<br>▪ Inhibition of intestinal P-gp (weak)<br>▪ Inhibition of OATP1B1/3 (weak) | ▪ **Weak** |

*Eley T et al, 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-13; Eley T et al, 2011, 62nd AASLD Abs 381; Eley T et al 2012, 7th Int Workshop on Clin Pharm of Hep Ther; Abs O-4; Kirby B et al 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-20; Mathias A, 14th Int Workshop on Clin Pharm of HIV Ther, Session 5*

German, AASLD 2014

## 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]

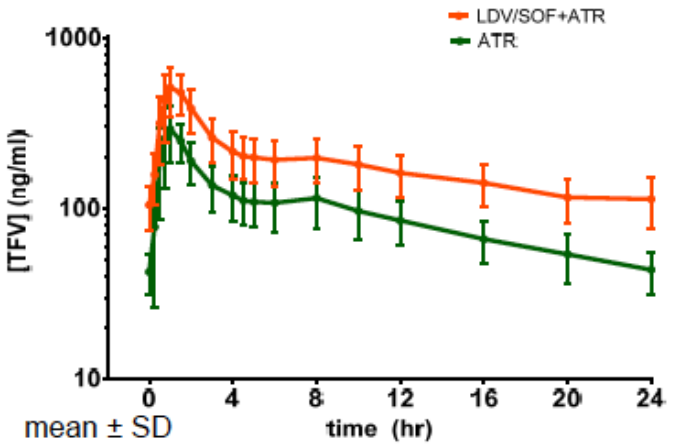
| Object | Perpetrator | AUC | $C_{max}$ |
|---|---|---|---|
| Pravastatin | LDV* | ↑ 168% | ↑ 166% |
| Rosuvastatin | | ↑ 699% | ↑ 1670% |

*LDV administered in combination with VDV and TGV.

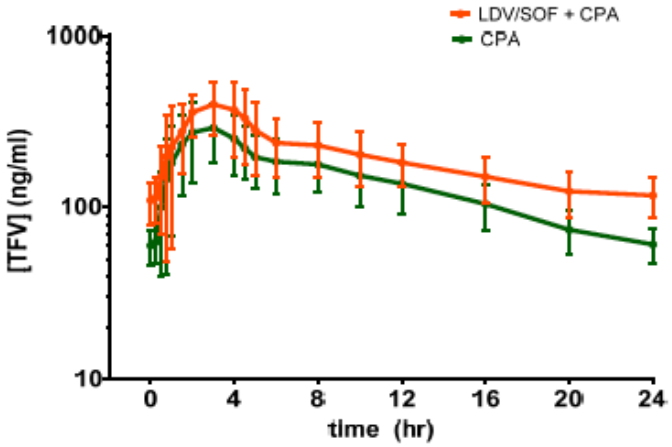
- VDV is a potent OATP inhibitor; LDV is a weak OATP inhibitor
- SOF and GS-331007 are not OATP inhibitors
- LDV/SOF may be administered with OATP substrates

- 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

# Effect of LDV/SOF on TFV (ATR or CPA)




mean ± SD




| TFV PK Parameter | Mean (%CV) | | GMR% (90% CI): LDV/SOF + ARV vs ARV | |
|---|---|---|---|---|
| | LDV/SOF + ATR | LDV/SOF + CPA | ATR | CPA |
| $AUC_{tau}$ (ng·h/mL) | 4400 (27.1) | 4780 (28.6) | 198 (177, 223) | 140 (131, 150) |
| $C_{max}$ (ng/mL) | 527 (29.9) | 490 (24.1) | 179 (156, 204) | 132 (125, 139) |
| $C_{tau}$ (ng/mL) | 113 (33.0) | 118 (26.4) | 263 (237, 297) | 191 (174, 210) |

Data presented to 3 significant figures; LDV/SOF + ATR: n=15; ATR: n=17; LDV/SOF + CPA: n=14; CPA: n=14.

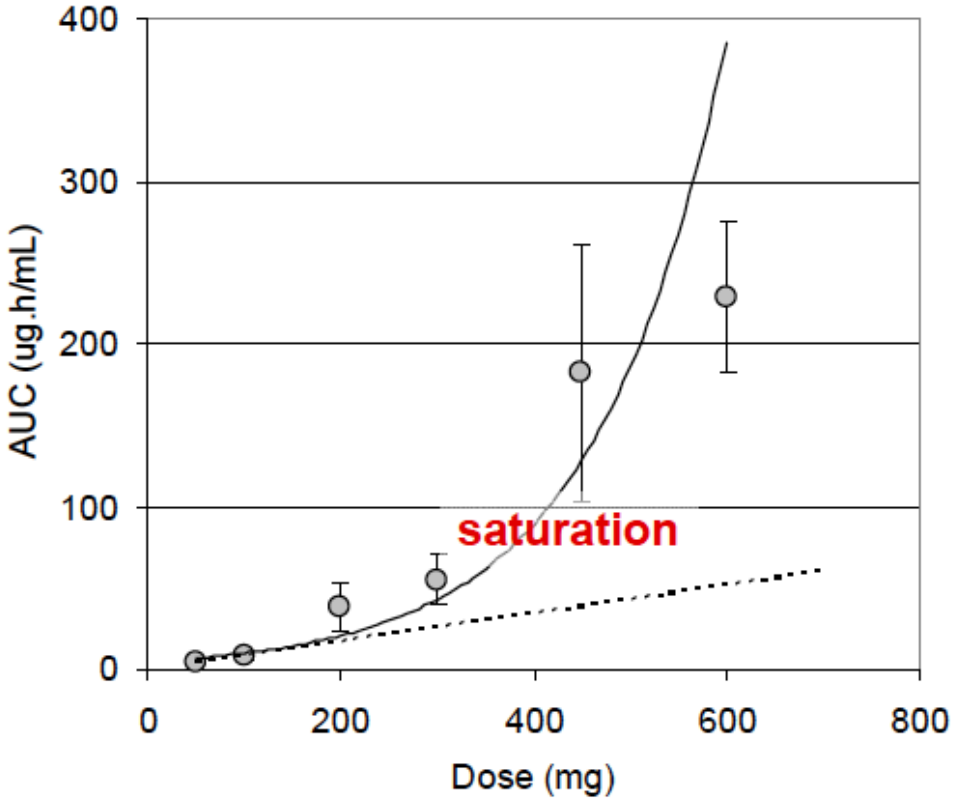
- LDV/SOF increased TFV exposure
  - Similar **absolute** TFV exposures (within ATR or CPA) with LDV/SOF
    - TFV exposures in LDV/SOF + NNRTI-based regimens are similar to those with boosted HIV PIs
  - Lack of marked changes in TFV $Cl_{renal}$ (data on file)

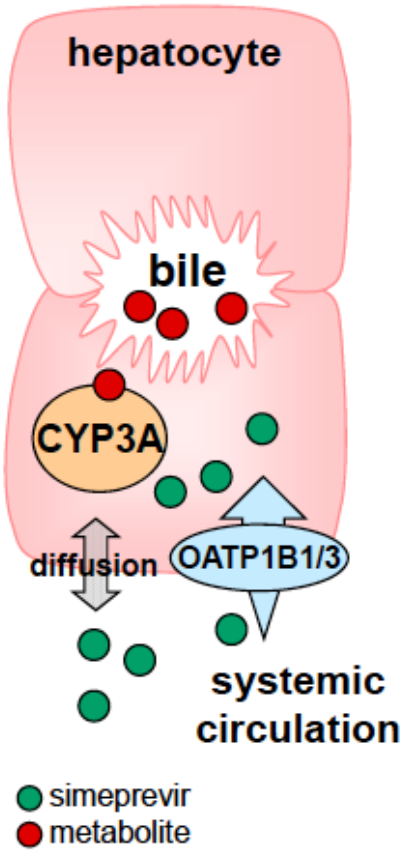
| DAA | Substrate | Effect | Clinical DDI extent | Comments |
|---|---|---|---|---|
| Simeprevir | CYP3A4<br>P-gp | Inhibits OATP1B1 and multi-drug resistant protein 2<br>Inhibits gut CYP3A4 and P-gp | Moderate | Bile elimination |
| Paritaprevir/r | CYP3A4<br>P-gp and OATP1B1/3 | Inhibits liver CYP3A4<br>Inhibits gut P-gp, BCRP<br>Inhibits OATP1B1/3 | Significant | Efavirenz and rilpivirine contraindicated<br>Hyperbilirubinemia |
| Sofosbuvir | Cathepsin A, esterases and kinases<br>P-gp and BCRP | Inhibits gut P-gp | Low | Urine elimination (80%) and bile (14%) |
| Dasabuvir | CYP2C8, 3A4 and 2D6<br>P-gp and BCRP | Inhibits UGT1A1<br>Inhibits OATP1B1 | Significant | |
| Daclatasvir | CYP3A4 and P-gp | Inhibits OATP1B1/3 and P-gp | Moderate | Increases statin exposure<br>Darunavir/r increases daclatasvir exposure |
| Ledipasvir | P-gp and BCRP | Inhibits gut P-gp and BCRP<br>Inhibits OATP1B1/3 | Low | Increases statin exposure |
| Ombitasvir | CYP3A4<br>P-gp and BCRP | Inhibits CYP2C8 and UGT1A1 | Significant | |

BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

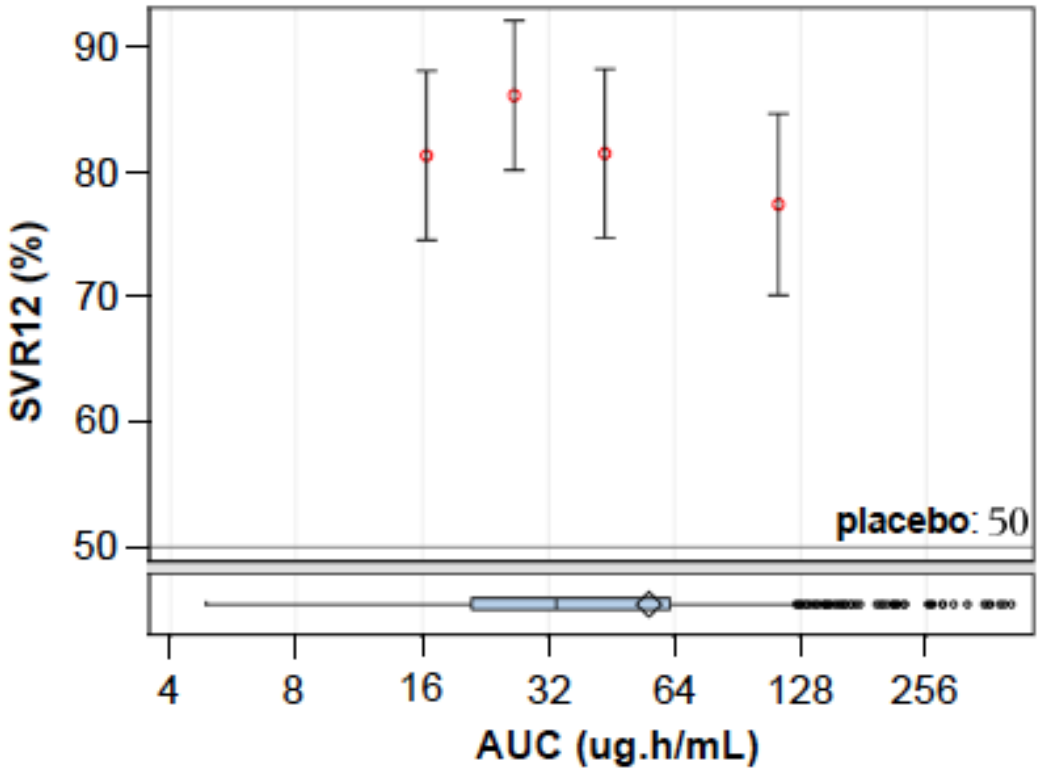
# Simeprevir Exhibits Non-Linear Pharmacokinetics



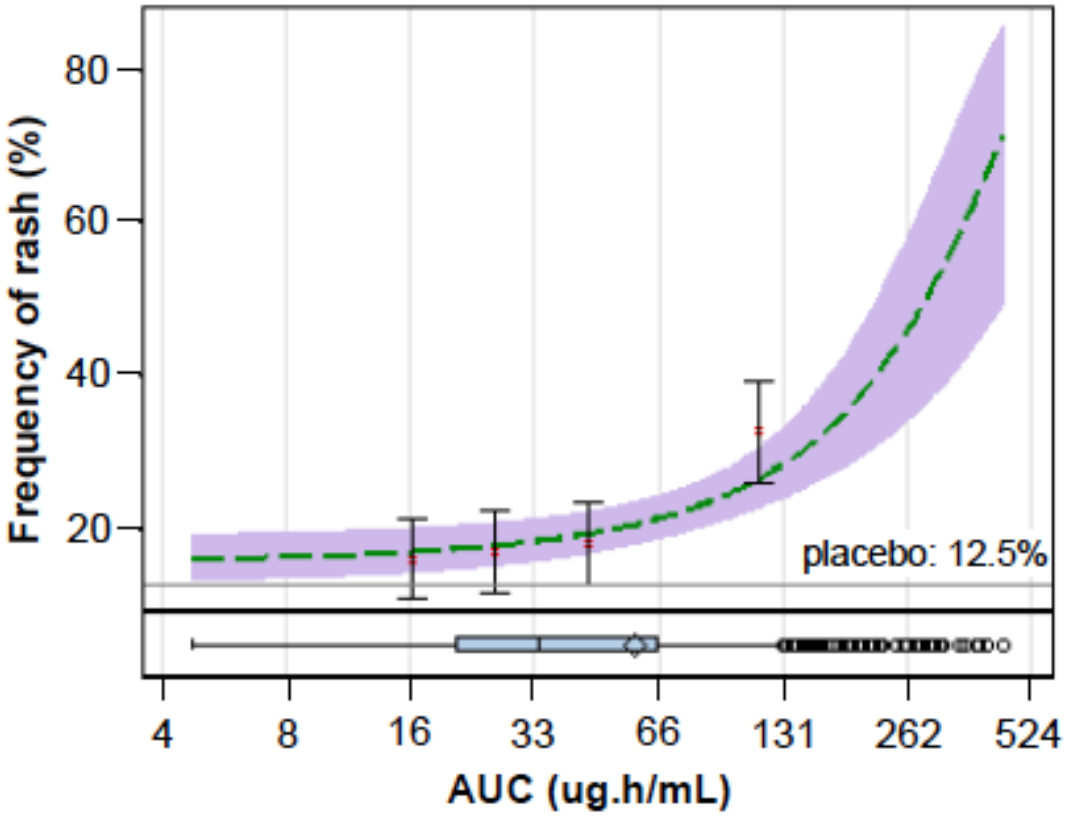

Trial C101 (healthy subjects)

# No Correlation Between Efficacy (SVR12) and Exposures Achieved with 150 mg QD




Phase 3 trials (C208, C216)

# An Increased Incidence of Rash was Associated with Higher Exposures in Phase 3

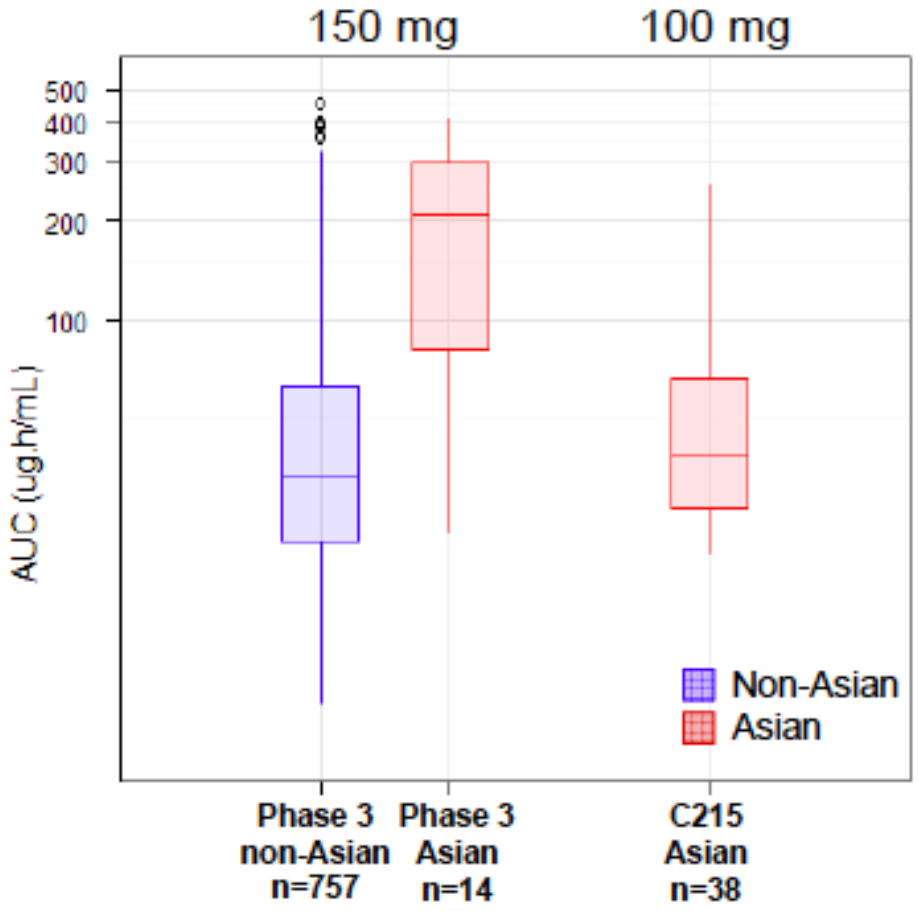



Similar relationships between exposures and:

- photosensitivity
- pruritus
- dyspnea
- increased bilirubin

Phase 3 trials (C208, C216, HPC3007)

# Systemic Exposures were Higher in Asian Patients in Phase 3 trials



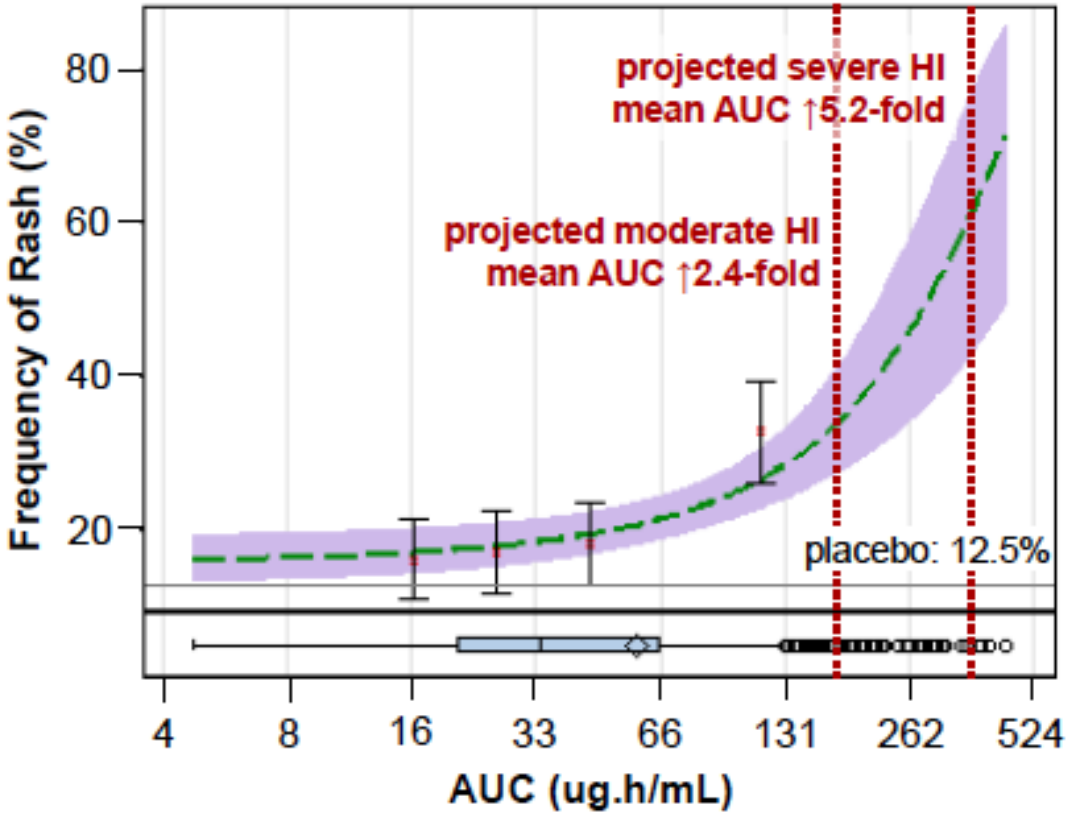

**Relative to Caucasian subjects, Asian subjects have:**

**smaller liver**
**less CYP3A**
**less OATP1B1**

**slower clearance**
**higher exposure**

Phase 3 trials (C208, C216, HPC3007); Yang et al. 2012, Tomita et al. 2013

# HCV-Uninfected Subjects with Moderate or Severe Hepatic Impairment had Higher Exposures Compared to Healthy Controls




- PegIFN is contraindicated in Child-Pugh class B or C
- Simeprevir PK will be evaluated in patients with moderate or severe hepatic impairment during ongoing IFN-free development

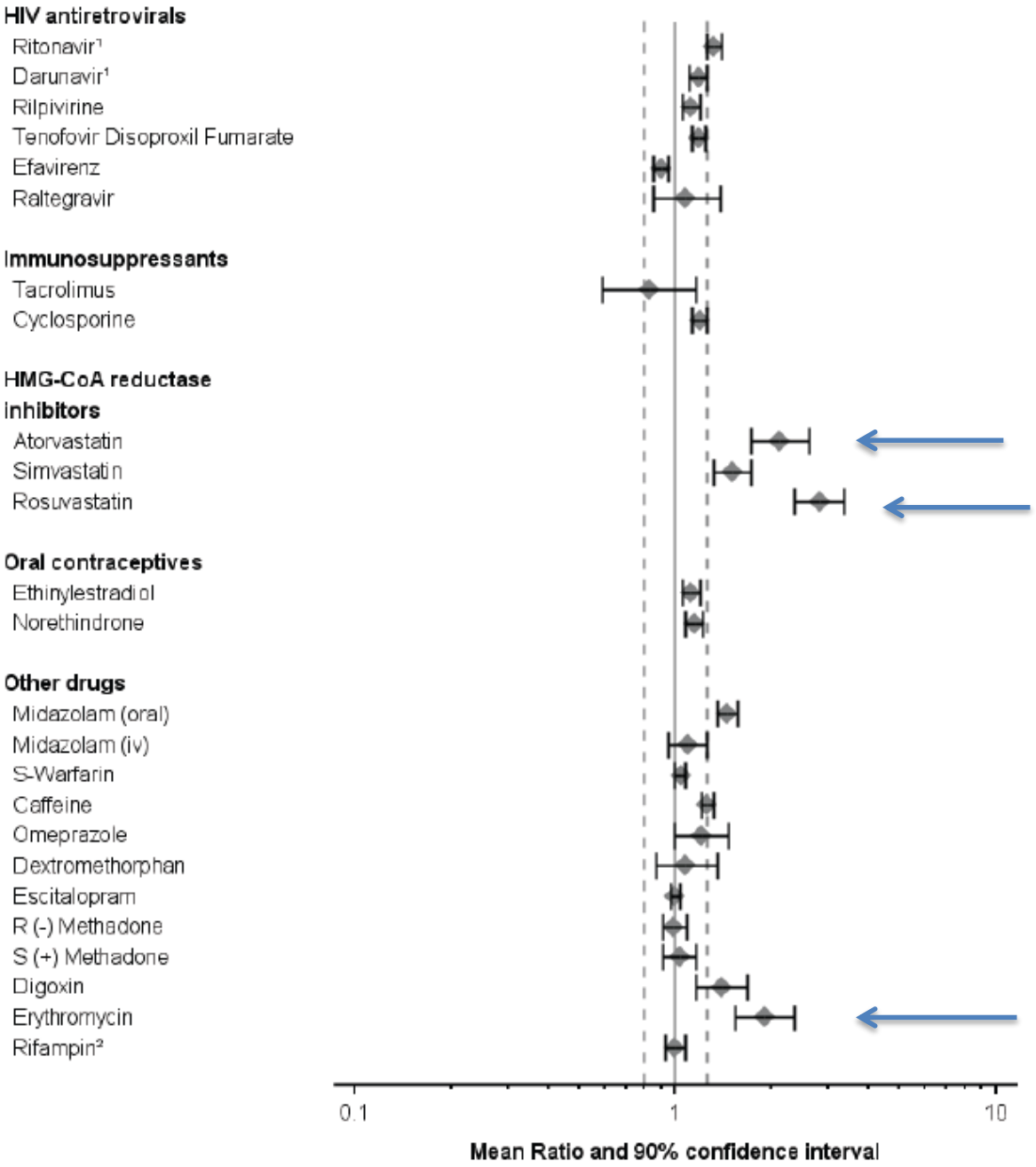
Phase 3 trials (C208, C216, HPC3007)

# Effect of ARVs on Simeprevir: *Victim*

| Drug | Effect on Simeprevir AUC (exposure) | Mechanism/ *Recommendation* |
|---|---|---|
| Darunavir/r | 2.6-fold increase (DRV increased 18%) | RTV Inhibits CYP3A4<br>*Not recommended* |
| Rilpivirine | No effect | *No dose adjustment* |
| Efavirenz | 70% decrease | EFV induces CYP3A4<br>*Not recommended* |
| Raltegravir | 11% decrease | *No dose adjustment* |
| Tenofovir | 14% decrease (TFV increased 18%) | Intestine or renal transport<br>*No dose adjustment* |

Ouwerkerk-Mahadevan S et al, IDSA 2012; Abs 1618; Ouwerkerk-Mahadevan S et al, CROI 2012; Abs 49 ; Simeprevir (Olysio) USPI

**Figure 6: Effect of SMV Administration at 150 mg Once Daily on Exposure of Coadministered Drugs**




Simeprevir, FDA Advisory Commitee Briefing Document

**Prevalence of Drug-Drug Interactions upon Addition of Simeprevir- or Sofosbuvir-Containing Treatment to Medication Profiles of Patients with HIV and Hepatitis C Coinfection.**

Patel N et al. AIDS Res Human Retrovir 2014

- DDIs were present in 20% of the 335 included patients.
- After the addition of **SIM-containing therapy**, the frequency of DDIs significantly **increased to 88.4%** ($p<0.001$).
- After adding **SOF-containing therapy**, the prevalence of DDIs increased to 24.5% ($p<0.001$).
- Variables independently associated with DDIs after the addition of **SIM-containing** therapy were **NNRT**I regimen (prevalence ratio, PR: 1.62; 95% confidence interval, CI: 1.38-1.91, $p<0.001$), **PI regimen** (PR: 1.64; 95% CI: 1.40-1.93, $p<0.001$), and **≥7 non-HIV medications** (PR: 1.06; 95% CI: 1.00-1.14, $p=0.09$).

- *The prevalence of DDIs was significantly lower for SOF-containing HCV therapy within various types of ART regimens.*

# Worthy to get PK data in real life?

- ✓ Simeprevir:
- No DDI data with DTG, ATV/r, LPV/r, COBI, MVC
- overdosing in cirrhotic patients and/or HIV coinfected treated with PI/r
  - increase risk of rash/photosensitivity?
  - dose decrease in cirrhotics?

| DAA | Substrate | Effect | Clinical DDI extent | Comments |
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| Simeprevir | CYP3A4<br>P-gp | Inhibits OATP1B1 and multi-drug resistant protein 2<br>Inhibits gut CYP3A4 and P-gp | Moderate | Bile elimination |
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| Dasabuvir | CYP2C8, 3A4 and 2D6<br>P-gp and BCRP | Inhibits UGT1A1<br>Inhibits OATP1B1 | Significant | |
| Daclatasvir | CYP3A4 and P-gp | Inhibits OATP1B1/3 and P-gp | Moderate | Increases statin exposure<br>Darunavir/r increases daclatasvir exposure |
| Ledipasvir | P-gp and BCRP | Inhibits gut P-gp and BCRP<br>Inhibits OATP1B1/3 | Low | Increases statin exposure |
| Ombitasvir | CYP3A4<br>P-gp and BCRP | Inhibits CYP2C8 and UGT1A1 | Significant | |

BCRP: Breast cancer resistance protein; DDA: Direct-acting antivirals; DDI: Drug-drug interactions; MRP: Multidrug resistance protein; OATP: Organ anion transporter protein; P-gp: P glycoprotein; UGT: Uridin-glucoronil-transferase.

Soriano, Exp Opin Drug Met Toxicol 2014

# Daclatasvir DDIs - *victim*

| | | |
|---|---|---|
| CYP3A4 and/or Pgp INDUCERS - anti-HIV | EFV | Increase to 90 mg/day |
| CYP3A4 and/or Pgp INDUCERS - other than EFV | *Etravirine*, Carbamazepine, oxacarbazepine, phenobarbital, dexame St John's wort | Not recommended |
| CYP3A4 and/or Pgp INHIBITORS Anti-HIV | ATV/RTV **DRV/r and LPV/R** | Decrease to 30 mg/day **Standard dose*** |
| CYP3A4 and/or Pgp INHIBITORS other than anti-HIV | charithromycin, itraconazole, quinidine, ranolazine | Caution or decrease to 30 mg/day |

*** Daclatasvir AUC increase by 40% (DRV/r) and 15% (LPV/R)- HEP DART meeting Dec 2014**

# Daclatasvir DDIs - *perpetrator*

- ✓ No effect of gastric acid modifiers, midazolam or oral contraceptives
- ✓ Caution with rosuvastatin (increase of AUC by 58%%)

*Bifano M et al, 2013, 8th Int Workshop on Clin Pharm of Hep Ther, Abs O-15; Bifano M et al AVT 2014; In Press; Bifano M et al 2013; EASL; Abs 794.*

# Worthy to get PK data in real life?

- ✓ **Simeprevir**:
- No DDI data with DTG, ATV/r, LPV/r, COBI, MVC
- overdosing in cirrhotic patients and/or HIV coinfected treated with PI/r
  - increase risk of rash/photosensitivity?
  - dose decrease in cirrhotics?

- ✓ **Daclatasvir**
- No DDIs data with ETV, DTG, COBI, MVC
- HIV-coinfected with dose reduction (ATV, COBI): underdosing?

DDIs of daclatasvir have been evaluated in healthy volunteeers

+

PK exposure was shown to be **lower in HCV+** as compared to healthy volunteers

+

Pk exposure was shown to be **lower in cirrhotics patients (**HCV-) as compared to heallthy volunteers (but unbound fraction equal)

+

=

- HIV/HCV cirrhotic,
- ATV/r or COBI-containing HAART
- Daclatasvir dose reduction (30 mg OD)

**Magnitude of DDI and drug exposure are not easy to predict**

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## Modelling clinical data shows active tissue concentration of daclatasvir is 10-fold lower than its plasma concentration

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# DAAs in Development

| Drug | CYP Activity | Transporters | Interaction Potential |
|---|---|---|---|
| **Asunaprevir** | ▪ CYP3A4 substrate<br>▪ Inducer of CYP3A4 (weak)<br>▪ Inhibition of CYP2D6 (weak) | ▪ P-gp, OATP1B1/3 substrate<br>▪ Inhibition of P-gp (weak), OATP1B1/3 | ▪ **Moderate** |

*Eley T et al, 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-13; Eley T et al, 2011, 62nd AASLD Abs 381; Eley T et al 2012, 7th Int Workshop on Clin Pharm of Hep Ther; Abs O-4; Kirby B et al 2013, 8th Int Workshop on Clin Pharm of Hep Ther; Abs O-20; Mathias A, 14th Int Workshop on Clin Pharm of HIV Ther, Session 5*

## DRUG INTERACTIONS WITH ABBVIE'S 3D REGIMEN (ABT450/RITONAVIR, OMBITASVIR AND DASABUVIR

| | ABT-450/r | Ombitasvir (ABT-267) | Dasabuvir (ABT-333) |
|---|---|---|---|
| Pharmacology | NS3/4A protease inhibitor | NS5A inhibitor | NS5B non-nucleoside inhibitor |
| Adult Dose | *Investigational*: 150 mg once daily with ritonavir 100 mg once daily<br><br>Co-formulated with ritonavir and ombitasvir as 150/100/25 mg tablet. | *Investigational*: 25 mg once daily<br><br>Coformulated with ABT-450 and ritonavir (150 mg ABT450, 100 mg ritonavir, 25 mg ombitasvir fixed dose tablet). | *Investigational*: 400 mg BID |
| Impact of Food | In healthy subjects, ABT-450 Cmax, and AUC were 11 to 19% higher under non-fasting conditions compared to fasting. ABT-450/r can be given with or without food.[1] | | |
| Kinetic Characteristics | Substrate of 3A4, P-gp, OATP1B1. Inhibits CYP2C8, UGT1A1, OATP1B1 and OATP1B3 | Substrate of 3A4, P-gp. Inhibits CYP2C8, UGT1A1. | Substrate of CYP2C8>3A4, 2D6, P-gp. Inhibits UGT1A1, OATP1B1. |

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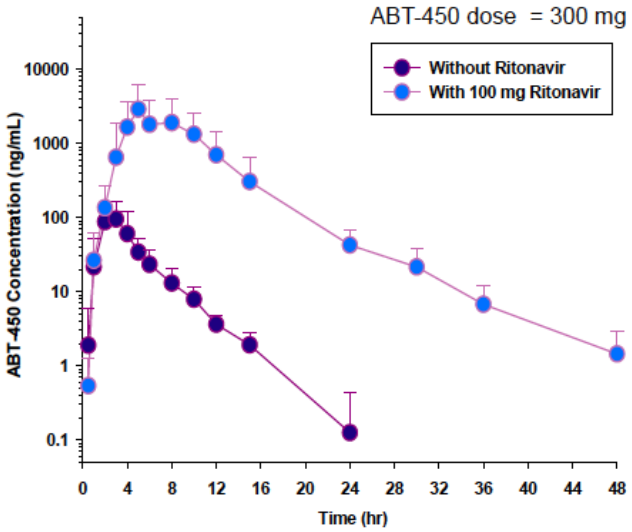
# Why is ABT-450 Dosed with Ritonavir?




| | |
|---|---|
| $C_{max}$ | ↑ 28-fold |
| AUC | ↑ 48-fold |
| $C_{12}$ | ↑ 200-fold |
| $C_{24}$ | ↑ 340-fold |
| $t_{½}$ | ↑ from 3 hours to 5 hours |

• Significant pharmacokinetic boosting allows for QD administration at lower ABT-450 doses while potentially improving the resistance profile.

•Changes in ABT-267 and ABT-333 exposures were ≤ ~50% when dosed with ABT-450 + ritonavir.

| DDI Study of 3D Regimen with | Effect of HIV PI on $C_{max}$ and AUC of 3D Regimen | Effect of 3D Regimen on $C_{max}$, AUC and $C_{trough}$ of HIV PI |
|---|---|---|
| ATV + RTV QD ✓ | ABT-450 ≤ 94% ↑ ; ombitasvir ≤ 23% ↓ ; dasabuvir ↔ | ATV ↔ |
| DRV + RTV QD ✓ | ABT-450 ≤ 54% ↑; ombitasvir ↔ ; dasabuvir ↔ | DRV $C_{max}$ and AUC ≤ 24% ↓ and $C_{trough}$ 48% ↓ |
| DRV + RTV BID ✓ | ABT-450 ≤ 41% ↓; ombitasvir ≤ 27% ↓ ; dasabuvir ≤ 27% ↓ | DRV $C_{max}$ and AUC ↔ and $C_{trough}$ 43% ↓ |
| LPV/r BID ✗ | ABT-450 ≤ 117% ↑ ; ombitasvir ↔ ; dasabuvir ↔ | LPV ↔ |

| DDI Study of 3D Regimen with | Effect of HIV-1 ARV Drugs on $C_{max}$ and AUC of 3D Regimen | Effect of 3D regimen on $C_{max}$, AUC and $C_{trough}$ HIV-1 ARV Drugs |
|---|---|---|
| FTC + TDF ✓ | ABT-450 ≤ 32% ↓; ombitasvir ↔ ; dasabuvir ↔ | FTC ↔; TDF $C_{max}$ and AUC ↔ , $C_{trough}$ 24% ↑ |
| RAL ✓ | ABT-450 ↔ ; ombitasvir ↔ ; dasabuvir ↔ | RAL ≤ 134% ↑ |
| RPV ✗ | ABT-450 ≤ 30% ↑ ; ombitasvir ↔ ; dasabuvir ↔ | RPV $C_{max}$ 155% ↑ , AUC 225% ↑ and $C_{trough}$ 262% ↑ |

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# MK-5172 e MK-8742

**DRUG INTERACTIONS WITH MK-5172 AND MK-8742**

| | **MK-5172 (Merck)** | **MK-8742 (Merck)** |
|---|---|---|
| Pharmacology | NS3/4A protease inhibitor | NS5A inhibitor |
| Adult Dose | *Investigational*: 100 mg once daily | *Investigational:* 50 mg once daily |
| Kinetic Characteristics | Substrate of CYP3A4, P-gp and OATP1B1.[1]<br><br>Inhibitor of CYP2C8, 3A4 (weak), UGT1A1 (weak) and possibly BCRP. | Substrate of CYP3A4, P-glycoprotein (P-gp) and the organic anion-transporting polypeptide (OATP) in vitro. No age effect observed in young (22-45 yrs) vs elderly (65-78 yrs) males; ~33% higher AUC in elderly female vs male subjects after adjusting for body weight.[2] |

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# Worthy to get PK data in real life?

- ✓ **Simeprevir**:
- No DDI data with DTG, ATV/r, LPV/r, COBI, MVC
- overdosing in cirrhotic patients and/or HIV coinfected treated with PI/r
  - increase risk of rash/photosensitivity?
  - dose decrease in cirrhotics?

- ✓ **Daclatasvir**
- No DDIs data with ETV, DTG, COBI, MVC
- HIV-coinfected with dose reduction (ATV, COBI): underdosing?

- ✓ **Asunaprevir, 3D –drugs, MK 5172 and 8742**
- Lack of DDI data with COBI, DTG, MVC and many not-HIV drugs
- PK variability (demographics, genetics, clinical stages)


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