Drug Interactions Between the Anti-HCV Regimen Ledipasvir/Sofosbuvir and Antiretrovirals

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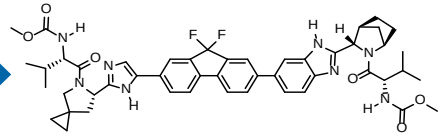
Disclosures

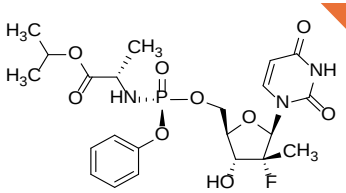
- I am an employee of Gilead Sciences, Inc.

Background

- **Ledipasvir**
  - Once-daily, oral, 90-mg NS5A inhibitor
- **Sofosbuvir**
  - Once-daily, oral, 400-mg NS5B inhibitor
  - GS-331007, predominant circulating metabolite

LDV
NS5A
inhibitor





SOF
nucleotide
polymerase
inhibitor

- **Ledipasvir/Sofosbuvir FDC**
  - Once-daily, oral, fixed-dose (90/400 mg) combination tablet for chronic hepatitis C for genotype 1 or 4*

LDV
NS5A
inhibitor

SOF
nucleotide
polymerase
inhibitor

* FDC, fixed-dose combination; genotype 4: LDV/SOF SPC.

Preclinical Profile

- LDV/SOF exhibits limited potential for clinically significant drug-drug interactions

Transporters/Enzymes	Substrate	Inhibitor
P-gp/BCRP	LDV SOF (not metabolite GS-331007)	LDV
Slow oxidative metabolism (oxidative pathway)	LDV	

- LDV or SOF are not substrates or clinically relevant inhibitors of OCT1, OATP1B1, OATP1B3 and BSEP or OAT1, OAT3 or OCT2
- GS-331007 is not a substrate for OAT1, OAT2, or OCT2
- LDV or SOF are not turned over by major CYP isoforms in vitro
- LDV, SOF and GS-331007 are not substrates or clinically relevant inhibitors of UGT1A1

LDV/SOF in HCV/HIV-Coinfection

HCV/HIV DDI Program

LDV or SOF Single-Agent DDI

NNRTI: RPV

InSTI: RAL

PI: DRV/r

NNRTI-based regimen: EFV/FTC/TDF

	Tenofovir (TFV)
LDV	AUC_{tau}: ↑38%; C_{tau}: ↑55%
SOF	C_{max}: ↑25%
FDC	• In vitro: SOF and LDV increase tenofovir DF absorption • Mediated by inhibition of efflux transporters (ie, Pgp, BCRP) by LDV

LDV/SOF in HCV/HIV Coinfection

HCV/HIV DDI Program

	LDV or SOF Single-Agent DDI
NNRTI	RPV
InSTI	RAL
PI	DRV/r
NNRTI-based regimens	EFV/FTC/TDF
PI-based regimens	
InSTI-based regimens	

LDV/SOF in HCV/HIV Coinfection

HCV/HIV DDI Program

	LDV or SOF Single-Agent DDI	LDV/SOF-regimen Based DDIs
NNRTI	RPV	ABC/3TC
InSTI	RAL	
PI	DRV/r	
NNRTI-based regimens	EFV/FTC/TDF	EFV/FTC/TDF FTC/RPV/TDF
PI-based regimens		ATV/r+FTC/TDF DRV/r+FTC/TDF
InSTI-based regimens		E/C/F/TAF DTG+FTC/TDF

Effect of HIV ARVs on LDV/SOF

NNRTI-Containing Regimens

Perpetrator	Object	AUC	C_{max}
EFV/FTC/TDF	SOF/GS-331007	↔	↔
	LDV	↓ 34%	↓ 34%
FTC/RPV/TDF	SOF/GS-331007/LDV	↔	↔
ABC/3TC	SOF/GS-331007/LDV	↔	↔

- No clinically relevant change in LDV/SOF with EFV/FTC/TDF, FTC/RPV/TDF and ABC/3TC

German et al, IWCPHHT 2014

Effect of HIV ARVs on LDV/SOF

Integrase-Containing Regimens

Perpetrator	Object	AUC	C_{max}	C_{tau}
RAL	SOF/GS-331007/LDV	↔	↔	↔
DTG + FTC + TDF	SOF/GS-331007/LDV	↔	↔	↔
EVG/COBI/FTC/TAF	SOF	↑47%	↑28%	NA
	GS-331007	↑48%	↔	↑66%
	LDV	↑79%	↑65%	↑93%

- No clinically relevant change with RAL and DTG + FTC/TDF

Kirby et al, AASLD 2012; German et al, IWCPHHT 2014; Garrison et al, IWCPHHT 2015

Effect of HIV ARVs on LDV/SOF

Protease Inhibitor-Containing Regimens

Perpetrator*	Object	AUC	C_{max}	C_{tau}
ATV/RTV+FTC/TDF	SOF	↔	↔	NA
	GS-331007	↔	↔	↑42%
	LDV	↑96%	↑68%	↑118%
DRV/RTV+FTC/TDF	SOF	↓ 27%	↓ 37%	NA
	GS-331007	↔	↔	↔
	LDV	↔	↔	↔

*Similar results when LDV/SOF and ATV/RTV+FTC/TDF or DRV/RTV+FTC/TDF were administered simultaneously or following a 12-hour stagger.

German et al, CROI 2015

Effect of LDV/SOF on HIV ARVs

NNRTI-Containing Regimens

Perpetrator	Object	AUC	C_{max}	C_{tau}
LDV/SOF	EFV	↔	↔	↔
	FTC	↔	↔	↔
	TFV	↑98%	↑79%	↑163%
LDV/SOF	RPV	↔	↔	↔
	FTC	↔	↔	↔
	TFV	↑40%	↔	↑91%
LDV/SOF	ABC	↔	↔	↔
	3TC	↔	↔	↔

- TFV exposure increases with NNRTI-containing regimens

German et al, IWCPHHT 2014

Effect of LDV/SOF on HIV ARVs

Integrase-Containing Regimens

Perpetrator	Object	AUC	C_{max}	C_{tau}
LDV	RAL	↓ 15%	↓ 18%	↑15%
SOF		↓ 27%	↓ 43%	↔
LDV/SOF	DTG	↔	↔	↔
	FTC	↔	↔	↔
	TFV	↑65%	↑61%	↑115%
LDV/SOF	EVG	↔	↔	↑46%
	COBI	↑53%	↔	↑225%
	FTC	↔	↔	↔
	TAF	↔	↔	NA
	TFV	↔	↔	↔

- TFV, administered as TDF and not TAF, increases with LDV/SOF

Kirby et al, AASLD 2012; German et al, IWCPHHT 2014; Garrison et al, IWCPHHT 2015

Effect of LDV/SOF on HIV ARVs

Protease Inhibitor-Containing Regimens

Perpetrator	Object*	AUC	C_{max}	C_{tau}
LDV/SOF	ATV	↔	↔	↑63%
	RTV	↔	↔	↑45%
	FTC	↔	↔	↔
	TFV	↔	↑47%	↑47%
LDV/SOF	DRV	↔	↔	↔
	RTV	↔	↔	↑48%
	FTC	↔	↔	↔
	TFV	↑50%	↑64%	↑59%

*Similar results observed when LDV/SOF and ATV/RTV+FTC/TDF or DRV/RTV+FTC/TDF were administered simultaneously or following a 12-hour stagger.

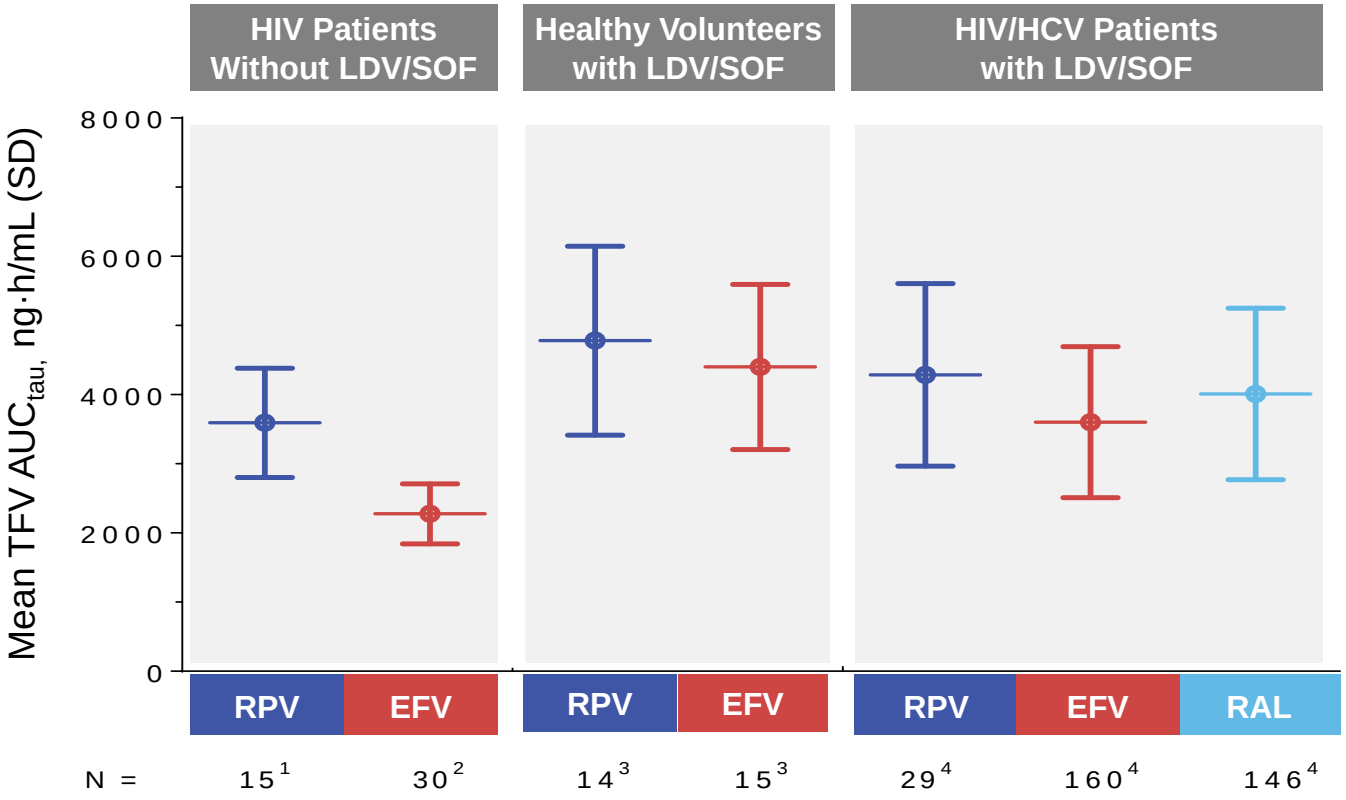
German et al, CROI 2015

LDV/SOF and ARV Regimen-based DDIs

Questions for investigation

- Understand TFV exposure within an
  - NNRTI Regimen?
  - Boosted-PI regimen?
    - TFV exposure is higher within boosted PI-regimens relative to TFV within NNRTI-based regimens

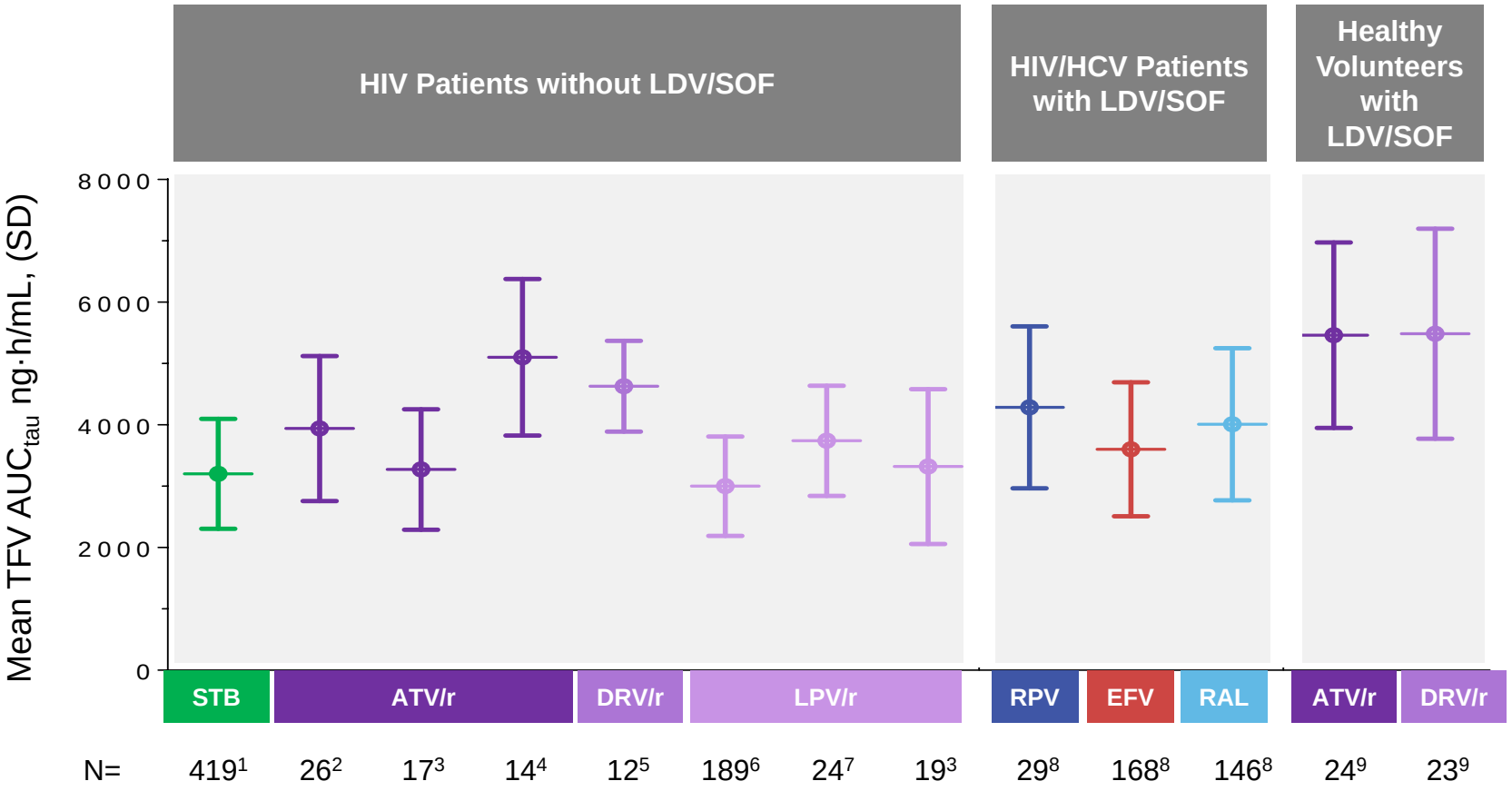
Tenofovir (TFV) PK With ARV Regimens With or Without LDV/SOF



- Lack of marked changes in TFV renal clearance in healthy volunteers

1. Hoetelmans et al, IAS 2005; 2. Gilead Study GS-US-236-0120; 3. German et al, IWCPHT 2014; 4. Gilead Study GS-US-337-0115 (ION-4).

Tenofovir (TFV) PK With ARV Regimens With or Without LDV/SOF



1. Ramanathan et al, IWCPHT 2013; 2. Gilead Study GS-US-216-0114; 3. Zhu et al, 9th IWCPHT. 2008. #023 (ATV+RTV & LPV/r); 4. Agarwala S, et al. 6th IWCPHT 2005. Abstr 16. (ATV+RTV); 5. Hoetelmans RMW, et al. *BJCP.* 2007;64(5):655-61 (DRV+RTV); 6. Jullien et al, AAC 2005;49; 7. Kearney et al, JAIDS 2006;43; 8. Gilead Study GS-US-337-0115 (ION-4); 9. German et al, CROI 2015.

Recommendations for Use

- Use of LDV/SOF is permitted in patients with HCV/HIV coinfection
- LDV/SOF has been shown to increase tenofovir exposure

Patients receiving tenofovir DF and LDV/SOF concomitantly should be monitored for adverse reactions associated with tenofovir DF.

- Refer to the tenofovir DF-containing product's prescribing information for recommendations on renal monitoring

Acknowledgments

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