Antiretroviral and Directly Acting Antiviral Drug Metabolism and Transporter Characteristics (Summary)

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
Tenofovir alafenamide[1]	P-gp, BCRP; minimal metabolism via 3A4	3A4 (weak – in vitro only; not an inhibitor in vivo). Does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or UGT1A.	Not an inducer of 3A4 in vivo.		
HIV Protease Inhibitors					
atazanavir[2]	Mainly CYP3A P-gp, MRP1	3A4, UGT1A1 >>2C8 (weak)* *Caution when unboosted atazanavir is coadministered with 2C8 substrates with narrow therapeutic indices (e.g., paclitaxel, repaglinide); clinically significant interactions with 2C8 substrates are not expected when atazanavir is boosted with ritonavir.		P-gp, MRP1, OATP1B1, OATP1B3, BCRP	
darunavir[3]	Mainly CYP3A, P-gp	CYP3A4		BCRP, OATP1B1[4]	
fosamprenavir[5], indinavir[6], lopinavir/ritonavir[7], saquinavir[8]	Mainly CYP3A, P-gp, MRP1 (LPV, SQV)	CYP3A4 (saquinavir is a weak inhibitor)		P-gp (LPV) OATP1B1, OATP1B3 (LPV, SQV)	
nelfinavir[9]	Mainly CYP3A, 2C19, P-gp	CYP3A4	UGT, 2B6, 2C8, 2C9/19[10]		
tipranavir[11]	Mainly CYP3A, P-gp	2D6[12]	CYP3A4 (potent)[11], UGT	OATP1B1	P-gp
PK Boosters					
ritonavir[13]	CYP3A4, P-gp, MRP1	CYP3A4 (potent)> >2D6* >2C9 >2C19 >2A6 >1A2>2E1. *negligible effect at boosting doses[7]	UGT, CYP1A2, CYP2C9/19, 2B6 (inhibits in vitro,[14] but induces in vivo[15])	P-gp, OATP1B1, OATP1B3, BCRP, OATP2B1, OCT2, MATE1[16]	
cobicistat[17]	CYP3A, 2D6 (minor)	CYP3A, CYP2D6		P-gp, BCRP, OATP1B1 and OATP1B3, MATE1[16, 18]	
HIV NNRTIs					
delavirdine[19]	CYP3A4	3A4 (potent)			
doravirine (MK-1439)	CYP3A4/5. Not a substrate of OATP1B1	Does not inhibit CYP3A4, 2D6, 1A2, 2B6, 2C8/9,	Unlikely to induce CYP enzymes to a clinically relevant extent.	Not anticipated to inhibit OATP1B1/3, OAT1, OAT3, OCT2,	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
		2C19, or UGT		BCRP in a clinically relevant manner.	
efavirenz[20]	CYP3A4, 2B6 (minor)	2C9, 2C19[20] (? Clinical significance).	3A4 (potent), 2B6[21], UGT1A1[22]		
etravirine[23]	CYP3A4, CYP2C9, and CYP2C19	CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak)	3A4 (weak)		
nevirapine[24]	CYP3A4, 2B6 (minor)		3A4, 2B6 (potent)		
rilpivirine[25]	CYP3A4 (major); CYP2C19, 1A2, 2C8/9/10 (minor).		2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[26] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.	OCT2	
HIV INSTIs					
bictegravir (GS-9883)[27, 28]	UGT1A1, CYP3A4 (similar contribution)	Does not inhibit CYP including CYP3A4 or UGT1A1.	Does not induce CYP3A4 or UGT1A1.	OCT2 (less than dolutegravir), MATE1. Does not inhibit OATP1B1/3, OCT1, BSEP, OAT1/3.	
cabotegravir[29]	UGT1A1, UGT1A9 (minor). Substrate of P-gp, BCRP (high intrinsic membrane permeability limits impact of these transporters on intestinal absorption).	Does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 2D6. Weakly inhibits CYP3A4 and inhibits UGT1A3 (not clinically relevant).	Does not induce CYP1A2, 2B6 or 3A4.	OAT1/3. Does not inhibit P-gp, BCRP, BSEP, MRP2, OACT1, OATP1B1, OATP1B3.	
dolutegravir[30]	UGT1A1, CYP3A4 (10-15%); also a substrate of UGT1A3, UGT1A9, P-gp and BCRP in vitro. Not a substrate of OATP1B1, OATP1B3, or OCT1.		Does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.	OCT2, MATE1; also MATE2 but low potential to affect transport of MATE2 substrates.	
elvitegravir[31]	CYP3A4		CYP2C9 (modest)		

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
raltegravir[32]	UGT1A1	Raltegravir has no inhibitory or inductive potential in vitro.	Raltegravir has no inhibitory or inductive potential in vitro.		
HIV CCR5 INHIBITORS					
cenicriviroc[33]	CYP3A4, 2C8. Not a substrate of OATP1B1/B3 or OCT2.	Not a known CYP inhibitor.	Not a known CYP inducer.	P-gp Not an inhibitor of OATP1B1/B3 or OCT2.	
maraviroc[34]	CYP3A4, P-gp	Does not inhibit major CYP isozymes at clinically relevant concentrations.		P-gp (in gut; systemic effects unlikely).	
HIV ATTACHMENT INHIBITOR					
Fostemsavir (BMS 663068, prodrug of 626529)	CYP3A4 (partial)	Not anticipated to inhibit UGT1A1, 1A4, 1A9 or CYP450 enzymes.	No CYP3A4 induction.	Inhibitor of OATP1B3. Not anticipated to inhibit other transporters including OCT2, OAT1, OAT3, MATE1, MRP2, BSEP, NTCP and P-gp.	
HIV MATURATION INHIBITOR					
GSK2838232	CYP3A4	UGT1A4. Inhibits intestinal CYP3A4 (when administered as GSK 200 mg/ritonavir).	CYP3A4 (weak)	Inhibits intestinal P-gp, BCRP (when administered as GSK 200 mg/ritonavir).	
CO-FORMULATED/COMBINATION HCV REGIMENS					
Epclusa®					
velpatasvir[35-37] (NS5A inhibitor)	CYP3A4, 2C8, 2B6; OATP1B1, OATP1B3, P-gp, BCRP.	No inhibiting or inducing effects on P450.	No inhibiting or inducing effects on P450.	P-gp, OATP1B1, OATP1B3, BCRP (limited to intestinal efflux and hepatic uptake – clinically relevant interactions in systemic circulation not expected).	
sofosbuvir[38]	P-gp, BCRP.GS-	No inhibiting or inducing	No inhibiting or inducing	No inhibiting or	No inhibiting or

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	**Inducer**	**Inhibitor**	**Inducer**
(NS5B inhibitor)	331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure): not a P-gp substrate	effects on P450 and UGT1A1.	effects on P450 and UGT1A1.	inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.	inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.
Harvoni®					
ledipasvir[39] (NS5A inhibitor)	P-gp (likely)	Not an inhibitor or inducer of P450 or UGT.	Not an inhibitor or inducer of P450 or UGT.	Weak inhibitor of P-gp and BRCP (intestinal, not systemic). Likely a weak inhibitor of OATP1B1/1B3.	
sofosbuvir[38] (NS5B inhibitor)	P-gp, BCRP.GS-331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure): not a P-gp substrate.	No inhibiting or inducing effects on P450 and UGT1A1.	No inhibiting or inducing effects on P450 and UGT1A1.	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.
Maviret® (Mavyret® – US)[40]					
glecaprevir (ABT-493) (NS3/4A PI) pibrentasvir (ABT-530) (NS5A inhibitor)	P-gp and/or BCRP. OATP1B1/3 (glecaprevir). Minimal metabolism and primary biliary excretion, negligible renal excretion (<1%).	CYP1A2, 3A4 and UGT1A1 (weak); do not inhibit CYP2D6, 2C19, 2C9. Significant interactions with substrates of these enzymes are not expected.[41]		P-gp, BCRP, OATP1B1/3.	
Vosevi®					
sofosbuvir[38] (NS5B inhibitor)	P-gp, BCRP. GS-331007 (primary systemic nucleoside metabolite, accounts for >90% of systemic drug exposure): not a	No inhibiting or inducing effects on P450 and UGT1A1.	No inhibiting or inducing effects on P450 and UGT1A1.	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.	No inhibiting or inducing effects on P-gp, BCRP, OATP1B1, OATP1B3, OCT1, BSEP.

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
	P-gp substrate				
velpatasvir[35-37] (NS5A inhibitor)	CYP3A4, 2C8, 2B6; OATP1B1, OATP1B3, P-gp, BCRP.	No inhibiting or inducing effects on P450.	No inhibiting or inducing effects on P450.	P-gp, OATP1B1, OATP1B3, OATP2B1, BCRP (limited to intestinal efflux and hepatic uptake – clinically relevant interactions in systemic circulation not expected).	
voxilaprevir (GS-9857)[42, 43] (NS3/4A PI)	P-gp, BCRP, OATP1B1, OAT1B3. CYP3A4>>CYP1A2, 2C8.	Does not inhibit CYP or UGT1A1 enzymes.		P-gp, BCRP, OATP1B1, OATP1B3. Does not inhibit OCT1, OCT2, OAT1, OAT3 or MATE1.	
Zepatier®[44]					
elbasvir[45, 46] (NS5A inhibitor)	CYP3A4, P-glycoprotein (P-gp) and OATP in vitro.	Does not inhibit CYP3A4	Does not induce CYP1A2, 2B6 or 3A4.[44]	BCRP (intestinal)[44], P-gp (in vitro only; not expected to cause clinically significant interactions via P-gp inhibition at usual clinical doses)[47] Does not inhibit OATP1B[44]	
grazoprevir[46, 48] (NS3/4A PI)	CYP3A4, P-gp and OATP1B1	CYP2C8 (not clinically meaningful),[49] 3A4 (weak), UGT1A1 (weak)	Does not induce CYP1A2, 2B6 or 3A4.[44]	BCRP (intestinal)[44]. Does not inhibit OATP1B[44]	
Holkira Pak®[50, 51]					
paritaprevir (NS3/4A PI)	3A4, P-gp, OATP1B1, OATP1B3, BCRP.	UGT1A1 *(net effect of 3D is UGT1A1 inhibition)*[52]		OATP1B1 and OATP1B3; P-gp, BCRP (potential).	
ombitasvir (NS5A inhibitor)	3A4, P-gp, BCRP.	UGT1A1 *(net effect of 3D is UGT1A1 inhibition)*[52]			
dasabuvir (NS5B inhibitor)	CYP2C8>3A4, P-gp, BCRP.	UGT1A1 *(net effect of 3D is UGT1A1 inhibition)*[52]		BCRP, P-gp (potential)	
ritonavir[13]	CYP3A4, P-gp, MRP1	CYP3A4 (potent)> >2D6* >2C9 >2C19 >2A6 >1A2>2E1.	UGT, CYP1A2, CYP2C9/19, 2B6 (inhibits in vitro,[14] but	P-gp, OATP1B1, OATP1B3, BCRP, OATP2B1, OCT2	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	**Inducer**	**Inhibitor**	**Inducer**
		*negligible effect at boosting doses[7]	induces in vivo[15])		
Daclatasvir-TRIO					
asunaprevir (NS3 PI)[53,54]	CYP3A4, P-gp; OATP1B/2B1	CYP2D6 (moderate)	CYP3A4 (weak)	P-gp, OATP1B1/2B1 (weak)	
beclabuvir[55, 56] (NS5B inhibitor)	CYP3A4, P-gp; OATP1B1/1B3		CYP3A4 (weak-moderate); 46-50% ↓ midazolam AUC	P-gp	
daclatasvir[57] (NS5A inhibitor)	CYP3A4, P-gp, OCT1. (*inhibition of P-gp alone with no/minimal CYP3A4 inhibition not expected to significantly increase daclatasvir exposure)		CYP3A4 (weak; no meaningful effect on midazolam kinetics)	P-gp (weak-moderate), weak inhibitor of OATP1B1, OCT1, and BCRP.	
HCV NS5A INHIBITORS					
daclatasvir[57]	CYP3A4, P-gp, OCT1. (*inhibition of P-gp alone with no/minimal CYP3A4 inhibition not expected to significantly increase daclatasvir exposure)		CYP3A4 (weak; no meaningful effect on midazolam kinetics)	P-gp (weak-moderate), weak inhibitor of OATP1B1, OCT1, and BCRP.	
HCV NS3/4A PIs					
simeprevir	CYP3A4, P-gp, OATP1B1.	Mild inhibitor of intestinal (but not hepatic) CYP3A4, and 1A2.[58] No clinically relevant effects on CYP2C9, 2C19 and 2D6.[59]		P-gp, OATP1B1/3	

Key: BCRP = breast cancer resistance protein; CYP= Hepatic Cytochrome P450 isoenzyme; Substrate= route of hepatic elimination of that specific drug (specified by a specific cytochrome P450 isoenzyme); inducer = leads to more rapid clearance of substrates of a specific hepatic isoenzyme (lowers serum concentrations of the respective drug and may lead to decreased efficacy); inhibitor= leads to decreased clearance of substrates of a specific hepatic isoenzyme (increases serum concentrations of a respective drug and may lead to toxicity). OCT2 = renal organic cation transporter; P-gp= P-glycoprotein; UGT= Uridine diphosphate glucuronyltransferase.

Please note: This chart summarizes currently available data, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV and HCV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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