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

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
ANTIRETROVIRALS					
HIV Reverse Transcriptase Nucleotide Inhibitors (NRTIs)/Translocation Inhibitor (NRTTI)					
islatravir[1]	Does not interact with CYP enzymes.	Does not inhibit CYP enzymes in vitro.	Does not induce CYP enzymes in vitro.	Does not interact with renal or hepatic transporters.	
tenofovir alafenamide (TAF)[2]	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.		
tenofovir disoproxil fumarate (TDF)[3]	OAT1, MRP4[4]	Does not inhibit CYP3A4, 2D6, 2C9, 2E1. Inhibits CYP1A but likely not clinically significant.			
HIV Protease Inhibitors (PIs)					
atazanavir[5]	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[6]	Mainly CYP3A, P-gp	CYP3A4		BCRP, OATP1B1[7]	
fosamprenavir[8], indinavir[9], lopinavir/ritonavir[10], saquinavir[11]	Mainly CYP3A, P-gp, MRP1 (LPV, SQV)	CYP3A4 (saquinavir is a weak inhibitor)		P-gp (LPV) OATP1B1, OATP1B3 (LPV, SQV)	
nelfinavir[12]	Mainly CYP3A, 2C19, P-gp	CYP3A4	UGT, 2B6, 2C8, 2C9/19[13]		
tipranavir[14]	Mainly CYP3A, P-gp	2D6[15]	CYP3A4 (potent)[14], UGT	OATP1B1	P-gp
PK Boosters					
ritonavir[16]	CYP3A4, P-gp, MRP1	CYP3A4 (potent)> >2D6* >2C9 >2C19 >2A6 >1A2>2E1. *negligible effect at boosting doses[10]	UGT, CYP1A2, CYP2C9/19, 2B6 (inhibits in vitro,[17] but induces in vivo[18])	P-gp, OATP1B1, OATP1B3, BCRP, OATP2B1, OCT2, MATE1[19]	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
cobicistat[20]	CYP3A, 2D6 (minor)	CYP3A, CYP2D6		P-gp, BCRP, OATP1B1 and OATP1B3, MATE1[19, 21]	
HIV NNRTIs					
dapivirine *administered via vaginal ring with low systemic concentrations, reducing likelihood of clinically relevant DDIs[22]	CYP3A4/5>2B6, 2C19; UGT isoenzymes[23]		Does not induce CYP1A2 or CYP3A4/5 activity (in cultured human hepatocytes).[23]		
delavirdine[24]	CYP3A4	3A4 (potent)			
doravirine[25]	CYP3A4/5. Not a substrate of OATP1B1	Does not inhibit CYP3A4, 2D6, 1A2, 2B6, 2C8/9, 2C19, or UGT1A1.	Unlikely to induce CYP1A2, 2B6 or 3A4 enzymes to a clinically relevant extent.	Not likely to inhibit P-glycoprotein, OATP1B1/3, OAT1, OAT3, OCT2, MATE1, MATE2K, BCRP, BSEP.	
efavirenz[26]	CYP3A4, 2B6 (minor)	2C9, 2C19[26] (? Clinical significance).	3A4 (potent), 2B6[27], UGT1A1[28]		OATP1B1, MRP2[29]
etravirine[30]	CYP3A4, CYP2C9, and CYP2C19	CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak)	3A4 (weak)	P-gp (weak; 19% increase Cmax of digoxin)[31]	
nevirapine[32]	CYP3A4, 2B6 (minor)		3A4, 2B6 (potent)		
rilpivirine[33]	CYP3A4 (major); CYP2C19, 1A2, 2C8/9/10 (minor).		2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[34] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.	OCT2	
HIV INSTIs					
bictegravir[35, 36]	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.	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
cabotegravir[37, 38]	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 (10% ↑ midazolam AUC) and inhibits UGT1A3 (not clinically relevant).	Does not induce CYP1A2, 2B6 or 3A4.	OAT1/3 (weak; not anticipated to cause clinically significant drug interactions).[39] Does not inhibit P-gp, BCRP, BSEP, MRP2, MRP4, OCT1, OCT2, MATE1, OATP1B1, OATP1B3.	
dolutegravir[40]	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[41]	CYP3A4		CYP2C9 (modest)		
raltegravir[42]	UGT1A1	Raltegravir has no inhibitory or inductive potential in vitro.	Raltegravir has no inhibitory or inductive potential in vitro.		
HIV ATTACHMENT INHIBITOR					
fostemsavir (BMS 663068, prodrug of temsavir/626529)[43]	Esterases (36.1%), CYP3A4 (21.2%), P-gp, BCRP	Not anticipated to inhibit UGT1A1, 1A4, 1A9 or CYP450 enzymes.	No CYP3A4 induction.	Inhibitor of OATP1B1, OATP1B3 and BCRP. Not anticipated to inhibit other transporters including OCT2, OAT1, OAT3, MATE1, MRP2, BSEP, NTCP and P-gp.	
HIV CAPSID INHIBITOR					
lenacapavir (GS-6207) *being investigated as a long acting SC injection	Low hepatic clearance (0.8%) in primary human hepatocytes[44]				
HIV CCR5 INHIBITORS					
cenicriviroc[45]	CYP3A4, 2C8. Not a substrate of	Not a known CYP inhibitor.	Not a known CYP inducer.	P-gp Not an inhibitor of OATP1B1/B3 or	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
	OATP1B1/B3 or OCT2.			OCT2.	
maraviroc[46]	CYP3A4, P-gp	Does not inhibit major CYP isozymes at clinically relevant concentrations.		P-gp (in gut; systemic effects unlikely).	
HIV MATURATION INHIBITOR (MI)					
GSK2838232[47]	CYP3A4, UGT	UGT1A4. Inhibits intestinal CYP3A4 (when administered as GSK232 200 mg/ritonavir).	CYP3A4 (weak)	Inhibits intestinal P-gp, BCRP (when administered as GSK232 200 mg/ritonavir).	
CO-FORMULATED/COMBINATION HEPATITIS C REGIMENS					
Epclusa®					
velpatasvir[48-50] (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[51] (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.
Harvoni®					
ledipasvir[52] (NS5A inhibitor)	P-gp, BCRP	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). Inhibitor of OATP1B1/1B3 only at concentrations exceeding those achieved in clinic.	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
sofosbuvir[51] (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)[53]					
glecaprevir (ABT-493) (NS3/4A PI) pibrentasvir (ABT-530) (NS5A inhibitor)	P-gp and/or BCRP. Also for glecaprevir: OATP1B1/3, CYP3A4 (secondary role). Minimal metabolism and primary biliary excretion, negligible renal excretion (<1%).	CYP1A2, 3A4 (27% ↑ midazolam AUC) and UGT1A1 (weak); do not inhibit CYP2D6, 2C19, 2C9. Significant interactions with substrates of these enzymes are not expected.[54]		P-gp (105% ↑ Cmax, 138% ↑ AUC dabigatran), BCRP, OATP1B1/3.	
Vosevi®					
sofosbuvir[51] (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.
velpatasvir[48-50] (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 (34% ↑ AUC, 88% ↑ Cmax digoxin), OATP1B1, OATP1B3, OATP2B1, BCRP (169% ↑ rosuvastatin AUC)).	
voxilaprevir (GS-9857)[55, 56] (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®[57]					
elbasvir[58, 59] (NS5A inhibitor)	CYP3A4, P-glycoprotein (P-gp) and	Does not inhibit CYP3A4	Does not induce CYP1A2, 2B6 or 3A4.[57]	BCRP (intestinal)[57], P-gp (in vitro only; not	

	Substrate	CYP450 and UGT		Transporters	
		Inhibitor	Inducer	Inhibitor	Inducer
	OATP in vitro.			expected to cause clinically significant interactions via P-gp inhibition at usual clinical doses)[60] Does not inhibit OATP1B[57]	
grazoprevir[59, 61] (NS3/4A PI)	CYP3A4, P-gp and OATP1B1	CYP2C8 (not clinically meaningful),[62] 3A4 (weak; 34% ↑ midazolam AUC), UGT1A1 (weak)	Does not induce CYP1A2, 2B6 or 3A4.[57]	BCRP (intestinal)[57]. Does not inhibit OATP1B[57]	
Daclatasvir-SOF					
daclatasvir[63] (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.	
sofosbuvir[51] (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.

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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