Actual and Predicted Pharmacokinetic Interactions Between Antihyperglycemic Agents and Antiretrovirals

Antiretroviral Pharmacokinetic Characteristics (summary):

	Protease Inhibitors (PIs) atazanavir (Reyataz®)[1], darunavir (Prezista®)[2], fosamprenavir (Telzir®)[3], indinavir (Crixivan®)[4], lopinavir/ritonavir (Kaletra®)[5], nelfinavir (Viracept®)[6], ritonavir (Norvir®)[7], saquinavir (Invirase®)[8], tipranavir (Aptivus®)[9]	**Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)** efavirenz (Sustiva®)[10], etravirine (Intelence®)[11], nevirapine (Viramune®)[12], rilpivirine (Edurant®)[13]	**Integrase Inhibitors** Dolutegravir (Tivicay®),[14] elvitegravir/cobicistat (Stribild®, single-tablet regimen with tenofovir/emtricitabine)[15], raltegravir (Isentress®)[16]
Metabolism	Mainly CYP3A4	Efavirenz, nevirapine: CYP3A4, 2B6 (minor) Etravirine: CYP3A4, CYP2C9, and CYP2C19. Rilpivirine: CYP3A4 (major), as well as CYP2C19, 1A2, 2C8/9/10 (minor).	Dolutegravir: UGT1A1, CYP3A4 (10-15%). Elvitegravir: CYP3A, UGT1A1/3 Cobicistat: CYP3A, 2D6 (minor) Raltegravir: UGT1A1
Hepatic Inhibitor	Mainly CYP3A4 (darunavir, indinavir, nelfinavir, amprenavir >> saquinavir) Atazanavir: 3A4, UGT1A1 >>2C8 (weak) Caution when unboosted atazanavir is coadministered with drugs that are 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. Nelfinavir: 2B6 in vitro. Ritonavir: CYP3A4 (potent)> >2D6 >2C9 >2C19 >2A6 >1A2>2E1. At low boosting doses, ritonavir has a negligible effect in CYP2D6 inhibition.[5] Ritonavir inhibits CYP2B6 in vitro,[17] but induces 2B6 in vivo.[18] Tipranavir: 2D6[19]	Efavirenz: 2C9, 2C19[10] (? Clinical significance). Etravirine[11]: CYP2C9 (weak), CYP2C19 (moderate), p-glycoprotein (weak) Delavirdine (Rescriptor®)[20]; 3A4 (potent)	Cobicistat: CYP3A, CYP2D6; also p-glycoprotein (P-gp), BCRP, OATP1B1 and OATP1B3. Dolutegravir inhibits the renal organic cation transporter, OCT2.[14] Raltegravir has no inhibitory or inductive potential in vitro.[16]

	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
Hepatic Inducer	Nelfinavir: UGT, 2B6, 2C8, 2C9/19[21] Ritonavir: UGT, CYP1A2, CYP2C9/19, 2B6 Tipranavir: mixed induction/inhibition effects; often acts as inducer of CYP3A4 (potent) and UGT, even when boosted with ritonavir[9]	Efavirenz: 3A4 (potent), 2B6[22] and UGT1A1[23] Etravirine[11]: 3A4 (weak) Nevirapine[12]: 3A4, 2B6 (potent) Rilpivirine: 2C19 (moderate), CYP1A2, 2B6 and 3A4 (weak).[24] A clinically relevant effect on CYP enzyme activity is considered unlikely with the 25 mg dose.[13]	Dolutegravir does not induce CYP1A2, CYP2B6, or CYP3A4 in vitro.[14] Elvitegravir: CYP2C9 (modest) Raltegravir has no inhibitory or inductive potential in vitro.[16]

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
α GLUCOSIDASE INHIBITORS					
Acarbose (Prandase®, Glucobay®)	Must be taken with first bite of a meal (if taken after meal, efficacy is significantly reduced). If no meal is to be eaten, dose should be omitted. To improve GI tolerability, start with a low dose and increase slowly every 3-5 days. Start with 25 mg 1-2 times/day; increase dose by 25-50 mg/day if tolerated every 3-5 days; usual max 150 mg/day (higher doses are poorly tolerated)	Acarbose is metabolized to inactive compounds in GI tract and < 2% reaches systemic circulation.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Miglitol (n/a in Canada)		Minimal absorption.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Voglibose		Minimal absorption.	Pharmacokinetic	Pharmacokinetic	Pharmacokinetic

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
(n/a in Canada)			interaction not expected.	interaction not expected.	interaction not expected.
BIGUANIDES					
Metformin (Glucophage®, Glumetza® extended release) Also combination products: • Avandamet® (rosiglitazone/ metformin) • Janumet® (sitagliptin/ metformin)	*To improve GI tolerability, start with a low dose and increase slowly every 3-5 days.* Metformin is taken 2-3 times per day with or after meals. Start with 500 mg once or twice daily; increase by 500 mg/day as tolerated; max 2.5 g /day. Glumetza is taken once daily with evening meal; start with 1 g and increase by 500 mg at weekly intervals; max 2 g/day.	No liver metabolism. Excreted 100% as unchanged drug by glomerular filtration plus active tubular secretion via OCT2 and MATE-1-2K.	Pharmacokinetic interaction not expected. In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis.	Pharmacokinetic interaction not expected. In healthy volunteers, coadministration of **rilpivirine 25 mg** and single dose metformin 850 mg did not result in significant alteration in metformin plasma and urine pharmacokinetics. Combination may be coadministered without dose adjustment.[33] In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis.	In patients at risk of/already experiencing mitochondrial toxicity (esp. secondary to prolonged NRTI use), use with caution due to risk of hyperlactatemia or lactic acidosis. In healthy subjects, coadministration of metformin 500 mg q12h plus either dolutegravir 50 mg q24h or 50 mg q12h for 7 days led to increases in metformin exposures (79% increase AUC, 66% increase Cmax and 145% increase AUC, 111% increase Cmax, respectively) compared to metformin administered alone. The combination was generally well tolerated.[34]

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
					Close monitoring for metformin side effects (primarily gastrointestinal) is recommended when starting or stopping dolutegravir and metformin together. A dose adjustment of metformin may be necessary.[14, 34]
DPP-4 INHIBITORS[31]					
Alogliptin (n/a in Canada or US)		Not metabolized. Excreted primarily as unchanged drug in urine (95%).	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Linagliptin (Trajenta®)	5 mg once daily without regard to mealtimes.	CYP3A4, Pgp substrate and weak inhibitor.[35] Primarily eliminated unchanged as parent compound (> 80%) via fecal route. Only 17% is metabolized to inactive compound.	In combination with ritonavir 200 mg BID, linagliptin Cmax and AUC ↑ to approximately 3-fold and 2-fold, respectively.[35] This increase may not be clinically significant, since linagliptin is primarily excreted unchanged, and has a large safety window.[35] The manufacturer does not consider this interaction to be clinically significant.	Potential ↓ linagliptin.	Potential ↑ linagliptin via inhibition by **elvitegravir/cobicistat,** but may not be clinically significant, since linagliptin is primarily excreted unchanged, and has a large safety window.

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
Saxagliptin (Onglyza®)	5 mg once daily without regard to mealtimes; 2.5 mg once daily if GFR 10-50 mL/min.	Extensively metabolized via CYP3A4/5 (1 active metabolite). Excreted primarily as inactive metabolites; 24% as unchanged drug; 26% as active metabolite.	Potential ↑ saxagliptin; clinical significance unknown since DPP-4 inhibitors have a large safety window. NB: 145% ↑ AUC with ketoconazole	Potential ↓ saxagliptin. . NB: 76% ↓ AUC with rifampin	Potential ↑ saxagliptin by **elvitegravir/cobicistat**; clinical significance unknown since DPP-4 inhibitors have a large safety window.
Sitagliptin (Januvia®)	100 mg once daily without regard to mealtimes. Janumet (sitagliptin + metformin) is taken BID with or after meals.	Pgp substrate, minor metabolism via CYP3A4 & 2C8 to inactive compounds. Excreted primarily as unchanged drug in urine (80%).	Potential ↑ sitagliptin, but may not be clinically significant, since sitagliptin is primarily excreted unchanged and has a large safety window.	Potential ↓ sitagliptin.	Potential ↑ sitagliptin by **elvitegravir/cobicistat**, but may not be clinically significant, since sitagliptin is primarily excreted unchanged and has a large safety window.
Vildagliptin (Galvux®) (n/a in Canada or US)		Extensively metabolized (55%) to inactive compounds via non-CYP hydrolysis. Excreted primarily as inactive metabolites (21-33% as unchanged drug).	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
HUMAN GLUCAGON-LIKE PEPTIDE (GLP-1 AGONISTS)					
Exenatide (Byetta®)	Exenatide is injected twice daily 0-60 min before breakfast & supper. Start with 5 mcg SC BID for first month; if tolerated, may increase to 10 mg SC BID.	Minimal metabolism. Excreted renally unchanged.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.	Pharmacokinetic interaction not expected.
Liraglutide (Victoza®)	Liraglutide is injected	Not metabolized via	Pharmacokinetic	Pharmacokinetic	Pharmacokinetic

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	once daily without regard to mealtimes. Start with 0.6 mg SC once daily for at least first week; if tolerated, increase to 1.2 mg SC once daily; max 1.8 mg/day.	P450. Extensively metabolized to inactive compounds by endogenous endopeptidases. Excreted as inactive metabolites.	interaction not expected. Liraglutide can cause PR prolongation; caution if coadministering with other drugs that can also cause PR prolongation, including PIs and rilpivirine.	interaction not expected. Liraglutide can cause PR prolongation; caution if coadministering with other drugs that can also cause PR prolongation, including PIs and rilpivirine.	interaction not expected.
MEGLITINIDES					
Repaglinide (GlucoNorm®)	Start with 0.5 to 1 mg TID; max 12 mg/day *Take within 30 min prior to a meal and only if patient will be eating. If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*	Extensively metabolized to inactive compounds primarily via CYP2C8 & to lesser extent via 3A4. Also handled by OATP1B1. Excreted as inactive metabolites primarily in the bile; very little excreted as unchanged in urine.	Potential ↑ repaglinide. Monitor and adjust repaglinide dose as needed. Caution with unboosted atazanavir, which inhibits 3A4 and 2C8; clinically significant interaction not expected when atazanavir is boosted with ritonavir.[1] **NB: ↑ repaglinide AUC with other inhibitors:** • 144% ↑ with cyclosporine (3A4)	Potential ↓ repaglinide. Monitor and adjust repaglinide dose as needed.	Potential ↑ repaglinide concentrations via 3A4 inhibition by **elvitegravir/cobicistat.** Monitor and adjust repaglinide dose as needed. **NB: ↑ repaglinide AUC with other inhibitors:** • 40% ↑ with itraconazole (3A4 & OATP1B1) • 712% ↑ with gemfibrozil (2C8 & OATP1B1); avoid coadministration
Nateglinide	Start with 120 mg TID;	Extensively metabolized	Potential ↓/↑	Potential ↓/↑	Potential ↓/↑

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
(Starlix®)	max 540 mg/day *Take within 30 min prior to a meal and only if patient will be eating. If a meal is delayed or will not be eaten, the dose should usually be delayed or omitted.*	to inactive compounds primarily via CYP 2C9 (70%) & to lesser extent via 3A4. Excreted primarily as metabolites; only 15% as unchanged drug in urine	nateglinide concentrations via 2C9 induction or 3A4 inhibition. Monitor and adjust nateglinide dose as needed.	nateglinide concentrations via 2C9 inhibition or 3A4 induction. Monitor and adjust nateglinide dose as needed.	nateglinide concentrations via 2C9 induction or 3A4 inhibition by **elvitegravir/cobicistat**. Monitor and adjust nateglinide dose as needed.
SGLT2 INHIBITORS					
Canagliflozin (Invokana®)	100 mg daily; maximum 300 mg daily if inadequate response or patient is on a UGT inducer and eGFR>60 mL/min/1.73m2[36]	Substrate of UGT1A9, UGT2B4, P-gp, BCRP, MRP2. Weak inhibitor of CYP3A4, 2B6, 2C8, 2C9, P-gp (in vitro); clinically relevant effects not observed in vivo.	51% ↓ AUC with rifampin (UGT inducer). Potential need for ↑ canagliflozin dose with ritonavir-boosted PIs.[36] NB: cobicistat does not induce UGT.	51% ↓ AUC with rifampin (UGT inducer). Potential need for ↑ canagliflozin dose with efavirenz.[36]	Pharmacokinetic interaction not expected. NB: cobicistat does not induce UGT.
Dapagliflozin (Forxiga®)	5 mg daily. May increase to 10 mg daily if inadequate response.	Substrate of UGT1A9, P-gp (minor). Unlikely to affect kinetics of P-gp, OCT2, OAT1 or OAT3 substrates.	Significant interaction not anticipated. A 7% reduction in dapagliflozin AUC was observed in the presence of rifampin, a potent UGT inducer. No dosing adjustment is required.[37] NB: cobicistat does not induce UGT.	Significant interaction not anticipated. A 7% reduction in dapagliflozin AUC was observed in the presence of rifampin, a potent UGT inducer. No dosing adjustment is required.[37]	Pharmacokinetic interaction not expected. NB: cobicistat does not induce UGT.
SULFONYLUREAS					
Gliclazide (Diamicron®)	BID before breakfast & supper; start with 80 mg	Metabolized via 2C9 to inactive compounds.	Nelfinavir and ritonavir may ↓	Etravirine, efavirenz may ↑ sulfonylurea	Elvitegravir may ↓ sulfonylurea

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	BID; max 160 mg BID. Gliclazide MR Once daily before breakfast; start with 30 mg *Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose.*		sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ gliclazide AUC 70%	concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed.	concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.
Glimepiride (Amaryl®)	Once daily before breakfast; start with 1 mg daily; increase every 1-2 weeks; max 8 mg daily. *Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose.*	Metabolized via 2C9, 2C19 to inactive compounds.	Nelfinavir and ritonavir may ↓ sulfonylurea concentrations. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ glimepiride AUC 34%	Etravirine, efavirenz may ↑ sulfonylurea concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed. NB: fluconazole ↑ glimepiride AUC 138%	Elvitegravir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.
Glyburide (Diabeta®)	Once daily or twice daily if the dose/day exceeds 10 mg; start with 2.5 to 5 mg daily; increase every 1-2 weeks; max 20 mg/day. *Most of the benefit of a sulfonylurea is achieved in most patients at half the max daily dose.*	Metabolized via 2C9 in part to weakly active metabolites that may accumulate in renal impairment.	Nelfinavir and ritonavir may ↓ sulfonylurea concentrations. Use with caution. Adjust sulfonylurea dose as needed. NB: rifampin ↓ glyburide AUC 39%	Etravirine, efavirenz may ↑ sulfonylurea concentrations via 2C9 inhibition. Use with caution. Adjust sulfonylurea dose as needed.	Elvitegravir may ↓ sulfonylurea concentrations via 2C9 induction. Use with caution. Adjust sulfonylurea dose as needed.
THIAZOLIDINEDIONES (TZDs)					
Pioglitazone (Actos®)	Once daily without regard to mealtimes; start with 15 or 30 mg	Extensive liver metabolism: 2C8, 3A4 >> 1A1.	Potential ↑ pioglitazone. Monitor and adjust pioglitazone dose as	Potential ↓ pioglitazone. Monitor and adjust pioglitazone dose as	Potential ↑ pioglitazone via 3A4 inhibition by **elvitegravir/cobici**

Drug	Initial (Max) Dose	Kinetics[25-32]	Protease Inhibitors (PIs)	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Integrase Inhibitors
	daily; max 45 mg/day. *Before increasing dose, allow 8-12 weeks to assess full benefit.*	Excreted as inactive metabolites primarily via fecal route.	needed. **NB: ↑ pioglitazone AUC with other inhibitors:** • 130% ↑ with gemfibrozil (2C8)	needed. NB: 54% ↓ with rifampin.	**stat.** Monitor and adjust pioglitazone dose as needed.
Rosiglitazone (Avandia®)	Once daily without regard to mealtimes; start with 4 mg daily; max 8 mg/day. *Before increasing dose, allow 8-12 weeks to assess full benefit.*	Extensive liver metabolism primarily to inactive compounds by 2C8, also 2C9 (minor). Excreted as inactive metabolites in urine.	An open label single sequence crossover study in healthy subjects (n=14) to evaluated the effect of **ATV 400mg** daily and **ATV/r 300mg/100mg** daily on the kinetics of rosiglitazone 4mg daily (CYP 2C8 probe). Atazanavir ↑ rosiglitazone AUC 35%; atazanavir/r ↓ rosiglitazone AUC 17%. ATV is a weak inhibitor of CYP2C8, while ATV/r appears to induce CYP2C8 and offset inhibition by ATV.[38] Monitor for ↑/↓ effect with PIs and adjust rosiglitazone dose as needed.	Potential ↓ rosiglitazone. Monitor and adjust rosiglitazone dose as needed. NB: 60% ↓ with rifampin. An open-label prospective trial in outpatients with HIV receiving backbone ARV therapy consisting of 2-3 NRTIs. In 4 patients taking nevirapine, rosiglitazone ↓ Cmax 44% and there was a trend to ↓ AUC 41% (not signif).[39]	Potential ↓ rosiglitazone concentrations via 2C9 induction by elvitegravir. Monitor and adjust rosiglitazone dose as needed.

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