Resource: ART Drug-Drug Interactions

April 2023

Table 24: Antidiabetic Drugs (also see drug package inserts)

→ Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors

Class or Drug	Mechanism of Action	Clinical Comments
• NRTIs [a] • Cabotegravir (CAB) • Raltegravir (RAL) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions are expected.	No dose adjustments are necessary.
• Dolutegravir (DTG) • Bictegravir (BIC)	• **Metformin:** – DTG inhibits renal OCT2, MATE1, and MATE2, which are involved in metformin elimination. – BIC inhibits renal OCT2 and MATE1, which are involved in metformin elimination. • **Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions are expected.	• **Metformin:** – Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects. – When coadministered with DTG, titrate to achieve clinical effect but do not exceed 1,000 mg daily; monitor for adverse effects, including lactic acidosis. – When coadministered with BIC, drug interaction studies suggest that prospective dose adjustment of metformin is not required. • **Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** levels may be increased via CYP3A inhibition. • **Canagliflozin** exposure could be reduced through EVG induction of UGT enzymes. • **TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions reported.	• **Metformin:** Monitor for metformin-related adverse effects; reduce dose as needed. • **Glyburide or alternative sulfonylureas:** Use lowest effective doses with boosted EVG; monitor for signs of hypoglycemia. • **Saxagliptin:** Limit dose to 2.5 mg once per day. • **Canagliflozin:** Monitor for glycemic control. – If glycemic control is inadequate in patient taking EVG/RTV, consider increasing canagliflozin dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 mL/min/1.73 m^2. • **TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.

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Class or Drug	Mechanism of Action	Clinical Comments
Boosted PIs [b]	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; thus, concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** is a substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with ATV or DRV may decrease canagliflozin concentrations. • **GLP-1 agonists:** Caution is needed when coadministering ATV or DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing PI absorption. Furthermore, exenatide may slow gastric emptying. • **TZDs, exenatide:** No significant interactions are expected.	• **Metformin:** Monitor for metformin-related adverse effects; reduce dose as needed. • **Glyburide or alternative sulfonylureas:** Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia. • **Saxagliptin:** Limit dose to 2.5 mg once per day. • **Canagliflozin:** If patient already tolerates canagliflozin 100 mg daily, increase dose to 200 mg daily. If patient already tolerates canagliflozin 200 mg daily and requires additional glycemic control, the management strategy should be based on renal function. – In patients with eGFR ≥60 mL/min/1.73 m^2, canagliflozin dose may be increased to 300 mg daily. – In patients with eGFR <60 mL/min/1.73 m^2, consider adding another antihyperglycemic agent. • **GLP-1 agonists:** May recommend ATV or DRV dosing 4 hours before. **TZDs:** No dose adjustments are necessary.
Rilpivirine (RPV)	• **GLP-1 agonists:** Caution needed when coadministering with RPV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing RPV absorption. Furthermore, exenatide may slow gastric emptying. • **Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors:** No significant interactions reported.	• **GLP-1 agonists:** May recommend RPV dosing 4 hours before. • **Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors:** No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR)	• **Pioglitazone:** EFV may increase concentrations through CYP2C8 inhibition. No significant interactions are expected. • **Saxagliptin, sitagliptin:** EFV and ETR may decrease concentrations. • **Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions reported.	• **Pioglitazone:** Monitor for signs of adverse effects with EFV; decrease dose if necessary. • **Saxagliptin, sitagliptin:** Monitor for efficacy; if necessary, increase dose of DPP-4 inhibitor. • **Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.

Abbreviations: ATV, atazanavir; COBI, cobicistat; CYP, cytochrome P450; GFR, glomerular filtration rate; MATE, multidrug and toxin extrusion; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Notes:

a. An increased risk for bone fractures has been reported with canagliflozin, particularly in patients with a history of or who are at high risk of cardiovascular disease; therefore, caution is recommended when coadministering SGLT-2 inhibitors in the long term with TDF due to potential additive bone toxicities.

b. RTV-boosted PIs are known to cause metabolic abnormalities, which may increase blood glucose and decrease insulin sensitivity.