Metabolism of and Drug Interactions with *Tivicay*

Summary

- *Tivicay* (dolutegravir [DTG]) is primarily metabolized via UGT1A1 with some contribution from CYP3A.[1]
- DTG is not expected to affect the pharmacokinetics (PK) of drugs dependent upon hepatic metabolism.[1] DTG is a substrate of CYP3A4, but is not an inhibitor or inducer of CYP3A4.
- Drugs that are potent inducers of UGT1A1 or CYP3A may decrease plasma concentrations of DTG.[1] Consult the Prescribing Information for dosing recommendations and/or adjustments for DTG.
- Due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events with concomitant use of DTG, the concomitant administration of dofetilide is contraindicated.[1]
- Important safety information can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

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CONTRAINDICATION

In vitro, DTG inhibited the renal organic cation transporter, OCT2.[1] Coadministration of DTG with dofetilide is contraindicated due to potential life-threatening toxicity resulting from increased dofetilide drug concentrations.

METABOLISM OF DTG

DTG is primarily metabolized via the hepatic enzyme UGT1A1 with some contribution from CYP3A.[1] DTG inhibits the renal organic cation transporter, OCT2, resulting in a decrease in the tubular secretion of creatinine along with some drugs eliminated via OCT2 (dofetilide, dalfampridine, and metformin).

In vitro, DTG did not inhibit the cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1, UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, or multidrug resistance protein (MRP)2, or MRP4.[1] Nor did DTG induce CYP1A2, CYP2B6, or CYP3A4 *in-vitro*. Therefore, DTG is not expected to affect the PK of drugs dependent on hepatic metabolism.

For inquires on interactions with other drugs that are not listed herein, it is recommended to consult the prescribing information of the drug in question to determine its metabolic profile and if that drug is an inducer or inhibitor of the enzymes listed above. Reputable drug interaction websites may also be consulted, such as http://www.hiv-druginteractions.org/checker.

EFFECT OF DTG ON THE PK OF OTHER AGENTS

In vitro, DTG inhibited the renal organic cation transporters, OCT2 (IC_{50} = 1.93 µM) and multidrug and toxin extrusion transporter (MATE) 1 (IC_{50} = 6.34 µM).[1] *In vivo*, DTG inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. DTG may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide, dalfampridine, and metformin).

Metformin concentrations may increase when concomitantly administered with DTG.[1] Refer to the Prescribing Information for metformin to assess the benefit and risk of concomitant use of DTG and metformin.

In vitro, DTG inhibited the basolateral renal transporters, organic anion transporter (OAT)1 (IC_{50} = 2.12 µM) and OAT3 (IC_{50} = 1.97 µM).[1] However, *in vivo*, DTG did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, DTG did not inhibit (IC_{50} greater than 50 µM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), BCRP, bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, MRP2, or MRP4.[1] *In vitro*, DTG did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, DTG is not expected to affect the PK of drugs that are substrates of these enzymes or transporters.

EFFECT OF OTHER AGENTS ON THE PK OF DTG

Drugs which are inducers of UGT1A1 and/or CYP3A hepatic enzymes may decrease plasma concentrations of DTG and may reduce the therapeutic effect.[1] Consult the prescribing information for dosing recommendations and/or adjustments for DTG.

Drugs that are substrates but not potent inducers of UGT1A1 and/or CYP3A such as midazolam, triazolam, sildenafil, simvastatin, and lovastatin are not expected to affect the PK of DTG.[1] Based on drug interaction trial results, the following drugs can be co-administered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir.[1-8]

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Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.



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