# Use of mechanistic PBPK modeling to predict the potential for renal transporter DDIs between Dolutegravir and Tenofovir/Metformin

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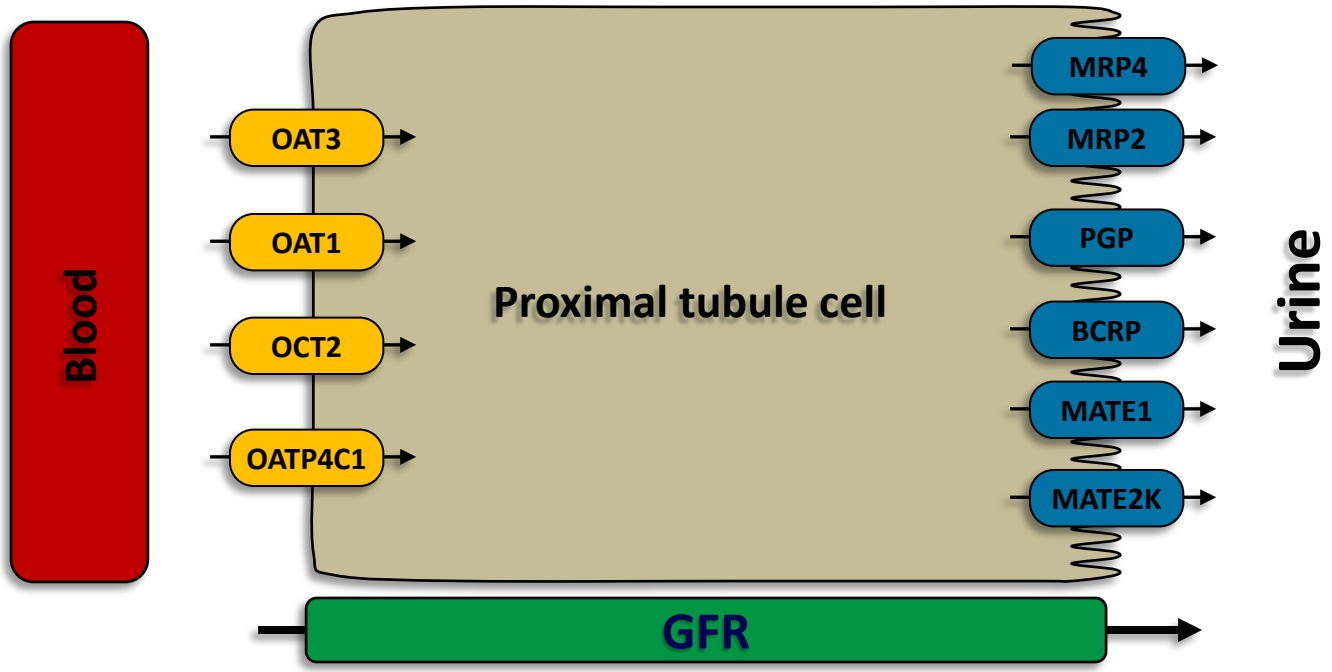
**15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; May 19-21, 2014; Washington, DC**

# Drug Transporters Present in the Kidney

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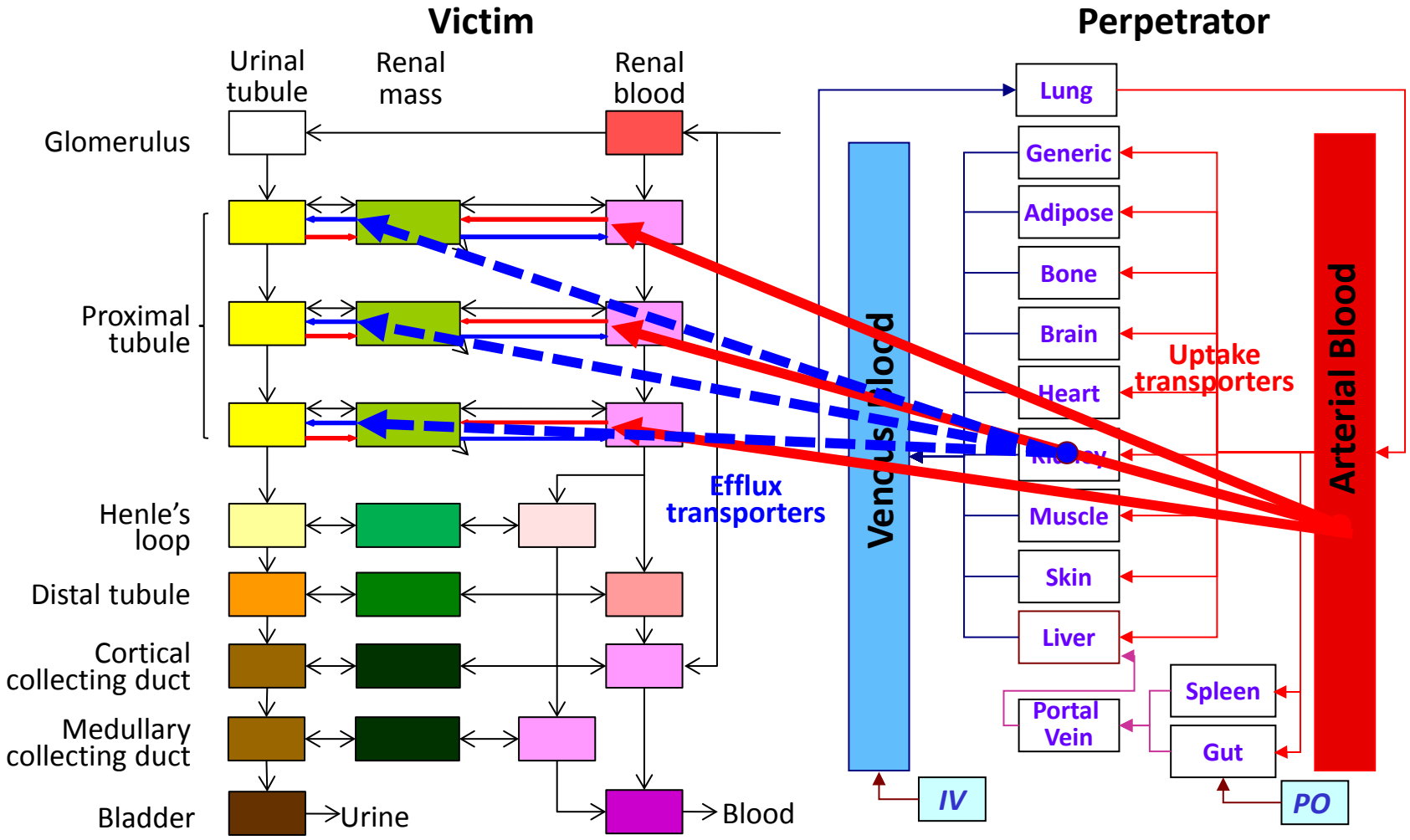
# SimCYP Mechanistic Kidney Model



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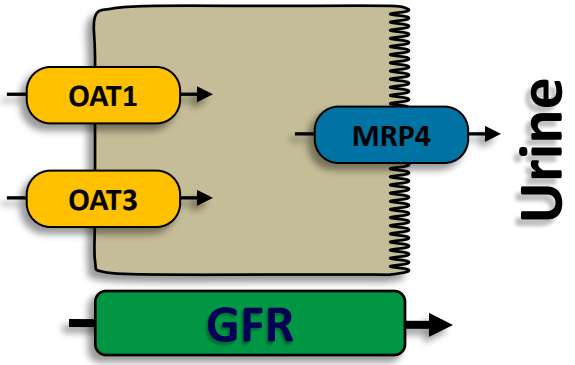
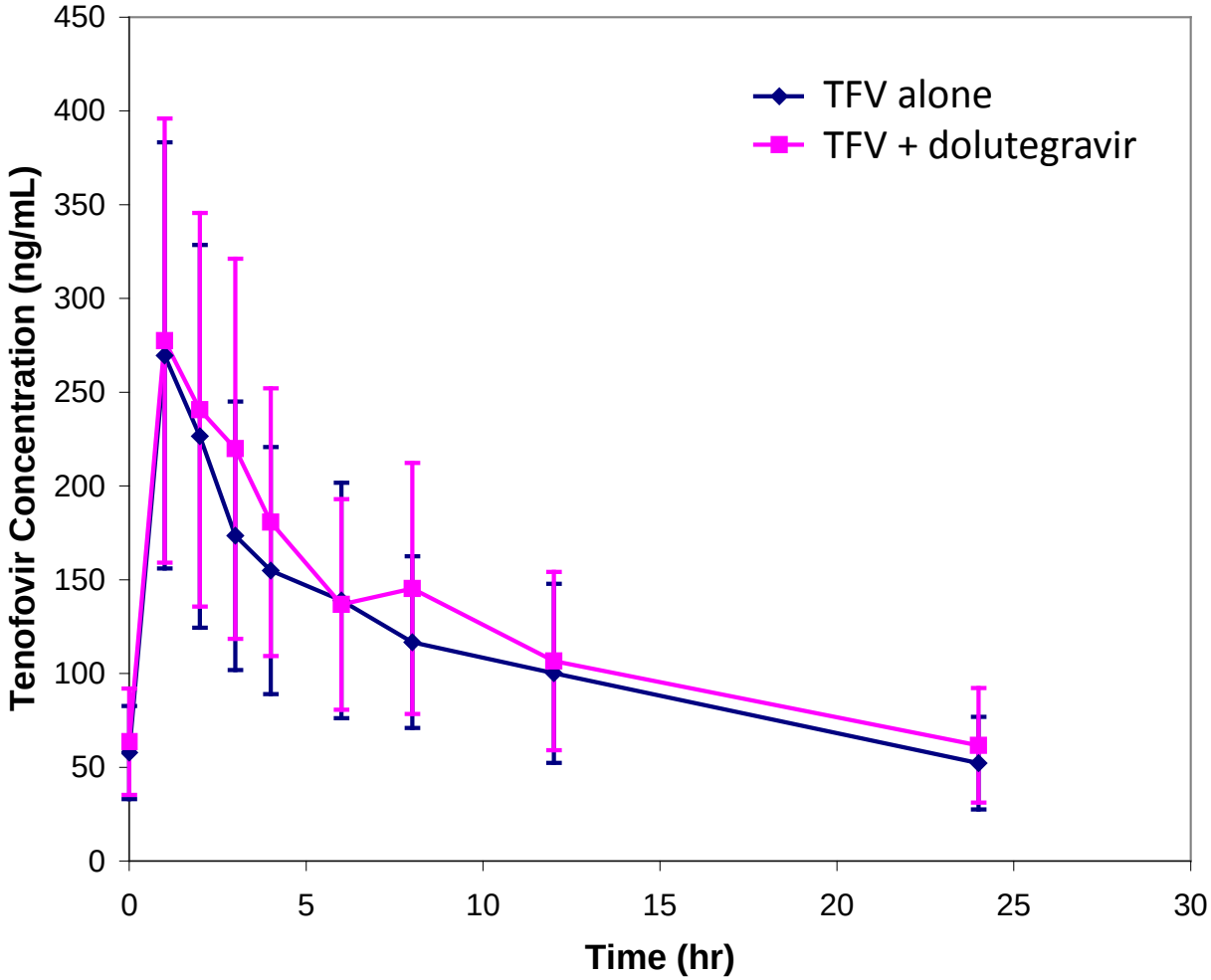
# Dolutegravir–Tenofovir

# Tivicay™ (Dolutegravir; DTG)

- DTG is an HIV integrase inhibitor approved for the treatment of HIV-1.
- *In vitro*, DTG weakly inhibits OAT1/3 ($IC_{50}$ = 2 µM) and MRP4 ($IC_{50}$ = 84 µM).
- Tenofovir is primarily renally cleared by OAT1/3 and MRP4.
- Use PBPK modeling to investigate the potential for DTG to impact the renal disposition of tenofovir.



# DTG Does Not Affect Tenofovir Plasma Pharmacokinetics[1]




**1.** Song et al. *J Acquir Immune Defic Syndr.* 2010;55:365-367.

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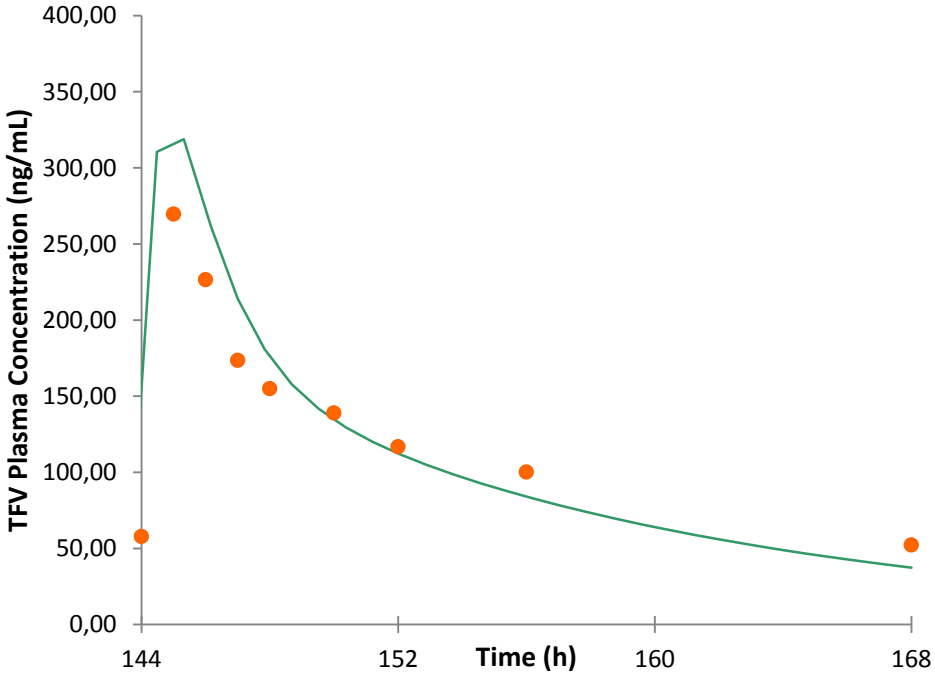
# How Do We Estimate *In Vivo* Tenofovir Clearance Due to OAT1/3 and MRP4 ?

# Optimize OAT1/3 $Cl_{int}$ to Tenofovir Plasma PK[1]

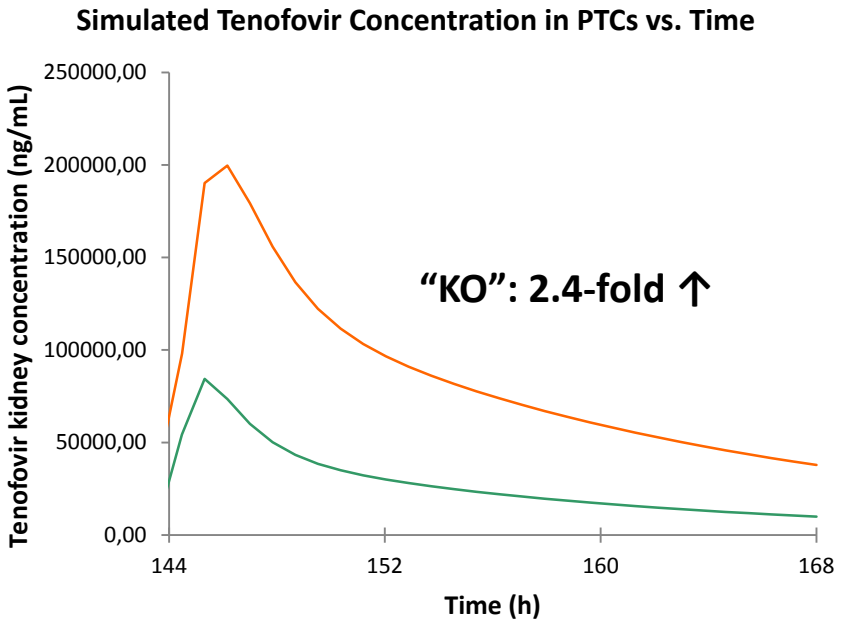



| Optimized Basolateral Uptake Clearance (L/hr) | Observed $Cl_{sys}$ (L/hr) |
|---|---|
| 18.6 | 15.7 |

1. Song et al. *J Acquir Immune Defic Syndr.* 2010;55:365-367.

# What is the Sensitivity of Tenofovir to MRP4 Inhibition?[1]

- In Mrp4 KO mice, TFV concentration in the kidney ↑ 2.3-fold
  - No significant change in plasma concentration

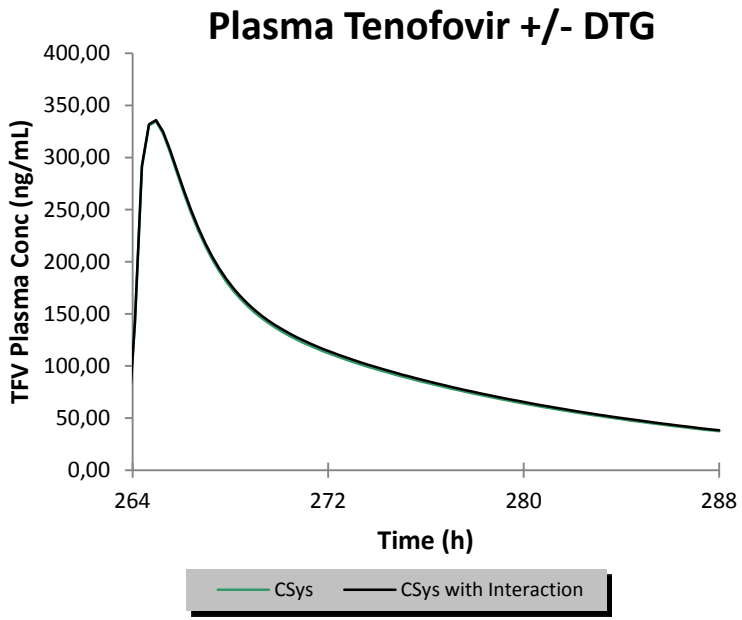


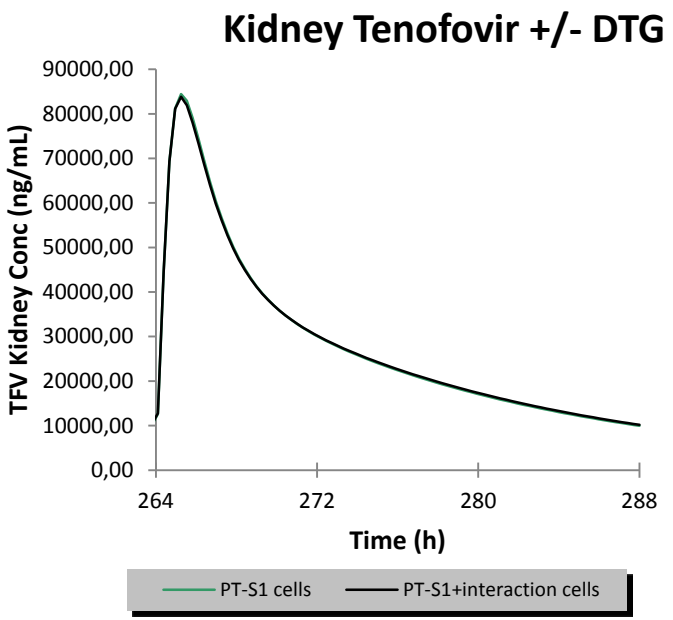

**1.** Imaoka et al. *Mol Pharmacol*. 2007;71:619-627.

# Tenofovir–Dolutegravir DDI Simulation Using SimCYP MechKim Model

**Dolutegravir** Day 8 →

**Tenofovir** Day 1 → Day 12

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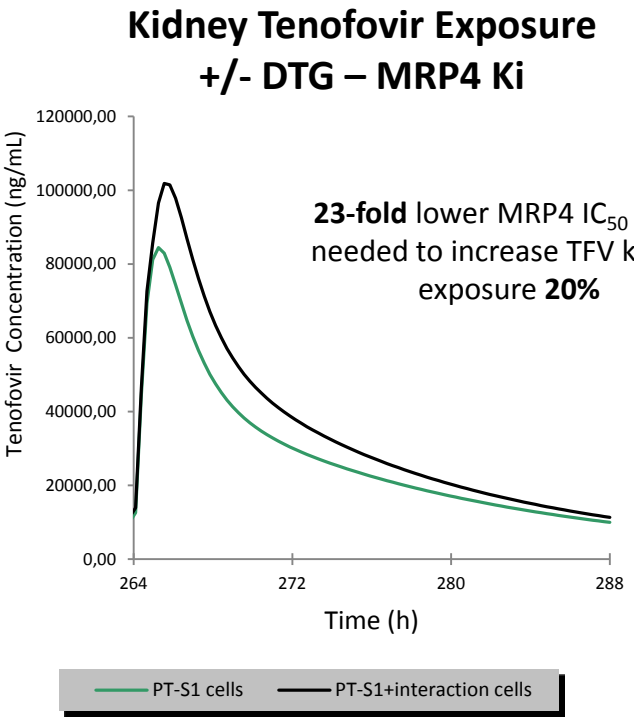
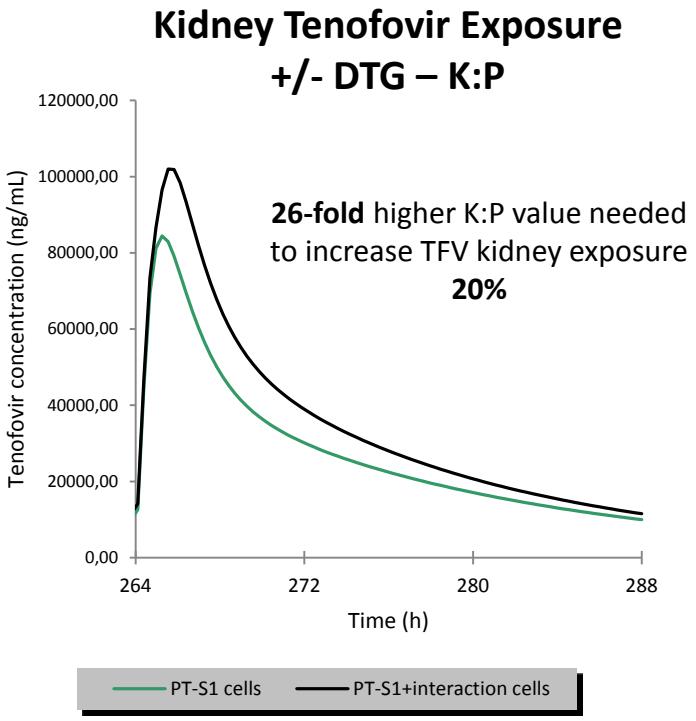
# Impact of MRP4 Ki Value and DTG Kidney:Plasma Ratio on Tenofovir Kidney Exposure

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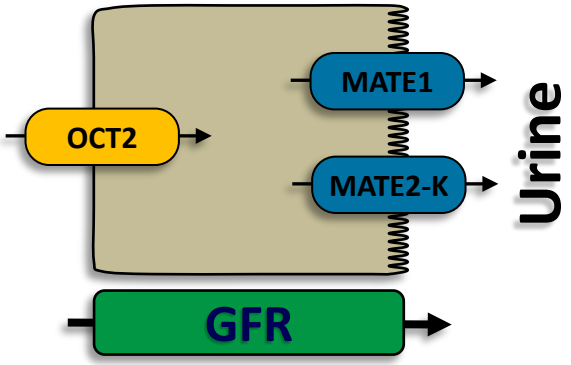
# Conclusions

- DTG does not impact the plasma pharmacokinetics of tenofovir
- PBPK modeling predicts that DTG coadministration will not affect tenofovir kidney disposition

# Dolutegravir–Metformin

# Transporters Involved in Metformin Disposition

- Metformin disposition and renal clearance are driven by membrane transporters.
  - OCT2 and MATE1/2-K in the kidney
  - OCT1 and MATE1 in the liver
  - PMAT and OCT1/3 in the intestine
- *In vitro*, DTG is an inhibitor of OCT2 ($IC_{50}$ = 1.9 µM) and MATE1 ($IC_{50}$ = 6.3 µM). It shows weak inhibition of OCT1 in the liver and MATE2-K in the kidney, and does not inhibit OCT3 in the intestine.

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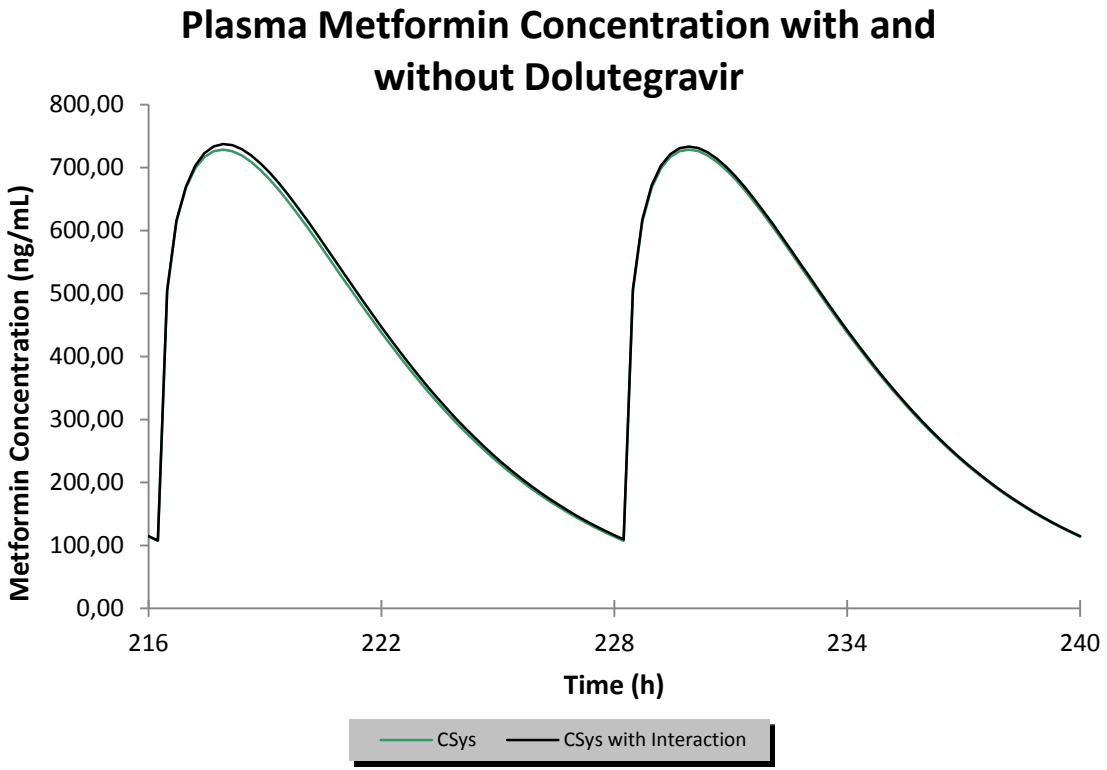
# Dolutegravir–Metformin DDI Simulation Using SimCYP PBPK Model

**Dolutegravir** Day 5 → Day 12

**Metformin** Day 1 → Day 22

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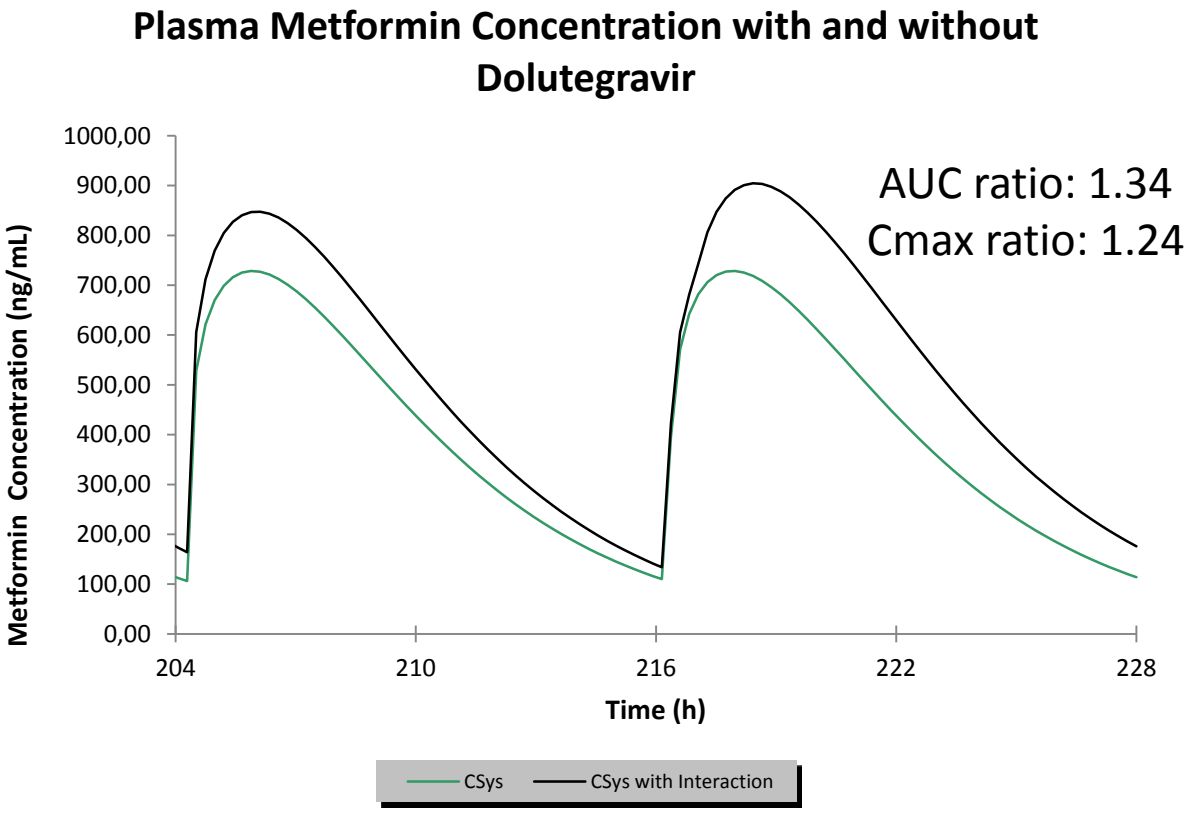
# Dolutegravir–Metformin DDI Simulation Using OCT2 $IC_{50}$ Value (0.066 µM) from Lepist et al., 2014[1]




**1.** Lepist et al. *Kidney Int.* 2014;doi: 10.1038/ki.2014.66

# Conclusions

- Mechanistic models can be used to predict and investigate complex investigations involving transporters.

- Role of membrane transporters in PK/PD is rapidly evolving, and best practices for the generation and application of transporter data are still being developed.

# Acknowledgments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