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Title of diploma thesis: *In vitro* and *ex vivo* study of drug-drug interactions of antivirals on intestinal membrane transporters

Tenofovir (TFV) is the first-line agent in the treatment of hepatitis B virus (HBV) infection for patients aged over 12 years and one of the first-line choices for the combination antiretroviral therapy (cART) of infections caused by human immunodeficiency virus (HIV).

Two commercially available prodrugs have been developed for oral administration of TFV, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). These prodrugs increase TFV membrane permeability and oral bioavailability.

One of the factors that can affect the bioavailability of orally administrated drugs is active transport mediated by efflux transporters, mainly by P-glycoprotein (ABCB1, P-gp) and Breast cancer resistance protein (ABCG2, BCRP). It has been already proved that TDF and TAF are substrates of both of these transporters.

The goal of this diploma thesis was to use *in vitro* and *ex vivo* models of intestinal barrier to assess the impact of the efflux transporters on TDF and TAF transport in the intestine and on their accumulation in rat precision-cut intestinal slices (rPCIS). We also focused on comparing the stability and metabolism of TDF and TAF in the rat intestine.

Data from our studies on Caco-2 cell line (human epithelial colorectal adenocarcinoma cells) confirmed that both TDF and TAF are substrates of efflux transporter ABCB1. Specific inhibition of ABCG2 did not affect TDF and TAF transport across Caco-2 cell monolayer. Effect of ABCB1 inhibition was also seen using rPCIS. ABCB1 inhibition resulted in increased accumulation of TDF and TAF metabolites in rPCIS. Data from our studies on rPCIS also confirmed that TDF is in intestine less stable than TAF and is rapidly metabolized by gut hydrolases.