Physiologically-Based Simulation of Daclatasvir Pharmacokinetics With Antiretroviral Inducers and Inhibitors of Cytochrome P450 and Drug Transporters

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Disclosures

- Tushar Garimella is an employee of Bristol-Myers Squibb
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- The following simulations based on PBPK analyses provide the most appropriate dose of DCV in certain complex HIV-1 treatment regimens and the recommendations based on this modeling are currently not in any approved Daklinza product labelling

Background

- Daclatasvir (DCV; pangenotypic HCV NS5A inhibitor) is a substrate of CYP3A4 and a substrate and inhibitor of P-gp
- DCV with sofosbuvir (SOF; pangenotypic NS5B inhibitor) is well tolerated and efficacious in HIV-HCV coinfected patients receiving commonly used antiretroviral (ARV) regimens
  - 97% SVR12 after 12 weeks DCV+SOF (HCV genotypes 1-4; ALLY-2 study)[1]
- Standard DCV dosing (60 mg daily) can be adjusted for use with ARVs affecting CYP 3A4[2]
  - 30 mg daily with boosted atazanavir with ritonavir or cobicistat (ATV/r, ATV/c), indinavir (IDV), saquinavir (SQV), nelfinavir (NFV), and fixed-dose combination elvitegravir/cobicistat/emtricitabine/tenofovir
  - 90 mg daily with efavirenz (EFV), nevirapine (NVP), etravirine (ETR)
- Establishing a DCV dose for complex ARV regimens remains a challenge
- Physiologically-based simulation allows complex drug-drug interactions to be modelled *in silico*

1. Wyles DL, *et al. N Engl J Med* 2015;373:714–25.
2. Daklinza Prescribing Information (USA). Accessed (25 May 2016) at: http://packageinserts.bms.com/pi/pi_daklinza.pdf

Objectives

- To use a physiologically-based PK (PBPK) model to simulate PK interactions between DCV and ARV regimens combining inducers and inhibitors of CYP and P-gp
- To explore appropriate DCV dose adjustments with complex ARV regimens, based on PBPK models and observed data

DCV PBPK Model Development

- Initial model development and validation was carried out in Simcyp simulator versions 13r1 and 14r1
- DCV base model was derived from *in vitro* parameters, *in silico* predictions, and *in vivo* ADME and bioavailability data[1]
- Key DCV assumptions
  - P-gp efflux in gut and liver but no influx transporters involved in gut absorption
  - Minor metabolism by an unknown CYP with similar properties to CYP 2C8
  - Passive tissue distribution according to partition and binding rules, except for the liver
- All simulations modelled a healthy, 50% female Caucasian population of ages 20–49 years
- Base model performance assessed by visual comparison of simulated PK profiles and parameters against observed data from SAD and MAD studies

1. Wang Q, *et al. American Conference on Pharmacometrics 6*; Washington, DC; October 4–7, 2015.

DCV PBPK Parameters

	Value	Method
Molecular Weight	738.96	
log $P_{o:w}$	4.05	Experimental
Compound Type	**Diprotic base**	
pKa 1	5.6	Experimental
pKa 2	4.9	Experimental
Blood/Plasma Ratio	0.8	Experimental
Fraction Unbound in Plasma	0.006	Experimental
PAMPA ($x10^{-6}$ cm/s)	49	Experimental
P-gp efflux in Gut		
J_{max} (pmol/min/million cells)	2.610	Experimental
K_m (µM)	8.160	Experimental
V_{ss} (L/kg)	0.556	Method 2 (Roger and Rowland)
Enzyme kinetics tab:	**Recombinant enzymes**	
CYP3A4		
V_{max} (pmol/min/pmol)	0.575	Experimental
K_m (µM)	2.53	Experimental
CYP3A5		
V_{max} (pmol/min/pmol)	0.0957	Experimental
K_m (µM)	9.14	Experimental
Unidentified CYP		
Cl_{int} (µl/min/pmol)	0.32	Model fitting
fu, mic	0.35	*in silico*
P-gp mediated canalicular efflux in liver		
J_{max} (pmol/min/million cells)	88.000	Sensitivity analysis, fitting
K_m (µM)	8.160	Sensitivity analysis, fitting
RAF/REF	1.600	Sensitivity analysis, fitting
% available for reabsorption	80%	Sensitivity analysis, fitting

Model Validation

- DCV PK was simulated and compared with clinical data for coadministration of DCV with:
  - Ketoconazole (KET; 400 mg QD) – Strong CYP3A4 and P-gp inhibitor
  - Cyclosporine (CSP; 400 mg QD) – Weak CYP3A4 inhibitor/ Strong P-gp inhibitor
  - Rifampin (RIF; 600 mg QD) – Strong CYP3A4/P-gp inducer
- In addition, single-dose midazolam (MDZ; 5 mg) PK was simulated with and without DCV 60 mg QD and compared with clinical data
- KET, CSP, RIF and MDZ parameters were as supplied within Simcyp, but with adjustment of P-gp inhibition for KET and CSP

Simulation of DCV PK with cART

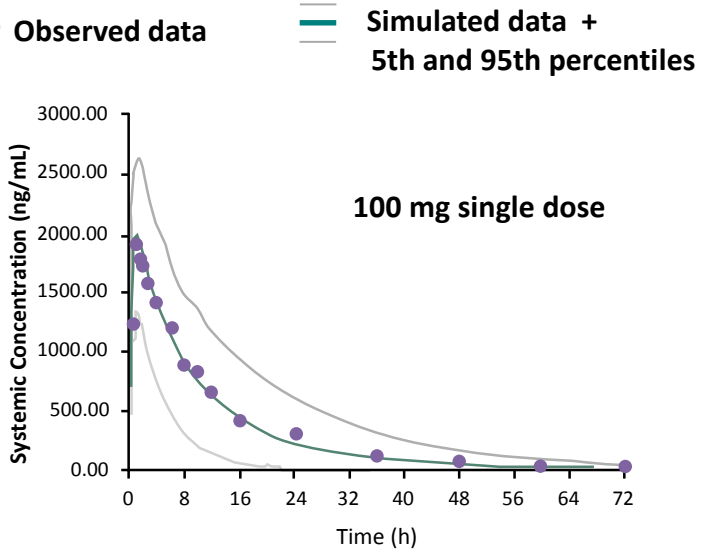
- All ARV simulations were performed in Simcyp version 14r1
- Model parameters for individual ARVs were derived from available physicochemical, *in vitro*, *in silico* and clinical data
  - ATV, EFV, tenofovir (TDF), emtricitabine (FTC), ritonavir (RTV), cobicistat (Cobi), darunavir (DRV)
  - Elvitegravir (EVG), maraviroc (MVC), raltegravir (RAL), and other nucleoside analogues were not modelled
- Six simulation trials of DCV 60 mg ($\leq$ 3 modelled ARVs/trial) were performed per regimen, each with 14 healthy subjects

Model Base Case: Single & Multiple Dose DCV

Single Dose DCV

Dose (mg)	DCV C_{max}			DCV AUC		
	Obs.	Sim.	Sim:Obs	Obs.	Sim.	Sim:Obs
1	16	17	1.1	160	169	1.1
10	200	182	0.9	2053	1811	0.9
25	406	471	1.2	3962	4683	1.2
50	1226	962	0.8	13255	9596	0.7
100	1921	1960	1.0	22241	19667	0.9
200	2816	3987	1.4	31473	40508	1.3

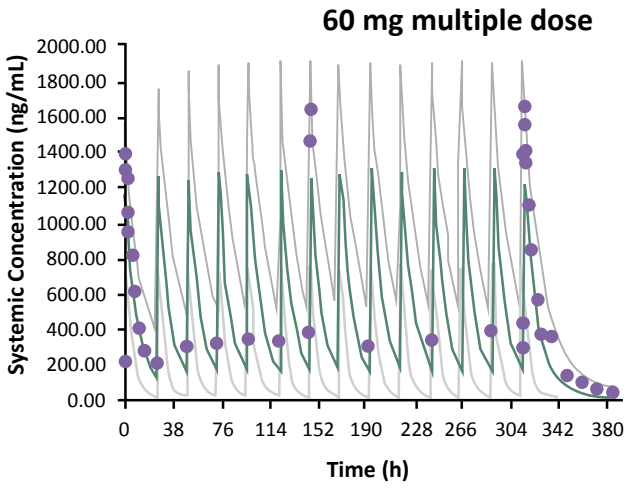
Obs., observed; Sim., simulated



Multiple Dose DCV

Dose (mg)	DCV C_{max}			DCV AUC		
	Obs.	Sim.	Sim:Obs	Obs.	Sim.	Sim:Obs
1	16	19	1.2	125	193	1.5
10	257	198	0.8	2454	2051	0.8
30	734	619	0.8	6275	6387	1.0
60	1582	1202	0.8	15666	11713	0.8

Obs., observed; Sim., simulated



Model Validation 1

DCV effect on MDZ PK

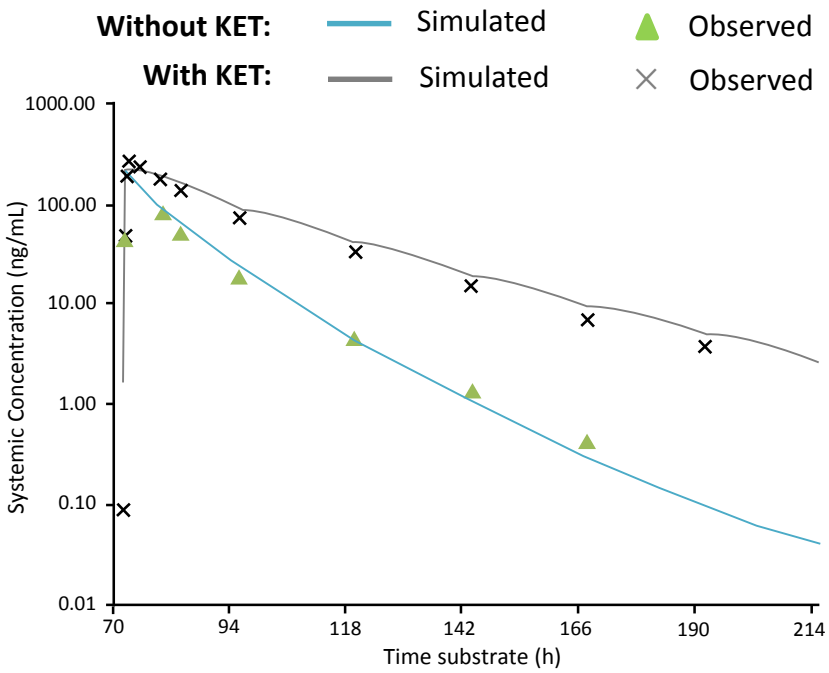
	GMR C_{max} (90% CI)	GMR AUC (90% CI)
Observed	0.95 (0.88–1.04)	0.87 (0.83–0.92)
Simulated	0.90 (0.87–0.94)	0.90 (0.87–0.94)

Three trial simulations of 10 healthy subjects each

14 days of DCV 60 mg QD with a single 5 mg MDZ dose at Day 10

- The simulated effect of DCV on MDZ exposure parameters was similar to observed data

Simulated vs Observed Plasma DCV ± KET



- Simulated PK profiles for DCV 20 mg ± KET 400 mg were similar to observed data
- The KET effect was mainly via CYP3A inhibition, with a minor contribution from inhibition of biliary P-gp clearance

Model Validation 2

Drug	DCV dose	GMR C_{max}			GMR AUC		
		Observed	Simulated	Sim:obs ratio	Observed	Simulated	Sim:obs ratio
RIF	60 mg SD	0.438	0.627	1.43	0.212	0.218	1.01
KET	20 mg SD	1.57	1.25	0.80	2.99	3.11	1.04
CSP	60 mg QD	1.04	1.03	0.99	1.4	1.04	0.74

SD, single dose

- Overall simulated GMR were similar to observed data
- Under-prediction of RIF C_{max} change may represent omission of gut P-gp induction from the model
- Under-prediction of CSP AUC change may represent underestimation of CSP inhibition of CYP3A4, DCV hepatic uptake or DCV renal clearance

ARV Regimen Models and DCV Dose Recommendations

- Modelling was performed for
  - TDF/FTC/EVG/Cobi fixed-dose combination – EVG not modelled (non-perpetrator)
  - ATV 300 mg or 400 mg alone, with ritonavir 100 mg, and with ritonavir + EFV 600 mg
  - ATV 300 mg + Cobi
  - DRV 800 mg + ritonavir 100 mg ± EFV 600 mg
- Non-perpetrator ARVs in the regimen (EVG, MVC, RAL, other NRTIs) were assumed to have no effect on modelled results for the above combinations
- DCV dose recommendations were made by comparing modelled GMR for DCV AUC and C_{max} against observed interaction data for which a dose adjustment is indicated[1]
  - Observed ATV/r (300/100 mg) : 2.1-fold AUC increase → **30 mg DCV QD**
  - Observed EFV (600 mg) : 32% AUC decrease→ **90 mg DCV QD**

1. Bifano M, *et al. Antivir Ther* 2013;18:931–40.

Simulated DCV PK with vs without ARVs

Regimen	DCV GMR Cmax (95% CI)	DCV GMR AUC (95% CI)	Recommended DCV Dose
TDF/FTC/EVG/Cobi (300/200/150/150 mg)[a]	1.46 (1.40–1.52)	2.09 (1.94–2.26)	30 mg
ATV 400 mg	1.90 (1.83–1.97)	2.69 (2.55–2.85)	30 mg
ATV 400mg + RTV	1.80 (1.71–1.89)	2.46 (2.27–2.67)	30 mg
ATV 400mg + RTV + EFV	1.75 (1.66–1.85)	2.36 (2.18–2.56)	30 mg
ATV 300mg + RTV	1.74 (1.65–1.83)	2.34 (2.15–2.55)	30 mg
ATV 300mg + RTV + EFV	1.69 (1.60–1.79)	2.24 (2.06–2.44)	30 mg
ATV 300mg + Cobi	1.97 (1.90–2.05)	2.92 (2.77–3.02)	30 mg
DRV 800 mg + RTV	1.31 (1.24–1.38)	1.56 (1.42–1.71)	60 mg
DRV 800mg + RTV + EFV	1.31 (1.25–1.39)	1.57 (1.44–1.72)	60 mg

ATV, atazanavir; Cobi, cobicistat; DRV, darunavir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; RIF, rifampin; RTV, ritonavir; TDF, tenofovir disoproxil fumarate. All Regimens were QD administration. All RTV was 100 mg, all Cobi was 150 mg, and all EFV was 600 mg.
[a]EVG not included in model

- Substitution of etravirine for EFV in the above is expected to give similar results due to similar CYP3A4 induction

Summary & Conclusions

- A validated, physiologically-based model was used to estimate PK interactions between DCV and complex combinations of ARVs not generally evaluated in clinical interaction studies
- The model predicts >2-fold elevations in DCV AUC and corresponding increases in C_{max} for administration with TDF/FTC/EVG/Cobi or with RTV- or Cobi-boosted ATV
  - Lesser (<1.6-fold) effect on AUC and C_{max} with RTV-boosted DRV
- The effect of boosted PIs on DCV is not significantly affected by concomitant EFV
- Based on this model, the predicted dose of DCV would be:
  - **30 mg QD** with ATV/r- or ATV/c-based regimens ± EFV
  - **60 mg QD** with DRV/r-based regimens ± EFV