Mechanistic Prediction of HIV Drug-Drug Interactions in Virtual Populations from *in vitro* Enzyme Kinetic Data: Ritonavir and Saquinavir

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INTRODUCTION

- Quantitative prediction of metabolic drug-drug interactions (mDDI) and the ability to identify patients most likely to experience such interactions is of clinical benefit.

- This is challenging in patient groups receiving multiple drugs, (e.g. HIV-infected individuals). However, the extrapolation of *in vivo* ADME properties from *in vitro* data (IVIVE) provides a useful framework to assess such mDDI.

- Ritonavir (RTV), a potent inhibitor of cytochrome P450 3A4 (CYP3A4), is used in many regimens as a pharmacoenhancer of other protease inhibitors metabolised by CYP3A4, including saquinavir (SQV).

- It is reported that at higher doses RTV may also induce CYP3A4 *in vivo*[1].

- Here, we report the prediction of the magnitude of interaction observed in a multiple dose study (Buss *et al.*, 2001)[2] of healthy volunteers taking either SQV alone (800 mg *b.d.* fortovase; n=8) or SQV/RTV (800/300 mg *b.d.*).

METHODS

- SQV V_{max}, K_m, K_i data and RTV K_i data were taken from multiple published sources and combined in meta-analyses (Table 1). A linear relationship between fold-induction *in vivo* and dose was assumed, and the fold value associated with continued administration of 500 mg RTV was scaled down to 3-fold for 300 mg RTV[1].

- The data were implemented in a physiologically-based pharmacokinetic model within Simcyp® Software (Version 7.0).

- Ten trials of 8 virtual subjects with genetic, physiological, and demographic variables relevant to IVIVE were generated (Figure 1). Simulations were performed assuming the absence and presence of CYP3A4 induction by ritonavir, in addition to its inhibitory effect.

- Mean fold error (MFE – ratio of predicted versus observed fold-changes) was used to assess the accuracy of the predicted magnitude of interaction.

Table 1 Kinetic parameters derived from meta-analyses of published sources.

Kinetic Data for SQV and RTV	value	fu_{mic}	reference
SQV			
V_{max} (pmol/min/mg)	3140		3, 4
K_m (uM)	0.85	0.87	3, 4
K_i - CYP3A4 (uM)	3.5	0.58	5, 6
CL_R (L/h)	0.95		7
RTV			
CLpo [%CV] (L/h)	9.1 [102]		8, 9, 10
K_i - CYP3A4 (uM)	0.025	0.66	5, 11, 12
Fold Induction	3		2
CL_R (L/h)	0.32		8, 9, 10, 13

Figure 1 Demographic and other parameters generated for virtual subjects.
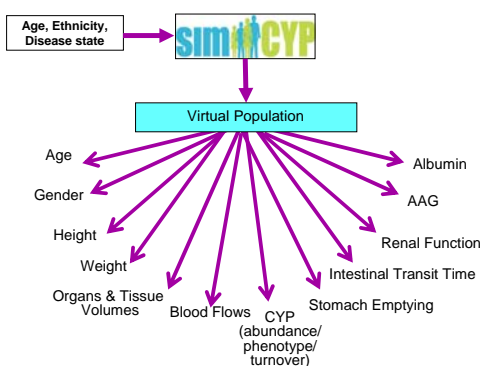

Figure 2 Simulated (—) and observed (- -) concentration-time profiles for SQV alone (800mg, *b.d.*; 14 days) and SQV/RTV (800/400mg, *b.d.*; 14 days). Data shown are from simulations run in the absence of enzyme induction. Data are expressed as geometric mean concentrations.
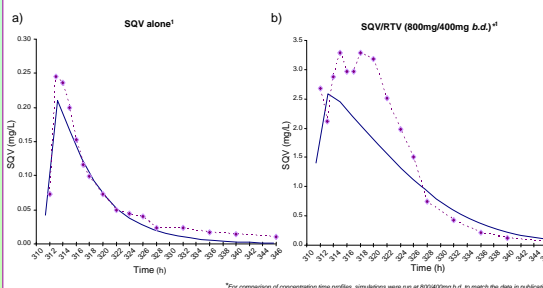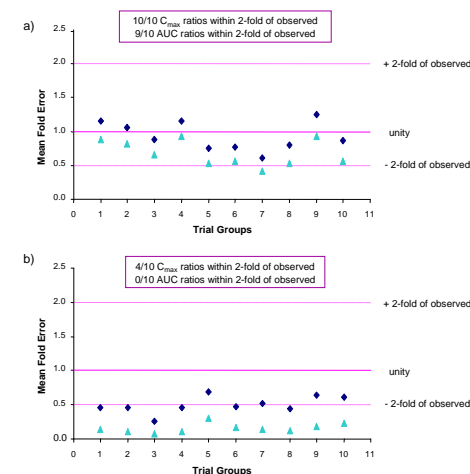

*For comparison of concentration time profiles, simulations were run at 800/400mg b.d. to match the data in publication

Figure 3 Accuracy of the prediction of interaction without (a) and with (b) incorporation of simultaneous induction and inhibition by RTV. Data are the mean fold error of Cmax (♦) and AUC (▲) ratios. The line of unity (—) and +/- 2-fold of observed data (- -) are also shown.

RESULTS

- Observed changes in maximum SQV plasma concentration (C_{max}) and the area under its concentration-time curve (AUC) were 10.0 and 21.5-fold, respectively.

- Corresponding predicted values for the 10 simulated trials ranged from 6.9 to 13.4 and from 9.6 to 19.9, respectively.

- Predicted and observed plasma concentration-time profiles for SQV in the absence and presence of RTV, and assuming no enzyme induction, are shown in Figure 2.

- When CYP3A4 induction was *not* considered, the MFE for prediction of C_{max} ratios was 0.9 and all values were within 2-fold of the observed values. The MFE for prediction of AUC ratios was 0.7 with 9/10 of the predicted values within 2-fold of the observed data (Figure 3a).

- Assuming simultaneous induction and inhibition of CYP3A4 by RTV led to under prediction of the interaction. C_{max} ratios for 4 of the 10 trials were within 2-fold of observed values, whereas none of the predicted AUC ratios were within 2-fold of observed values (Figure 3b).

CONCLUSIONS

- Simcyp was able to predict the magnitude of inhibition of the clearance of SQV (fortovase) by RTV, indicating that IVIVE is a useful tool for assessing HIV mDDIs.

- The simulations indicate that, at a dose of 300 mg, enzyme induction by RTV does not appear to contribute to the interaction. However, a robust relationship between concentration and induction *in vivo* has yet to be established.

- In addition, without knowing the free concentrations of SQV in the observed study it is not possible to accommodate potential changes in plasma binding (displacement or induction) as a complicating factor.

- Incorporation of *in vitro* solubility data into the Simcyp Advanced Dissolution, Absorption and Metabolism (ADAM) model may help to predict mDDIs involving alternative formulations of SQV.

REFERENCES

[1]Hsu *et al.*, 1997; *Antimicrob Agents Chemother*, **41**: 898-905
[2]Buss *et al.*, 2001; *Br J Clin Pharmacol*, **52**: 255-264
[3]Cazali *et al.*, 2003; *Xenobiotica*, **34**: 151-178
[4]Eagling *et al.*, 2002; *Xenobiotica*, **32**: 1-17
[5]Eagling *et al.*, 1997; *Br J Clin Pharmacol*, **44**: 190-194
[6]Lillibridge *et al.*, 1998; *Drug Metab Dispos*, **26**: 609-616
[7]Mikus *et al.*, 2004; *Clinical Pharmacokinet* **43**: 1015-1024
[8]Khaliq *et al.*, 2001;*J Clin Pharmacol*, **51**: 591-600
[9]Hsu *et al.*, 1998; *Clin Pharmacol Ther*, **63**: 453-464
[10]Gutierrez *et al.*, 2003; *Clin Ther*, **25**: 1200-1210
[11]Iribarne *et al.*, 1998; *Drug Metab Dispos*, **26**: 257-260
[12]Koudriakova *et al.*, 1998; *Drug Metab Dispos*, **26**:552-561
[13]Denissen *et al.*, 1997; *Drug Metab Dispos*, **25**: 489-501