HIGH DOSE RIFAMPICIN FOR THE TREATMENT OF LEPROSY IN HIV PATIENTS TAKING DOLUTEGRAVIR

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Background

High dose rifampicin (RIF) is being investigated for shortening TB therapy (1) as well as in other indications such as leprosy (2). At the end of 2018 the World Health Organisation (WHO) reported 184,212 registered cases and 208,619 new cases of leprosy worldwide, with approximately 75% of these cases being reported in India (50%), Brazil (15%) and Indonesia (10%) (3). Previously published studies have indicated a higher prevalence of leprosy in HIV-positive individuals (4). RIF is a potent inducer of cytochromes P450 3A4 (CYP3A4) and UDP-glucuronosyltransferase 1A1 (UGT1A1) (5) which are involved in the metabolism of the first-line ARV dolutegravir (DTG) (6). There are currently no data on how to manage the drug-drug interaction (DDI) between DTG and RIF administered at 1200 mg once monthly (QMT) for the treatment of leprosy (3). The present study used physiologically-based pharmacokinetic (PBPK) modelling to predict the magnitude of DDI between QMT high dose RIF and multiple DTG dosing regimens.

Objective 1

To verify a RIF PBPK induction model for CYP3A4 and UGT1A1 against clinical DDI data and to describe the strength and duration of induction with 1200mg versus 600mg QMT doses of RIF.

Objective 2

To simulate the magnitude of the DDI between RIF 1200mg QMT and various DTG dosing regimens and to predict dosage adjustment to overcome the DDI.

Method

A whole-body PBPK model was designed in Simbiology v. 9.4.0 (MATLAB R2018a) and used to simulate DDI scenarios in 100 adults. The DTG model was qualified against reported clinical data for DTG 50mg once daily (QD) and twice daily (BID). The CYP3A4 and UGT1A1 induction model was verified using in vitro and clinical data for the CYP3A4 substrates midazolam (MDZ) and nifedipine (NIF), as well as the UGT1A1 substrates raltegravir (RAL) and DTG in the presence and absence of RIF (figures 1-3 legend). As per convention, PBPK models were assumed to be qualified if the simulated values were within 2-fold of the mean reported clinical values and if the absolute average-fold error (AAFE) was below 2. The verified DTG and RIF models were used to simulate the magnitude of DDI between: RIF 600mg QMT with DTG 50mg BID (regimen 1), RIF 1200mg QMT with DTG 50mg BID (regimen 2), RIF 1200mg QMT with DTG 100mg BID (regimen 3), RIF 1200mg QMT with DTG 50mg three times daily (TID) (regimen 4) and RIF 1200mg QMT with DTG 50mg BID for 7 days followed by DTG 50mg QD for 21 days (regimen 5).

Figure 1: PBPK Model AUC Verification

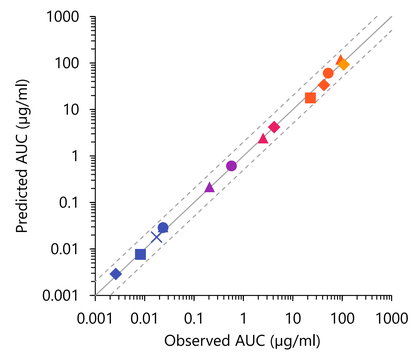


Figure 2: PBPK Model C_{max} Verification

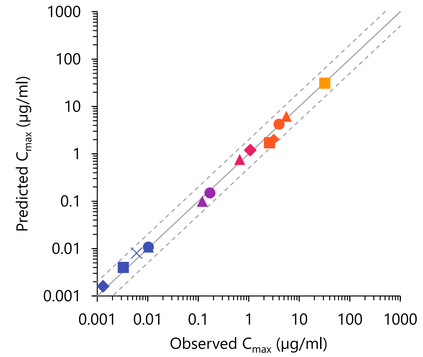
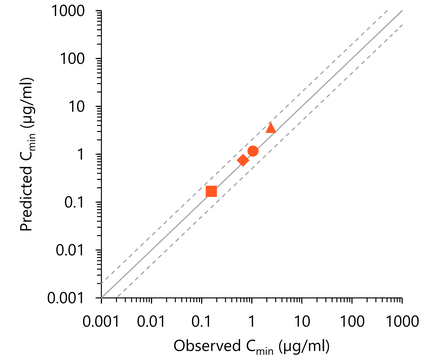


Figure 3: PBPK Model C_{min} Verification



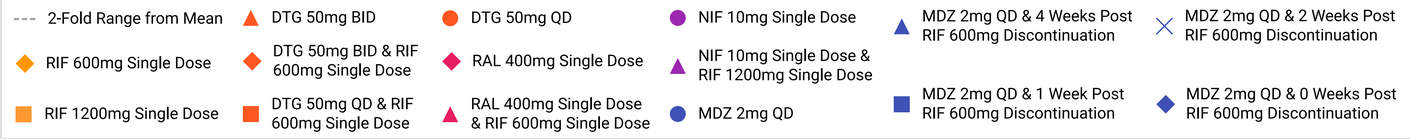


Figure 4: Single Dose RIF Induction of CYP3A4 & UGT1A1

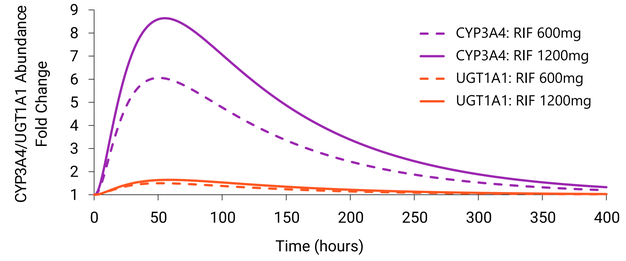
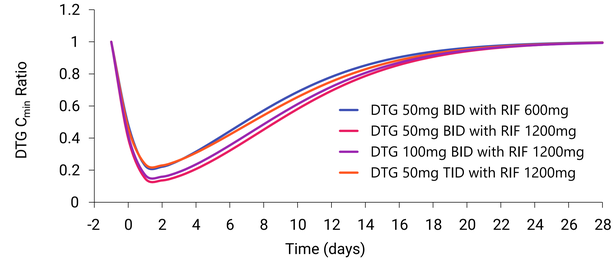


Figure 5: Ratio of DTG C_{min} Versus the DTG RIF DDI C_{min}



Results

The PBPK model was successfully qualified according to the criteria (figures 1-3). For RIF 600mg and 1200mg QMT the PBPK model simulated a maximum abundance fold-change of 6.1 and 8.6 for CYP3A4 and 1.5 and 1.6 for UGT1A1, respectively (figure 4). There was a tendency to overpredict the magnitude of RIF induction for regimen 1 relative to DTG 50 mg BID alone. The ratios of simulated versus observed area under the curve (AUC), maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) for regimen 1 were 0.63, 0.58 and 0.74, respectively. The simulated C_{min} of DTG in the presence of RIF are summarised in table 1. As expected, regimen 1 predicted C_{min} minus one standard deviation (-1 SD) values greater than 4 x DTG's protein adjusted (PA) IC_{90} (0.256µg/ml). For regimen 2, the C_{min} -1 SD fell 84% below 4 x PA-IC_{90} 1-day post RIF dose and recovered above 4 x PA- IC_{90} 4-days later. Both regimen 3 and 4 predicted C_{min} -1 SD values greater than 4 x PA-IC_{90}. Regimen 5's C_{min} -1 SD fell up to 30% below 4 x PA-IC_{90} on days 1-3 and up to 85% below on days 7-10 post RIF dose. The ratios of DTG C_{min} versus the DTG RIF DDI C_{min} are shown in figure 5. The C_{min} for all regimens was substantially reduced during the co-administration of RIF and took up to 28 days to return to their steady state values.

Conclusion

The PBPK model predicted marked reductions in the C_{min} of several DTG dosing regimens when co-administered with 600mg and 1200mg RIF QMT. Of interest, the return of DTG plasma concentrations to steady state C_{min} was predicted to be considerably delayed after coadministration of both 600mg and 1200mg RIF QMT. This was due to the enzyme degradation rates which were verified with the DDI of MDZ up to 4 weeks after the discontinuation of RIF during model verification. The PBPK model tendency to overpredict the magnitude of induction for RIF 600mg with DTG BID must be carefully considered when analysing the simulated RIF 1200mg QMT regimens.

Table 1: Pharmacokinetic Summary of Simulated DDIs Between Various Doses of RIF and DTG

Days Post RIF Dose	1	2	3	4	5	6	7	8	9	10	11	12	13	14
DTG RIF Regimen	**C_{min} (µg/ml)**													
1: DTG 50mg BID & RIF 600mg QMT	0.92 ± 0.58	0.89 ± 0.51	1.04 ± 0.56	1.26 ± 0.63	1.51 ± 0.71	1.77 ± 0.79	2.04 ± 0.87	2.29 ± 0.95	2.53 ± 1.02	2.75 ± 1.10	2.95 ± 1.17	3.13 ± 1.24	3.28 ± 1.30	3.41 ± 1.35
2: DTG 50mg BID & RIF 1200mg QMT	0.61 ± 0.57	0.55 ± 0.48	0.67 ± 0.54	0.84 ± 0.62	1.06 ± 0.72	1.31 ± 0.82	1.57 ± 0.91	1.84 ± 1.01	2.11 ± 1.10	2.37 ± 1.19	2.61 ± 1.28	2.83 ± 1.36	3.03 ± 1.44	3.20 ± 1.51
3: DTG 100mg BID & RIF 1200mg QMT	1.61 ± 0.81	1.55 ± 0.74	1.77 ± 0.80	2.09 ± 0.90	2.46 ± 0.99	2.86 ± 1.10	3.27 ± 1.20	3.67 ± 1.29	4.07 ± 1.38	4.44 ± 1.47	4.78 ± 1.56	5.09 ± 1.63	5.37 ± 1.71	5.61 ± 1.77
4: DTG 50mg TID & RIF 1200mg QMT	1.13 ± 0.82	1.06 ± 0.74	1.26 ± 0.81	1.57 ± 0.93	1.95 ± 1.05	2.36 ± 1.17	2.80 ± 1.29	3.24 ± 1.41	3.67 ± 1.52	4.07 ± 1.62	4.45 ± 1.73	4.80 ± 1.82	5.10 ± 1.91	5.37 ± 1.99
5: DTG 50mg BID for 7 days and DTG 50mg QD for 21 days with RIF 1200mg QMT	0.63 ± 0.45	0.59 ± 0.41	0.71 ± 0.46	0.90 ± 0.53	1.12 ± 0.61	1.37 ± 0.68	0.38 ± 0.34	0.40 ± 0.30	0.48 ± 0.33	0.57 ± 0.36	0.66 ± 0.40	0.74 ± 0.43	0.81 ± 0.46	0.88 ± 0.49

C_{min} values are presented as mean ± SD (µg/ml) of 100 simulated adults. Black text - mean C_{min} - 1 SD is above 4 x PA-IC_{90} (0.256µg/ml), pink text - mean C_{min} - 1 SD is below 4 x PA-IC_{90}.

References

1. Dooley, K.E. Am J Respir Crit Care Med. 2018. **2.** Milstein, M. et al. BMC Infect Dis. 2016. **3.** www.WHO.int **4.** Massone, C. et al. Expert Rev Anti Infect Ther. 2011. **5.** Chen, J. Ann Clin Microbiol Antimicrob. 2006. **6.** Castellino, S. et al. Antimicrob Agents Chemother. 2013.

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