Dose rationale for bedaquiline in paediatric patients with multi drug-resistant tuberculosis

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Introduction

Multi-drug resistant tuberculosis (MDR-TB) is a leading cause of death globally, manifesting severely in children[1]. In 2022, the World Health Organisation (WHO) conditionally recommended bedaquiline (BDQ), a novel mycobacterial ATP synthase inhibitor, to treat MDR-TB in all children[2]. However, these recommendations are based on limited evidence due to the lack of pharmacokinetic (PK) data available in children[3,4]. Moreover, efficacy has been extrapolated from adults without further understanding of the required target attainment in this population.

In addition, a high proportion of the population are co-infected with HIV and are often administered efavirenz (EFV), a first line NNRTI[5] or, ritonavir-boosted lopinavir (LPV/r), a HIV-1 protease inhibitor[6], which are known to induce and inhibit drug metabolism, respectively. Accordingly, a dose rationale is needed to ensure high probability of target attainment (PTA), safety and efficacy profiles, considering concurrent antiretroviral use.

Aim

To utilise a model-based framework to identify optimised dosing regimens for BDQ in the presence of anti-retroviral drugs in paediatric MDR-TB patients aged 2-17 years old.

Methods

A previously published population PK model[7] was adapted for the analysis. It was assumed that the underlying concentration-antibacterial activity relationship across populations is similar.

PK model

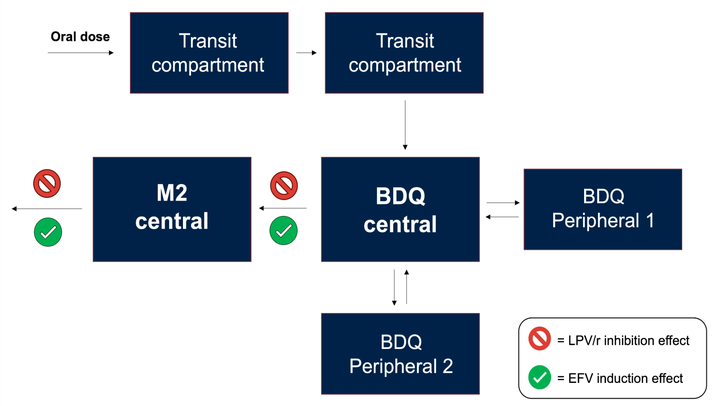


Figure 1. Final structural PK model for BDQ and M2. The model included 3 compartments for BDQ and 1 for M2. The model also included black race and age as covariates on the clearance of BDQ and M2. Allometric scaling coefficients were fixed at 0.75 (CL, Q) and 1 (V). For co-administration of EFV or LPV/r, metabolic induction or inhibition of CYP3A4 pathway, respectively and changes in both BDQ and M2 CL were considered[8,9]. Figure adapted from[7].

Allometric principles were considered for extrapolation purposes. A virtual cohort of adult (N=105, weight range 40.3kg-80kg) and paediatric patients (N=400, weight range 16kg-50kg) was selected and several dosing scenarios were simulated. The aim of the optimization step was to maximise BDQ exposure and maintain safe M2 maximum concentrations.

Simulation scenarios

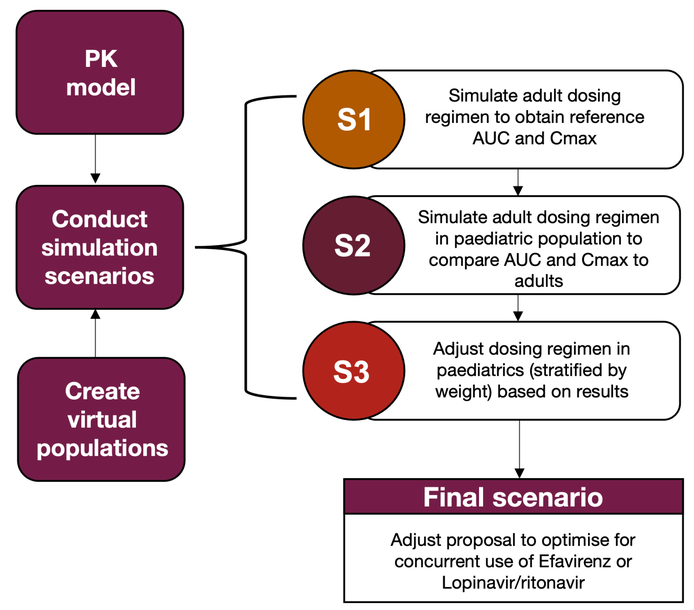


Figure 2. Simulation scenarios and analysis workflow.

Results

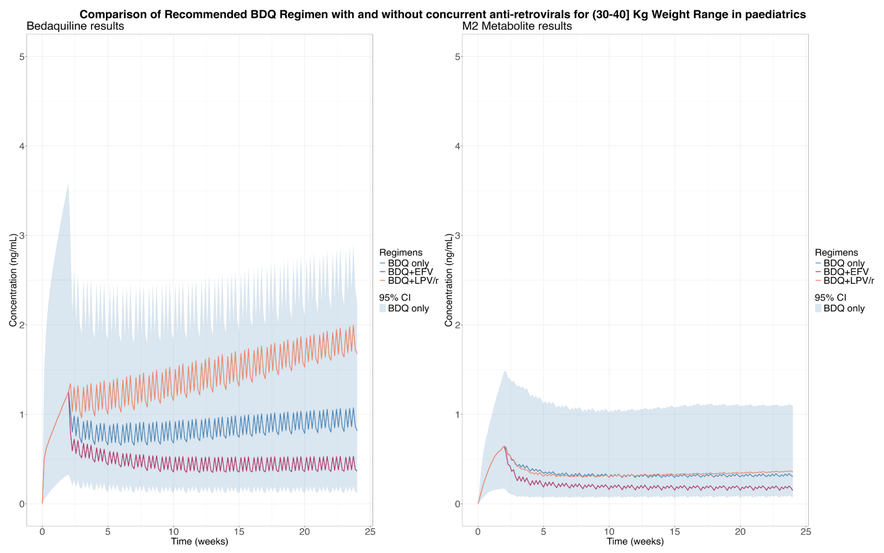
TABLE 1: *Proportion of paediatric patients within the adult reference range (5th-95th prediction intervals)*

Bedaquiline AUC at week 24		
	AUC (µg*h/mL)	
Anti-retroviral Comedications	**Recommended regimen**	**Optimised for anti-retroviral**
EFV comedication	75.5%	85.8%
LPV/r comedication	61.3%	92.6%

TABLE 2: *Median Cmax (5th-95th prediction intervals) at steady state for the M2 metabolite*

M2 steady state Cmax		
	Cmax (µg/mL)	
Anti-retroviral Comedications	**Recommended regimen**	**Optimised for anti-retroviral**
EFV comedication	0.18 (0.07-0.52)	0.28 (0.11-0.79)
LPV/r comedication	0.31 (0.12-0.85)	0.17 (0.07-0.46)

Figure 2a: Simulated concentration-time profiles



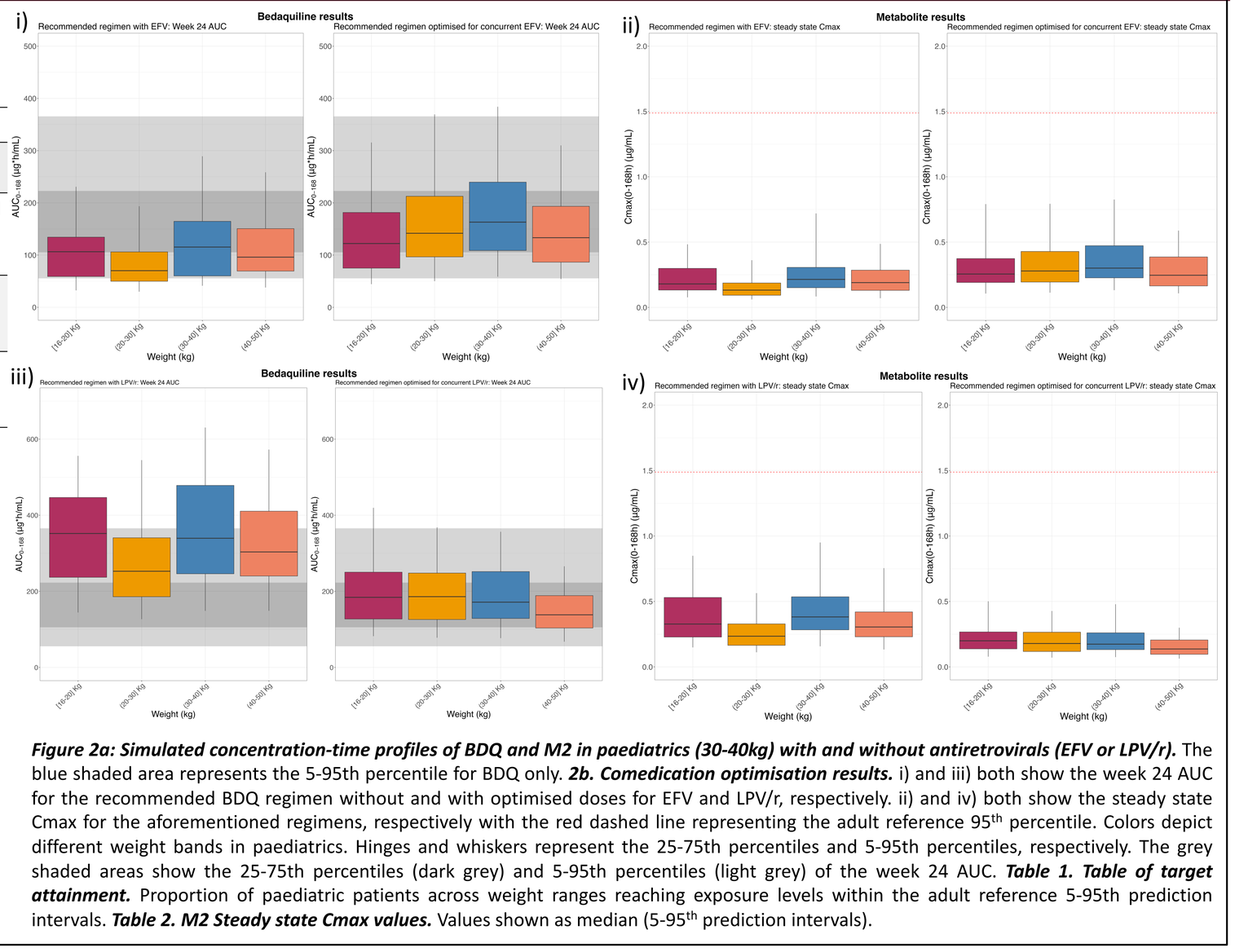


Figure 2a: Simulated concentration-time profiles of BDQ and M2 in paediatrics (30-40kg) with and without antiretrovirals (EFV or LPV/r). The blue shaded area represents the 5-95th percentile for BDQ only. ***2b. Comedication optimisation results.*** i) and iii) both show the week 24 AUC for the recommended BDQ regimen without and with optimised doses for EFV and LPV/r, respectively. ii) and iv) both show the steady state Cmax for the aforementioned regimens, respectively with the red dashed line representing the adult reference 95th percentile. Colors depict different weight bands in paediatrics. Hinges and whiskers represent the 25-75th percentiles and 5-95th percentiles, respectively. The grey shaded areas show the 25-75th percentiles (dark grey) and 5-95th percentiles (light grey) of the week 24 AUC. ***Table 1. Table of target attainment.*** Proportion of paediatric patients across weight ranges reaching exposure levels within the adult reference 5-95th prediction intervals. ***Table 2. M2 Steady state Cmax values.*** Values shown as median (5-95th prediction intervals).

Conclusions

Our study incorporates current understanding of BDQ interactions with EFV and LPV/r, establishing a dose rationale for paediatric patients often excluded from clinical trials due to HIV co-infection. We recommend the use of a three weight bands (<20 kg, 20-30 kg, 30-50 kg), with maintenance doses of 150/200/300 mg thrice weekly for 22 weeks with EFV co-administration, and 50/60/70 mg thrice weekly for 22 weeks with LPV/r co-administration. These doses ensure efficacious levels of BDQ, with a higher proportion of paediatric patients reaching target adult reference exposures. However, our findings also highlight the need for clinical decisions to balance the benefits against the risk of QT prolongation associated with higher M2 levels in patients co-administered EFV.

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