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ARTICLE

Optimizing the design of a pharmacokinetic trial to evaluate the dosing scheme of a novel tuberculosis drug in children living with or without HIV

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Abstract

Pharmacokinetic (PK) studies in children are usually small and have ethical constraints due to the medical complexities of drawing blood in this special population. Often, population PK models for the drug(s) of interest are available in adults, and these models can be extended to incorporate the expected deviations seen in children. As a consequence, there is increasing interest in the use of optimal design methodology to design PK sampling schemes in children that maximize information using a small sample size and limited number of sampling times per dosing period. As a case study, we use the novel tuberculosis drug delamanid, and show how applications of optimal design methodology can result in highly efficient and model-robust designs in children for estimating PK parameters using a limited number of sampling measurements. Using developed population PK models based on available data from adults living with and without HIV, and limited data on children without HIV, competing designs for children living with HIV were derived and assessed based on robustness to model uncertainty.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Multidrug-resistant tuberculosis (TB) is a serious infectious disease affecting children worldwide, with especially serious outcomes among those living with HIV. Pharmacokinetic (PK) studies of novel TB drugs found to be efficacious in adults are needed for children, and they require minimal sampling collection in this vulnerable population.

WHAT QUESTION DID THIS STUDY ADDRESS?

With an aim to maximize efficiency, this study seeks to apply optimal design methodology to determine sparse PK sampling times in the design of a PK trial of the novel TB drug delamanid (DLM) in children living with and without HIV.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provides a few optimal designs for studying DLM exposure in children, particularly among those with HIV when there is uncertainty in the population PK model.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT AND/OR THERAPEUTICS?

The approach presents efficient PK sampling designs robust to model uncertainty when extended to pediatric populations and subgroups (such as children living with HIV) and can thus provide alternatives or benchmarks for competing practical designs.

INTRODUCTION

Multidrug-resistant (MDR) tuberculosis (TB) is TB that is resistant to two drugs, isoniazid and rifampicin, which constitute the backbone of the first line regimen for treating drug-susceptible TB. This is a continuing global health emergency with an estimation of 450,000 new cases of MDR-TB worldwide in 2021, out of the 10 million new TB cases, as estimated by the World Health Organization (WHO).[1] Pediatric TB comprised about 8% of all new TB case notifications but there are limited published estimates on actual pediatric MDR-TB cases, with model-based methods suggesting between 25,000 and 32,000 estimated new cases annually.[2,3] Moreover, an estimated 22% of children who develop MDR-TB will die.[4] MDR-TB is also a particularly challenging issue among those living with the human immunodeficiency virus (HIV), which ranks among the top five risk factors of developing TB in 2021,[1] as this is not only a highly immunocompromised population but most are also taking antiretrovirals that may significantly interact with TB medications. These are alarming statistics that support a critical need to pay attention to children with MDR-TB, especially those living with HIV. MDR-TB has been known to be hard to treat, requiring a long duration of treatment (up to 24 months), and dependent on regimens that cause serious and potentially permanent side effects. In recent years, novel drugs have been evaluated in late phase clinical trials and have shown significant improvements in efficacy in adults when they were added to the optimized background regimen.[5,6] Moreover, these drugs have the potential to replace the more toxic drugs as well as dramatically shorten treatment duration. One such drug is delamanid (DLM).[5,7]

A strategy that has been adopted in pediatric TB drug research, including that for the novel drug DLM, is to conduct small pediatric pharmacokinetic (PK) studies to identify doses that achieve drug levels similar to adults, as well as evaluate safety at the proper dose.[8] A pediatric age de-escalation PK trial in four age groups called Otsuka 232 was conducted by the drug developer Otsuka (ClinicalTrials.gov identifier NCT01856634) to determine the appropriate dosing scheme from children without HIV. Extension of dosing recommendations to children living with HIV is a critical component of the research, and IMPAACT 2005 (ClinicalTrials.gov identifier NCT03141060) is one study that was originally designed for this purpose. This latter study uses sparse PK sampling as this requires a minimal number of blood draws over a dosing interval.[9] Estimated PK parameters are obtained by fitting data from these sparse samples to population PK models.[10,11]

Our goal in this work is to determine optimal PK sampling times, under a fixed prespecified number of PK sampling times per dosing interval and fixed number of participants in each of four prespecified pediatric age groups in IMPAACT 2005. At the design stage, simulation work will rely on an assumed pediatric population PK model that is extended from fitted models determined from all available previous studies. If available, fitted models are based only on adult data, extensions involve the use of allometric scaling and maturation functions to account for differences in age, weight, and organ function between children and adults.[12–16] We apply optimal design methodology in the determination of the optimal sampling times.[17,18] Examples of this have recently been presented in the literature for PK modeling of antipsychotic drugs, antimalarial drugs, and a cocktail of phenotyping drugs, among others.[19–21] This is also becoming an active area of investigation in the design of pediatric studies.[22–28] In this case study, optimality will be with respect to prespecified precision criteria on estimation of PK parameter effects of interest, including that corresponding to the main exposure parameter (area under the curve from 0 to 24 h [AUC_{0-24}]) that will be compared to target exposure in adults.[29,30]

We use the drug DLM as a case study to show how application of optimal design methodology[31] can lead to highly efficient designs for estimation of PK parameters using a limited number of measurements or, at the minimum, provide a benchmark to gauge efficiency of competing

designs. Further, these methods can be used to assess if a design meets the US Food and Drug Administration (FDA) suggestions regarding precision of the PK parameter estimates, as described in Wang et al.[12]

METHODS

We first describe the design and PK sampling schemes used in the two pediatric PK trials mentioned earlier, Otsuka 232 and IMPAACT 2005. We then describe the pediatric PK model that was developed based on: (1) the structural model derived from PK collected in adults with MDR-TB (with and without HIV co-infection), and (2) available PK data from children living without HIV who completed the Otsuka 232 trial plus a 6-month safety and tolerability extension trial (Otsuka 233). In extending the model to include children living with HIV and on an efavirenz (EFV)-based regimen, we also consider the plausibility of a difference in clearance and relative bioavailability due to HIV infection status in the pediatric model, as suggested by PK data in adults. Next, we derive the optimal design for the extended model to estimate the PK parameters relevant to the primary objective of the proposed pediatric PK trial. Finally, with the intention of augmenting the PK data from each of these derived designs to Otsuka 232 PK data, we compare the derived optimal design with the original IMPAACT 2005 design. In addition, we evaluate the robustness of these designs under various model misspecification cases.

Otsuka 232 design

The first pediatric study[29] had a target enrollment of 24 HIV uninfected children with MDR-TB ages zero to less than 18 years old, with six children in each of four age groups, and with the following dosing/formulation scheme:

Age group (years)	12 to less than 18	6 to less than 12	3 to less than 6	0 to less than 3
Dose/ formulation	100 mg b.i.d. (2 × 50 mg tablets)	50 mg b.i.d. (1 × 50 mg tablets)	25 mg b.i.d. (DPF)	5.5–8 kg: 5 mg q.d. DPF greater than 8–10 kg: 5 mg b.i.d. DPF greater than 10 kg: 10 mg b.i.d. DPF

b.i.d., twice per day; q.d., once per day; DPF, dispersible pediatric formulation.

Children received DLM with background TB regimen for 10 days, at doses expected to achieve similar exposure (AUC_{0-24h}) as adults. PK data were collected at five different occasions with the following intensive sampling scheme at days 1 and 11:

Dose day	1	11
Hours post-morning dose	0, 2, 4, 10, 12, 14, 24	0, 2, 4, 10, 12, 14, 24, 72, 120, and 192

IMPAACT 2005 design

The second pediatric study has a target enrollment of 36 children with MDR-TB ages zero to less than 18 years old, with or without HIV infection. Nine children will be enrolled in each of the same four age groups described in Section "Otsuka 232 design," six HIV-infected and on EFV-based regimen and three HIV uninfected. Children are also receiving DLM with background TB regimen for 24 weeks, at doses expected to achieve similar exposure (AUC_{0-24h}) as adults, with the following dosing/formulation scheme:

Weight band	Greater than or equal to 40 kg	30 to less than 40 kg	15 to less than 30 kg	Less than 15 kg
Dose (formulation)	100 mg b.i.d. (2 × 50 mg tablet)	50 mg b.i.d. (1 × 50 mg tablet)	25 mg b.i.d. (1 × 25 mg DPF)	15 mg b.i.d. (3 × 5 mg DPF)

b.i.d., twice per day; DPF, dispersible pediatric formulation.

To allow for evaluation of exposure metrics while reducing patient burden, a sparse PK data design was used, collecting samples from days 1, 11, 29 ± 3, 57 ± 3, 85 ± 7, 113 ± 7, 169 ± 7, and 197 ± 7, with blood drawn for PK at only four different timepoints on day 11, three different time points on days 1 and 57 ± 3, and only one timepoint for the other days:

Week	1	2	5	9	13	17	25	29
Day	1	11	29 ± 3	57 ± 3	85 ± 7	113 ± 7	169 ± 7	197 ± 7
Hours post-dose	0, 4, 8	0, 2, 4, 8	0	0, 4, 8	0	0	0	4

Pediatric model for children living without HIV (model 1)

A population PK model for DLM was developed by Sasaki et al.[29] based on PK data obtained from previous trials, including PK data from children with MDR-TB but living without HIV (Otsuka 232) and a 6-month safety and tolerability extension trial in the same population (Otsuka 233). This nonlinear mixed-effect PK model (model 1) is a two-compartment linear model with a transit compartment absorption model (4 compartments), parameterized by clearance (CL), central volume of distribution (V_1), peripheral volume of distribution (V_2), intercompartmental clearance (Q), mean absorption time, and the relative bioavailability of DLM

in the patient (F). See Appendix S1 (Supplement A) for more details.

Extended pediatric models for children with HIV (and on EFV-based regimen) and those without HIV

With the inclusion of children with HIV, specifically limited to those who are on an EFV-based antiretroviral regimen, we extend the pediatric model to reflect that drug clearance differs between HIV uninfected and HIV infected children on EFV (model 2), as in the adult model.[30] A further extension with presence of effect of HIV infection and/or EFV administration on CL and F was also investigated (model 3). Because all children living with HIV who will be enrolled in IMPAACT 2005 will also be on EFV-based regimen, data obtained from this design does not have the ability to tease out the effects HIV infection from the effect of EFV administration. See Appendix S1 (Supplement A) for technical descriptions of these models.

Optimal designs for a pediatric population

We now investigate how the choice of PK sampling times in the design for IMPAACT 2005, with the intention to pool data from this design with data from the Otsuka 232 trial, can potentially improve statistical inference by using optimal design methodology. We assume that doses and number of individuals in the study are fixed and not available for optimization. For this application, the main PK exposure metric of interest is the AUC_{0-24} of DLM at steady-state, achieved at around week 2 from treatment initiation, because this is the PK exposure we want to compare to adult exposure. For the typical individual exposed to the drug, AUC_{0-24} can be derived from the computed values for the typical values of CL and relative F, through the formula $AUC = Dose \bullet F/CL$. Thus, the ability to accurately determine the typical values of AUC across pediatric subgroups can be one guide for design optimality.

Further, a precision criterion specified by the FDA, states that pediatric studies should be designed to have sufficient statistical power (>80%) to target a 95% confidence interval that is within 60% and 140% of the geometric mean estimates of CL and volume of distribution in each pediatric subgroup.[12] In our evaluations, because we have relative F in our models, we compute the expected 95% confidence intervals for the geometric mean of apparent clearance, $CL_{app} = \frac{CL}{F}$, and apparent volume of distribution, $V_{1,app} = \frac{V_1}{F}$. In the models we investigate here, log-normal distributions are assumed for the parameters' random effects, so the geometric mean of these parameters is just the typical value ($\vec{\eta}_i = 0$) for any vector of covariates, whereas the confidence intervals of the geometric mean can be calculated via the delta method using the expected uncertainty of the estimated parameters.

If one assumes that there is no HIV effect on drug exposure (model 1) then, according to the above considerations, a design objective could be to determine the PK sampling timepoints that would enable estimation of the subset of coefficients $\left(\theta_{CL}, \theta_{V_1}, \text{and } \theta_{AGE-F}\right)$, associated with the typical values of the parameters $\left(CL_i, V_{1i}, \text{and } F_i\right)$, with highest precision, while still estimating all parameters with some precision. To achieve this using optimal design methodology, we use the Ds-optimality criterion.[31–33] See Appendix S1, Supplement B, for details of our approach and design constraints for this paper.

Under the same distribution of participants per age group and design space constraints described for the Ds-optimal design under model 1, we also obtained Ds-optimal designs under the following models: (1) model 2 with $\theta_{HIV-CL} = 0.20$ (20% increase in DLM clearance for children with HIV and on EFV); and (2) model 3 with $\theta_{HIV-CL} = 0.20$ and $\theta_{HIV-F} = 0.20$ (20% increase in DLM clearance and 20% decrease in bioavailability for children living with HIV and on EFV). We consider a 20% change in values from model 1, for the clearance and/or bioavailability parameters under models 2 and 3, as this is commonly used as a cutoff influence of a covariate which may have clinical significance and in line with bioequivalence criteria.[34] The Ds-optimal design for model 2 estimates the subset of coefficients $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}, \theta_{CL-HIV}\right)$, associated with the typical values of the parameters $\left(CL_i, V_{1,i}, F_i, Z_{HIV-CL,i}\right)$, as "interesting" and the rest as "uninteresting." The Ds-optimal design for model 3 estimates the subset of coefficients $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}, \theta_{CL-HIV}, \theta_{F-HIV}\right)$, associated with the typical values of the parameters $\left(CL_i, V_{1,i}, F_i, Z_{HIV-CL,i}, Z_{HIV-F,i}\right)$, as "interesting" and the rest as "uninteresting." Additionally, these designs have the same distribution constraints on participant HIV status in each age group as in IMPAACT 2005 with three living without HIV and six living with HIV (and on EFV).

Evaluation of pediatric designs with full covariate distributions

The Ds-optimal pediatric PK designs for models 1, 2, and 3 are determined using the approximation that each cohort of patients have the same covariate values (i.e., dosing, weight, and age are the same for all patients in a cohort, defined in Table S2, Appendix S1, Supplement B). To obtain a more complete design

evaluation, the final, optimized designs are evaluated more accurately, after incorporating the additional variation in covariates expected in these designs. Specifically, (1) we simulate ages and weights for individuals in the study, within the expected ranges (see below), and (2) we compute the expected parameter uncertainty, via the *FIM*, given the realized covariates and the study design. We then repeat (1) and (2) 100 times and report the average of the parameter uncertainty calculations. The simulated ages were sampled randomly from a uniform distribution within the age cohorts that the individual is assigned (12 to <18 years, 6 to <12 years, 3 to <6 years, and 0 to <3 years), and the simulated weights were random samples taken from an adjusted growth reference for age-weight distribution for children with pulmonary TB (based on WHO references for children <10 years old, and NHANES reference for children ≥10 years old).[35] These more accurate assessments of expected model uncertainty are then used to compute the 95% confidence interval of the geometric mean estimates of the apparent CL and apparent volume of distribution in each pediatric subgroup and to see if these confidence intervals lie within 60% and 140% of the geometric mean, as described above. See Appendix S1, Supplement C for technical details.

RESULTS

Evaluation of the existing designs

Original design for IMPAACT 2005 and Otsuka 232

Table 1 shows the expected parameter relative standard error (RSE) values (in percentages) for estimating each parameter in the pediatric model with no HIV/EFV effect on DLM exposure (model 1), for the original IMPAACT 2005 design, the original Otsuka design, and when data from both designs are combined (pooled data analysis). As expected, given that the assumed pediatric model was fitted to data from it, and with a more intensive PK sampling collection, the Otsuka design shows at least as good as, or better, precision for estimating almost all model parameters. Although the IMPAACT 2005 design shows better precision in estimating the clearance parameter, the Otsuka design has much lower RSE in estimating volume and intercompartmental clearance parameters.

For the original IMPAACT design, the FDA precision criterion for CL_{app} is met throughout the entire age range under models 1 and 2 (Figure 1). However, this was not met under model 3 throughout the entire age range. The precision criterion for V_1 was far from being met under all models.

TABLE 1 Expected RSE (in %) of parameters for the model with no HIV effect (model 1) for the original design for IMPAACT 2005, the design for Otsuka 232, and when both designs are pooled.

Parameter	Original design IMPAACT 2005	Original design Otsuka 232	Pooled data
θ_{CL}	3	4	2
θ_{V_1}	64	6	6
θ_Q	152	21	17
θ_{V_2}	55	14	12
θ_{MAT}	30	4	4
$\theta_{\text{AGE}-F}$	21	19	14
ω_{CL}	30	36	23
ω_{V_2}	98	32	31
σ	7	8	5

Abbreviations: CL, clearance; *F*, bioavailability; MAT, mean absorption time; RSE, relative standard error; V_1, central volume of distribution; V_2, peripheral volume of distribution.

Estimation when data pooled with Otsuka 232 trial

When data from the Otsuka trial and IMPAACT 2005 under the original design are pooled, there is improvement in precision of all model parameters in all three models compared to the original IMPAACT 2005 design, as expected (Table 2). The RSE for estimating θ_{CL} decreases by 33% and 40% under model 1, and models 2 and 3, respectively, whereas the RSE for estimating θ_{V_1} decreases by 91% under all models. The RSE for estimating $\theta_{\text{CL}-\text{HIV}}$ decreases by 26% and 28% under model 2 and model 3, respectively, and the RSE for estimating $\theta_{F-\text{HIV}}$ is 30% lower under model 3. The FDA precision criteria are met for all specified parameters of interest under the three model scenarios when pooling the data (Figure 2).

Ds-optimal designs for the pediatric models

We use data from the Otsuka 232 trial (i.e., data from the optimal design and the Otsuka 232 design are pooled) to optimize the Ds-optimality criterion under the different model assumptions. For example, if HIV/EFV has no effect on DLM exposure in children, that is, the population PK model described by model 1 is

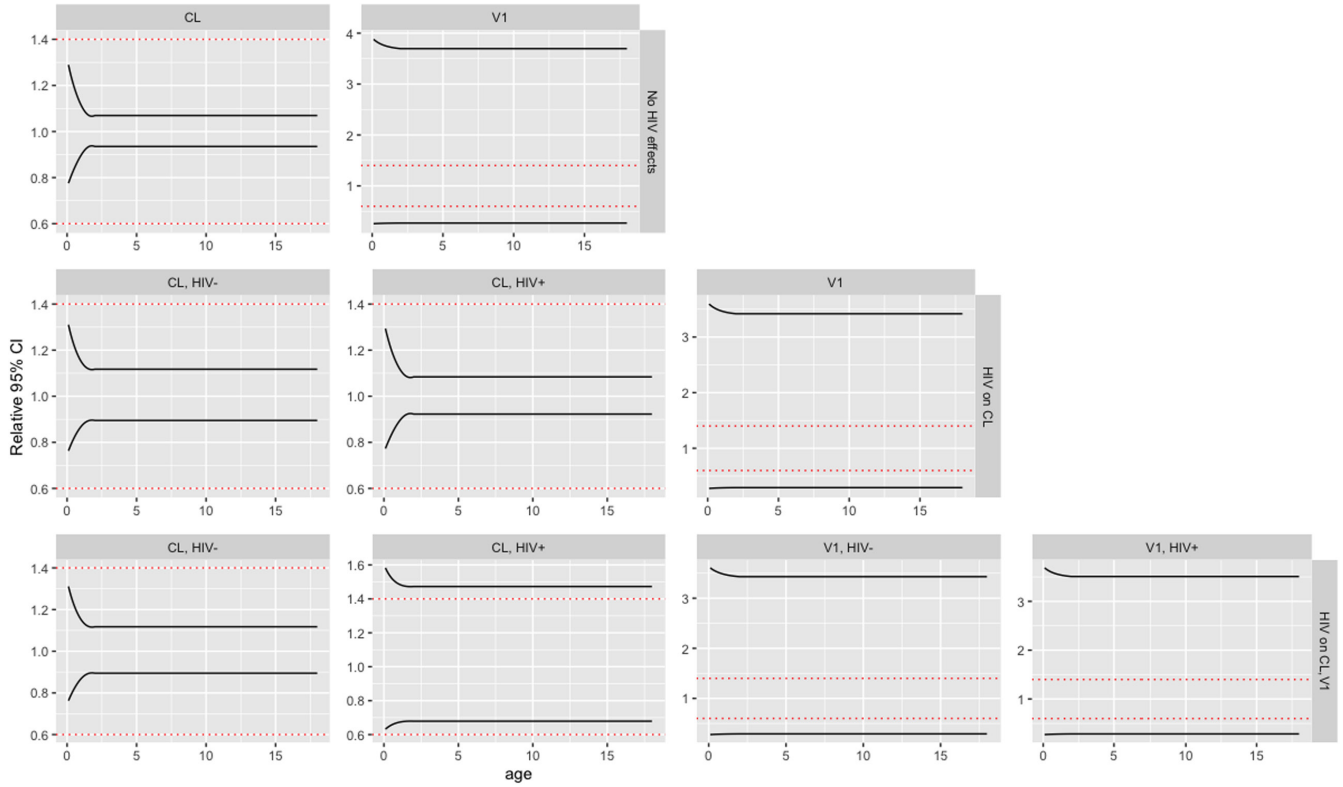

FIGURE 1 FDA criteria for apparent CL and V_1 each from model 1 (first row), model 2 (second row), and model 3 (third row) using the original IMPAACT 2005 design. (Relative 95% CI for geometric mean estimate should be between 0.6 [bottom red line] and 1.4 [top red line] to pass the criteria). CI, confidence interval; CL, clearance; FDA, US Food and Drug Administration; *V*1, central volume of distribution.

TABLE 2 Expected RSE (in %) of parameters for the three model scenarios when Otsuka trial data is pooled with data from the original design for IMPAACT 2005.

	Original IMPAACT 2005 design			Pooled data from Otsuka 232 trial and original IMPAACT 2005 design		
Parameter	Model 1 (no HIV effect)	Model 2 (20% higher CL if HIV+)	Model 3 (20% higher CL and 20% lower F if HIV+)	Model 1 (no HIV effect)	Model 2 (20% higher CL if HIV+)	Model 3 (20% higher CL and 20% lower F if HIV+)
θ_{CL}	3	5	5	2	3	3
θ_{V_1}	68	64	64	6	6	6
θ_Q	165	153	154	17	17	19
θ_{V_2}	56	52	53	12	12	12
θ_{MAT}	32	29	29	4	4	4
θ_{AGE-F}	36	36	36	14	14	14
ω_{CL}	30	30	30	23	23	23
ω_{V_2}	99	98	98	31	31	31
σ	7	7	7	5	5	5
θ_{CL-HIV}		39	66		29	47
θ_{F-HIV}			37			26

Abbreviations: CL, clearance; *F*, bioavailability; MAT, mean absorption time; *Q*, intercompartmental clearance; RSE, relative standard error; V_1, central volume of distribution; V_2, peripheral volume of distribution.

the true model, then the Ds-optimal design for the coefficients $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}\right)$, associated with the typical values of the parameters $\left(CL_i, V_{1,i}, F_i\right)$ in model 1, should provide the most efficient estimates of these three parameters overall when combined with data from the Otsuka 232 trial.

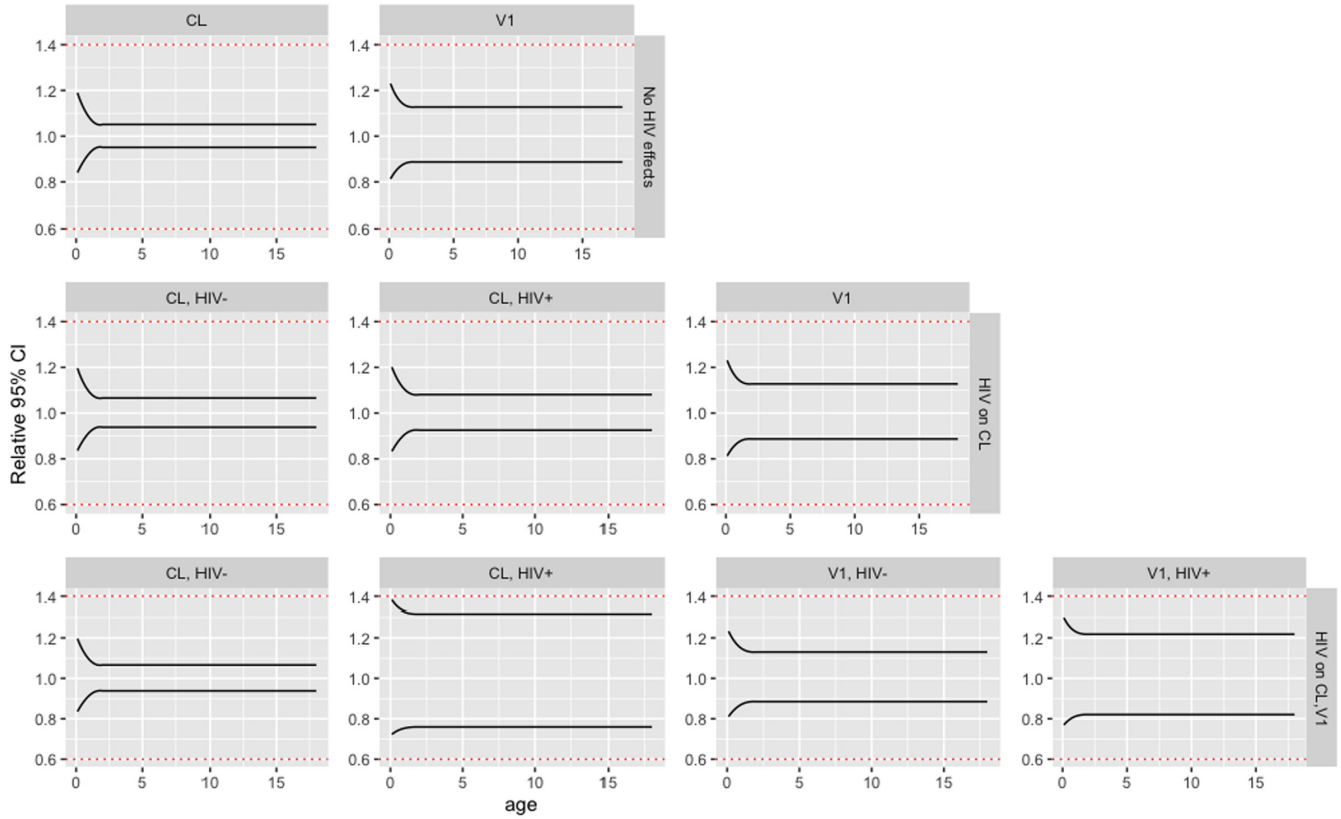

FIGURE 2 FDA criteria for CL and V_1 based on model 1 (first row), model 2 (second row), and model 3 (third row) under the original IMPAACT 2005 design pooled with data from the Otsuka trial. (Relative 95% CI for geometric mean estimate should be between 0.6 [bottom red line] and 1.4 [top red line] to pass the criteria). CI, confidence interval; CL, clearance; FDA, US Food and Drug Administration.

TABLE 3 Ds-optimal designs for the pediatric models (sampling times shown in hours postdose).

Week	1	2	5	9	13	17	25	29
Day	1	11	29 ± 3	57 ± 3	85 ± 7	113 ± 7	169 ± 7	197 ± 7
IMPAACT 2005	0, 4, 8	0, 2, 4, 8	0	0, 4, 8	0	0	0	4
Model 1	0, 0.17, 3	3, 4, 5, 8	0	3, 4, 8	0	0	0	4
Model 2	0, 0.17, 3	0, 4, 7, 8	0	0, 3, 4	0	0	0	4
Model 3	0, 0.17, 4	0, 3, 4, 5	0	0, 4, 5	0	0	0	4

With a target enrollment of nine children in each of the four age groups, with six children with HIV and on EFV and three children without HIV in each age group, and restricting the search to the design space described in the previous section, Table 3 provides the derived set of optimal sampling times that optimize the Ds-optimality criterion for each model. For the days with multiple sample collection, the sampling times within each dosing period shifted closer to each other compared to the original IMPAACT 2005 design. Moreover, for many of the multi-sample days, all samples would be collected before 8 h from dosing. All these features make this optimal design easier to perform, especially during day 1 when all samples would be collected within, at most, only 4 h after dosing.

Evaluation of the Ds-optimal designs (pooled with Otsuka 232 trial data)

Relative efficiency

In terms of performance, compared to the original IMPAACT 2005 design, the relative efficiency (RE) of the Ds-optimal design for model 1 is 1.05 for estimating the typical model parameters describing $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}\right)$ of the pediatric model with no HIV

TABLE 4 Expected RSE (in %) of parameters of interest for the three model scenarios for the different Ds-optimal designs (ngroup = 6 using typical covariate values for AGE and WT).

Model	Parameter	Original design	Ds-optimal for model 1	Ds-optimal for model 2	Ds-optimal for model 3
Model 1	θ_{CL}	2.4	2.4	2.4	2.4
	θ_{V_1}	5.8	5.5	5.5	5.5
	θ_{AGE-F}	14.2	13.4	13.6	13.5
Model 2	θ_{CL}	3.1	3.1	3.1	3.1
	θ_{V_1}	5.8	5.5	5.5	5.5
	θ_{AGE-F}	14.2	13.4	13.6	13.5
	θ_{CL-HIV}	28.9	29.2	29.0	29.0
Model 3	θ_{CL}	3.1	3.1	3.1	3.1
	θ_{V_1}	5.9	5.5	5.5	5.6
	θ_{AGE-F}	14.2	13.4	13.6	13.5
	θ_{CL-HIV}	47.0	44.8	43.7	43.6
	θ_{F-HIV}	26.1	22.8	22.8	22.4

Abbreviations: CL, clearance; *F*, bioavailability; RSE, relative standard error; V_1, central volume of distribution; WT, weight.

effect (model 1). That is, for the original IMPAACT 2005 design to match the Ds-optimal design for model 1 in terms of information content, we would need 5% more participants. Compared to the original IMPAACT 2005 design, using the Ds-optimal for model 2 will result in an RE of 1.04 for model parameters describing $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}, \theta_{CL-HIV}\right)$ in model 2; using the Ds-optimal for model 3 will result in a 9% improvement in estimation efficiency (RE = 1.09) for model parameters describing $\left(\theta_{CL}, \theta_{V_1}, \theta_{AGE-F}, \theta_{CL-HIV}, \theta_{F-HIV}\right)$ in model 3. Another interesting observation is that any pairwise comparison of the three Ds-optimal designs under each of the three competing models result in a relative efficiency that is ~1.0, which means that any of these Ds-optimal designs is almost Ds-optimal for estimating parameters of interest in any of these models.

Expected RSE

Table 4 shows the expected RSE values when estimating the corresponding parameters of interest of each of the potential models, for each of the designs. The Ds-optimal designs provide, roughly, the same precision under any of the three model scenarios. The Ds-optimal designs have approximately the same RSE value as the original IMPAACT 2005 design for estimating θ_{CL}, whereas the Ds-optimal designs show modest improvement in estimation precision for θ_{V_1} and θ_{AGE-F} compared to the original IMPAACT 2005 design. Under model 3, improvements in estimation precision are also observed with the Ds-optimal designs (compared to the original IMPAACT 2005 design) for θ_{CL-HIV} and θ_{F-HIV}.

FDA criteria

Given the increased precision seen in the Ds-optimal designs, these designs, naturally, also pass the FDA criterion for apparent CL and volume of distribution, because the criterion was already passed with the non-optimized IMPAACT trial design pooled with data from Otsuka 232 (not shown). For example, see Figure 3 for model 3 apparent clearance and volume under the Ds-optimal design for model 3.

DISCUSSION

With the original IMPAACT 2005 design alone, all the model parameters are not well-estimated, as reflected by the RSE and the FDA criterion.[12] Of note, the FDA criterion is never passed for the V_1 parameter with this design under any model scenario. Although this design allows for relatively good estimation of CL, it is not the case for estimation of HIV/EFV effect on CL and *F* at the same time. The Otsuka trial was designed exclusively for children without HIV and, thus, can only provide information for model 1. This design allows for relatively better estimation of almost all model 1 parameters (as expected, because the model was developed from these data), but lower precision for estimation of θ_{CL}.

As the intent of the IMPAACT 2005 study has been to combine information with the Otsuka trial data, design optimization included information from the Otsuka design in the objective function to be optimized. Pooled with Otsuka data, the original IMPAACT 2005 design is, of course, expected to perform better than each of these two

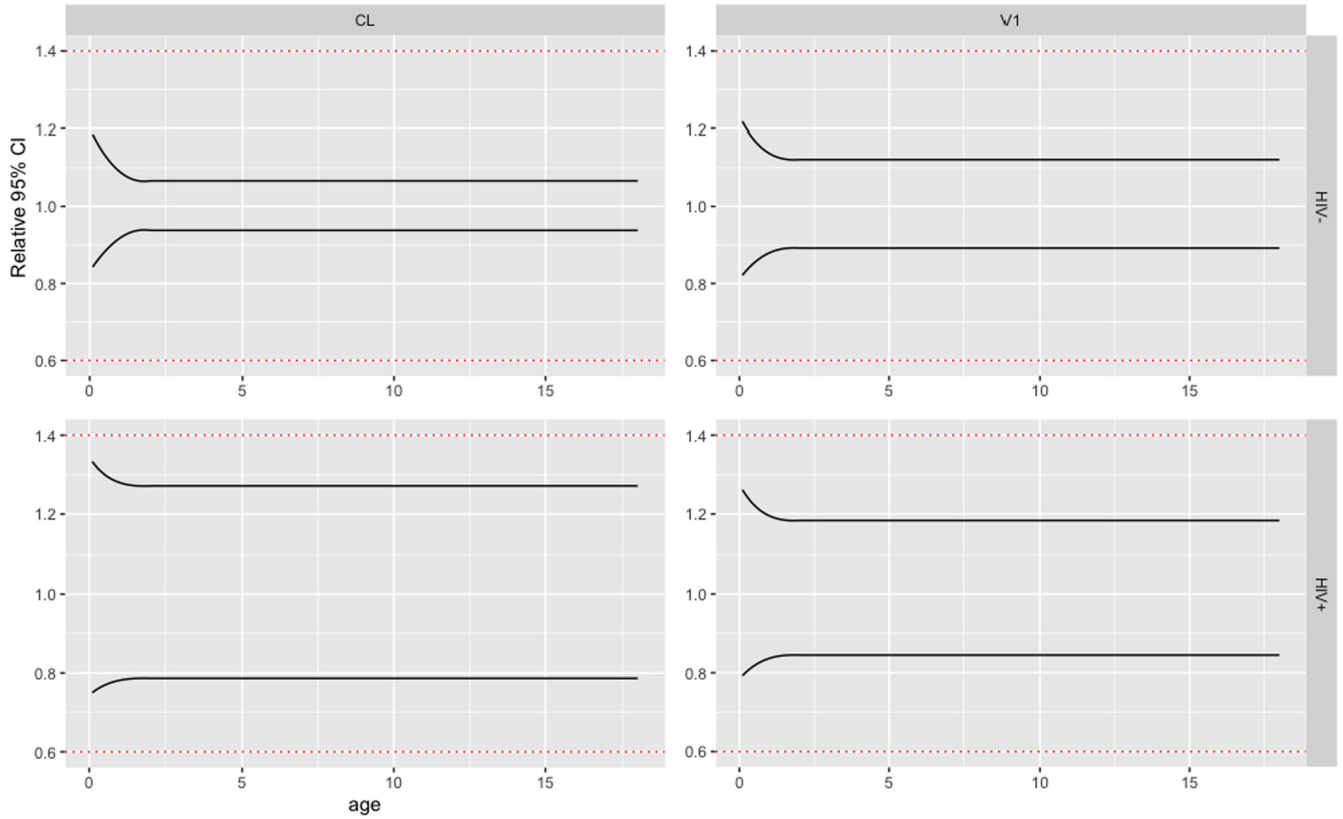

FIGURE 3 FDA criteria for apparent CL and V_1 based on model 3 under the Ds-optimal design pooled with Otsuka trial data. (Relative 95% CI for geometric mean estimate should be between 0.6 [bottom red line] and 1.4 [top red line] to pass the criteria). CI, confidence interval; CL, clearance; FDA, US Food and Drug Administration; $V1$, central volume of distribution.

designs alone, and was able to fulfill the FDA criteria for both CL and V_1, including the corresponding HIV effects on these parameters (if relevant) under each of the three candidate models.

The Ds-optimal designs are also able to fulfill the FDA criteria under all scenarios. Moreover, these optimal designs provided the same improved precision with nearly equivalent RSE values for the subset of parameters of interest under each of the models (their efficiencies relative to each other are approximately one under all three models). For the original IMPAACT 2005 design to match the information content of these Ds-optimal designs (that is, to achieve the same estimation precision for $\theta_{\mathrm{CL}}, \theta_{V_1}, \theta_{\mathrm{AGE}-F}, \theta_{\mathrm{CL}-\mathrm{HIV}}, \theta_{F-\mathrm{HIV}}$. the sample size would have to increase by 4%–9%. Under model uncertainty, it makes sense to use any of these Ds-optimal designs. Because the Ds-optimal design for model 3 seems to have a slightly better practical advantage (all the PK samples during the multi-sampling periods are collected within the shortest period), this would perhaps be the best design to use.

A technical challenge observed in this case study is the long run time it takes to evaluate the designs with even a modest number of simulations from the covariate distribution, primarily due to the complexity of the models. This issue makes derivation of the Ds-optimal design prohibitive (for example, for model 1 it takes about 3 weeks), if it incorporates variability in the covariate values of participants within age groups. Nature-inspired meta-heuristic search algorithms,[36,37] notably swarm-based algorithms, like particle swarm optimization (PSO) and many of its variants, may be potentially useful when optimizing with many potential realizations of the covariate values. This is because PSO, like other metaheuristic algorithms, are general purpose optimization algorithms that virtually require no technical assumptions for it to work well. They have been shown in the computer science and engineering literature to optimize hundreds or thousands of variables, work fast, and extricate themselves from a local optimum.

One can also expand robustness of the optimal design search to accommodate uncertainty in assumed model parameters, including HIV parameter effects, by considering distributional assumptions on these parameters and then derive designs based on composite criteria such as ED-optimality. ED-optimal designs optimize a function of the expectation of the FIM over some specified prior distribution of these parameters.[38,39] As this approach will introduce further computational burden, PSO can be a potential solution.

This case study shows how optimal design tools can systematize design optimization and avoid implementation of cumbersome trial and error simulation-based assessments.

We can examine many more designs and model assumptions, as well as allow flexibility and/or relaxations in design specifications, such as, for example, removal of noninformative observations, addition of more observations, etc. We also derived Ds-optimal designs that allowed optimization of accrual proportion per age group, which led to significant increases in proportions allocated to the oldest and youngest age groups; however, this would not be ideal with minimum safety data requirements in each age group.

AUTHOR CONTRIBUTIONS

G.M., A.C.H., E.M.S., and W.K.W. wrote the manuscript. G.M., E.M.S., and A.C.H. designed the research. G.M. and A.C.H. performed the research. A.C.H. contributed new analytical tools.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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