Model-Based Once-Daily Darunavir/Ritonavir Dosing Recommendations in Pediatric HIV-1-Infected Patients Aged ≥3 to <12 Years

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An existing population pharmacokinetic model of darunavir in adults was updated using pediatric data from two studies evaluating weight-based, once-daily dosing of darunavir/ritonavir (ARIEL, NCT00919854 and DIONE, NCT00915655). The model was then used to provide once-daily dosing recommendations for darunavir/ritonavir in pediatric patients aged ≥3 to <12 years. The final model comprised two compartments with first-order absorption and apparent clearance dependent on the concentration of α1-acid glycoprotein. The recommended darunavir/ritonavir once-daily dosing regimens in children aged ≥3 to <12 years are: 35/7 mg/kg from 10 to <15 kg, 600/100 mg from 15 to <30 kg, 675/100 mg from 30 to <40 kg, and 800/100 mg for ≥40 kg. These doses should result in exposures similar to the adult exposure after treatment with darunavir/ritonavir 800/100 mg once daily, while minimizing pill burden and allowing a switch from suspension to tablet(s) as early as possible.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC? Darunavir/ritonavir is administered once daily in combination with other antiretroviral agents, for treatment-naive adolescents aged >12 years and adults, and for treatment-experienced patients who have no darunavir RAMs. Dosing recommendations for darunavir/ritonavir were needed for once-daily dosing in children 3 to <12 years old. • WHAT QUESTION DID THIS STUDY ADDRESS? This analysis used a model-based approach to provide darunavir once-daily dose recommendations for treatment-naive (or treatment-experienced with no darunavir RAMs) pediatric patients aged ≥3 to <12 years to achieve exposures comparable to those achieved with darunavir/ritonavir 800 mg/100 mg once daily in adults. • WHAT THIS ANALYSIS ADDS TO OUR KNOWLEDGE This analysis gives guidance for once-daily darunavir/ritonavir dosing for treatment-naive (or treatment-experienced with no darunavir RAMs) children aged ≥3 to <12 years according to weight band. • HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS This analysis used a model-based approach to interpolate once-daily dosing recommendations for children 6 to <12 years old using pharmacokinetic data from children 3 to <6 years old and adolescents 12 to <18 years old.

There has been a dramatic decrease in the morbidity and mortality of human immunodeficiency virus (HIV)-1-infected children since the introduction of HIV-1 protease inhibitor (PI)-containing antiretroviral regimens.1,2 However, more treatment options in suitable formulations are still needed for HIV-1-infected children, especially those aged under 6 years. Determination of appropriate dosing regimens in this age group requires specific trials, particularly as there are significant risks associated with underdosing,3 such as treatment failure and development of resistance.

Darunavir is a PI that, when used in combination with low-dose ritonavir or cobicistat, significantly reduces viral load in treatment-naive and experienced HIV-1-infected adults.3–10 Darunavir is available as an oral suspension (100 mg/ml), with comparable bioavailability to the tablet formulations.11 Tablets for pediatric administration are available in strengths of 75, 150, and 600 mg; an 800 mg tablet is also available.12 A fixed-dose combination tablet of darunavir 800 mg with cobicistat 150 mg is currently only available for use in adults6; there is no fixed-dose combination of darunavir and ritonavir. Ritonavir is available as an oral 80 mg/ml solution and 100 mg capsule and tablet. A study of darunavir/cobicistat for pediatric use is currently ongoing (GS-US-216-0128: NCT02016924).

DELPHI studied the pharmacokinetics, efficacy, and safety of darunavir/ritonavir twice-daily dosing in treatment-experienced children and adolescents (6 to <18 years old).13 Two further pediatric trials examining the safety and efficacy of darunavir/ritonavir given with ≥2 active antiretroviral agents, ARIEL (NCT00919854)14 and DIONE (NCT00915655),15 have been conducted. The pharmacokinetics of once-daily darunavir/ritonavir have also been evaluated in a substudy of ARIEL14,16 and in DIONE. Once-daily dosing for darunavir/ritonavir was initially developed for adults, based on darunavir’s relatively long elimination half-life, the desirability of regimen simplification, and the reduction of the required ritonavir daily dose.17 Clinical trials have established the efficacy and safety of once-daily
Darunavir/ritonavir for treatment-naive adults and for
treatment-experienced adults who harbor no darunavir
resistance-associated mutations.7–10 The ARIEL substudy
included treatment-experienced, HIV-1-infected, pediatric
patients aged ≥3 to <6 years, and weighing between 10
and <20 kg. DIONE included treatment-naive, HIV-1-
infected, adolescent patients aged ≥12 to <18 years and
weighing ≥40 kg. Toxicity observed in juvenile rats prevents
darunavir/ritonavir use in children aged <3 years old.18

A population pharmacokinetic model for darunavir/
ritonavir was previously established in adults.19 The model
was shown to have adequate predictive performance and
was, for example, able to describe darunavir pharmacoki-
netics following administration of a different formulation
when a correction factor for bioavailability was included.19

For the present study, the structural model was conserved
and the model parameters were adjusted with a dataset
containing richly sampled plasma concentration–time pro-
files from adult data from the DUET-1 and -2 studies
(NCT00255099 and NCT00254046, respectively)20–23 and
from children aged ≥3 to <18 years receiving twice-daily
darunavir based on data from DELPHI (NCT00355524)13
and ARIEL.14 The final model comprised two compart-
ments with first-order absorption and apparent clearance depend-
ent on the concentration of z1-acid glycoprotein (AAG). In
the current analysis, the model was further adjusted using
richly sampled darunavir plasma concentration–time profiles
in the ARIEL substudy and in DIONE. The main objective
of this analysis was to evaluate and recommend a once-
daily darunavir/ritonavir dosing regimen in children aged ≥3
to <12 years to achieve exposures within the limits of 80%
to 130% of the geometric mean exposure in adults receiv-
ing darunavir/ritonavir 800/100 mg once daily.

METHODS

Study objective

The main objective was achieved by: first, adjusting the
population pharmacokinetic model of darunavir to include
data from treatment-experienced, HIV-1-infected children
between the ages of ≥3 to <6 years (ARIEL substudy)14,16
and treatment-naive, HIV-1-infected, adolescent patients
between the ages of ≥12 to <18 years (DIONE study),15

who received once-daily darunavir/ritonavir. Second, provid-
ing individual estimates and summary statistics of AUCtau,
\( C_{\text{oh}} \), average concentration at steady state calculated from
AUCtau (\( C_{\text{SS,ave}} \)), and CL/F for once-daily darunavir/ritonavir
for these age groups. Lastly, performing simulations using
the adjusted model parameters for various once-daily
darunavir/ritonavir dosing scenarios to provide the pediatric
dosing recommendations in HIV-1-infected children aged
≥3 to <12 years. For children aged 6 to <12 years, once-
daily dosing recommendations were to be derived from
model-based simulations.

Studies included in the analysis

The database used in this analysis included existing
plasma concentration–time datasets from two pediatric
studies: ARIEL;14 DELPHI13 after 2 weeks of treatment;
two adult studies, DUET-1 and DUET-2 studies after 4 weeks
of treatment,24 and also incorporated datasets from the pediat-
cic DIONE study and the ARIEL once-daily substudy after
2 weeks of treatment14–16 (Table 1). Patients who had miss-
ing darunavir concentrations (one patient) or no pharmaco-
kinetic observations (four patients) were omitted from the
analysis. Darunavir concentrations without a time-matching
quantifiable ritonavir concentration were excluded because
such samples likely demonstrate nonadherence by the patient
and no pharmacoenhancement of darunavir could, there-
therefore, be expected.

The database included an adult dataset from the DUET-1
and DUET-2 trials because these data had similar sampling
frequencies (five samples taken in children, eight in adults),
and a similar timeframe after treatment (2 weeks in chil-
dren, 4 weeks in adults) compared with the pediatric stud-
ies. The data from DUET came from patients who received
darunavir/ritonavir without coadministration of etravirine (but
with other concomitant antiretrovirals from the NRTI class
with optional use of enfuvirtide).

Dosing

In the ARIEL trial14 darunavir was given as an oral
100-mg/ml suspension while ritonavir was administered
as an oral 80-mg/ml solution. The ARIEL substudy14,16 eval-
uated the pharmacokinetics of once-daily darunavir/ritonavir
in treatment-experienced children ≥3 to <6 years old and

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Table 1 Overview of the datasets used to adjust the darunavir population pharmacokinetic model

| Dataset        | DUET-1 and DUET-2 | DELPHI | ARIEL | ARIEL substudy | DIONE |
|----------------|-------------------|--------|-------|----------------|-------|
| Patients (n)   | 30                | 41     | 24    | 10*            | 12    |
| Dose of darunavir/ritonavir | 600/100 mg BID | 300–600/50–100 mg BID | 20/3 mg/kg BID | 40/7 mg/kg QD for <15 kg | 600/100 mg BID for ≥15 kg |
| Age range (years) | 18–66            | 6–17   | 3–5   | 3–5            | 12–17 |
| Bodyweight, range (kg) | 45–96            | 20–49  | 12–19 | 13–19          | 40–62 |
| AAG, range (mg/dL) | 54–347           | 48–312 | 63–156| 56–125         | 52–120|
| Samples per patient (n) | 8               | 5      | 5     | 6              | 6     |
| Time, range (h)  | 0–12             | 0–12   | 0–12  | 0–24           | 0–24  |
| Darunavir formulation | Tablets 300 mg  | Tablets 300 mg & 75 mg | Suspension 100 mg/mL | Suspension 100 mg/mL | Tablets 400 mg |

*The 10 patients in the ARIEL QD substudy are also included in the 24 patients of the main ARIEL BID study.
Table 2 Dosing table for darunavir/ritonavir once daily intake per weight band for both the ARIEL and DIONE trials

| Bodyweight (kg) | Darunavir dose, QD (mg) | Ritonavir dose, QD (mg) |
|-----------------|------------------------|------------------------|
| 10–10.9         | 400                    | 66                     |
| 11–11.9         | 440                    | 72                     |
| 12–12.9         | 480                    | 76                     |
| 13–13.9         | 520                    | 86                     |
| 14–14.9         | 560                    | 92                     |
| 15–19.9         | 640                    | 100                    |
| ≥40             | 800                    | 100                    |

Weighing between 10 and <20 kg. The total darunavir/ritonavir dose was 40/7 mg/kg once daily for those weighing <15 kg and 600/100 mg once daily for those weighing ≥15 kg. This dosing was based on previous simulation of darunavir exposures using data from the main ARIEL trial, taking into account bodyweight, AAG levels, dosing convenience, and minimizing risk of underdosing. The DIONE study\(^{15,16}\) evaluated the pharmacokinetics of darunavir/ritonavir 800/100 mg once daily in treatment-naïve adolescent patients ≥12 to <18 years old, weighing ≥40 kg. Darunavir was given as 400 mg tablets and ritonavir was given as capsules. The dosing data for both the ARIEL and DIONE trials are presented in Table 2.

Bioanalysis

Plasma concentrations of darunavir and ritonavir were assessed using a previously validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 5.00 ng/ml for both compounds.\(^{25}\)

Model

The model was run using NONMEM 7 level 1.0 (ICON Development Solutions, Ellicott City, MD) with a GFortran (http://gcc.gnu.org/) compiler (Supplementary Information). Parameter estimations were done with the First-Order Conditional Estimation method with interaction using untransformed concentrations. All data management, evaluation of goodness-of-fit, and visual predictive checks and simulations were performed using R version 3.0.1.\(^{26}\)

The initial model was an update of a previous population pharmacokinetic model of darunavir/ritonavir established in adults and adjusted for the clinical trial/commercial tablet formulation\(^{19}\) and for children ≥3 to <18 years old receiving twice-daily darunavir. It is a two-compartment model with first-order absorption (parameterized as KA, and fixed to twice-daily darunavir. It is a two-compartment model with

\[ \text{CL/F} = \frac{\text{CL}_{\text{int}}/F \cdot \left( \frac{1}{1 + K_{AAG} \cdot \text{AAG}} \right) \cdot \left( \frac{\text{WT}}{70} \right)^{\theta} \cdot e^{\eta}}{F_{\text{rel}}} \]

where \(\text{CL/F}_i\) = individual apparent oral clearance, \(\text{CL}_{\text{int}}/F\) = population estimate of apparent intrinsic clearance, \(K_{AAG} = \) affinity constant for AAG, given a fixed value of 0.0304, \(\text{AAG}_i = \) individual AAG concentration, \(\theta = \) influence of bodyweight [WT] on apparent clearance, \(\eta = \) individual random effect, \(F_{\text{rel}} = \) relative bioavailability correction for commercial tablet formulation and oral suspension compared with the formulation used in the previous model, given a fixed value of 1.18.

The apparent volume of distribution of the central compartment \((V2/F_i)\) is assumed to be dependent on bodyweight, as described by the following equation:

\[ V2/F_i = \frac{V2/F \cdot (\text{WT}/70)^{\theta} \cdot e^{\eta}}{F_{\text{rel}}} \]

After incorporating DIONE and ARIEL once-daily substudy datasets into the model, from the graphical exploration (Supplementary Figure 1) it was concluded that no modification of the structural model was deemed necessary. However, longer sampling times due to the 24-hour dose interval after once-daily darunavir administration allowed more reliable information on the distribution of the compound to be obtained, expressed as \(V2/F, Q/F,\) and \(V3/F.\) Hence, all the pharmacokinetic parameters were determined with the exception of \(K_{AAG}\) and \(F_{\text{rel}},\) which were fixed to the values obtained during the original model development. The interindividual variability on \(CL/F, Q/F,\) and \(KA\) were determined, together with the multiplicative residual error.

The model-building dataset was then used for visual predictive check simulations \((N = 100)\) using the newly estimated parameters, and \(CL/F\) was determined using noncompartmental approaches for both observed and simulated data. A standard visual predictive check would not be informative. However, this visual predictive check is deemed important because the purpose of the model is to investigate the influence of covariates on model-inferred clearance. The simulated and observed values of the parameters were compared for bodyweight, AAG concentration, age, and total once-daily darunavir dose.

Individual pharmacokinetic parameter estimates

Individual darunavir pharmacokinetic parameters for patients administered with once-daily darunavir/ritonavir were derived by means of post hoc estimates. Simulation records were added to the dataset at the exact time of trough \((0 h)\) to obtain a precise estimation of the darunavir plasma concentration at the trough for each visit where a plasma concentration was available and for all patients. This allows steady-state \(C_{oh}\) to be captured without being biased by the actual sampling time relative to the dose intake, which can vary from one patient to another.

For the ARIEL once-daily substudy, only one visit where rich sampling occurred was available, and the individual pharmacokinetic parameters were determined directly during the model parameter estimation step. For the week 24 analysis of the DIONE trial, richly (2 weeks) and sparsely sampled (8 and 24 weeks) concentrations were used. The
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RESULTS

Patients

Rich sampling data were taken from a pooled dataset of patients across five studies (ARIEL, DELPHI, DIONE, DUET-1, and DUET-2) (Table 1). The overall dataset for pharmacokinetic parameter estimation consisted of a total of 659 darunavir plasma concentration–time observations, of which 423 derived from pediatric patients. The observations were from 102 patients: 72 children (≥3 to <18 years old) and 30 adults (≥18 years old). The dataset used to evaluate the individual darunavir exposures in the DIONE study after 24 weeks of treatment consisted of 115 darunavir plasma concentration–time observations from 12 children.

Pharmacokinetic parameter estimation

All structural parameters were well estimated, and interindividual variability could be detected for population estimates of apparent intrinsic clearance (CLint/F), apparent intercompartmental clearance (Q/F), and the first-order absorption rate constant (KA) (Table 3). The similarities and differences between the published model (developed for children from ≥3 to <18 years old after twice-daily darunavir administration) and the model update reported here (developed for children aged ≥3 to <18 years after both twice-daily and once-daily darunavir administration) are as follows:

1. There were only slight changes in CLint/F (from 51.2 l/h to 51.0 l/h) and apparent central volume of distribution (V2/F) parameter estimates (from 127 l to 137 l).
2. There was no change in the effect of bodyweight on apparent oral clearance (CL/F) and V2/F.
3. There were substantial changes in apparent peripheral volume of distribution (V3/F) (from 84.3 l to 254 l) and Q/F (from 15.0 l to 19.1 l/h) due to an improved estimation achieved with the extra information gathered from the once-daily dosing.
4. The interindividual variability on V2/F and V3/F was too small to be compared with the previous model.

There were minimal differences between the observed and expected trend of the data, with no noticeable structural bias (Figure 1). Distributions for individual estimates for the random effects of CLint/F, Q/F, and KA are shown in Figure 2. Minimal shrinkage was detected for CLint/F, while shrinkage was more substantial for population estimates of Q/F and KA. This shrinkage was likely due to Q/F and KA being estimated at steady-state, which yields little information on these parameters. However, this had no impact on the exposure simulations and therefore the model was fit for purpose.

Visual predictive checks

The visual predictive checks of CL/F vs. all four covariates are shown in Figure 3. The model performed well over the range of covariates of interest: AAG concentration, bodyweight, darunavir dose, and age. Furthermore, the parameter values obtained from noncompartmental analysis based on the simulated profiles agreed well with model input data.

Individual pharmacokinetic parameter estimates

The goodness-of-fit plots from the model adjustment containing only the data from the ARIEL once-daily substudy showed that the model predictions appeared to be accurate for children aged ≥3 to <6 years and weighing between 10 and <20 kg, with no detectable bias present for individual
A population pharmacokinetic model of darunavir was adjusted for children aged ≥3 to <18 years receiving twice-daily darunavir from a previous model in adults. The update to the model presented here was successfully performed using pharmacokinetic data from the DIONE (treatment-naïve adolescent patients ≥12 to <18 years old) and ARIEL substudy (treatment-experienced children ≥3 to <6 years old) to enable weight-based, once-daily darunavir dosing recommendations to be given in children from ≥3 to <12 years. While ritonavir levels were measured in DIONE and ARIEL and simultaneous population pharmacokinetic modeling of darunavir and ritonavir once daily has been described by other groups, ritonavir dosing was not modeled in the current analysis. The model had adequate predictive performance and was deemed suitable for simulation purposes. The model was confirmed with pharmacokinetic parameters estimated using data from the ARIEL substudy and DIONE. The geometric mean exposure in pediatric patients would be deemed comparable to that in adults receiving darunavir/ritonavir 800/100 mg once daily if it fell within the predefined limits of 80% to 130% of the target adult exposure. This limits the risk of overexposure without compromising efficacy, because the lower range of AUC_{tau} and trough plasma concentration (C_{min}) are within observations from adult data. The geometric mean darunavir AUC_{tau} was 77.8 μg·h/ml, which represents 86.7% of the target geometric mean in adults treated with darunavir/ritonavir 800/100 mg once daily.

Exposure simulations

The expected darunavir exposures (AUC_{tau}) are shown in Figure 4 with darunavir once-daily dosing of: 35 mg/kg dose, 10 to 15 kg bodyweight; 600 mg dose, 15 to 30 kg bodyweight; 675 mg dose, 30 to 40 kg bodyweight; 800 mg dose, 40 to 65 kg. The expected exposures with darunavir/ritonavir once-daily dosing that most closely matched adult exposure, based on visual inspection of the plots, formed the basis for treatment recommendations. The mean exposures of the regimens shown in Figure 4 are expected to be in the 80% to 130% range of the adult target (dosed with darunavir/ritonavir 800/100 mg once daily for average AAG concentrations). Simulation plots of all dosing strategies are shown in Supplemental Figure 2.

DISCUSSION

A population pharmacokinetic model of darunavir was adjusted for children aged ≥3 to <18 years receiving twice-daily darunavir from a previous model in adults. The update to the model presented here was successfully performed using pharmacokinetic data from the DIONE (treatment-naïve adolescent patients ≥12 to <18 years old) and ARIEL substudy (treatment-experienced children ≥3 to <6 years old) to enable weight-based, once-daily darunavir dosing recommendations to be given in children from ≥3 to <12 years. While ritonavir levels were measured in DIONE and ARIEL and simultaneous population pharmacokinetic modeling of darunavir and ritonavir once daily has been described by other groups, ritonavir dosing was not modeled in the current analysis. The model had adequate predictive performance and was deemed suitable for simulation purposes. The model was confirmed with pharmacokinetic parameters estimated using data from the ARIEL substudy and DIONE. The geometric mean exposure in pediatric patients would be deemed comparable to that in adults receiving darunavir/ritonavir 800/100 mg once daily if it fell within the predefined limits of 80% to 130% of the target adult exposure. This limits the risk of overexposure without compromising efficacy, because the lower range of AUC_{tau} and trough plasma concentration (C_{min}) are within observations from adult data. The geometric mean darunavir AUC_{tau} was 77.8 μg·h/ml, which represents 86.7% of the target geometric mean in adults treated with darunavir/ritonavir 800/100 mg once daily.
Figure 1. Basic goodness-of-fit plots for the model adjustment. (a) Observed vs. population prediction; (b) observed vs. individual prediction; (c) conditional weighted residuals vs. population prediction; (d) conditional weighted residuals vs. time after dose. Black dots represent adult DUET data, red dots DELPHI data, green dots ARIEL data, blue dots ARIEL QD substudy data, and pink dots DIONE data. Opacity is applied so that if points overlap, the overlapping area is darker.

Figure 2. Random effects for (a) $\text{CL}_\text{int/F}$, (b) $Q/F$, and (c) $K_A$. The blue line represents the expected individual parameter distribution, and the red line the density line of the observed individual parameter distributions. $\text{CL}_\text{int/F}$, population estimate of apparent intrinsic clearance; $Q/F$, intercompartmental clearance; $K_A$, first-order absorption rate constant.
Simulations of potential darunavir/ritonavir once-daily regimens were applied to explore the resultant exposures. These, together with efficacy and safety data from the trials mentioned, were used to develop optimal once-daily darunavir/ritonavir dosing recommendations for treatment-naive and treatment-experienced children aged ≥3 to <12 years old (with no darunavir resistance-associated mutations) (as in ODIN\textsuperscript{10}).

For children weighing 10 to <15 kg, simulations from this model indicate that the dose should be 35/7 mg/kg darunavir/ritonavir once daily. From the ARIEL data, a darunavir/ritonavir dose of 40/7 mg/kg for children weighing 10 to <15 kg appeared to be appropriate to reach the target exposure in adults when treated with darunavir/ritonavir 800/100 mg once daily. However, a darunavir/ritonavir dose of 35/7 mg/kg is preferred in children weighing 10 to <15 kg, since the simulations show a better match with the adult exposure than those with 40/7 mg/kg, which may lead to overexposure (115% of geometric mean adult exposure vs. 100% of geometric mean adult exposure for 40/7 mg/kg and 35/7 mg/kg, respectively). In addition, limited safety data are available in this particular

**Figure 3** Visual predictive checks of CL/F vs. (a) α1-acid glycoprotein concentration (AAG); (b) bodyweight; (c) total daily darunavir dose; and (d) age. The dots represent the observed parameters determined by a noncompartmental analysis, the black lines represent the 5\textsuperscript{th}, 50\textsuperscript{th} (median), and 95\textsuperscript{th} percentile (with smoothing applied) of the parameters based on simulated values. Black dots represent adult DUET data, red dots DELPHI data, green dots ARIEL data, blue dots ARIEL QD substudy data, and pink dots DIONE data.
subpopulation as studied in ARIEL. For children weighing 15 to <30 kg, the dose should be 600/100 mg darunavir/ritonavir once daily to reach the target exposure in adults. Although this dose may seem high in patients weighing 15 to 20 kg, this regimen offers the opportunity to switch from a darunavir suspension to the tablet for patients weighing >15 kg, using only one 600 mg tablet. For children weighing 30 to <40 kg, the dose should be 675/100 mg darunavir/ritonavir once daily (75 and 600 mg tablets). A higher dose (800 mg) leads to high AUC_{tau} and C_{0h}, and could exceed values observed in adults receiving darunavir/ritonavir 800/100 mg once daily. For children weighing ≥40 kg, the dose should be 800/100 mg darunavir/ritonavir once daily. This dose was deemed appropriate for these children (≥12 to <18 years) to reach the target exposure in adults.

In conclusion, we have adapted a pharmacokinetic two-compartment model with first-order absorption, and containing bodyweight and AAG as covariates, to provide recommendations on dosing in children aged ≥3 to <12 years dosed once daily with darunavir boosted with ritonavir and given with two other antiretroviral agents for the treatment of HIV-1. The model performed well, and allowed regimens to be recommended that should result in target pediatric exposure close to that observed in adults treated with darunavir/ritonavir 800/100 mg once daily. Using the model to interpolate once-daily dose recommendations for children aged 6 to <12 years, allowed optimal doses to be derived without the need to conduct a specific once-daily dosing study in this age group. Recommended pediatric doses are 35/7 mg/kg from 10 to <15 kg, 600/100 mg from 15 to <30 kg, 675/100 mg from 30 to <40 kg, and 800/100 mg for ≥40 kg.

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Conflict of Interest. A.B., T.N.K., T.V.D.C., M.O., F.L.T., A.V., and P.V. are full-time employees of Janssen. P.V. was a full-time employee of Janssen Pharmaceuticals at the time of the analyses.

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