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Adequate exposure of 50 mg dolutegravir in children weighing 20 to 40 kg outside of sub-Sahara Africa

Hylke Waalewijn[a], Kim Stol[b,c], Linda van der Knaap[c], Pieter L.A. Fraaij[c,d], Clementien Vermont[c], Annemarie M.C. van Rossum[c,e], Riet Strik-Albers[b], David M. Burger[a], Elin M. Svensson[a,f] and Angela Colbers[a]

Dolutegravir 50 mg is registered for use in children weighing 20–40 kg. This approval is based on data from an African paediatric cohort, and no pharmacokinetic data was available from children outside of Africa. This study provides further evidence of the effective use of dolutegravir 50 mg in children weighing 20 to 40 kg by showing that concentration data gathered in clinical practice shows adequate concentration levels in Dutch children without a safety signal.

The viral integrase enzyme inhibitor dolutegravir is currently used as a first-choice antiretroviral for treating HIV infection in adults and children. However, dolutegravir treatment was inaccessible for most children living with HIV because the 50 mg film-coated tablet registered for use in adults and adolescents weighing >40 kg, was the only formulation available in sub-Saharan Africa. This changed when data from the ODYSSEY trial showed that 50 mg dolutegravir, taken by children weighing more than 20 kg, achieved drug exposures comparable to adult reference values [1]. Based on these data, in 2020, the FDA and European Medicines Agency have adopted this dose change [2,3].

We investigate whether this dose would also achieve appropriate dolutegravir exposure in children outside of Africa. We study plasma concentration data gathered in routine clinical practice in children weighing 20–40 kg treated with dolutegravir 50 mg once-daily in the Netherlands.

This was a retrospective multicentre pharmacokinetic study, investigating dolutegravir concentration data, which was collected from children who gave written informed consent (or caretaker consented), weighing 20–40 kg, who had been on antiretroviral treatment for at least 1 year. The study was reviewed by the relevant ethics review committees (METC no.: 2019-6039), and approved as a retrospective study not interfering with clinical practice.

The primary objective of the study was to compare the trough concentration (C_{trough}) of 50 mg dolutegravir administered to children with HIV in the Netherlands weighing 20–40 kg to C_{trough} values of adults taking 50 mg dolutegravir with food (1.11 mg/l) [3], and C_{trough} data from the ODYSSEY trial of children weighing 20–40 kg taking dolutegravir without food (0.72 mg/l) [1]. In addition, safety and efficacy data was explored through a retrospective review of clinical records. Individual C_{trough} predictions and the proportion of samples below the 90% effective concentration (EC_{90}: 0.32 mg/l) were reported [4].

Dolutegravir plasma concentration data was gathered according to local drug-monitoring practices, recording at least the dose, time and date of the last taken dose, co-medication, and time and date of the therapeutic drug monitoring (TDM) sample as well as weight and height of the child. All samples were measured with a validated analysis method [5]. All grade 3 and 4 adverse events (AE), serious adverse events (SAE), and any event resulting in discontinuation of dolutegravir were reported. Viral blip is defined as a single viral load between 40 and 200 copies/ml followed by viral suppression. Missing information on patients' weight was handled by taking the weight of a visit within 4 weeks of the sampling visit or by assuming linear weight change between two visits.

Plasma samples were taken during scheduled periodic clinic visits at arbitrary time after a self-reported dolutegravir dose. These samples were used to predict the concentration at 24 h after dose (C_{trough}) using a paediatric pharmacokinetic population model in NONMEM (see model control stream, Supplementary Digital Content 1, http://links.lww.com/QAD/C641, which describes the model control stream of the population-pharmacokinetic model) [6,7]. This method was accurate and precise for the purpose of our analysis (see model validation section, Supplementary Digital Content 2, http://links.lww.com/QAD/C641, which shows the accuracy and precision of the used method).

Children could have multiple samples taken at different occasions on the same dose. To prevent giving more weight to children that had TDM samples at multiple occasions, a single geometric mean (GM) C_{trough} for each individual was calculated by combining predicted C_{trough} from the available samples. GM C_{trough} from individuals were combined in a GM C_{trough} for the cohort.

In total, 20 participants were enrolled in this study (Table 1 for demographics information). In total, 76 TDM visits

were included in the analysis. Children contributed a median (range) of four (1–9) samples with six children contributing only one sample (see Figure 1, Supplementary Digital Content 3, http://links.lww.com/QAD/C641, which shows distribution of sample data in time after dose).

GM C_{trough} with coefficient of variation (CV%) was 1.93 (32) mg/l, which is higher than reference values: 1.1 mg/l of adults taking dolutegravir 50 mg once-daily with food, and 0.72 of children weighing 20–40 kg in the ODYSSEY trial, taking dolutegravir without food (Table 1). Two of 76 (2.6%) of individual estimated C_{trough} were below dolutegravir EC_{90} of 0.32 mg/l. One was from a child with a history of nonadherence to therapy.

Two out of 20 children had a detectable viral load >40 copies/ml in the period of observation: one blip of 40 copies/mL followed by viral suppression after 1 month and one child, with a history of non-adherence to therapy, remained detectable during 6 months of 50 mg dolutegravir treatment. There was no apparent relation to measured C_{trough} and the child continued to be suppressed from 8 months after start of therapy and onwards. All other children had an undetectable viral load during the studied period. No dolutegravir doses where changed based on plasma concentrations.

One AE resulted in dolutegravir discontinuation: nocturnal nose bleeds combined with loss of concentration, possibly related to dolutegravir use (GM C_{trough}: 0.4 mg/l). One SAE was reported: increased lipid and amylase levels, attributed to lopinavir/ritonavir use. Lipid and amylase levels normalized after stopping lopinavir/ritonavir. Dolutegravir was continued without further adverse events.

Table 1. Demographics and trough concentration results of children taking 50 mg dolutegravir

Dose (as film-coated tablet)	50 mg
Number of children with TDM samples on dose (female)	20 (13)
Ethnicity Black African; mixed Black African-white	18; 2
Means of infection (MTCT; unknown)	9; 11
Total plasma concentration samples	76
Weight (kg)	30.65 (27.68–34.06)
Age (years) [IQR; range]	10.0 (10.0–10.25; 5.9–13.8)
The median (range) follow-up*	1.65 (0–2.07) years
Total follow-up time	23.8 treatment years
DTG C_{trough} (mg/l)**	1.93 (32)
Reference C_{trough} fasted children (mg/l)†	0.72 (44)
Reference C_{trough} fed adults (mg/l)¼	1.11 (46)
Individuals with viral blip	2/20

Median (IQR) for weight and age and geometric mean C_{trough} (CV%); C_{trough}: concentration at the end of dosing interval ($T = 24$ h); MTCT: mother to child transmission. For our study this concentration is extrapolated to $T = 24$ h from a TDM sample. *Time between the first TDM sample and last data entry. **Mostly without regards to food. †Calculated from fasted children receiving 50 mg in the ODYSSEY trial. ¼Fed adults [3].

We report adequate exposure in children 20–40 kg, living in the Netherlands, receiving 50 mg dolutegravir once-daily. GM C_{trough} was higher than DTG reference values established in adults and children, without concerning safety issues in our observational period (Table 1). The reference paediatric cohort took dolutegravir without food, while, in our study, almost all children took dolutegravir with food. In adults, food intake increases dolutegravir exposure by 70% [7]. The difference in food intake and nutritional status of the two paediatric cohorts potentially explains the difference between the studies.

No relation between C_{trough} parameters and toxicity has been reported in the literature and paediatric studies have confirmed long-term safety of dolutegravir in children [8,9]. Moreover, GM C_{trough} of 2.12 mg/l was safe in adults receiving 50 mg dolutegravir twice-daily [3]. The low number of adverse events related to dolutegravir in our study suggests that these exposures remain safe.

In conclusion, 50 mg dolutegravir provides adequate exposure to dolutegravir in children above 20 kg, living in the Netherlands. We report the first pharmacokinetic data on 50 mg dolutegravir used clinically in children weighing 20–40 kg outside of sub-Sahara Africa and provide confirmation that the 50 mg dolutegravir dose provides adequate exposure and was well tolerated when taken by children in different settings.

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Conflicts of interest

There are no conflicts of interest.

[a]*Radboud University Medical Center, Department of Pharmacy, Radboud Institute for Health Sciences (RIHS), Nijmegen, The Netherlands;* [b]*Radboud University Medical Center, Amalia Children's Hospital, Department of Pediatrics, Division of Infectious Diseases and Immunology, Nijmegen, The Netherlands;* [c]*Erasmus MC University Medical Center-Sophia Children's Hospital, Department of Pediatrics, Division of Infectious Diseases and Immunology, Rotterdam, The Netherlands;* [d]*Department of Viroscience, Erasmus-MC University Medical Center, Rotterdam, The Netherlands;* [e]*Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands; and* [f]*Department of Pharmacy, Uppsala University, Uppsala, Sweden.*

Correspondence to Angela Colbers, PhD, Department of Pharmacy 864, Radboud University Nijmegen Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands.
Tel: +31 625248088;
e-mail: Angela.colbers@radboudumc.nl

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References

1. Bollen PDJ, Moore CL, Mujuru HA, Makumbi S, Kekitiinwa AR, Kaudha E, *et al*. **Simplified dolutegravir dosing for children with HIV weighing 20 kg or more: pharmacokinetic and safety substudies of the multicentre, randomised ODYSSEY trial.** *Lancet HIV* 2020; **7**:e533–e544.
2. European Medicines Agency. Tivicay: dolutegravir. https://www.ema.europa.eu/en/medicines/human/EPAR/tivicay [Accessed 5 February 2022].
3. US Food and Drug Administration. New Drug Application (NDA): 213983. Products on NDA 213983: Tivicay PD. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=213983 [accessed 22 April 2022]
4. Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, *et al*. **Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults.** *AIDS* 2011; **25**:1737–1745.
5. Bollen PDJ, de Graaff-Teulen MJA, Schalkwijk S, van Erp NP, Burger DM. **Development and validation of an UPLC-MS/MS bioanalytical method for simultaneous quantification of the antiretroviral drugs dolutegravir, elvitegravir, raltegravir, nevirapine and etravirine in human plasma.** *J Chromatogr B Analyt Technol Biomed Life Sci* 2019; **1105**:76–84.
6. Singh R, Baker M, Thapar M, Gibb D, Turkova A, Ford D, *et al*. **Pediatric dolutegravir (DTG) dosing recommendations derived from combined P1093 and ODYSSEY Population Pharmacokinetic analysis**. In: *International Workshop on HIV & Pediatrics 2020*. San Francisco; 2020.
7. US Food and Drug Administration. **Clinical pharmacology and biopharmaceutics review(s)**. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213983Orig1s000ClinPharmR.pdf [Accessed 5 February 2022].
8. Lugemwa A, Mujuru H, Wynne B, Violari A, Kekitiinwa A, Kity C, et al. **A randomised comparison of DTG-based ART vs standard of care in infants and young children living with HIV weighing 3 to 14 kg: results from the ODYSSEY trial**. [conference proceeding PEBLB18] In: International AIDS society (IAS) 18–21 July 2021.
9. Turkova A, White E, Mujuru HA, Kekitiinwa AR, Kityo CM, Violari A, *et al*. **Dolutegravir as first- or second-line treatment for HIV-1 infection in children.** *N Engl J Med* 2021; **385**:2531–2543.

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Effect of weekly 17-hydroxyprogesterone caproate on small for gestational age among pregnant women with HIV in Zambia

Madelyn G. Conner[a], Bellington Vwalika[b], Bethany L. Freeman[a], Yuri V. Sebastião[a], Chileshe M. Mabula-Bwalya[c], Stephen R. Cole[a], Elizabeth M. Stringer[a], Margaret P. Kasaro[c], Jeffrey S.A. Stringer[a] and Joan T. Price[a]

The IPOP trial demonstrated a reduced risk of severe small for gestational age among infants born to women with HIV who received weekly intramuscular 17 alpha-hydroxyprogesterone caproate. This secondary analysis examined the 17P treatment effect in subgroups of maternal BMI, parity, timing of antiretroviral therapy (ART) initiation, and ART regimen. We found that 17P was more effective among nulliparous women, women who started ART before pregnancy, and those taking protease inhibitors.

Small for gestational age (SGA) infants are at a high risk of morbidity and mortality. Women with HIV are more likely to deliver an SGA infant, and antiretroviral therapy (ART) does not appear to reduce this risk [1]. Second-line ART regimens that include protease inhibitors have been linked to SGA [2]. In mice, antenatal exposure to protease inhibitor containing ART promotes dysregulated placental vascularization, which progesterone supplementation can counteract [3].

The Improving Pregnancy Outcomes with Progesterone (IPOP) trial compared weekly intramuscular 17 alpha-hydroxyprogesterone caproate (17P) to placebo in pregnant women with HIV in Zambia. We have previously reported no effect of 17P on the primary composite outcome of preterm birth less than 37 gestational weeks or stillbirth [4]. Here, we examine the effect of 17P on the prespecified outcome of severe SGA (<third percentile) in the overall trial population and within the following subgroups: women on ART containing protease inhibitor vs. no protease inhibitor, women who initiated ART before vs. during pregnancy, underweight (BMI $<18.5\,kg/m^2$) vs. normal or overweight (BMI $18.5–29.9\,kg/m^2$) vs. obese (BMI $\geq 30\,kg/m^2$) women, and nulliparous vs. parous women.

IPOP randomized 800 pregnant women with HIV to weekly injections of either 17P or placebo starting at 16–24 gestational weeks by ultrasound. Study procedures [5] and primary results [4] have been published. Birthweight was recorded within 24 h of birth and sex-specific birthweight percentile was calculated by INTERGROWTH-21st standards [6]. We defined our outcome of SGA as birthweight for age less than third percentile, as most newborns less than tenth percentile are not pathologically growth restricted. In an intent-to-treat analysis between randomization groups overall and in subgroups of protease inhibitor use, timing of ART initiation, BMI, and parity, we estimated the SGA risk (proportion), relative risk, and risk difference, along with Wald-type 95% confidence intervals (CIs).

Baseline characteristics between randomization groups were similar as previously reported [4]. Overall, 7.1% of participants randomized to 17P delivered a severe SGA infant compared with 11.9% randomized to placebo [risk ratio (RR) 0.60, 95% confidence interval (95% CI): 0.38–0.94; Table 1]. In subgroup analyses, estimates of the protective effect of 17P on severe SGA risk were