



Published in final edited form as:

Lancet HIV. 2022 January ; 9(1): e24–e31. doi:10.1016/S2352-3018(21)00266-6.

Abacavir dosing in neonates from birth to 3 months of life: a population pharmacokinetic modelling and simulation study

Adrie Bekker¹, Edmund V. Capparelli², Avy Violari³, Mark F. Cotton¹, Mae Cababasay⁴, Jiajia Wang⁴, Ruth Mathiba³, Lubbe Wiesner⁵, Andrew Wiznia⁶, Pearl Samson⁷, Renee Browning⁸, Jack Moye⁹, Firdose L. Nakwa¹⁰, Eric Decloedt¹¹, Helena Rabie¹, Mark Mirochnick¹², Tim R. Cressey^{13,14,15} **IMPAACT P1106 team**

¹Family Centre for Research with Ubuntu, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

²University of California San Diego, San Diego, CA, USA

³Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

⁴Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA

⁵Division of Clinical Pharmacology, University of Cape Town, Cape Town, South Africa

⁶Jacobi Medical Centre, Bronx, New York

⁷Frontier Science Foundation, Amherst, NY, USA

⁸Division of AIDS, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA

⁹Division of Extramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA

¹⁰Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa

Corresponding author: Adrie Bekker, Department of Pediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Tygerberg, 7505, South Africa. adrie@sun.ac.za. Tel: +27 21 938 9198. Fax +27 21 938 4179.

Contributors:

AB, TRC, EVC, MM, and MFC conceptualized the manuscript. AB, MM, AV, RM, FLN, ED, HR were responsible for the project administration and research activity execution. AB, MC, JW, RB, PS and JM led safety data analysis. TRC and EVC led the pharmacokinetic analysis. Data were verified by AB and TRC. AB and TRC prepared the original draft and all authors reviewed and edited the manuscript. Oversight was provided by EVC, MM, AV and MFC.

Declaration of interests:

AB, EVC, AV, MFC, RM, HR and MM received funding from the IMPAACT Network. MM received funding from Gilead Sciences, Merck & Co, and ViiV Healthcare. AV received funding from ViiV Healthcare, MSD, Gilead Sciences and from Jansen for participation in a DSMB. HR received funding from Abbvie. All other authors declare no competing interests

Data Sharing

The data cannot be made publicly available because of the ethical restrictions in the study's informed consent documents and in the International Maternal Adolescent Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human participants protection plan; public availability might compromise participant confidentiality. However, data are available to all interested researchers upon request to the IMPAACT Statistical and Data Management Centre's data access committee (sdac.data@fstrf.org) with the agreement of the IMPAACT Network.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

¹¹Division of Clinical Pharmacology, Department of Medicine, Stellenbosch University, Cape Town, South Africa

¹²Boston University Sch of Med, Boston, MA, USA

¹³AMS/PHPT Research Collaboration, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand

¹⁴MIVEGEC, University of Montpellier, CNRS, IRD, Montpellier, France

¹⁵Department of Molecular & Clinical Pharmacology, University of Liverpool, UK

Summary

Background: No evidence-based optimal dosing guidance is available for abacavir liquid formulation use from birth. We used abacavir pharmacokinetic data from neonates and infants to determine an exact abacavir dosing strategy (mg/kg) for infants aged 0–3 months and to propose dosing by WHO weight band for neonates.

Methods: Abacavir pharmacokinetic and safety data were pooled from three completed studies (1997–2020): PACTG 321 (USA), the Tygerberg Cohort (South Africa), and IMPAACT P1106 (South Africa). PACTG 321 and the Tygerberg Cohort were performed in neonates exposed to HIV receiving a single dose of abacavir. IMPAACT P1106 included predominantly low birthweight (<2500 g) infants on antiretroviral therapy enrolled when they were younger than 3 months. We developed a population pharmacokinetic model and performed simulations to achieve abacavir exposures (area under the curve for 0–12 h) within the target range of 3.2–25.2 µg·h/mL, previously reported in older children.

Findings: 45 infants contributed 308 abacavir concentrations; 21 neonates were younger than 15 days. At first pharmacokinetic assessment, median postnatal age for PACTG 321 was 1 day and median bodyweight was 3.1 kg; for the Tygerberg Cohort it was 10 days and 3.3 kg; and for IMPAACT P1106 it was 73 days and 3.8 kg. Our model predicted a slow abacavir clearance of 2.51 mL/min per kg at birth, which doubled by 4 weeks of age. Therapeutic targets were achieved with exact abacavir doses of 2.0 mg/kg twice daily from 0 weeks to 4 weeks and 4.0 mg/kg twice daily from 4 weeks to 12 weeks. A fixed weight-band dosing strategy of 8 mg (for 2–3 kg), 10 mg (3–4 kg), and 12 mg (4–5 kg) abacavir twice daily achieved target exposures throughout the first 4 weeks of life without the need for dose adjustment due to age or bodyweight changes. No adverse events of grade 3 or higher were related to abacavir.

Interpretation: Integration of these dosing recommendations into National and International guidelines for the abacavir liquid formulation will expand antiretroviral options from birth and simplify the clinical management of neonates with HIV.

Funding: National Institute of Allergy and Infectious Diseases, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Mental Health (NIMH), and the Collaborative Initiative for Paediatric HIV Education and Research Programme.

Introduction

Initiation of antiretroviral therapy (ART) in infants with HIV before 3 months of age significantly reduces disease progression and mortality.¹ However, administering ART from birth is challenging because few antiretroviral drugs are recommended for use in neonates (aged <4 weeks). Of the five antiretroviral drugs recommended for neonates, only zidovudine, lamivudine, nevirapine, and raltegravir can be used from birth, with ritonavir boosted lopinavir given from 2 weeks postnatal age and 42 weeks post-menstrual age.²

Abacavir is a nucleoside reverse transcriptase inhibitor that could provide an additional antiretroviral option from birth. A paediatric liquid abacavir formulation is currently licensed for use in infants aged 3 months and older at a dose of 8 mg/kg twice daily.³ Generic paediatric dispersible tablets containing abacavir are also available. WHO guidelines from 2016 recommend weight-band dosing for abacavir liquid and tablet formulations in infants and children with HIV weighing at least 3 kg from age 4 weeks.⁴ However, using abacavir in neonates is restricted due to the scarcity of available pharmacokinetic and safety data to guide dosing. Extrapolating dosing information from infants to neonates is complicated by the rapid growth and organ maturation during early life.⁵ On average, the birthweights of neonates double within 5 months and triple by 1 year.⁶ Abacavir is metabolised via uridine diphosphate glucuronyltransferase 2B7 (UGT2B7) and alcohol dehydrogenase (ADH) enzymes,⁷ both of which are not fully developed in young infants;^{8,9} thus, the initial dosing and when to increase dosage require investigation.

Abacavir is recommended by WHO as first-line ART for young infants and children from 1 month of age, whereas zidovudine is recommended instead of abacavir for neonates (<4 weeks of age) starting ART.³ The favourable safety profile of abacavir in children¹⁰ might make it suitable for use in neonates.^{11,12} The use of abacavir as part of first-line ART in neonates would simplify ART regimens by avoiding a switch from zidovudine to abacavir at age 4 weeks.

To inform abacavir dosing during the first months of life, we pooled abacavir data generated from three pharmacokinetic studies performed in neonates and young infants. A population pharmacokinetic model was developed to describe abacavir concentrations that incorporate both bodyweight changes and maturation of drug elimination pathways during early life. Our objectives were to determine an exact abacavir dosing strategy (mg/kg) for infants aged 0–3 months and to propose dosing per WHO weight bands for neonates.

Methods

Study Design

Data were pooled from three completed pharmacokinetic studies conducted between 1997 and 2020 administering abacavir liquid formulation to neonates and young infants: the Pediatric AIDS Clinical Trials Group (PACTG 321; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00000864), NCT00000864), the Tygerberg Cohort,¹³ and the International Maternal Pediatric and Adolescent AIDS Clinical Trials Network (IMPAACT P1106; [NCT02383849](https://clinicaltrials.gov/ct2/show/study/NCT02383849)). In the first two studies, intensive pharmacokinetic sampling was done after a single dose of abacavir in term neonates (≥37

weeks gestational age) born to women with HIV. In both studies, all neonates were negative for HIV and single doses of abacavir were administered on top of the standard-of-care infant antiretroviral prophylaxis (ie, nevirapine or zidovudine, or a combination of both), with the goal of providing initial pharmacokinetic and safety data to guide multi-dose studies. The third study made use of a sparse pharmacokinetic sampling strategy evaluating multi-dose abacavir in low birthweight (<2500 g) and normal birthweight (2500–4000 g) infants aged between 0 months and 3 months with HIV on ART.

PACTG 321 was a phase 1, multicentre study of the safety, tolerance, and pharmacokinetics of abacavir combined with 6 weeks of standard zidovudine therapy in term neonates born to women living with HIV at US sites. A single 2 mg/kg dose of abacavir was given to term neonates (aged 0–7 days) followed by intensive pharmacokinetic sampling at 1 h, 2 h, 3 h, 6 h, 8 h, and 24 h post abacavir dose. Clinical, haematology, and chemistry investigations were performed at screening, and at 2 days, 7–14 days, and 6 weeks.

The Tygerberg Cohort was an open-label, single-centre, pharmacokinetic and safety study of abacavir in neonates exposed to HIV and receiving nevirapine with or without zidovudine for HIV prophylaxis, conducted in Cape Town, South Africa.¹³ A single 8 mg/kg dose of abacavir was given to term neonates followed by intensive pharmacokinetic sampling at 1 h, 2 h, 4 h, 6 h, and 8 h post abacavir dose. Clinical evaluations were done on the day of pharmacokinetic sampling and mothers were contacted by telephone 1 month later to enquire about any adverse events.

IMPAACT P1106 was a phase 4 prospective, multiarm trial conducted in South Africa, evaluating pharmacokinetics and safety of antiretrovirals and antituberculosis medication in low birthweight and normal birthweight infants younger than 3 months born to women living with HIV. All infants who received abacavir as part of ritonavir-boosted lopinavir-based ART at any time were included. Abacavir was dosed according to standard-of-care South African weight-band dosing (appendix p 4).¹⁴ The first sparse blood sampling for pharmacokinetic assessment was performed 2 weeks after ritonavir-boosted lopinavir initiation. Pharmacokinetic measurements were collected before the dose and at 1.5 h and 4 h after the dose at study weeks 2, 10, and 24; pre-dose samples were also collected at weeks 6 and 16. Adverse events were classified as expected (for low-birthweight infants) or unexpected. Because normal developmental physiology of premature infants commonly results in clinical conditions and laboratory values classified as adverse events when using standard adverse event reporting tables, events commonly associated with prematurity or low birthweight, and which were present on the day of a study visit, were categorised as expected adverse events according to a pre-identified table that incorporated grading criteria (appendix pp 5, 6). Unexpected adverse events were defined as unanticipated events not commonly associated with prematurity and were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Adverse events were evaluated by study site investigators and the study team from entry to week 24. Point and 90% Clopper-Pearson CI estimates were generated for the proportion of infants meeting the composite safety endpoint of death and grade 3–4 adverse events.

Each study was approved by the institutional ethics review board responsible for study oversight; these included Stellenbosch University, University of the Witwatersrand, and US IMPAACT sites. Written informed consent was obtained from all infants' mothers or legal caregivers before entry.

Procedures

Abacavir plasma concentrations were quantified using validated liquid chromatography assays with a lower limit of quantification (LLOQ) between 0.02 and 0.03 µg·h/mL. PACTG 321 samples were measured at the Glaxo-Wellcome Research and Development Laboratory (Research Triangle Park, NC, USA), Tygerberg Cohort samples at the AMS-PHPT Laboratory, Chiang Mai University (Chiang Mai, Thailand), and IMPAACT P1106 samples at the Division of Clinical Pharmacology (University of Cape Town, Cape Town, South Africa). The laboratories in Thailand and South Africa are ISO certified and participate in the Division of AIDS-funded external quality control programme.¹⁵

Statistical Analysis

Population Pharmacokinetic Model Development: Population means and variances of abacavir pharmacokinetic parameters were estimated using a non-linear mixed-effects regression model. NONMEM software (version 7.4) was used to fit abacavir concentration–time data using the first-order conditional estimation method with interaction. Pharmacokinetic structural and residual models were assessed using both statistical and graphical methods (RStudio version 1.3.959). Exponential error models were used to describe inter-individual variability in pharmacokinetic parameters; a combined additive and proportional error model was initially used to estimate residual variability; and inter-occasion variability was assessed. Samples below the LLOQ were imputed as LLOQ/2.¹⁶ Nested models were compared using the minimal value of the objective function provided by NONMEM. The influence of infant covariates on pharmacokinetic parameters was tested using the standard stepwise forward inclusion and backward elimination procedure.¹⁷ Infant covariates assessed included bodyweight, postnatal age, and post-menstrual age. Postnatal age or chronological age is the time elapsed after birth and post-menstrual age is defined as gestational age at birth plus postnatal age.¹⁸ The final model was evaluated using the bootstrap resampling technique and a visual predictive check.

Model Simulations: Monte Carlo simulations were run in NONMEM¹⁹ for infants receiving abacavir liquid formulation twice daily. To assess the exact mg/kg dosing for infants aged 0–3 months, a population of virtual infants with birthweights of 2.0 kg, 3.0 kg, and 4.0 kg were simulated up to age 12 weeks. WHO dosing guidelines include three weight bands for infants younger than 4 weeks: 2–3 kg, 3–4 kg, and 4–5 kg. To determine the optimal weightband dosing for neonates, a population of virtual neonates with birthweights of 2.0 kg, 2.5 kg, 3.0 kg, 3.5 kg, 4.0 kg, and 4.5 kg was simulated up to age 4 weeks. A dose requiring no adjustment up to age 4 weeks (ie, independent of weight gain) was considered advantageous. For both scenarios, bodyweights were adjusted weekly based on the UK-WHO Growth Chart,⁶ contingent on their birthweights. Per US Food and Drug Administration (FDA) guidance, the efficacy of antiretrovirals in children can be extrapolated from adult trials based on achieving comparable plasma exposures. Here,

predicted abacavir drug exposures (area under the curve for 0–12 h) were compared with the target abacavir drug exposure range of 3.2–25.2 µg·h/mL reported in older children using WHO weight-band dosing included in the FDA filing.²⁰ Summary statistics were calculated using STATA software (version 13).

Role of the Funding Source

The funder of the study contributed to study design but had no role in data collection, data analysis, data interpretation, or writing of the report.

Results

48 infants younger than 3 months were included in this analysis: 11 infants in PACTG 321, ten in the Tygerberg Cohort, and 27 in IMPAACT P1106. Three infants in IMPAACT P1106 had no pharmacokinetic samples collected; one infant died, one discontinued abacavir after a negative HIV result, and one started abacavir after seroconversion. Safety data were missing for three infants in PACTG 321. Table 1 summarises the three studies and the infant characteristics at birth and first pharmacokinetic visit. Of the 45 infants included in the pharmacokinetic analysis, 21 (47%) from PACTG 321 and the Tygerberg Cohort were sampled before 15 days postnatal age, and 24 (53%) from IMPAACT P1106 on ritonavir-boosted lopinavir, lamivudine, and abacavir were younger than 3 months. None of these 24 infants received rifampicin. The majority (21 [88%] of 24) were pre-term (gestational age <37 weeks) and 18 (75%) of 24 had low birthweight. Infants in IMPAACT P1106 were older than in the other studies at first pharmacokinetic sampling, with a median postnatal age of 73 days (table 1).

308 abacavir plasma concentrations were available from 45 infants for model development. All plasma samples collected in PACTG 321 and the Tygerberg Cohort had quantifiable abacavir plasma concentrations, whereas 33 of 198 samples in IMPAACT P1106 (all pre-dose) were below LLOQ. Abacavir plasma concentrations were best described by a one-compartment model with first order absorption and elimination. Accurate estimation of the absorption rate constant was not possible and was fixed to 2.07 h⁻¹.²¹ Residual variability was described by a proportional error model. Oral clearance (CL/F) and volume of distribution (Vd/F) were allometrically scaled according to bodyweight *a priori* with the exponents fixed to 0.75 and 1.00, respectively.²² Maturation of abacavir CL/F was assessed using postnatal age and post-menstrual age, including attempts to differentiate between young and older infants; however, this process was best described using an exponential model as a function of postnatal age (table 2). Abacavir CL/F was low at birth but approximately doubled by 4 weeks of age (figure 1). Abacavir CL/F in all 18 low-birthweight and pre-term infants at 6 weeks postnatal age was similar to any term infant of the same chronological age. The final population pharmacokinetic parameter estimates with bootstrap results are shown in table 2. Goodness-of-fit plots and a visual predictive check are shown in the appendix (pp 1, 2).

Abacavir drug exposures were predicted for virtual infants from birth until age 12 weeks receiving abacavir doses between 2.0 mg/kg and 6.0 mg/kg twice daily. Abacavir exposures rapidly decreased from a median of 12.6 µg·h/mL on day 1 to 4.5 µg·h/mL by day 28,

indicating the need for a dose increase. The optimal abacavir dose selected was 2·0 mg/kg from 0 weeks to 4 weeks, then 4·0 mg/kg thereafter. This dosing strategy provided abacavir exposures within the expected range for infants with birthweights of 2·0 kg, 3·0 kg, and 4·0 kg (figure 2; appendix p 3).

To determine the optimal abacavir doses for neonates per WHO weight bands, plasma drug exposures were simulated for neonates with birthweights of 2·0 kg, 2·5 kg, 3·0 kg, 3·5 kg, 4·0 kg, and 4·5 kg receiving abacavir doses between 8 mg and 12 mg twice daily. To ensure comparable abacavir exposures between weight bands, the preferred abacavir doses were 8 mg for birthweights of 2–3 kg, 10 mg for 3–4 kg, and 12 mg for 4–5 kg (figure 3). Abacavir exposures rapidly decreased after birth across all weight bands, falling by around 25% at week 2, and around 55% by week 4. Abacavir exposures remained within the reported range, except for 5% of infants weighing 2·0 kg and 12% weighing 3·0 kg with high exposures during the first week of life.

For PACTG 321, safety and toxicity data were available for eight neonates who received a single dose of abacavir during standard zidovudine prophylaxis. Two participants developed grade 3 neutropenia, deemed possibly related to zidovudine. All other clinical and laboratory abnormalities were grade 2 or lower and deemed unrelated to study medication. For the Tygerberg Cohort, no adverse events were documented in ten neonates on the day of single dose abacavir administration. Nine of ten mothers could be contacted after 1 month, reporting healthy infants with no skin rash, fever, or vomiting observed in the 2 weeks after pharmacokinetic sampling.

27 infants in IMPAACT P1106 received multi-dose abacavir-containing ART for a median duration of 24·0 weeks (range 0·6–28·7). 15 infants (55·6%; 90% CI 38·3–72·0) met the safety endpoint of death or a grade 3 or higher adverse event. None of these were assessed by the study site investigators to be related to abacavir, and none led to any interruptions or adjustments of abacavir dosing. One 8-week-old infant (3·7%; 0·2–16·4) died at home due to an unknown cause 1 day after hospital discharge for gastroenteritis, which was considered unrelated to abacavir. Five infants (18·5%; 7·6–35·1) had grade 3 or 4 expected adverse events, which included sepsis in three infants and single instances of five other adverse events (appendix p 7). 12 infants (44·4%; 28·0–61·8) had grade 3 or 4 unexpected adverse events which included increased blood potassium in seven infants, gastroenteritis in four infants, and single instances of 16 other adverse events (appendix p 8). All infants with grade 3 or 4 unexpected adverse events had resolution to grade 2 or better by the final study visit, with the exception of one infant with tracheobronchitis and upper respiratory tract infection who withdrew consent, and two infants with weight loss or underweight. No hypersensitivity reactions were reported with the multi-dose treatment. One grade 2 alanine aminotransferase concentration led to an 8-day temporary hold of ART; however, this infant had a history of hepatotoxic traditional medicine ingestion. Unchanged ART was restarted without further complications.

Discussion

In this study, we report the first abacavir population pharmacokinetic model developed using data collected in neonates and young infants to inform abacavir liquid dosing from birth to age 3 months. Our proposed abacavir dosing strategy and weight-band dosing for neonates achieved exposures in the range reported in older children. No major safety concerns for abacavir were seen, although care should be taken when interpreting the safety of PACTG 321 and the Tygerberg Cohort because only a single dose was administered. In IMPAACT P1106, with the administration of multi-dose abacavir to infants older than 1 month, no grade 3 or higher adverse events were considered to be related to abacavir.

A detailed understanding of abacavir metabolism is essential for age-appropriate abacavir dosing guidance. Abacavir is primarily metabolised in the liver via UGT2B7 and ADH enzymes, with metabolic enzyme activities and organ function typically slow at birth and increasing rapidly during early life.⁷ A strength of the current analysis is the inclusion of neonates and older low-birthweight and pre-term infants, enrolled when they were younger than 3 months at the time of pharmacokinetic sampling, providing a robust dataset to describe oral clearance during this period of rapid maturation and bodyweight changes. Our abacavir population pharmacokinetic model adequately described the abacavir concentration data for this young population. Although one-compartmental²¹ and two-compartmental pharmacokinetic models²³ have been reported, we selected a one-compartmental model because our data could not identify a peripheral compartment, probably due to the sparse nature of the IMPAACT P1106 pharmacokinetic data. Both bodyweight and postnatal age were identified as important covariates in our model, but a previous paediatric model of abacavir pharmacokinetics included only bodyweight.²¹ Our model predicts an abacavir clearance of 2.51 mL/min per kg for a 3 kg child at birth, which is almost five times lower than adults²⁴ and consistent with minimal UGT2B7 and ADH enzyme activities at birth. We found abacavir clearance to rapidly increase after birth, by about two times by week 4 and 3.5 times by week 12, signifying that dose adjustments are likely necessary at the ages of 1 month and 3 months to ensure therapeutic concentrations. Indeed, we found exact abacavir dosing of 2.0 mg/kg twice daily at 0–4 weeks, increasing to 4.0 mg/kg twice daily at 4–12 weeks and to 8.0 mg/kg twice daily after 12 weeks achieved similar exposures to those observed in older children.

In the context of a public health approach, precise dosing of abacavir liquid is not feasible and WHO weight-band dosing is preferable. Although WHO recommends a weight-band dose for children older than 4 weeks and weight at least 3 kg, abacavir weight-band dosing is not available for infants younger than 4 weeks of age. Based on our simulations, we propose an optimal abacavir weight-band dosing strategy for term neonates of 8 mg (for 2–3 kg), 10 mg (3–4 kg), and 12 mg (4–5 kg) twice daily. This strategy uses the same dose of abacavir liquid from birth to 4 weeks, which simplifies treatment during this challenging period. Moreover, if we administer abacavir in the first 4 weeks of life following an HIV diagnosis, the switch from zidovudine to abacavir at age 1 month, as recommended by South African guidelines for infants on ART,¹⁴ will not be needed. In addition, the use of abacavir in the neonatal period will better align with current WHO first-line ART guidelines.

A single dose of abacavir in term neonates and chronic abacavir use in infants older than 1 month appeared to be safe. However, the safety of multiple doses of abacavir has not yet been confirmed in neonates. Across all three studies, no adverse events of grade 3 or higher were deemed to be related to abacavir. Despite large differences in abacavir doses and plasma concentrations between studies, no relationship with safety effects was observed. No hypersensitivity reactions were reported. Abacavir hypersensitivity reactions are uncommon in children, especially in sub-Saharan Africa, where the HLA*B5701 allele is rare.¹⁰ A systematic review reported a pooled incidence of 2.2% (95% CI 0.4–5.2) for hypersensitivity reactions observed in 1769 children (aged 0–18 years) from Europe, North America, and Africa on ART.¹⁰ Two grade 3 neutropenia adverse events in the Tygerberg Cohort were attributed to zidovudine. The IMPAACT P1115 trial evaluating early nevirapine-based ART for neonates, published in 2021, also reported zidovudine related haematological toxicity leading to its permanent discontinuation in nine (2%) of 438 neonates and temporary discontinuation in four neonates.²⁵ Findings from two large observational cohorts further support abacavir's low toxicity when started in infants before 3 months of age. Of 139 European infants (20 neonates) given 2–8 mg/kg twice daily, only 19 (14%) discontinued abacavir by 1 year, four of whom discontinued due to a possible abacavir adverse event (one metabolic acidosis, one diarrhoea, and two possible hypersensitivity reactions).¹¹ Of 931 South African infants (96 neonates), only 61 (8%) of 798 discontinued abacavir permanently with one hypersensitivity reaction reported;¹² no abacavir doses were provided.

Although the abacavir liquid formulations remain in use in several settings, there is an urgent need to determine whether available paediatric solid formulations can be used from birth. A paediatric fixed dose combination with abacavir and lamivudine co-formulated in a 2:1 ratio is available. As expected, the abacavir dose imposed by the paediatric fixed-dose combination tablets can lead to higher mg/kg dosing than current licensed doses. However, the well established safety margin of abacavir in children and adolescents¹⁰ offers some reassurance for a similar good safety profile in neonates. The ongoing *PETITE* study in South Africa (Pan African Clinical Trials Registry, PACTR202007806554538) is studying the safety, pharmacokinetics, and acceptability of paediatric solid fixed-dose combinations of abacavir, lamivudine, and ritonavir-boosted lopinavir from birth, for which the data will build upon the information generated with the liquid formulation to guide the optimal use of abacavir in neonates.

Our study had several limitations. The abacavir assays were not performed at the same facility and this could potentially be an additional source of variability. For the pharmacokinetic model, samples from 15 days to 41 days postnatal age and beyond 9 months were absent, as were samples at steady state in neonates. Including these samples would have benefited the model. Indeed, results should be interpreted with some caution, especially if extrapolating dosing outside of the age range studied. Similarly, the first pharmacokinetic sampling for pre-term and low-birthweight infants was at a more advanced postnatal age (41–190 days); therefore, care should be taken not to use this proposed abacavir dosing in preterm and low-birthweight infants at birth. The effects of common concomitant medications on abacavir exposure, particularly ritonavir-boosted lopinavir, for which lower abacavir exposures have been reported,²⁶ also need further assessment in this population.

In summary, abacavir is an alternative nucleoside reverse transcriptase inhibitor option for neonates and we propose both exact and weight-band dosing from birth for the abacavir liquid formulation. Such dosing guidance can facilitate early abacavir use in neonates both for HIV treatment or as a component of prevention in neonates at high risk of HIV acquisition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

For PACTG321 and IMPAACT P1106, overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The Tygerberg Cohort study was supported by the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) - Growing the Leaders of Tomorrow Fellowship Programme. The teams thank the participants, their families and the study staff conducting the protocol.

References

1. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med* 2008; 359(21): 2233–44. [PubMed: 19020325]
2. Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at <https://clinicalinfo.hiv.gov/sites/default/files/inline-files/pediatricguidelines.pdf>. Accessed (August 24, 2021)
3. ZIAGEN (abacavir sulfate): Package Insert, Full Prescribing Information: Revised: 11/2020. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Ziagen/pdf/ZIAGEN-PI-MG.PDF. Accessed (August 24, 2021).
4. WHO: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach - Second edition 2016. <https://apps.who.int/iris/handle/10665/208825>. Accessed (August 24, 2021) 2016.
5. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349(12): 1157–67. [PubMed: 13679531]
6. Royal College of Paediatrics and Child Health. BOYS UK–WHO Growth Chart 0–4 years https://www.rcpch.ac.uk/sites/default/files/Boys_0-4_years_growth_chart.pdf. Accessed (August 24, 2021).
7. Yuen GJ, Weller S, Pakes GE. A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; 47(6): 351–71. [PubMed: 18479171]
8. Onishi S, Kawade N, Itoh S, Isobe K, Sugiyama S. Postnatal development of uridine diphosphate glucuronyltransferase activity towards bilirubin and 2-aminophenol in human liver. *Biochem J* 1979; 184(3): 705–7. [PubMed: 120201]
9. Pikkariainen PH, Raiha NC. Development of alcohol dehydrogenase activity in the human liver. *Pediatric research* 1967; 1(3): 165–8. [PubMed: 6080860]
10. Jesson J, Dahourou DL, Renaud F, Penazzato M, Leroy V. Adverse events associated with abacavir use in HIV-infected children and adolescents: a systematic review and meta-analysis. *Lancet HIV* 2016; 3(2): e64–75. [PubMed: 26847228]

11. Crichton S, Collins IJ, Bamford A, et al. Abacavir use in young infants in the UK and Ireland national paediatric cohort. 11th International Workshop on HIV Pediatrics. Mexico City, Mexico; 2019.
12. De Waal R, Rabie H, Technau K, et al. Abacavir safety and efficacy in young infants in South African observational cohorts [abstract no. 845]. Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA; 2020.
13. Bekker A, Decloedt EH, Slade G, Cotton MF, Rabie H, Cressey TR. Single Dose Abacavir Pharmacokinetics and Safety in Neonates Exposed to HIV. Clin Infect Dis 2020.
14. South African HIV Clinicians Society (SAHCS): Antiretroviral Drug Dosing Chart for Children: https://sahivsoc.org/Files/PaedDosingChart_Final2019.pdf. Accessed (August 24, 2021).
15. DiFrancesco R, Tooley K, Rosenkranz SL, et al. Clinical pharmacology quality assurance for HIV and related infectious diseases research. Clin Pharmacol Ther 2013; 93(6): 479–82. [PubMed: 23588323]
16. Bergstrand M, Karlsson MO. Handling data below the limit of quantification in mixed effect models. AAPS J 2009; 11(2): 371–80. [PubMed: 19452283]
17. Wahlby U, Jonsson EN, Karlsson MO. Comparison of stepwise covariate model building strategies in population pharmacokinetic-pharmacodynamic analysis. AAPS PharmSci 2002; 4(4): E27. [PubMed: 12645999]
18. Engle WA, American Academy of Pediatrics Committee on F, Newborn. Age terminology during the perinatal period. Pediatrics 2004; 114(5): 1362–4. [PubMed: 15520122]
19. Beal SL, Sheiner LB, Boeckmann AJ. NONMEM users guide: ICON. PLC. <https://nonmem.iconplc.com/nonmem720/guides/>. Accessed (August 24, 2021). 1994-2011.
20. ZIAGEN® (abacavir sulfate) Epivir® (lamivudine). U.S FDA OFFICE OF CLINICAL PHARMACOLOGY REVIEW. Submission date: 5/23/14. <https://www.fda.gov/media/92051/download>. Accessed (August 24, 2021).
21. Jullien V, Urien S, Chappuy H, et al. Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. J Clin Pharmacol 2005; 45(3): 257–64. [PubMed: 15703361]
22. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48: 303–32. [PubMed: 17914927]
23. Archary M, McLlaron H, Bobat R, et al. Population pharmacokinetics of abacavir and lamivudine in severely malnourished human immunodeficiency virus-infected children in relation to treatment outcomes. Br J Clin Pharmacol 2019; 85(9): 2066–75. [PubMed: 31141195]
24. McDowell JA, Chittick GE, Stevens CP, Edwards KD, Stein DS. Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 2000; 44(6): 1686–90. [PubMed: 10817729]
25. Ruel TD, Capparelli EV, Tierney C, et al. Pharmacokinetics and safety of early nevirapine-based antiretroviral therapy for neonates at high risk for perinatal HIV infection: a phase 1/2 proof of concept study. Lancet HIV 2021; 8(3): e149–e57. [PubMed: 33242457]
26. Waters LJ, Moyle G, Bonora S, et al. Abacavir plasma pharmacokinetics in the absence and presence of atazanavir/ritonavir or lopinavir/ritonavir and vice versa in HIV-infected patients. Antivir Ther 2007; 12(5): 825–30. [PubMed: 17713166]

Research in Context

Evidence before the study

WHO recommends abacavir for first-line antiretroviral treatment in infants and children. Abacavir is licensed at 8 mg/kg twice a day from age 3 months and the 2016 WHO weight-band dosing guideline recommends abacavir from age 1 month in infants weighing at least 3 kg. To date, insufficient abacavir pharmacokinetic and safety data in neonates have been available to support dosing recommendations from birth. We performed a literature search using PubMed with the terms “pharmacokinetics”, “safety”, “abacavir”, and “neonates” for research published up to May 20, 2021, and found no studies with the exception of one from our research team, reporting on the pharmacokinetics of single-dose abacavir in ten term neonates born to women living with HIV. Two other studies (PACTG 321 and IMPAACT P1106) reported abacavir pharmacokinetics and safety data in neonates and infants at scientific conferences, but were not published. Each of these three independent studies alone is not able to provide sufficient information to guide abacavir dosing through the first 3 months of life.

Added value of the study

Conducting large pharmacokinetic and safety clinical trials in neonates is challenging, often delaying dosing guidance in this vulnerable population. Pooling data from these three independent studies performed in neonates and infants provided the opportunity to delineate abacavir dosing from birth through to age 3 months using a population pharmacokinetic modelling and simulation approach. To our knowledge, no previous pharmacokinetic model of abacavir has included data in neonates. This analysis extends our understanding of abacavir metabolism during early life and its impact on drug exposures. The pharmacokinetic model simulations provided the opportunity to explore multiple abacavir dosing options to support and ultimately recommend both exact (mg/kg) and WHO weight-band dosing from birth with the liquid formulation. Safety data on abacavir use from birth are scarce. Data from these three studies provide some reassurance that abacavir is safe, based on a single dose in term neonates and with chronic use in infants older than 1 month.

Implications of all the available evidence

The proposed abacavir dosing strategy is the first evidence based optimal dosing guidance for infants younger than 3 months receiving abacavir liquid formulation. We expect that this dosing information will expand antiretroviral options during the neonatal period. In terms of public health, use of abacavir from birth aligns with current WHO first-line antiretroviral therapy guidelines, which would eliminate the switch from zidovudine to abacavir at age 1 month, simplifying the treatment for both health-care providers and parents or caregivers. These new data should support national and international experts and policy makers when revising and simplifying HIV treatment guidelines for neonates in all settings.

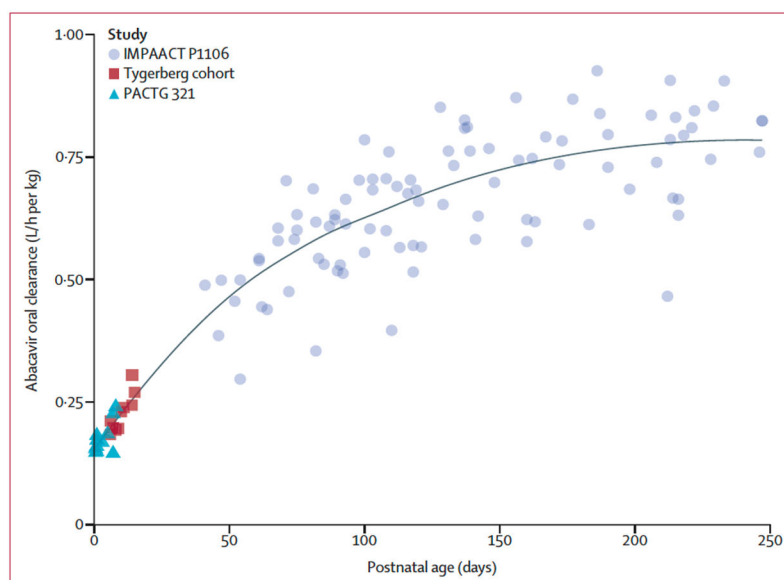


Figure 1:
Individual predicted abacavir oral clearance versus postnatal age for neonates and infants enrolled in 3 pharmacokinetic studies administering abacavir liquid formulation

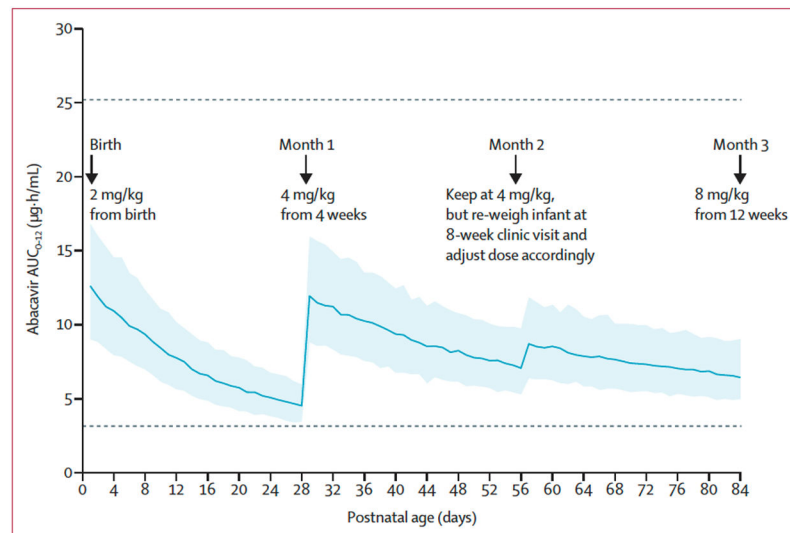


Figure 2: Predicted abacavir exposure for a 3.0 kg infant at birth: 2 mg/kg BID from 0-4 weeks of life, 4 mg/kg BID until 12 weeks and 8 mg/kg BID thereafter.

Solid line median and shaded area 5th to 95th percentile. Dotted lines represent the upper and lower ranges for AUC₀₋₁₂ (3.2 to 25.2 µg.hr/mL) observed in older children receiving abacavir twice daily.

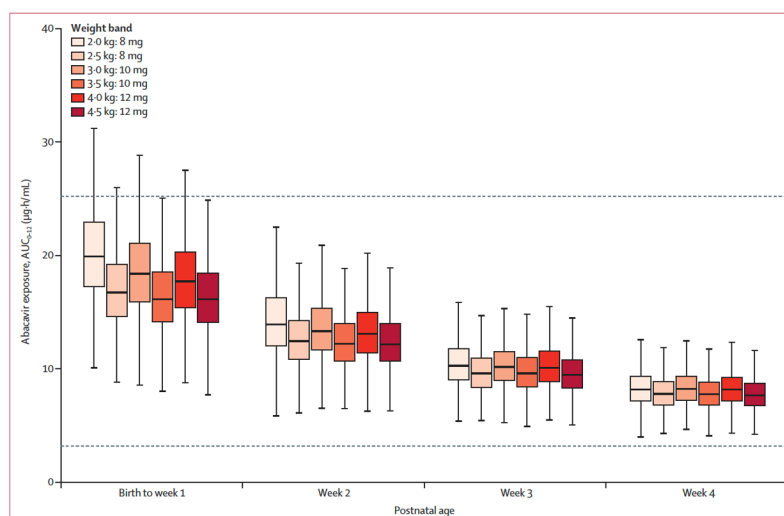


Figure 3. Box-whisker plots of predicted abacavir exposure for neonates from 0-4 weeks of life dosed per WHO weight-bands.

Infants at birth weighing 2.0 and 2.5 kg received 8 mg (0.4 mL), 3.0 and 3.5 kg received 10 mg (0.5mL), and 4.0 and 4.5 kg received 12 mg (0.6mL) of abacavir liquid BID for 28 days. Dotted lines represent the upper and lower ranges for AUC₀₋₁₂ (3.2 to 25.2 µg·hr/mL) observed in older children receiving abacavir twice daily.

Table 1:Study and infant characteristics at birth and first pharmacokinetic visit (*n*=45)

	PACTG 321	Tygerberg Cohort	IMPAACT P1106	Total
Study design				
Participant HIV status	Exposed to HIV	Exposed to HIV	Living with HIV	..
Dates	1997–99	2019–20	2015–20	..
Number of infants	11	10	24	45
Number of doses	Single	Single	Multiple (twice daily)	..
Abacavir dose, mg/kg	2.0 (1.9–2.1)	8.1 (8.0–8.4)	10.8 (4.1–13.2)	..
Number of samples	60	50	198	308
Infant characteristics				
Sex				
Female	6	3	12	26
Male	5	2	12	19
Ethnicity				
Black	8	10	21	39
Mixed *	0	0	3	3
Hispanic	3	0	0	3
Birthweight, kg	3.1 (2.2–4.0)	3.2 (2.5–4.2)	2.2 (1.4–3.3)	2.6 (1.4–4.2)
Low birthweight (<2500 g)	3 (27)	0 (0)	18 (75)	21 (47)
Gestational age at birth, weeks	39 (39–39)	39 (38–42)	35 (27–39)	38 (27–42)
Weight at first pharmacokinetic visit, kg	3.1 (2.2–4.0)	3.3 (2.9–4.4)	3.8 (2.4–5.8)	3.5 (2.2–5.8)
Postnatal age at first abacavir dose, days	1 (1–8)	10 (6–15)	60 (25–174)	31 (1–174)
Postnatal age at first pharmacokinetic visit, days	1 (1–8)	10 (6–15)	73 (41–190)	46 (1–190)

Data are n (%) or median (range).

* In South Africa, this term is used to refer to anyone from a Mixed White and Black or Asian background.

Table 2:

Final population pharmacokinetic parameter estimates for abacavir

	Final model		Bootstrap*	
	Estimated value	Relative SE[†]	Median	5th–95th percentile
Absorption rate constant (Ka), h ⁻¹	2.07 (fixed)	..	..	..
Oral clearance (CL/F), L/h per 4.2 kg	0.583	11.4	0.567	0.410–0.673
Maturation parameters				
Mat	3.63	17.4	3.65	2.69–4.96
K _{Mat} , days ⁻¹	0.0086	25.5	0.0086	0.0060–0.150
Oral volume of distribution (Vd/F), L/4.2	6.88	8.0	6.89	6.10–7.94
Inter-individual variability				
IIVCL, %CV	18.2	29.2	17.1	11.0–28.3
IIVV, %CV	15.2	51.9	14.0	0.10–28.2
Residual variability				
Proportional	0.265	13.0	0.256	0.201–0.315

Maturation function: $\text{Mat} \times [1 - e^{(-\text{PNA} \times K_{\text{Mat}})}]$. CL/F: $\{0.583 + [3.63 \times (1 - e^{-\text{PNA} \times 0.0086})]\} \times (\text{bodyweight}/4.2)^{0.75}$. Vd/F: $6.88 \times (\text{bodyweight}/4.2)$. IIVCL=inter-individual variability for clearance. IIVV=inter-individual variability for volume of distribution. %CV=percent coefficient variation. Mat=maturation. PNA=postnatal age in days. K_{Mat}=maturation rate constant.

* Statistics from 1000 bootstrap analyses.

[†] Relative SE was defined as: $(\text{SE}_{\text{estimate}}/\text{estimate}) \times 100$.