## Title

Pharmacokinetics, safety, tolerability, and antiviral activity of dolutegravir dispersible tablets in infants and children with HIV-1 (IMPAACT P1093): results of an open-label, phase 1–2 trial



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# Pharmacokinetics, safety, tolerability and antiviral activity of dolutegravir dispersible tablets in infants and children with HIV-1: results of the IMPAACT P1093 study, a phase I/II open-label trial

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TDR and AW led the writing of the manuscript; TDR, AW and EA accessed, verified and analysed the pharmacokinetic data; KPG, and JPL had access to safety, tolerability and efficacy data and performed all statistical analyses; KPG accessed and verified all data. All authors (TR, EA, JPL, KPG, KG, NM, SP, AMB, MB, DD, PA, CB, CV, RS, LK, TV, BM, JP, ED, MA, KC, PO, JD, RH, ET, AW) contributed to the protocol development, implementation, data collection, drafting of the manuscript; all had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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## Abstract

**Background:** Safe and potent antiretroviral medications in child-friendly formulations are needed to treat young children living with HIV-1 The primary objective of this study was to select dosing for a dispersible tablet formulation of dolutegravir that achieved pharmacokinetic exposures similar to those in adults, and was safe and well-tolerated in young children.

**Methods:** IMPAACT P1093 is a Phase I/II ongoing multi-centre, open-label, non-comparative study of dolutegravir treated with 5mg dispersible tablet formulation. Children 4 weeks to < 6 years old, weighing ≥ 3kg, with HIV RNA > 1000 copies/mL and no prior integrase-strand-transfer-inhibitor treatment were recruited in Africa, Asia and the Americas from 2017 to 2020. Doses were selected based on intensive pharmacokinetic evaluation on day 5–10, with safety and tolerability assessed through 48 weeks.

**Findings:** The analysis included 73 (48% female) participants with median (range) age of 1 (0·1, 6·0) years, weight of 8·5 (3·7, 18·5) kg, plasma HIV-1 RNA level of 4·2 (2·1, 7·0) (log10 copies/mL), and CD4% was 24·0 (0·3, 49·0); 64 (87·7%) were treatment-experienced. The selected dose within each age cohort (≥ 2 to < 6 years, ≥ 6 months to < 2 years of age and ≥ 4 weeks to < 6 months) achieved geometric mean trough (ng/mL) of 688, 1179, and 1446, and 24-hour area-under-the-curve (hr*mg/L) of 53, 74, and 65, respectively. No grade 3 or worse adverse events were attributed to dolutegravir. Dispersible tablet palatability was rated as good or better in 97% of reports from 73 responders.

**Interpretation:** In this study, the proposed once-daily dosing of dolutegravir dispersible tablets provided drug exposures comparable to adults, and was safe and well-tolerated. These data support the use of dolutegravir dispersible tablets as first- or second-line treatment for infants and children < 6 years old with HIV-1.

**Trial Registration:** This trial is registered at ClinicalTrials.gov (NCT01302847)

### Keywords

Dolutegravir; infants; children; HIV-1; HIV

## Introduction

Despite progress in the prevention of vertical transmission, 1·8 million children were estimated to be living with human immunodeficiency virus (HIV) in 2019 globally, with only 53% receiving antiretroviral treatment.[1] Potent and well-tolerated formulations of antiretrovirals are particularly needed to treat infants and young children, who have challenges with adherence, poor treatment outcomes and a small number of options with approved dosing. Since 2018, the World Health Organization has recommended dolutegravir, an integrase-strand-transfer-inhibitor, with a high barrier to resistance and good safety profile as first line treatment of HIV-1.[2] However, global implementation of dolutegravir has been limited to adults and children weighing enough to utilize the film-coated tablet formulation.

The objective of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1093 trial is to evaluate the pharmacokinetics, safety, tolerability and antiviral activity of dolutegravir in order to determine dosing for the treatment of infants, children, and adolescents living with HIV-1. Data from IMPAACT P1093 established dosing of dolutegravir film-coated tablets to treat adolescents and children weighing at least 30 kg.[3,4] A dispersible tablet formulation of dolutegravir was developed for the treatment of infants and younger children and was first evaluated within the IMPAACT P1093 trial.

Here we present data on the pharmacokinetics, safety, tolerability, and antiviral activity of a proposed dose for a 5 mg dispersible tablet dolutegravir formulation to treat infants and young children with HIV-1, 4 weeks to 6 years of age and weighing at least 3 kg.

## Methods

### Study design and participants

IMPAACT P1093 is a Phase I/II, multi-centre, open-label, non-comparative study of the pharmacokinetics, safety, tolerability, and antiviral activity of dolutegravir in infants, children, and adolescents living with HIV-1 (NCT01302847). As per guidance from the United States Federal Drug Administration and the European Medicines Agency guidance for HIV drug development in paediatric populations, this trial focused on pharmacokinetics and safety.[5–7] The primary objectives of this ongoing study are, for infants, children and adolescents living with HIV-1: 1) to evaluate the steady-state pharmacokinetics of dolutegravir in combination with optimized background therapy and to determine the dose of dolutegravir that achieves the targeted 24-hour trough concentration ($C_{24h}$) and 24-hour area-under-the-curve ($AUC_{24}$) in this population, 2) to determine the safety and tolerability of dolutegravir at 24 and 48 weeks; 3) to select a dose for each formulation of dolutegravir for dosing that achieves similar exposure to the dolutegravir 50 mg once daily dose in adults. Secondary objectives include evaluating the virologic and immunologic responses of infants and children after 24 and 48 weeks of treatment, and evaluating the pharmacokinetic (PK) profile of dolutegravir dispersible tablets dosed according to World Health Organization (WHO) weight-bands.[2] The analysis presented here included the cohorts of participants who received the dispersible tablet formulation.

To enrol, infants and children had to be 4 weeks to less than 6 years old, have confirmed HIV-1 infection, weigh at least 3 kg, and have HIV-1 RNA > 1000 copies per mL. For background treatment, participants had to have at least one fully active drug based on genotype evaluation that could be used for combination therapy with dolutegravir. Infants < 2 years of age could be antiretroviral treatment naïve or have had initiated treatment within the prior 4 weeks, in which case dolutegravir was added to the treatment regimen. Exclusion criteria included prior exposure to an integrase strand transfer inhibitor, use of medications predicted to interact with dolutegravir metabolism, and evidence of liver toxicity or any grade 3 or 4 toxicity as per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1·0) at screening.[8] We recruited participants into P1093 at IMPAACT network clinical research sites from April 20th, 2011 to February 19th, 2020; the first participant who received dolutegravir dispersible tablets was enrolled on June 1st, 2017.

The National Institutes of Health (NIH), applicable national authorities and local Institutional Review Boards (IRB) reviewed the protocol. Written informed consent was obtained from each participant's parent or legal guardian for participation, in their local language.

## Procedures

Dolutegravir dispersible tablet dosing was evaluated in two stages for each of the three age-based cohorts (≥ 2 to < 6 years, ≥ 6 months to < 2 years and ≥ 4 weeks to < 6 months). In Stage I, we examined intensive pharmacokinetics and short-term (4-week) safety of a dose. If safety and pharmacokinetic criteria were met with the first 4 participants, enrolment was continued until a minimum of 10 participants within each age-based cohort and a minimum of 8 participants in each weight-band (3 to < 6 kg, 6 to < 10 kg, 10 to < 14 kg, 14 to < 20 kg) with evaluable data had been enrolled. If predetermined Stage I criteria (see below) for intensive pharmacokinetic and safety metrics were met, enrolment into Stage II was opened for additional participants to be treated at the final proposed dose (without intensive pharmacologic studies), in order to achieve a minimum of 22 participants in each age cohort for the assessment of 24- and 48-week safety and secondary objectives.

Participants initiated dolutegravir dispersible tablet(s) on the day of enrolment. Intensive pharmacokinetic evaluations were performed between days 5 and 10; samples were obtained after dolutegravir was ingested in a fasted state, generally defined as no high fat food or liquid 2 hours prior or 1 hour after dolutegravir administration (See protocol in supplemental material for more details). The optimized background antiretroviral regimen included at least two additional agents, at least one of which was predicted to have antiviral activity by genotype; the initiation of background agents with potential interaction with study drug was delayed until after intensive pharmacokinetic evaluations. Every adverse event was reviewed by the site investigator, including consideration of association with study drug; every grade 3 or greater event was additionally reviewed by protocol team. After enrolment, participants were evaluated at day 10 and weeks 4, 8, 12, 16, 24, 32, 40 and 48, with history, physical examination, and laboratory studies including plasma HIV-1 RNA levels. Caregivers reported palatability at day 10 and weeks 4 and 24 (Table S1, Appendix, page 1–3).

Dolutegravir plasma concentrations were determined using liquid chromatography with tandem mass spectrometry, as previously described.[9] Whole blood was collected at time 0 (pre-dose) and at 1, 2, 3, 4, 6, 8 and 24 hours after ingestion. Dolutegravir steady-state pharmacokinetic parameters were calculated using Phoenix WinNonlin version 8·3 (Certara USA, Inc., Princeton, New Jersey, USA) and were performed in real-time at the IMPAACT Pharmacology Support Laboratory at the University of Alabama at Birmingham.

The 5 mg dolutegravir dispersible tablets were dosed using weight-band tables; dosing was once daily, or twice daily if a participant was taking other antiretroviral medications that altered metabolism. The pharmacokinetic targets for population exposure were a geometric mean (range) $C_{24h}$ of 995 ng/mL (697–2,260 ng/mL) and $AUC_{24}$ of 46 μgxh/mL (37–134 μgxh/mL) based on data from adult Phase III trials.[10–12] Dosing was evaluated for Stage 1 by the protocol team for the extent to which they approximated exposures in adults, based primarily on target ranges for the geometric means of $C_{24h}$ and $AUC_{24}$, but also considering variability and the EC90. Dosing must also not have not triggered safety concerns, defined as having a life-threatening drug-related adverse event, a grade 4 event that is probably or definitely attributable to the study medication, or no more than 25% having terminated dolutegravir due to a grade 3 or higher drug-related event. The initial dosing (Table S2, Appendix, page 4] evaluated for children ≥ 2 years to < 6 years and ≥ 6 months to < 2 years raised no safety concerns but did not achieve acceptable drug exposures. The proposed dolutegravir dispersible tablet dosing ultimately studied in Stage I and II is presented with the results. While the protocol-specific primary analysis was based on dosing by age cohort, Version 5·0 included an additional secondary objective to assess pharmacokinetic exposures among children dosed according to WHO weight-bands: 3 to < 6 kg: 5 mg; 6 to < 10 kg: 15 mg; 10 to < 14 kg: 20 mg; 14 to < 20kg: 25 mg.

## Outcomes

The primary pharmacokinetic outcomes were dolutegravir $C_{24}$ and $AUC_{24}$. The primary safety outcome was toxicity, defined as grade 3 or 4 adverse events, termination of treatment due to drug-related adverse event, or death. Secondary outcomes included additional pharmacokinetic variables and tolerability, and clinical efficacy. Clinical efficacy variables included plasma HIV-1 RNA at week 24 and 48, respectively, and CD4 absolute cell counts and percentage through week 48. Virologic success was defined as achieving a plasma HIV-1 RNA < 400 copies per mL. Other efficacy outcomes included the proportion achieving HIV-1 RNA < 50 copies per mL and the change from baseline in CD4 cell count and percentage.

## Statistical Analysis

Pharmacokinetic, safety, tolerability, and efficacy analyses were conducted in participants treated with the proposed dose of dolutegravir dispersible tablets in Stages I and II. We included all available data for participants until the last enrolled participant reached 48 weeks of study in the safety analysis and the pharmacokinetic analyses were performed on the participants from the proposed dose dispersible tablet cohorts. Descriptive statistics were used to summarize the participant characteristics and tolerability. Unless otherwise stated, median and range were used to summarize continuous variables and proportion and

95% confidence intervals for categorical variables. The main efficacy analysis examined the proportion with plasma HIV-1 RNA < 400 copies per mL and HIV-1 RNA-1 < 50 copies per mL after 24 and 48 weeks of treatment among those with available data.

### Role of Funding Source

Overall support for this trial and 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), by NICHD contract number HHSN275201800001l, and from ViiV Healthcare/GlaxoSmithKline. All sponsors contributed to study design; data collection, analysis, and interpretation were completed by the IMPAACT network; writing of the manuscript was completed by the authors (see Contributors, below). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH

## Results

A total of 181 participants living with HIV-1 from nine countries in North America, South America, Africa, and Asia were enrolled in IMPAACT P1093 and received dolutegravir. In the early phase of the study, 85 children and adolescents received formulations other than the dispersible tablets; 96 received dolutegravir dispersible tablets. Twenty-three children received initial failed doses that resulted in concentrations that did not pass Stage I review (Table S2, Appendix page 4). Seventy-three participants received the final proposed dose (Figure 1). The analysis cohort included the 73 children treated with the proposed dosing of dolutegravir dispersible tablets, of whom 35 (48%) participants were female with median (range) age of 1 (0·1, 6·0) year, weight of 8·5 (3·7, 18·5) kg, plasma HIV-1 RNA level of 4·2 (2·1, 7·0) ($log_{10}$ copies per mL), CD4 count (cells/mm3) of 1691 (1, 8255) and CD4% of 24·0 (0·3, 49·0); 64 (87·7%) were treatment-experienced and 18 (19%) had a Grade 2 or 3 comorbidities on enrolment (Table 1 and Table S3, Appendix page 4). Among the optimized background regimens prescribed, most included two nucleoside-reverse transcriptase inhibitors, with the most common regimen being lamivudine or emtricitabine plus abacavir (46·6%) (Table S4, Appendix page 5).

The primary analysis includes Stage I assessment of 43 participants at the final proposed doses (Table 2). Age cohorts (≥ 2 to < 6 years, ≥ 6 months to < 2 years of age and ≥ 4 weeks to < 6 months) achieved geometric mean dolutegravir $C_{24h}$ (ng/mL) of 688, 1179, and 1446, and $AUC_{24}$ (hr*mg/L) of 53, 74, and 65, respectively, with other parameters summarized in Table S5 (Appendix page 5) and Figure 2. Stage 1 assessment of WHO dosing by weight-band (independent of age) also resulted in acceptable exposures, with geometric mean $C_{24h}$ (ng/mL) concentrations ranging from 883 to 1453 and $AUC_{24}$ (hr*mg/L) ranging from 49·0 to 70·0 (Table S6, Appendix page 5).

Among 73 participants who received the proposed dispersible tablet dose, 5 had early discontinuations. One died at Week 8 (gastroenteritis believed unrelated to dolutegravir), one withdrew per site physician recommendation at Week 12 due to other comorbidities that complicated protocol participation. Two participants discontinued due to site physician concerns about medication adherence (Weeks 24 and 40), and one due to consent withdrawn because family relocated away from study site (Week 24). (Additional details in Table S7, appendix page 6)

Dolutegravir was well tolerated, with no grade 3 or greater adverse events judged to be possibly, probably, or definitely related to dolutegravir, and no events that led to permanent discontinuation. Overall, thirty-eight (52·1%) participants experienced an adverse event of grade 3 or higher; 12 (16·4%) experienced a clinical adverse event of grade 3 or higher and 29 (39·7%) experienced a laboratory adverse event of grade 3 or higher (Table 3). The most frequently reported events involved infections that commonly occur in these age groups and study settings (e.g., pneumonia); one participant experienced grade 4 clinical adverse event and one participant experienced grade 5 clinical adverse event or death (Table S8, appendix page 7). Nineteen participants experienced grade 3 laboratory adverse events and ten participants experienced grade 4 laboratory adverse events, with the most frequent adverse events being neutrophil count decreased. There were no grade 5 laboratory adverse events (Table S9, appendix page 8).

Dolutegravir dispersible tablet formulation palatability was rated “average” (45·8%), “good” (41·7%), or “very good” (12·5%) for 72 of 73 (98·7%) caregiver respondents; no participants rated palatability as “very bad” (Table S10, Appendix page 8); impressions were stable over time (Figure S1, Appendix page 9).

Virologic responses were assessed based on the available HIV-1 RNA data at week 24 and 48, respectively. By week 24, HIV-1 RNA data were available for 70 participants, of which 60 (85·7%) participants with 95% CI (75·3%–92·9%) achieved virologic success based on the plasma HIV-1 RNA of <400 copies per mL target and 36 (51·4%); 95%CI: 39·2%–63·6%) achieved an HIV-1 RNA level <50 copies per mL (Table S11, Appendix page 9), respectively. At week 48, the HIV-1 RNA data were available for 68 participants, of which 62 (91·2%) participants with 95% CI (81·8%–96·7%) achieved virologic success based on plasma HIV-1 RNA <400 copies per mL target and 46 (67·6%) participants with 95% CI (55·2%–78·5%) achieved plasma HIV-1 RNA <50 copies per mL (Table S12, Appendix page 10). The estimates of the virologic success rates at different time points are also shown in Figure 3. Through 48 weeks, CD4 counts (%) recovered a median of 243 cells/$mm^3$ (8·9 % points).

## Discussion

We describe the results of a multicentre, non-comparative, phase I/II clinical research trial of the pharmacokinetics, safety, tolerability, and efficacy of a dispersible tablet formulation of dolutegravir among children living with HIV-1, ages 4 weeks to 6 years. Whether analysed by the pre-specified age-cohorts (Table S6, Appendix page 5), or by the age-independent weight-band dosing utilized by the WHO (Table S7, Appendix page 5), the selected doses

of dolutegravir dispersible tablets provided drug exposures that have been shown efficacious in adults. Across participants of all ages and weights, the dispersible tablet formulation was found to be safe and well-tolerated, and resulted in high rates of plasma HIV-1 RNA suppression over 48 weeks of treatment. These data formed the basis of regulatory approvals by the U.S. Food and Drug Administration (FDA) in June of 2020[13] and the European Medicines Agency (EMA) in January of 2021,[14] representing the first approvals for dolutegravir dosing in this age range and for the dispersible tablet formulation in any population.

The IMPAACT P1093 study first generated data about the film-coated tablet formulation of dolutegravir for the treatment of adolescents and children older than 6 years of age, leading to regulatory approval.[4,3] For the evaluation of this novel dispersible tablet formulation among children younger than 6 years, we made several changes to the protocol. First, $C_{24h}$ was elevated to be a primary parameter and the target concentration was increased to 995 ng/mL from 750 ng/mL. Both concentrations are well above the minimum concentration to achieve 90% of maximal virologic response ($EC_{90}$) of 300 ng/mL, which is estimated from the Phase II-derived $EC_{50}$ of 36 ng/mL, in adults.[15] However, the study team and regulatory bodies felt a higher target for the geometric mean of the study cohorts would more accurately reflect adult exposure and, importantly, would be more forgiving and result in reliable drug concentrations in real world populations of children across ages when medication adherence can be challenging and metabolic clearance of dolutegravir can vary dramatically.[16] The upper limit of the target range for $AUC_{24}$ (hr*mg/L) was also widened from 37–86 to 37–134, to accommodate the variability and the potential increase from higher drug doses aiming to meet the target $C_{24h}$. The dispersible tablet is approximately 60% more bioavailable than the film coated tablet, suggesting equivalence of 30 mg dispersible tablet to the 50 mg film coated tablet, which is the recommended dose for adults.[17] As such, a child weighing 20 kg or more would receive 30 mg dispersible tablet dose which is the equivalent of the recommended adult daily dose.

It is also important to note that while the intensive pharmacokinetic studies in this study were performed under fasted conditions, infants and children in real life situations are likely to take dolutegravir with food. Ingestion with food would be anticipated to increase the absorption of dolutegravir.[18] Thus while the geometric mean C24 observed in children aged ≥ 2 years to < 6 years was just below the lower limit of the target range under fasted conditions, it is likely that levels will be achieved in clinical practice. Higher concentrations would be anticipated to increase virologic control, but raise concern for potential toxicity. However, despite the high drug levels observed (under fasted conditions) and anticipated higher exposures (during the study course, when there were no food restrictions), the safety profile of the dolutegravir dispersible tablet formulation in children was similar to adults, with no new laboratory or clinical safety signals or intolerance observed.

When the IMPAACT P1093 study began in 2011, the protocol had been designed to determine dosing separately for each age cohort, with an aim to accurately accommodate age-based changes in metabolism. This resulted in the proposed dosing shown in Table 2, in which a lower dose was determined for infants < 6 months of age. However, dosing based on weight-bands alone, independent of age, is simpler for providers and families; this

weight-band approach has been adapted by the WHO[19] and was officially recommended by the FDA in 2019[5] for children with HIV-1. We therefore modified the most recent version of the protocol to include additional secondary analyses for dosing by weight-band independent of age, and expanded enrolment to ensure those analyses were adequately powered. Table S6 (Appendix, page 5) summarizes the results of these additional analyses that supported the FDA and WHO-approved weight-band dosing of dolutegravir dispersible tablets independent of age. The EMA approved the dosing of the protocol, which differs from the WHO and FDA dosing by inclusion of a lower dose of 10 mg for infants aged ≥ 4 weeks to < 6 months weighing 6 to < 10 kg; the pharmacokinetic results of this population are shown in Table S15 (Appendix page 11).[14]

Dolutegravir dosing and formulations are now available for children, starting from the age of 4 weeks and weight of 3 kg and extending seamlessly into adulthood. The data presented here suggest that a dolutegravir dispersible tablet dose of 30 mg (6 tablets) is appropriate for children once they weigh at least 20 kg. Comparative pharmacokinetic studies suggest that the dispersible tablets are 60–80% more bioavailable than the film-coated tablets.[20] The ODYSSEY trial (NCT02259127) demonstrated that the 50 mg dolutegravir film-coated tablet taken once daily among children weighing 20 to < 40kg resulted in good drug concentrations and was safe and well tolerated.[21] Taken together, these data suggest that when children grow to reach 20 kg they can transition from 25 mg (5 dispersible tablets) to 30 mg (6 dispersible tablets) or directly to the standard adult dose of one 50 mg film-coated tablet daily, if able to swallow a tablet.

Our results also underscore the clinical efficacy of dolutegravir-based regimens in children. Overall, 85% and 63% of participants achieved virologic suppression with a plasma HIV-1 RNA less than 400 and 50 copies per mL, respectively, at week 48. The proportion of participants achieving a plasma HIV-1 RNA of < 50 increased from week 24 to 48, possibly reflecting the slower declines of HIV-1 RNA that can be seen among infants who start with very high viral burdens.[22] The overall virologic suppression rates in this study were also likely lowered due to adherence challenges among participants who had prior treatment experience (87.7% of the study population). Enrolment criteria required viremia of at least 1,000 copies/mL; this led to enrolment of many children who had failed multiple prior regimens, and selected for children with adherence challenges. In support of this interpretation, there was a trend towards lower virologic suppression rates at 24 and 48 weeks among ARV-experienced participants, compared to ARV-naïve participants (Tables S13 an S14, Appendix pages 10–11). Participants experienced a CD4% increase of 8·9 points at week 48 suggesting impressive immunologic reconstitution.

Interpretation of the safety and clinical efficacy findings in this study is limited by the small number of participants enrolled, who were also spread across several age and weight-band groupings, and without a formal comparator group. Our study design and sample size were consistent with FDA and EMA guidance; to accelerate approval of HIV therapies for HIV infected paediatric populations, they suggests that if paediatric trials can demonstrate drug concentrations similar to those in adults that are safe, efficacy can be extrapolated from larger adult trials.[5–7] The high frequency of Grade 3 neutropenia (36%, Table S7, appendix page 8) we found in the youngest cohort is likely to reflect, as least in part, differences

in haematologic normal values for infants in sub-Saharan Africa;[23] all cases resolved spontaneously and with opportunistic infection complications. No unusual toxicities were noted, but post approval surveillance for rare events will be important. Questions about integrase inhibitor related excessive weight gain, as seen in adults,[24] could not be rigorously evaluated given the size and small single arm design of our trial; however, data from P1093 will be combined with data from other IMPAACT trials to facilitate robust comparison weight changes by antiretroviral regiments.

Dolutegravir is now recommended for the first line treatment of infants and children with HIV-1 in the USA[25] and Europe[26], and by the WHO,[19] in harmony with recommendations for adults. Ongoing research will likely further facilitate the roll out of dolutegravir to children globally. We believe this positive outcome underscores the importance of close collaboration among clinical researchers, regulators and stakeholders and of adapting protocols to address changes that occur in the clinical landscape over time. The ODYSSEY trial recently demonstrated that dolutegravir resulted in superior virologic suppression compared to standard-care with protease inhibitors or efavirenz among children with HIV-1,[27] and will generate data about dosing in the context of treatment for tuberculosis.[28] Studies are underway to determine dosing for neonates less than 4 weeks of age.[29] A dispersible fixed-dose combination formulation of dolutegravir, abacavir and lamivudine, suitable for infants and young children is also being studied.[30] To better meet the needs of children globally, dolutegravir has been licensed to generic manufacturers who are developing a 10 mg scored dispersible tablet formulation.[31]

The proposed, once-daily dosing of dolutegravir dispersible tablets provided drug exposures comparable to adults and was safe, well-tolerated and virologically efficacious and supports the use of dolutegravir dispersible tablets as first- or second-line treatment for infants and children < 6 years old with HIV-1. Greater worldwide dolutegravir availability and inclusion in national treatment programs, including research limited settings, of this therapy will be a major treatment advance leading to a future of healthy infants, children and adolescents living into adulthood with HIV.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments.

We thank the entire IMPAACT P1093 protocol team, site investigators, participants and their families for their contribution to this study. Individual contributors are listed in the appendix, page 11.

### Declaration of Interests

TDR, AW, SP, PA, MB, DD, KG, KPG, JL, RH, NM, LK, TV, EA, BM, JP, ED, MA, KC, PO, JD, and ET reported no conflicts of interest. MO and JP have served on the advisory board for ViiV Healthcare. JP has received research funding from GlaxoSmithKline (through his institution). RS held stock and was an employee of GlaxoSmithKline. CV, CB, AB hold stock and are employees of ViiV Healthcare, the manufacturer of dolutegravir.

## Data sharing statement

The data cannot be made publicly available due to the ethical restrictions in the study's informed consent documents and in the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network's approved human subjects protection plan; public availability may 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 (email address: sdac.data@fstrf.org) with the agreement of the IMPAACT Network.

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## Putting research into context

### Evidence before this study

Potent and well-tolerated antiretroviral medications are needed for infants and young children living with HIV-1. These populations have few treatment options, inadequate virologic responses, poor clinical outcomes, and unique challenges with adherence. Dolutegravir has been shown to be potent with an acceptable safety profile in adults, and has been recommended as first and second line treatment for adults by the World Health Organization since 2018. A granule formulation of dolutegravir was first developed for the treatment of young children. However, in response to feedback from the World Health Organization and other stakeholders, ViiV Healthcare/ GlaxoSmithKline shifted drug development to a 5 mg dispersible tablet formulation of dolutegravir. The IMPAACT P1093 protocol was then amended to determine dosing of this formulation for children ages 4 weeks to < 6 years living with HIV-1. We searched PubMed for publications on September 13, 2021 using the search terms “dolutegravir,” “S/GSK1349572,” and “children” and identified no studies prior reporting the pharmacokinetics of this formulation.

### Added value of this study:

IMPAACT P1093 evaluated the pharmacokinetics, safety, tolerability, and antiviral activity of a dispersible tablet dolutegravir formulation (S/GSK1349572) to treat infants and young children with HIV-1, aged 4 weeks to 6 years of age and weighing at least 3 kg. The proposed weight-band based dosing with a 5mg dispersible tablet of dolutegravir resulted in pharmacokinetic exposures comparable to adults receiving the 50mg film-coated tablet, and was safe, well-tolerated, and efficacious among participants. Supplemented by data from the ODYSSEY trial, the data presented here formed the basis for regulatory approvals by the US Food and Drug Administration and the European Medicines Authority, and for current World Health Organization recommendations for this formulation of dolutegravir to be used as first- and second-line treatment for children living with HIV-1.

### Implications of all the available evidence:

The combined data about the dispersible and film-coated tablet formulations of dolutegravir, make dosing now possible for people living with HIV-1 from infancy through adulthood, facilitating the harmonization of country guidelines and supply chains. Through unprecedented partnership among ViiV/GlaxoSmithKline, the World Health Organization, the IMPAACT Treatment Network (P1093 Trial), the Penta ID Network (ODYSSEY Trial) and the Clinton Health Access Initiative (CHAI) and with technology transfer to generic manufacturers, many children living with HIV-1 globally will now gain access to dolutegravir.

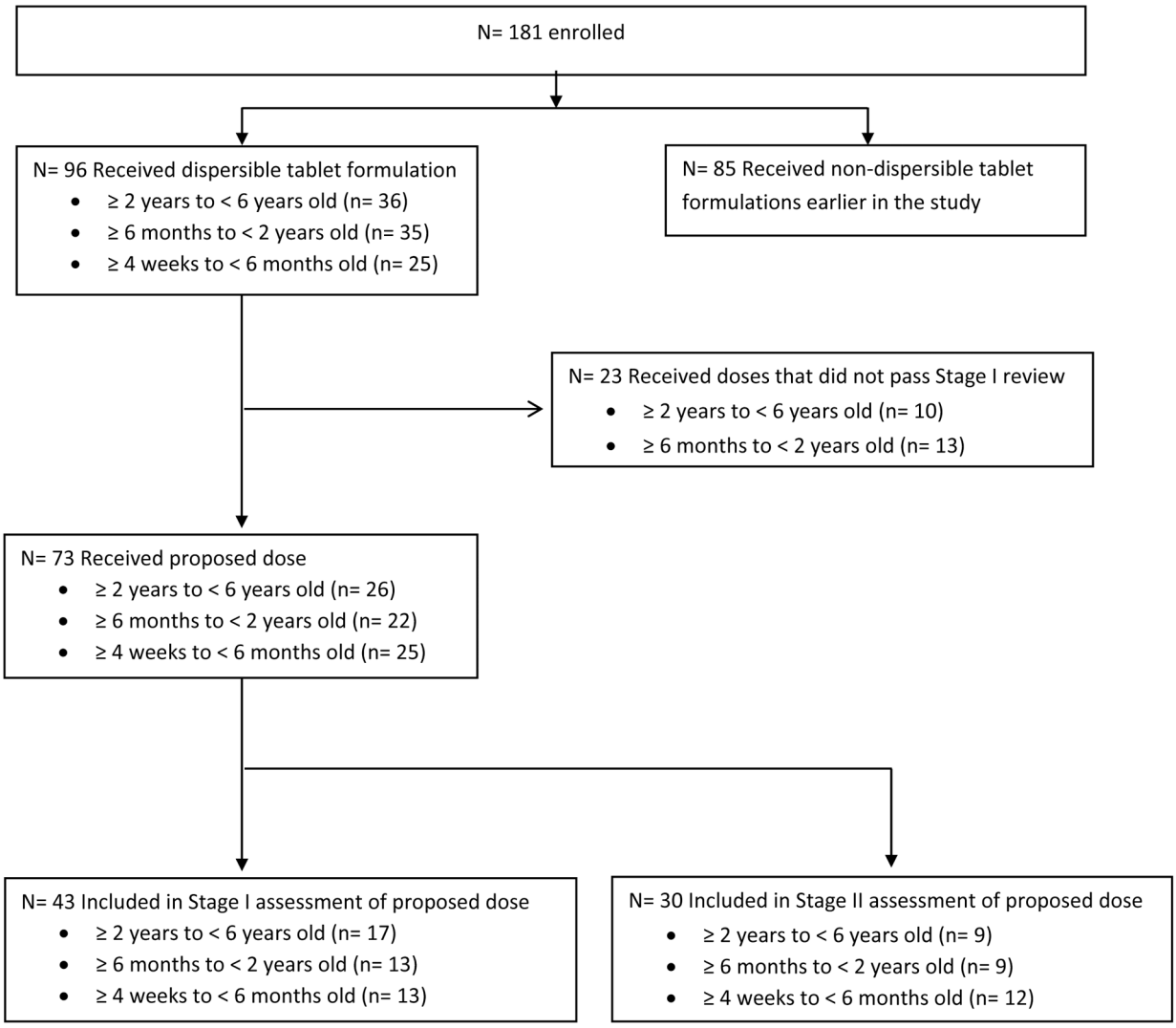


**Figure 1.**

Participant flow chart

Doses were evaluated in Stage I by examining intensive pharmacokinetic and safety results through one month; in Stage II, additional participants were enrolled to assess safety through 48 weeks. This analysis included only participants who received the dispersible tablet formulation.

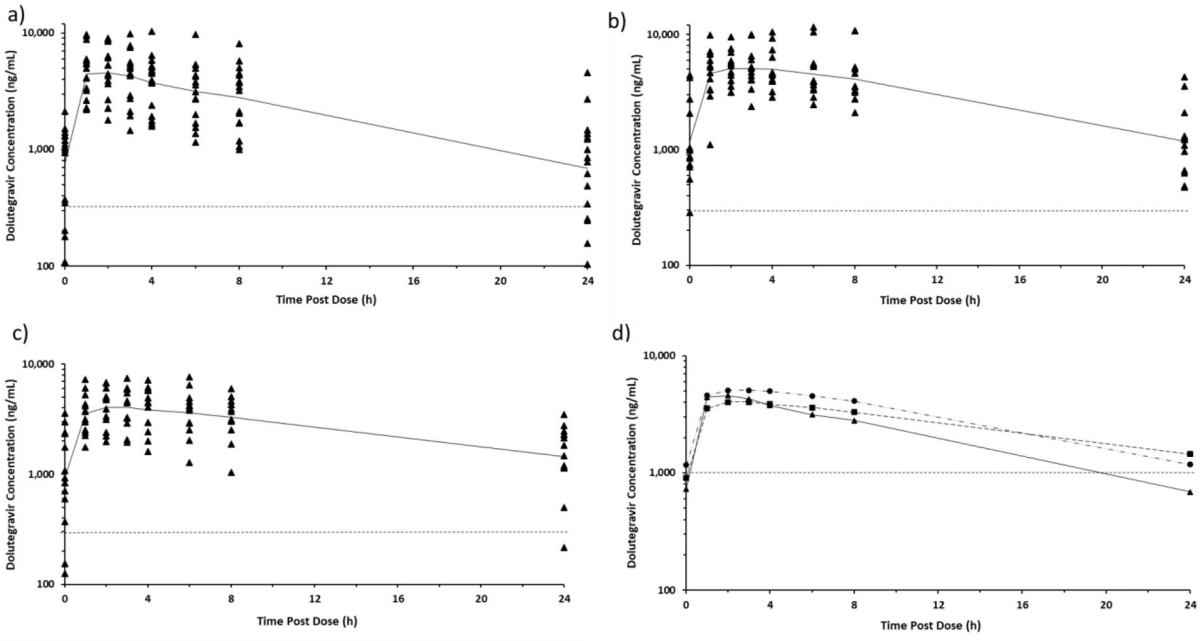


**Figure 2.**

Dolutegravir steady state concentrations

a) cohort ≥ 2 years to < 6 years; b) ≥ 6 months to < 2 years, c) ≥ 4 weeks to < 6 months; d) composite of all three cohorts with triangles for ≥ 2 years to < 6 years, circles for ≥ 6 months to < 2 years, and square for ≥ 4 weeks to < 6 months. The solid line connects geometric mean values at each time point and the dashed line represents the EC90 of 300 ng/mL. For d) the solid line connects the geometric means for each cohort, and the dashed line represents the target of 995 ng/mL.

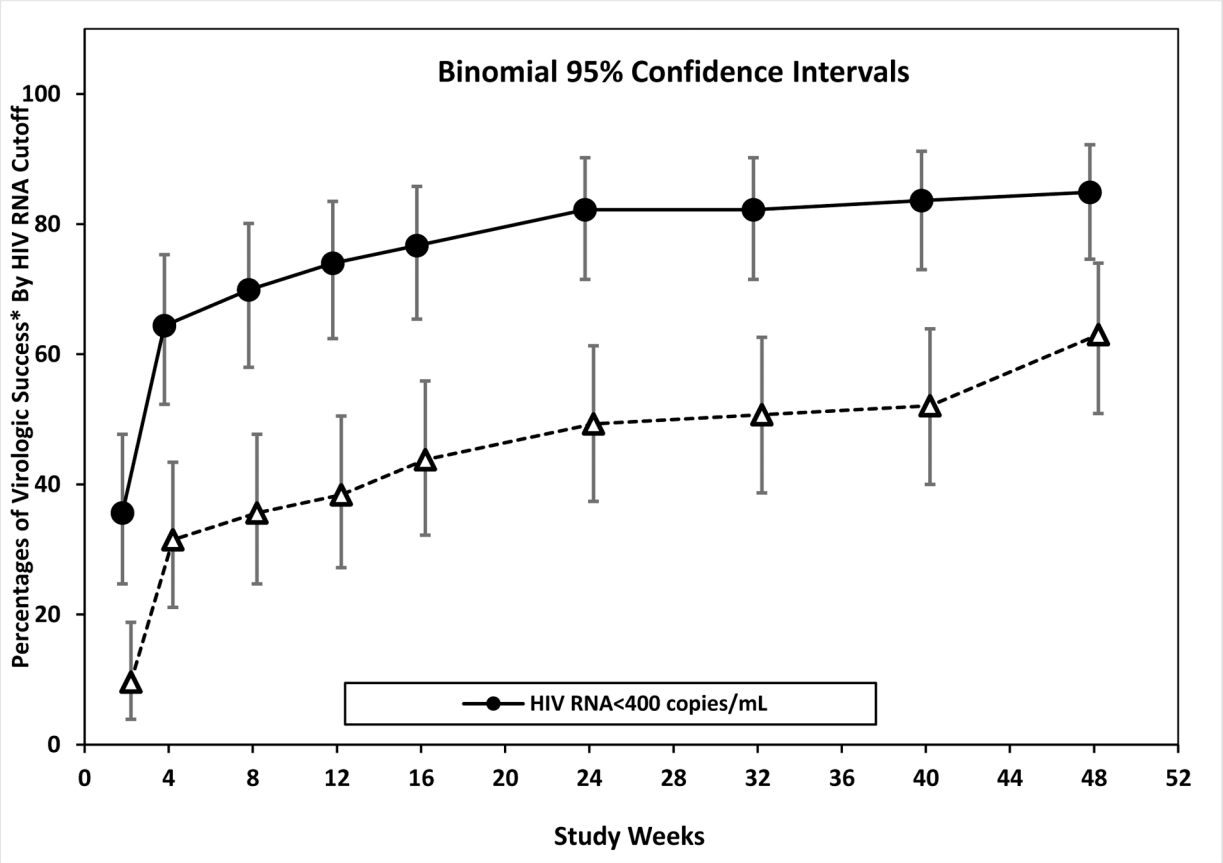


**Figure 3.**
Proportion of participants with HIV RNA<400 copies/mL and <50 copies/mL

**Table 1:**

Participant demographic and baseline characteristics, by age cohort

| | ≥ 2 years to < 6 years (N=26) | ≥ 6 months to < 2 years (N=22) | ≥ 4 weeks to < 6 months (N=25) | Total (N=73) |
|---|---|---|---|---|
| Age (year) | | | | |
| Median (Min, Max) | 3·2 (2·2, 6·0) | 1·0 (0·5, 2·0) | 0·3 (0·1, 0·5) | 1·0 (0·1, 6·0) |
| Q1, Q3 | 2·5, 4·3 | 0·8, 1·4 | 0·3, 0·4 | 0·4, 2·6 |
| Sex (n (%)) | | | | |
| Male | 16 (62%) | 9 (41%) | 13 (52%) | 38 (52%) |
| Geography (n (%)) | | | | |
| Asia (Thailand) | 6 (23%) | 0 (0%) | 3 (12%) | 9 (12%) |
| Africa (Botswana, Kenya, South Africa, Tanzania, Uganda, Zimbabwe) | 13 (50%) | 19 (86%) | 19 (76%) | 51 (70%) |
| North America (USA) | 2 (8%) | 1 (5%) | 0 (0%) | 3 (4%) |
| South America (Brazil) | 5 (19%) | 2 (9%) | 3 (12%) | 10 (14%) |
| Enrollment Weight (kg) | | | | |
| Median (Min, Max) | 14·3 (9·3, 18·5) | 8·4 (5·6, 14·5) | 5·6 (3·7, 7·7) | 8·5 (3·7, 18·5) |
| Median (Q1, Q3) | 14·3 (11·7, 15·2) | 8·4 (7·3, 9·1) | 5·6 (5·0, 6·4) | 8·5 (6·3, 12·2) |
| Weight Band (%)) | | | | |
| 3 to <6 kgs | 0 (0%) | 1 (5%) | 15 (60%) | 16 (22%) |
| 6 to <10 kgs | 2 (8%) | 18 (82%) | 10 (40%) | 30 (41%) |
| 10 to <14 kgs | 10 (38%) | 2 (9%) | 0 (0%) | 12 (16%) |
| 14 to <20 kgs | 14 (54%) | 1 (5%) | 0 (0%) | 15 (21%) |
| Plasma HIV RNA (log10 copies/mL) | | | | |
| Median (Min, Max) | 4·5 (2·1, 6·5) | 4·0 (2·5, 6·1) | 4·1 (2·3, 7·0) | 4·2 (2·1, 7·0) |
| Q1, Q3 | 3·6, 5·3 | 3·3, 5·4 | 3·5, 5·8 | 3·4, 5·7 |
| Plasma HIV RNA Categories (copies/mL) (n (%)) | | | | |
| <400 | 2 (8%) | 1 (5%) | 1 (4%) | 4 (5%) |
| 400 – <1,000 | 2 (8%) | 1 (5%) | 0 (0%) | 3 (4%) |
| 1,000 – <10,000 | 4 (15%) | 9 (41%) | 10 (40%) | 23 (32%) |
| 10,000 – <100,000 | 9 (35%) | 5 (23%) | 3 (12%) | 17 (23%) |
| >=100,000 | 9 (35%) | 6 (27%) | 11 (44%) | 26 (36%) |
| CD4 Cell Count (cells/mm^^3) | | | | |
| Median (Min, Max) | 999·5 (1, 2,489) | 2,101·5 (429, 8,255) | 1,916 (909, 4,174) | 1,691 (1, 8,255) |
| Q1, Q3 | 474·0, 1,711·0 | 1,373·0, 2,384·0 | 1,357, 2,680 | 1,001, 2,281 |
| CD4 Cell Count Categories (cells/mm^3) (n (%)) | | | | |
| <50 | 1 (4%) | 0 (0%) | 0 (0%) | 1 (1%) |
| 50 – <200 | 2 (8%) | 0 (0%) | 0 (0%) | 2 (3%) |
| 350 – <500 | 4 (15%) | 1 (5%) | 0 (0%) | 5 (7%) |
| >=500 | 19 (73%) | 21 (95%) | 25 (100%) | 65 (89%) |
| CD4 Percent | | | | |

| | ≥ 2 years to < 6 years (N=26) | ≥ 6 months to < 2 years (N=22) | ≥ 4 weeks to < 6 months (N=25) | Total (N=73) |
|---|---|---|---|---|
| Median (Min, Max) | 22·5 (0·3, 42·0) | 24·6 (15, 49) | 22·7 (11·0, 37·7) | 24·0 (0·3, 49·0) |
| Q1, Q3 | 16·4, 31·0 | 21·0, 36·0 | 20·6, 30·4 | 19·8, 31·0 |
| CD4 Percent Categories (n (%)) | | | | |
| <=14 | 5 (19%) | 0 (0%) | 1 (4%) | 6 (8%) |
| >14 – <25 | 11 (42%) | 11 (50%) | 13 (52%) | 35 (48%) |
| >=25 | 10 (38%) | 11 (50%) | 11 (44%) | 32 (44%) |

Q1, Q3: first quartile (Q1) and third quartile (Q3) respectively

**Table 2.**

Final proposed dolutegravir dispersible tablet dosing, once daily

| Age | Weight Band (kg) | Dose (mg) |
|---|---|---|
| ≥ 4 weeks to < 6 months | 3 to < 6 | 5 |
| | 6 to < 10 | 10 |
| ≥ 6 months to < 6 years | 3 to < 6 | 10 |
| | 6 to < 10 | 15 |
| | 10 to < 14 | 20 |
| | 14 to < 20 | 25 |

**Table 3.**

Summary of grade 3 or greater adverse events through week 48

| | ≥ 2 years to < 6 years (N=26) | | ≥ 6 months to < 2 years (N=22) | | ≥ 4 weeks to < 6 months (N=25) | | Total (N=73) | |
|---|---|---|---|---|---|---|---|---|
| | n (%) | (95% CI) | n (%) | (95% CI) | n (%) | (95% CI) | n (%) | (95% CI) |
| With Grade 3 or greater events | 10 (38·5) | (20·2, 59·4) | 12 (54·5) | (32·2, 75·6) | 16 (64) | (42·5, 82·0) | 38 (52·1) | (40·0, 63·9) |
| With Grade 3 or greater clinical events | 5 (19·2) | (6·6, 39·4) | 4 (18·2) | (5·2, 40·3) | 3 (12) | (2·6, 31·2) | 12 (16·4) | (8·8, 27·0) |
| With Grade 3 or greater laboratory events | 6 (23·1) | (9·0, 43·7) | 9 (40·9) | (20·7, 63·7) | 14 (56) | (34·9, 75·6) | 29 (39·7) | (28·5, 51·9) |
| With Grade 3 or greater drug related * events | 0 (0) | (0·0, 13·2) | 0 (0) | (0·0, 15·4) | 0 (0) | (0·0, 13·7) | 0 (0) | (0·0, 4·9) |
| With Grade 3 or greater drug related * clinical events | 0 (0) | (0·0, 13·2) | 0 (0) | (0·0, 15·4) | 0 (0) | (0·0, 13·7) | 0 (0) | (0·0, 4·9) |
| With Grade 3 or greater drug related * laboratory events | *0 (0)* | (0·0, 13·2) | 0 (0) | (0·0, 15·4) | 0 (0) | (0·0, 13·7) | 0 (0) | (0·0, 4·9) |

N = Number of participants in each cohort.

n (%) = Number (percent) of participants in each subcategory.

* Drug related adverse events were determined by site investigators to be possibly, probably or definitely related to study drug.

95% CI = Exact 95% Confidence Interval.