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Safety and efficacy at 240 weeks of different raltegravir formulations in children with HIV-1: a phase 1/2 open label, non-randomised, multicentre trial

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Contributors

SN, CA, HT, BH, BLG, TF, LMF, and AAW developed the initial study design. CA, TF, AJR, and BLG extracted data. SN, CA, and TF analysed the findings. SN wrote the first draft of the manuscript. All authors collaboratively discussed key decisions throughout the course of the review, provided critical feedback on preliminary drafts and interpretation of results, and approved the final manuscript.

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Declaration of interests

HT, BH, and AJR are employees of Merck & Co, Kenilworth, NJ, USA, and might own stock or stock options, or both, in the company. CA, TF, and BLG report grants from the National Institutes of Health and from Merck Pharmaceuticals during the conduct of the study. All other authors declare no competing interests.

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Summary

Background—Raltegravir is an integrase inhibitor approved for use in adults and children with HIV-1 infection, but there are no data on the long-term use of this medication in children. We aimed to assess the long-term safety, tolerability, pharmacokinetics, and efficacy of multiple raltegravir formulations in children aged 4 weeks to 18 years with HIV-1 infection.

Methods—In this phase 1/2 open-label multicentre trial (IMPAACT P1066), done in 43 IMPAACT network sites in the USA, South Africa, Brazil, Botswana, and Argentina, eligible participants were children aged 4 weeks to 18 years with HIV-1 infection who had previously received antiretroviral therapy (ART), had HIV-1 RNA higher than 1000 copies per mL, and no exposure to integrase inhibitors. Participants were separated into five age groups and enrolled in six cohorts. Three formulations of open-label raltegravir—adult tablets, chewable tablets, and granules for oral suspension—were added to individualised optimised background therapy, according to the age and weight of participants. The primary outcome at 48 weeks has been previously reported. In the 240-week follow-up, outcomes of interest included graded clinical and laboratory safety of raltegravir formulations during the study and virological efficacy (with virological success defined as HIV-1 RNA reduction of $>1 \log_{10}$ from baseline or HIV-1 RNA <400 copies per mL) at week 240. The primary analysis group for safety and efficacy comprised patients treated only with the final selected dose of raltegravir. This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT00485264.

Findings—Between August, 2007, and December, 2012, 220 patients were assessed for eligibility, and 153 were enrolled and treated. Of these patients, 122 received only the final selected dose of raltegravir (63 received adult tablets, 33 chewable tablets, and 26 oral granules), and one was not treated. There were few serious clinical or laboratory safety events noted, with two patients having a drug-related adverse event (skin rash), which led one patient to discontinue the study treatment. The addition of raltegravir to an individually optimised ART regimen resulted in virological success at week 240 in 19 (44.2%, 95% CI 29.1–60.1) of 43 patients receiving 400 mg tablets, 24 (77.4%, 58.9–90.4) of 31 patients receiving the chewable tablets, and 13 (86.7%, 59.5–98.3) of 15 patients receiving oral granules. Among patients with virological failure, raltegravir resistance was noted in 19 (38%) of 50 patients who had virological rebound after initial suppression and had samples at virological failure available for testing.

Interpretation—Our study suggests that raltegravir can be used for the treatment of HIV-1 infection in children as young as 4 weeks, with the expectation of long-term safety and efficacy, but should be used with caution among older children who had previous extensive antiretroviral therapy.

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Introduction

Raltegravir was the first integrase inhibitor approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in adults with HIV-1 infection. The addition of raltegravir to optimised antiretroviral therapy (ART) has shown high virological success rates, with 72.3% (332 of 459 participants) success at 48 weeks among highly treatment-experienced adults¹ and 86.1% (241 of 280) success at 48 weeks among treatment-naïve adults.² Raltegravir, as part of an optimised background therapy, had a 42% (193 of 462) success rate at 240 weeks in treatment-experienced adults³ and 71% (198 of 279) success among treatment-naïve adults.⁴

On the basis of 24-week and 48-week pharmacokinetic, safety, and efficacy data, three formulations of raltegravir have now been licensed and approved for use in children younger than 18 years: a 400 mg tablet, for twice-daily use in children who weigh 25 kg or more; and chewable tablets (100 mg and 25 mg) and granules for suspension (100 mg sachet), for twice-daily weight-based dosing in children older than 4 weeks. In 2017, raltegravir in granules for suspension was approved for use in neonates. This IMPAACT P1066 trial was designed to assess the pharmacokinetics and both short-term (24 weeks and 48 weeks) and long-term (240 weeks) safety and efficacy of these different formulations. Data on intensive pharmacokinetics and 48-week safety and efficacy have been previously published.^{5–7} This report focuses on the long-term safety and efficacy of three formulations of raltegravir added to an optimised ART in patients after 240 weeks of follow-up.

Methods

Study design and participants

The IMPAACT P1066 trial was a phase 1/2 open-label, non-randomised, multicentre study done at 43 IMPAACT network sites in the USA, South Africa, Brazil, Botswana, and Argentina. Local institutional review boards or in country ethics committees responsible for oversight of the study granted ethics and regulatory approvals (including for all versions and amendments of the protocol). The full IMPAACT 1066 study protocol is available online.

Participants were separated into five age groups and enrolled in six cohorts (1, 2A, 2B, 3, 4, and 5) with three different raltegravir formulations. Participants in cohort 1 (age 12 to 18 years) and cohort 2A (6 to <12 years) received the 400 mg adult tablet formulation twice per day, whereas cohort 2B (6–12 years) and cohort 3 (2 to <6 years) received a dose of approximately 6 mg/kg with the chewable tablet formulation twice per day. Cohort 4 (6 months to <2 years) and cohort 5 (4 weeks to <6 months) received the granules for suspension formulation, at approximately 6 mg/kg per dose. Participants who were eligible for this study were 18 years or younger, had plasma HIV-1 RNA higher than 1000 copies per mL, and had received ART but were naïve to raltegravir and other integrase inhibitors. Patients were required to have entry laboratory values lower than the Division of AIDS table for grading the severity of paediatric grade 3 toxicity criteria,⁸ and absence of active opportunistic infection or concurrent cancer. For cohort 5, unsuccessful prophylaxis to prevent mother-to-child transmission (MTCT) was required, but no direct ART was allowed. Exclusion criteria included previous exposure to raltegravir, ongoing treatment for active

tuberculosis, pregnancy or lactation, or an inability to access clean water, as defined by local standards. Both written and oral informed consent by parent or guardian was obtained as per standard of each country and documented as accepted in the participant's file.

Procedures

We did a clinical examination, safety laboratory assessment, HIV RNA viral load and CD4 testing, and collected data on safety events (graded according to the Division of AIDS table for severity grading) at each study visit. Safety parameters included haematology, liver and renal function testing, and lipid panels. Fasting lipid panels were done only when non-fasting lipid panels were abnormal. Virological parameters included HIV-1 viral load testing (Roche 1.5 Quantitative HIV-1 RNA PCR [Indianapolis, IN, USA] for cohorts 1, 2A, 2B, and 3; and Abbott Real Time HIV-1 assay [Chicago, IL, USA] for cohorts 4 and 5) and CD4 testing with Division of AIDS-certified flow cytometry. We assessed integrase inhibitor resistance at study entry and at any timepoint associated with virological rebound after having achieved virological success (defined as HIV-1 RNA <400 copies per mL or >1 log₁₀ reduction from baseline).

Caregivers were taught how to suspend the oral granules and administer the chewable tablets. We monitored adherence with self-reported surveys completed at each study visit (at 4, 8, 12, 24, 36, and 48 weeks, and every 4 months afterwards); pill bottles were collected, but unused pills were not counted. Directly observed therapy and therapeutic drug monitoring were not a part of this study. After 48 weeks of therapy, patients were allowed to transition from oral granules for suspension to chewable tablets and from chewable tablets to 400 mg adult tablets, if they met the respective weight and age requirements. By the data cutoff date (July 24, 2017), all patients enrolled had either completed 240 weeks of study or prematurely discontinued the study and were no longer in follow-up. Therefore, this report presents the safety and efficacy results of the complete 240 weeks of follow-up.

We monitored the emergence of resistance mutations by extracting plasma RNA from all patients with virological failure, by Sanger sequencing of HIV-1 *pol* gene, which encodes integrase, reverse transcriptase, and protease,⁹ on available samples that were adequate for testing. All patients had reverse transcriptase and protease sequencing done at baseline. Additionally, for patients identified with virological failure, we assessed resistance (for integrase, reverse transcriptase, and protease) on samples taken at or near the time of virological failure, and integrase resistance on a stored baseline sample.

Outcomes

Initial patients were enrolled in a previous pharmacokinetics (dose selection) and safety phase of the study, but this report only includes patients who received what would become the final selected dose. The primary analysis group for safety and efficacy comprised patients treated only with the final selected dose of raltegravir, referred to as the final dose population, in a pre-planned long-term follow-up of 240 weeks after enrolment.

Efficacy responses were secondary objectives. The virological secondary outcome was virological success, defined as achieving either an HIV-1 RNA lower than 400 copies per mL or a reduction in concentration higher than 1 log₁₀ from baseline at 24 weeks. This

definition was also used for timepoints at 48, 96, 144, 192, and 240 weeks. Other secondary efficacy endpoints included the proportion of patients achieving HIV-1 RNA concentrations lower than 50 copies per mL and lower than 400 copies per mL and change from baseline in CD4 percentage at 48, 96, 144, 192, and 240 weeks.

Statistical analysis

The minimum sample size per age group was determined on the basis of requirements outlined by the FDA and EMA. Additionally, we targeted a minimum of 100 patients with exposure to raltegravir for assessment of safety, across the entire paediatric age range (4 weeks to 18 years). We did descriptive analyses for each formulation; there were no comparisons between groups. Although our protocol prespecified that patients were followed up after premature discontinuation of therapy, these data are not included in this report because the patients switched to regimens that did not contain raltegravir.

We used an observed failure approach for handling missing data. For virological endpoints, missing values were considered to be virological failures if they were due to discontinuation of study treatment for lack of efficacy or non-treatment-related reasons, with virological success not achieved at the last available HIV-1 RNA value; otherwise, missing data were excluded. For change from baseline in CD4 percentage, baseline values were carried forward for missing data, as described above. Other missing values were excluded.

Virological failure was defined as non-response (not achieving either HIV-1 RNA reduction of $>1 \log_{10}$ from baseline or HIV-1 RNA <400 copies per mL at each prespecified timepoint after 48 weeks) or virological rebound (confirmed HIV-1 RNA of >400 copies per mL after initial response [ie, HIV-1 RNA of <400 copies per mL] or confirmed HIV-1 RNA increase of $>1.0 \log_{10}$ above nadir; confirmation required two consecutive measurements at least 1 week apart).

All analyses were done with SAS software, version 9.4. A data safety monitoring committee oversaw the conduct of this study.

This trial is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00485264), number [NCT00485264](https://clinicaltrials.gov/ct2/show/study/NCT00485264).

Role of the funding source

Merck supplied funding, the study drug, and scientific input via participation in the study team, and NIH supplied funding, had overall scientific decision making, and was the investigational new drug sponsor for the study. The corresponding author had access to all study data and final responsibility for the decision to submit for publication.

Results

Between August 2007, and December, 2012, 220 patients were assessed for eligibility, and 153 were enrolled, including 110 from the USA, 27 from South Africa, 12 from Brazil, three from Botswana, and one from Argentina. The first participant enrolled on Sept 14, 2007, and the last patient's follow-up was on May 18, 2017. Of the 153 enrolled patients, 122 were included in the final dose population (figure 1). One patient never received the study drug

and was excluded from all analyses. Safety and efficacy data of 30 patients who received doses other than the final selected dose were similar to data of patients in the final dose population (data not shown).

Of the 122 patients in the final dose population, 58 (48%) were girls; and 80 (66%) were black, 35 (29%) were white, and 43 (35%) were Hispanic or Latino. The age range of patients was 8–18 years (mean 14·9 years) for those receiving adult tablets, 2–11 years (mean 5·4 years) for chewable tablets, and 4 weeks to 1·9 years (mean 35·7 weeks) for oral granules. In the final dose population, 33 (52%) of 63 patients who received adult tablets, 25 (76%) of 33 who received chewable tablets, and 14 (54%) of 26 who received oral granules completed 240 weeks of study treatment. The final dose population was classified at enrolment according to US Centers for Disease Control and Prevention (CDC) HIV clinical classification criteria;¹⁰ patients in the oldest age cohorts, those receiving 400 mg tablets, were disproportionately classified as category C, severely symptomatic (table 1).

Details of previous ART exposure have been previously published,^{5,6} but are highlighted here. 121 patients in the final dose population had drug exposure before enrolling in the study, with many having extensive drug exposure (table 1). The age cohorts who received adult tablets had the most extensive ART drug exposures (of nucleoside reverse-transcriptase inhibitors [NRTIs], 57 [91%] of 63 were exposed to zidovudine, 56 [89%] to lamivudine, 57 [91%] to didanosine, and 52 [83%] to stavudine; of non-NRTIs, 33 [52%] of 63 were exposed to efavirenz and 34 [54%] to nevirapine; of protease inhibitors: 44 [70%] of 63 were exposed to ritonavir, 38 [60%] to nelfinavir, and 42 [67%] to lopinavir–ritonavir). Similar patterns were noted in patients older than 2 years; cohorts receiving oral granules had the fewest previous ART drug exposure (due to having the fewest treatment options), often limited to prevention of MTCT (zidovudine and nevirapine; data not shown).

All patients received raltegravir plus at least two other ARTs. 64 unique optimised background regimens were selected by site investigators, ranging from two NRTIs to as many as five ARTs of multiple classes added to raltegravir, with the greatest diversity of therapies among the older cohorts. Among patients in the final dose population at study entry, 61 (50%) of 122 had HIV-1 RNA between 4000 and 50 000 copies per mL, whereas 47 (39%) had HIV-1 RNA higher than 50 000 copies per mL. None of the site investigators had the study-run genotypic sensitivity scores (GSS) before initiation of optimised background therapy. The GSS were calculated during analysis of the data and, apart from raltegravir, background therapy contributed GSS 0–1 in 33 (34%) of 96 patients receiving tablet and chewable formulations and in one (4%) of 26 receiving oral granules.

The mean CD4 percentage at the start of the study was 23·0% (SD 10·1) overall, 20·0% (9·6) for patients receiving adult tablets, 28·5% (9·0) for patients receiving chewable tablets, and 20·7% (9·9) for patients receiving oral granules. At study week 240, the increase in CD4 percentage was 4·7% (95% CI 2·8–6·6) overall, 2·8% (0·4–5·2) for adult tablets, 5·2% (1·8–8·7) for chewable tablets, and 8·6% (3·2–14·0) for oral granules (figure 2).

Two patients died during the study period because of events not considered related to raltegravir by the study investigator: one patient, a 15-year-old girl who was not on the

selected final recommended dose, died from pneumonia at study week 85; another patient, a 2-year-old boy who was on the final selected recommended raltegravir dose, died from gastroenteritis at study week 59.

Four of 122 patients had serious laboratory adverse events that were not considered to be drug related. One patient had a transient liver function enzyme elevation (elevation of both alanine aminotransferase and aspartate aminotransferase) at week 20 that was possibly related to treatment; the study drug was not interrupted, and the abnormal elevation resolved within 12 days (for alanine aminotransferase) and 31 days (for aspartate aminotransferase). Overall, there were no discontinuations due to laboratory adverse events. Two participants (1%) had serious clinical adverse events possibly related to the study drug: one participant had a possibly drug-related rash on study day 17, but continued treatment with the study drug, and a second participant had a serious grade 3 drug-related allergic rash on study day 7; this participant was the only one who discontinued the study drug because of a possible drug-related adverse event. We observed no differences between age cohorts or formulations regarding reported adverse events (table 2).

118 of 122 patients had one or more clinical adverse events after 240 weeks of study (table 2). These included typical illnesses of childhood such as fever, diarrhoea, cough, rhinorrhoea, and nasal congestion. Raltegravir therapy was not stopped for any of these events. One adolescent with pre-existing psychiatric issues had one episode of psychomotor hyperactivity, abnormal behaviour, and insomnia. This episode was considered serious, but judged to not be drug related, and raltegravir therapy was not interrupted.

There were some important infections recorded, including two events of *Pneumocystis jirovecii* pneumonia; one event each of *Mycobacterium avium* complex infection, tuberculosis, sepsis or septic shock, bacterial meningitis, and pneumococcal pneumonia; and 18 pneumonia events in which the pathogen was not specified. All these events occurred in 17 patients, with some patients having more than one event. Raltegravir therapy was continued in all 17 patients. None of the serious infections coincided with meeting virological failure endpoints at the time of the infection. One patient, a 21-week-old boy receiving oral granules, had one event of immune reconstitution inflammatory syndrome occurring 29 days after initiation of therapy. He remained on raltegravir therapy throughout this event, which resolved on day 134. One patient, receiving the adult tablets, had an abnormal electrocardiogram (first-degree heart block) at week 144, which was judged not to be related and the patient continued on raltegravir through week 240. There were few lipid abnormalities noted during the study, with only two patients reported to have hyperlipidaemia, which was judged not to be related to raltegravir. Background therapy for these patients included etravirine plus ritonavir-boosted darunavir in one, and efavirenz plus ritonavir-boosted darunavir in the other.

Among the final dose recipients, seven participants transitioned from chewable tablets to adult tablets formulation of raltegravir, whereas 12 participants transitioned from oral granules to chewable tablets.

Patients receiving either the chewable tablets (ages 2–12 years) or oral granules (ages 4 weeks to 2 years) had sustained efficacy at week 240, with virological success of 77·4% (95% CI 58·9–90·4; 24 of 31) for patients receiving chewable tablets and 86·7% (59·5–98·3; 13 of 15) for patients receiving oral granules (figure 3). By contrast, patients who received adult tablets had virological success of 44·2% (29·1–60·1; 19 of 43) at week 240. Results for the proportion of patients achieving HIV-1 RNA lower than 400 copies per mL are in the appendix (p 2).

In the final dose population, 60 (49%) patients had documented virological failure (table 3): 19 (32%) of 60 participants had raltegravir-resistant virus, 31 (52%) had raltegravir-sensitive virus, and ten (17%) participants had missing specimens at the time of virological failure. Among patients with virological failure, raltegravir resistance was noted in 19 (38%) of 50 patients who had virological rebound after initial suppression and had samples at virological failure available for testing. We did not observe raltegravir resistance at study entry among any patients tested, although two patients had major accessory resistance mutations (as defined by the Stanford Drug Resistance Database),¹¹ one with Thr97Ala, the other with Val151Ile.

Among the 19 patients who developed raltegravir resistance, major primary resistance mutations (according to the Stanford Drug Resistance Database) at the time of virological failure included: 14 isolates with Asn155His, ten isolates with Gln148His, Gln148Lys, or Gln148Arg, and nine isolates with Gly140Ser, Gly140Ala, or Gly140Cys mutations. Tyr143 and Glu92Gln (major resistance mutations to integrase inhibitors) and Leu74Ile, Leu74Met, Thr97Ala, and Val151Ile (polymorphic accessory mutations) were present in less than five isolates. At the time of virological failure, three of 19 patients had only raltegravir accessory mutations that encoded potential or low-level resistance.

Case report forms of self-reported adherence were completed at each study visit. Compliance data were calculated on the basis of all available data and are not available for every participant or for every timepoint. Adherence reports were either self-reported by adolescents or reported by caregivers of patients on the study. Participants who switched raltegravir formulations were included in their originally assigned formulation. Assessing only patients receiving raltegravir in adult tablets, overall compliance data (either self-reported or caregiver report) were available for the 23 patients receiving adult tablets who had raltegravir-sensitive virus at the start of study. At virological failure, 16 (70%) of 23 reported compliance greater than 90% (considered to be excellent adherence), four (17%) reported 80–89% compliance, two (9%) reported 70–79% compliance, and one (4%) did not report any adherence data. These data suggest that reported excellent adherence is an unreliable predictor of either virological failure or development of virological resistance.

Discussion

In this population with substantial previous ART exposure, at week 240, virological success was noted in most patients who received either raltegravir chewable tablets (77%) or oral granules (87%). By contrast, in patients receiving the 400 mg adult tablets, virological success was noted in 44% of patients at week 240. This older group of patients had been

heavily pretreated with ART and—with fewer choices for optimised background therapy because of limited approved formulations for young patients—had higher rates of previous CDC C categorisation at study entry. These older patients also appeared to be less adherent to therapy, with 61% having documented raltegravir-sensitive virus at the time of virological failure. Raltegravir was well tolerated and associated with few safety events related to drug exposure, with only one patient discontinuing raltegravir because of study drug toxicity (rash). There were few grade 3 or 4 adverse events across all formulations of raltegravir and we found no differences in the frequency or severity of these events that were specific to the formulation used. These results reflect the age-based and weight-based raltegravir doses proposed and now approved for commercial use. Furthermore, since the study was designed, the accepted definitions of virological control have evolved, but had we used a more stringent cutoff of 50 copies per mL (appendix p 2), our interpretation of raltegravir efficacy in the present study would not have changed.

There are two licensed integrase inhibitors available for children, raltegravir and dolutegravir. Raltegravir has been licensed for use in children aged 2–18 years with HIV-1 infection since 2011, in children aged 4 weeks to 2 years since 2013, and, in 2017, was licensed for use in infants born at term,¹² on the basis of data from the IMPAACT 1110 and 1097 studies.^{13,14} All these studies have been done in collaboration with the IMPAACT network. To date, dolutegravir is indicated in combination with other antiretroviral medicines for the treatment of adults and adolescents with HIV infection; for children older than 6 years, dolutegravir is indicated in the USA for children weighing at least 30 kg and in the EU for children weighing at least 15 kg. As with raltegravir, dolutegravir was studied in children with HIV-1 infection with documented previous virological failure.^{15,16} Among 45 patients aged 6–18 years with HIV-1 infection followed up for 48 weeks, dolutegravir was associated with few safety events and virological success (HIV-1 RNA <400 copies per mL) was achieved by 74% of patients aged 12–18 years and 78% of those aged 6–12 years in the first 48 weeks of treatment. Raltegravir has a lower genetic barrier than that of dolutegravir, and care should be used when sequencing the use of integrase inhibitor therapy. The favourable safety profile of integrase inhibitors in children and their virological success, as shown by the data at 240 weeks of raltegravir in this study, suggests that integrase inhibitors can be successfully used to achieve long-term virological success in children with HIV-1 infection.

ART is often used in combination with other non-HIV-1 therapies in populations with HIV-1 infection and comorbid conditions, which includes the need to simultaneously treat HIV-1 and tuberculosis. Raltegravir has been studied¹⁷ in adult populations in combination with tuberculosis therapies—including rifampin, a broad and potent inducer of hepatic metabolism—and was shown to have an excellent safety profile and good virological success. On the basis of previous establishment of pharmacokinetic targets in adults and children with HIV-1 infection and data on raltegravir dosing in adults and children with tuberculosis,¹⁸ we believe that raltegravir can also be dosed correctly in children with HIV and tuberculosis co-infection. However, further pharmacokinetic and efficacy studies are needed in infants with tuberculosis.

For a therapy to be used in younger children, success is often measured by drug acceptability or palatability. We have shown in previous reports⁶ that families of children younger than 2 years who received oral granules did not report any problems with taking the granule suspension; spitting or vomiting of medication and medication refusal were also uncommon. These results are supported by data presented here on the virological success among infants taking the oral granule formulation of raltegravir. This success is in contrast with study patients receiving the 400 mg adult tablet formulation (for children weighing >25 kg) for whom, despite having adherence data available, virological failure was a sign of non-adherence and not viral resistance, with only seven (21%) of 34 having documented raltegravir resistance at the time of virological failure.

As seen in adults among whom resistance to integrase inhibitor therapy develops, typical resistance mutations were seen in the patients on this study, including mutations at Asn155His, Gln148, and Gly140 codons. The absence of resistance in more than half of participants with virological failure is typical of non-adherence to antiretrovirals, as is the transient selection of resistance followed by overgrowth by wildtype viral variants that was observed in one participant. We did not detect major resistance mutations to raltegravir among any study participants. Additionally, there was no previous raltegravir exposure among the two older study cohorts, nor among the infants who did not have prevention of MTCT, which suggests that the raltegravir resistance detected during the study was newly selected, rather than due to re-emergence of minority variants in the viral reservoirs of patients.

Because the primary objectives of this study were focused on pharmacokinetics for dose finding and safety, and did not use comparator groups, there are limitations to the interpretation of efficacy. Additionally, the absence of long-term therapeutic drug monitoring to compare reported adherence, virological success, and development of resistance, limits our ability to fully understand the development of resistance in this population.

The addition of raltegravir to optimised ART in this population aged 4 weeks to 18 years with HIV-1 infection and substantial previous ART exposure showed a favourable safety profile and long-term virological success. Non-adherence in older children and adolescents continues to be a major challenge in treatment of HIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

The treatment of people younger than 18 years with HIV-1 infection is evolving. Few data exist on the short-term use of integrase inhibitors in all children and no data exist regarding their long-term use. We searched PubMed for studies published from Jan 1, 2010, to Dec 30, 2017, with the search terms “integrase inhibitors”, “children”, “youth”, “adolescents and infants”, and “long term”, but restricted studies to those published in the English language. We found no indication that such data had been published to date.

Added value of this study

This long-term follow-up study of 122 young patients (aged 4 weeks to 18 years) with HIV-1 infection receiving three different, age-appropriate, formulations of raltegravir showed that this integrase inhibitor was well tolerated and had favourable virological outcomes. Older children, who were often highly treatment experienced, had lower proportions of virological success than did children younger than 12 years.

Implications of all the available evidence

Our study suggests that raltegravir can be used for the treatment of HIV-1 infection in children as young as 4 weeks, with the expectation of long-term safety and efficacy, but should be used with caution among older children who have had previous extensive antiretroviral therapy.

Figure 1. Trial profile and enrolment across cohorts

*Disallowed medications are phenobarbital, rifampin, rifabutin, and phenytoin.

Figure 2. Changes in CD4 percentage by raltegravir formulation
Vertical bars are 95% CI.

Figure 3. Virological success by raltegravir formulation
Vertical bars are 95% CI.

Table 1:

Baseline US Centers for Disease Control and Prevention classification and previous antiretroviral therapy exposure

	Cohorts 1 and 2A (adult tablets; n=63)	Cohorts 2B and 3 (chewable tablets; n=33)	Cohorts 4 and 5 (oral granules; n=26)	Total (n=122)
CDC classification				
Category A: mildly symptomatic HIV	16 (25%)	11 (33%)	10 (38%)	37 (30%)
Category B: moderately symptomatic HIV	24 (38%)	4 (12%)	3 (12%)	31 (25%)
Category C: severely symptomatic HIV	22 (35%)	7 (21%)	3 (12%)	32 (26%)
Category N: asymptomatic HIV	1 (2%)	11 (33%)	10 (39%)	22 (18%)
Previous antiretroviral therapy exposure				
NRTI exposure	63 (100%)	32 (97%)	12 (46%)	107 (88%)
NNRTI exposure	54 (86%)	21 (64%)	19 (73%)	94 (77%)
PI exposure	60 (95%)	20 (61%)	5 (19%)	85 (70%)

Data are n (%). CDC=US Centers for Disease Control and Prevention. NRTI=nucleoside reverse-transcriptase inhibitor. NNRTI=non-NRTI. PI=protease inhibitors.

Table 2:

Clinical adverse events by formulation

	Cohorts 1 and 2A (adult tablets; n=63)	Cohorts 2B and 3 (chewable tablets; n=33)	Cohorts 4 and 5 (oral granules; n=26)	Total (n=122)
Blood and lymphatic system disorders				
Lymphadenopathy	9 (14%)	8 (24%)	9 (35%)	26 (21%)
Gastrointestinal disorders				
Abdominal pain	17 (27%)	3 (9%)	3 (12%)	23 (19%)
Diarrhoea	19 (30%)	10 (30%)	16 (62%)	45 (37%)
Nausea	20 (32%)	3 (9%)	1 (4%)	24 (20%)
Vomiting	21 (33%)	13 (39%)	9 (35%)	43 (35%)
General disorders and administration site conditions				
Pyrexia	32 (51%)	17 (52%)	14 (54%)	63 (52%)
Infections and infestations				
Gastroenteritis	5 (8%)	10 (30%)	10 (38%)	25 (20%)
Impetigo	0	9 (27%)	2 (8%)	11 (9%)
Otitis media	8 (13%)	12 (36%)	6 (23%)	26 (21%)
Pharyngitis	4 (6%)	4 (12%)	10 (38%)	18 (15%)
Metabolism and nutrition disorders				
Decreased appetite	6 (10%)	6 (18%)	7 (27%)	19 (16%)
Nervous system disorders				
Headache	29 (46%)	3 (9%)	1 (4%)	33 (27%)
Respiratory, thoracic, and mediastinal disorders				
Cough	43 (68%)	21 (64%)	19 (73%)	83 (68%)
Nasal congestion	31 (49%)	14 (42%)	15 (58%)	60 (49%)
Oropharyngeal pain	25 (40%)	7 (21%)	1 (4%)	33 (27%)
Rhinorrhoea	26 (41%)	18 (55%)	16 (62%)	60 (49%)
Skin and subcutaneous tissue disorders				
Rash	9 (14%)	6 (18%)	16 (62%)	31 (25%)

Data are n (%) by formulation administered for each adverse event category, for the 240 weeks of study, for adverse events that had prevalence greater than 25% of patients in one or more cohorts.

Table 3:

Raltegravir resistance across formulations in final dose population

	Overall virological failure	No raltegravir-associated drug-resistance mutations found in plasma virus at virological failure [*]	Raltegravir-associated drug-resistance mutations found in plasma virus at virological failure ^{*†}
Cohorts 1 and 2A (n=63)	34 (53%)	23 (68%)	7 (21%)
Cohorts 2B and 3 (n=33)	15 (45%)	4 (27%)	11 (73%)
Cohorts 4 and 5 (n=26)	11 (42%)	4 (36%)	1 (9%)
Total (n=122)	60 (49%)	31 (52%)	19 (32%)

Data are n (%). Cohorts 1 and 2A received adult tablets, cohorts 2B and 3 received chewable tablets, and cohorts 4 and 5 received oral granules.

^{*} Excludes participants with a missing specimen at virological failure.

[†] All but five participants had plasma HIV RNA sequence pre-raltegravir showing no raltegravir-associated mutations, except two participants who had polymorphic accessory mutations (one with Thr97Ala, the other with Val151Ile).