



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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## Raltegravir (RAL, Isentress) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/daf/>

### Formulations

**Tablet:** 400 mg (film-coated poloxamer tablet)

**HD Tablet:** 600 mg (film-coated poloxamer tablet)

**Chewable Tablets:** 100 mg (scored) and 25 mg

**Granules for Oral Suspension:** Single-use packet of 100 mg of raltegravir, suspended in 10 mL of water for final concentration of 10 mg/mL.

**Note:** Film-coated tablets, chewable tablets, and oral suspension **are not interchangeable**.

### Dosing Recommendations

**Note:** No dosing information is available for preterm infants or **infants weighing <2 kg at birth**. (See [Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV](#) and [Table 12](#) for information about using raltegravir for the prevention of perinatal HIV transmission).

#### Neonate (Weighing $\geq 2$ kg) Dose

**Raltegravir Oral Suspension Dosing Table for Full-Term Neonates from Birth to Age 4 Weeks: Neonates Aged  $\geq 37$  Weeks and Weighing  $\geq 2$  kg**

Body Weight	Volume (Dose) of Suspension
<b>Birth to 1 Week of Age: Once-Daily Dosing</b>	<b>Approximately 1.5 mg/kg/dose</b>
2 kg to <3 kg	0.4 mL (4 mg) once daily
3 kg to <4 kg	0.5 mL (5 mg) once daily
4 kg to <5 kg	0.7 mL (7 mg) once daily
<b>1–4 Weeks of Age: Twice-Daily Dosing</b>	<b>Approximately 3 mg/kg/dose</b>
2 kg to <3 kg	0.8 mL (8 mg) twice daily
3 kg to <4 kg	1 mL (10 mg) twice daily
4 kg to <5 kg	1.5 mL (15 mg) twice daily

**Note:** If the mother has taken raltegravir 2 hours to 24 hours prior to delivery, the neonate's first dose should be delayed until 24 hours to 48 hours after birth.

**Note:** Metabolism by uridine diphosphate glucuronyl transferase (UGT1A1) is low at birth and increases rapidly during the next 4 to 6 weeks of life.

#### Infant and Child (Weighing $\geq 3$ kg to <20 kg) Dose

### Selected Adverse Events

- Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis
- Nausea, diarrhea
- Headache, dizziness, fatigue
- Insomnia
- Fever
- Creatine phosphokinase elevation, muscle weakness, and rhabdomyolysis

### Special Instructions

- Raltegravir can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any raltegravir formulations.
- Significant drug interactions are more likely to occur when the raltegravir HD formulation is used once daily. **The following drugs should not be coadministered:** calcium carbonate, rifampin, tipranavir/ritonavir, and etravirine.
- Chewable tablets can be chewed, crushed (before administration), or swallowed whole.
- Film-coated tablets, including HD tablets, must be swallowed whole.
- The chewable tablets and oral suspension have better bioavailability than the film-coated tablets. Because the formulations are not interchangeable, **do not substitute** chewable tablets or oral suspension for film-coated tablets. See specific recommendations for proper dosing of different formulations.

### Raltegravir Oral Suspension Dosing Table for Patients Aged $\geq 4$ Weeks<sup>a</sup>

Body Weight	Volume (Dose) of Suspension to be Administered Twice Daily
3 kg to <4 kg	2.5 mL (25 mg)
4 kg to <6 kg	3 mL (30 mg)
6 kg to <8 kg	4 mL (40 mg)
8 kg to <11 kg	6 mL (60 mg)
11 kg to <14 kg	8 mL (80 mg)
14 kg to <20 kg	10 mL (100 mg)

<sup>a</sup> The weight-based dosing recommendation for the oral suspension is based on approximately raltegravir 6 mg/kg per dose twice daily.

**Note:** The maximum dose of oral suspension is 10 mL (raltegravir 100 mg) twice daily.

**Note:** For children weighing 11 kg to 20 kg, either oral suspension or chewable tablets can be used.

### Child and Adolescent Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

*Children Weighing  $\geq 11$  kg:*

- Weighing <25 kg: Chewable tablets twice daily. See table below for chewable tablet dose.
- Weighing  $\geq 25$  kg: Raltegravir 400-mg, film-coated tablet twice daily **or** chewable tablets twice daily. See table below for chewable tablet dose.

*Children and Adolescents Weighing  $\geq 50$  kg:*

- Two raltegravir 600-mg HD tablets (1,200 mg) once daily
- This dose is for treatment-naïve or virologically suppressed patients who are on an initial dose of raltegravir 400 mg twice daily.
- See the Approval section under the Pediatric Use heading below for more information.

### Chewable Tablet Dosing Table<sup>a</sup>

Body Weight	Dose	Number of Chewable Tablets
11 kg to <14 kg	Raltegravir 75 mg twice daily	Three 25-mg tablets twice daily
14 kg to <20 kg	Raltegravir 100 mg twice daily	One 100-mg tablet twice daily
20 kg to <28 kg	Raltegravir 150 mg twice daily	One and a half 100-mg tablets <sup>b</sup> twice daily
28 kg to <40 kg	Raltegravir 200 mg twice daily	Two 100-mg tablets twice daily
$\geq 40$ kg	Raltegravir 300 mg twice daily	Three 100-mg tablets twice daily

<sup>a</sup> The weight-based dose recommendation for the chewable tablet is based on approximately raltegravir 6 mg/kg per dose twice daily.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.
- The chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- The oral suspension comes in a kit that includes mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document. Each foil packet is single-use and contains 100 mg of raltegravir, which will be suspended in 10 mL of water for a final concentration of raltegravir 10 mg/mL. Gently swirl the mixing cup for 45 seconds in a circular motion to mix the powder into a uniform suspension.
- **Do not shake the oral suspension.** Dose should be administered within 30 minutes of mixing; unused solution should be discarded as directed in the Instructions for Use document.

### Metabolism/Elimination

- UGT1A1-mediated glucuronidation

### Raltegravir Dosing in Patients with Hepatic Impairment:

- No dose adjustment is necessary in patients who have mild-to-moderate hepatic insufficiency and are receiving twice daily dosing of raltegravir.
- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving either raltegravir 1,200 mg once daily or 400 mg twice daily.
- No studies have been conducted on the use of raltegravir HD in patients with hepatic impairment. Therefore, administration of raltegravir HD **is not recommended** in patients with hepatic impairment.
- The effect of severe hepatic impairment on raltegravir pharmacokinetics has not been studied.

### Raltegravir Dosing in Patients with Renal Impairment:

- No dose adjustment is necessary in patients with any degree of renal impairment.

<sup>b</sup> The raltegravir 100-mg chewable tablet can be divided into equal halves.

**Note:** Maximum dose of chewable tablets is raltegravir 300 mg twice daily.

**Drug Interactions** (see also the [Adult and Adolescent Antiretroviral Guidelines](#) and the [HIV Drug Interaction Checker](#))

- *Metabolism:* The major route of raltegravir elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT1A1).
- Coadministering raltegravir with inducers of UGT1A1, such as rifampin and tipranavir, may result in reduced plasma concentrations of raltegravir. Inhibitors of UGT1A1, such as atazanavir, may increase plasma concentrations of raltegravir. No dosing modifications are recommended when raltegravir is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, raltegravir HD tablets **should not be coadministered** with TPV/r (see the text below).
- In adults, an increased dose of raltegravir is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily raltegravir HD tablets. **In children aged 2 years to <12 years who had tuberculosis/HIV coinfection and who were taking rifampin, raltegravir 12 mg/kg per dose twice daily of the chewable tablet formulation safely achieved pharmacokinetic (PK) targets.**<sup>1,2</sup>
- Aluminum-containing antacids and magnesium-containing antacids may reduce raltegravir plasma concentrations and **should not be coadministered** with raltegravir.
- Significant drug interactions may be more likely to occur with raltegravir HD once daily.  $C_{\text{trough}}$  concentrations in adults are approximately 30% lower with raltegravir HD 1,200 mg once daily than with raltegravir 400 mg twice daily. A lower  $C_{\text{trough}}$  increases the potential for clinically significant drug interactions with interfering drugs that decrease raltegravir exposure and further lower  $C_{\text{trough}}$ . In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the raltegravir HD formulation: calcium carbonate, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on raltegravir is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.
- Before administering raltegravir, clinicians should carefully review a patient's medication profile for potential drug interactions with raltegravir.

**Major Toxicities**

- *More common:* Nausea, headache, dizziness, diarrhea, fatigue, itching, insomnia.
- *Less common:* Abdominal pain, vomiting. Patients with chronic active hepatitis B virus infection and/or hepatitis C virus infection are more likely to experience a worsening adverse events grade from baseline for laboratory abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than patients who are not coinfecting.
- *Rare:* Moderate to severe increase in creatine phosphokinase levels. Use raltegravir with caution in patients who are receiving medications associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with prior history. Rash, including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

## **Resistance**

The International Antiviral Society-USA (IAS-USA) maintains [a list of updated resistance mutations](#) and the [Stanford University HIV Drug Resistance Database](#) offers a discussion of each mutation.

## **Pediatric Use**

### *Approval*

Raltegravir is an integrase strand transfer inhibitor (INSTI) that is approved by the Food and Drug Administration (FDA) for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV in pediatric patients weighing  $\geq 2$  kg. The current pediatric FDA approval and dose recommendations are based on evaluations of 122 patients aged  $\geq 4$  weeks to 18 years who participated in IMPAACT P1066 and 42 full-term neonates who were treated for  $\leq 6$  weeks starting from birth and followed for a total of 24 weeks during IMPAACT P1110.<sup>3</sup>

The FDA has approved raltegravir HD, which allows for once-daily dosing, for use in children and adolescents weighing  $\geq 40$  kg. However, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends using raltegravir HD in children weighing  $\geq 50$  kg, since there are no clinical data on the use of raltegravir HD once-daily dosing in children or adolescents weighing  $< 50$  kg.

### *Efficacy in Clinical Trials*

Raltegravir has been evaluated in adults in three, large, randomized clinical trials: STARTMRK, SPRING-2, and ACTG A5257. STARTMRK compared the safety and efficacy of a raltegravir-containing regimen and an efavirenz-containing regimen. At 48 weeks, raltegravir was noninferior to efavirenz. However, more patients discontinued efavirenz during the longer follow-up periods of 4 and 5 years, and raltegravir was found to be virologically and immunologically superior compared to efavirenz.<sup>4-6</sup> Results from SPRING-2 study in treatment-naïve adults showed that raltegravir and dolutegravir were equally effective and had similar safety profiles.<sup>7</sup> ACTG A5257 compared raltegravir to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but raltegravir had better tolerability.<sup>8</sup>

Raltegravir was studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated PKs, safety, tolerability, and efficacy. In 96 participants aged 2 years to 18 years who were mostly treatment-experienced, 79.1% of the patients achieved a favorable viral load response (i.e., viral loads  $< 400$  copies/mL or  $\geq 1$  log<sub>10</sub> decline in viral load) while receiving the currently recommended dose of raltegravir. Infants and toddlers aged  $\geq 4$  weeks to  $< 2$  years were also enrolled in IMPAACT P1066 and received treatment with raltegravir oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads  $< 400$  copies/mL.<sup>9-11</sup> **FDA approval for the use of raltegravir in infants as young as 4 weeks of age was based on the results of this study.**

The ONCEMRK study compared raltegravir 1,200 mg once daily (taken as two 600-mg HD tablets) to raltegravir 400 mg twice daily in treatment-naïve adults. Once-daily dosing of raltegravir using the HD tablets was approved by the FDA for adults and children weighing  $\geq 40$  kg who are either treatment-naïve or virologically suppressed on a twice-daily raltegravir regimen. While the HD tablets are approved by the FDA for use in children weighing  $\geq 40$  kg, the Panel **does not recommend** using HD tablets in children weighing  $< 50$  kg (see below).

### ***Efficacy and Pharmacokinetics of Once-Daily Dosing in Children and Adults***

Raltegravir PKs exhibit considerable intrasubject and intersubject variability.<sup>12,13</sup> Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naïve patients with HIV were randomized to receive raltegravir 800 mg once daily or raltegravir 400 mg twice daily. After 48 weeks of treatment, the percentage of patients who achieved HIV RNA viral loads  $< 50$  copies/mL was 83% in the once-daily group compared to 89% in the twice-daily group. Patients in the once-daily arm with C<sub>trough</sub> concentrations below 45 nM were at the greatest risk of experiencing treatment failure.<sup>12,13</sup> Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower



$C_{\text{trough}}$  concentrations suggests that maintaining raltegravir trough plasma concentrations above 45 nM is important for efficacy.<sup>12,13</sup>

Once-daily dosing with raltegravir 1,200 mg was found to be as effective as dosing with raltegravir 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either raltegravir 1,200 mg once daily (taken as two 600-mg tablets) or raltegravir 400 mg twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 89% of participants on the once-daily dose and 88% of participants on the twice-daily dose reached viral loads of <40 copies. There was no difference in discontinuation rates due to side effects between the two groups.<sup>14</sup> In May 2017, once-daily dosing of raltegravir using the HD tablets was approved by the FDA for adults and children weighing  $\geq 40$  kg who are either treatment-naive or virologically suppressed on a twice-daily raltegravir regimen. The use of once-daily dosing with the HD tablets has not been studied in pediatric patients. Population PK modeling and simulations of once-daily dosing with raltegravir HD tablets predict that this dosing schedule will produce drug exposures that are similar to those observed in adult patients during ONCEMRK.<sup>3,15</sup>

Dosing with three 400-mg tablets once daily and dosing with two 600-mg HD tablets once daily are expected to produce similar PK profiles. In adults enrolled in ONCEMRK, the  $C_{\text{trough}}$  concentrations were approximately 30% lower in participants taking once-daily raltegravir HD tablets than in those taking raltegravir 400 mg twice daily. Because of this, the potential for significant drug interactions is greater with once-daily dosing, as interfering drugs that decrease drug exposure may further decrease  $C_{\text{trough}}$ .  $C_{\text{max}}$  is approximately six times higher in patients receiving raltegravir 1,200 mg once daily than in those receiving raltegravir 400 mg twice daily, with a two-fold higher area under the curve (AUC).

While modeling and simulations for pediatric patients may indicate that PK targets are met using the once-daily raltegravir 1,200 mg dose, safety cannot be extrapolated for children weighing <50 kg. There were six children in IMPAACT P1066 who had drug exposures that were similar to those observed in ONCEMRK, but all six children weighed >50 kg. Potential dose-related central nervous system toxicities, such as insomnia or hyperactivity, might occur in children exposed to very high concentrations of raltegravir.<sup>3</sup> The Panel recommendations differ from those of the FDA because there are no clinical data on once-daily dosing with raltegravir HD tablets in children or adolescents weighing <50 kg. While the FDA has approved the use of once-daily dosing with raltegravir HD tablets in children weighing  $\geq 40$  kg, the Panel recommends using once-daily dosing with raltegravir HD tablets only in children and adolescents who weigh  $\geq 50$  kg.

### ***Efficacy and Pharmacokinetics in Children***

IMPAACT P1066 evaluated the PKs, safety, and efficacy of raltegravir in children aged 4 weeks to 18 years. A description of the study cohorts and a summary of the PK parameters can be found in Tables A and B.<sup>10,11</sup>

**Table A. Summary of IMPAACT P1066 Cohorts and Participation<sup>10,11</sup>**

<b>Age</b>	<b>Cohort</b>	<b>Formulation</b>	<b>Number of Participants Who Received the Final Recommended Dose</b>
<b>12 Years to &lt;19 Years</b>	I	Film-coated tablet	59
<b>6 Years to &lt;12 Years</b>	IIA	Film-coated tablet	4
<b>6 Years to &lt;12 Years</b>	IIB	Chewable tablet	13
<b>2 Years to &lt;6 Years</b>	III	Chewable tablet	20
<b>6 Months to &lt;2 Years</b>	IV	Oral suspension	14
<b>4 Weeks to &lt;6 Months</b>	V	Oral suspension	12

**Table B. Summary of IMPAACT P1066 PK Results by Cohort<sup>10,11</sup>**

Age	Cohort	Formulation	Intensive PK	Mean Dose	GM (CV%) <sup>a</sup> AUC <sub>0-12h</sub> $\mu\text{M}\cdot\text{hr}$	GM (CV%) <sup>b</sup> C <sub>12h</sub> nM
12 Years to <19 Years	I	Film-coated tablet	11	9.3 mg/kg	15.7 (98%)	333 (78%)
6 Years to <12 Years	IIA	Film-coated tablet	11	13.5 mg/kg	15.8 (120%)	246 (221%)
6 Years to <12 Years	IIB	Chewable tablet	10	6.5 mg/kg	22.6 (34%)	130 (88%)
2 Years to <6 Years	III	Chewable tablet	12	6.2 mg/kg	18.0 (59%)	71 (55%)
6 Months to <2 Years	IV	Oral suspension	8	5.9 mg/kg	19.8 (34%)	108 (52%)
4 Weeks to <6 Months	V	Oral suspension	11	5.7 mg/kg	22.3 (40%)	117 (68%)

<sup>a</sup> PK targets for Cohorts I–III: AUC<sub>0-12h</sub> 14–25  $\mu\text{M}\cdot\text{hr}$  (6–11 mg\*h/L); C<sub>12h</sub> nM  $\geq$ 33 nM (14.7 ng/mL)

<sup>b</sup> PK targets for Cohorts IV–V: AUC<sub>0-12h</sub> 14–45  $\mu\text{M}\cdot\text{hr}$  (6–20 mg\*h/L); C<sub>12h</sub> nM  $\geq$ 75 nM (33.3 ng/mL)

**Key to Acronyms:** AUC = area under the curve; C<sub>12h</sub> = concentration at 12 hours (trough); CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic

### Children Aged 2 Years to 18 Years

IMPAACT P1066 was a Phase 1/2 open-label multicenter study that evaluated the PK profile, safety, tolerability, and efficacy of various formulations of raltegravir in antiretroviral treatment (ART)-experienced children and adolescents with HIV aged 2 years to 18 years. Raltegravir was administered in combination with an optimized background ART regimen.<sup>11,16</sup> Subjects received either the raltegravir 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing  $\geq$ 25 kg) or the chewable tablet formulation at a dose of raltegravir 6 mg/kg twice daily (patients aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included an intensive PK evaluation in various age cohorts (Cohort I: 12 years to <19 years; Cohort II: 6 years to <12 years, Cohort III: 2 years to <6 years). Doses were selected with the aim of achieving target PK parameters similar to those seen in adults: PK targets were a geometric mean (GM) AUC<sub>0-12h</sub> of 14  $\mu\text{M}\cdot\text{hr}$  to 25  $\mu\text{M}\cdot\text{hr}$  and a GM 12-hour concentration (C<sub>12h</sub>)  $>$ 33 nM. Additional participants were then enrolled in each age cohort to evaluate the long-term efficacy, tolerability, and safety of raltegravir.

A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of raltegravir. Only treatment-experienced patients were eligible to enroll, and the optimized regimen was determined by the site investigators. Adolescents tended to be more treatment-experienced and have more advanced disease than those in the younger cohorts, with 75% having CDC Category B or C classification. Ninety-six participants completed 48 weeks of treatment. Seventy-nine percent of participants achieved HIV RNA  $<$ 400 copies/mL and 57% of participants achieved HIV RNA  $<$ 50 copies/mL, with a mean CD4 T lymphocyte (CD4) cell count increase of 156 cells/mm<sup>3</sup> (4.6%).<sup>11</sup> Of 36 subjects who experienced virologic failure, the development of drug resistance and/or poor adherence were contributing factors. Genotypic resistance data were available for 34 patients who experienced virologic failure, and raltegravir-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of adverse events (AEs) through Week 48 were comparable to those observed in adult studies. AEs were commonly reported, but few serious AEs were considered to be drug-related. AEs that were considered to be drug-related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia; and one patient with a Grade 2 allergic rash on Day 17 and Grade 3 ALT and Grade 4 AST laboratory elevations after Day 122. There were no discontinuations due to AEs and no drug-related deaths.<sup>11</sup> Overall, raltegravir was well tolerated when it was administered as a film-coated tablet twice daily in subjects aged 6 years to <19 years and as chewable tablets at a dose of approximately 6 mg/kg twice daily in subjects aged 2 years to <12 years, with favorable virologic and immunologic responses.<sup>17</sup>

Among 19 children and adolescents who were non-responders with multidrug-resistant virus in the HIV Spanish Cohort (CoRISe), all had good virologic response and improved CD4 counts when raltegravir was

included in an optimized regimen.<sup>9</sup> Experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.<sup>18,19</sup> Overall virologic and immunologic outcomes have been good among additional cohorts of treatment-experienced children and adolescents from low-income and middle-income countries.<sup>20,21</sup>

### ***Children Aged at Least 4 Weeks to <2 Years***

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for raltegravir oral suspension in combination with an optimized background regimen. All subjects had previously received ARV drugs to prevent perinatal transmission and/or treat HIV, and 69% had baseline plasma HIV RNA exceeding 100,000 copies/mL. PK targets for Cohorts IV and V were modified to a GM AUC<sub>0-12h</sub> of 14  $\mu\text{M}\cdot\text{hr}$  to 45  $\mu\text{M}\cdot\text{hr}$  and a GM C<sub>12h</sub>  $\geq 75$  nM (33.3 ng/mL). These targets were modified so that >90% of patients would be predicted to have C<sub>12h</sub> above the 45 nM threshold. By Week 48, two subjects experienced AEs thought to be related to the study drug: one patient with a serious erythematous rash that resulted in permanent discontinuation of raltegravir, and one patient with immune reconstitution inflammatory syndrome. Virologic success, defined as  $\geq 1$  log<sub>10</sub> decline in HIV RNA or <400 copies/mL at 48 weeks, was achieved in >87% of participants. At 48 weeks of follow up, 45.5% of subjects had HIV RNA <50 copies/mL and mean CD4 cell count increases of 527.6 cells/mm<sup>3</sup> (7.3%). There were four subjects in Cohort IV who experienced virologic failure by Week 48 and one subject with a raltegravir-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately 6 mg/kg twice daily, were well tolerated and had good efficacy.<sup>10</sup>

### ***Long-Term Follow Up in Children***

The IMPAACT P1066 study team recently reported results regarding the safety and efficacy of different raltegravir formulations at 240 weeks in children enrolled in this multicenter trial.<sup>22</sup> Eligible participants were children aged 4 weeks to 18 years who had previously been treated with ART and who were experiencing virologic failure at the time of enrollment. Raltegravir was added to an optimized ART regimen in all participants. Raltegravir was well tolerated, and there were few serious clinical or laboratory safety events noted during the study.<sup>22</sup>

The proportion of participants who achieved virologic success at 240 weeks varied by the raltegravir formulation used: 19 of 43 children (44.2%) who received raltegravir 400-mg tablets; 24 of 31 children (77.4%) who received chewable tablets; and 13 of 15 children (86.7%) who received the oral granules for suspension. Raltegravir resistance was documented in 19 of 50 patients (38%) who experienced virologic rebound after initial suppression. These results suggest that younger children with less treatment experience are more likely to have sustained virologic suppression, while older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to raltegravir. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the raltegravir 400-mg tablets.<sup>22</sup> In the accompanying commentary, the authors conclude that these findings support the use of raltegravir in infants and young children, who have few treatment options.<sup>23</sup> However, in older children and adolescents, INSTIs such as dolutegravir (which has a higher genetic barrier to resistance than raltegravir) would be preferred.<sup>23</sup>

### ***Neonates Aged <4 Weeks***

Raltegravir is metabolized by UGT1A1, the same enzyme responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and raltegravir elimination is prolonged in neonates. In addition, bilirubin and raltegravir may compete for UGT and albumin binding sites.<sup>24</sup> Washout PKs of raltegravir in neonates born to pregnant women with HIV was studied in IMPAACT P1097.<sup>25</sup> The neonatal plasma half-life was highly variable, ranging from 9.3 hours to 184 hours, suggesting potential roles for developmental aspects of neonatal UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of raltegravir.

IMPAACT P1110 is a Phase 1, multicenter trial enrolling full-term neonates with or without *in utero*



raltegravir exposure who were exposed to HIV and who are at risk of acquiring HIV. **Raltegravir-exposed neonates were those whose mothers received raltegravir within 2 hours to 24 hours of delivery.** For raltegravir-exposed neonates, the initial dose of raltegravir was delayed until 12 hours to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two raltegravir doses administered 1 week apart and Cohort 2 infants received daily raltegravir dosing for the first 6 weeks of life. PK data from Cohort 1 and from older infants and children were combined in a population PK model, and simulations were used to select the following raltegravir dosing regimen for evaluation in infants in Cohort 2: 1.5 mg/kg daily, starting within 48 hours of life through Day 7; 3 mg/kg twice daily on Days 8 to 28 of life; 6 mg/kg twice daily after 4 weeks of age.<sup>26,27</sup> Protocol exposure targets for each subject were AUC<sub>0-24hr</sub> 12 mg\*h/L to 40 mg\*h/L, AUC<sub>0-12hr</sub> 6 mg\*h/L to 20 mg\*h/L, and C<sub>12hr</sub> or C<sub>24hr</sub> >33 ng/mL. Safety was assessed based on clinical and laboratory evaluations.<sup>25,28,29</sup> Twenty-six raltegravir-naïve infants and 10 raltegravir-exposed infants were enrolled in Cohort 2; 25 raltegravir-naïve infants and 10 raltegravir-exposed infants had evaluable PK results and safety data. Results for the raltegravir-naïve infants and raltegravir-exposed infants who were enrolled in Cohort 2 are contained in the summary table below.

**Table C. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naïve and Raltegravir-Exposed Neonates<sup>29,30</sup>**

PK Parameter	After Initial Dose: 1.5 mg/kg Once Daily RAL-Naïve (N = 25)		After Initial Dose: 1.5 mg/kg Once Daily RAL-Exposed (N = 10)		Days 15–18: 3.0 mg/kg Twice Daily RAL-Naïve (N = 24)		Days 15–18: 3.0 mg/kg Twice Daily RAL-Exposed (N = 9)	
	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target	Geometric Mean (CV%)	Target
AUC (mg*h/L) <sup>a</sup>	38.2 (38.4%)	Above: 11 Met: 13 Below: 0	42.9 (24.6%)	Above: 6 Met: 4 Below: 0	14.3 (43.3%)	Above: 8 Met: 14 Below: 1	18.3 (48.8%)	Above: 5 Met: 3 Below: 1
Trough (ng/mL) <sup>b</sup>	948 (64.2%)	Above: 25 Below: 0	946.3 (49.7%)	Above: 10 Below: 0	176 (93.8%)	Above: 22 Below: 1	273.6 (75.5%)	Above: 8 Below: 1
C <sub>max</sub> (ng/mL) <sup>c</sup>	2,350 (35.0%)	Above: 0 Below: 25	2,565.3 (24.3%)	Above: 0 Below: 10	2,850 (41.9%)	Above: 0 Below: 24	3,667.4 (46.7%)	Above: 0 Below: 9
T <sub>max</sub> (hours)	5.4 (57.5%)	N/A	3.8 (58.3%)	N/A	2.3 (67.1%)	N/A	1.9 (59.4%)	N/A
T <sub>1/2</sub> (hours)	15.8 (174.8%)	N/A	14.4 (58.3%)	N/A	2.5 (33.5%)	N/A	2.9 (20.1%)	N/A

<sup>a</sup> The PK targets were AUC<sub>24</sub> 12–40 mg\*h/L and AUC<sub>12</sub> 6–20 mg\*h/L.

<sup>b</sup> The trough concentration target was >33 ng/mL.

<sup>c</sup> The C<sub>max</sub> target was <8,724 ng/mL.

**Key to Acronyms:** AUC = area under the curve; C<sub>max</sub> = maximum concentration; CV = coefficient of variation; PK = pharmacokinetic; RAL = raltegravir; T<sub>1/2</sub> = half-life; T<sub>max</sub> = time to reach maximum concentration

Daily raltegravir was safe and well tolerated during the first 6 weeks of life. Infants were treated for up to 6 weeks from birth and followed for a total of 24 weeks. All GM protocol exposure targets were met. In some infants, AUC<sub>0-24hr</sub> following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in raltegravir metabolism during the first week of life. The PK targets and the safety guidelines were met for both raltegravir-naïve and raltegravir-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory adverse reactions were reported among the raltegravir-naïve infants: Grade 4 transient neutropenia occurred in one infant receiving a zidovudine-containing regimen; two bilirubin elevations (one Grade 1 and one Grade 2) were considered nonserious and did not require specific therapy.<sup>3</sup> Among the raltegravir-exposed infants, there were four infants with Grade 3 or 4 toxicities: anemia in one infant, neutropenia in one infant, and hyperbilirubinemia in two infants. No specific therapy was required to treat these toxicities and no infants

required phototherapy or exchange transfusion for hyperbilirubinemia.

Results from P1110 confirmed the PK modeling and simulation submitted for FDA approval and labeling. Neonates born to mothers who received raltegravir 2 hours to 24 hours prior to delivery should have their first dose of raltegravir delayed until 24 hours to 48 hours after birth.<sup>30</sup>

Dosing in preterm infants has not been well studied. Two case reports of preterm infants dosed with raltegravir to prevent perinatal transmission have been published.<sup>31,32</sup> These case reports involved one infant born at a gestational age of 24 weeks and 6 days who weighed 800 g and another infant born at 33 weeks gestation who weighed 1,910 g. In both infants, intermittent dosing of raltegravir was done using real-time therapeutic drug monitoring (TDM) in the neonatal intensive care unit.<sup>31,32</sup> Less frequent dosing was required because raltegravir elimination was significantly delayed in these preterm infants. A revised version of P1110 that will determine the PKs and safety of raltegravir in low birth weight neonates at risk of perinatal transmission of HIV is in development.

### Formulations

The PKs of raltegravir in adult patients with HIV who swallowed intact 400-mg tablets were compared to those observed in patients who chewed the 400-mg, film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher among patients who chewed the tablets, although the palatability was rated as poor.<sup>33</sup> In adult volunteers, the PKs of raltegravir 800 mg taken once daily by chewing was compared to the PKs of two doses of raltegravir 400 mg taken every 12 hours by swallowing. Participants who took raltegravir by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets as currently recommended.<sup>34</sup> According to the manufacturer, the film-coated tablets must be swallowed whole.

The raltegravir chewable tablet and oral suspension have higher oral bioavailability than the 400-mg, film-coated tablet, according to a comparative study in healthy adult volunteers.<sup>35</sup> Compared with the raltegravir 400-mg tablet formulation, the raltegravir 600-mg tablet has higher relative bioavailability.<sup>3,36</sup> Interpatient and inpatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.<sup>3,37</sup> Because of differences in the bioavailability of various formulations, the dosing recommendations for each formulation differ, and the formulations **are not interchangeable**. When prescribing raltegravir, clinicians should refer to the appropriate dosing table for the chosen formulation. While the raltegravir chewable tablets are not yet approved for use in children aged <2 years, a recent study has investigated whether these tablets may be dispersed and administered to younger children and infants.<sup>38</sup> An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including breast milk. A follow-up evaluation of chewable tablets used as dispersible tablets for young children is planned.

Palatability was evaluated as part of IMPAACT P1066. Both chewable tablets and oral granules for suspension were thought to have acceptable palatability. Seventy-three percent of those surveyed reported no problems with chewable tablets; 82.6% reported no problems with administering the oral granules.<sup>10,11</sup>

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