Raltegravir (RAL, Isentress)  (Last updated May 22, 2018; last reviewed May 22, 2018)

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

Formulations

Tablets: 400 mg (film-coated poloxamer tablet)
HD Tablets: 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

See Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV and Table 12, Newborn Antiretroviral Dosing Recommendations for prevention of perinatal transmission.

Neonate Dose:

Neonates ≥ 37 Weeks of Gestation (Weighing ≥ 2 kg):
- No dosing information is available for preterm or low birthweight infants.

Oral Suspension Dosing Table

Full-Term Neonates (Birth to 4 Weeks [28 Days] of Age):

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume (Dose) of Suspension to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 1 Week: Once-Daily Dosing</td>
<td>Approximately 1.5 mg/kg/dose</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>0.4 mL (4 mg) once daily</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>0.5 mL (5 mg) once daily</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>0.7 mL (7 mg) once daily</td>
</tr>
<tr>
<td>1–4 Weeks: Twice-Daily Dosing</td>
<td>Approximately 3 mg/kg/dose</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td>0.8 mL (8 mg) twice daily</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td>1 mL (10 mg) twice daily</td>
</tr>
<tr>
<td>4 to &lt;5</td>
<td>1.5 mL (15 mg) twice daily</td>
</tr>
</tbody>
</table>

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

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

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

- Can be given without regard to food.
- Co-administration or staggered administration of aluminum- 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 co-administered: 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.
- 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 preparations.
- Chewable tablets should be stored in the
Infant and Pediatric Dose

Oral Suspension Dosing Table

*Children Aged ≥4 Weeks and Weighing ≥3 kg to <20 kg:

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Volume (Dose) of Suspension to be Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to &lt;4</td>
<td>2.5 mL (25 mg) twice daily</td>
</tr>
<tr>
<td>4 to &lt;6</td>
<td>3 mL (30 mg) twice daily</td>
</tr>
<tr>
<td>6 to &lt;8</td>
<td>4 mL (40 mg) twice daily</td>
</tr>
<tr>
<td>8 to &lt;11</td>
<td>6 mL (60 mg) twice daily</td>
</tr>
<tr>
<td>11 to &lt;14</td>
<td>8 mL (80 mg) twice daily</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>10 mL (100 mg) twice daily</td>
</tr>
</tbody>
</table>

*a The weight-based dosing recommendation for the oral suspension is based on approximately 6 mg/kg/dose twice daily.

Note: Maximum dose of oral suspension is 10 mL (100 mg) twice daily.

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

Pediatric Dose for Chewable Tablets, Film-Coated Tablets, and HD Tablets

*Children Weighing ≥11 kg:

- <25 kg: Chewable tablets twice daily. See table below for chewable tablet dose.
- ≥25 kg: 400-mg film-coated tablet twice daily or chewable tablets twice daily. See table below for chewable tablet dose.

*Child and Adolescent Weighing ≥50 kg (HD), see Pediatric Use, Approval:

- 1200 mg (two 600 mg HD) once daily
- For treatment-naive or virologically suppressed patients on an initial regimen of 400 mg twice daily.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose</th>
<th>Number of Chewable Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 to &lt;14</td>
<td>75 mg twice daily</td>
<td>3 X 25 mg twice daily</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>100 mg twice daily</td>
<td>1 X 100 mg twice daily</td>
</tr>
<tr>
<td>20 to &lt;28</td>
<td>150 mg twice daily</td>
<td>1.5 X 100 mg * twice daily</td>
</tr>
<tr>
<td>28 to &lt;40</td>
<td>200 mg twice daily</td>
<td>2 X 100 mg twice daily</td>
</tr>
<tr>
<td>≥40</td>
<td>300 mg twice daily</td>
<td>3 X 100 mg twice daily</td>
</tr>
</tbody>
</table>

*a The weight-based dose recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.

*b The 100-mg chewable tablet can be divided into equal halves.

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

original package with desiccant to protect them from moisture.

- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.

- Oral suspension is provided in kits that include mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions 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 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 for standard-dose raltegravir in patients with mild-to-moderate hepatic insufficiency. No dosing studies of raltegravir HD have been done 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 necessary in patients with any degree of renal impairment.
Drug Interactions (see also the Adult and Adolescent Guidelines and the HIV Drug Interaction Checker)

- **Metabolism:** The major route of raltegravir elimination is mediated through glucuronidation by uridine diphosphate glucotransferase (UGT1A1).

- 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 co-administered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r) (except with HD tablets—see note below).

- In adults, an increased dose of raltegravir is recommended when it is co-administered with rifampin. For adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. Do not co-administer rifampin with once-daily raltegravir HD tablets. The appropriate dose adjustment is not known in children and is currently being studied in IMPAACT P1101.

- Aluminum- and magnesium-containing antacids may reduce raltegravir plasma concentrations and should not be co-administered.

- Significant drug interactions may be more likely to occur with raltegravir HD once daily. Concentrations in adults are approximately 30% lower with raltegravir HD 1200 mg once daily than with raltegravir 400 mg twice daily. A lower concentration increases the potential for clinically significant drug interactions with interfering drugs that decrease raltegravir exposure and further lower concentration. In addition to aluminum- and magnesium-containing antacids, the following drugs should not be co-administered with raltegravir: calcium carbonate, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug metabolizing enzymes on raltegravir is unknown; co-administration with phenytoin, phenobarbital, and carbamazepine is not recommended.

- Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with raltegravir.

Major Toxicities

- **More common:** Nausea, headache, dizziness, diarrhea, fatigue, itching, and 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 Grade from baseline for laboratory abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than are patients who are not co-infected.

- **Rare:** Moderate to severe increase in creatine phosphokinase. Use raltegravir with caution in patients 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 AIDS 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 that is Food and Drug Administration (FDA)-approved for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection in pediatric patients weighing ≥2 kg. Current pediatric FDA approval and dose recommendations are based on
evaluations in 122 patients aged ≥4 weeks to 18 years enrolled in IMPAACT P1066 and 42 neonates treated for ≤6 weeks starting from birth and followed for a total of 24 weeks in IMPAACT P1110.1

Overall, raltegravir has a favorable safety profile and is available in formulations suitable for administration to neonates, infants, and young children.

The FDA has approved raltegravir HD, which allows once daily dosing, for use in children and adolescents ≥40 kg, but the Panel recommends using it in children ≥50 kg since there are no clinical data on raltegravir HD once-daily dosing in children or adolescents <50 kg.

Efficacy in Clinical Trials (Adults and Children):

• Raltegravir has been evaluated in adults in three large randomized clinical trials: STARTMRK, SPRING-2, and ACTG A5257. In STARTMRK, a raltegravir-containing regimen was compared to an efavirenz-containing regimen. At 48 weeks, raltegravir was non-inferior to efavirenz. However, more patients discontinued efavirenz during the longer follow-up periods of 4 and 5 years, and raltegravir was found to be superior.2-4 SPRING-2 compared raltegravir to dolutegravir and demonstrated non-inferiority of dolutegravir.5 ACTG A5257 compared raltegravir to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but raltegravir had better tolerability.6

• Raltegravir has been studied in infants, children, and adolescents in IMPAACT P1066, an open-label trial that evaluated pharmacokinetics (PK), 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., HIV viral load <400 copies/mL or ≥1 log₁₀ decline in viral load) while receiving the currently recommended dose of raltegravir. Infants and toddlers aged ≥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 (14/23 infants and toddlers) had an HIV viral load <400 copies/mL.7-9

• The ONCEMRK study compared raltegravir 1200 mg once daily (taken as two 600-mg HD tablets) to raltegravir 400 mg twice daily in treatment-naive adults. Once-daily dosing of raltegravir using the HD tablets was approved by the FDA for adults and children weighing ≥40 kg who are either treatment-naive or virologically suppressed on a twice-daily raltegravir regimen. While the HD tablets are FDA-approved for children weighing ≥40 kg, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend using HD tablets in children weighing <50 kg (see below).

Efficacy and Pharmacokinetics of Once-Daily Dosing (Children and Adults)

Raltegravir PK exhibit considerable intrasubject and intersubject variability.10,11 Current PK targets are based on results from a clinical trial in adults (QDMRK) in which treatment-naive patients with HIV were randomized to receive raltegravir 800 mg once daily versus raltegravir 400 mg twice daily (BID). After 48 weeks of treatment, the percentage of patients achieving 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≤₄₅ trough concentrations below 45 nM were at the greatest risk of treatment failure.10,11 Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower C≤₄₅ concentrations suggests that maintaining raltegravir trough plasma concentrations above 45 nM is important for efficacy.10,11

Higher, once-daily dosing with raltegravir 1200 mg was found to be as effective as 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either 1200 mg of raltegravir once daily (taken as two 600-mg tablets) or 400 mg of raltegravir twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 89% of participants on the once-daily dose versus 88% of participants on the twice-dose reached viral loads of <40 copies. There was no difference in discontinuation rates due to side effects.12 In May 2017, once-daily dosing of raltegravir using the HD tablets was approved by the FDA for adults and children weighing ≥40 kg who are either treatment-naive or virologically suppressed on a twice-daily raltegravir regimen. The use of once-daily HD tablets has not been studied in pediatric patients.
Population PK modeling and simulations of once daily raltegravir HD tablets predict similar drug exposures to those observed in adult patients in ONCEMRK.\textsuperscript{1,13}

No significant differences in PK are anticipated with the administration of two 600-mg HD tablets (1200 mg) given once daily compared to three 400-mg (1200 mg) tablets given once daily. 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 with raltegravir 1200 mg once daily when compared to 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 1200 mg regimen, safety cannot be extrapolated for children weighing <50 kg. There were six children in IMPAACT P1066 who had similar drug exposures as those observed in ONCEMRK, but all weighed >50 kg. Potential dose-related central nervous system toxicities, such as insomnia or hyperactivity, might occur with very high raltegravir concentrations in children.\textsuperscript{4} The Panel recommendations differ from those of the FDA because there are no clinical data on once-daily raltegravir HD tablet dosing in children or adolescents weighing <50 kg. While the FDA has approved once-daily raltegravir HD tablets for use in children weighing ≥40 kg, the Panel recommends that once-daily raltegravir HD tablets only be used in children and adolescents weighing ≥50 kg.

**Efficacy and Pharmacokinetics in Children**

IMPAACT P1066 was conducted to evaluate the PK, safety, and efficacy of raltegravir in children aged 4 weeks to 18 years. Enrollment by cohort and PK parameters are summarized in Tables A and B.\textsuperscript{8,9}

### Table A. Summary of IMPAACT P1066 Cohorts and Participation\textsuperscript{8,9}

<table>
<thead>
<tr>
<th>Age</th>
<th>Cohort</th>
<th>Formulation</th>
<th>Participants Receiving the Final Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Years to &lt;19 Years</td>
<td>I</td>
<td>Film-coated tablet</td>
<td>N = 59</td>
</tr>
<tr>
<td>6 Years to &lt;12 Years</td>
<td>IIA</td>
<td>Film-coated tablet</td>
<td>N = 4</td>
</tr>
<tr>
<td>6 Years to &lt;12 Years</td>
<td>IIB</td>
<td>Chewable tablet</td>
<td>N = 13</td>
</tr>
<tr>
<td>2 Years to &lt;6 Years</td>
<td>III</td>
<td>Chewable tablet</td>
<td>N = 20</td>
</tr>
<tr>
<td>6 Months to &lt;2 Years</td>
<td>IV</td>
<td>Oral suspension</td>
<td>N = 14</td>
</tr>
<tr>
<td>4 Weeks to &lt;6 Months</td>
<td>V</td>
<td>Oral suspension</td>
<td>N = 12</td>
</tr>
</tbody>
</table>

### Table B. Summary of IMPAACT P1066 PK Results by Cohort\textsuperscript{8,9}

<table>
<thead>
<tr>
<th>Age</th>
<th>Cohort</th>
<th>Formulation</th>
<th>Intensive PK</th>
<th>Mean Dose mg/kg</th>
<th>GM (CV%)\textsuperscript{a} AUC\textsubscript{0-12h} µMxhr</th>
<th>GM (CV%)\textsuperscript{b} C\textsubscript{12h} nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Years to &lt;19 Years</td>
<td>I</td>
<td>Film-coated tablet</td>
<td>N = 11</td>
<td>9.3</td>
<td>15.7 (98)</td>
<td>333 (78)</td>
</tr>
<tr>
<td>6 Years to &lt;12 Years</td>
<td>IIA</td>
<td>Film-coated tablet</td>
<td>N = 11</td>
<td>13.5</td>
<td>15.8 (120)</td>
<td>246 (221)</td>
</tr>
<tr>
<td>6 Years to &lt;12 Years</td>
<td>IIB</td>
<td>Chewable tablet</td>
<td>N = 10</td>
<td>6.5</td>
<td>22.6 (34)</td>
<td>130 (88)</td>
</tr>
<tr>
<td>2 Years to &lt;6 Years</td>
<td>III</td>
<td>Chewable tablet</td>
<td>N = 12</td>
<td>6.2</td>
<td>18.0 (59)</td>
<td>71 (55)</td>
</tr>
<tr>
<td>6 Months to &lt;2 Years</td>
<td>IV</td>
<td>Oral suspension</td>
<td>N = 8</td>
<td>5.9</td>
<td>19.8 (34)</td>
<td>108 (52)</td>
</tr>
<tr>
<td>4 Weeks to &lt;6 Months</td>
<td>V</td>
<td>Oral suspension</td>
<td>N = 11</td>
<td>5.7</td>
<td>22.3 (40)</td>
<td>117 (68)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} PK targets for Cohorts I–III: AUC\textsubscript{0-12h} 14–25 µMxhr; C\textsubscript{12h} nM ≥33 nM

\textsuperscript{b} PK targets for Cohorts IV–V: AUC\textsubscript{0-12h} 14–45 µMxhr; C\textsubscript{12h} nM ≥75 nM

**Key to Acronyms:** AUC = area under the curve; C\textsubscript{12h} = concentration at 12 hours (trough); CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic
Children Aged 2 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 in combination with an optimized background ART regimen. Subjects received either the 400-mg, film-coated tablet formulation twice daily (patients aged 6–18 years and weighing ≥25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 years to <12 years). In IMPAACT P1066, the initial dose-finding stage included intensive PK evaluation in various age cohorts (Cohort I: aged 12 years to <19 years; Cohort II: 6 years to <12 years, Cohort III: 2 years to <6 years). Dose selection was based on achieving target PK parameters similar to those seen in adults: PK targets were geometric mean (GM) \( \text{AUC}_{0-12h} \) of 14 to 25 \( \mu \text{Mxhr} \) and GM 12-hour concentration (\( C_{12h} \)) >33 nM. Additional subjects were then enrolled in each age cohort to evaluate long-term efficacy, tolerability, and safety. A total of 126 treatment-experienced participants were enrolled, with 96 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. 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 (percent [%]) increase of 156 cells/mm\(^3\) (4.6%). Of 36 subjects who experienced virologic failure, development of drug resistance and/or poor adherence were contributing factors. Genotypic resistance data were available for 34 patients with virologic failure, and raltegravir-associated mutations were detected in 12/34 of those subjects. 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 there were few serious AEs considered to be drug-related. Observed AEs 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. Overall, raltegravir administered as a film-coated tablet twice daily in subjects aged 6 to <19 years and as chewable tablets at a dose of approximately 6 mg/kg twice daily in subjects aged 2 to <12 years was well tolerated, with favorable virologic and immunologic responses.

In 19 children and adolescents non-responders with multidrug-resistant virus in the HIV Spanish Cohort (CoRISe), had good virologic response and improved CD4 counts when raltegravir was included in an optimized regimen. Additional experience from the French expanded access program in treatment-experienced adolescents supports the good virologic and immunologic results observed in IMPAACT P1066.

Infants and Toddlers 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 received prior ARV drugs as part of prevention of perinatal transmission and/or treatment of HIV, and 69% had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL. PK targets for Cohorts IVand V were modified to GM \( \text{AUC}_{0-12h} \) of 14 to 45 \( \mu \text{Mxhr} \) and GM 12-hour concentration (\( C_{12h} \)) ≥75 nM (33.3 ng/mL). These targets were modified so that greater than 90% of patients would be predicted to have \( C_{12h} \) 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 ≥1 log\(_{10}\) decline in HIV RNA or <400 copies/mL at 48 weeks, was achieved in more than 87% of subjects. At 48 weeks of follow-up, 45.5% of subjects had HIV RNA <50 copies/mL and mean CD4 cell count (percent [%]) increases of 527.6 cells/mm\(^3\) (7.3%) There were four subjects in Cohort IV with virologic failure by Week 48 and one subject with a raltegravir-associated resistance mutation on genotype. Overall, the granules for oral suspension, at a dose of approximately 6 mg/kg twice daily, were well tolerated with good efficacy.
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. Washout PK of raltegravir in neonates born to pregnant women with HIV was studied in IMPAACT P1097. The neonatal plasma half-life was highly variable, ranging from 9.3 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 exposed to HIV and at risk of acquiring HIV-infection, with or without (i.e., raltegravir-naive) in utero raltegravir exposure. Study design included two cohorts: Cohort 1 infants received two single raltegravir doses 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 daily raltegravir dosing regimen for evaluation in raltegravir-naive 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. Protocol exposure targets for each subject are AUC0-24hr 12 to 40 mg*h/L, AUC0-12hr 6 to 20 mg*h/L, C12hr or C24hr >33 ng/mL. Safety was assessed based on clinical and laboratory evaluations. Twenty-six raltegravir-naive infants were enrolled in Cohort 2. Evaluable PK results and safety data are available for 25 infants. Results for raltegravir-naive infants enrolled in Cohort 2 are contained in the summary table below.

Table C. IMPAACT P1110 Cohort 2 Intensive PK Results

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>After Initial Dose: 1.5 mg/kg Once Daily (N = 25)</th>
<th>Days 15–18: 3.0 mg/kg Twice Daily (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean (CV)</td>
<td>Target</td>
<td>Geometric Mean (CV)</td>
</tr>
<tr>
<td>AUC (mg*h/L)</td>
<td>38.2 (38.4%)</td>
<td>Above: 11 Met: 13 Below: 0</td>
</tr>
<tr>
<td>Trough (ng/mL)</td>
<td>948 (64.2%)</td>
<td>Above: 25 Below: 0</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>2,350 (35.0%)</td>
<td>Above: 0 Below: 25</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>5.4 (57.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>T1/2 (hrs)</td>
<td>15.8 (174.8%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**PK Targets:** AUC24h 12–40 mg*h/L; AUC12h 6–20 mg*h/L

**Trough Concentrations:** >33 ng/mL

**Key to Acronyms:** AUC = area under the curve; Cmax = maximum concentration; CV = coefficient of variation; PK = pharmacokinetic; T1/2 = half-life; Tmax = 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, AUC0-24hr following initial dose was slightly above target range, but this is considered acceptable given the rapid increase in raltegravir metabolism over the first week of life. The PK targets and the safety guidelines were met for raltegravir-unexposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory adverse reactions were reported: Grade 4 transient neutropenia occurred in one infant receiving the zidovudine-containing regimen; two bilirubin elevations.
(one each, Grade 1 and Grade 2) were considered non-serious and did not require specific therapy.\textsuperscript{1} The safety and PK data for daily dosing collected from IMPAACT P1110 are from raltegravir-naive infants in Cohort 2; data collection from infants born to mothers who were receiving raltegravir is ongoing. However, the Panel believes that the FDA-approved dosing (including delaying the first dose for infants born to mothers who received raltegravir) is reasonable based on current data about clearance from premature and raltegravir-exposed infants.

**Formulations**

The PK of raltegravir was compared in adult patients with HIV who swallowed intact, whole 400-mg tablets and patients who chewed the 400-mg film-coated tablets because of swallowing difficulties. Drug absorption was significantly higher in the group who chewed the tablets, although the palatability was rated as poor.\textsuperscript{24} In adult volunteers, the PK of raltegravir 800 mg taken once daily by chewing was compared to two doses of raltegravir 400 mg taken every 12 hours by swallowing. Subjects taking raltegravir by chewing had significantly higher drug exposure and reduced PK variability than swallowing whole tablets as currently recommended.\textsuperscript{25} 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, based on a comparative study in healthy adult volunteers.\textsuperscript{26} Compared with the raltegravir 400-mg tablet formulation, the 600-mg tablet has higher relative bioavailability.\textsuperscript{1} Intertpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets.\textsuperscript{1,27} Because of differences in the bioavailability of various formulations, the dosing recommendations differ and the formulations are not interchangeable. When prescribing raltegravir, clinicians should refer to the appropriate dosing table for the various formulations. 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.\textsuperscript{28} An in vitro evaluation demonstrated that the chewable tablets are stable in various liquids, including breastmilk. A follow-up evaluation of chewable tablets used as dispersible tablets in 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.\textsuperscript{8,9}

**References**


4. Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. 


12. Cahn P. Raltegravir (RAL) 1200 mg once daily (QD) is non-inferior to RAL 400 mg twice daily (BID), in combination with tenofovir/emtricitabine, in treatment-naive HIV-1-infected subjects: week 48 results. Presented at: 21st International AIDS Conference. 2016. Durban, South Africa.


