Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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**Dosing Recommendations**

**Neonate Dose:**
- Not approved for use in neonates.
- Investigational dose for neonates ≥37 weeks of gestation and weighing ≥2 kg under study in IMPAACT P1110:
  - Birth to age 7 days: 1.5 mg/kg once daily
  - Aged 8–28 days: 3 mg/kg twice daily
  - Aged ≥4 weeks: 6 mg/kg twice daily (see below for approved infant and pediatric dose)
- No dosing information is available for preterm or low birthweight infants.

**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>1 mL (20 mg) twice daily</td>
</tr>
<tr>
<td>4 to &lt;6</td>
<td>1.5 mL (30 mg) twice daily</td>
</tr>
<tr>
<td>6 to &lt;8</td>
<td>2 mL (40 mg) twice daily</td>
</tr>
<tr>
<td>8 to &lt;11</td>
<td>3 mL (60 mg) twice daily</td>
</tr>
<tr>
<td>11 to &lt;14</td>
<td>4 mL (80 mg) twice daily</td>
</tr>
<tr>
<td>14 to &lt;20</td>
<td>5 mL (100 mg) twice daily</td>
</tr>
</tbody>
</table>

*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 5 mL (100 mg) twice daily.

**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.
- Avoid taking aluminum and/or magnesium containing antacids.
- Chewable tablets can be chewed, crushed (before administration), or 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 original package with desiccant to protect from moisture.
- Chewable tablets contain phenylalanine. Therefore, patients with phenylketonuria should make the necessary dietary adjustments.
- Oral suspension is provided with a kit that includes two mixing cups, two dosing syringes, and 60 foil packets. Detailed
Drug Interactions (see also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents and http://www.hiv-druginteractions.org/)

- **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, whereas inhibitors of UGT1A1 such as atazanavir may increase plasma concentrations of raltegravir (no dosing modifications are recommended when raltegravir is co-administered with tipranavir/ritonavir or atazanavir/ritonavir).
- In adults, an increased dose of raltegravir is recommended when co-administered with rifampin. In adults receiving rifampin, the recommended raltegravir dose is 800 mg twice daily. The appropriate dose adjustment is not known in children and is currently being studied in IMPAACT P1101.
- Efavirenz and etravirine may decrease raltegravir concentrations (no dosing modifications are recommended when raltegravir is co-administered with efavirenz or etravirine).
• Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions with raltegravir.

• Raltegravir plasma concentrations may be reduced when administered with antacids containing divalent metal cations such as magnesium hydroxide, aluminum hydroxide, or calcium carbonate:
  • Co-administration or administration of raltegravir within 6 hours of aluminum and/or magnesium hydroxide-containing antacids resulted in significantly reduced raltegravir plasma levels and is not recommended.
  • Calcium carbonate decreased raltegravir plasma concentrations to a lesser extent, thus no dose adjustment is recommended with calcium-containing antacids.

**Major Toxicities**

• *More common:* Nausea, headache, dizziness, diarrhea, fatigue, itching, and insomnia.

• *Less common:* Abdominal pain, vomiting. Patients with chronic active hepatitis B and/or hepatitis C are more likely to experience worsening 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. Myopathy and rhabdomyolysis: Use raltegravir with caution in patients receiving medications associated with these toxicities. Anxiety, depression, and paranoia especially in those with prior history. Rash including Stevens-Johnson syndrome, hypersensitivity reaction, and toxic epidermal necrolysis have been reported. Thrombocytopenia. Cerebellar ataxia. Hepatic failure (with and without associated hypersensitivity) in patients with underlying liver disease and/or concomitant medications.

**Resistance**


**Pediatric Use**

**Approval**

Raltegravir is an integrase strand transfer inhibitor indicated in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection for use in infants and children aged ≥4 weeks and weighing ≥3 kg. Current pediatric Food and Drug Administration approval and dosing recommendations are based upon evaluations in 122 patients aged ≥4 weeks to 18 years enrolled in IMPAACT P1066.1

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

**Efficacy in Clinical Trials (Adults and Children):**

• Raltegravir has been evaluated in three large randomized clinical trials in adults, 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. However, with longer follow-up of 4 and 5 years, more patients discontinued efavirenz 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 DRV/r; all regimens had equivalent virologic efficacy but raltegravir had better tolerability.6

• Raltegravir has been studied in infants, children and adolescents in an open-label trial, IMPAACT P1066, to evaluate pharmacokinetic (PK), safety, tolerability, and efficacy. In 96 children and adolescents aged 2 through 18 years, who were mostly treatment-experienced, 79.1% of the patients achieved a favorable viral load response (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 P1066 and received treatment with raltegravir oral suspension. At Weeks 24 and 48, 61% of the infants (14 of 23 infants) had an HIV viral load <400 copies/mL.7,9

Efficacy and Pharmacokinetics of Once-Daily Dosing (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 \( C_{\text{trough}} \) 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 \( C_{\text{trough}} \) concentrations suggests that maintaining raltegravir trough plasma concentrations above 45 nM is important for efficacy.10,11

Higher once-daily doses of raltegravir may be as effective as 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either 1200 mg of once daily (two, 600 mg tablets) versus 400 mg twice daily plus tenofovir disoproxil fumarate plus emtricitabine. After 48 weeks, 88.9% on the once-daily dose versus 88.1% twice-daily reached viral loads <40 copies. There was no difference in discontinuation rates due to side effects.12

Efficacy and Pharmacokinetics (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.8,9

Table A: Summary of P1066 Cohorts and Participation8,9

<table>
<thead>
<tr>
<th>Age (years)</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 P1066 PK Results by Cohort8,9

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Cohort</th>
<th>Formulation</th>
<th>Intensive PK</th>
<th>Mean Dose ( \text{mg/kg} )</th>
<th>( \text{GM (CV%)}^a ) ( \text{AUC}_{0-12h} ) ( \text{µMxh} )</th>
<th>( \text{GM (CV%)}^b ) ( C_{12h} ) ( \text{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>

\(^a\) PK targets for Cohorts I-III: \( \text{AUC}_{0-12h} \) 14-25 \( \text{µMxh} \); \( C_{12h} \) \( \text{nM} \) ≥33 \( \text{nM} \)

\(^b\) PK targets for Cohorts IV-V: \( \text{AUC}_{0-12h} \) 14-45 \( \text{µMxh} \); \( C_{12h} \) \( \text{nM} \) ≥75 \( \text{nM} \)

Key to Acronyms: AUC = area under the surve; GM = geometric mean; PK = pharmacokinetic
Children Aged 2 to 18 Years

IMPAACT P1066 is a Phase I/II open-label multicenter study to evaluate the PK profile, safety, tolerability, and efficacy of various formulations of raltegravir in antiretroviral treatment (ART)-experienced children and adolescents with HIV aged 2 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 at least 25 kg) or the chewable tablet formulation at a dose of 6 mg/kg twice daily (aged 2 to <12 years). In IMPAACT P1066, the initial dose-finding stage included intensive PK evaluation in various age cohorts (Cohort I: aged 12 to <19 years; Cohort II: 6 to <12 years, Cohort III: 2 to <6 years). Dose selection was based on achieving target PK parameters similar to those seen in adults: PK targets were geometric mean (GM) area under the curve (AUC0-12h) of 14–25 µMxh and GM 12-hour concentration (C12h) >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 subjects 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 subjects completed 48 weeks of treatment with 79% achieving HIV RNA <400 copies/mL and 57% achieving HIV RNA <50 copies/mL, with a mean CD4 T lymphocyte (CD4) cell count (percent [%]) increase of 156 cells/µL (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 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 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 with HIV and multidrug-resistant virus in the HIV Spanish Pediatric Cohort (CoRISe), good virologic response and improved CD4 counts were observed 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/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 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 infection, and 69% had baseline plasma HIV-1 RNA exceeding 100,000 copies/mL. PK targets for Cohorts IV and V were modified to GM AUC0-12h of 14 to 45 µMxh and GM 12-hour concentration (C12h) ≥75 nM (33.3 ng/mL). These targets were modified so that greater than 90% of patients would be predicted to have C12h above the 45 nM threshold. By week 48, 2 subjects experienced AEs thought to be related to study drug: 1 patient with a serious erythematous rash that resulted in permanent discontinuation of raltegravir, and 1 patient with immune reconstitution inflammatory syndrome. Virologic success defined as ≥1 log10 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 [%]) increase of 527.6 cells/mm³ (7.3%) There were 4 subjects in Cohort IV with virologic failure by week 48 and 1 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

There are limited data on the safety and dosing of raltegravir in 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 it is likely that 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 I, multicenter trial enrolling full-term neonates exposed to HIV at high risk of acquiring HIV-1-infection, with or without in utero raltegravir exposure. Study design included 2 cohorts; Cohort 1 infants received 2 single raltegravir doses 1 week apart and Cohort 2 infants received daily raltegravir dosing for 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 daily raltegravir dosing regimen for evaluation in raltegravir-naive infants enrolled in Cohort 2. 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:

**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></td>
<td>Geometric Mean (CV)</td>
<td>Target</td>
</tr>
<tr>
<td><strong>AUC (mg*h/L)</strong></td>
<td>38.2 (38.4%)</td>
<td>Above: 11 Met: 13 Below: 0</td>
</tr>
<tr>
<td><strong>Trough (ng/mL)</strong></td>
<td>948 (64.2%)</td>
<td>Above: 25 Below: 0</td>
</tr>
<tr>
<td><strong>C_{max} (ng/mL)</strong></td>
<td>2,350 (35.0%)</td>
<td>Above: 0 Below: 25</td>
</tr>
<tr>
<td><strong>T_{max} (ng/mL)</strong></td>
<td>5.4 (57.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>T_{1/2} (hrs)</strong></td>
<td>15.8 (174.8%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**PK Targets:** AUC_{24}, 12–40 mg*h/L; AUC_{12}, 6–20 mg*h/L

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

**Key to Acronyms:** AUC = area under the curve; C_{max} = maximum concentration; PK = pharmacokinetic

Daily raltegravir was safe and well tolerated during the first 6 weeks of life. All GM protocol exposure targets were met. In some infants AUC_{24} 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.

**Formulations**

The PK of raltegravir was compared in adult patients with HIV receiving 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 palatability was rated as poor. In adult volunteers, the PK of raltegravir 800 mg taken once daily by chewing was compared to 2 doses of 400 mg 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. 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 film-coated tablet based on a comparative study in healthy adult volunteers. Interpatient and intrapatient variability for PK parameters of raltegravir are considerable, especially with the film-coated tablets. Because of the differences in the bioavailability of the film-coated tablets and each of the other formulations, the dosing recommendations for the film-coated tablets are different and not interchangeable with the chewable tablets or oral granules for suspension.

Palatability was evaluated as part of 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.

References


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