Raltegravir (RAL, Isentress)

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Formulations

Tablet: 400 mg (film-coated poloxamer tablet)

High-Dose (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 a final concentration of 10 mg/mL

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

For additional information, see Drugs@FDA or DailyMed.

Dosing Recommendations

Note: No dosing information is available for preterm infants or infants weighing <2 kg at birth. See Table 13 in Antiretroviral Management of Newborns With Perinatal HIV Exposure or HIV Infection for information about using raltegravir (RAL) for the prevention of perinatal HIV transmission.

Neonate **(Weighing ≥2 kg)** Dose[a,b]

Raltegravir Oral Suspension Dosing Table for Full-Term Neonates **From Birth to Age 4 Weeks**

Neonates Aged ≥37 Weeks and Weighing ≥2 kg

Weight	Volume (Dose) of Suspension[b]
Birth to 1 **Week** of Age: Once-Daily Dosing	Approximately 1.5 **mg/kg** per dose
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
1–**4 Weeks** of Age: Twice-Daily Dosing	Approximately 3 **mg/kg** per dose
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

[a] RAL is metabolized by uridine diphosphate glucuronyl transferase (UGT) 1A1, and enzyme activity is low at birth; enzyme activity increases rapidly during the next 4–6 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

- RAL can be given without regard to food.
- Coadministration or staggered administration of aluminum-containing and magnesium-containing antacids **is not recommended** with any RAL formulations.
- Significant drug interactions are more likely to occur when the RAL HD formulation is used once daily. **The following drugs should not be coadministered with once-daily RAL HD dosing:** calcium carbonate antacids, 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

[b] For neonates, most of the prepared oral suspension will be discarded. The volume for the required dose is much smaller than the 10 mL suspension that is prepared.

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

Infant >4 W**eeks of** Age and Child **(Weighing ≥3 kg to <20 kg)** Dose

- For children weighing 3–20 kg, either oral suspension or chewable tablets can be used.

Raltegravir Oral Suspension Dosing Table for Patients Aged **>4 Weeks**[a]

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

Weight	Twice-Daily Volume (Dose) of Suspension[b]
3 kg to <4 kg	2.5 mL (25 mg) twice daily
4 kg to <6 kg	3 mL (30 mg) twice daily
6 kg to <8 kg	4 mL (40 mg) twice daily
8 kg to <10 kg	6 mL (60 mg) twice daily
10 kg to <14 kg	8 mL (80 mg) twice daily
14 kg to <20 kg	10 mL (100 mg) twice daily

[a] The weight-based dose recommendation for the oral suspension is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

[b] For neonates, most of the prepared oral suspension will be discarded, because the volume for the required dose is much smaller than 10 mL.

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

Children Weighing ≥3 kg

- Weighing <25 kg
  - Chewable tablets twice daily. See the table below for chewable tablet doses.
- Weighing ≥25 kg
  - RAL 400-mg, film-coated tablets twice daily **or** chewable tablets twice daily. See the table below for chewable tablet doses.

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.

- The chewable tablets should be stored in the original package with a desiccant to protect them from moisture.
- **Instructions for preparing and administering the chewable tablet as a crushed tablet are as follows:** Place the tablet(s) in a small, clean cup. For each tablet, add a teaspoon (~5 mL) of liquid (e.g., water, juice, or breast milk). Within 2 minutes, the tablet(s) will absorb the liquid and fall apart. Using a spoon, crush any remaining pieces of the tablet(s). Immediately administer the entire dose orally. If any portion of the dose is left in the cup, add another teaspoon (~5 mL) of liquid, swirl, and administer immediately.
- The chewable tablets contain phenylalanine, a component of aspartame. Phenylalanine can be harmful to patients with phenylketonuria, and the necessary dietary adjustments should be made in consultation with a metabolic specialist.
- The oral suspension comes in a kit that includes instructions for use, mixing cups, oral dosing syringes, and 60 foil packets. Detailed instructions for preparation are provided in the Instructions for Use document.[1] Each single-use foil packet contains 100 mg of RAL, which will be suspended in 10 mL of water for a final concentration of RAL 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. For neonates, most of the prepared oral suspension will be discarded, because the volume for the required dose is much smaller than 10 mL.

Metabolism/Elimination

- UGT1A1-mediated glucuronidation

Raltegravir Dosing in Patients With Hepatic Impairment

- No dose adjustment is necessary for patients with mild-to-moderate hepatic insufficiency who are receiving RAL twice daily.

Children and Adolescents Weighing ≥40 kg

- Two RAL 600-mg HD tablets (1,200 mg) once daily
- This dose is for antiretroviral therapy–naive or virologically suppressed patients who are on an initial dose of RAL 400 mg twice daily.

Chewable Tablet Dosing Table[a]

Note: The maximum dose of chewable tablets is RAL 300 mg twice daily.

Weight	Twice-Daily Dose	Number of Chewable Tablets
3 kg to <6 kg	RAL 25 mg	1 tablet (25 mg)
6 kg to <10 kg	RAL 50 mg	2 tablets (25 mg)
10 kg to <14 kg	RAL 75 mg	3 tablets (25 mg)
14 kg to <20 kg	RAL 100 mg	1 tablet (100 mg)
20 kg to <28 kg	RAL 150 mg	1½ tablets[b] (100 mg)
28 kg to <40 kg	RAL 200 mg	2 tablets (100 mg)
≥40 kg	RAL 300 mg	3 tablets (100 mg)

[a] The weight-based dose recommendation for the chewable tablet is based on a dose of approximately RAL 6 mg/kg per dose twice daily.

[b] The RAL 100-mg chewable tablet can be divided into equal halves.

- No studies have been conducted on the use of RAL HD in patients with hepatic impairment. Therefore, administering RAL HD is not recommended in patients with hepatic impairment.
- The effect of severe hepatic impairment on RAL 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.

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker.

- *Metabolism:* The major route of raltegravir (RAL) elimination is mediated through glucuronidation by uridine diphosphate glucuronyl transferase (UGT) 1A1.
- Coadministering RAL with inducers of UGT1A1—such as rifampin and tipranavir—may result in reduced plasma concentrations of RAL. Inhibitors of UGT1A1—such as atazanavir (ATV)—may increase plasma concentrations of RAL. No dosing modifications are recommended when RAL is coadministered with atazanavir/ritonavir (ATV/r) or tipranavir/ritonavir (TPV/r). However, RAL high-dose (HD) tablets **should not be coadministered** with TPV/r.
- In adults, an increased dose of RAL is recommended when it is coadministered with rifampin. For adults receiving rifampin, the recommended RAL dose is 800 mg twice daily. **Do not coadminister** rifampin with once-daily RAL HD tablets. In children aged 4 weeks to <12 years who had tuberculosis (TB)/HIV coinfection and were taking rifampin, RAL 12 mg/kg per dose twice daily of the chewable tablet formulation safely achieved pharmacokinetic (PK) targets.[2,3] In a single case report of a 6-month-old infant receiving RAL oral granules for suspension and

rifampicin for TB prophylaxis, 3 to 4 times the currently recommended dose of 12 mg/kg twice daily was needed[4] to achieve target trough concentrations (C_{trough}) >0.022 mg/L.

- Aluminum-containing antacids and magnesium-containing antacids may reduce RAL plasma concentrations and **should not be coadministered** with RAL.
- Significant drug interactions may be more likely to occur with RAL HD once daily. C_{trough} in adults is approximately 30% lower with RAL HD 1,200 mg once daily than with RAL 400 mg twice daily. A lower C_{trough} increases the potential for clinically significant drug interactions with interfering drugs that decrease RAL exposure and further lower C_{trough}. In addition to aluminum-containing and magnesium-containing antacids, the following drugs **should not be coadministered** with the RAL HD formulation: calcium carbonate antacids, rifampin, TPV/r, and etravirine. The impact of other strong inducers of drug-metabolizing enzymes on RAL is unknown; coadministration with phenytoin, phenobarbital, and carbamazepine **is not recommended**.
- Before administering RAL, clinicians should carefully review a patient's medication profile for potential drug interactions with RAL.

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 (AEs) grade from baseline for laboratory abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin than patients who are not coinfected.
- *Rare:* Moderate-to-severe increase in creatine phosphokinase levels. Use RAL with caution in patients who are receiving medications that are associated with myopathy and rhabdomyolysis. Anxiety, depression, and paranoia, especially in those with a history of these conditions. 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 maintains a list of updated HIV resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

RAL is an integrase strand transfer inhibitor that is approved by the U.S. Food and Drug Administration (FDA) for use in combination with other antiretroviral (ARV) drugs for the treatment of HIV in pediatric patients weighing ≥2 kg. The current pediatric FDA approval and dose recommendations are based on evaluations of 122 patients aged ≥4 weeks to 18 years who participated in IMPAACT P1066 and 42 full-term neonates who were treated for ≤6 weeks starting from birth and followed for a total of 24 weeks during IMPAACT P1110.[5]

The FDA has approved RAL HD, which allows once-daily dosing, for use in children and adolescents weighing ≥40 kg.

Efficacy in Clinical Trials

RAL has been evaluated in adults in three large, randomized clinical trials: STARTMRK, SPRING-2, and AIDS Clinical Trials Group (ACTG) A5257. STARTMRK compared the safety and efficacy of a RAL-containing regimen and an efavirenz (EFV)-containing regimen. At 48 weeks, RAL was noninferior to EFV. However, more patients discontinued EFV during the longer follow-up periods of 4 and 5 years, and RAL was found to be virologically and immunologically superior to EFV.[6-8] Results from the SPRING-2 study in treatment-naive adults showed that RAL and dolutegravir (DTG) were equally effective and had similar safety profiles.[9] ACTG A5257 compared RAL to ATV/r and darunavir/ritonavir; all regimens had equivalent virologic efficacy, but RAL had better tolerability.[10] The ONCEMRK study compared RAL 1,200 mg once daily (taken as two 600-mg RAL HD tablets) to RAL 400 mg twice daily in treatment-naive adults (see the results for the ONCEMRK study in the following section). Once-daily dosing of RAL 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 RAL regimen.

RAL 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 to 18 years who were mostly antiretroviral therapy (ART) experienced, 79.1% of the patients achieved a favorable viral load response (i.e., viral loads <400 copies/mL or ≥1 $\log_{10}$ decline in viral load) while receiving the currently recommended dose of RAL. Infants and toddlers aged ≥4 weeks to <2 years also were enrolled in IMPAACT P1066 and received treatment with RAL oral suspension. At Weeks 24 and 48, 61% of the participants (14 of 23 infants and toddlers) had HIV viral loads[11-13] <400 copies/mL.

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

RAL PKs exhibit considerable intrasubject and intersubject variability.[14,15] 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 RAL 800 mg once daily or RAL 400 mg twice daily. After 48 weeks of treatment, the percent of patients who achieved HIV RNA viral loads <50 copies/mL was 83% in the once-daily group, compared with 89% in the twice-daily group. Patients in the once-daily arm with C_{trough} concentrations <45 nM (20 ng/mL) were at greater risk of experiencing treatment failure.[14,15] Overall drug exposures were similar in both groups, but the association between higher risk of treatment failure and lower C_{trough} concentrations suggests that maintaining RAL trough plasma concentrations >45 nM (20 ng/mL) is important for efficacy.[14,15]

Once-daily dosing with RAL 1,200 mg was found to be as effective as dosing with RAL 400 mg twice daily. In the ONCEMRK study, 797 treatment-naive adults were randomized to receive either RAL 1,200 mg once daily (taken as two 600-mg tablets) or RAL 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/mL. Discontinuation rates due to AEs were not different between the two groups.[16] In May 2017, once-daily dosing of RAL 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 RAL 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 RAL HD tablets predict that this

dosing schedule will produce drug exposures similar to those observed in adult patients during ONCEMRK.[5,17]

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

Although modeling and simulations for pediatric patients indicate that PK targets are met using the once-daily RAL 1,200-mg dose, no clinical data exist on the use of this dose in children weighing <50 kg. Six children in IMPAACT P1066 had drug exposures that were similar to those observed in ONCEMRK, but all six children weighed >50 kg. Dose-related central nervous system toxicities—such as insomnia or hyperactivity—may occur in children who are exposed to very high concentrations of RAL.[5]

Efficacy and Pharmacokinetics in Children

IMPAACT P1066 evaluated the PKs, safety, and efficacy of RAL in treatment-experienced children aged 4 weeks to 18 years. A summary of RAL steady-state PK parameters, following administration of the recommended twice-daily doses (approximately 6 mg/kg twice daily), can be found in Table A below.[12,13]

Table A. Raltegravir Steady-State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Twice-Daily Doses: IMPAACT P1066

Body Weight	Formulation	Dose	N[a]	Geometric Mean (% CV[b]) $AUC_{0\text{-}12h}$ (μM·h)[c,d]	Geometric Mean (% CV[b]) C_{12h} (nM)[c,d]
≥25 kg	Film-coated tablet	400 mg twice daily	18	14.1 (121%)	233 (157%)
≥25 kg	Chewable tablet	Weight-based dosing[e]	9	22.1 (36%)	113 (80%)
11 **kg to <25 kg**	Chewable tablet	Weight-based dosing[e]	13	18.6 (68%)	82 (123%)
3 **kg to <20 kg**	Oral suspension	Weight-based dosing[e]	19	24.5 (43%)	113 (69%)

[a] Number of patients with intensive PK results at the final recommended dose

[b] Geometric coefficient of variation

[c] Pharmacokinetic targets for film-coated tablets and chewable tablets: $AUC_{0–12h}$ 14–25 μM·h (6–11 mg·h/L); C_{12h} nM ≥33 nM (14.7 ng/mL)

[d] Pharmacokinetic targets for oral suspension: $AUC_{0–12h}$ 14–45 μM·h (6–20 mg·h/L); C_{12h} nM ≥75 nM (33.3 ng/mL)

[e] To approximate 6 mg/kg twice daily

Key: AUC = area under the curve; $AUC_{0–12h}$ = AUC from time zero to 12 hours after drug administration; C_{12h} = concentration at 12 hours (trough); CV = coefficient of variation

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 RAL in ART-experienced children and adolescents with HIV aged 2 to 18 years. RAL was administered in combination with an optimized background ARV regimen.[13,18] Subjects received either the RAL 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 RAL 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 1: 12 years to <19 years; Cohort 2: 6 years to <12 years; Cohort 3: 2 years to <6 years). Doses were selected with the aim of achieving target PK parameters that were similar to those seen in adults: PK targets were a geometric mean (GM) $AUC_{0–12h}$ of 14 µM·h to 25 µM·h and a GM 12-hour concentration (C_{12h}) >33 nM. Additional participants were then enrolled in each age cohort to evaluate the long-term efficacy, tolerability, and safety of RAL.

A total of 126 treatment-experienced participants were enrolled, with 96 participants receiving the final recommended dose of RAL. 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 the Centers for Disease Control and Prevention Category B or C classification of HIV infection. 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) count increase[13] of 156 cells/mm^3 (4.6%). Among 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 RAL-associated mutations were detected in 12 out of 34 of those patients. The frequency, type, and severity of 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. Patients with AEs that were considered to be drug related included one patient with Grade 3 psychomotor hyperactivity, abnormal behavior, and insomnia, as well as 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.[13] Overall, RAL was well tolerated when 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.[19]

Children Aged ≥4 Weeks to <2 Years

IMPAACT P1066 studied 26 infants and toddlers aged 4 weeks to <2 years who were administered the granules for RAL oral suspension in combination with an optimized background ARV 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 Cohort IV (6 months to <2 years) and Cohort V (4 weeks to <6 months) were modified to a GM $AUC_{0–12h}$ of 14 µM·h to 45 µM·h and a GM C_{12h} ≥75 nM (33.3 ng/mL). These targets were modified so that an estimated >90% of patients would have C_{12h} above the 45 nM threshold. By Week 48, two subjects experienced AEs that were thought to be related to the study drug: one patient experienced a serious erythematous rash that resulted in permanent discontinuation of RAL, and one patient experienced 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 >87% of participants. At 48 weeks of

follow up, 45.5% of subjects had HIV RNA <50 copies/mL and mean CD4 count increases of 527.6 cells/mm^3 (7.3%). Four subjects in Cohort 4 experienced virologic failure by Week 48, and one participant had a RAL-associated resistance mutation. Overall, the granules for oral suspension, at a dose of approximately RAL 6 mg/kg twice daily, were well tolerated and had good efficacy.[12]

Long-Term Follow Up in Children

The IMPAACT P1066 study team reported results regarding the safety and efficacy of different RAL formulations at 240 weeks in children enrolled in this multicenter trial.[20] 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. RAL was added to an optimized ARV regimen in all participants. RAL was well tolerated, and few serious clinical or laboratory safety events were noted during the study.[20]

The proportion of participants who achieved virologic success at 240 weeks varied by the RAL formulation used: 19 of 43 children (44.2%) who received RAL 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. RAL 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, whereas older children with an extensive treatment history are more likely to experience treatment failure and develop resistance to RAL. Poor adherence among adolescents may have contributed to the lower efficacy observed in older children who received the RAL 400-mg tablets.[20]

Neonates Aged <4 Weeks

RAL is metabolized by UGT1A1, the same enzyme that is responsible for the elimination of bilirubin. UGT enzyme activity is low at birth, and RAL elimination is prolonged in neonates. Washout PKs of RAL in neonates born to pregnant women with HIV were studied in IMPAACT P1097.[21] The neonatal plasma half-life of RAL was highly variable, ranging from 9.3 to 184 hours. This suggests that neonatal development may impact UGT1A1 enzyme activity, redistribution, and/or enterohepatic recirculation of RAL. RAL competes with unconjugated bilirubin for albumin binding sites. When RAL plasma concentrations are extremely high, unconjugated bilirubin may be displaced from albumin by RAL and cross the blood–brain barrier, leading to bilirubin-induced neurologic dysfunction. The effect of RAL on neonatal bilirubin binding is unlikely to be clinically significant, unless concentrations that are 50-fold to 100-fold higher than typical peak concentrations are reached (approximately 5,000 ng/mL).[22]

IMPAACT P1110 was a Phase 1, multicenter trial that enrolled full-term neonates with or without *in utero* RAL exposure at risk of acquiring HIV. RAL-exposed neonates were those whose mothers received RAL within 2 to 24 hours of delivery. For RAL-exposed neonates, the initial dose of RAL was delayed until 12 to 60 hours after delivery. The study design included two cohorts: Cohort 1 infants received two RAL doses that were administered 1 week apart, and Cohort 2 infants received daily RAL doses 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 RAL dosing regimen for evaluation in infants in Cohort 2: RAL 1.5 mg/kg daily, starting within 48 hours of life and continuing through Day 7; RAL 3 mg/kg twice daily on Days 8 to 28 of life; and RAL 6 mg/kg twice daily after 4 weeks of age.[23] Protocol exposure targets for each subject were

$AUC_{0–24hr}$ 12 mg·h/L to 40 mg·h/L, $AUC_{0–12hr}$ 6 mg·h/L to 20 mg·h/L, and C_{12h} or C_{24h} >33 ng/mL. Safety was assessed using clinical and laboratory evaluations.[21,24,25]

Twenty-six RAL-naive infants and 10 RAL-exposed infants were enrolled in Cohort 2; 25 RAL-naive infants and 10 RAL-exposed infants had evaluable PK results and safety data. Results for the RAL-naive infants and RAL-exposed infants who were enrolled in Cohort 2 are contained in Table B below.[25]

Table B. Raltegravir Pharmacokinetic Parameters for Raltegravir-Naive and Raltegravir-Exposed Neonates

PK Parameter	Initial Dose: **RAL 1.5 mg/kg** Once Daily RAL-Naive **(n = 25)**[d]	Initial Dose: **RAL 1.5 mg/kg** Once Daily RAL-Exposed **(n = 10)**	Days 15–18: **RAL 3.0 mg/kg** Twice Daily RAL-Naive **(n = 24)**[e]	Days 15–18: **RAL 3.0 mg/kg** Twice Daily RAL-Exposed **(n = 10)**[f]
	GM (CV%)	GM (CV%)	GM (CV%)	GM (CV%)
AUC_{0-24h} (mg·h/L)[a]	38.2 (42.0%)	42.9 (25.3%)	—	—
AUC_{0-12h} (mg·h/L)	—	—	14.3 (49.5%)	18.3 (62.8%)
C_{trough} (ng/mL)[b]	948 (84.0%)	946 (74.0%)	176 (162.1%)	274 (176.4%)
C_{max} (ng/mL)[c]	2,350 (36.5%)	2,565 (23.1%)	2,849 (47.5%)	3,667 (46.3%)
T_{max} (hours)	5.4 (71.5%)	3.8 (88.8%)	2.3 (77.1%)	1.9 (52.3%)
$T_{1/2}$ (hours)	15.8 (101.4%)	14.4 (69.5%)	2.5 (34.1%)	2.9 (20.7%)

[a] AUC targets: AUC_{0-24h} 12–40 mg·h/L and AUC_{0-12h} 6–20 mg·h/L.

[b] C_{trough} concentration >33 ng/mL. For initial dose, C_{last} collected at 24 hours was used. For Days 15–18, C_{12h} was estimated when the 12 hours post-dose sample was collected earlier than 12 hours after dosing (the protocol specified a sample collection time of 8–12 hours post dose).

[c] C_{max} <8,724 ng/mL

[d] AUC_{0-24h} could not be estimated for one infant.

[e] AUC_{0-12h} and C_{trough} could not be estimated for one infant with delayed absorption.

[f] AUC_{0-12h} and C_{max} could not be estimated for one infant with incomplete sample collection.

Key: AUC = area under the curve; AUC_{0-12h} = AUC from time zero to 12 hours after drug administration; AUC_{0-24h} = AUC from time zero to 24 hours after drug administration; C_{last} = last measurable plasma concentration; C_{max} = maximum concentration; C_{trough} = trough concentration; CV = coefficient of variation; GM = geometric mean; PK = pharmacokinetic; RAL = raltegravir; $T_{1/2}$ = half-life; T_{max} = time to reach maximum concentration

Daily RAL 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_{0-24h} following the initial dose was slightly above the target range, but this is considered acceptable given the rapid increase in RAL metabolism during the first week of life. The PK targets and the safety guidelines were met for both RAL-naive and RAL-exposed infants in Cohort 2 using the specified dosing regimen. No drug-related clinical AEs were observed. Three laboratory AEs were reported among the RAL-naive infants: Grade 4 transient neutropenia occurred in one infant who received a zidovudine-containing regimen; two bilirubin elevations (one Grade 1 and one Grade 2) were considered nonserious and did not require specific therapy.[5] Among the RAL-exposed infants, four infants exhibited 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 IMPAACT P1110 confirmed the PK modeling and simulation submitted for FDA approval and labeling. Neonates born to mothers who received RAL 2 to 24 hours prior to delivery

should have their first dose of RAL delayed until 24 to 48 hours after birth.[24,25] The timing of administration of the initial dose of RAL to infants born to patients receiving DTG- or bictegravir-containing regimens has not been studied. In a single case report of a neonate born to a mother receiving an intensified regimen of DTG 50 mg twice daily for viremia close to the time of delivery, prolonged neonatal DTG concentrations were observed.[26] These findings suggest that a similar delay in the first dose of RAL until 24 to 48 hours after birth may be indicated in neonates born to patients receiving an INSTI-containing oral regimen to avoid potential toxicity. Results of ongoing studies IMPAACT 2023 (DTG neonatal PK and safety study) and IMPAACT 2026 (washout PK in infants born to mothers receiving bictegravir) may provide PK data that can inform future recommendations.

The current RAL dosing regimen with two dose changes in the first month of life may be challenging for some families. To simplify medication teaching and minimize dosing changes, some experts increase to the 3 mg/kg twice-daily dose on Day 4 or 5 of life. Because many infants receiving RAL as part of presumptive HIV therapy will have a longer hospital stay following birth by cesarean section, this dosing change can generally be made at the time of hospital discharge.

RAL can be safely administered to full-term infants using the daily dosing regimen that was studied in IMPAACT P1110. This regimen **is not recommended** for use in preterm infants. RAL elimination kinetics in preterm and low-birth-weight neonates after maternal dosing was studied in IMPAACT P1097.[27] Sixteen mothers and their 18 low-birth-weight neonates (<2.5 kg) were enrolled. Median (range) RAL elimination half-life was 24.4 hours (10.1–83) hours (n = 17). A PK model incorporating slower clearance in preterm neonates demonstrated that a reduction in RAL dosing is required in this population.[27]

Two case reports of preterm infants who received RAL to prevent perinatal transmission have been published.[28,29] 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 RAL was done using real-time therapeutic drug monitoring in the neonatal intensive care unit.[28,29] Less-frequent dosing was required because RAL elimination was significantly delayed in these preterm infants. RAL PKs and safety must be studied in preterm infants before RAL can be safely used without real-time PK monitoring in this population.

Formulations

The PKs of RAL in adult patients with HIV who swallowed intact 400-mg tablets were compared with 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.[30] In adult volunteers, the PKs of RAL 800 mg taken once daily by chewing was compared with the PKs of two doses of RAL 400 mg taken every 12 hours by swallowing. Participants who took RAL by chewing had significantly higher drug exposure and reduced PK variability than those who swallowed whole tablets according to current recommendations.[31] According to the manufacturer, the film-coated tablets must be swallowed whole.

The RAL 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.[32] Compared with the RAL 400-mg tablet formulation, the RAL 600-mg tablet has higher relative bioavailability.[5,33] Interpatient and intrapatient variability for PK parameters of RAL are considerable, especially with the film-coated tablets.[5,34] Because of differences in the bioavailability of various formulations, the

dosing recommendations for each formulation differ, and the formulations **are not interchangeable.** When prescribing RAL, clinicians should refer to the appropriate dosing table for the chosen formulation. The use of RAL chewable tablets as dispersible tablets in children aged <2 years has been studied in IMPAACT P1101 for infants and toddlers with TB/HIV coinfection who received rifampin as part of their TB treatment. The use of RAL chewable tablets dispersed in water at a dose of RAL 12 mg/kg per dose twice daily safely achieved PK targets.[2,35] The RAL chewable tablets are now approved for use in infants and young children 4 weeks of age and older and weighing at least 2 kg.[36] An *in vitro* evaluation demonstrated that the chewable tablets are stable in various liquids, including water, apple juice, and breast milk.[36] The chewable tablets may be crushed and mixed with a small amount of liquid to facilitate administration (see Special Instructions above).

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.[12,13] The acceptability and feasibility of administering RAL granules for oral suspension in a low-resource setting has been studied in clinics in South Africa and Zimbabwe. With proper training by health care personnel, caregivers were able to prepare the suspension safely and accurately.[37,38]

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