

Selected Properties of Raltegravir

Other names	Isentress®, MK-0518
Manufacturer	MERCK & CO., INC.
Pharmacology/Mechanism of Action	<p>Raltegravir is a novel HIV-1 integrase strand transfer inhibitor. The bulk drug is a potassium salt of raltegravir with a molecular weight of 482.52.</p> <p>Raltegravir potently inhibits integrase catalyzed strand transfer, with an IC₅₀ of 10 nM, close to the limit of the sensitivity of the assay. Inhibition of integrase prevents the covalent insertion, or integration, of unintegrated linear HIV-1 DNA into the host cell genome preventing the formation of the HIV-1 provirus. Raltegravir is selective for strand transfer, having much reduced activity on either assembly or 3' end processing when analyzed in staged enzymatic assays.</p>
Activity	<ul style="list-style-type: none"> • HIV1: EC₉₅: 31 ± 20 nM (in vitro) • HIV 1 - diverse, primary clinical isolates including isolates resistant to reverse transcriptase inhibitors & protease inhibitors: EC₉₅: 6 to 50 nM (in vitro) • HIV 2: EC₉₅ value = 6 nM (in vitro)
Resistance - genotypic	<p>Resistance data are preliminary and limited. Raltegravir has a low genetic barrier (similar to the 1st generation NNRTI class).</p> <p>Resistance is associated with mutations at positions 148 (Q148H/K/R) or 155 (N155H) plus ≥ 1 additional substitution (i.e., L74M/R, E92Q, T97A, E138A/K, G140A/S, V151I, G163R, H183P, Y226D/F/H, S230R and D232N). Both of the integrase variants, Q148K and E138A/G140A/Q148K, engender a substantial loss of susceptibility to raltegravir.</p> <p>Another resistance pathway involves a mutation at position 143 (Y143C/H/R)</p>
Resistance - phenotypic	
Cross-Resistance	<p>There seems to be cross-resistance between raltegravir and elvitegravir. Viruses with integrase inhibitor resistance mutations remain fully sensitive to the effects of non-nucleoside reverse transcriptase inhibitors as well as nucleosides and protease inhibitors.</p>
Oral Bioavailability	<p>The absolute bioavailability of raltegravir has not been established.</p> <p>Based on a formulation comparison study in healthy adult volunteers, the chewable tablet has higher oral bioavailability than the film-coated tablet.</p> <p>The absorption of raltegravir, etravirine, emtricitabine, and tenofovir was not compromised when the drugs were crushed, dissolved in 60 mL warm water, and administered by gastrostomy tube to a 52 year old HIV-positive male with ulcerative esophagitis. [Sandkovsky et al. 2012]</p>

Effect of Food	<p><u>Film-coated tablets:</u> A single dose pharmacokinetic study in healthy subjects (n = 20) showed that a high fat meal affected the rate but not the extent of absorption of raltegravir. Data from Phase II trials suggest that the effect of food on C_{12hr} is not clinically important [Wenning et al. ICAAC 2007]. Raltegravir was administered without regard to food in Benchmrk-1 and Benchmrk-2 studies.</p> <p>In healthy volunteers who received raltegravir 400 mg BID for 10 days in conjunction with various meal types, a low-fat meal appeared to modestly decrease absorption with little effect on trough concentrations (C_{12h}), a moderate-fat meal had little to no effect, and a high-fat meal appeared to modestly increase absorption, although none of these effects appear clinically meaningful.[Brainard et al. J Clin Pharmacol 2010].</p> <p><u>Chewable tablets:</u> Administration of chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in C_{max} and 188% increase in C_{12hr} compared to administration in the fasted state. Administration of the chewable tablet with a high fat meal does not affect raltegravir pharmacokinetics to a clinically meaningful degree and the chewable tablet can be administered without regard to food.</p> <p>Raltegravir may be administered twice daily without regard to meals.</p>
Protein Binding	83% protein bound (over concentration range of 2 to 10 µM)
Vd	
Tmax	Raltegravir is rapidly absorbed with median T _{max} 3 hours in the fasted state.
serum T ½	Concentrations declined in a biphasic manner with initial phase t _½ ~1 hr and terminal phase t _½ ~9 hours.
Drug Concentrations	<p>Raltegravir displays dose proportional pharmacokinetics over the clinically relevant dose range (100 to 800 mg).</p> <p><u>Adults:</u> In a single dose pharmacokinetic study in healthy subjects (n = 20), AUC_{0-∞} & C_{max} of raltegravir were dose proportional for the dose range 100-1600 mg. Raltegravir C_{12h} increased proportionally from 100-800 mg, and slightly less than proportionally from 100-1600mg [Wenning et al. ICAAC 2007]. Considerable intersubject and intrasubject variability was observed in the kinetics.</p> <p>Subjects who received 400mg BID: AUC 14.3 uM•hr, C_{12hr} 142 nM. Gender, age, body mass index, race, and HIV status had no clinically meaningful effect on raltegravir pharmacokinetics. Similarly, in a study of 44 treatment-naïve African-American patients administered RAL 400 mg BID plus tenofovir/FTC, mean raltegravir AUC 5159 ng.hr/mL (CV 78%), C_{max} 1315 ng/mL (CV 109%), C_{12h} after 2nd dose was 166 ng/mL (CV</p>

94%); these results were comparable to historical controls, suggesting no influence of race on raltegravir pharmacokinetics.[Wohl et al. 2010]

The pharmacokinetics of single dose raltegravir was studied in subjects with generally **low UGT1A1 activity** (UGT1A1*28/*28 genotype) compared to subjects with normal activity (UGT1A1*1/*1 genotype). Raltegravir AUC ↑ 41%, C_{max} ↑ 40% and C_{min} ↑ 91% in individuals with the UGT1A1*28/*28 genotype relative to the UGT1A1*1/*1 genotype. However, these differences are not considered to be clinically important, and the T_{max} and t_{1/2} values were similar for both genotypes. No dose adjustment of raltegravir is required for individuals with the UGT1A1*28/*28 genotype.[Petry A et al. ICAAC 2008]

Simultaneous plasma and **cervicovaginal fluid (CVF)** samples were obtained in 7 HIV-negative women taking raltegravir for 7 days. Raltegravir was detectable in CVF 6 hours post-dose, T_{max} 12h, CVF t_{1/2} 17 hours (vs. plasma t_{1/2} 7 hours), with CVF:plasma AUC ratio of 64% on day 1 and 93% on day 7. Raltegravir CVF concentrations were C_{12h} 607 ng/mL, AUC 1677 ng.hr/mL.[Jones A et al. 10th IWCPHT 2009, #O_06]. In 6 HIV-positive women taking raltegravir 400 mg BID for at least 4 weeks, similar raltegravir CVF concentrations were observed.[Patterson et al. IAC 2010]

Raltegravir concentrations and HIV-1 RNA levels were measured in simultaneous **semen** and plasma samples from 10 treatment-experienced patients on 24 weeks of raltegravir-based therapy. In all samples, semen RNA was <100 copies/mL and plasma RNA was <50 copies/mL. Median raltegravir concentration was 345 (83-707) ng/mL in semen and 206 (106-986) ng/mL in plasma, yielding a median semen:plasma ratio of 1.42 (0.52-6.66).[Barau et al. AAC 2010].

Plasma and **intracellular raltegravir** concentrations after single dose raltegravir 400 mg were measured for 48 hours in healthy subjects. Intracellular raltegravir concentrations were 24% of plasma concentrations, and intracellular:plasma ratios were stable without significant time-related trends suggesting no intracellular accumulation.[Wang et al. ICAAC 2010]

Concentrations of raltegravir in gut-associated lymphoid tissue (GALT) were compared to blood plasma concentrations in healthy male volunteers who received raltegravir 400 mg BID for 7 days. After multiple doses, raltegravir AUCs in the terminal ileum, splenic flexure and rectal tissue were 84-fold, 679-fold and 239-fold higher than blood concentrations, respectively. The raltegravir accumulation ratio was 0.9 for terminal ileum, 8.4 for splenic flexure and 5.5 for rectal tissue. These data suggest that RAL may also have a role in PEP/PrEP and treatment of primary HIV infection.[Patterson et al. HIV PK 2012, #O_11]

Pediatrics:

	<p>Preliminary dose finding study suggest HIV infected adolescents (≥ 12 and < 19 yrs) receiving RAL 8mg/kg BID achieve systemic exposure similar to adults receiving 400mg BID. RAL well tolerated in this preliminary study.(Acosta et al. 2008)</p>
Minimum target trough concentrations (for wildtype virus)	<p>IC95 = 15 ng/mL</p> <p>In vitro simulations suggest that antiviral effect is consistent with AUC rather than trough [McSharry J et al. 10th IWCPHT 2009, #O_09].</p> <p>Based on data from two healthy volunteer studies, C_{2h} or AUC_{0-3h} may be used to reliably predict AUC_{0-12h}, which may be a better PK parameter for raltegravir TDM.[Burger et al. 2010]</p>
CSF (% of serum)	<p>In 18 HIV-positive patients, raltegravir concentrations were measured in matched CSF and plasma samples. Raltegravir was present in all CSF specimens with a median concentration of 13.9 ng/mL (IQR 8.9, 24.6). The median CSF-to-plasma ratio was 7.3% (IQR 2.2%, 17%). CSF concentrations correlated with plasma concentrations ($\rho = 0.47$, $p = 0.03$) but not with post-dose sampling time. Raltegravir concentrations in CSF exceeded the IC50 of wild-type HIV in all but 1 specimen by a median of 4.1-fold (IQR 2.6, 7.2).[Letendre S et al. ICAAC 2009]</p> <p>In 3 HIV-positive patients who started a raltegravir-based regimen and underwent lumbar punctures for clinical reasons, raltegravir CSF trough concentrations were above or very close to in-vitro 95% inhibitory concentration (IC95) (14.6 ng/ml).[Calcagno et al. 2010]</p> <p>In 27 HIV-positive patients on raltegravir who underwent lumbar punctures for clinical reasons, the median raltegravir CSF:plasma ratio was 0.25 (IQR 0.10-0.42). At the end of the dosing interval, patients on boosted PIs had higher CSF trough concentrations compared to those on other ARVs (difference not significant). Patients with altered BBB function had higher CSF:plasma ratios (0.57 vs. 0.18, $p=0.01$). In 4 patients on rifampin (3 on RAL 800 mg BID), CSF:plasma ratio was 0.31.[Calcagno et al. 2012]</p> <p>2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]</p>
Metabolism	<p>Raltegravir is not an inhibitor of cytochrome P450 enzymes, major UGTs, or P-glycoprotein and does not induce CYP3A. The major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation.</p>
Excretion	<p>Feces: 51% (only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile).</p> <p>Urine: 32% (raltegravir + raltegravir glucuronide)</p>

<p>Dosing – Adult</p>	<p>400 mg BID with or without food.</p> <p>Raltegravir film-coated tablets must be swallowed whole. Raltegravir chewable tablets may be chewed or swallowed whole.</p> <p>Because the formulations are not bioequivalent, do not substitute chewable tablets for the 400 mg film-coated tablet.</p>																		
<p>Dosing – Pediatric</p>	<p>12 years of age and older:</p> <ul style="list-style-type: none"> One 400 mg film-coated tablet orally, twice daily <p>6 to less than 12 years of age:</p> <ul style="list-style-type: none"> <i>If at least 25 kg in weight:</i> <ul style="list-style-type: none"> One 400 mg film-coated tablet orally, twice daily OR Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 <i>If <25 kg in weight:</i> <ul style="list-style-type: none"> Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 <p>2 to less than 6 years of age, at least 10 kg in weight:</p> <ul style="list-style-type: none"> Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified in Table 1 <p>Table 1. Dosing of raltegravir chewable tablets for pediatric patients 2 to <12 years of age:</p> <table border="1" data-bbox="669 1037 1427 1234"> <thead> <tr> <th>Weight (kg)</th> <th>Dose</th> <th># of Chewable Tablets</th> </tr> </thead> <tbody> <tr> <td>10 to <14</td> <td>75 mg BID</td> <td>3 x 25 mg BID</td> </tr> <tr> <td>14 to <20</td> <td>100 mg BID</td> <td>1 x 100 mg BID</td> </tr> <tr> <td>20 to <28</td> <td>150 mg BID</td> <td>1.5* x 100 mg BID</td> </tr> <tr> <td>28 to <40</td> <td>200 mg BID</td> <td>2 x 100 mg BID</td> </tr> <tr> <td>At least 40</td> <td>300 mg BID</td> <td>3 x 100 mg BID</td> </tr> </tbody> </table> <p>The weight-based dosing recommendation for the chewable tablet is based on approximately 6 mg/kg/dose twice daily.</p> <p>The 100 mg chewable tablet can be divided into equal halves.</p> <p>The safety and effectiveness of raltegravir in pediatric patients less than 2 years of age have not been established.</p>	Weight (kg)	Dose	# of Chewable Tablets	10 to <14	75 mg BID	3 x 25 mg BID	14 to <20	100 mg BID	1 x 100 mg BID	20 to <28	150 mg BID	1.5* x 100 mg BID	28 to <40	200 mg BID	2 x 100 mg BID	At least 40	300 mg BID	3 x 100 mg BID
Weight (kg)	Dose	# of Chewable Tablets																	
10 to <14	75 mg BID	3 x 25 mg BID																	
14 to <20	100 mg BID	1 x 100 mg BID																	
20 to <28	150 mg BID	1.5* x 100 mg BID																	
28 to <40	200 mg BID	2 x 100 mg BID																	
At least 40	300 mg BID	3 x 100 mg BID																	

Summary of Raltegravir Dosing in Pediatrics (studies)			
Age		RAL Dose	Ref
2-5 yo		6 mg/kg BID, max 300 mg BID (OCT)	Nachman et al. CROI 2011, #715
6-11 yo	<25 kg	6 mg/kg BID, max 300 mg BID (OCT)	Nachman et al. CROI 2010, #161LB
	≥25 kg	400 mg BID (AF)	Nachman et al. CROI 2010, #873
12-18		400 mg BID (AF)	ICAAC 2008; Wiznia et al. CROI 2009; Frenkel et al. ICAAC 2009.

OCT = oral chewable tablet; AF = adult formulation (400 mg tab)

Special instructions for pediatric patients

Raltegravir film-coated tablets must be swallowed whole. Raltegravir chewable tablets may be chewed or swallowed whole. The 100 mg chewable tablet can be divided into equal halves.

Because the formulations are not bioequivalent, **do not substitute chewable tablets for the 400 mg film-coated tablet.**

Raltegravir chewable tablets contain phenylalanine, a component of aspartame.

- each 25 mg chewable tablet contains approximately 0.05 mg phenylalanine.
- each 100 mg chewable tablet contains approximately 0.10 mg phenylalanine.

Phenylalanine can be harmful to patients with **phenylketonuria**.

<p>Adjust in Liver Dysfunction</p>	<p>Moderate hepatic insufficiency (Child Pugh score 7 to 9) has no clinically meaningful effect on raltegravir pharmacokinetics (14% ↓ AUC, 37% ↓ Cmax and 26% ↑ C12 vs. healthy matched control subjects).(Iwamoto et al. 2009)</p> <p>No dosage adjustment is necessary for patients with mild to moderate hepatic impairment.</p> <p>The kinetics of raltegravir and darunavir were studied in five HIV-HCV co-infected patients with moderate to severe hepatic impairment (2 with chronic active hepatitis, 3 with cirrhosis). Plasma Ctrough samples were collected at days 14 and 30 after this new regimen was initiated; 24 matched HIV-1 patients with normal liver function treated with raltegravir and darunavir were used as a control group. Mean raltegravir Ctrough was 637 vs. 221 ng/mL in controls. Patients with cirrhosis had higher mean raltegravir Ctrough than patients with active non-cirrhotic hepatitis (665 vs. 581 ng/mL). No differences in viral/immunologic outcome or safety parameters were found between cirrhotic and non-cirrhotic patients. Use raltegravir with caution in patients with moderate to severe liver impairment because of the risk of additive toxicity.(Tommasi et al. 2010)</p> <p>The kinetics of multi-dose raltegravir 400 mg BID were studied in HIV/HCV coinfecting patients with Child-Pugh grade C hepatic cirrhosis on stable cART (LPVr, FPVr or DRVr) with controlled viremia (<50 copies/ml) for at least 6 months. Compared to patients with no histologic liver damage, patients with advanced cirrhosis (Child-Pugh C) showed higher RAL exposure, with mean 72% ↑ AUC and 6.5-fold ↑ C12. No safety issues were identified and RAL was well tolerated by all patients.(Hernandez-Novoa et al. CROI 2012).</p>
<p>Adjust in Renal Failure/Dialysis</p>	<p>Severe renal insufficiency (Clcr<30 mL/min) has no clinically meaningful effect on pharmacokinetics of 400 mg raltegravir (15% ↓ AUC, 32% ↓ Cmax and 28% ↑ C12 vs. healthy matched control subjects). Raltegravir half-life (↑ t1/2α ~24%, ↑ t1/2β ~51%) was slightly prolonged in renal insufficiency, but these changes were not clinically important. No serious adverse events were observed.(Iwamoto et al. 2009) No dosage adjustment is necessary in patients with renal insufficiency.</p> <p>Antiretroviral pharmacokinetics were studied in a 49-year old HIV-positive man virologically suppressed on darunavir/ritonavir 600/100 mg twice daily, etravirine 200 mg twice daily and raltegravir 400 mg twice daily while undergoing hemodialysis three times weekly. The morning dose of the antiretrovirals was taken after completion of the 4-hour morning hemodialysis session. After dialysis, darunavir, etravirine, raltegravir and ritonavir concentrations were decreased by 57%, 29%, 82% and 60%, respectively compared to predialysis levels. A supplemental dose of 600 mg darunavir administered prior to the hemodialysis session was successful in restoring darunavir concentrations approximately equal to expected levels, while administration of a supplemental dose of raltegravir 400 mg was not, likely due to wide intra- and inter-patient variability. Dose</p>

	<p>supplementation of etravirine was not deemed necessary given the relatively low amount removed during hemodialysis. After 1 year of therapy, the patient maintained viral suppression.[Giguere et al. 2009]</p> <p>Pre- and post-dialysis raltegravir concentrations were measured in 2 ESRD HIV-infected patients. The hemodialysis extraction ratio and raltegravir hemodialysis clearance were 5.5% and 9.1 ml/min in patient 1, and 9.5% and 19.1 ml/min in patient 2. These results suggest minimal raltegravir removal by hemodialysis with no specific raltegravir dosage adjustments required.[Molto et al. 2010]</p> <p>An HIV-positive patient on continuous venovenous hemodiafiltration (CVVHDF) received raltegravir 400 mg BID, darunavir 600/100 mg BID, zidovudine 300 mg BID and 3TC 50 mg q24h in suspension via gastric port and simultaneous enteral feeding via the duodenal port of a double-lumen nasogastrroduodenal tube. Pharmacokinetic sampling and analysis indicated that darunavir and raltegravir were removed by CVVHDF with approximately the same clearance as provided by a normally functioning kidney. Absorption of both drugs after suspension and application via the gastric port with continued administration of feed via the duodenal port of the double-lumen tube was good. As such, dose adjustments are not required for patients receiving darunavir and/or raltegravir while undergoing CVVHDF and that absorption of darunavir and raltegravir is not significantly affected by postpyloric enteral feeding.[Taegtmeier et al. 2011]</p>
<p>Toxicity</p>	<p>Single dose PK study in healthy subjects (n = 20), single doses of raltegravir up to 1600 mg were generally well tolerated [Wenning et al. ICAAC 2007].</p> <p>In the Benchmrk studies, the rate of side effects was similar for the raltegravir and placebo treatment groups. The most common ADRs (>10%) in these studies were: nausea, headache, diarrhea and pyrexia. CK elevations with myopathy and rhabdomyolysis have been reported. The relationship of Raltegravir to these events is not known. No lipid abnormalities have been reported so far with raltegravir.</p> <p>Severe, potentially life-threatening, and fatal skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Hypersensitivity reactions have also been reported, characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure. Discontinue raltegravir and other suspect agents immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated.</p>

Overdose	<ul style="list-style-type: none"> • Doses as high as 1600-mg single dose and 800-mg twice-daily multiple doses were studied in healthy volunteers without evidence of toxicity. • Occasional doses of up to 1800 mg per day were taken in the P005/P018 & P019 studies without evidence of toxicity
Pregnancy & Lactation	<p><i>Pregnancy</i></p> <ul style="list-style-type: none"> • Third trimester and postpartum raltegravir pharmacokinetics were studied in 10 HIV-positive women receiving raltegravir 400 mg BID. Raltegravir kinetics showed extensive variability (consistent with observations in other populations), but exposure was not consistently altered during the 3rd trimester compared to post-partum and historical data. The cord blood:maternal plasma ration (n=6) was 0.98 (0.09-2.26).[Best et al. ICAAC 2010] Similar results were observed in 3rd trimester and post-partum concentrations in a cohort of 5 HIV-positive women on raltegravir 400 mg BID.[Colbers et al. 12th IWCPHT 2011] • Thus, raltegravir appears to readily cross the placenta and standard dosing may be used in pregnancy • High raltegravir concentrations were observed in 3 newborns whose mothers received raltegravir during pregnancy. Raltegravir concentrations in the neonates were disproportionately higher (209-3634 ng/mL at 5.5-13 hours post dose) compared to maternal raltegravir concentrations (22-493 ng/mL at 7-12 hours post dose), indicating effective placental transfer and possibly immature neonatal UGT1A1 mediated glucuronidation.[Rosenvinge M et al. 2010] • Placenta transfer of drug was demonstrated in both rats and rabbits. • Treatment related increases in the incidence of supernumerary ribs were seen in rats (exposures 3 fold the exposure at the recommended human dose) <p><i>Lactation</i></p> <ul style="list-style-type: none"> • It is not know if raltegravir is secreted in human milk. • Raltegravir is secreted in the milk of lactating rats. • It is recommended that HIV infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV

Drug Interactions	<p><i>See Drug interaction tables for more details</i></p> <p><i>Effect of Raltegravir on the Kinetics of Other Agents</i></p> <ul style="list-style-type: none"> • Does NOT inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A <i>in vitro</i> • Does NOT induce CYP3A4 <i>in vitro</i> <p><i>Effect of Other Agents on the Pharmacokinetics of Raltegravir</i></p> <ul style="list-style-type: none"> • Strong inducers of UGT1A1 (ex Rifampin) will reduce plasma concentrations of Raltegravir • Less strong inducers (e.g., efavirenz, nevirapine, rifabutin, St. John's wort) may be used without dose adjustment of Raltegravir. • Strong inhibitors of UGT1A1 (Ex ATV/r) will increase plasma concentrations of Raltegravir. In trials the combination of Raltegravir with ATV/r did not result in toxicity concerns. Therefore may use combination without dose adjustment.
Baseline Assessment	CD4, viral load
Routine Labs	CD4, viral load
Dosage Forms	<p>400 mg tablets, DIN 02301881</p> <p>Chewable tablets (<i>available in US</i>):</p> <ul style="list-style-type: none"> ○ 100 mg, pale orange, oval-shaped, orange-banana flavoured ○ 25 mg, pale yellow, round, orange-banana flavoured
Storage	Store at room temperature (20-25°C); excursions permitted to 15-30°C.

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