Selected Properties of Raltegravir

Other names	Isentress®, MK-0518 Fixed dose combination: • Dutrebis® (lamivudine 150 mg/raltegravir 300 mg tablet) • *Licensed but not commercially available in U.S.*
Manufacturer	Merck Canada Inc.
Pharmacology/Mechanism of Action	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. 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.
Activity	• 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	Resistance data are preliminary and limited. Raltegravir has a low genetic barrier (similar to the 1st generation NNRTI class). 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. Another resistance pathway involves a mutation at position 143 (Y143C/H/R)
Resistance - phenotypic	
Cross-Resistance	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.
Oral Bioavailability	The absolute bioavailability of raltegravir has not been established. The pharmacokinetics of raltegravir were compared in 67 patients who swallowed the intact tablet with 13 HIV-infected patients who chewed the raltegravir tablet due to swallowing difficulties. HIV-infected patients receiving raltegravir by chewing the tablet showed higher drug absorption and reduced pharmacokinetic variability compared with patients swallowing the intact tablet. Crushed tablets tested in water or in a pH 6.8

	buffer exhibited prompt and complete dissolution of RAL.[Cattaneo et al. AAC 2012] 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]
Effect of Food	Film-coated tablets: 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 C12hr is not clinically important [Wenning et al. ICAAC 2007]. Raltegravir was administered without regard to food in Benchmrk-1 and Benchmrk-2 studies. 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 (C12h), 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]. Chewable tablets: Administration of chewable tablet with a high fat meal led to an average 6% decrease in AUC, 62% decrease in Cmax and 188% increase in C12hr 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. **Raltegravir may be administered twice daily without regard to meals.**
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	Raltegravir displays dose proportional pharmacokinetics over the clinically relevant dose range (100 to 800 mg). Adults: In a single dose pharmacokinetic study in healthy subjects (n = 20), AUC $_{0-\infty}$ & Cmax 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.

Subjects who received **400mg BID**: AUC 14.3 uM•hr, C12hr 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%), Cmax 1315 ng/mL (CV 109%), C12h after 2nd dose was 166 ng/mL (CV 94%); these results were comparable to historical controls, suggesting no influence of race on raltegravir pharmacokinetics.[Wohl et al. 2013]

Pediatrics:
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)

Raltegravir Steady State Pharmacokinetic Parameters in Pediatric Patients Following Administration of Recommended Doses:

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

*Number of patients with intensive pharmacokinetic (PK) results at the final recommended dose.
†Geometric coefficient of variation.

The pharmacokinetics of raltegravir in infants under 4 weeks of age has not been established.

Chewing vs. swallowing tablets
The pharmacokinetics of raltegravir were compared in 67 patients who swallowed the intact tablet with 13 HIV-infected patients who **chewed the raltegravir tablet** due to swallowing difficulties. HIV-infected patients receiving raltegravir by chewing the tablet showed higher drug absorption and reduced pharmacokinetic variability compared with patients swallowing the intact tablet.[Cattaneo et al. 2012]

In 12 healthy volunteers, the pharmacokinetics of raltegravir 400

mg BID by swallowing was compared to raltegravir 800 mg QD where the tablets were chewed. While large inter-patient variability was observed with the BID dosing, variability was reduced by 20-1500% when raltegravir tablets were chewed. Chewing raltegravir also led to significantly higher raltegravir AUC (40722 ± 14843 vs. 21753 ± 12229 ng*h/mL, p<0.0001) and no difference in Cmin (36 ± 23 vs. 43 ± 23 ng/mL, p=0.298). compared to swallowing the tablets.[Cattaneo et al. 2013][Rizk et al. 2014]

Reformulated 600 mg tablet
In healthy volunteers, the effect of food on single dose pharmacokinetics of raltegravir 1200 mg, administered as either 3 x 400 mg marketed tablet or 2 x 600 mg reformulated tablet. For the reformulated tablet, administration with a low fat meal resulted in 40% ↓ AUC, 52% ↓ Cmax and 16% ↓ C24h, while administration with a high fat meal resulted in 3% ↑ AUC, 28% ↓ Cmax and 12% ↓ C24h.[Krishna et al. 2013]

In healthy subjects, **raltegravir 1800 mg daily** for 28 days was well tolerated, and resulted in mean RAL Cmax, C24h and AUC of 29 uM, 88.5 nM and 74.5 hr.uM, respectively.[Krishna et al. 2014]

Dutrebis fixed dose combination tablet:
One tablet was shown to provide comparable lamivudine and raltegravir exposures to one Epivir 150 mg tablet plus one Isentress 400 mg tablet. Due to the higher bioavailability of raltegravir contained in Dutrebis, the exposures provided by the 300 mg dose of raltegravir are comparable to 400 mg of ralegravir given as the raltegravir poloxamer formulation (Isentress), which accounts for the difference in raltegravir dose.

Concentrations in UGT1A1*28/*28 genotype
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 gentoype). Raltegravir AUC ↑ 41%, Cmax ↑ 40% and Cmin ↑ 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 $t_{½}$ 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]

Cervicovaginal fluid concentrations
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, Tmax 12h, CVF t½ 17 hours (vs. plasma t½ 7 hours), with CVF:plasma AUC ratio of 64% on day 1 and 93% on day 7. Raltegravir CVF concentrations were C12h 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]

Semen concentrations

A total of 96 blood and 96 semen samples were collected within 1 hour of each other in 16 HIV-infected men virally suppressed on raltegravir-based therapy for a median of 21 months. The median seminal plasma to blood plasma ratios and AUC_{0-12h} seminal plasma to blood plasma ratios of raltegravir were 3.25 (interquartile range 1.46 to 5.37) and 2.26 (interquartile range 1.05 to 4.45), respectively. Concentrations of raltegravir in seminal plasma are several fold-higher than those attained in blood plasma and those required to inhibit viral replication in this compartment.[Antoniou et al. 2014]

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].

Intracellular concentrations

Paired plasma and intracellular samples were obtained from 12 HIV-infected adults taking raltegravir BID and after switching to once daily. With BID dosing, no plasma trough concentrations were below the IC_{95}, in contrast to 33% for once daily dosing. Fifty percent of the once daily group had intracellular trough concentrations below the inhibitory concentration 95 (IC_{95}), 25% in the b.i.d. group. Lower plasma and intracellular concentrations may contribute to inferior virologic suppression rates observed with once daily raltegravir dosing.[Sandkovsky et al. AIDS 2012].

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]

Gut-associated lymphoid tissue concentrations

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]
Minimum target trough concentrations (for wildtype virus)	IC95 = 15 ng/mL In vitro simulations suggest that antiviral effect is consistent with AUC rather than trough [McSharry J et al. 10th IWCPHT 2009, #O_09]. 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]
CSF (% of serum)	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] 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] 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] 2010 CNS Penetration Effectiveness (CPE) Score: 3 [Letendre S et al. 2010]
Metabolism	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.
Excretion	Feces: 51% (only raltegravir was present, most of which is likely derived from hydrolysis of raltegravir-glucuronide secreted in bile). Urine: 32% (raltegravir + raltegravir glucuronide)
Dosing – Adult	400 mg BID with or without food. Raltegravir film-coated tablets must be swallowed whole. Raltegravir chewable tablets may be chewed or swallowed whole. Because the formulations are not bioequivalent, **do not**

substitute chewable tablets for the 400 mg film-coated tablet.

Dutrebis® (lamivudine 150 mg/raltegravir 300 mg tablet):
1 tablet twice daily with or without food.

Dosing – Pediatric

If at least 25 kg in weight:

- One 400 mg film-coated tablet orally, twice daily **OR**
- Chewable tablets: weight based to maximum dose 300 mg, twice daily as specified:

Weight (kg)	Dose	# of Chewable Tablets
25 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

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

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

At least 4 weeks of age and weighing at least 3 kg to less than 25 kg:

Body weight (kg)	Volume (Dose) of Suspension	# of Chewable Tablets
3 to <4	1 mL (20 mg) BID	
4 to <6	1.5 mL (30 mg) BID	
6 to <8	2 mL (40 mg) BID	
8 to <11	3 mL (60 mg) BID	
11 to <14†	4 mL (80 mg) BID	3 x 25 mg BID
14 to <20†	5 mL (100 mg) BID	1 x 100 mg BID
20 to <25		1.5 x 100 mg‡ BID

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

†For weight between 11 and 20 kg either formulation can be used.

Note: The chewable tablets are available as 25 mg and 100 mg tablets.

‡The 100 mg chewable tablet can be divided into equal halves.

The maximum dose of chewable tablets is 300 mg twice daily. The maximum dose of oral suspension is 100 mg twice daily.

The safety and effectiveness of raltegravir in pediatric patients less than 4 weeks of age have not been established.

Summary of Raltegravir Dosing in Pediatrics (studies)

Age		RAL Dose	Ref
4 wks-<2 yo		Oral suspension	IMPAACT P1066
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

	<table><tr><td>12-18</td><td></td><td>400 mg BID (AF)</td><td>ICAAC 2008; Wiznia et al. CROI 2009; Frenkel et al. ICAAC 2009.</td></tr></table> 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. **The maximum dose of chewable tablets is 300 mg twice daily.** 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**. Each single-use packet for oral suspension contains 100 mg of raltegravir which is to be suspended in 5 mL of water giving a final concentration of 20 mg/mL. Pour packet contents into 5 mL of water and mix. Once mixed, measure the recommended volume (dose) of suspension with a syringe and administer the dose orally. The oral suspension should be administered orally within 30 minutes of mixing. **The maximum dose of oral suspension is 100 mg twice daily.** Because the formulations are not bioequivalent**, do not substitute chewable tablets or oral suspension for the 400 mg film-coated tablet.**
Adjust in Liver Dysfunction	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) **No dosage adjustment is necessary for patients with mild to moderate hepatic impairment.** 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) The kinetics of multi-dose raltegravir 400 mg BID were studied in HIV/HCV coinfected 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). The kinetics of raltegravir 400 mg BID plus either abacavir/3TC or tenofovir/FTC were studied in 10 HIV+ patients (80% HCV) with end-stage liver disease: median age 50 (39-63) yrs, 58 (48-81) kg, CD4 258 (57-604) cells/mm^3, MELD and CP scores at screening were 12 [5; 26] and 10 [6; 14], respectively. Median MELD at M1 was 11 [7; 33]. Albumin concentration at M1 was 27 [24; 36] g/L. Raltegravir was well tolerated in all subjects. Raltegravir pharmacokinetics exhibited wide variability, but were within the range historically reported in patients or volunteers with normal liver function.(Barau et al. CROI 2013)
Adjust in Renal Failure/Dialysis	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.** 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 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] 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] 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 nasogastroduodenal 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.[Taegtmeyer et al. 2011]
Toxicity	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]. 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. 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.
Overdose	• 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	*Pregnancy* • 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.[McKeown 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) *Lactation* • 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 *Use in preventing vertical transmission* • Case series of 31 pregnant women: raltegravir was virologically effective and caused no adverse events in women or their newborns (France) [Jeantils et al. ICAAC 2013]. • Three cases in which raltegravir was used late in pregnancy to rapidly reduce maternal HIV-1 viral load in women with multidrug resistant virus. In all three cases, addition of raltegravir to the mother's regimen was associated with rapid reduction in maternal viral load. The much higher raltegravir concentrations in neonates compared with their mothers suggests effective placental transfer. [Hegazi et al. 2012]
Drug Interactions	*See Drug interaction tables for more details* *Effect of Raltegravir on the Kinetics of Other Agents* • Does NOT inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A *in vitro* • Does NOT induce CYP3A4 *in vitro* *Effect of Other Agents on the Pharmacokinetics of Raltegravir* • 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 or 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	400 mg tablets, DIN 02301881 Chewable tablets: ○ 100 mg, pale orange, oval-shaped, orange-banana flavoured, DIN 02392437 ○ 25 mg, pale yellow, round, orange-banana flavoured, DIN 02392429 Oral suspension *(approved in U.S.)*: ○ single-use packet for oral suspension contains 100 mg of raltegravir which is to be suspended in 5 mL of water giving a final concentration of 20 mg/mL Fixed dose combination: • Dutrebis® (lamivudine 150 mg/raltegravir 300 mg tablet). Approved in U.S. but not commercially available.
Storage	Store at room temperature (20-25°C); excursions permitted to 15-30°C. The oral suspension should be administered orally within 30 minutes of mixing.

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