

## LIQUID DRUG FORMULATIONS

Drug	Liquid available?	Formulation	Status	Cost	Comments
<b>ANTIRETROVIRALS – FIXED DOSE COMBINATION PRODUCTS</b>					
Atripla® (efavirenz/ emtricitabine/ tenofovir)	No	Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral vehicle. The solution was prepared within 24 hours of administration to ensure drug stability in solution.			<p>Bioequivalence of Atripla tablet and compounded oral liquid formulation in HIV-negative volunteers was <b>not</b> demonstrated. The 90% CI for FTC C<sub>max</sub> and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz C<sub>max</sub> fell below the range of bioequivalence while efavirenz AUC<sub>∞</sub> fell slightly above the range and tenofovir C<sub>max</sub> and AUC<sub>∞</sub> fell above the range. Tenofovir C<sub>max</sub> and AUC<sub>∞</sub> were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown. [King et al. JAIDS 2011;56(5):e131-2].</p> <p>Splitting EFV/FTC/TDF tablets has not been studied and it is not recommended. There are no studies evaluating the pharmacokinetics of a split EFV/FTC/TDF tablet versus a whole tablet.</p>
Combivir® (lamivudine/ zidovudine)	yes (individual components)	Use lamivudine & zidovudine liquid products	facilitated access		No data, but likely OK to crush tablets; crush immediately before ingestion. May have bitter taste.
Complera® (emtricitabine/ tenofovir/ rilpivirine)	no				Splitting or crushing Complera tablets into a liquid medium has not been studied and is not recommended. Rilpivirine hydrochloride is insoluble in water over a wide pH range. (Email communication, Gilead July 2012).
Kivexa® (abacavir/ lamivudine)	yes (individual components)	Use abacavir & lamivudine liquid products	facilitated access		
Stribild® (elvitegravir/ cobicistat/ emtricitabine/ tenofovir)	no				Crushing STRIBILD tablets into a liquid medium has not been studied and is not recommended. While emtricitabine and tenofovir are soluble in water, cobicistat and elvitegravir are practically insoluble in water. Currently, there are no studies evaluating the pharmacokinetics (e.g., oral bioavailability) of a crushed STRIBILD tablet dispersed into a liquid

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Trizivir® (abacavir/ lamivudine/ zidovudine)	yes (individual components)	Use abacavir, lamivudine & zidovudine liquid products	facilitated access		medium (e.g., milk, water, juice) compared to a whole tablet.  Splitting STRIBILD tablets has not been studied and it is not recommended. (Communication from Gilead Canada, April 2013)
Truvada® (tenofovir/ emtricitabine)	yes (individual components)				May split tablets. May crush and stir into water, grapefruit juice or orange juice. The stability of the mixture is unknown. (Email communication, Gilead, May 2008).  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]
<b>ANTIRETROVIRALS – INDIVIDUAL AGENTS</b>					
abacavir	yes	20 mg/mL oral solution; 240 mL bottle	facilitated access	\$100.00/ bottle	Yellow, strawberry-banana flavoured liquid; store oral solution at room temperature.  Tablet is film-coated, no data on whether can be crushed.
amprenavir	yes	15 mg/ml oral liquid; 240 mL bottle	section 8	\$46.08/bottle	Yellow, grape/bubblegum flavoured liquid. Oral solution contains: vitamin E 46 IU/ml, propylene glycol 550 mg/ml, PEG400 170mg/ml, , saccharin Store at room temperature in original bottle. NB: due to high propylene glycol content, avoid in pregnancy, children <4 years, renal or hepatic dysfunction.
atazanavir	yes	50 mg/1.5 g dispersible oral powder, 180 g bottle	investigational only (PACTG 1020)	available in Europe	<b>Powder</b> may be mixed with small amount of water, applesauce, milk, or yogurt (consume within 3 hours of mixing). Do not mix with juices or foods with high pH.  In an open label, multicentre study of atazanavir and

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darunavir	yes	100 mg/mL oral suspension	Licensed in U.S. and Europe		<p>atazanavir/ritonavir in children 91 days-21 years, the pharmacokinetics of atazanavir capsules and atazanavir orange-vanilla flavoured powder were studied. Day 7 atazanavir kinetics were compared in children of similar age receiving powder vs. capsules; the powder was found to be 40% less bioavailable at the same BSA-based dose. Therefore, suggest converting from powder to capsule by multiplying the powder dose by 0.6 and rounding up to the nearest 50 mg.[Kiser J et al. 2011]</p> <p><b>Atazanavir capsules</b> may be opened and the contents mixed with applesauce for immediate ingestion with a light meal. In-house study showed that the bioavailability of the contents of two 200-mg atazanavir capsules mixed with applesauce was 91.7% relative to atazanavir capsules taken intact. In addition, administration of the contents of two 200-mg capsules was well tolerated (Bristol Myers Squibb, Personal Communication, October 22, 2008).</p> <p>No pharmacokinetic data are available on chewing or crushing of PREZISTA film-coated tablets. However, since the tablets are not formulated as an extended release formulation, no potential problem is anticipated if the tablets are chewed or crushed for administration through a nasogastric (NG) tube. It is unlikely that chewing or crushing PREZISTA tablets would have a significant impact on pharmacokinetics (Data on File, Tibotec, November 2006).</p> <p>In two patients, one with dysphagia and Candida esophagitis and one with a stomach tube, who received darunavir tablets crushed and dissolved and administered with ritonavir oral solution, adequate plasma darunavir levels were achieved along with good virologic response.(Scholten et al. 2010)</p> <p>Can dissolve 100 mg tablets in water to make slurry (20% ↑ bioavailability). Disperse tablets in at least 90 mL of water, allow to stand for a few minutes, stir and consume.</p>
delavirdine	no				

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didanosine (ddl)	yes	2 g and 4 g oral powder (pediatric solution); 10 mg/mL final concentration	SAP	\$67.84/4 g bottle; \$30/2 g bottle	<p>Reconstitute oral powder with sterile water, then Mylanta TC suspension; stable for 30 days in fridge; available via SAP (call Maggie Jackson at 514-333-2287).</p> <p>(can also crush/dissolve buffered tablets in water, apple juice, or chocolate milk)</p>
dolutegravir	no	Pediatric oral granule formulation in development.			<p>In comparison to the commercially available tablet, dolutegravir exposures following administration of the granule formulation alone, with different types of water and with formula exceeded that of the tablet, demonstrating the dolutegravir oral granule DTG granule can be given without restriction on the type of liquid, or can be administered directly to mouth (e.g., when potable water is not available).[Patel et al. CROI 2012, #N-161]</p> <p>Tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. [ViiV data on file, November 18, 2013].</p>
efavirenz	yes	30 mg/mL; 180 mL bottle	pediatric suspension available via Sustiva Oral Liquid Expanded Access Program at 1-877-372-7097 (Massachusetts)		<p>Strawberry-mint flavour. Store liquid at room temperature in original container; stable for 30 days after opening.</p> <p>Can open <b>capsules</b> and mix powder with two teaspoons of one of four possible food vehicles: applesauce, grape jelly, yogurt, or infant formula (but may result in hot "jalapeno" sensation). Specific instructions [Kaul et al. AJHP 2010;67:217-22]:</p> <ol style="list-style-type: none"> <li>1. Hold the capsule vertically with the cap facing up.</li> <li>2. Pull the cap away from the body of the capsule carefully, sprinkle and mix the contents with the food in a 100-mL container.</li> <li>3. Administer the mixture with a spoon as soon as possible but no more than 30 minutes after mixing.</li> <li>4. After administration of the efavirenz–food mixture,</li> </ol>

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emtricitabine (FTC)	Yes (in US)		investigational only in Canada		<p>rinse the container three times with 50 mL of water, patient should swallow each rinse.</p> <p>5. After the three rinses, patient should consume an additional 90 mL of water.</p> <p>For nasogastric administration, may open capsules and mix with either 5 mL MCT oil or 15 mL Ora-Sweet (grind powder first to enhance dissolution). Powder is insoluble in water; do NOT mix with polyethylene glycol (will ↓ bioavailability).</p>
etravirine	No				<p>200 mg capsules may be opened and mixed with water.</p> <p>Patients who are unable to swallow etravirine tablets whole may disperse the tablets in a glass of water. A bioavailability study has shown that the PK of etravirine tablets when swallowed whole and when taken after dispersion in a glass of water are comparable. Both the 100 mg and 200 mg tablet formulations of etravirine may be dispersed in water [Kakuda et al. 2012].</p> <p>Stir the tablet in 100ml of cold water until a homogenous, white, cloudy, suspension is obtained. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed. (Data on File, Tibotec)</p> <p>Do not chew the tablets (product monograph); no PK data available for crushing/chewing 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>

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fosamprenavir	yes	50 mg/mL oral suspension, 225 mL bottle.	Section 8		Grape bubblegum and peppermint flavour. Suspension must be taken on an empty stomach. Store oral suspension between 2-30°C. Do not freeze. Discard the suspension 28 days after first opening. No information on crushing or dissolution of 700 mg tablets.
indinavir	no		liquid being formulated		do NOT open capsules (bitter taste; stability?); NB: 10 mg/mL indinavir syrup complex compounding formulation . Stable for 14 days in refrigerator, store in glass bottle. (Hugen et al. Am J Health Syst Pharm 2000; 57(14):1332-9).
lamivudine (3TC)	yes	10 mg/mL oral solution; 240 mL bottle	facilitated access	\$70.40/ bottle	Pale yellow, strawberry-banana flavoured solution; stable at room temperature. (Note:contains 6% v/v ETOH & 3g sugar) Can also crush tablets.
lopinavir/ritonavir	yes	80 mg/20 mg per mL; 160 mL bottle	facilitated access	\$316.27/ bottle	Cotton-candy flavoured yellow-orange oral solution; stable in refrigerator until expiry date; stable at room temperature for 42 days. Oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Increased risk of toxicity in preterm infants.  NB: tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed. Administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC by 45% and 47%, respectively. Therefore, the use of crushed lopinavir/ritonavir tablets should be avoided, if possible.[Best et al. JAIDS 2011;58:385-91]
maraviroc	no				No PK data available for crushing/chewing tablet. (Data on File, Pfizer) . While the company does not have any specific kinetic information, crushing or cutting the tablets is not expected to negatively affect bioavailability.

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nelfinavir	yes	50 mg/g oral powder; 144 g bottle. (1g = 1 level scoop).	facilitated access	\$52.42/ bottle	Can also dissolve tablets (i.e. 250 mg tablet in 5 mL sterile water to yield a 50 mg/mL liquid. Use syringe with 1 mL increments to measure. Round dose to nearest 50mg); tablet or powder may be mixed with food or liquid up to 6 hours (refrigerated) before dose is taken.
nevirapine	yes	10 mg/mL;240 mL bottle	SAP		Sweet-flavoured syrup; stable at room temperature. Can crush immediate-release (200 mg) tablets in water. NB: Extended-release (400 mg XR) tablets must be swallowed whole; they must not be chewed, crushed or divided.
raltegravir	Yes (approved in U.S.)	20 mg/mL (single-use packet of 100 mg raltegravir)  100 mg & 25 mg pediatric chewable tablets (available in U.S).			<p>NB: Because the formulations are not bioequivalent, do not substitute raltegravir chewable tablets or oral suspension for the 400 mg film-coated tablet. The maximum dose of chewable tablets is 300 mg twice daily. The maximum dose of oral suspension is 100 mg twice daily.</p> <p>The oral suspension should be administered orally within 30 minutes of mixing.</p> <p>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]</p> <p>Crushing tablets is not recommended; granules (sub-units of the tablet) dissolve faster than intact tablets and may result in faster release of drug which could affect in-vivo performance (Data on File, Merck Frosst, May 2008). Drug has bitter taste which is masked by the film coating.</p>

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ritonavir	yes	80 mg/mL oral liquid; 240 mL bottle	facilitated access	\$256.35/ bottle	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. Pharmacotherapy 2012; 32: 142-7.] Orange-coloured oral solution, peppermint & caramel-flavoured. 43% v/v alcohol. Shake well before each use. Stable at room temperature; do not refrigerate.
saquinavir	no		liquid not being formulated due to unpalatability		6 x 200 mg Fortavse whole caps mixed with 50 mL of whole milk or Advera nutritional supplement took 5-15 minutes to dissolve when heated to 40, 60 or 80 degrees C. The mixture remained in solution for up to 1 hour at room temperature. If refrigerated for 24 hours, it turned into a gel, but reliquified after reheating to 30 degrees C. The drug was still stable at 24 hours. (data on file, Hoffmann-LaRoche)
stavudine (d4T)	yes	1 mg/mL oral suspension; 200 ml bottle	SAP	no charge	Fruit-flavoured; stable 30 days in fridge; can also open up capsules give in small portion of food or 5-10 mL cool tap water
tenofovir	yes		40 mg per 1 gram of oral powder formulation (available in US)		Crushed tablet dissolves in 100 mL water in 20 minutes; grape juice may also be used. NB: crushed tablets have very disagreeable taste. May also try splitting tablets and inserting into empty gelatin capsules to mask taste.
tipranavir	no		investigational only in Canada		250 mg capsule. No information on opening or dissolution.
zalcitabine (ddC)	no				Investigational oral solution is no longer available.
zidovudine (AZT)	yes	10 mg/mL oral syrup; 240 mL bottle	ODDMP	\$43.39/bottle	Strawberry-flavoured; stable at room temperature. May open capsules & give in small portion of food or 5-10 mL cool tap water.



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OTHER MEDICATIONS:					
acyclovir	yes	200 mg/5 mL; 125 mL bottle	Facilitated access	\$30,72/ bottle	Banana-flavoured suspension; store between 15-25C.
azithromycin	yes	pediatric oral powder/suspension 100 mg/5 mL (300 mg bottle) OR 200 mg/5 mL (600 & 900 mg bottles)	limited use	\$23.77/ 600mg bottle	Cherry-flavoured suspension. Dispose unused suspension after 10 days; may also open capsules and mix with water (ingest immediately on empty stomach, follow with full glass of water)
clarithromycin	yes	125 mg/5 mL & 250 mg/5mL; 55, 105 and 150 mL bottles			Fruit-flavoured suspension. Shake well before use. Store reconstituted liquid at room temperature.
Fenofibrate (Lipidil Supra, Lipidil EZ)	no				Tablets are not enteric-coated or sustained-release. Therefore while the company does not have any specific kinetic information, crushing or cutting the tablets is not expected to negatively affect bioavailability.
hydroxyurea	no				Can open up capsules and mix with water; take immediately. Some inert material (used as a vehicle in capsule) may not dissolve, and may float on top. Do not allow powder to come in contact with skin and mucous membranes. Avoid inhalation of powder when opening capsules.
rifabutin	no				Can open capsules (experience in pediatrics: OK to mix with applesauce, syrup, cherry syrup); drug not soluble in water
sofosbuvir	no				Sofosbuvir tablets can be disintegrated in water, juice, or milk with minor stirring and pressure with a spoon. However, the stability of sofosbuvir in these liquids is unknown at this time. Furthermore, there are no studies evaluating the pharmacokinetic parameters of the disintegrated or crushed sofosbuvir tablet versus the whole tablet. In addition, a disintegrated or crushed sofosbuvir tablet may have an unpleasant taste.(Personal communication, Gilead Sciences Canada, December 2013).

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TMP/SMX	yes	pediatric suspension 40 mg/200 mg per 5 mL (= ½ SS tablet); 400 & 800 mL bottles	formulary	\$0.20/10 mL (=1 SS tablet)	Cherry-flavoured. Store at Room temperature (Septra brand)

Key: ODDMP: Ontario Drug Distribution/Monitoring Program, SAP= Special Access Program, Health Protection Branch, Ottawa (ph: 613-941-2108; fax: 613-941-3194; [http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sap\\_requestform\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sap_requestform_e.html) )