ORAL ANTIRETROVIRAL ADMINISTRATION: INFORMATION ON CRUSHING AND LIQUID DRUG FORMULATIONS

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
Combination Products:					
Atripla® (efavirenz/ emtricitabine/ tenofovir)	no	Consider use of Truvada® tabs and efavirenz caps as alternate formulations (see separate entries)		Atripla® tablet was 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. Bioequivalence of Atripla tablet and compounded oral liquid formulation (above) in HIV-negative volunteers was **not** demonstrated. The 90% CI for FTC Cmax and AUC fell within the range of 0.8-1.25 thus, bioequivalence was met, but the 90% CI for efavirenz Cmax fell below the range of bioequivalence while efavirenz AUC∞ fell slightly above the range and tenofovir Cmax and AUC∞ fell above the range. Tenofovir Cmax and AUC∞ were approximately 40% and 20% higher, respectively with the liquid formulation. The clinical implications of these data are unknown, however the authors state that crushed Atripla® may be a viable option in certain patients and risks vs. benefits should be carefully considered. [King et al. JAIDS	See information on crushing Atripla® in the Case Reports section. Although Truvada® tablets may be split, splitting Atripla® tablets has not been studied. There are no studies evaluating the pharmacokinetics of a split tablet vs. a whole tablet. Efavirenz is not water soluble.

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				2011;56(5):e131-2].	
Combivir® (lamivudine/ zidovudine)	yes (individual components)	Use lamivudine & zidovudine liquid products			No data, but likely OK to crush tablets (film-coated); 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).
Genvoya® (elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide)	no			*see case reports for Stribild	Splitting or crushing Genvoya tablets into a liquid medium has not been studied and is not recommended. TAF is soluble in water but has a bitter and burnt aromatic taste. Emtricitabine is soluble in water, but cobicistat and elvitegravir are practically insoluble.(email communication, Gilead, November 2015).
Kivexa® (abacavir/ lamivudine)	yes (individual components)	Use abacavir & lamivudine liquid products			Film-coated immediate release tablet; however no studies regarding stability of split or crushed tablets. (Email communication, GlaxoSmithKline, May 2008) Tablet may be split or crushed and added to a small amount of food or water. (European

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					Medicines Agency, EPAR summary for the public, Ziagen updated 05-2010)
Prezcobix® (darunavir/ cobicistat)	no	See darunavir and ritonavir for potential liquid formulations (substitution of cobicistat with ritonavir may be required)			Splitting Prezcobix® film-coated tablets has not been studied. Tablets should be swallowed whole without breaking or crushing to ensure administration of the entire dose. (Prezcobix Product Monograph, 2014)
Stribild® (elvitegravir/ cobicistat/ emtricitabine/ tenofovir)	no			Case report describing successful virological suppression with crushed Stribild in juice (Fulco et al. AJHP 2014;71(10);784-6).	Pharmacokinetics of crushed Stribild® tablets were studied in healthy volunteers. Crushed tablets followed by breakfast, or administered suspended after a breakfast or a drip feed (Nutrison) was shown to be bioequivalent for elvitegravir, tenofovir and emtricitabine. Elvitegravir Cmax failed to fall within bioequivalence range (100-120%), but this difference is unlikely to be clinically significant. Cobicistat AUC was reduced by 10%.(de Hoon et al. CROI 2016, #431).
Triumeq® (abacavir/ lamivudine/ dolutegravir)	no	Use abacavir & lamivudine liquid products. Dolutegravir tablets may be crushed (see dolutegravir). See Crushing &Splitting section also.			Triumeq® is film-coated, non-scored, and non-sustained released formulation. Although not studied, splitting or crushing tablets is not expected to affect the dissolution or absoprtion. Tablets may be crushed and added to a small amount of

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					semi-solid food or liquid, and consumed immediately. (Data on File, ViiV Healthcare, Oct 2014)
Trizivir® (abacavir/ lamivudine/ zidovudine)	yes (individual components)	Use abacavir, lamivudine & zidovudine liquid products.			Film coated immediate release tablet however no studies regarding stability of split or crushed tablets.
Truvada® (tenofovir/ emtricitabine)	yes (individual components- US only)	See tenofovir & emtricitabine.		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. Pharmacother 2012;32(2):142-7).	May split tablets. May crush and stir into water, grape juice or orange juice. The stability of the mixture is unknown. (Email communication, Gilead, July 2012).
INDIVIDUAL ANTIRETROVIRAL AGENTS:					
abacavir	yes	20 mg/mL oral solution; 240 mL bottle. Yellow, strawberry-banana flavoured liquid.	Store oral solution at room temperature.		Tablet is film-coated; no data on whether can be crushed.
amprenavir	no-product discontinued	See fosamprenavir for liquid formulation.			

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atazanavir	yes (US only)	50 mg/1.5 g dispersible oral powder packet	**Powder:** mix with food such as applesauce or yogurt (1 TBSP minimum). Mixing with a beverage (milk, formula, water-30 mL + additional 15 mL after to consume residual drug) can be used if infant is able to drink from a cup. For younger infants who cannot eat solid food, mix with infant formula (10 mL + additional 10 mL after to consume residual drug) and administer via oral syringe. Stable for 1 hour at room temperature once mixed in food or beverage. (Refer to Reyataz® US Product Monograph for	**Capsules**: In an open label, multicentre study of atazanavir and 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. AIDS 2011;25:1489-96.)	**Capsules:** 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, November 20, 2015).

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			additional information on mixing/administration).		
darunavir	yes (US only)	100 mg/mL oral suspension	Store oral suspension at room temperature. Shake well before use.	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. J Int AIDS Soc 2010;13(Suppl 4):P114). A case report describes an intubated 44 year old man on tenofovir/emtricitabine, darunavir, and ritonavir in ICU who was given darunavir tablets via orogastric tube crushed and dissolved in 15-20mls of water. Viral load did not change significantly and adequate darunavir trough levels were achieved. (Kim et al. CJHP 2014;67(1):39-42).	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).
delavirdine	no				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

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didanosine (ddI)	yes (SAP)	4 g oral powder (pediatric solution); 10 mg/mL final concentration. Take on an empty stomach. Do not give with fruit juices or acidic drinks, feeds or milk.	30 days	Reconstitute with commercially available antacid that contains as active ingredients aluminum hydroxide (400 mg per 5 mL), magnesium hydroxide (400 mg per 5 mL), and simethicone (40 mg per 5 mL)) If above strength not available, reconstitute with similar antacid of ½ strength using these alternative instructions: Add 400 mL of antacid in two, 200 mL portions, shaking the contents after each addition of 200 mL. The admixture may be dispensed in flint-glass or plastic bottles. Shake well before using. Stable for 30 days in fridge. Available via SAP (call Maggie Jackson from BMS at 514-333-2287).	and consume.
dolutegravir	no	50 mg/10g pediatric oral granule formulation in development		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 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).	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).

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efavirenz	no Note: pediatric suspension is no longer available internationally (2014)	30 mg/mL; 180 mL bottle- not available Consider use of capsule formulation as described in Clinical Compounding		(Patel et al. Antivir Ther 2014;19(3):229-33.) **Tablets**: A pediatric pharmacokinetic intensive study that utilized weight band dosing and a combination of capsules or half of a 600 mg tablet reported low overall plasma efavirenz concentrations in both groups (higher doses need to be investigated). They found no significant differences across weight bands, suggesting no discernible effect of using half tablets. (Fillekes et al. JAIDS 2011;58(4):392-298). **Capsules**: Can open capsules 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(3):217-22]. 1. Hold the capsule vertically with the cap facing up. 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.	Splitting efavirenz tablets has not been well studied. With the exception of the study by Fillekes et al (JAIDS 2011;58(4):392-298), there are no well controlled pharmacokinetic studies evaluating a split tablet vs. a whole tablet. Efavirenz is not water soluble. The use of the capsule formulation is preferred when possible. (see Case Reports/Clinical Compounding)

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				3. Administer the mixture with a spoon as soon as possible but no more than 30 minutes after mixing. 4. After administration of the efavirenz–food mixture, rinse the container three times with 50 mL of water, patient should swallow each rinse. 5. After the three rinses, patient should consume an additional 90 mL of water. For nasogastric administration, may open **capsules** and mix with either 5 mL MCT oil or 15 mL Ora-Sweet/any aqueous vehicle (grind powder first to enhance dissolution). Do NOT mix with polyethylene glycol (will ↓ bioavailability). Splitting **tablets** is not recommended (Email communication, Bristol-Myers Squibb, June 1, 2011).	
elvitegravir	no			Case report describing successful virological suppression with crushed Stribild in juice (Fulco et al. AJHP 2014 71(10);784-6).	No information on crushing in product monograph. See Stribild® for more information.
emtricitabine (FTC)	no (US only)	10 mg/mL oral solution	Store oral solution refrigerated; stable for 3 mos		200 mg capsules may be opened and mixed with water.

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	Commercial Oral Liquid Available?	Formulation	Stability		
			at room temperature.		
etravirine	no	See Crushing and Splitting section for dispersion information.	Consume immediately.	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. Pharmacother 2012;32(2):142-7).	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. Int J Clin Pharmacol Ther 2013;51(9):725-37). Place the tablet in 5 mL of cold water or at least enough liquid to cover the medication. Stir until a homogenous, white, cloudy, suspension is obtained. If desired, add more water or alternatively orange juice or milk. Once dispersed, patients should stir the dispersion well and drink it immediately. The glass should be rinsed with water, orange juice or milk several times and each rinse completely swallowed to ensure the entire dose is consumed. Avoid the use of grapefruit juice, warm liquids (> 40°C) or carbonated beverages. (Intelence® Product

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					Monograph, 2014).
fosamprenavir	yes	50 mg/mL oral suspension, 225 mL bottle. 0.6% propylene glycol Grape bubblegum and peppermint flavour. In adults, oral suspension should be taken on an empty stomach (1 hr before or 2 hours after food). In pediatric patients, oral suspension should be given with food.	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. Fosamprenavir calcium tablets and suspension are equivalent on a mg per mg basis.
indinavir	no			10 mg/mL indinavir syrup complex compounding formulation. Stable for 14 days in refrigerator, store in glass bottle. (Hugen et al. AJHP 2000; 57(14):1332-9).	Do NOT open capsules (bitter taste; stability uncertain).
lamivudine (3TC)	yes	10 mg/mL oral solution; 240 mL bottle. Pale yellow, strawberry-banana flavoured solution); (NB: contains 6% v/v ETOH & 3g sugar).	Store at room temperature.		Can also crush or split tablets.
lopinavir/ ritonavir	yes	80 mg/20 mg per mL; 160 mL bottle. Cotton-candy flavoured yellow-	Stable in refrigerator until expiry date; stable at room	Administration of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir	NB: Adult and pediatric Kaletra® tablets should be swallowed whole and not chewed, broken, or crushed.

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		orange oral solution. Oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Increased risk of toxicity in preterm infants.	temperature for 42 days.	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).	Risk of tablets shattering if broken/crushed.
maraviroc	no				Film coated immediate release tablet. No pharmacokinetic 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.
nelfinavir	yes (US only); discontinued in Canada	50 mg/g oral powder; 144 g bottle. (1g = 1 level scoop). Take with food or close to time of feeds.	**Oral Powder:** mix with small amount of water, milk, formula, or dietary supplements (acidic food or juice such as apple juice, orange juice, apple sauce not recommended- bitter taste); consume immediately; may be stored in		For infants, 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 50 mg and consume immediately. Tablets also readily dissolve in water and produce a dispersion that can be mixed with milk/chocolate milk. Tablets can be crushed and given with pudding. Tablet may be mixed with food or liquid and taken immediately. Do not mix with acidic food/juice (orange or

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			fridge for up to 6 hours.		apple juice) due to bitter taste.
nevirapine	yes-SAP	10 mg/mL;240 mL bottle 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 (US only)	20 mg/mL oral banana flavoured granular powder (single-use packet of 100 mg raltegravir) 25 mg & 100 mg pediatric chewable tablets (Canada & US)	The oral suspension should be administered orally within 30 minutes of mixing	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. 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	Crushing film coated tablets 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 a bitter taste which is masked by the film coating. Chewable tablet may be chewed or swallowed whole. Oral suspension, chewable tablets and film-coated tablets are NOT interchangeable. The maximum dose of the chewable tablets is 300 mg BID and the maximum dose of the oral suspension is 100 mg BID.

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	Commercial Oral Liquid Available?	Formulation	Stability		
				exhibited prompt and complete dissolution of RAL.(Cattaneo et al. AAC 2012;56(12):6132-6.) In healthy volunteers, RAL 800 mg daily (chewed) vs. 400 mg BID (swallowed intact) resulted in a 2-fold increase AUC, 4-fold increase in Cmax, similar Cmin concentrations, and less pharmacokinetic variability in the 800 mg daily group. (Cattaneo et al. Ther Drug Monit 2014 Jul1. (Epub ahead of print). 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).	
rilpivirine	no				Film coated tablet. No data available on stability of splitting or crushing rilpivirine tablets. Rilpivirine is insoluble in water over wide pH range. (Email communication, Janssen, July 2012).
ritonavir	yes	80 mg/mL oral liquid; 240 mL bottle.	Stable at room temperature; do		Tablets may not be split or crushed (Norvir® Product

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		Orange-coloured oral solution, peppermint & caramel-flavoured. 43% v/v alcohol. Shake well before each use	not refrigerate. See tips for taking liquid in Crushing & Splitting section.		Monograph). Liquid is unpalatable, bad aftertaste. Tips: - Mix oral solution with milk/chocolate milk or pudding - Give after popsicle/frozen juice to dull taste buds - Give after grape jelly, maple syrup, or peanut butter which coats mouth -Give strong flavour after dose: syrup, cheese, chewing gum
saquinavir	no		Liquid not being formulated due to unpalatability	In an open-label, randomized, 4 period study in adults, the bioavailability of 1000 mg opened saquinavir capsules suspended in simple syrup, baby formula and jelly jam (plus ritonavir 100 mg oral solution) was approximately 10%, 60% and 40% higher, respectively, than 1000 mg unopened saquinavir capsules plus ritonavir. In terms of palatability, saquinavir suspended in simple syrup or jelly jam ranked higher than saquinavir suspended in baby food.(McKay et al. 8th Int Workshop Clin Pharm HIV Ther 2007, abstract 6).	Hard gel caps (Invirase®) may be opened and powder sprinkled on food, simple syrup or water (unpleasant taste). Take with food. 6 x 200 mg Fortovase® (soft-gel caps) 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°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	yes- SAP	1 mg/mL oral	Stable 30 days		Can also open up capsules give

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(d4T)		suspension; 200 ml bottle. Fruit-flavoured. Shake well.	in fridge.		in small portion of food or 5-10 mL cool tap water.
tenofovir	yes (US only)	40 mg per 1 gram of oral powder formulation. Oral powder should be mixed in a container with 2 to 4 ounces (60 to 120 mL) of soft food not requiring chewing (e.g., applesauce, baby food, yogurt). Do not attempt to mix in a liquid as the powder may float on top even after stirring.	Administer immediately to avoid a bitter taste.		Crushed tablet dissolves in 100 mL water in 20 minutes; grape juice may also be used. Consume immediately. NB: crushed tablets have very disagreeable taste. May also try splitting tablets and inserting into empty gelatin capsules to mask taste.
tipranavir	yes (US only)	100 mg/mL oral solution; contains 116 IU/mL vitamin E.	Store oral solution and room temperature (25ºC). Use solution within 60 days of opening the bottle.		250 mg capsule. Avoid splitting or crushing capsule.
zalcitabine (ddC)	no	Investigational oral solution is no longer available.			
zidovudine (AZT)	yes	10 mg/mL oral syrup; 240 mL bottle. Strawberry-flavoured.	Store at room temperature.		May open capsules & give in small portion of food or 5-10 mL cool tap water.

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OTHER:					
acyclovir	yes	200 mg/5 mL;125 mL bottle. Banana-flavoured suspension.	Store between 15-25 ºC		
azithromycin	yes	pediatric oral powder/suspension 100 mg/5 mL (300 mg bottle) OR 200 mg/5 mL (600 & 900 mg bottles). Cherry-flavoured suspension.	Store reconstituted suspension between 5-30ºC. 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.		
daclatasvir	no				Manufacturer recommends not chewing or crushing the tablet as it has a very unpleasant taste.(Daklinza Summary of Product Characteristics, EU, September 2014).
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

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					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).
telaprevir	no				Manufacturer recommends not breaking, chewing or crushing the tablet as it has a bitter taste.(Incivek Product Monograph, Canada, December 2013).
TMP/SMX	yes	pediatric suspension 40 mg/200 mg per 5 mL (= ½ SS tablet); 400 & 800 mL bottles	Store at room temperature		

Key: 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)