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 DF)	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.	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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				benefits should be carefully considered. [King et al. JAIDS 2011;56(5):e131-2].	
Biktarvy® (bictegravir/ emtricitabine/ tenofovir alafenamide)	no				Note that Biktarvy tablets should be administered whole. Crushing BIC/FTC/TAF tablets into a liquid medium has not been studied and is not recommended. While TAF is soluble in water, it has a bitter and burnt aromatic taste flavor profile. While FTC is soluble in water, BIC is practically insoluble (solubility of 0.1 mg/mL in water at 20 °C). Currently, there are no studies evaluating the pharmacokinetics (e.g., oral bioavailability) of a crushed BIC/FTC/TAF tablet dispersed into a liquid medium (e.g., milk, water, juice) compared to a whole tablet. (Data on File, Gilead US, May 2018) Similarly, splitting BIC/FTC/TAF tablets has not been studied and it is not recommended. Currently, there is no study evaluating the pharmacokinetics of a split tablet versus a whole tablet. (Data on File, Gilead US, May 2018).
Combivir®	yes (individual	Use lamivudine &			No data, but likely OK to crush

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(lamivudine/ zidovudine)	components)	zidovudine liquid products			tablets (film-coated); crush immediately before ingestion. May have bitter taste. Tablets can be crushed and added to small amount of liquid or semi-solid food; consume immediately. (Duggan et al. Am J Health-Syst Pharm. 2015; 72:1555-65)
Complera® (tenofovir DF/ emtricitabine/ 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).
Descovy® (tenofovir AF emtricitabine)	no				Crushing or splitting Descovy® tablets has not been studied and is not recommended. TAF is soluble in water. However, it has a bitter and burnt aromatic flavor profile. Emtricitabine is soluble in water. (Email communication, Gilead January 2017).
Evotaz					The manufacturer recommends to swallow the tablet whole; do not crush or chew tablets (Evotaz Product Monograph, Sept 2015).

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Genvoya® (elvitegravir/ cobicistat/ tenofovir AF/ emtricitabine)	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, March 2016). See Stribild® for more information.
Juluca® (dolutegravir/ rilpivirine)	no				The efficacy, safety and pharmacokinetics of crushing dolutegravir/rilpivirine have not been evaluated. The tablet should be swallowed whole and taken with a meal to ensure administration of the entire dose. Based on clinical judgment if the Juluca tablet requires splitting, it should be split in half and both halves ingested immediately with a meal. If the Juluca tablet requires crushing, it should be crushed and added to a small amount of liquid or semi-solid food and the full tablet content consumed immediately with a meal. (Data

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					on File, ViiV Healthcare, May 2018)
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 Medicines Agency, EPAR summary for the public, Ziagen updated 05-2010)
Odefsey® (tenofovir AF/ emtricitabine/ rilpivirine)	no				Crushing or splitting Odefsey® tablets has not been studied and is not recommended. TAF is soluble in water. However, it has a bitter and burnt aromatic flavor profile. Rilpivirine hydrochloride is insoluble in water over a wide pH range. (Email communication, Gilead January 2017).
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) Tablets are immediate-release

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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).	formulation; no anticipated absorption issues if the tablets are chewed, split or crushed. (Huesgen et al. Pharmacother 2016;36(11):1145-65). Pharmacokinetics of crushed Stribild® tablets were studied in healthy volunteers. Whole tablets with breakfast were compared to: I. Crushed and suspended with breakfast II. Crushed and suspended with enteral nutrition (Nutrison). The groups were 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% for intervention I only. (Jongbloed-de Hoon et al. JAIDS. 2017;74(5):571-574.)
Symtuza® (darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide)					Symtuza should be swallowed whole. The manufacturer does not recommend breaking or crushing Symtuza to ensure administration of the entire dose. Film-coated tablets. The relative bioavailability of

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Triumeq® (abacavir/ lamivudine/ dolutegravir (DTG))	no	Use abacavir & lamivudine liquid products. Dolutegravir tablets may be crushed (see dolutegravir). See Crushing &Splitting section also.			darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single tablet regimen was compared with the tablet administered whole, split or crushed. In the split group there was an 11% decrease in TAF Cmax only (not clinically relevant). In the crushed group there was a 17% decrease in the emtricitabine Cmax and TAF Cmax and AUC were decreased by 29% and 18%, respectively (clinical relevance not assessed, but impact expected to be minimal based on wide therapeutic window for TAF). (Brown et al. EACS 2017, #PS8/3) 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 absorption. Tablets may be crushed and added to a small amount of semi-solid food or liquid, and consumed immediately. (Data on File, ViiV Healthcare, Oct 2014) **Nasogastric or gastric feeding tubes:** No clinical or pharmacokinetic studies done to evaluate. The administration

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					of crushed Triumeq® tablets should not have an effect on the absorption of the components of Triumeq®. The absorption of Triumeq® is thought to occur in the proximal small intesting (duodenum/jejunum). (Data on File, ViiV Healthcare, March 2017) Pharmacokinetics of crushed Triumeq® tablets were studied in healthy volunteers. Whole tablets in fasting state were compared to: I. Crushed and suspended in fasting state II. Crushed and suspended with enteral nutrition (Nutrison). Intervention I showed 26% and 30% increase in DTG AUC and Cmax. Intervention II showed an 18 % and 21 % increase in DTG AUC and Cmax, respectively. Although bio-equivalence was not demonstrated, the increase in DTG exposure was not considered to be clinically relevant. However, caution is warranted if crushed DTG is given once daily or BID with food, as DTG exposure will likely be higher. (Roskam-Kwint et al. CROI 2017, #P-429)
Trizivir®	yes (individual	Use abacavir,			Film coated immediate release

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(abacavir/ lamivudine/ zidovudine)	components)	lamivudine & zidovudine liquid products.			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). Case report of complex HIV patient with MAC with intractable nausea/vomiting requiring ARVs (tenofovir DF 300 mg/emtricitabine 200 mg as Truvada® and dolutegravir 50 mg daily) via jejunostomy (J)-tube. ARVs were crushed, mixed with 3-5 mL or water, administered, and flushed with 10 mL of water. Concentrations of oral and J-tube administration of ARVs were assessed. DTG and TDF exposures were similar between J-tube and oral administration. FTC AUC was 38% lower for J-tube vs. oral. Compared to a reference population, overall AUC was	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).

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				lower for both routes- DTG 75-76% lower and TDF 55-61% lower. However, FTC via J-tube AUC was similar to the reference population and 71% higher when given orally. Reduced drug absorption was the primary cause for decreased drug exposure. TDM is recommended to assess drug concentrations in patients with the potential for impaired absorption (Brooks et al. Pharmacother 2017 May 27, epub ahead of print). Case report of an HIV patient with difficulty swallowing pills who preferred ARV formulations that he could crush. Tenofovir DF-emtricitabine (Truvada®) 1 tab daily and dolutegravir 50 mg daily were crushed using a pill crusher, added to applesauce, and consumed immediately. The 4- week viral load decreased from 10,800 to < 20 copies/mL (Buscemi L. Am J Health-Syst Pharm 2016;73(15):1125-26).	
INDIVIDUAL ANTIRETROVIRAL AGENTS:					
abacavir	yes	20 mg/mL oral solution; 240 mL bottle. Yellow,	Store oral solution at room temperature.		Tablet is film-coated. Tablet can be crushed and added to a small amount of

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		strawberry-banana flavoured liquid. Contains sorbitol 340 mg/mL (E-mail communication, ViiV, April 2017)			liquid or semi-solid food; consume immediately (Duggan et al. Am J Health-Syst Pharm. 2015; 72:1555-65).
amprenavir	no-product discontinued	See fosamprenavir for liquid formulation.			
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	**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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			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 additional information on mixing/administration).		
darunavir	yes (US only) or compassionate access through Janssen (e-mail communication, Janssen, February 2017)	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	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).

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				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).	
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 and consume.
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	

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dolutegravir	no	Pediatric film-coated tablets (10, 25 mg) available via compassionate access. (ViiV Healthcare communication, February 2017) 5 mg dispersible tablet under investigation. Pediatric granules no longer under development.		514-333-2287). 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). (Patel et al. Antivir Ther 2014;19(3):229-33.) Case report of a critically ill patient with lymphoma requiring enteral administration of ARVs. Both abacavir and 3TC solutions were administered enterally. Crushed **dolutegravir 50 mg BID** (separated from enteral nutrition by 2 hours) and rilpivirine 25 mg daily (given with a 240-mL bolus of an enteral formula (2 kcal/mL)) were administered via orogastric tube. Crushed tablets were each mixed with 10 mL of water and flushed down the tube at separate administration	10, 25 and 50 mg tablets should ideally be swallowed whole. All tablet strengths may also be split into halves followed by immediate ingestion of both halves or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. (ViiV Healthcare communication, February 2017) See Triumeq® for more information.

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				times. Trough concentrations were: day 8, rilpivirine 30 ng/mL (reference range 40-120 ng/mL), and day 9, dolutegravir 820 ng/mL (reference range 830 ng/mL steady-state trough concentration for 50 mg once daily dose). Virologic suppression was maintained after ARV enteral administration (hospital day 29). Given somewhat decreased levels of these ARVs, the authors recommended consideration to increase dolutegravir to 150-200 mg total daily dose, particularly in integrase-experienced patients, and rilpivirine 50 mg daily (similar to dosing with an inducer such as rifabutin). (Turley et al. JIAPAC 2017;16(2):117-119). Case report of complex HIV patient with MAC with intractable nausea/vomiting requiring ARVs (tenofovir DF 300 mg/emtricitabine 200 mg as Truvada® and **dolutegravir 50 mg daily)** via jejunostomy (J)-tube. ARVs were crushed, mixed with 3-5 mL or water, administered, and flushed with 10 mL of water. Concentrations of oral and J-tube administration	

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				of ARVs were assessed. DTG and TDF exposures were similar between J-tube and oral administration. FTC AUC was 38% lower for J-tube vs. oral. Compared to a reference population, overall AUC was lower for both routes- DTG 75-76% lower and TDF 55-61% lower. However, FTC via J-tube AUC was similar to the reference population and 71% higher when given orally. Reduced drug absorption was the primary cause for decreased drug exposure. TDM is recommended to assess drug concentrations in patients with the potential for impaired absorption (Brooks et al. Pharmacother 2017 May 27, epub ahead of print). Case report of an HIV patient with difficulty swallowing pills who preferred ARV formulations that he could crush. Tenofovir DF-emtricitabine (Truvada®) 1 tab daily and **dolutegravir 50 mg daily** were crushed using a pill crusher, added to applesauce, and consumed immediately. The 4- week viral load decreased from 10,800 to	

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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		< 20 copies/mL (Buscemi L. Am J Health-Syst Pharm 2016;73(15):1125-26). **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:** may be opened and added to 1-2 tsp of liquids or foods (e.g. applesauce, grape jelly, yogurt, reconstituted infant formula at room temperature) but may result in peppery taste. Grape jelly may mask taste. Specific instructions: (Kaul et al. AJHP 2010;67(3):217-22; DHHS 2017). 1. Hold the capsule horizontally over a small container and twist open to avoid spillage. 2. Pull the capsule away from the body of the capsule carefully, sprinkle and mix the	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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				contents with 1-2 tsp of food or formula. 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, an additional 2 tsp of food or infant formula must be added to the container, stirred, and given to the patient. 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).	Crushing or splitting Genvoya® tablets has not been studied and is not recommended. While emtricitabine and TAF are soluble in water, cobicistat and elvitegravir are practically insoluble in water. See Genvoya® for more information. (Communication from Gilead Canada, March 2016). See Stribild® for more

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					information.
emtricitabine (FTC)	no (US only)	10 mg/mL oral solution	Store oral solution refrigerated; stable for 3 mos at room temperature.		200 mg capsules may be opened and mixed with water.
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

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					completely swallowed to ensure the entire dose is consumed. Avoid the use of grapefruit juice, warm liquids (> 40ºC) or carbonated beverages. (Intelence® Product 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 2-30ºC. 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	Store at room temperature.		Can also crush or split tablets. Pharmacokinetic study in

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		bottle. Pale yellow, strawberry-banana flavoured solution); (NB: contains 6% v/v ETOH & 3g sugar). Does not contain sorbitol.			adults on co-administration of 3TC 300 mg and sorbitol solution (low (3.2 g), medium (10.2 g) and high (13.4 g) sorbitol doses) given with 240 mL water in the fasting state. A dose-dependent decrease in 3TC exposure was seen and is likely due to decreased absorption and bioavailability of 3TC (accelerated small intestinal transit time mediated by sorbitol). Higher doses of sorbitol resulted in lower 3TC concentrations (decreased $AUC_{0-\infty}$ by 14%, 32%, and 36%, respectively). Caution is warranted with chronic administration of 3TC solution and other liquid drugs containing sorbitol (e.g. abacavir, nevirapine, cotrimoxazole). (Adkison et al. CROI 2017, #428) In addition, in pediatric patients, ensure lamivudine dose is optimized based on weight.
lopinavir/ ritonavir	yes	80 mg/20 mg per mL; 160 mL bottle. Cotton-candy flavoured yellow-orange oral solution. Oral solution contains the excipients	Stable in refrigerator until expiry date; stable at room temperature for 42 days.	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	NB: Adult and pediatric Kaletra® tablets should be swallowed whole and not chewed, broken, or crushed. Risk of tablets shattering if broken/crushed.

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		alcohol (42.4% v/v) and propylene glycol (15.3% w/v). Increased risk of toxicity in preterm infants.		tablets should be avoided, if possible. (Best et al. JAIDS 2011;58:385-91).	
maraviroc	Yes (US only)	20 mg/ml clear, colourless, strawberry flavoured oral solution			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 fridge for up to 6		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 apple juice) due to bitter taste.

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			hours.		
nevirapine	Yes (SAP)	10 mg/mL;240 mL bottle suspension Contains sorbitol 162 mg/mL (Personal communication, Boehringer Ingelheim Canada, April 2017).	Stable at room temperature. Shake well before use.		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 (SAP)	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	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.

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
				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;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	Dispersible tablet (2.5 mg) and granule (2.5 mg/g)			Case report of a critically ill patient with lymphoma requiring enteral administration of ARVs. Both abacavir and 3TC	Film coated tablet. No data available on stability of splitting or crushing rilpivirine tablets. Rilpivirine is insoluble in water

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
	formulations under investigation- Janssen Ireland (https://clinicaltrials.gov/ct2/show/NCT02561936)			solutions were administered enterally. Crushed dolutegravir 50 mg BID (separated from enteral nutrition by 2 hours) and rilpivirine 25 mg daily (given with a 240-mL bolus of an enteral formula (2 kcal/mL)) were administered via orogastric tube. Crushed tablets were each mixed with 10 mL of water and flushed down the tube at separate administration times. Trough concentrations were: day 8, rilpivirine 30 ng/mL (reference range 40-120 ng/mL), and day 9, dolutegravir 820 ng/mL (reference range 830 ng/mL steady-state trough concentration for 50 mg once daily dose). Virologic suppression was maintained after ARV enteral administration (hospital day 29). Given somewhat decreased levels of these ARVs, the authors recommended consideration to increase dolutegravir to 150-200 mg total daily dose, particularly in integrase-experienced patients, and rilpivirine 50 mg daily (similar to dosing with an inducer such as rifabutin). (Turley et al. JIAPAC 2017;16(2):117-119).	over wide pH range. (Email communication, Janssen, July 2012). Crushed tablets added to a small amount of semisolid food or liquid is not expected to have an adverse effect if consumed immediately. Since tablets are small, ensure the whole dose is consumed. (Huesgen et al. Pharmacother 2016;36(11):1145-65).
ritonavir	yes	80 mg/mL oral	Stable at room		Tablets may not be split or

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
		liquid; 240 mL bottle. Orange-coloured oral solution, peppermint & caramel-flavoured. 43.2% v/v alcohol, propylene glycol 26.57% w/v. Shake well before each use. 100 mg Oral Powder (100 mg/packet)- Available in the US only.	temperature; do not refrigerate. See tips for taking liquid in Crushing & Splitting section.		crushed (Norvir® Product 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 Oral powder (100 mg/packet): The entire packet should be mixed with soft food such as apple sauce or vanilla pudding, or mixed with liquid such as water, chocolate milk, or infant formula. All soft food or liquid should be consumed within 2 hours of preparation. The bitter taste may be decreased if taken with food. The powder should be used in 100 mg increments only. The oral powder can also be administered via feeding tube after being mixed with water.
saquinavir	no		Liquid not being	In an open-label, randomized, 4	Hard gel caps (Invirase®) may

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
			formulated due to unpalatability	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).	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 (d4T)	yes- SAP	1 mg/mL oral suspension; 200 ml bottle. Fruit-flavoured. Shake well.	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 (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.,	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.

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
		applesauce, baby food, yogurt). Do not attempt to mix in a liquid as the powder may float on top even after stirring.			
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.
OTHER:					
acyclovir	yes	200 mg/5 mL;125 mL bottle. Banana-flavoured suspension.	Store between 15-25 ºC		

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
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 powder when opening capsules.
rifabutin	no				Can open capsules (experience

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
					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); 100 & 400	Store at room temperature. Shake well before use.		

Drug	Oral Liquid Preparation			Case Reports/Clinical Compounding	Information on Crushing or Splitting Tablets
	Commercial Oral Liquid Available?	Formulation	Stability		
		mL bottles Contains sorbitol. Example : Teva-Trimel suspension contains sorbitol 4 g/5 mL- (Personal communication, Teva Canada, April 2017)			

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)