Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Abacavir (ZIAGEN®, ABC)

Dose	Neonatal/Infant: • Not approved for infants < 3 months. Pediatric (≥3 months): • 8 mg/kg/dose (maximum 300 mg) po BID • If clinically stable with undetectable viral load and stable CD4 cell count for > 24 weeks (6 months), may consider once daily ABC as 16 mg/kg/day to maximum of 600 mg po once daily. Dosing regimen with scored tablets for pediatric patients weighing over 14 kg: Weight-band BID dosing (FDA approved label revisions, Mar 2015): • 14 to < 20 kg: 150 mg po BID or 300 mg once daily • ≥ 20 to < 25 kg: 150 mg po QAM and 300mg po QPM or 450 mg po once daily • ≥ 25 kg: 300 mg po BID or 600 mg once daily Adolescent (weight ≥ 25 kg)/Adult: • 300 mg po BID or 600 mg once daily
How Supplied/ Storage	• 20 mg/mL banana-strawberry liquid (240 mL bottle). Store at room temperature. • 300 mg tablet (Ziagen® Product Monograph, Canada) (300 mg scored tablet only available in the US) • Combination tablet: – TRIZIVIR® = 300 mg zidovudine; 150 mg lamivudine; 300 mg abacavir – KIVEXA® = 600 mg abacavir; 300 mg lamivudine – TRIUMEQ® = 50 mg dolutegravir; 600 mg abacavir; 300 mg lamivudine
Food Restrictions	May take with or without food.
Comments	• Test patients for HLA-B*5701 allele before starting therapy to predict risk of hypersensitivity. If positive for HLA-B*5701, do not use abacavir. • Watch for hypersensitivity reaction (~ 5% incidence; usually within first 6 weeks): fever, rash, fatigue, n/v, diarrhea, abdominal pain and respiratory symptoms. • **Do NOT rechallenge if suspect hypersensitivity.** • KIVEXA®: Film coated immediate release 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 02-2015) • TRIZIVIR®: Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. • TRIUMEQ®: 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 semi-solid food or liquid, and consumed immediately. (Data on File, ViiV Healthcare, Oct 2014)

Didanosine (VIDEX®, VIDEX EC®, ddI)

Antiretroviral Drug Dosing in Pediatric Patients
July 2017

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
Dose	Neonatal/Infant (2 weeks to less than 3 months): • 50 mg/m^2/dose po BID is the preferred dose based on current pharmacokinetic knowledge[1] Infant (≥ 3 months to 8 months): 100 mg/m^2/dose po BID Pediatric dose of oral solution (> 8 months): • 120 mg/m^2/dose po BID (range 90 – 150 mg/m^2/dose po BID, maximum 200 mg BID) • In treatment-naïve patients aged 3-21 years, 240 mg/m^2 once daily (oral solution or capsules) has shown effective viral suppression Pediatric dose of Videx EC for ages 6 to 18 years and body weight ≥ 20 kg (2017 Pediatric DHHS guidelines): 20 to < 25 kg: 200 mg po once daily 25 to < 60 kg: 250 mg po once daily ≥ 60 kg: 400 mg po once daily Adult/Adolescent: Oral solution: < 60 kg: 125 mg po BID (preferred) or 250 mg once daily ≥ 60 kg: 200 mg po BID (preferred) or 400 mg once daily Videx EC: 25 to < 60 kg: 250 mg once daily ≥ 60 kg: 400 mg once daily Didanosine combined with tenofovir DF (2017 DHHS Pediatric Guidelines) < 60 kg: 200 mg once daily (limited data in adults) ≥ 60 kg: 250 mg once daily
How Supplied/ Storage	• 4 g pediatric powder for oral solution (final concentration of 10 mg/mL). Refrigerate for up to 30 days (shake well before using). Available through Special Access Program[2]. • VIDEX EC delayed release capsules: 125 mg, 200 mg, 250 mg and 400 mg
Food Restrictions	• Take on an empty stomach. Do not give with fruit juices or acidic drinks, feeds or milk. To improve adherence some practitioners administer ddI without regard to timing of food.
Comments	4 g bottle (product monograph revised 8/2014): • 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. • Note: The admixture may be dispensed in flint-glass or plastic bottles. • Didanosine oral solution contains antacids which may interfere with absorption of some medications if given at the same time. • Combination of stavudine and didanosine is not recommended (unless benefits outweigh the risks) due to increased risk of

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
	serious toxicities. • Combination of didanosine and tenofovir should be avoided due to drug interaction and increased risk of pancreatitis
Emtricitabine (FTC, Emtriva®)	
Dose	Neonate (0 to < 3 months): • 3 mg/kg/dose po once daily Pediatric (≥ 3 months to 17 years): • Oral solution: 6 mg/kg/dose (maximum dose 240 mg)* once daily • Capsules (children weighing > 33 kg): 200 mg once daily Adult/Adolescent (≥ 18 years): • Oral solution: 240 mg daily* • Capsules: 200 mg daily *Higher maximum dosage with oral solution because 20% lower plasma exposure
How supplied/ Storage	Oral solution: 10 mg/mL (store at room temperature up to 25°C if used within 3 months, otherwise refrigerate for longer-term storage) – Only available in US Capsules: 200 mg – Only available in US Combination Tablet: TRUVADA® = 200 mg emtricitabine + 300 mg tenofovir DF ATRIPLA® = 200 mg emtricitabine + 300 mg tenofovir DF + 600 mg efavirenz COMPLERA® = 200 mg emtricitabine + 300 mg tenofovir DF + 25 mg rilpivirine ODEFSEY®= 200 mg emtricitabine + 25 mg tenofovir AF + 25 mg rilpivirine STRIBILD®= 200 mg emtricitabine + 300 mg tenofovir DF +150 mg elvitegravir + 150 mg cobicistat GENVOYA®= 200 mg emtricitabine + 10 mg tenofovir AF + 150 mg elvitegravir + 150 mg cobicistat DESCOVY®= 200 mg emtricitabine + 10 mg tenofovir AF **or** 200 mg emtricitabine + 25 mg tenofovir AF
Food restrictions	May be taken with or without food.
Comments	• 200 mg capsules may be opened and mixed with water • Screen patients for HBV prior to starting emtricitabine • TRUVADA®: 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) • ATRIPLA®: Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours did not meet bioequivalence of Atripla® whole tablet however clinical implications unknown. The authors stated that crushed Atripla® may be a viable option in certain patients and risks vs. benefits should be carefully considered (King et al. JAIDS 2011; 56:e131-2). 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 soluble in water. (Email communication, Gilead, July 2012). • COMPLERA®: Crushing Complera tablets into a liquid medium has not been studied and is not recommended. Rilpivirine is

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
	practically insoluble in water over a wide pH range. (Email communication, Gilead, July 2012). • STRIBILD®: No data on crushing or splitting Stribild and is not recommended by manufacturer. Cobicistat is practically insoluble in water. (Email communication, Gilead, July 2012). Case report describing successful virological suppression with crushed Stribild in juice (Fulco et al. AJHP 2014; 71(10);784-6). • GENVOYA®: No data on crushing or splitting Genvoya and is not recommended by manufacturer. While emtricitabine and tenofovir are soluble in water, cobicistat and elvitegravir are practically insoluble in water. (Communication from Gilead Canada, March 2016). • ODEFSEY®: Crushing and splitting Odefsey tablets has not been studied and is not recommended. Rilpivirine is practically insoluble in water over a wide pH range. (Communication from Gilead, January 2017). • DESCOVY®: Crushing or splitting FTC/TAF tablets has not been studied and is not recommended. Emtricitabine is soluble in water. TAF is soluble in water; however, it has a bitter and burnt aromatic flavour (Communication from Gilead Canada, January 2017).
Lamivudine (3TC®, EPIVIR®)	
Dose	<u>Neonate/Infant (age < 4 weeks):</u> • 2 mg/kg/dose po BID <u>Pediatric (age ≥ 4 weeks):</u> • 4 mg/kg/dose po BID; maximum 150 mg po BID (give BID; avoid use of liquid formulation as once daily in this age category)* <u>Pediatric dosing (patients weighing ≥ 14 kg) for scored 150 mg tablet</u> • 14 to < 20 kg: 75 mg po BID • ≥ 20 to < 25 kg: 75 mg po QAM, 150 mg po QHS • ≥ 25 kg: 150 mg po BID <u>Pediatric dosing (patients weighing ≥ 14 kg and ≥3 years of age) with scored 150 mg tablet for patients until clinically stable, with a stable CD4 count and undetectable viral load:</u> • 14 to < 20 kg: 150 mg once daily • ≥ 20 to < 25 kg: 225 mg once daily • ≥ 25 kg: 300 mg once daily <u>Adult/Adolescent (age ≥ 16 years): (2017 DHHS Pediatric Guidelines)</u> • Weight < 25 kg: 4 mg/kg/dose po BID (maximum 150 mg po BID) • ≥ 25 kg: 150 mg po BID or 300 mg po once daily
How Supplied/ Storage	• 10 mg/mL strawberry-banana oral liquid (240 mL bottle). Store at room temperature. • 3TC®: 150 mg (scored) and 300 mg tablets • 100 mg tablet (Heptovir®) but restricted access due to HBV indication • Generic tablets: 100 mg, 150 mg, and 300 mg <u>Combination tablets:</u> COMBIVIR® = 300 mg zidovudine + 150 mg lamivudine (Generic tablet may be split) TRIZIVIR® = 300 mg zidovudine + 150 mg lamivudine + 300 mg abacavir

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	
	KIVEXA® = 600 mg abacavir + 300 mg lamivudine TRIUMEQ® = dolutegravir 50 mg; abacavir 600 mg; lamivudine 300 mg
Food Restrictions	Take with or without food.
Comments	• Lamivudine 150 mg scored tablet. Tablets may be split or crushed. Screen patients for HBV infection before administering 3TC. • *Liquid formulation of lamivudine generally not recommended given as once daily in infants and young children due to potentially lower drug concentrations than BID (also not well-studied). • Pharmacokinetic study in 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. • COMBIVIR®: Film-coated immediate release tablet however no studies, but likely acceptable to crush immediately before ingestion. May have a bitter aftertaste. • Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. • crushing tablets is not expected to affect the dissolution or absoprtion. 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)

Stavudine (ZERIT®, d4T)	
Dose	<u>Neonate/Infant (birth up to 13 days):</u> • 0.5 mg/kg/dose po BID <u>Pediatric (≥14 days and weighing < 30 kg):</u> • 1 mg/kg/dose po BID <u>Adult/Adolescent (body weight ≥ 30 kg): (2017 DHHS Pediatric Guidelines)</u> • 30 mg po BID[1]
How Supplied/ Storage	• 1 mg/mL fruit flavored suspension (200 mL bottle). Available through Special Access program[2]. Stable for 30 days in fridge. Shake well. • 15, 20, 30, 40 mg capsules
Food Restrictions	Take with or without food.
Comments	• May open capsule and give in small portion of food or 5-10 mL cool tap water. • Should not be administered with zidovudine due to poor antiretroviral effect. • Combination of stavudine and didanosine is not recommended (unless benefits outweigh the risks) due to increased risk of

	serious toxicities. • Dosage adjustment required for renal dysfunction based on CrCl
	Tenofovir alfenamide (TAF)
Dose	Neonate/Infant: (2016 DHHS Pediatric Guideline, Canada and US monographs) • Not approved for use. Pediatric: • Not recommended for use in children less than 12 years Adolescent (≥ 12 years and weight ≥ 35 kg)/Adult: • Genvoya® 1 tablet po once daily • Odefsey® 1 tablet po once daily • Descovy® 1 tablet po once daily
How Supplied/ Storage	TAF only available as fixed dose combination tablet Combination tablets: ODEFSEY®= 200 mg emtricitabine + 25 mg tenofovir AF + 25 mg rilpivirine GENVOYA®= 200 mg emtricitabine + 10 mg tenofovir AF + 150 mg elvitegravir + 150 mg cobicistat DESCOVY®= 200 mg emtricitabine + 10 mg tenofovir AF **OR** 200 mg emtricitabine + 25 mg tenofovir AF
Food Restrictions	Take Genvoya with food and Odefsey with a meal. May take Descovy with or without food.
Comments	• TAF not recommended for use with CrCl < 30 mL/min. • TAF 25 mg dose is recommended as the standard dose when not given with a pharmacokinetic booster (ritonavir or cobicistat). TAF 10 mg dose is recommended with pharmacokinetic boosters such as ritonavir or cobicistat (Canadian Descovy monograph, April 2016). • TAF is soluble in water; however, it has a bitter and burnt aromatic flavour (Communication from Gilead Canada, January 2017). • Screen patients for HBV infection before use of TAF. • ODEFSEY® must be given with at least a 500 calorie meal (2017 DHHS Pediatric guidelines). (Note: Odefsey® Canadian product monograph recommends to take with a meal; calories not specified). • GENVOYA®: No data on crushing or splitting Genvoya and is not recommended by manufacturer. While emtricitabine and tenofovir are soluble in water, cobicistat and elvitegravir are practically insoluble in water. (Communication from Gilead Canada, March 2016). • ODEFSEY®: Crushing and splitting Odefsey tablets has not been studied and is not recommended. Rilpivirine is practically insoluble in water over a wide pH range. (Communication from Gilead, January 2017). • DESCOVY®: Crushing or splitting FTC/TAF tablets has not been studied and is not recommended. Emtricitabine is soluble in water. TAF is soluble in water; however, it has a bitter and burnt aromatic flavour (Communication from Gilead Canada, January 2017).
	Tenofovir disoproxil fumarate (VIREAD®, TDF)
Dose	Neonate/Infant: • Not approved for use.

	Pediatric (≥ 2 years to < 12 years): • Not approved for use in children less than 2 years. • Recommended oral dose is 8 mg/kg/dose (up to a maximum dose of 300 mg) once daily as powder or tablets (see Viread product monograph, US and 2017 DHHS Pediatric Guidelines[1]) Adolescent (≥ 12 years and weight ≥35 kg)/Adult: • 300 mg once daily
How Supplied/ Storage	• 300 mg tablet (150 mg, 200 mg, 250 mg and 300 mg tablet available in US) • Oral powder (40 mg per 1 g of powder)- available in the US only Combination tablets: TRUVADA® = 200 mg emtricitabine + 300 mg tenofovir DF ATRIPLA® = 200 mg emtricitabine + 300 mg tenofovir DF + 600 mg efavirenz COMPLERA® = 200 mg emtricitabine + 300 mg tenofovir DF + 25 mg rilpivirine STRIBILD®= 200 mg emtricitabine + 300 mg tenofovir DF +150 mg elvitegravir + 150 mg cobicistat
Food Restrictions	Take with food if possible for increased absorption. May take without food.
Comments	• Tenofovir DF: Dissolve crushed tablets in 100 mL of water, or grape juice and take immediately. • Unpalatable bitter taste. May split tablet and insert in empty gelatin capsule to mask bitter taste. • Decreases in Bone Mineral density (BMD) have been reported in both adult and pediatric studies. • 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). Administer immediately to avoid a bitter taste. Do not attempt to mix in a liquid as the powder may float on top even after stirring. • Tenofovir may decrease atazanavir (ATV) plasma concentrations. In adults, a boosting dose of 100 mg ritonavir is recommended (ATV 300 mg/RTV 100 mg) if co-administered with tenofovir. • TRUVADA®: 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) • ATRIPLA®: Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours did not meet bioequivalence of Atripla® whole tablet however clinical implications unknown. The authors stated that crushed Atripla® may be a viable option in certain patients and risks vs. benefits should be carefully considered (King et al. JAIDS 2011; 56:e131-2). 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 soluble in water. (Email communication, Gilead, July 2012). • COMPLERA®: Crushing Complera tablets into a liquid medium has not been studied and is not recommended. Rilpivirine is practically insoluble in water over a wide pH range. (Email communication, Gilead, July 2012). • STRIBILD®: No data on crushing or splitting Stribild and is not recommended by manufacturer. Cobicistat is practically insoluble in water. (Email communication, Gilead, July 2012). Case report describing successful virological suppression with crushed Stribild in juice (Fulco et al. AJHP 2014; 71(10);784-6).
Zidovudine (RETROVIR®, AZT, ZDV)	
Dose	Neonate/infant (< 6 weeks of age) dose for prevention of transmission or treatment: • For prevention of transmission, start ZDV immediately (preferably within 2 to 6 hours but no longer than 6 - 12 hours after

	birth) and administer for 6 weeks.[3] • *Less than 30 weeks gestation*: – PO: 2 mg/kg/dose po q12h for 4 weeks, then increase to 3 mg/kg/dose q12h for last 2 weeks – IV: 1.5 mg/kg/dose IV q12h for 4 weeks, then increase to 2.3 mg/kg/dose q12h for last 2 weeks • ≥ *30 to < 35 weeks gestation:* – PO: 2 mg/kg/dose po q12h for 2 weeks, then increase to 3 mg/kg/dose q12h for last 4 weeks – IV: 1.5 mg/kg/dose q12h for 2 weeks, then increase to 2.3 mg/kg/dose q12h for last 4 weeks • ≥ *35 weeks gestation:* – PO: 4 mg/kg/dose po q12h for 4-6 weeks – IV: 3 mg/kg/dose IV q12h <u>Infant/child dose (age ≥ 35 weeks post-conception and at least 4 weeks post-delivery):</u> • PO: 240 mg/m^2/dose po q12h <u>or:</u> • MG/KG DOSING: – 4 to < 9 kg: 12 mg/kg/dose po BID – 9 to < 30 kg: 9 mg/kg/dose po BID – ≥ 30 kg: 300 mg po BID <u>Adult/Adolescent (18 years or older):</u> • 300 mg po BID
How Supplied/ Storage	• 10 mg/mL strawberry syrup (240 mL bottle). Store at room temperature. • 100 mg capsules • 200 mg/20 mL vial (intravenous) <u>Combination tablets:</u> COMBIVIR® = 300 mg zidovudine + 150 mg lamivudine TRIZIVIR® = 300 mg zidovudine + 150 mg lamivudine + 300 mg abacavir
Food Restrictions	Take with or without food.
Comments	• Should not be administered with d4T due to poor antiretroviral effect. • May open capsule and give in small portion of food or 5 – 10 mL cool tap water. • COMBIVIR®: Film-coated immediate release tablet however no studies, but likely acceptable to crush immediately before ingestion. May have a bitter aftertaste. • TRIZIVIR®: Film coated immediate release tablet however no studies regarding stability of split or crushed tablets.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	
Efavirenz (SUSTIVA®, EFV)	
Dose	Neonate/Infant: • Not approved for use. Dosing for Children 3 months to < 3 years based on CYP 2B6 Genotype (CYP 2B6 516 G/G or G/T and CYP 2B6 516 T/T) currently being investigated. Pediatric (3 months to < 3 years and weight ≥ 3.5 kg) without regard to CYP 2B6 Genotype: • Generally not recommended to use. FDA approved dosing in this age group as follows: 3.5 to < 5 kg: 100 mg daily 5 to < 7.5 kg: 150 mg daily 7.5 to < 15 kg: 200 mg daily 15 to < 20 kg: 250 mg daily Pediatric (≥3 years and weight ≥ 10 kg): • Give once daily (po) 10 to < 15 kg: 200 mg 15 to < 20 kg: 250 mg 20 to < 25 kg: 300 mg 25 to < 32.5 kg: 350 mg 32.5 to < 40 kg: 400 mg ≥ 40 kg: 600 mg • Pediatric patients with virologic rebound or lack of response may require higher doses (367 mg/m^2/dose to maximum of 600 mg po once daily) Adult/Adolescent (weight ≥ 40 kg): • 600 mg po once daily
How Supplied/ Storage	• 50, 200 mg capsules • 600 mg tablet; Note: efavirenz 30 mg/L oral solution is no longer available internationally Combination tablet: ATRIPLA® = 300 mg tenofovir + 200 mg emtricitabine + 600 mg efavirenz
Food Restrictions	May take with or without food but do not take with high fat meal (significantly increases AUC and side effects).
Comments	• Dose at bedtime recommended first 2-4 weeks to decrease CNS side effects. • **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 cap away from the body of the capsule carefully, sprinkle and mix the 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.

	• **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). Since data is limited on splitting tablets, the use of the capsule formulation is preferred when possible. • ATRIPLA®: Atripla FDC tablet crushed, dissolved in 5 mL of water and diluted to 20 mL with Ora-Sweet oral solution and used within 24 hours did not meet bioequivalence of Atripla® whole tablet however clinical implications unknown. 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 2011; 56:e131-2). 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 soluble in water. (Email communication, Gilead, July 2012). • Mixed inducer/inhibitor of CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • Use with caution in adolescent women of childbearing potential because of the risk of teratogenicity.
Etravirine (Intelence® ETR)	
Dose	Neonate/ Infant: • Not approved for use. Pediatric (antiretroviral-experienced children 6 to <18 years of age and weighing at least 16 kg): Not approved for use in children < 6 years. Studies in infants and children aged 2 months to 6 years are currently underway (NCT01504841). • 16 to < 20 kg: 100 mg po BID • 20 to < 25 kg: 125 mg po BID • 25 to < 30 kg: 150 mg po BID • ≥ 30 kg: 200 mg po BID Adult (antiretroviral experienced): • 200 mg po BID
How Supplied/ Storage	• 25 mg tablets • 100 mg tablets • 200 mg tablets • Tablets sensitive to moisture. Store in original container with desiccant at room temperature.
Food Restrictions	• Take with food.
Comments	• Inducer of CYP3A4; Inhibitor of CYP2C9/2C19. **CHECK FOR DRUG INTERACTIONS.** • 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^{o}C) or carbonated beverages. (Intelence® Product Monograph, 2014)
Nevirapine (VIRAMUNE®, NVP)	

Dose	Newborn Perinatal Prophylaxis (see Perinatal guidelines for more information on use of NVP for prophylaxis of mother to child transmission of HIV): **Weight-Band Prophylaxis Dosing** (NICHD-HPTN 040/PACTG 1043 Study): 3 doses in first week of life (1st dose within 48 hours of birth; 2nd dose 48 hours after 1st dose; 3rd dose 96 hours after 2nd dose): • Birth weight < 1.5 kg: 2 **mg/kg per dose po (note: dose per kg for this weight only) X 1** • Birth weight 1.5 – 2 kg: 8 mg **per dose** po X 1 • Birth weight > 2 kg: 12 mg **per dose po** X 1 **Part of 3-Drug Combination ARV Prophylaxis Regimen** (Investigational- IMPAACT P1115) (2017 DHHS Perinatal Guidelines): No lead-in dosing recommended • ≥ 37 weeks gestational age: 6 mg/kg/dose po BID from birth through to 2-6 weeks • 34 to < 37 weeks gestational age: 4 mg/kg/dose po BID for the first week, then 6 mg/kg/dose po BID (no lead-in) through 2-6 weeks - *The optimal duration of nevirapine is unknown; many experts recommend continuation of nevirapine x 6 weeks and others recommend 2 weeks if the HIV amplification test NAAT is negative at birth.* - *In children < 2 years old some experts initiate nevirapine without 2-week lead-in (rash not as prevalent as with older children).* **Alternate prophylaxis dosing strategy** (Sick Kids in Toronto: Lau et al. JAIDS, 2017): Lead-in dosing used • ≥ 32 weeks gestational age: 150 mg/m^2/dose po once daily x 2 weeks (lead-in), then 150 mg/m^2/dose po BID x 2 weeks (total 4 weeks) *** TDM is essential in this strategy due to large inter/intra patient variability *** Patients with a lower birth weight required a lower NVP dose to achieve target trough levels (3-8 mg/L) **Premature infant < 34 weeks gestation prophylaxis dosing** (Investigational): Various dosing strategies under study • 2 mg/kg/dose po once daily x 2 weeks, then 4 mg/kg/dose po once daily (IMPAACT P1106- Bekker, CROI 2016, #758) Treatment of HIV Infection: Investigational dose age < 1 month[1]: (2017 DHHS Pediatric Guidelines) • 34-37 weeks gestational age: 4 mg/kg/dose po BID for the first week, then 6 mg/kg/dose BID (no lead in) • ≥ 37 weeks gestational age: 6 mg/kg/dose po BID (no lead in) Pediatric (immediate release tablet): *≥ 1 month to < 8 years:* • 200 mg/m^2/dose po once daily x 14 days, then 200 mg/m^2/dose po BID (if no rash or ADRs; maximum 200 mg per dose BID) *≥ 8 years:* • 120 - 150 mg/m^2/dose po once daily X 14 days, then 120 - 150 mg/m^2/dose po BID (if no rash or ADRs; maximum 200 mg

	per dose BID or extended release 400 mg po once daily) Pediatric (extended release tablet): • ≥ 6 years who are already taking immediate release nevirapine BID can be switched to extended release without lead in dosing Adult/Adolescent: • 200 mg po BID (Note: Initiate dose at 200 mg po once daily x 14 days then increase dose to 200 mg po BID) • 400 mg extended release po once daily (Note: initiate therapy with 200 mg immediate release tablet po once daily for the first 14 days, then increase to 400 mg po once daily if no rash) • Nevirapine is not approved for children less than 15 years of age in Canada; however, dosing recommendations are well-established for immediate release tablets and suspension)
How Supplied/ Storage	• 10 mg/mL sweet flavoured syrup (240 mL bottle). Available through Special Access program[2]. Store at room temperature. • 200 mg tablet; 400 mg extended release tablet
Food Restrictions	May take with or without food.
Comments	• Do not increase dose if rash occurs within first 14 days. • May crush immediate release (IR) tablets, mix in water and give orally or by G-tube; liquid formulation available via SAP. • Do not crush, chew or divide extended release (ER) tablet (400 mg XR); they may be swallowed whole. • Shake suspension well before administering. • If nevirapine dosing is interrupted for > 14 days, should be restarted with once daily dosing with immediate release tablets or suspension for 14 days followed by dose escalation. • Patients ≥ 6 years taking IR tablet BID may be switched to ER tablet without lead-in dosing • When switching from efavirenz to nevirapine, the 14-day escalation of nevirapine is not required. Full doses of nevirapine can be used as of the first day. • Remnants of extended release polymer matrix may be found in feces but may only contain part of original nevirapine content • Induces CYP450 3A4 – may need to increase dose of other drugs metabolized by P450 enzymes in the liver. **CHECK FOR DRUG INTERACTIONS.**
Rilpivirine (EDURANT®, RPV)	
Dose	Neonate/infant: • Rilpirivine is not approved for use in neonates/infants. Pediatric Rilpivirine is not approved in Canada for use in children less than 12 years of age. Antiretroviral-naïve children 12 to <18 years of age weighing at least 35 kg: (2017 DHHS Pediatric Guidelines) • 25 mg po once daily • COMPLERA® 1 tablet po once daily (with a 400 calorie meal) • ODEFSEY® 1 tablet po once daily (with a meal) • Trial underway investigating use in pediatric patients ≥ 6 to 18 years (NCT00799864)

	Adult >18 years (avoid in antiretroviral-naïve patients with viral load ≥100,000 copies/mL): • 25 mg po once daily
How Supplied/ Storage	• 25 mg tablet • Dispersible tablet (2.5 mg) and granule (2.5 mg/g) formulations are under investigation (https://clinicaltrials.gov/ct2/show/NCT02561936) Combination tablet: COMPLERA® = 300 mg tenofovir DF + 200 mg emtricitabine + 25 mg rilpivirine ODEFSEY®= 200 mg emtricitabine + 25 mg tenofovir AF + 25 mg rilpivirine
Food Restrictions	Must take with food (at least ~400 kcal recommended).
Comments	• 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). • COMPLERA®: Crushing Complera tablets into a liquid medium has not been studied and is not recommended. Rilpivirine is practically insoluble in water over a wide pH range. (Email communication, Gilead, July 2012). • ODEFSEY®: Crushing and splitting Odefsey tablets has not been studied and is not recommended. Rilpivirine is practically insoluble in water over a wide pH range. (Communication from Gilead, January 2017). • Use RPV with caution in patients with baseline VL > 100,000 copies/mL. • RPV is metabolized by CYP4503A4. CHECK FOR DRUG INTERACTIONS. • Caution when administered with a drug with a known risk of Torsades de Pointes (QT prolongation) • Do not use with proton pump inhibitors and caution with H2 receptor antagonists. Antacids should only be taken at least 2 hours before or 4 hours after rilpivirine.

Protease Inhibitors (PIs)	
Atazanavir (Reyataz®, ATV)	
Dose	Neonate/infant: • Not approved for use. Should not be administered to neonates and infants < 3 months due to risk associated with hyperbilirubinemia and kernicterus. Pediatric (≥ 3 months to <18 years and weight ≥ 5 kg : (2017 DHHS Pediatric Guidelines) • Boosted atazanavir USA FDA approved for ARV-naïve infants at least 3 months of age. In Canada, dosing guidelines approved for use in children ≥ 6 years. ATV powder: – 5 to < 15 kg: ATV 200 mg/rtv 80 mg po once daily – 15 to < 25 kg: ATV 250 mg/ rtv 80 mg po once daily ATV capsules (capsule not approved for use < 6 years or < 15 kg) – 15 to < 20 kg: ATV150 mg/rtv 100 mg po once daily – 20 to < 40 kg: ATV 200 mg/rtv 100 mg po once daily (note: some experts would increase atazanavir to 300 mg at > 35 kg to avoid under-dosing, especially when administered with TDF) – ≥ 40 kg: ATV 300 mg/rtv 100 mg po once daily Adult/Adolescent (≥18 years) and Weighing at least 40 Kg: • *Antiretroviral naïve:* ATV 300 mg/rtv 100 mg po once daily or ATV 400 mg po once daily (if unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels) • *Antiretroviral experienced*: 300 mg ATV/rtv 100 mg po once daily • *Atazanavir in combination with efavirenz*: 400 mg ATV/rtv 100 mg both po once daily but at separate times (*naïve only*) • *Atazanavir in combination with tenofovir:* 300 mg ATV/rtv 100 mg both po once daily. • *Atazanavir in combination with* H2 receptor antagonist: 400 mg ATV/rtv 100 mg po once daily.
How Supplied/ Storage	• 150, 200, and 300 mg capsules • 50 mg in 1.5 g of powder packet (contains aspartame, sucrose, and orange-vanilla flavour)- for > 3 months and between 10 to < 25 kg – available in US or via Special Access Program[2] Combination tablet: • Evotaz® = 300 mg atazanavir + 150 mg cobicistat – available in the US only (approved in Canada but not yet marketed)
Food Restrictions	Take with food.
Comments	• Capsules and powder packets are not interchangeable. • Capsules: may be opened and mixed with applesauce for immediate ingestion with food. • Oral 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. If > 1 packet per dose, repeat these steps for each packet. 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. • Antacids and buffered medications (including didanosine buffered tablets) decrease ATV concentrations if taken at the same time –Administer ATV 2 hours before these medications. H_2 receptor antagonists decrease ATV levels. Check drug interaction resource for recommendations on dosing ATV when co-administered with H2 receptor antagonists. • Proton pump inhibitors decrease ATV levels. Omeprazole (≤ 20 mg) may be used in treatment I patients taking boosted ATV– take 12 hours before ATV. Otherwise coadministration of atazanavir and proton pump inhibitors is **NOT** recommended. • ATV inhibits UGT1A1 and may increase levels of raltegravir. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • Atazanavir in combination with cobicistat (Evotaz®) in children and adolescents aged 3 months to 18 years is currently under investigation. Cobicistat use is currently not recommended for use in children and adolescents less than 18 years. Some experts consider that cobicistat boosted regimens may be appropriate in certain children aged < 18 years and weighing ≥ 35 kg; consultation with an HIV pediatric expert is advised (2017 DHHS Pediatric Guidelines).
Darunavir (Prezista®, DRV)	

Dose	<u>Neonate/ Infant:</u>
	• Not approved for use.
	• DRV is not recommended in pediatric patients < 3 years or ≤ 10 kg
	
	<u>Pediatric (3 years to <18 years) Treatment naïve or treatment-experienced with or without one or more darunavir-associated mutations:</u>
	• Take with food.
	• 10 to < 11 kg: 200 mg DRV/32 mg rtv po BID
	• 11 to < 12 kg: 220 mg DRV/32 mg rtv po BID
	• 12 to < 13 kg: 240 mg DRV/40 mg rtv po BID
	• 13 to < 14 kg: 260 mg DRV/40 mg rtv po BID
	• 14 to < 15 kg: 280 mg DRV/48 mg rtv po BID
	• 15 to < 30 kg: 375 mg DRV/48 mg rtv po BID
	• 30 to < 40 kg: 450 mg DRV/100 mg rtv po BID
	• ≥ 40 kg: 600 mg DRV/100 mg rtv po BID
	
	<u>Adult/Adolescent (≥ 12 years):</u>
	• Take with food.
	• Treatment naïve or experienced; no DRV resistance-associated mutations:
	  • ≥ 30 to < 40 kg: 675 mg DRV/rtv 100 mg po once daily
	  • ≥ 40 kg: 800 mg DRV/rtv 100 mg po once daily
	• Treatment experienced; at least one DRV associated-resistance mutation:
	  • ≥ 30 to < 40 kg: 400 mg DRV/rtv100 mg po both BID
	  • ≥ 40 kg: 600 mg DRV/rtv 100 mg po both BID

	Adult (> 18 years): • At least one DRV resistance associated mutation: 600 mg darunavir/rtv 100 mg po BID with food • Treatment naïve or treatment-experienced with no DRV resistance associated mutations: 800 mg darunavir/150 mg cobicistat (Prezcobix ®) po once daily
How Supplied/ Storage	• 75 mg, 150 mg, 600 mg, 800 mg tablets • 100 mg/mL Oral suspension- available in Canada via compassionate access through Janssen (email communication, Janssen, February 2017). Store oral suspension at room temperature. Shake well before use. • PREZCOBIX®: 800 mg darunavir; 150 mg cobicistat co-formulated tablet
Food Restrictions	Must be taken with food.
Comments	• Darunavir specific mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V • In patients with one or more darunavir resistance-associated mutations, darunavir should only be given twice daily • Darunavir contains a sulfonamide moiety. The potential cross-sensitivity with other drugs in the sulfonamide class is unknown – caution in patients with sulfonamide allergy. • Limited data available on chewing or crushing. No problems anticipated if tablets chewed or crushed for administration through a nasogastric (NG) tube (Data on file, Tibotec, May 2008). 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 15-20 mL of water. Viral load did not change significantly and adequate darunavir trough levels were achieved. (Kim et al. CJHP 2014;67(1):39-42). Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.** • PREZCOBIX®: Splitting film-coated tablets has not been studied. Tablets should be swallowed whole without breaking or crushing to ensure administration of the entire dose. • PREZCOBIX® safety and efficacy has not been established in pediatric patients, thus use is not recommended. (Prezcobix Product Monograph, 2015)**.** Pharmacokinetics, efficacy and safety of darunavir/cobicistat is currently under study in children aged 12 to 18 years. Some experts consider that cobicistat boosted regimens may be appropriate in certain children aged < 18 years and weighing ≥ 35 kg; consultation with an HIV pediatric expert is advised (2017 DHHS Pediatric Guidelines).
Fosamprenavir (TELZIR®, f-APV)	
Dose	Neonate: • Not approved for use. Pediatric (≥ 6 months to 18 years): • Boosted fosamprenavir USA FDA approved for ARV-naïve infants at least 4 weeks of age and treatment experienced infants at least 6 months of age. Pediatric guidelines do not recommend using in infants < 6 months. In Canada, dosing guidelines approved for use in children ≥ 6 years. • *Oral suspension* – < 11 kg: f-APV 45 mg/kg/dose plus rtv 7 mg/kg/dose both po BID – 11 to < 15 kg: f-APV 30 mg/kg/dose plus rtv 3 mg/kg/dose both po BID – 15 to < 20 kg: f-APV 23 mg/kg/dose plus rtv 3 mg/kg/dose both po BID

	– ≥ 20 kg f-APV 18 mg/kg/dose plus rtv 3 mg/kg/dose both po BID – Do not exceed recommended adult dose: f-APV 700 mg plus rtv 100 mg po BID <u>Adult/Adolescent (> 18 years):</u> • *Antiretroviral naïve:* – 1400 mg f-APV BID **without** ritonavir (unboosted regimen not recommended due to inferior potency) – 1400 mg f-APV/rtv 100-200 mg, both once daily – 700 mg f-APV/rtv 100 mg, both BID • *Protease-inhibitor experienced*: – 700 mg f-APV/rtv 100 mg, both BID
How Supplied/ Storage	• 700 mg tablet (prodrug, equivalent to 600 mg amprenavir) • 50 mg/mL oral suspension (225 mL bottle) [calcium prodrug, equivalent to 43 mg/mL amprenavir]. Contains 1% w/w propylene glycol. Verbal communication ViiV May 2017. Store suspension between 2 – 30°C. Discard 28 days after opening. Shake well.
Food Restrictions	• F-APV tablets without rtv may be taken with or without food. F-APV with rtv should be taken with food. • 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.
Comments	• Fosamprenavir calcium tablets and suspension are equivalent on a mg per mg basis. • No data available regarding stability of crushed or dissolved tablet. • APV is a sulfonamide. In pivotal studies there was no evidence of increased rash in patients with a history of sulfonamide allergy. Caution in patients with sulfonamide allergy. • The suspension contains propyl and methyl parahydroxybenzoate which may cause allergic reactions (delayed in some cases). • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Lopinavir/ Ritonavir (KALETRA®, LPV/rtv)	
Dose	<u>Neonate (age < 14 days):</u> • Do not administer to neonates before a postmenstrual age of 42 weeks and a post-natal age of at least 14 days because of potential toxicities. <u>Infant dose (age 14 days to 12 months – US FDA Approved):</u> • *Without nevirapine or efavirenz*: – 300 mg/m^2 LPV/ 75 mg rtv/m^2/dose po BID (~16 mg/kg/dose LPV/ 4 mg/kg/dose rtv po BID) – Plasma levels among patients < 12 months were lower than those observed in adults or older children. LPV dosing should be adjusted for growth at frequent intervals. – LPV/rtv is not recommended in combination with nevirapine, efavirenz, fosamprenavir, or nelfinavir in patients < 12 months of age. – Once daily dosing is not recommended.

	Pediatrics/Adolescent (> 12 months to 18 years) (2017 DHHS Pediatric guidelines): • *Treatment naïve and without nevirapine or efavirenz:* – 230 mg/m^2/dose LPV/ 57.5 mg/m^2/dose rtv po BID to a maximum of 400 mg LPV/100 mg rtv BID ○ < 15 kg: approximately 12 mg/kg/dose LPV/3 mg/kg/dose rtv po BID ○ ≥ 15 to 40 kg: approximately 10 mg/kg/dose LPV/2.5 mg/kg/dose rtv po BID – Dose based on weight for number of 100 mg LPV/ 25 mg rtv tablets: ○ 15 to 25 kg: 2 tablets (200/50 mg) po BID ○ > 25 to 35 kg: 3 tablets (300/75 mg) po BID ○ > 35 kg: 4 tablets (400/100 mg) po BID • *Treatment experienced or patients taking nevirapine or efavirenz:* – 300 mg/m^2/dose LPV/75 mg/m^2/dose rtv BID to a maximum of 400 mg LPV/100 mg rtv po BID ○ < 15 kg: approximately 13 mg/kg/dose LPV/3.25 mg/kg/dose rtv po BID ○ ≥ 15 to 45 kg: approximately 11 mg/kg/dose LPV/2.75 mg/kg/dose rtv po BID – Dose based on weight for number of 100 mg LPV/25 mg rtv tablets: ○ 15 to 20 kg: 2 tablets (200/50 mg) po BID ○ > 20 to 30 kg: 3 tablets (300/75 mg) po BID ○ > 30 to 45 kg: 4 tablets (400/100 mg) po BID ○ > 45 kg: 5 tablets (500/125 mg) po BID → can be given as combination of 2 tablets of 200/50 mg LPV/rtv and 1 tablet of 100 mg/25 mg LPV/rtv – Once daily dosing is not recommended. Adult (> 18 years): – < 3 LPV associated mutations: 800 mg LPV/200 mg rtv po once daily or 400 mg LPV/100 mg rtv po BID – > 3 LPV associated mutations: 400 mg LPV /100 mg rtv po BID – LPV associated mutations: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T and I84V – LPV/rtv once daily is not recommended with NVP or EFV
How Supplied/ Storage	• Cotton candy flavoured oral solution: 80 mg LPV/20 mg rtv per mL (160 mL bottle). Contains alcohol 42.4% v/v and 15.3% propylene glycol weight/volume. Solution should be refrigerated until dispensed and then stored up to 42 days at room temperature. • 100 mg lopinavir/25 mg ritonavir **pediatric** tablet; 200 mg lopinavir/50 mg ritonavir **adult** tablet, may be used in children capable of swallowing larger tablets. Tablets should be stored at room temperature. Tablets must be swallowed whole; they cannot be broken, chewed, or 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].
Food Restrictions	• Solution: Take with food to enhance absorption. • Tablets: Take with or without food.

Comments	• Liquid formulation contains alcohol therefore avoid co-medication with metronidazole. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Nelfinavir (Viracept®, NFV)	
Dose	Neonatal/Infant (less than 6 weeks): • in Canada or USA *NICHD/HPTN 040/PACTG 1043:* – 50-75 mg/kg/dose po BID; Less than 1.5 kg- not studied (note: Alberta Health Services perinatal protocol recommends 50 mg/kg/dose po q12 h in infants with birth weight < 1.5 kg) Pediatric (2 – 13 years): • 50 mg/kg/dose po BID (range 45 – 55 mg/kg/dose); Canadian monograph recommends 25-35 mg/kg/dose po TID Adult/Adolescent: • 1250 mg po BID
How Supplied/ Storage	250 mg and 625 mg tablets; Note: 50 mg/g oral powder (144 g bottle) only available in US and is no longer available in Canada
Food Restrictions	Give with food or shortly after food for optimal absorption.
Comments	• **Tabs:** Dissolve a 250 mg tablet in 5 mL of sterile water (50 mg/mL). Measure out dose with a syringe that has 1 mL increments. Round doses to closest 50 mg. Do not mix with formula. • For older children, tablets 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. • **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 hours. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Ritonavir (NORVIR®, rtv)	
Dose	• Ritonavir is now used solely as a pharmacokinetic enhancer of other protease inhibitors. For dosing, see specific protease inhibitors.
How Supplied/ Storage	• 80 mg/mL peppermint/caramel liquid (240 mL bottle). Recommended to be stored at room temperature and to use by product expiration date (limited shelf-life). (43% v/v ethanol) • 100 mg Oral Powder (100 mg/packet)- Available in the US only. • 100 mg tablet. Store at room temperature. • 100 mg soft elastic capsule – Available in the US only. Refrigerate until dispensed then stable at room temperature for 30 days. (12% v/v ethanol)
Food Restrictions	Take with food.
Comments	• 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 to coat 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. • During encapsulation process, exposure to soya protein lecithin and fractionated coconut oil occurs. As peanut and soy are from the same plant family, some patients allergic to peanuts may also be allergic to soy. Consult an allergist prior to taking capsules. • Liquid formulation contains alcohol therefore avoid co-medication with metronidazole. • Tablets may not be split or crushed (Norvir® Product Monograph). • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**
Protease Inhibitors (PIs)	
Tipranavir (APTIVUS®, TPV)	
Dose	<u>Neonate/Infant:</u> • Not approved in USA for children less than 2 years of age and in Canada for children less than 18 years of age. <u>Pediatric (2-18 years):</u> • 14 mg/kg/dose TPV + 6 mg/kg/dose rtv po BID (375 mg/m^2/dose TPV + 150 mg/m^2/dose rtv, both po BID) (max. 500 mg TPV + 200 mg RTV po BID) <u>Adult/Adolescent:</u> • 500 mg TPV + 200 mg RTV po BID
How Supplied/ Storage	• 250 mg capsule • Refrigerate the capsules until dispensed then stable at room temperature for 60 days • 100 mg/mL oral solution available in the US only. Note: solution contains 116 international units/mL vitamin E. • Store oral solution at room temperature (25ºC). Use solution within 60 days of opening the bottle.
Food Restrictions	Take with food.
Comments	• Capsule cannot be split or crushed (Verbal communication, Boehringer Ingelheim, May 2008). • Indicated for adults who are highly treatment experienced or have resistance to multiple PIs. • TPV is a sulfonamide. The potential cross-sensitivity with other sulfonamide drugs is unknown – caution in patients with sulfonamide allergy. • Protease inhibitors are extensively metabolized by as well as inhibit CYP450 3A4. **CHECK FOR DRUG INTERACTIONS.**

Antiretroviral Drug Dosing in Pediatric Patients
July 2017

Entry and Fusion Inhibitors	
Enfuvirtide (Fuzeon®, T-20)	
Dose	Neonate/ Infant/ Pediatrics (less than 6 years): • Not approved for use in children less than 6 years in US or Canada. Pediatric/Adolescent (6 - 16 years): • For children 6 years or more: 2 mg/kg/dose twice daily, maximum dose 90 mg (1 mL) twice daily injected subcutaneously into upper arm, anterior thigh, or abdomen. Monitor weight closely and adjust dose accordingly. Adult/Adolescent (more than 16 years): • 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.
How Supplied/ Storage	• Injection: lyophilized powder for injection 108 mg of enfuvirtide, when reconstituted with 1.1 mL sterile water to deliver 90 mg/mL. • Convenience kit: 60 single use vials of enfuvirtide (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3 mL), 60 administration syringes (1 mL), alcohol wipes • Reconstituted vial should be allowed to stand until the powder goes completely into solution (may take up to 45 min). Do not shake. • Once reconstituted, enfuvirtide should be injected immediately or stored in the fridge in the original vial until use. Must be used within 24 hours after reconstitution
Comments	Injection sites should be rotated. Enfuvirtide should not be injected into moles, scar tissue, bruises, or the navel.
Maraviroc (Celsentri®, MVC)	
Dose	Neonate/ Infant/ Pediatric/ Adolescent (≥-2 years and weighing ≥ 10 kg): • Not approved for use in children less than 2 years in US and less than 18 years in Canada. • NCT00791700 Trial investigating use in children aged 2 to < 18 years Pediatric (≥ 2 years and weighing ≥ 10 kg) without CYP 3A inhibitor: (US product monograph) 10 to < 20 kg: use not recommended 20 to < 30 kg: use not recommended 30 to < 40 kg: 300 mg po BID (tablets or solution) > 40 kg: 300 mg po BID (tablets or solution) Pediatric (≥ 2 years and weighing ≥ 10 kg) with CYP 3A inhibitor: 10 to < 20 kg: 50 mg po BID (tablets or solution) 20 to < 30 kg: 75 mg po BID (tablets) or 80 mg po BID (solution) 30 to < 40 kg: 100 mg po BID (tablets or solution) BID > 40 kg: 150 mg po BID (tablets or solution) * Use not recommended with potent CYP 3A inducers Adult/Adolescent (≥16 years): • With CYP 3A inhibitor (i.e. protease inhibitors (except TPV), ketoconazole, itraconazole, clarithromycin: 150 mg po BID

	• No CYP 3A inducer/inhibitor (i.e. TPV, NVP, T-20, NRTIs): 300 mg po BID • With CYP 3A inducer (i.e. EFV, ETR, rifampin, carbamazepine, phenobarbital, phenytoin) and not taking potent CYP3A inhibitor: 600 mg po BID
How Supplied/ Storage	150 mg and 300 mg film-coated tablets (25 mg and 75 mg tablets – US only). Store between 15-30°C in a USP tight container. 20 mg/mL strawberry flavored oral solution (US only); store at room temperature (20°C - 25°C).
Food Restrictions	Take with or without food.
Comments	• CYP450 3A and p-glycoprotein (Pgp) substrate. **CHECK FOR DRUG INTERACTIONS.** • Must have HIV tropism checked to exclude CXCR4/mixed tropic strain. Use MVC only in patients with CCR5-tropic virus. • Film coated immediate release tablet however no studies regarding stability of split or crushed tablets. (Verbal communication, Pfizer, May 2008).

Integrase Inhibitors	
Dolutegravir (Tivicay®, DTG)	
Dose	Neonate/Infant: Not approved for neonates/infants Pediatric/Adolescent: Treatment naïve or treatment experienced/INSTI-naïve: (US & Canadian product monographs; DHHS 2017 Pediatric Guidelines) • < 30 kg: not approved • 30 to < 40 kg: 35 mg po once daily (1x10 mg tablet + 1x25 mg tablet) • ≥ 40 kg: 50 mg po once daily • Treatment naïve or treatment experienced/INSTI-naïve when co-administered with potent UGT1A1/CYP3A inducers (i.e. EFV, f-APV/RTV, TPV/RTV, or rifampin): Increase weight-based dose to BID instead of once daily (double the daily dose) Adult: • Treatment naïve or treatment experienced/INSTI-naïve: 50 mg po once daily • Treatment naïve or treatment experienced/INSTI-naïve, when co-administered with potent UGT1A1/CYP3A inducers (i.e. EFV, f-APV/rtv, TPV/rtv, or rifampin): 50 mg po BID • INSTI-experienced with INSTI associated resistance or clinically suspected INSTI resistance: 50 mg po BID
How Supplied/ Storage	• 50 mg tablet • DTG 10 mg and 25 mg tablets available (Compassionate Access- Canada) • DTG pediatric 5 mg dispersible tablets currently under investigation; pediatric granules no longer under study (ViiV Healthcare communication, February 2017) • TRIUMEQ®: 50 mg dolutegravir; 600 mg abacavir; 300 mg lamivudine fixed dose combination tablet
Food Restrictions	Take with or without food
Comments	• DTG 10, 25 and 50 tablets may be split into halves followed by immediate ingestion of both halves of the tablet, or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately. [ViiV data on file, February, 2017] • 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) • 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 semi-solid food or liquid, and consumed immediately. (Data on File, ViiV Healthcare, Oct 2014)

	• UGT1A1 and CYP3A substrate. **CHECK FOR DRUG INTERACTIONS** • Take DTG 2 hours before or 6 hours after cation containing medications (antacids, laxatives, sucralfate, oral zinc or iron supplements, oral calcium supplements or buffered medications); DTG also can be administered **with food** at the same time as calcium or iron containing supplements. • Poor virologic response to DTG 50 mg po BID may occur if INSTI-resistance Q148 substitution is present, along with 2 or more additional INSTI-resistance mutations • Use DTG with caution with INSTI-experienced patients with CrCl < 30 mL/min because DTG concentrations will be decreased (cause unknown).
Elvitegravir (fixed dose in Stribild® and Genvoya®, EVG)	
Dose	• Pediatric dosing: Stribild® not recommended for <18 years in US and Canada (under study in 12-18 years old; Study GS-US-236-0112/NCT01721109). Genvoya® preferred INSTI regimen for adolescents aged ≥ 12 years and weighing ≥ 35 kg. • Adolescent (≥ 12 years and weighing ≥ 35kg): – Genvoya® 1 tablet po once daily with food (2017 DHHS Pediatric Guideline) – Trial underway investigating use of Stribild® in adolescents >12 to 18 years (NCT01721109) • Adult (≥ 18 years): – Stribild® or Genvoya®- 1 tablet po once daily with food
How Supplied/ Storage	• Fixed dose combination tablet, Stribild® – Elvitegravir 150 mg + cobicistat 150 mg + emtricitabine 200 mg + tenofovir DF 300 mg • Fixed dose combination tablet, Genvoya® – Elvitegravir 150 mg + cobicistat 150 mg + emtricitabine 200 mg + tenofovir AF 10 mg
Food Restrictions	With food
Comments	• 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 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) • Case report describing successful virological suppression with crushed Stribild in juice (Fulco et al. AJHP 2014 71(10);784-6). • Crushing GENVOYA 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 GENVOYA tablet dispersed into a liquid medium (e.g., milk, water, juice) compared to a whole tablet (Communication from Gilead Canada, March 2016). • Splitting GENVOYA tablets has not been studied and is not recommended. Currently, there are no studies evaluating the pharmacokinetics of a split versus whole tablet (Communication from Gilead Canada, March 2016) • TAF is soluble in water; however, it has a bitter and burnt aromatic flavour profile.

	• Elvitegravir and cobicistat are metabolized by or impact CYP450 isoenzymes and Pgp. **CHECK DRUG INTERACTIONS** • Do not initiate Stribild® in patients with CrCl < 70 mL/min, discontinue if CrCl < 50 mL/min • No dosage adjustment required for Genvoya® if CrCl ≥ 30 mL/min • Monitor creatinine clearance, urine glucose and urine protein • Separate from antacids by at least 2 hours, no adjustments with H2 blockers or PPI • Abrupt discontinuation may cause Hepatitis B flare. Monitor hepatic function for several months after discontinuation.
	Raltegravir (Isentress®, RAL)
Dose	Neonate: Not approved for neonates. In Canada, not approved for children less than 2 years of age. IMPAACT P1110 investigational dose for Term Infants of at least 37 weeks and birth weight of at least 2 kg: (2017 DHHS Pediatric Guidelines) Birth to age 7 days: 1.5 mg/kg/dose po once daily Age 8 to 28 days: 3 mg/kg/dose po BID Age > 4 weeks: 6 mg/kg/dose po BID (see dosing below) <u>Infant/Pediatric Dosing:</u> at least 4 weeks of age and ≥ 3 kg and < 20 kg (2017 DHHS Pediatric Guidelines) • Weight based dosing for **oral suspension** (approximately 6 mg/kg/dose po BID) – 3 to < 4 kg 1 mL (20 mg) po BID – 4 to < 6 kg 1.5 mL (30 mg) po BID – 6 to < 8 kg 2 mL (40 mg) po BID – 8 to < 11 kg 3 mL (60 mg) po BID – 11 to < 14 kg 4 mL (80 mg) po BID – 14 to < 20 kg 5 mL (100 mg) po BID • Maximum dose of oral suspension is 5 mL (100 mg) po BID • For children weighing 11 to 20 kg, either the oral suspension or chewable tablets can be used. <u>Children ≥ 11 kg:</u> • Weight based dosing for **chewable tablets** (approximately 6 mg/kg/dose po BID) - 11 to < 14 kg 75 mg po BID 3 x 25 mg po BID - 14 to < 20 kg 100 mg po BID 1 x 100 mg po BID - 20 to < 28 kg 150 mg po BID 1.5 x 100 mg BID (or 1 x 100 mg + 2 x 25 mg po BID) - 28 to < 40 kg 200 mg po BID 2 x 100 mg po BID - ≥ 40 kg 300 mg po BID 3 x 100 mg po BID • Maximum dose of chewable tablets is 300 mg po BID • The 100 mg chewable tablets can be divided into equal halves. <u>Children/adolescents ≥ 25 kg and Adults</u>: • 400 mg film coated tablet po BID
How Supplied/ Storage	• 400 mg film-coated tablet. Store at room temperature (15-30°C). • Orange-banana flavoured 25 mg and 100 mg scored pediatric chewable tablet. • Chewable tablets should be stored in in original package with desiccant to protect from moisture. • 100 mg banana flavoured oral granular powder for suspension (final concentration 20 mg/mL) (single-use foil packet). Store

	in original container and do not open foil packet until ready for reconstitution. Available in US or in Canada through the Special Access Program[2] (Phone communication, Merck, July 2015).
Food Restrictions	Take with or without food
Comments	• 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, crushed or swallowed whole. • Oral suspension, chewable tablets and film-coated tablets are NOT interchangeable. The chewable tablets and oral suspension have better bioavailability than the film-coated tablets. The maximum dose of the chewable tablets is 300 mg BID and the maximum dose of the oral suspension is 100 mg BID. • Chewable tablets contain phenylalanine, which could be harmful to patients with phenylketonuria. • Oral Powder: Each foil package contains 100 mg of RAL, which should be suspended in 5 mL of water (final concentration = 20 mg/mL). The appropriate dose (volume) should be measured with an oral syringe and should be ingested within 30 minutes of mixing. • Clearance through UGT1A1. **CHECK FOR DRUG INTERACTIONS.**

Additional References:

1. Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Updated April 27, 2017. Available at https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv-guidelines/47/introduction
2. Contact one of the outpatient pharmacies (UAH or RAH) to initiate the ordering process. For nevirapine, didanosine and stavudine liquids, additional paperwork is required in addition to the special access request forms which are available on the Health Canada website (http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/sapf1_pasf1-eng.php). Special Access Program ph: 613-941-2108.
3. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Updated Oct 26, 2016. Available at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0
4. Canadian and US Product Monographs for individual antiretrovirals.

Updated by: Michelle Foisy, Pharm.D., Pam Nickel,BScPharm, Christine Hughes, Pharm.D, Sarah Lamb, PharmD Student, Northern Alberta HIV Program (NAP), Alberta Health Services, Edmonton, Alberta; and Natalie Dayneka Pharm.D. FCSHP, Children's Hospital of Eastern Ontario (CHEO), Ottawa, Ontario. July 2017