Table 1. Dosing guidance in children

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| --- | --- | --- | --- | --- | --- | --- |
| Nucleoside reverse transcriptase inhibitor NRTI | Licensing restrictions | Guideline status | Available formulation | Dose from PENTA Guideline1 | Dose from DHHS guideline2 | Dose from WHO dosing annex 20183 |
|  | EMA / FDA |  |  |  |  |  |
| Abacavir (ABC) | ≥3 months/ ≥3 months | WHO:First line ≥2 weeksPENTA: First line ≥3 monthsif viral load (VL) >100.000 and child >12 years old, ABC is not preferred. | Liquid: 20 mg/mlTablets: 300 mg *scored* | Liquid:<25 kg ≥3 months old: 8 mg/kg BD or 16 mg/kg QD (max dose 600 mg/day)Tablets:14-21 kg: 150mg, ½ tablet BD or 1 tablet QD>21-30 kg: ½ tablet AM + 1 tablet PM or 1½ tablet QD>30 kg: 1 tablet BD or 2 tablets QD (max dose 600 mg/day)  | Liquid:<25 kg ≥3 months old: 8 mg/kg BD or 16 mg/kg QD (max dose 600 mg/day)Tablets (300 mg):14 to <20 kg: ½ tablet BD or 1 tablet QD20 to <14 kg: ½ tablet AM + 1 tablet PM>25 kg: 1 tablet BD or 2 tablets QD (max dose 600 mg/day) | ABC/3TC 60/30 mg tablets (dispersible)3-5.9 kg: 2 tablets QD or 1 tablet BD6-9.9 kg: 3 tablet QD or 1.5 tablets BD10-13.9 kg: 4 tablets QD or 2 tablets BD14-19.9 kg: 5 tablets QD or 2.5 tablets BD20-24.9 kg: 6 tablets QD or 3 tablets BDABC/3TC 120/60 mg (dispersible)3-5.9 kg: 1 tablet QD6-9.9 kg: 1.5 tablet QD10-13.9 kg: 2 tablets QD14-19.9 kg: 2.5 tablets QD20-24.9 kg: 3 tablets QDABC/3TC 600/300 mg tablets25-34.9 kg: 1 tablet QDABC liquid 20 mg/mL3-5.9 kg: 3 mL BD6-9.9 kg: 4 mL BD10-13.9 kg: 6 mL BD |
| Zidovudine (AZT) | Birth /Birth | WHO: First line 0 to <3 yearsAlternative in children ≥3 yearsPENTA: Alternative <12 years in combination with 3TC.DHHS:First line - birth to <6 yearsAlternative - ≥6 years  | Liquid: 10 mg/mlCapsules: 100 mgDispersible tablets: 60 mgIV infusion: 10 mg/ml | Child dosing liquid (from birth):4-9 kg: 12 mg/kg BD9-30 kg: 9 mg/kg BD≥30 kg: 300 mg BDChild dosing for capsules:8-13 kg: 100 mg BD14-21 kg: 100 mg AM + 200 mg PM22-30 kg: 200 mg BD; (≥30 kg): 300 mg BD | Liquid:4 to <9 kg: 12 mg/kg BD (max dose: 300 mg/day)9 to <30 kg: 9 mg/kg BD (max dose: 300 mg/day)≥30 kg: 300 mg BD IV: 120 mg/m2 every 6 hours (QDS)Dosing for premature newbornsGestational age <30 weeks:Oral dose:Weeks 0 to <4: 2 mg/kg BDWeeks 4 to <8: 3 mg/kg BDWeeks 8 to <10: 12 mg/kg BDFor ≥30 to <35 Weeks Gestation at Birth:Oral dose:Week 0 to <2: 2 mg/kg BDWeek 2 to <6: 3 mg/kg BDWeek 6 to <8: 12 mg/kg BDIV dose:1.5 mg/kg every 6 hours (QDS) | AZT 60 mg tablets (dispersible)3-5.9 kg: 1 tablet BD6-9.9 kg: 1.5 tablets BD10-13.9 kg: 2 tablets BD14-19.9 kg: 2.5 tablets BD20-24.9 kg: 3 tablets BDAZT 300 mg tablets25-34.9 kg: 1 tablet BDFor children <4 weeks of age:AZT liquid 10 mg/mL2-3 kg: 1 mL BD3-4 kg: 1.5 mL BD4-5 kg: 2 mL BD |
| Emtricitabine (FTC) | ≥4 months/ Birth | WHO: Second line <10 years, First line >10 yearsPENTA: Second line <12 years First line ≥12 years DHHS: First line ≥6 years with estimated CrCl ≥30 mL/min | Liquid: 10 mg/mlCapsules: 200 mg | Liquid≥4 months: 6 mg/kg QD (max dose: 240 mg/day)Capsules ≥33 kg: 200 mg QD (liquid and capsules not bioequivalent) | Liquid: 0 to <3 months: 3 mg/kg QD (max dose: 240 mg/day)≥4 months: 6 mg/kg QD (max dose: 240 mg/day)≥33 kg: 240 mg QD Capsules: ≥33 kg: 200 mg QD (liquid and capsules not bioequivalent) | No dose in annex |
| Lamivudine (3TC) | ≥3 months/ Birth | WHO: First line in all childrenPENTA: First line in all childrenDHHS:First line in all children | Liquid: 10mg/mlTablets: 150mg s*cored* 300mg, 100mg | Liquid:Child dosing (≥3 months): 4 mg/kg BD, or 8 mg/kg QD (max 300 mg/day)Tablets (≥3 years): 14-21 kg: ½ tablet BD or 1 tablet QD>21-30 kg: ½ tablet AM and 1 tablet PM or 1½ QD>30 kg: 1 tablet BD or 2 tablets QD  | Neonates (≥32 weeks gestation at birth)Liquid:0 to <4 weeks: 2 mg/kg BD4 weeks to <3 months: 4 mg/kg BDChild dosing (≥3 months):≥3 months to 3 years: 5 mg/kg BD (max 150 mg BD)≥3 years: 5 mg/kg BD (max 150 mg BD) or 10 mg/kg QD (max 300 mg)Tablet 150 mg (≥ 3 years):14 to <21 kg: ½ tablet BD or 1 tablet QD;21 to <30 kg: ½ tablet AM + 1 tablet PM or 1½ tablet QD≥30 kg: 1 tablet BD or 2 tablets QDTablet 300 mg (≥12 years):150 mg BD or 300 mg QD | ABC/3TC 60/30 mg tablets (dispersible)3-5.9 kg: 2 tablets QD or 1 tablet BD6-9.9 kg: 3 tablet QD or 1.5 tablets BD10-13.9 kg: 4 tablets QD or 2 tablets BD14-19.9 kg: 5 tablets QD or 2.5 tablets BD20-24.9 kg: 6 tablets QD or 3 tablets BDABC/3TC 120/60 mg (dispersible)3-5.9 kg: 1 tablet QD6-9.9 kg: 1.5 tablet QD10-13.9 kg: 2 tablets QD14-19.9 kg: 2.5 tablets QD20-24.9 kg: 3 tablets QDABC/3TC 600/300 mg tablets25-34.9 kg: 1 tablet QD3TC liquid 10 mg/mL3-5.9 kg: 3 mL BD6-9.9 kg: 4 mL BD10-13.9 kg: 6 mL BDFor children <4 weeks of age:AZT liquid 10 mg/mL2-3 kg: 0.5 mL BD3-4 kg: 0.8 mL BD4-5 kg: 1 mL BD |
| Tenofovir Disoproxil fumarate (TDF) | ≥2 years / ≥2 years | WHO: alternative >3 yearsFirst line ≥10 yearsPENTA:Alternative <12 years old.First line ≥12 years old DHHS:Alternative <12 years oldFirst line ≥12 years in combination with FTC | Oral powder: 40mg TDF/gTablets: 150mg, 200mg, 250mg, 300mg | Child dosing granule (1 scoop (scp) = 40mg)(≥2 years – 12 years):10-12 kg: 8 mg/kg QD10-12 kg: 2 scp QD12-14 kg: 2.5 scp QD14-17 kg): 3 scp QD17-19 kg: 3.5 scp QD19-22 kg: 4 scp QD22-24 kg: 4.5 scp QD24-27 kg: 5 scp QD27-29 kg: 5.5 scp QD29-32 kg: 6 scp QD32-34 kg: 6.5 scp QD34-35 kg: 7 scp QD≥35 kg: 7.5 scp QDChild dosing tablet (≥2 yrs):17-22 kg: 150 mg QD22-28 kg: 200 mg QD28-35 kg: 250 mg QD≥35 kg: 300 mg QD | Child dosing granule (1 scoop (scp) = 40mg) (≥2 years – 12 years):10-12 kg: 8 mg/kg QD10-12 kg: 2 scp QD12-14 kg: 2.5 scp QD14-17 kg): 3 scp QD17-19 kg: 3.5 scp QD19-22 kg: 4 scp QD22-24 kg: 4.5 scp QD24-27 kg: 5 scp QD27-29 kg: 5.5 scp QD29-32 kg: 6 scp QD32-34 kg: 6.5 scp QD34-35 kg: 7 scp QD≥35 kg: 7.5 scp QDChild dosing tablet (≥2 yrs):17-22 kg: 150 mg QD22-28 kg: 200 mg QD28-35 kg: 250 mg QD≥35 kg: 300 mg QD | No dose in annex |
| Tenofovir Alafenamide (TAF) | ≥6 years / ≥6 years in children >35 kgOr in children >25 kg without a PI | WHO: Not includedPENTA: Not preferredDHHS: First line for children ≥6 years with estimated CrCl ≥30 mL/min | For HIV only available in combination tablets | Not recommended in children | For HIV only available in fixed dose combination (FDCs) tablets In combination tablet:≥25 kg: 1 tablet QD not to be used with PIs ≥35 kg: 1 tablet QD | No dose in annex |
| Non-nucleoside reverse transcriptase inhibitor (NNRTI) | Licensing restrictions | Guideline status | Available formulation | Dose from PENTA Guideline1 | Dose from DHHS guideline2 | Dose from WHO dosing annex 20183 |
|  | EMA / FDA |  |  |  |  |  |
| Efavirenz (EFV) | ≥ 3 months/≥ 3 months (weighing at least 3.5 kg) | WHO: First line in children ≥3 years oldPENTA: First line in children ≥3 years oldDHHS: Alternative in children ≥3 years old | Capsule: 50 mg, 200 mg (scored)Tablet: 600 mg  | Child dosing liquid≥3-5 years13-15 kg: 360 mg QD15-20 kg: 390 mg QD20-25 kg: 450 mg QD25-32.5 kg: 510 mg QD≥ 5 years13-15 kg: 270 mg QD15-20 kg: 300 mg QD20-25 kg: 360 mg QD25-32.5 kg: 450 mg QD32.5-40 kg: 510 mg QD≥40 kg: 720 mg (max dose)Child dosing capsules (≥3 years):13-15 kg: 200 mg QD15-20 kg: 250 mg QD20-25 kg: 300mg QD25-32.5 kg: 350 mg QD32.5-40 kg: 400 mg QD≥40 kg: 600 mg QD | EFV not recommended for children <3 years old.Capsules:(≥3 months to 3 years)3.5-5 kg: 100 mg QD5-7.5 kg: 150 mg QD7.5-10 kg: 200 mg QD≥ 3 years10-15 kg: 200 mg QD15-20 kg: 250 mg QD20-25 kg: 300 mg QD25-32.5 kg: 350 mg QD32.5-40 kg: 400 mg QD≥40 kg: 600 mg QDTablets:≥40 kg: 600 mg QD | EFV 200mg tablets (scored)3-5.9 kg: -6-9.9 kg: -10-13.9 kg: 1 tablet QD14-19.9 kg: 1.5 tablets QD20-24.9 kg: 1.5 tablets QDEFV 200 mg tablets25 - 34.9 kg: 2 tablets QD |
| Nevirapine (NVP) | ≥ birth/15 days | WHO: First line in children <2 weeksAlternative in children ≥2 weeksPENTA: First line in children <3 years if unexposed to NVP perinatally and with three NRTI (ABC,3TC, ZDV)Alternative in children ≥3 years oldDHHS: First line in children aged <2 weeksAlternative in children 2 weeks to <3 years | Immediate release: tablets: 200 mgOral suspension: 10 mg/ml Extended release (XR) tablet: 100 mg, 400mg  | ALL doses of NVP are QD for 14 days then BD (lead-in)Immediate release (tablets or suspension): Dosed on BSA:150-200 mg/m2Dosed on Weight:≥1 month to <8 years: 7 mg/kg (lead-in with 4mg/kg)>8 years: 4 mg/kg BD (lead in with 4 mg/kg QD) Extended release tablets (no lead-in with XR tablets) (≥3 years):0.58-0.83 m2: 200 mg QD0.84-1.16m2: 300 mg QD≥1.17m2: 400mg QD (all patients must initiate therapy with immediate-release formulations for 14 days). | ALL doses of NVP are QD for 14 days then BD (lead-in)Immediate release (tablets or suspension): Dosed on BSA:≥1 month to <8 years: 150-200 mg/m2≥8 years: 120-150 mg/m2Extended release tablets (no lead-in with XR tablets): 6 to <18 years0.58-0.83 m2: 2x100 mg QD0.84-1.16 m2: 3x100 mg QD≥1.17 m2: 1x 400 mg QDChildren aged < 1 month; (not FDA approved)Gestational age 34 – 37 weeks: 4 mg/kg BD for the first week, increasing to 6 mg/kg BD thereafterGestational age ≥37 weeks: 6 mg/kg BD | NVP 50 mg tablets (dispersable)3-5.9 kg: 1 tablet BD6-9.9 kg: 1.5 tablets BD10-13.9 kg: 2 tablets BD14-19.9 kg: 2.5 tablets BD20-24.9 kg: 3 tablets BDNVP 200mg tablets25-34.9 kg: 1 tablet BDFor children <4 weeks of age:NVP liquid 10 mg/mL2-3 kg: 1.5 mL BD3-4 kg: 2 mL BD4-5 kg: 3 mL BD |
| Rilpivirine (RPV) | ≥12 years/≥12 years | WHO/PENTA:Not includedDHHS:Alternative in children >12 years old | Film coated tablet 25 mg | Not recommended in children  | Film coated tablet≥12 years and 35 kg or more: 25 mg QD | No dose in annex |
| Protease inhibitors (PIs) | Licensing restrictions | Guideline status | Available formulation | Dose from PENTA Guideline1 | Dose from DHHS guideline2 | Dose from WHO dosing annex 20183 |
|  | EMA / FDA |  |  |  |  |  |
| Atazanavir (ATV) | ≥ 3 months (≥ 5 kg)/ ≥ 3 months (≥ 5 kg | WHO:Alternative in children ≥3 months for 2nd linePENTA:First line for children >6 yearsDHHS:First line in children ≥3 years | Oral powder formulation: 50 mg/sachetCapsules: 150 mg, 200 mg, 300 mg | Boosted atazanavir (≥6 years):Capsules15-20 kg: 150 mg + 100 mg ritonavir (RTV) QD20-40 kg: 200 mg + 100 mg RTV QD≥40 kg: 300 mg QD + 100 mg RTV QD | Boosted atazanavir:(ART naïve and experienced)Oral powder: (≥ 3 months)5 to <15 kg: 200 mg + 80 mg RTV QD15 to <25 kg:250 mg +80 mg RTV QDCapsules: (≥ 6 years)15 to <35 kg: 200 mg + RTV 100 mg QD >35 kg: 300 mg + RTV 100 mg QDUnboosted atazanavir:(>13 years)ART naïve only400 mg QD | ATV 100 mg capsules 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: 2 capsules + 100 mg RTV QD14-19.9 kg: 2 capsules + 100 mg RTV QD20-24.9 kg: 2 capsules + 100 mg RTV QDATV 200 mg capsules 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: 1 capsule + 100 mg RTV QD14-19.9 kg: 1 capsule + 100 mg RTV QD20-24.9 kg: 1 capsule + 100 mg RTV QDATV 300 mg tablet25-34.9 kg: 1 tablet QD |
| Darunavir (DRV) | ≥ 3 years (≥ 15 kg)/≥ 3 years (≥ 10 kg) | WHO:alternative in children ≥3 years for 3rd linePENTA:Alternative in children 3 to <12 yearsFirst line in children >12 yearsDHHS:First line in children 3 to <6 years as BD regimen. Alternative in children 6 to <12 years (due to availability of other QD regimens at this age).First line in children >12 years old as QD regimen | Oral suspension: 100 mg/ml Tablets: 75 mg, 150 mg, 300 mg, 400 mg, 600 mg, 800 mg. | ART-naïve or ART-experienced:Child dosing liquid: (≥3 years, ≥10 kg):10-11 kg: 200 mg BD + 32mg RTV BD11-12 kg: 220 mg BD + 32mg RTV BD12-13 kg: 240 mg BD + 40mg RTV BD13-14 kg: 260 mg BD + 40mg RTV BD14-15 kg: 280 mg BD + 48mg RTV BD15-30 kg: 380 mg BD + 50mg RTV BD30-40 kg: 460 mg BD + 60mg RTV BD≥40 kg: 600 mg BD + 100mg RTV BD Child dosing tablets (≥3 years):15-30 kg: 375 mg BD + 50 mg RTV BD30-40 kg: 450 mg BD + 60 mg RTV BD≥40 kg: 600 mg BD + 100 mg RTV BD | ART-naïve or ART-experienced:Suspension (≥3 years, ≥10 kg):10 to <11 kg: 200 mg BD + 32 mg RTV BD11 to <12 kg: 220 mg BD + 32 mg RTV BD12 to <13 kg: 240 mg BD + 40 mg RTV BD13 to <14 kg: 260 mg BD + 40 mg RTV BD14 to <15 kg: 280 mg BD + 48 mg RTV BDSuspension/tablets (≥3 years, ≥15 kg):Twice-daily15 to <30 kg: 375 mg DRV + 48 mg RTV BD30 to <40 kg: 450 mg DRV + 60 mg RTV BDNo darunavir resistance-associated mutations≥40 kg: 800 mg DRV + 100 mg RTV QDWith ≥1 DRV resistance-associated mutations≥40 kg: 600 mg DRV + 100 mg RTV BD | DRV 75 mg tablet 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: 5 tablets BD20-24.9 kg: 5 tablets BDDRV 400 mg tablet25-34.9 kg: 1 tablet BDDRV 150 mg tablet 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: 4 tablets QD20-24.9 kg: 4 tablets QD DRV 600 mg tablet 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: 1 tablet QD20-24.9 kg: 1 tablet QD25-34.9 kg: 1 tablet QDDRV liquid 100 mg/mL3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: 2.5 mL BD20-24.9 kg: .3.5 mL BD25-34.9 kg: -RTV with QD DRV: 100 mg RTV tabletRTV with BD DRV:<15 kg: 0.5 mL RTV liquid 80 mg/mL (40 mg)15-30 kg: 25 or 50 mg RTV tablets |
| Lopinavir (LPV) | ≥2 weeks | WHO:Alternative regimen for children for whom an approved DTG dose is available. First line in children for whom an approved DTG dose is not available. PENTA:First line for children <6 yearsAlternative for children >6 yearsDHHS:First line in children 14 days to <3 yearsAlternative in children 3 to <12 years | Oral solution:LPV/r 80/20 mg/mlTablets:LPV/r 100/25 mg, 200/50 mg | Oral solution:Dosed on BSA:14 days to <6 months: 300/75 mg/m2 BD (max 400/100 BD)6 months to <18 years: 230/57.5 mg/m2 BD (max 400/100 BD)Dosed on weight:14 days to <6 months: 16/4 mg/kg BD (max 400/100 BD)6 months to <18 years: 10/2.5 mg/kg BD (max 400/100 BD)Tablets:15 to <25 kg: 200/50 mg BD25 to <35 kg: 300/75 mg BD>35 kg: 400/100 mg BDWith EFV/NVP:Oral solution:6 months to <18 months: 300/75 mg/m2 BDTablet:15 to <20 kg: 200/50 mg BD20 to <30 kg: 300/75 mg BD30 to <45 kg: 400/100 mg BD>45 kg: 500/125 mg BD | Oral solution:Dosed on BSA:ART-naïve or ART-experienced:14 days to <12 months: 300/75 mg/m2 BD (max 400/100 BD)ART naïve only:1 to <18 years: 230/57.5 mg/m2 BD (max 400/100 BD)Dosed on weight:14 days to <12 months: 16/4 mg/kg BD (max 400/100 BD)1 to <18 years: <15 kg: 13/3.25 mg/kg>15 kg: 10/2.5 mg/kg BD (max 400/100 BD)Tablets:Target mg/m2 230 mg/m2 (ART-naïve only):15 to <20 kg: 200/50 mg BD20 to <25 kg: 200/50 mg BD (230 mg/m2)25 to <30 kg: 300/75 mg BD30 to <35 kg: 300/75 mg BD35 to 45 kg: 400/100 BD>45 kg: 400/100 mg BDTarget mg/m2 300 mg/m2:15 to <20 kg: 200/50 mg BD20 to <25 kg: 300/75 mg BD (300 mg/m2)) 25 to <30 kg: 300/75 mg BD30 to <35 kg: 400/100 BD35 to 45 kg: 400/100 BD>45 kg: 400/100 mg BD or 500/100 BDWith EFV/NVP:12 months to <18 years: 300/75 mg/m2 BD | LPV/r 100/25 mg tablet 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: 2 tablets AM, 1 tablet PM14-19.9 kg: 2 tablets BD20-24.9 kg: 2 tablets BD25-34.9 kg: 3 tablets BDLPV/r 40/10 mg pellets3-5.9 kg: 2 tablets BD6-9.9 kg: 3 tablets BD10-13.9 kg: 4 tablets BD14-19.9 kg: 5 tablets BD20-24.9 kg: 6 tablets BDLPV/r liquid 80/20 mL3-5.9 kg: 1 mL BD6-9.9 kg: 1.5 mL BD10-13.9 kg: 2 mL BD 14-19.9 kg: 2.5 mL BD20-24.9 kg: 3 mL BDFor children 2 to <4 weeks of age:2-3 kg: 0.6 mL BD3-4 kg: 0.8 mL BD4-5 kg: 1 mL BD |
| InSTI | Licensing restrictions | Guideline status | Available formulation | Dose from PENTA Guideline | Dose from DHHS guideline | Dose from WHO dosing annex 20183 |
|  | EMA / FDA |  |  |  |  |  |
| Dolutegravir (DTG) | ≥ 6 years (≥15 kg) /≥ 30 kg | WHO:First line in children for whom an approved dose is availablePENTA:Alternative regimen children >12 yearsDHHS:First line in children >30 kg | Solid film coated Tablets: 50 mg, 25 mg, 10 mg | Without integrase resistance:≥ 12 years and ≥40 kg: 50mg QDWith integrase resistance: 50 mg BD | InSTI naïveTablets:30 kg to <40 kg: 35 mg QD>40 kg: 50 mg QD(InSTI naïve with UGT1a/Cyp3A inducers)>40 kg: 50 mg BD(InSTI experienced or with suspected INTSI resistance)>40 kg: 50 mg BD | DTG 25 mg tablets 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: -20-24.9 kg: 2 tablets QD\*DTG 50 mg tablets 3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: -20-24.9 kg: 1 tablet QD\*25-34.9 kg: 1 tablet QD |
| Elvitegravir(EVG) | >12 years old | WHO/PENTA:not includedDHHS:First line in children >12 yearsAlternative in children 6 to <12 years | Film coated tablets: 150 mg(150/150/200/10 EVG/cobicistat/3TC /TAF) | Not recommended in children | Adult film coated tablet:>25 kg: 150 mg (1 tablet) | No dose in annex |
| Raltegravir (RTG) | Birth/Birth | WHO:Preferred regimen for neonateAlternative for older children for whom an approved DTG dose is not availablePENTA:Alternative regimen children >12 yearsDHHS:First line in children from birth to <6 yearsAlternative in children >6 years | Film coated tablet: 400 mg, 600mgChewable tablet: 25 mg, 100 mg *scored*Granules for Suspension: 20 mg/mlNB. Suspension and chewable tabs are not bioequivalent to film-coated tabs. | Child dosing chewable tab:11 to <14 kg: 75 mg BD14 to <20 kg: 100 mg BD20 to <28 kg: 150 mg BD28 to <40 kg: 200 mg BD≥40 kg: 300 mg BDFilm coated tab (≥6 years and >25 kg or ≥12 years):400 mg BD | Oral suspension:Birth to < 1 week:2 to <3 kg: 4 mg QD3 to <4 kg: 5 mg QD4 to <5 kg: 6 mg QD1 to < 4 weeks2 to < 3 kg: 8 mg BD3 to < 4 kg: 10 mg BD4 to < 5 kg: 15 mg BDAged ≥4 weeks:3 to <4 kg: 25 mg BD4 to <6 kg: 30 mg BD6 to <8 kg: 40 mg BD 8 to <11 kg: 60 mg BD11 to <14 kg: 80 mg BD14 to <20 kg: 100 mg BD Child dosing chewable tab:11 to <14 kg: 75 mg BD14 to <20 kg:100 mg BD20 to <28 kg: 150 mg BD28 to <40 kg: 200 mg BD≥40 kg: 300 mg BDFilm coated tab (≥6 years and >25 kg or ≥12 years):400 mg BD | RTG 25 mg tablets (chewable)3-5.9 kg: 1 tablet BD6-9.9 kg: 2 tablets BD10-13.9 kg: 4 tablets BD14-19.9 kg: 5 tablets BD20-24.9 kg: 6 tablets BDRTG 100 mg tablets (chewable)3-5.9 kg: -6-9.9 kg: -10-13.9 kg: -14-19.9 kg: 1 tablet BD20-24.9 kg: 1.5 tablets BDRTG 400 mg tablet25-34.9 kg: 1 tablet BDRTG liquid 10 mg/mL3-5.9 kg: 3 mL BD6-9.9 kg: 5mL BD10-13.9 kg: 8mL BD14-19.9 kg: 10 mL BD20-24.9 kg: -For children <1 weeks of age:2-3 kg: 0.4 mL QD3-4 kg: 0.5 mL QD4-5 kg: 0.7 mL QDFor children 1 to <4 weeks of age:2-3 kg: 0.8 mL BD3-4 kg: 1 mL BD4-5 kg: 1.5 mL BD |

\*: At the time of writing, this dose is based on predicted exposures derived from PK results from the Odyssey4,5 and IMPAACT 10936 trials
EMA: European Medicines Agency

FDA: US-Food and Drug Administration

PENTA: Pediatric European Network for treatment of Aids

DHHS: Department of Health and Human Services

WHO: World Health Organization

NRTI: nucleoside (/nucleotide) reverse transcriptase inhibitors

NNRTI: non-nucleoside reverse transcriptase inhibitors

PI: protease inhibitors

InSTI: integrase strand transfer inhibitors
VL: viral load

PM: in the evening
AM: in the morning

QD: dosed once daily
 BD: dosed twice daily
 QDS: dosed four times daily (dosed every 6 hours)
Scp: Scoop (a scoop measuring 40 mg of pediatric TDF granules)

Table 2. Pharmacokinetic studies of NNRTIs in HIV infected pediatric patients

|  |
| --- |
| **Efavirenz (EFV)** |
| **Reference**  | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **BSA (m2)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **C trough (mg/l)** | **Cmax (mg/l)****Or C mid-dose interval****(CMDI)**  |
| EFV once-daily |  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Star et al 2002.7,8 | EFV Liquid formulation in combination with nelfinavir QDDose = (subject weight in kg/70)0.7 x 720 mgMean dose: 284 mg/day | N=488ART naive and experienced 3 to <10 years old | Median (range):5.1 (3.1 – 9.6) 8 | Not reported | Not reported | 63% VL <400 copies/mL at week 4858% VL <50 copies/mLAt week 48 | Mean (SD):68.818 (±32.831)9 | Mean (SD):1.768 (1.294)8 | Mean (SD):4.483 (1.831)8 |
| Von Hentig et al. 2006.9 | EFV capsules QDDose ranged between 375 and 480 mg/m2 (12.5 and 17.0mg/kg body weight) | N=11,NNRTI naive children4 to <10 years oldWeighing >13 kg | Median (range):8.7 ( 4.3 - 12.0) | Median (range)1.01 (0.72 – 1.51) | Median (range):25 (16 -50) | 80% VL <50 copies/mL10 | Mean (range):63.608 (44.222 – 82.989) | Mean (range):1.293 (0.889 -1.697) | Mean (range):5.552 (3.951-7.153) |
| Ren et al 2007.11  | EFV capsule formulation QD13to <15 kg:200 mg15 to <20 kg:250 mg20 to <25 kg:300 mg25 to <32.5 kg:350 mg32.5 to <40 kg:400 mg>40 kg: 600 mg | N=15,Information on prior ART use was not reported3-15 years, weighing >10 kg | Median (SD):7.2 (2.7) | Not reported | Median (SD):19.4 (4.2) | 67% VL <50 copies/mL after at least 6 months of ART | Not reported | Median (IQR):1.18 (0.46–1.70) | Median (IQR)**CMDI**:1.58 (0.67-2.20) |
| Fletcher et al. 200812 | EFV capsules dosed in combination with nelfinavir QDInitial dose:child dose (mg/day) =(child weight in kg/70 kg) 0.7 × 600 mg/day. Rounded off to the nearest 25 mg increment dose.Median dose (SD) [CV%]Week 2:12 mg/kg (1.4)[12%]Week 56:13 mg/kg (5) [36%] | N=50,At week 2N=34,At week 56 (after dose adjustment)3 to <16 years at initiation, NNRTI and PI based ART-naive.  | Median (range):Week 27 (3-16)Week 568 (5–17) | Median (range):Week 20.9 (0.6-2.1)Week 561 (0.7 - 2.0) | Median (range):Week 224 (13.4-98.0)Week 5626.2 (16.6–93.7) | 81% VL <400 copies/mL at week 4870% VL <50 copies/mL at week 48 | Median (SD)[CV%]:Week 260 (58) [77%]Week 5660 (33) [59%] | Median (SD)[CV%]:Week 21.45 (2.16)[103.1%]Week 561.30 (1.27) [77.3%] | Median (SD)[CV%]Cmax:Week 24.09 (2.67) [58.3]Week 564.55 (1.73) [39.5] |
| Wintergerst et al. 200813 | EFV dose median(range):Dose in mg300 mg (200–800)Dose in mg/kg13.3 (9.7–22.5)EFV capsule formulation QD13to <15 kg:200 mg15 to <20 kg:250 mg20 to <25 kg:300 mg25 to <32.5 kg:350 mg32.5 to <40 kg:400 mg>40 kg: 600 mg | N=33,ART experienced and naive childrenNo age or weight limit reported.  | Median (range):8.2 (2.1–16.7) | Not reported  | Median (range):24 (12–62) | 81.1% VL <50 copies/mL treated under TDM(intend to treat) | Not reported | Not reported | Not reported |
| Hirt et al. 200914 | EFV capsules 200 mgEFV capsule formulation QD13 to <15 kg: 200 mg15 to <20 kg: 250 mg20 to <25 kg: 300 mg25 to <32.5 kg: 350 mg32.5 to <40 kg: 400 mg>40 kg: 600 mgAverage dose:250 mg | N=48,ART naive30 months to <15 years old Weighing at least 10 kg | Median (range):6.35 (2.77–14.70) | Not reported | Median (range):16.4 (11–37) | 86% VL <400 copies/mL with AUC >49h\*mg/LAt week 850% VL <400 copies/mL with AUC <49h\*mg/LAt week 8 | Median (no range reported):65.2 | Median (no range reported):1.64 | Median Cmax (no range reported):3.71 |
| Ren et al. 200915 | EFV capsule formulation QD13to <15 kg: 200 mg15 to <20 kg: 250mg20 to <25 kg: 300 mg25 to <32.5 kg: 350 mg32.5 to <40 kg: 400 mg>40 kg: 600 mgAfter rifampicin-based therapyDose mg/kg Median (IQR):14.0 (12.8–14.5) | N= 15,Receiving EFV based therapy after TB treatment with rifampicin,aged 3–15 years and weighing >10 kg | Median (IQR):7.1 (5.7–9.2) | Not reported | Median (IQR):20.5 (17.3–24.8) | 81.1% VL <50 copies/mL treated under TDM(intend to treat) | Not reported | Median (IQR):0.86 (0.61–3.56) | Median (IQR)**CMDI**:1.23 (0.85 -4.18) |
| Pavia-Ruz et al. 201516 | EFV Oral solution 30 mg/ml (QD)EFV capsule sprinkles QD,Dose Oral solutionGroups 1-3 <10 kg: 390 mg10 <17 kg: 600 mgGroups 410 to <15 kg: 360 mg15 to <20 kg: 390 mg20 to <25 kg: 450mg25 to <32.5 kg: 510 mg32.5 to <40 kg: 630mg>40 kg: 720 mgDose capsule sprinkles:Groups 1-2<10 kg: 300 mg10 to <17 kg: 400 mgGroup 3<10 kg:400 mg10 to <17 kg: 600 mgGroup 4<10 kg: 150 mg10 to <15 kg: 200 mg15 to <20 kg: 250 mg20 to <25 kg: 300 mg25 to <32.5 kg: 350 mg32.5 to <40 kg: 400 mg>40 kg: 600mg | N=37,ART naive and experienced3 months to <6 yearsGroup 1: N=15 (3 -<6 months) Group 2: N=10 (26 months - <2 years)Group 3: N=4 (2 -<3 years)Group 4: N=8 (3 -<6 years) | Median (IQR):All children0.663 (0.430–2.324)Group 1:0.392 (0.334–0.441)Group 2: 0.825 (0.608–1.851)Group 3: 2.313 (2.198–2.660)Group 4: 3.922 (3.543–4.786) | Not reported | Not reported | 77.8% Vl <400 copies/mL at week 4863.0% VL <50 copies/mL at week 48 | Median (CV%):Oral solutionGroup 1:130 (98%)Group 2:71.4 (49%)Group 3:93.8 (68%)Group 4:131 (98%)Capsule sprinklesGroup 1:353 (68%)Group 3 (N=1):742 (N/A) | Median (CV%):Oral solutionGroup 1:0.391 (141%)Group 2:0.445 (57%)Group 3:0.648 (7%)Group 4:1.185 (111%)Capsule sprinklesGroup 1:2.229 (103%)Group 3 (N=1):5.650 (N/A) | Median (CV%) Cmax::Oral solutionGroup 1:3.790 (76%)Group 2:1.998 (51%)Group 3:2.167 (68%)Group 4:2.632 (83%)Capsule sprinklesGroup 1:10.543 (45%)Group 3 (N=1):14.400 (N/A) |
| Moore et al. 201717 | ~1600mg \*(weight in kg/70)0.7rounded for weightband dosingDose increased after week 2 PK exposure measurement if below target range.capsule formulation QD | N=47,Aged 3 to 36 monthsART naiveGroup:1A: N=221B: N=162A: N=72B: N=2Group 1: Extensive metabolizers Group 2: Slow metabolizers Group A: aged 3-24 monthsGroup B: aged 24 – 36months | Median (IQR):All children19 months (13–27)Group 1: 19 (13- 27)Group2: 20 (18-26) | Not reported | Not reported | 82% [95% CI (68 - 92)] VL< 400 copies/mL and <1 log10 decrease in VL from baseline | Median (IQR):Extensive metabolisersGroup 1A:108.58(58.85- 135.92)Group 1B:106.84(35.55- 132.17)Poor metabolizersGroup 2A:490.20(339.48- 650.25)Group 2B:83.11(63.71-102.50) | Median (IQR):Extensive metabolisersGroup 1A:1.80(1.01- 2.48)Group 1B:2.63 (0.83- 3.74)Poor metabolizersGroup 2A:20.78(12.29- 24.25)Group 2B:3.11(2.18- 4.03) | Median (IQR) Cmax::Extensive metabolisersGroup 1A9.19(6.02, 10.72)Group 1B7.533.49, 10.25Poor metabolizersGroup 2A21.8518.37, 33.39Group 2B4.784.48, 5.07 |
| Adult data8  | EFV 600 mg QD |  |  |  |  |  | Mean (SD):58.148 (23.013) | Mean (SD):1.768 (1.010) | Mean (SD):4.072 (1.168) |
| **Nevirapine (NVP)** |
| **Reference** | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **BSA (m2)** | **Weight(kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough****(mg/L)** | **Cmax (mg/L)** |
| NVP twice-daily  |  |  |  |  |  |  | AUC0-12 (h\*mg/L) |  |  |
| Chokephaibulkit et al. 2005 18 | Median dose (SD)164 (27) mg/m2 BDIn adult fixed dose combination tablets containing 200mg NVP | ART naive and experienced children taking adult fixed dose combinationN=34 (14 ART naive) | Median (range):8.4 (3–15) | Not reported | Not reported | Naive:92% VL <400 copies/mL after 26 weeksExperienced: Not reported | Median (range):78.4(50 – 306.6) | Median (range):Cmin5.98 (2.57-24.37) | Not reported |
| King et al. 2005 19 | Capsule and liquid formulation120 mg/m2 BD,Median dose mg/kg (range):4.4 (2.2–5.5) | N=20 (PK study: N=10) 5 months – 21 years oldART experienced and virologically suppressed | Median (range):7.0 (0.4–20.8) | Not reported | Median (range):22.8 (8–126.4) | 28% retained VL <400 copies/mL | Median (range):41.8 (25.4–102.4) | Median (range):2.2 (1.4–7.6) | Median (range):5.1 (3.1–10.9) |
| L’Homme et al. 200820 | Mean (range):370 (317, 486) mg/m2/day3 to <6 kg: 100 mg NVP In two doses6 to <10 kg: 150 mg NVP in two doses10 to <15 kg: 200 mg NVP in two doses15 to <20 kg: 250 mg NVP in two doses20 to <25 kg: 300 mg NVP in two doses25 to <30 kg: 400 mg NVP in two doses | 3 to <6 kg: N=26 to <10 kg: N=1310 to <15 kg: N=915 to <20 kg: N=1920 to <25 kg: N=1225 to <30 kg: N=10Naive childrenAged 3 months to <14 years | Mean (range):All children:6.9 (0.5, 14.9)3 to <6 kg:0.8 (0.7, 0.8)6 to <10 kg:1.3 (0.5, 4.2)10 to <15 kg: 5.2 (2.2, 6.8)15 to <20 kg:7.0 (4.8, 12.6)20 to <25 kg:10.2 (7.7, 13.5)25 to <30 kg:12.9 (10.2, 14.9) | Not reported | Mean (range):All children:16.0 (3.4, 29.0)3 to <6 kg:4.3 (3.4, 5.2)6 to <10 kg:7.7 (6.0, 9.8)10 to <15 kg: 11.2 (10.0, 13.0)15 to <20 kg:16.5 (15.0, 19.0)20 to <25 kg:21.5 (20.0, 24.0)25 to <30 kg:27.0 (25.0, 29.0) | 78% VL <250 copies/mL at week 4821 | Mean (range) [SD]:All children94.4 (32.1, 232) [39.4]3 to <6 kg:76.1 (40.4, 112)6 to <10 kg:102 (55.3, 232)10 to <15 kg: 80.8 (42.0, 158)15 to <20 kg:90.6 (61.3, 141)20 to <25 kg:85.9 (41.3, 169)25 to <30 kg:118 (32.1, 208) | **Mean C12** (range) [SD]:All children6.0 (1.4, 16.9) [3.0]3 to <6 kg:5.7 (1.8, 9.7)6 to <10 kg:6.4 (3.5, 16.9)10 to <15 kg: 5.0 (2.2, 10.5)15 to <20 kg:5.6 (3.2, 8.9)20 to <25 kg:5.6 (2.9, 11.0)25 to <30 kg:7.9 (1.4, 14.9) | Mean(range) [SD]:All children10.0 (3.8, 22.5) [3.8]3 to <6 kg:8.5 (5.3, 11.7)6 to <10 kg:10.7 (5.6, 22.5)10 to <15 kg: 9.1 (4.1, 16.8)15 to <20 kg:9.6 (6.5, 15.3)20 to <25 kg:9.0 (4.1, 17.6)25 to <30 kg:12.0 (3.8, 21.2) |
| Pollock et al. 200922 | TRIOMUNE 30 (200 mg NVP)Receiving tablets to achieve8 mg NVP/kg/dayDose (range in mg/kg)<8 kg: 50mg in two doses(>6.2) (n=1)8 to <12 kg: 100 mg in two doses(8.3-12.5) (n=10)12 to <18 kg: 150 mg in two doses(8.3-12.5) (n=7)18 to <22 kg:200 mg in two doses(9.1-11.1) (n=1)22 to <28 kg: 250 mg in two doses(8.9-11.4) (n=4)28 to <32 kg:300 mg in two doses(9.4-10.7) (n=10)32 to <38 kg:350mg in two doses(9.2-10.9) (n=1)>38 kg: 400 mg in two doses (<10.5) (n=3)  | N=37,ART naive and experienced,Malnourished children: N=25Normal weigh children: N=120 to 16 years | Median (range):All children:4.4 (0.7, 16.0)Malnourished:2.6 (0.7, 14.7)Normal weight:6.3 (0.8, 16.0) | Median (range):All children:0.52 (0.25, 1.23)Malnourished:0.40 (0.25, 0.96)Normal weight:0.62 (0.32, 1.23) | Median (range):All children:12.3 (3.9, 38.9)Malnourished:7.8 (3.9, 24.0)Normal weight:15.9 (6.3, 38.9) | 54% VL<400 copies/mL | Median (range):All children:-Malnourished:60.082 (35.328–166.629)Normal weight:79.861 (43.922–14.6376) | Median (range):All children:-Malnourished:5.084 (1.645–8.489)Normal weight:5.881 (2.305–9.097) | Median (range):All children:-Malnourished:6.719 (3.401–18.947)Normal weight:9.483 (5.099–22.453) |
| Chokephaibulkit et al. 201123 | Generic FDC tablets vs liquid, dosed to achieve300–400mg NVP/m2/day | N-=42,Thai childrenClinically stable on NVP treatment 5 months to <13 yearsChildren were randomized 1:1 to start with either Liquid formulation or generic FDC with NVP/ZDV/3TC and crossed over to the other formulation after PK analysis. After, PK analysis was done with the new formulation.6 to <8 kg: N=68 to <16 kg: N=1216 to <23 kg: N=1223 to <30 kg: N=12 | Median (range):All children6 years (0.5–12) | Not reported | Median (range):All children19 kg (6–29) | Not reported | Geometric Mean (90%CI):Liquid:81.88 (74.59-89.89)Generic FDC tablet68.88 (62.13–76.36) | Geometric Mean (90%CI):Liquid:4.94 (4.32–5.65)Generic FDC tablet4.19 (3.66–4.81) | Geometric Mean (90%CI):Liquid:8.39 (7.75–9.08)Generic FDC tablet7.67 (7.04–8.34) |
| Fillekes et al. 201224 | FDC tablet 50 mg NVPMedian (IQR) NVP dose348 (326385) mg/m2 | N=15,Children >1 month oldweighing 3 to <6 kg | Median (IQR):4.8 (4.2, 8.4) months | Not reported | Median (IQR):5.3 (4.3, 5.5) | Not reported | Median (IQR) [CV]:70 (56, 104) [31] | Median (IQR) [CV]:4.3 (2.9, 6.9) [2.8] | Median (IQR) [CV]:7.5 (6.2, 10) [2.6] |
| Gopalan 201725 | Lead-in dose: 120-150 mg/m2 QDTherapeutic dose (after week 2): 120-150 mg/m2 BD. | N=20,ART experienced and naive initiating NVP therapy2 to <18 years | Median (IQR):9 (6 -11) | Not reported | Not reported | 70% VL <200 copies/mL | Not reported | Median (IQR):Week1:4.8 (3.5- 6.1)Week 2:3.4 (2.1 -7.9)Week 4:8 (5.6 -10.7) | Not reported |
| Adult data26  | NVP 200 mg BD |  |  |  |  |  | Median (range):54.5 (48.0–71.8) | Median (range):3.73 (3.20–5.08) | Median (range):5.7 (5.00–7.44) |
| NVP Once-daily  |  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Giaquinto 201427 | NVP extended release (NVP-XR) VersusNVP immediate release (NVP-IR)Dosed to achieve14 mg/kg/day for children <8 years oldand8 mg/kg/day for children >8 years old | N= 45Virologically suppressed on NVP-immediate release formulationAged 3 to <18 years old3 to <6 years: N=166 to <12 years: N=1612 to <18 years: N=17 | Not reported | 100% remained virally suppressed(VL <50 copies/mL) after 48 weeks28 | Not reported | Not reported | Geometric mean:aNVP-XR:112.61NVP-IR:124.58Ratio XR:IR % (90%CI) [CV]:90.39(82.39–99.17)[26.8] | Geometric mean:aNVP-XR:3.474NVP-IR:3.814Ratio XR:IR % (90%CI) [CV]:91.08(82.28–100.81)[29.5] | Geometric mean:aNVP-XR:6.055NVP-IR:7.055Ratio XR:IR % (90%CI) [CV]:85.82(75.90–97.03)[36.2] |
| Adult data29 | NVP-XR 400mg QD |  |  |  |  |  | Median (IQR)101.8 (92.6–145.3) | Geometric mean: 2.88 (2.33–4.09) | Geometric mean: 6.69 (5.95–8.64) |
| **Rilpivirine (RPV)** |
| **Reference**  | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **BSA (m2)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough****(mg/L)** | **Cmax (mg/L)** |
| RPV once-daily |  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Crauwels et al. 201430Group 1: >12 to ≤15Group 2:>15 to ≤18 | Adult tablets25 mg RPV QD | Group 1: N=12Group 2: N=13Aged 12 to <18 years weighing >32 kg | Median (range):15 (13–17) | Not reported | Median (range):44 (35–58) | Not reported | Geometric mean (range):All children:1.750 (0.887–3.573)Group 1:1.488Group2:2.032 | Geometric mean (range):All children:0.0636 (0.0328–0.1620)Group 1:0.0553Group2:0.0722 | Geometric mean (range):All children:0.1023 (0.0485–0.1820)Group 1:0.085Group2:0.1212 |
| Foca et al. 201631Group 1: RPVGroup 2: RPV +DRV/r | Adult tabletsRPV 25 mg QDCombined with or without DRV/r  | Group 1: N=15,Group 2: N=14ART naïve and experienced12 to <24 years old | Median (range):Group 1:20.4 (12.4 - 22.8)Group 2: 19.7(14.6 - 22.9) | Median (range):Group 1:1.8 (1.3 - 3.9)Group 2:1.7 (1.5 - 2.2) | Median (range):Group 1:69.3 (38.4,115.6)Group 2:60.2 (49.5, 95.0) | Not reported | Geometric mean(90% CI):Group 1:2.38 (1.92-2.94)Group 2:6.74 (4.89-9.28) | Geometric mean(90% CI):Group 1:0.07 (0.03-0.10)Group 2:0.23 (0.17-0.32) | Geometric mean(90% CI):Group 1:0.14 (0.12, 0.18)Group 2:0.39 (0.27, 0.57) |
| Lombaard et al. 201632 | Adult tabletsRPV 25 mg QD | N=34,ART naive adolescentsAged 12 to <18 years | Median (range):14.5 (12–17)  | Not reported | Median (range):45.2 (33–93) | Week 48Baseline VL <100.000 copies/mL (N=28)N (%, 90% CI):22 (79, 63-94)Baseline VL >100.000 copies/mL (N=8)N (%, 90% CI): 4 (50, 15-85)Baseline VL <100.000 (N=28): 79% (63-94) VL <50 copies/mL at Week 48Baseline VL >100.000 (N=8):50% (15-85) VL <50 copies/mL at Week 48 | Mean (SD):2.391 (0.991) | Mean (SD):0.0835 (0.0387) | Not reported |
| Adult data33 | 25 mg QD |  |  |  |  |  | Median (range):2.204 (0.482-8.601) Mean (SD):2.397 (1.032)  | Median (range):0.074 (0.001-0.300) Mean (SD):0.080 (0.037) | Mean (no range reported): 0.220 mg/L |

a: geometric mean calculated on 45 children in the intensive PK substudy
AUC: area under the concentration-time curve
BSA: body surface area
Ctrough: concentration at the end of the dosing interval
Cmax: maximum concentration in the dosing interval
Cmdi: concentration at mid-dose interval
IQR: inter quartile range
95% CI: 95% confidence interval
CV%: coefficient of variation
SD: standard deviation
QD: dosed once daily
BD: dosed twice daily
XR: extended release formulation
IR: immediate release formulation
VL: viral load

Table 3. Pharmacokinetic studies of protease inhibitors in HIV infected pediatric patients.

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| --- |
| **Atazanavir (ATV)** |
| **Reference** | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **BSA (m2)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough****(mg/L)** | **Cmax (mg/L)** |
| ATV once daily |  |  |  |  |  |  | AUC0-24 (h\*mg/L)(calculated as AUC (12) \*2) |  |  |
| Kiser et al 2011 34IMPAACT 1020 | **Powder formulation**IMP1: 310 mg/m2 (boosted) IMP3a: 310 mg/m2 (boosted)**Capsules**IMP3b: 205 mg/m2 (boosted)IMP5: 205 mg/m2 (boosted)IMP6: 620 mg/m2 (**un**boosted) | N=195 (172 evaluable PK)**Powder formulation**3 to 6 months (n=11)(IMP0)91 days - <2 years old (n=17)(IMP1)2 to 13 years (n=21)(IMP3)**Capsules**2 years to 13 years (n=21)(IMP3)13 years to <21 years, boosted (n=14)(IMP5)13 years to <21 years, **un**boosted (n=21)(IMP6)64% American, 36% South-AfricanPI experienced (42%) & naive  | Median(range):Total8.7 years (0.3–21.3)Median (IQR):IMP0: 0.4 (0.1)IMP1: 1.3 (0.9)IMP3a: 4.5 (1.8)IMP3b: 8.8 (4.2)IMP5: 17.1 (2.4)IMP6: 14.6 (2.9) | Median(range):Total0.98m2 (0.27–2.32)Median (IQR):IMP0: 0.32 (0.02)IMP1: 0.42 (0.06)IMP3a: 0.64 (0.13) IMP3b: 0.98 (0.32)IMP5: 1.73 (0.55)IMP6: 1.54 (0.29) | Median (range):Total26.6 (4.3–121.9)Median (IQR):IMP0: 6.2 (0.5)IMP1: 8.5 (1.4)IMP3a: 15 (4.1)IMP3b: 28.8 (12.5)IMP5: 62.3 (34.9)IMP6: 52 (18.8) | 58.5% at week 48(69.5% of ART naive, 43.3% of ART experienced patients were <400 copies/ml at 48 weeks after initiation) | Median (IQR):IMP0: 38.928 (42.778)IMP1:44.243 (41.664)IMP3a: 52.199 (37.148)IMP3b: 45.680 (20.028)IMP5: 42.835 (18.910)IMP6: 51.781 (25.659) | Median (IQR):IMP0: 0.596 (0.672)IMP1: 0.482 (0.433) IMP3a: 0.947 (0.759)IMP3b:0.575 (0.469)IMP5: 0.885 (0.799)IMP6: 0.510 (0.516) | Median (IQR):IMP0: 4.952 (4.706) IMP1: 6.501 (5.865) IMP3a: 5.593 (3.397)IMP3b:5.013 (2.301)IMP5: 4.095 (2.616)IMP6: 7.006 (3.399) |
| Bunupuradah 2014 35 | 200 mg ATV / 100mg RTV+ TDF/FTC | N = 18 Thai childrenAged 6-18 yearsPI experienced & naive ATV taken with TDF | Median (IQR):13 years (11-14)  | Median (range):1.21 m2 (0.96-1.35): | median (range):35 (25-42)  | 75% at week 48 | Geometric Mean (SD):35.05 (1.06)  | Geometric Mean (SD):0.31 (1.13)  | Geometric Mean (SD):3.93 (1.06) |
| Cressey 2016 36 | 400 mg ATV QD&600 mg ATV QD | ATV 400: N= 18 (14 African, American, 1 White, 3 Hispanic) ATV 600: N= 6(4 African American, 1 white, 1 Hispanic)Adolescents 6 to < 24 years oldWith min BSA: >0.85 m2 | Median (95%CI):ATV 400 mg:20.3 (6-23)ATV 600 mg:16.9 (13-23)  | Median (CI 95%):ATV 400 mg:1.79 (0.85–2.29) m2ATV 600:1.72 (1.43-2.1) m2 | Median (95%CI):ATV 400: 70 (22-111) kg ATV 600:65 (45-86) kg | ATV 400 mg: 82% < 200 copies/mlATV 600 mg:80% <200 copies/ml | Geometric Mean (95% CI):ATV 400:19.9 (14.1-28.1)ATV 600:29.3 (13.7-62.9)  | Geometric Mean (95% CI):ATV 400: 0.18 (0.09-0.36)ATV 600:0.13 (0.03-0.61) | Geometric Mean (95% CI):ATV 400: 2.6 (1.8–3.7)ATV 600:4.0 (1.9–8.1) |
| Sevinsky et al.37 PRINCE I & PRINCE II | **ATV powder formulation**5 to <10 kg: 150/80 ATV/r [n=43] (group 1)5 to <10 kg: 200/80 ATV/r [n=10] (group 2)10 to <15 kg: 200/80 ATV/r [n=37] (group 3)15 to <25 kg: 250/80 ATV/r [n=48] (group 4)25 to <35 kg: 300/100 ATV/r [n=8] (group 5) | Children 3 months – <6 years: PRINCE IChildren 3 months to <11 yearsPrince IITotal amount of children involved in the study: 146 (used to inform on group age and weight parameters) (62.3% ART-experienced)56.8% Black/African AmericanInvolved in PK study: 88(used to inform on AUC, Ctrough and Cmax) | Age in months Median (range):All children41 (3–120)Group 1:6.0 (3–25)Group 2:4.0 (3–30)Group 3:35.0 (15–54)Group 4:61.5 (34–115)Group 5:86.5 (79–120) | Not reported | Median (range):Group 1:6.9 (5.4-9.7)Group 2:6.9 (6.0–9.9)Group 3:12.5 (10.4–14.8)Group 4:17.6 (15.0–24.8)Group 5:26.0 (25.1–34.9) | ART naive: 79% <400copies/ml at week 48ART-experienced: 62% <400 copies/ml at week 48 | Geometric Mean (CV%)Group 1: 32.503 (61%)Group 2:39.519 (54%)Group 3:50.305 (67%)Group 4:55.687 (45%)Group 5:44.329 (63%) | Geometric Mean (CV%):Group 1:0.336 (76%) Group 2:0.550 (60%)Group 3:0.572 (111%)Group 4:0.686 (68%)Group 5:0.468 (104%) | Geometric Mean (CV%):Group 1:4.131 (55%) Group 2:4.466 (59%)Group 3:5.197 (53%)Group 4:5.394 (46%)Group 5:4.210 (52%) |
| Adult refrence data38 | 400/100 mg QD |  |  |  |  |  | GM (CV%):46.073 (66%) | GM (CV%):0.636 (97%) |  |
| **Darunavir (DRV)** |
| **Reference** | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough (mg/l)** | **Cmax (mg/L)** |
| DRV/r twice-daily  |  |  |  |  |  |  AUC0-24 (h\*mg/L)(calculated as AUC (12)\*2) |  |  |
| Blache et al. 200939,40(DELPHI) | DRV tablets +ritonavir liquid (<40 kg) or capsules (>40 kg)11-19 mg/kg darunavir BDWith 2.5 mg/kg ritonavir BD | N = 76, (as reported for PK results)6-12 years: N=2412-17 years: N=76(as reported in baseline demographics)Weighing >20 kgART experienced | Mean (range not reported)14  | Not reported | 59% VL<400 copies/mL48% VL<50 copies/mL  | Mean (range):123.3 (71.9–201.5)6-12 years:112.8 (range not reported)12 to <18 years: 132.8 (range not reported) | Mean (range):3.7 (1.8–7.2)6-12 years: 3.3(range not reported)12 to <18 years: 4.1(range not reported) | Not reported |
| Chokephaibulkit et al. 201241 | DRV tablets + ritonavir capsules20 to <30 kg: 375/100 DRV/r BD30 to <40 kg:450/100 DRV/r BD>40 kg:600/100 DRV/r BD | N=19,Thai children >7 years, >20 kg20% ART experienced20 to <30 kg: N=1230 to <40 kg: N=2>40 kg: N=5 | Median (range):13 (7-16) | Median (range):29.4 (20–67.6) | Not reported | Median (CV%):All children120.6 (2\*60.3)20 to <30 kg:117.0 (85%)(2\*58.5)30 to <40 kg:117.0 (18%)(2\*58.5)>40 kg:131.6 (44%)(2\* 65.8)) | Median (CV%):All children3.1 (76%)20 to <30 kg:3.0 (96%)30 to <40 kg: 3.2 (60%)>40 kg:3.1(44%) | Median (CV%):All children8.3 (55%)20 to <30 kg:8.1 (65%)30 to <40 kg: 8.2 (1%)>40 kg:9.0 (46%) |
| Violari et al. 201542,43 ARIEL trial | Oral suspensionPart I20/3mg/kg DRV/r BD10 to <15 kg, 15 to <20 kgPart II25/3mg/kg DRV/r BD10-15 kg375/50mg DRV/r BD15-20 kg | N= 213 to <6 years oldART experiencedPart I 10 to <15 kg n=10b15 to <20 kg n=14bPart II10 to <15 kg n=9b15 to <20 kg n=12b | Median (range):4.4 (3.0, 6.0) a | Median (range):14.9 (12, 20) a | 71.4% VL<50 copies/mL | Mean (SD):Overall78.5 (25.1)Part I10 to <15 kg (20/3mg/kg): 137.4(2\*68.7 (25.5)) b15 to <20 kg (20/3mg/kg): 158.0 (2\*79.0(31.4))bPart II10 to <15 kg (25/3mg/kg): 190.8(2\*95.4 (33.4)) b15 to <20 kg (375/50mg drv/r): 163.2(2\*81.6 (33.7))b | Part I10 to <15 kg 4.429(2.064) b15 to <20 kg 4.848 (2.526) bPart II10 to <15 kg 6.414(2.637)b15 to <20 kg 5.027 (2.828) b | Not reported |
| Adult refrence data40,44 | 600/100 mg DRV/r BD |  |  |  |  | Median (range):111.632 (64.874-355.360) | Median (range):3.307(1.517-13.198) | Mean (CV%):8,390 (21%)44 |
| DRV/r once-daily  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Flynn et al. 201445DIONE trial | DRV tablet + ritonavir tablet>40 kg: 600/100 QD | N=12,Aged 12 to <18 yearsWeighing >40 kgART naive patients | Median (range):14.4 (12.6-17.3) | Median (range):50.5 (40.0-61.6) | 92% VL <50 copies/mL at week 2483% VL <50 copies/mL at week 48 | Median (SD):80.7 (23.6)  | Median (SD):1.93 (0.87)  | Not reported |
| Chokephaibulkit et al. 201446 | DRV tablet + ritonavir tablet20-30 kg: 450/100 mg QD30-40 kg: 600/100 mg QD>40 kg: 900/100 mg QD | N= 8,Thai childrenEligible 6 to <18 years (≥11years were enrolled)Weighing >40kgART naive patients | Median (range):16 (11.0-18.9) | - | 75% VL <50 copies/mL at week 48 | Median (range):51.2 (20.7-117.7) | Median (range):0.70 (0.2-2.4) | Median (range):5.88 (2.36–10.5) |
| Violari et al. 201542ARIEL trial | DRV oral suspension + ritonavir oral suspension<15 kg: 40/7 mg/kg QD>15 kg: 600/100 mg QD | N=10,Aged 3 to < 6 yearsART experienced | Median (range):4.4 (3.0-6.0) | Median (range):14.9 (12-20) | Not reported | Median (SD):115 (40.6)  | Not reported | Not reported |
| Larson et al. 201647 | DRV/r (formulation not reported) >40 kg: 800/100 mg DRV/r QD | N= 16,Eligible 9 to <24 years (≥ 13.7 years were enrolled)>40kgART experienced but without DRV RAM. | Median (range):20.1 (13.7-23.2) | Median (range):66.7 (40.0-92.3) | Not reported | Median (range):57.9 (49.6-67.6) | Median (range):1.0 (0.8-1.3)  | Median (range):5.5 (4.6–6.5) |
| Bastiaans et al. 201848DAPHNE trial | DRV/r tablet 15-30 kg: 600/100 mg QD30-40 kg: 675/100 mg QD>40 kg: 800/100 mg QD | N=12,Aged 6 to <12 yearsWeighing >15 kgART experienced but without DRV RAM. | Median (range):8.9 (6.3-11.7) | Median (range):26.6 (22.4-45.0) | 91% VL <50 copies/mL at 11.6 months | Median (CV%):63.1 (33%) | Median (CV%):1.5(44%)  | Median (CV%):5.6 (34%) |
| Adult refrence data40,49 | 800/100 mg QD |  |  |  |  | Median (range):87.854(45.000-219.240) | Median (range):2.041(0.368-7.242) | Mean (CV%):7.460 (20.3)49 |
| **Lopinavir (LPV)** |
| **Reference** | **Intended dose and formulation** | **Population** | **Age (years, unless stated differently)** | **BSA (m2)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough (mg/l)** | **Cmax (mg/L)** |
| LPV twice-daily  |  |  |  |  |  |  | AUC0-12 (h\*mg/L) |  |  |
| Sáez-Llorens 200350 | LPV Oral solution230/57.5 mg/m2 LPV/r BD300/75mg/m2 LPV/r BDCo administrated with and without NVP  | N=44ART naïve children6 months to <12 yearsN= 66, ART experienced (co administrated NVP) | **Mean** (Range):ART Naïve (no NVP)4.8 months (6-10.2)ART experienced (with NVP)5.7 months (8 -12.6) | Not reported | Not reported | 79% had VL <400copies/mL at Week 48 | Mean (SD)230/57.5 No NVP:72.6 (31.1)230/57.5 With NVP:51.6 (27.8)300/75 No NVP:116.4 (57.1)300/75 With NVP:85.8 (36.9) | Mean (SD)230/57.5 No NVP:3.35(2.14)230/57.5 With NVP:1.80 (1.68)300/75 No NVP:6.53 (4.57)300/75 With NVP:3.56 (3.45) | Mean (SD)230/57.5 No NVP:8.16 (2.94)230/57.5 With NVP:6.71 (3.32)300/75 No NVP:12.45 (5.77)300/75 With NVP:10.04 (3.26) |
| Rosso et al. 200651 | Oral solution230/57.5 mg/m2 BD | N=21ART naïve | Median (range):7.43 (3.50–13.46) | Not reported | Median (range):24.9 (8.3–39.0) | 100% VL <400 copies/mL at 24 weeks | Not reported | Median (IQR):7.90 (5.45-9.77) | Median (IQR)14.60 (10.83–15.98) |
| Verweel et al. 200752 | Soft gel capsule and oral solution230/57.5 mg/m2 BD | N= 23ART naïve, with PI mutations, and PI experienced (with no previous virological failure) | Median (range):5.6 (0.4-13.2 | Median (range):0.75 (0.30–1.31) | Median (range):18.1 (5.4–43.9) | Naïve:97% VL <50 copies/mL at 48 weeksPI resistance at baseline:66% VL <50 copies/mLAt 48 weeksPi experienced without prior virological failure:100% VL <50 copies/mL | Mean (SD):75.3 (33.7) | Mean (SD):3.68 (2.48) | Mean (SD):9.33 (3.27) |
| Chadwick et al. 200853 | LPV Oral solution300/75 mg/m2 LPV/r BD | N=18ART naïve cAged 6 weeks to <6 months | Median (SD):3.4 months (1.4) | Median (SD):0.31(0.05) | Median (SD):5.5(1.5) | 53% had VL<400copies/mL at week 24 | Median (SD):67.52(37.94) | Median (SD):2.37(2.7) | Not reported |
| La Porte 200954 | Soft gel capsule and oral solution 230/57.5 mg/m2 BD | N= 6Virologically suppressed on LPV BD | Median (range):9.8 (5.8-15.5) | Median (range):0.98 (0.73–1.54) | Not reported | Not reported | Median (range):161.8 (46.6–271.8) | Median (range):5.7 (1.7–9.7) | Median (range):9.8 (3.4-15.2) |
| Puthanakit 2009 55 | Oral solution**Low dose mg LPV/r: \*** 8 to 16.9 kg: 120/30 n= (3)17 to 19.9 kg: 144/36 n= (1)20 to 24.9 kg: 160/40 n= (4)25- 29.9 kg: 200/50 n= (1)30 to34.9 kg: 240/60 n= (1)>35 kg: 280/70 n= (2)**Standard dose: \***8 to 16.9 kg: 160/40 n= (2)17 to 19.9 kg: 200/50 n= (0)20 to 24.9 kg: 240/60 n= (5)25 to 29.9 kg: 280/70 n= (2)30 to34.9 kg: 320/80 n= (0)>35 kg: 400/100 n= (3) | N=22Aged 2 to <18 yearsLow dose: n=11Standard dose: n=11ART naïve **Thai** children | Median (IQR):All children:9.5 (7.0–12.3)Standard dose:9.6 (8.4-14.7)Low dose:8.6 (6.7-11.8) | Median (IQR):All children:0.9 (0.8–1.1)Standard dose:0.9 (0.8–1.2)Low dose:0.8 (0.7–1.1) | Median (IQR):Standard dose:24 (20-37)Low dose:21 (17-31) | Low dose efficacy:100% VL <50 copies/mL at 48 weeksStandard dose efficacy:75% VL <50 copies/mL at 48 weeks | Median (range)[%CV]:Low dose:83.1 (56.0–112.9) [35%]Standard dose117.6 (74.0–128.5) [32%] | Median (range)[%CV]:Low dose:3.4 (2.7–5.4) [46%]Standard dose4.9 (2.7–8.0) [54%] | Median (range)[%CV]:Low dose:10.1 (7.1–13.7) [33%]Standard dose11.9 (10.6–14.4) [25%] |
| Chadwick et al. 200956 | LPV Oral solution300/75 mg/m2 LPV/r BD | N=9ART Naïve childrenAged 14 days to <6 weeksWeighing >2.5kg | Median (SD):5.7 weeks (0.8) | Median (SD):0.27(0.04) | Median (SD):4.7(0.88) | 71% had VL <400 copies/mL at week 48 for cohort57 | Median (SD):36.6(14.8) | Median (SD):2.22 (1.34) | Median (SD):4.76 (1.84) |
| Chadwick et al. 201157 | LPV Oral solution300/75 mg/m2 LPV/r BD | N=20aged <6 months oldART Naïve children | Median (range):12.4 months (12.0-15.5) | Median (range):0.43(0.33-0.50) | Not reported | 71% had VL <400 copies/mL at week 48 | Median (IQR):99.1 (82.4-124.5)(for children starting ART at age 14 days to <6 weeks)112.0 (95.0-148.8)(for children starting ART at age 6 weeks to <6 months) | Not reported | Not reported |
| Chokephaibulkit et al. 2012 58 | Adult tablets 230/57.5 mg/m2 BD | N=6Virologically suppressed | Median (range):13.1 (9.3–17.7) | Not reported | Median (range): 40.8 (26.8–50.3) | Children where virologically suppressed (baseline) | Median (range):172 (125–201) | Median (range):4.2 (2.0–6.5) | Median (range):8.8 (7.4–9.8) |
| Bastiaans et al 201459 | Pediatric tablets (100/25mg)≥15 to ≤25kg: 200/50 mg>25 to ≤35kg: 300/75 mg >35kg: 400/100 mg | N=53ART experiencedMixed ethnicities | Median (IQR):Whole group:11.0 (8.8–14.7)≥15 to ≤25:7.4 (6.8–8.8)>25 to ≤35:10.9 (10.1–13.9)>35:15.0 (13.7–15.7) | Not reported  | Median(IQR):All children:31.0 (23.6–40.0)≥15 to ≤25:20.5 (19.3–23.5)>25 to ≤35:30.2 (29.1–32.1)>35:41 (38.3–49.5) |  | GM (95% CI):All children:106.9 (97.8–116.9)≥15 to ≤25:104.1 (84.9–127.5)>25 to ≤35:116.9 (100.6–135.8)>35:101.9 (89.1–116.6) | GM (95% CI):All children:4.9 (4.14–5.80)≥15 to ≤25:4.2 (3.07–5.78)>25 to ≤35:5.1 (3.53–7.36)>35:5.4 (4.16–6.97) | GM (95% CI):All children:12.0 (11.1–12.9)≥15 to ≤25:12.2 (10.4–14.5)>25 to ≤35:13.0 (11.4–14.8)>35:11.0 (10.0–12.2) |
| Lyall et al. 2015 60(PENTA 18) | Pediatric tablets (100/25mg)≥15 to ≤25 kg: 200/50 mg>25 to ≤35 kg: 300/75 mg >35 kg: 400/100 mg | N=26Suppressed for at least 24 weeks on LPV/r containing therapyMixed ethnicity≥15 to ≤25: N=7>25 to ≤35: N=8 >35: N=11 | Median (IQR):Whole group:12.8 (8.7, 14.7)≥15 to ≤25:7.1 (6.7, 8.7)>25 to ≤35:10.6 (9.5, 15.0)>35:14.3 (13.5, 15.4) | Not reported  | Median (IQR):All children:32.1 (24.1, 41.0)≥15 to ≤25:19.4 (19.0, 23.1)>25 to ≤35:30.7 (29.8, 32.1)>35:42.0 (38.5, 49.5) | 8% rebound at 48 weeks | GM (95% CI) **AUC0-24 (double AUC0-12)**:All children:223.9 (194.8, 257.4)≥15 to ≤25:232.1 (153.3, 351.4)>25 to ≤35:256.8 (209.3, 315.2) >35:198.1 (159.8, 245.5) | GM (95% CI):All children:5.69 (4.58, 7.07)≥15 to ≤25:4.92 (2.65, 9.16)>25 to ≤35:6.65 (5.22, 8.47) >35:5.57 (3.73, 8.32) | GM (95% CI):All children:5.69 (4.58, 7.07)≥15 to ≤25:4.92 (2.65, 9.16)>25 to ≤35:6.65 (5.22, 8.47) >35:5.57 (3.73, 8.32) |
| Adult refrence data61  | Adult tablets400/100 mg/m2 LPV/r BD |  |  |  |  |  | Median(SD):92.6 (36.7) | Median(SD):5.5 (2.7) | Mean (SD):9.8 (3.7) |
| Once-daily LPV/r |  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Rosso 200651 | 460/115 mg/m2 QD | N=7ART naïve | Median (range):8.67 (3.83–14.98) | Not reported | Median (range)24.9 (8.3–39.0) | 100% VL <400 at 24 weeks | Not reported | Median (IQR):1.59 (0.77-6.85) | Median (IQR):11.80 (11.15-16.35) |
| Van der Lee 200662 | 460/115 mg/m2 QD | N=19Virologically suppressed on LPV BDPre-treatment status unknown | Median (range):4.5 (1.4-12.9) | Median (IQR):0.76 (0.58–1.08) | Median (IQR):19.8 (13.6-30.0) | - | Median (SD):149.8 (58.8) | Mean (SD):2.88 (3.74)(53% of children Ctrough <1.0mg/L) | Mean (SD): 10.77 (2.90) |
| Van der Flier 200763 | Adult tablets (200/50 mg)460/115 mg/m2 QD | N=15Aged 4 to <15 years ART experienced without relevant mutationsVirologically suppressed on LPV BD | Median (range):8.7 (4.4-15.0) | Median (range):1.12 (0.79-1.56) | Median (range):33.8 (19.1–56.8) |  100% VL <50 copies/mL after 24 weeks | Mean (SD):217.9 (44.9) | Mean (SD):3.1 (2.4) | Mean (SD):14.8 (2.4) |
| La Porte 200954 | Soft gel capsule and oral solution 460/115mg/m2 QD | N= 7Virologically suppressed on LPV BD | Median (range):9.8 (5.8-15.5) | Median (range):0.98 (0.73–1.54) | Not reported | Viral load of one patient blipped to 666 copies/mL but regained viral suppression | Median (range):214.6 (114.2-289.2) | Median (range):3.4 (0.6-7.4) | Median (range): 13.5 (8.3-17.5) |
| Chokephaibulkit et al. 2011 58 | Adult tablets (200/50 mg)460/115 mg/m2 QD | N=6Virologically suppressed on LPV BD | Median (range):13.1 (9.3–17.7) | Not reported | Median (range): 40.8 (26.8–50.3) | 100% VL <40 copies/mL at 48 weeks | Median (range):200 (95–228) | Median (range):3.9 (0.2–7.3) | Median (range):12.1 (8.5–15.0) |
| Lyall et al. 2015 60(PENTA 18) | Pediatric tablets (100/25 mg)≥15 to ≤25: 200/50 mg>25 to ≤35: 300/75 mg >35: 400/100 mg | N=26Suppressed for at least 24 weeks on LPV/r containing therapyMixed ethnicity≥15 to ≤25: N=7>25 to ≤35: N=8 >35: N=11 | Median (IQR):Whole group:12.8 (8.7, 14.7)≥15 to ≤25:7.1 (6.7, 8.7)>25 to ≤35:10.6 (9.5, 15.0)>35:14.3 (13.5, 15.4) | Not reported | Median (IQR):Whole group:32.1 (24.1, 41.0)≥15 to ≤25:19.4 (19.0, 23.1)>25 to ≤35:30.7 (29.8, 32.1)>35:42.0 (38.5, 49.5) | 8% rebound at 48 weeks | GM (95% CI)Whole group:160.9 (138.4, 187.0)≥15 to ≤25:172.6 (121.3, 245.7)>25 to ≤35:159.3 (120.6, 210.5)>35:155.0 (116.8, 205.6) | GM (95% CI):Whole group:5.69 (4.58, 7.07)≥15 to ≤25:4.92 (2.65, 9.16)>25 to ≤35:6.65 (5.22, 8.47)>35:5.57 (3.73, 8.32) | GM (95% CI):Whole group:14.0 (12.7, 15.6)≥15 to ≤25:15.5 (12.4, 19.4)>25 to ≤35:15.0 (12.2, 18.5)>35:12.5 (10.7, 14.7) |
| Adult refrence data61,64 | 800/200 mg/m2 LPV/r QD |  |  |  |  |  | Mean (SD):154.1 (61.4) | Mean (SD):Cmin 1.7 (1.6)   | Mean (SD):11.8 (3.7) |

a: based on data from Violari et al. 93
b: based on data from FDA pharmacology review94
c: not reported which children were used for PK study
AUC: area under the concentration-time curve
BSA: body surface area
Ctrough: concentration at the end of the dosing interval
Cmax: maximum concentration in the dosing interval
ART: antiretroviral therapy
PI: protease inhibitor
DRV RAM: darunavir resistance associated mutations
IQR: inter quartile range
95% CI: 95% confidence interval
CV%: coefficient of variation
SD: standard deviation
GM: geometric mean
QD: dosed once daily
BD: dosed twice daily
VL: viral load
IMP: IMPAACT study group (1-6)

Table 4. Pharmacokinetic studies of integrase inhibitors and TAF in HIV infected pediatric patients

|  |
| --- |
| **Dolutegravir (DTG)** |
| **Reference** | **Dose DTG and formulation** | **Population** | **Age (years, unless stated differently)** | **Weight (kg)** | **Suppression rates %****(95%CI)** | **AUC** | **Ctrough (mg/l)** | **Cmax (mg/L)** |
| DTG once-daily |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Viani et al. 201565 IMPAACT P1093 | Film coated tablets (FCT)15 to <20 kg: 20 mg QD20 to <30 kg: 25 mg QD30 to <40 kg: 35 mg QD>40 kg: 50 mg QDCohort 1: (FCT) | Aged 12 to <18: N=23 ART experienced Weighing >15 kg**Fasted** | Median (range):12 to <18 years14.6 (12.2-17.9) | Median (range):12 to <18 years old50.8 (37.1-91.4) | 12 to <18 years:74% (52-90) <400copies/mL at week 4861% (39-80) <50copies/mL at week 48 | Median (range):12 to <18 years 52.9 (13.1-85.0) | Median (range):12 to <18 years 1.14 (0.21-2.12) | Median (range):12 to <18 years 4.01 (1.15-6.08) |
| Viani et al 201466 | Film coated tablets (FCT)20 to <30 kg: 25 mg QD30 to <40 kg: 35 mg QD>40 kg: 50mg QDCohort 2: (FCT) | Aged 6 to <12:N=11 Cohort 2A: 6 to <12 yearsCohort 2B: 6 to <12 yearsART experienced Weighing >15 kg**Fasted** | Median (range):6 to <12 years:10 (8-11) | Median (range):6 to <12 years:30.0 (18-54) | 6 to <12 years:78.3% (56.3-92.5)<400 copies/mL at week 4873.9% (51.6-89.8) <50 copies/mL at week 48 | Median (range):6 to <12 years:50.46 (46%) | Median (range):6 to <12 years:0.92 (89%) | Median (range):6 to <12 years:Not reported |
| Ruel et al. 20186 IMPAACT P1093 | Dispersible tablets (DT)3 to <6 kg: 5 mg QD6 to <10 kg: 10 mg QD10 to <14 kg: 15 mg QD14 to <20 kg: 20 mg QD20 to <20 kg: 25mg QD | N=30,ART experienced 4 weeks to 2 years:Weighing >3 kg**Fasted** | Median (range):Cohort 3 -DT:0.34 (0.28-0.39)Cohort 4 -DT:1.2 (0.9-1.9)Cohort 5 -DT:4.0 (2.1-5.9) | Not reported | 4 weeks to 2 years:81% VL <400 copies/mL at week 48 | Geometric mean (CV%) :Cohort 3 -DT:61 (44%)Cohort 4 -DT:51 (38%)Cohort 5 -DT:40 (36%) | Geometric mean (CV%):Cohort 3 -DT:1.207 55(%)Cohort 4 -DT:0.711 (60%)Cohort 5 -DT:0.461 (59%) | Not reported |
| Bollen et al. 4 Odyssey | Film coated tablets14 to <20 kg: 20 mg QD20 to <25 kg: 25 mg QD | Aged <18 yearsWeighing 14 to <25 kg 14 to <20 kg: n=1920 to <25 kg: n=14**Fasted** | Median (IQR):14 to <20 kg: 6.2 (5.1-7.4)20 to <25 kg: 9.5 (7.6-10.6)  | Median (IQR):14 to <20 kg:17 (16.0-18.6)20 to <25 kg:23.4 (22.9-23.9) | Not reported | Geometric mean (CV%):14 to <20 kg:39.6 (32%)20 to <25 kg:30.1 (41%) | Geometric mean (CV%):14 to <20 kg:0.48 (67%)20 to <25 kg:0.29 (97%) | Geometric mean (CV%):14 to <20 kg:4.03 (31%)20 to <25 kg:3.20 (40%) |
| Turkova et al.5 Odyssey | Film coated tablets25 to <30 kg: 25 mg QD (PK1)25 to <30 kg: 50 mg QD (PK2)30 to <40 kg: 35 mg QD (PK1)30 to <40 kg: 50 mg QD (PK2) | Aged <18 yearsWeighing 25 to <40 kg25 to <30 kg: n=1830 to < 40 kg: n=10**Fasted** | Median (range):25 to <30 kg:10.7 (7.5-17.9)30 to <40 kg:11.2 (9.8-17.8)  | Median (range):25 to <30 kg:27.5 (25.0-30.7)30 to <40 kg:31.0 (29.9-38.2) | Not reported | Geometric mean (CV%):25 to <30 kg (25mg):33.1(23%)25 to <30 kg (50mg):58.7 (27%)30 to <40 kg (35mg):40.3 (35%)30 to <40 kg (50mg):53.5 (32%) | Geometric mean (CV%):25 to <30 kg (25mg):0.38 (48%)25 to <30 kg (50mg):0.75 (42%)30 to <40 kg (35mg):0.45 (63%)30 to <40 kg (50mg):0.63 (49%) | Geometric mean (CV%):25 to <30 kg (25mg):3.16 (24%)25 to <30 kg (50mg):5.41 (25%)30 to <40 kg (35mg):3.98 (28%)30 to <40 kg (50mg):5.22 (25%) |
| Bollen et al. (Ref.)Odyssey (CROI 2019) | Film coated tablets (FCT) and Dispersible tablets (DT)20 to <25 kg: 50 mg FCT QD 20 to <25 kg: 30 mg DT QD  | Aged <18 yearsWeighing 20 to <25 kg20 to <25 kg FCT: n=720 to <25 kg DT: n=8**Fasted** | Median (range):20 to <25 kg FCT:9.7 (8.1-11.7)20 to <25 kg DT:  8.6 (6.8-11.3) | Median (range):20 to <25 kg FCT:22.4 (20.5-24.5)20 to <25 kg DT: 21.8 (20.3-22.7) | Not reported | Geometric mean (CV%):20 to <25 kg FCT:62.8 (30%)20 to <25 kg DT: 71.8 (28%) | Geometric mean (CV%):20 to <25 kg FCT:0.77 (51%)20 to <25 kg DT: 0.71 (74%) | Geometric mean (CV%):20 to <25 kg FCT:6.07 (29%)20 to <25 kg DT: 7.42 (25%) |
| Adult refrence data67  | 50 mg DTG QD | **Fasted** |  |  |  | GM (CV%):43.4 (20%) | GM (CV%):0.83 (26%) | GM (CV%):3.34 (16%) |
| **Raltegravir (RTG)** |
| **Reference** | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough (mg/l)** | **Cmax (mg/L)** |
| RTG twice-daily  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Nachmann et al. 201468 | Chewable tablet (CT)Film-coated tablet (FCT)Group 1: FCTGroup 2A: FCTGroup 2B: CTGroup3: CTFCT: 400mg BD (children weighing at least 25 kg)CT: 6 mg/kg BD maximum of 300 mg/day | N=96ART experienced and naive,Aged 2 to <19 yearsN (N in intensive PK sub-study)12 to <19 years FCT (Group 1): N=59 (11)6 to <12 years FCT (Group 2A): N=4 (11)6 to <12 years CT (Group 2B): N=13 (10)2 to <6 years CT (Group 3): N=20 (12) | Mean (SD):aGroup 1: 15.2 (1.9)Group 2A: 10 (1.4) Group 2B: 8.8 (1.6)Group3: 3.2 (1.2) | Mean:bGroup 1: 43.55Group 2A: 34.54Group 2B: 36.36Group 3: 14.24Median (CV%):aGroup 1: 39.8 (30.8%)Group 2A: 32.4 (23.2%)Group 2B: 35.1 (31.3%)Group3: 13.4 (15.7%) | 79.1% VL <400 copies/ mL or >1 log10 decline from baseline at week 4873.6% VL <400 copies/mL at 48 weeks 57.1% VL<50 copies/mL at week 48 | Median (CV%):bFilm coated tablets:Group 1: 7.4 (97.6%)Group 2A:6.7 (120.4%)Chewable tablets:Group 2B:10.5 (33.6%)Group 3:7.3 (58.6%) | Median (CV%):bFilm coated tablets:Group 1:  0.1376 (78.3%)Group 2A: 0.1075 (220.5%)Chewable tablets:Group 2B:0.0434 (87.6%)Group 3: 0.0358 (55.5%) | Median (CV%):bFilm coated tablets:Group 1:  1384.1 (95.1%)Group 2A:  2.247 (129.9%)Chewable tablets:Group 2B: 4.524 (53.3%)Group 3:  5.143 (56.5%) |
| Nachmann et al. 201569 | Granules for suspensionGroup 4: 6 mg/kg BDGroup 5: 6 mg/kg BD | N=96ART experienced and naive,Aged 4 weeks to <2 yearsGroup 4: 6 months to <2 years Group 5: 4 weeks to <6 months | Not reported | Mean (no range reported):Group 4: 8.49Group 5: 5.50 | 87.5% VL <400 copies/mL or >1 log10 reduction from baseline at week 4866.7%VL<400copies/mL at week 48 45.5% VL<50copies/mL at week 48 | Geometric Mean (CV%)Group 4:8.8 (34%)(19.8 µmol\*h)Group 5:9.9 (40%)(22.3 µmol\*h) | Geometric Mean (CV%):Group 4:0.0479 (52%)(108.2 nmol/L)Group 5:0.0517 (68%)(116.6 nmol/L) | Geometric Mean (CV%):Group 4:4.7009 (64.8%) (10,600 nmol/L)Group 5:2.4832 (38.7%)(5,600 nmol/L) |
| Clarke et al. 201770 | Oral granules for suspensionDay 1 to 7: 1.5 mg/kg QDDay 8 to 28: 3.0 mg/kg BD>4 weeks: 6.0 mg/kg BD | N=24Full term infants <48 hours of ageGestational age at birth >37 weeksWeighing >2 kg | Mean (range):38.5 weeks (37.0-40.9) | Mean Birth weight:2.93 (2.39-3.75) | All HIV NAT results were negative | Geometric mean (CV%):1.5mg/kg QD (infants):38.2 (38.4%)3.0 mg/kg:14.3 (43.3%) | Geometric mean (CV%):1.5mg/kg QD (infants):0.948 (64.2%)3.0 mg/kg:0.176 (93.8%) | Geometric mean (CV%):1.5mg/kg QD (infants):2.350 (35.0%)3.0 mg/kg:2.850 (41.9%) |
| Adult reference data71  | 400mg BD |  |  |  |  | Geometric Mean7.67 (17.3 µmol\*h) | Geometric Mean:0.0717(161.6 nmol/L) | Geometric Mean:2.749(6,200 nmol/L) |
| **Elvitegravir (EVG) and TAF** |
| **Reference** | **Dose and formulation** | **Population** | **Age (years, unless stated differently)** | **Weight (kg)** | **Suppression rates****(%)** | **AUC** | **Ctrough (mg/l)** | **Cmax (mg/L)** |
| EVG once-daily  |  |  |  |  |  | AUC0-24 (h\*mg/L) |  |  |
| Gaur et al. 201672 | EVG within FDC: 150 mg QD | N=24,Virologically unsupressed (>1000 copies/mL)Aged 12 to <18 years, | Median (range): 15 (12–17) | Median (range):52.0 (35.0–88.8) | Not reported | Mean (CV%):23.840 (25.5%) | Mean (CV%):0.301 (81.0%) | Mean (CV%):2.230 (19.2%) |
| Natukunda et al. 201773 | EVG within FDC: 150 mg QD | N=23,Virologically suppressed for more than 6 monthsAged 6 to <11 years, weighed at least 25 kg  | Median (IQR):10 (8–11) | Median (IQR):30.5 (27.5–33.0) | 100% stayed suppressed VL<50 copies/mL | Mean (CV%)33.814 (58%) | Mean (CV%):0.370 (119%) | Mean (CV%):3.055 (39%) |
| Adult reference data73 | EVG within FDC: 150 mg QD |  |  |  |  | Mean (CV%):22.797 (35%) | Mean (CV%):0.287 (62%) | Mean (CV%):2.113 (34%) |
| TAF once-daily |  |  |  |  |  | AUC0-12 (h\*mg/L) |  |  |
| Gaur et al. 201672 | TAF: 10 mg | N=24,Aged 12–18 years, | Median (range): 15 (12–17) | Median (range):52.0 (35.0–88.8) | Not reported | Mean (CV%):0.189 (55.8%) | Not reported | Mean (CV%):0.167 (64.4%) |
| Natukunda et al. 201773  | TAF: 10 mg | N=23,Virologically suppressed for more than 6 monthsAged 6–11 years, weighed at least 25 kg  | Median (IQR):10 (8–11) | Median (IQR):30.5 (27·5–33·0) | 100% stayed suppressed VL<50 copies/mL | Mean (CV%):TAF:0.333 (45%)TNF:0.440 (21%) | Mean (CV%):TAF:Not available due to short half-life of TAFTNF:0.015 (25%) | Mean (CV%):0.313 (61%)TNF:0.026 (21%) |
| Adult reference data73 | TAF: 10 mg |  |  |  |  | Mean (CV%)TAF:0.206 (72%)TNF:0.293 (27%) | Mean (CV%):TAF:Not available due to short half-life of TAFTNF:0.011 (29%) | Mean (CV%):0.162 (51%)TNF:0.015 (26%) |

a: data from full cohort
b: data from intensive PK studies only
AUC: area under the concentration-time curve
BSA: body surface area
Ctrough: concentration at the end of the dosing interval
Cmax: maximum concentration in the dosing interval
ART: antiretroviral therapy
IQR: inter quartile range
95% CI: 95% confidence interval
CV%: coefficient of variation
SD: standard deviation
GM: geometric mean
QD: dosed once daily
BD: dosed twice daily

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