Pharmacokinetics and Safety of the Abacavir/Lamivudine/Lopinavir/Ritonavir Fixed-Dose Granule Formulation (4-in-1) in Neonates: PETITE Study

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Background: Antiretroviral options for neonates (younger than 28 days) should be expanded. We evaluated the pharmacokinetics, safety, and acceptability of the "4-in-1" fixed-dose pediatric granule formulation of abacavir/lamivudine/lopinavir/ritonavir (30/15/40/10 mg) in neonates.

Methods: The PETITE study is an ongoing phase I/II, open-label, single-arm, 2-stage trial conducted in South Africa. In stage 1, term neonates exposed to HIV on standard antiretroviral prophylaxis (nevirapine ± zidovudine) received single dose(s) of the 4-in-1 formulation, followed by intensive pharmacokinetic sampling and safety assessments. At each PK visit, blood was drawn after an observed dose at 1, 2, 4, 8, and 12 hours postdose. In this study, we have reported the planned interim pharmacokinetic and safety analysis after completion of the single-dose administration.

Results: Sixteen neonates, with a median (range) birth weight of 3130 g (2790–3590 g), completed 24 pharmacokinetic visits. The 4-in-1 formulation imposed relatively high doses of abacavir [8.6 mg/kg (6.6–11.4)] and lamivudine [4.3 mg/kg (3.3–5.7)] but lower doses of lopinavir [11.5 mg/kg (8.8–15.2)]. The geometric means (GM, 90% CI) AUC0–12 of abacavir, lamivudine, and lopinavir were 29.87 (26.29–33.93), 12.61 (10.72–14.83), and 3.49 (2.13–5.72) µg.h/mL, respectively. Lopinavir GM AUC0–12 was below the predefined target (20–100 µg.h/mL), and ritonavir concentrations were only detectable in 4 of the 120 (3%) samples. No adverse events were related to study drugs. No neonate had difficulty swallowing the 4-in-1 formulation.

Conclusions: The high doses of abacavir and lamivudine (in mg/kg) and AUCs were safe, and the formulation was well tolerated; however, lopinavir/ritonavir exposures were extremely low, preventing its use in neonates use in neonates. Alternative pediatric solid antiretroviral formulations must be studied in neonates.

Key Words: neonates, HIV, pharmacokinetics, abacavir, lamivudine, lopinavir

INTRODUCTION

The clinical benefits of early antiretroviral therapy (ART) for young children living with HIV are well established, but appropriate antiretroviral formulations that are safe, efficacious, and acceptable for neonates (younger than 28 days) are lacking. Initiating ART at birth or in the first few weeks of life for HIV treatment or prevention is challenging in all settings. In sub-Saharan Africa, only zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) liquid formulations are readily available for use from birth. Lopinavir/ritonavir (LPV/r) is widely used in pediatric HIV treatment, but there are no formulations approved for use from birth. LPV/r liquid formulation was initially approved for use in neonates aged 14 days or older, but the US Food and Drug Administration revised its 2013 labeling to specify for older than 42 weeks postmenstrual age as well, following reports of cardiac toxicity, acute renal failure, and respiratory complications in preterm neonates. Liquid LPV/r contains 42% alcohol and 15% propylene glycol, and it is unknown whether these...
toxicities are due to LPV/r or excessive exposure to the alcohol and/or propylene glycol in the formulation. Solid LPV/r formulations without these excipients could be advantageous for neonates, and expanding antiretroviral options for exposed neonates (born to women with HIV) remains a high priority.\textsuperscript{3}

The first solid pediatric LPV/r formulation developed was the oral “pellets” (Cipla Ltd, India.) composed of mini-meltrex tablets (1.8 mm) stored in capsules containing LPV/r at 40/10 mg.\textsuperscript{4} The oral pellets were approved for use for infants not only older than 14 days but also weighing >5.0 kg because of swallowability uncertainties in neonates. Building on this formulation, Cipla in partnership with the Drugs for Neglected Disease initiative recently developed a taste-masked fixed-dose combination (FDC) pediatric granule formulation of abacavir (ABC/3TC/LPV/r—coated LPV/r capsule is up to 9-fold smaller than the pellets and considered safe to swallow. The 4-in-1 capsules are simple to open, have no cold chain requirements, and the strawberry-flavored granules can be given with liquids, for example, breastmilk. The drug doses and ratios of ABC/3TC/LPV/r in the 4-in-1 capsule were designed for use in infants aged 4 weeks or older and weighing 3.0 kg for dosing per WHO weight bands.\textsuperscript{6} Multidosing pharmacokinetics (PK) and safety for the 3TC liquid formulation in neonates are available but none for solid pediatric formulations. Administering the 4-in-1 to neonates with immature drug elimination pathways may potentially lead to overexposure or underexposure of individual drug components. However, given the multiple advantages of this FDC granule formulation over individual liquid formulations, coupled with the favorable safety profiles of these drugs in children,\textsuperscript{9–11} we designed this study to evaluate the PK, safety, and acceptability of the 4-in-1 in term neonates.

**METHODS**

**Study Design**

The "PETITE" study is an ongoing phase I/II, open-label, single-arm, 2-stage clinical trial conducted at the Family Center for Research with Ubuntu at Tygerberg Hospital in Cape Town, South Africa (PACTR202007806554538). The study was designed to enroll 50 neonates exposed to HIV with birth weights between ≥2000 and ≤4000 g in 2 stages. In stage 1, the safety and single-dose PK of the 4-in-1 were assessed in 2 sequential cohorts: cohort 1A (n = 8) and cohort 1B (n = 8). Clinical and laboratory safety criteria had to be met before moving from cohort 1A to 1B. If both safety and predefined PK criteria were met following stage 1 single-dose PK, stage 2 would open to assess multidosing in neonates (cohort 2, n = 34). The study was approved by the Stellenbosch University Health Research Ethics Committee and the World Health Organization Research Ethics Review Committee. In this study, we have reported the planned interim safety and PK analysis after completion of stage 1.

**Stage 1**

All mothers provided written informed consent, and healthy term (gestational age: 38 weeks or older) neonates exposed to HIV were screened for enrollment. All neonates received HIV nucleic acid tests (NATs) at birth and standard antiretroviral prophylaxis (NVP with or without ZDV) per South African guidelines.\textsuperscript{12} Neonates were excluded based on the following criteria: (1) their baseline-corrected QT (QTc) intervals were >450 milliseconds (msec) on electrocardiogram (ECG); (2) aspartate transaminase (AST) or alanine aminotransferase value >1.25 the upper limit of normal (ULN); (3) creatinine value above the ULN; (4) hemoglobin level <13 g/dL; (5) hypokalemia (<3.6 mmol/L), hyperkalemia (>6.7 mmol/L), hypernatremia, (<135 mmol/L), and any other grade 3 or higher adverse event (AE) on the DAIDS toxicity table; (5) confirmed HIV infection; (6) receipt of tuberculosis treatment; or (7) if their mother was receiving LPV-containing ART. All ECGs were assessed by the study investigators and an independent pediatric cardiologist. A single 4-in-1 (ABC/3TC/LPV/r—coated LPV/r capsule was opened and mixed with expressed breastmilk or formula milk for oral administration on the PK sampling day. Acceptability and swallowability evaluations were performed at PK visits.

**Cohort 1A**

Screening and entry visits were performed in neonates younger than 14 days exposed to HIV with birth weights of ≥2500 to ≤4000 g. Enrolled neonates received a single observed dose of the 4-in-1 between neonates aged 14 days or older and those younger than 21 days. Thereafter, blood was drawn at 1, 2, 4, 8, and 12 hours postdose. An ECG was performed 4 hours after dosing [time to maximum concentration (T\textsubscript{max}) for LPV]. A clinical and laboratory safety visit (including HIV NAT) was performed 1 week after the PK visit. If 1 participant experienced a QTc interval of >500 msec, 1 participant a fatal or life-threatening–related AE, 2 participants the same related grade 3 or higher AE; or 3 participants with different related grade 3 or higher AEs (safety hold criteria), cohort 1A would be paused until the data safety and monitoring board (DSMB) assessed causality and advised on either study continuation or termination. If no major safety concerns were identified, cohort 1B would open to accrual.

**Cohort 1B**

Screening and entry visits of neonates were performed within the first 72 hours of life. Neonates exposed to HIV with birth weights ≥2000 to ≤4000 g were screened for enrollment. Enrolled neonates received a single dose of the 4-in-1 between ≥3 days and <14 days of age. After an observed dose, blood was drawn at 1, 2, 4, 8, and 12 hours postdose. An ECG was performed 4 hours after dosing. Ten to 14 days later, another single dose of the 4-in-1 was administered, followed by identical PK sampling and assessments. Clinical and laboratory safety visits were also performed 1 week after each PK visit. The safety hold criteria for cohort 1B were the same as those for cohort 1A.
Quantification of Plasma Drug Concentrations

Antiretroviral plasma concentrations were measured using liquid chromatography triple quadrupole mass spectrometry assays validated per US Food and Drug Administration guidelines at Bioanalytical Testing Laboratory of the Faculty of Associated Medical Sciences, Chiang Mai University. The lower limit of quantification (LLOQ) was 0.02 µg/mL for ABC/3TC and 0.05 µg/mL for LPV/RTV. This laboratory participates in the US NIH Clinical Pharmacology Quality Control program.13

Pharmacokinetic and Statistical Analysis

A noncompartmental pharmacokinetic analysis was performed to calculate the PK parameters using Phoenix WinNonLin (Certara). Maximum concentration (Cmax), Tmax, and 12-hour postdose concentration (C12) were taken directly from the observed concentration–time data. AUC0–12 was determined using the linear trapezoidal method. When possible, from the data, AUC12–∞ was estimated as the C12/λz, where λz was determined from the terminal slope. Apparent clearance (CL/F) was calculated as dose/AUC0–inf. If concentrations after the peak were <LLOQ, the first LLOQ value was set to LLOQ/2 and subsequent values to zero.

Interim Safety and Pharmacokinetic Analysis

An interim analysis was planned after completion of stage 1 to review the safety parameters and predefined PK criteria before proceeding to stage 2. Because no clear plasma exposure–response relationships exist for ABC and 3TC, the interim PK criteria focused on achieving LPV exposures comparable with those observed in adults and children on a multidose schedule. A mean LPV area under the concentration–time curve (AUC0–12 between approximately 40 and 100 µg·h/mL is safe and effective in adults and children.5,14 A mean LPV AUC0–12 between 30 and 150 µg·h/mL, that is, approximately 70%–150% of the reference range was selected as the predefined steady-state target for the multidose strategy. If the geometric mean (GM) of LPV AUC0–12 fell between 20 and 100 µg·h/mL (assuming an AUC0–12/AUC0–∞ ratio of 0.6515,16) after a single dose, it was expected that steady-state target exposures would be achieved.

RESULTS

Twenty-one term neonates exposed to HIV were screened. Three were ineligible due to grade 1 hypernatremic event, grade 1 AST (AST > 1.25 × ULN) event, and a mother on LPV-based ART. The baseline characteristics for the 18 enrolled neonates are listed in Table 1. The median (range) birth weight of neonates in stage 1 was 3143 g (2790–3590). Two neonates were withdrawn before receiving the 4-in-1, one because of new neurological signs (hypotonia, lethargy, and absence of eye contact) and one mother withdrew consent.

Pharmacokinetics of the 4-in-1 in Neonates

Sixteen neonates completed stage 1. In cohort 1A, 8 neonates had intensive PK assessment at a median (range) of 15 (14–19) days of life, with a body weight of 3413 g (3020–4240 g). After no safety hold criteria were met, cohort 1B opened to accrual. In cohort 1B, 8 neonates had both intensive PK assessments, the first at a median of 8 (7–9) days of life, with a body weight of 3288 g (2640–3740 g). The second PK assessment was performed at 20 (18–22) days of life, with a body weight of 3715 g (3015–4525 g). At the PK visits (n = 24), the dose in mg/kg for ABC, 3TC, and LPV/RTV was 8.6 (6.6–11.4), 4.3 (3.3–5.7), and 11.5/2.9 (8.8/2.2–15.2/3.8), respectively.

All 120 PK samples were successfully collected per protocol and analyzed. ABC and 3TC plasma concentrations were above the LLOQ in all samples. LPV concentrations were greater than LLOQ in 93 of the 120 (78%) samples, but only 4 of the 120 (3.3%) samples had quantifiable RTV concentrations. The mean concentration versus time curves for ABC, 3TC, and LPV at each PK visit are shown in (Fig. 1). The GM (90% CI) for ABC AUC0–12 decreased with postnatal age: 35.90, 28.02, and 26.50 µg·h/mL at 7–9, 14–19, and 18–22 days of life, respectively. A relatively smaller decrease in 3TC AUC0–12 from 13.34 to 11.90 µg·h/mL was observed over the same period. Lopinavir and ritonavir concentrations were extremely low at each PK visit and did not allow estimation of λz and AUC0–inf. No neonates had an LPV concentration above 4.10 µg/mL at any time point. The LPV AUC0–12 was low and variable, ranging between 0 and 26.33 µg·h/mL. A summary of the PK parameters for ABC, 3TC, and LPV is summarized in Table 2. Combining all PK visits, the GM (90% CI) AUC0–12 of ABC, 3TC, and LPV was 29.87 (26.29–33.93) µg·h/mL, 12.61 (10.72–14.83) µg·h/mL, and 3.49 (2.13–5.72) µg·h/mL, respectively. The GM LPV AUC0–12 in cohort 1A/1B did not fall within the predefined target of 20–100 µg·h/mL necessary to assess multidoses of the 4-in-1 in cohort 2.

Safety of the 4-in-1 in Neonates

No deaths or life-threatening events occurred. Twenty-one AEs were reported in the 16 neonates who received a least one dose of the 4-in-1; all were assessed as not related. Of the 21 AEs, 16 were classified as grade 1, 4 as grade 2, and 1 as grade 3. The grade 3 serious AE was hospitalization for respiratory syncytial virus pneumonia, with full recovery 9 days after onset of illness. Electrolyte disturbances without clinical sequela were common. Thirteen hyperkalemic episodes, primarily grade 1 and likely due to hemolysis, were reported in 11 neonates: 10 episodes were of grade 1 (5.6 to <6.0 mmol/L) and 3 grade 2 (6.0 to ≤6.7 mmol/L). Three episodes of grade 1 hyponatremia, 3 grade 1 anemia, and 1 grade 2 oral candidiasis were also reported. No neonates showed abnormal creatinine, alanine aminotransferase, AST, or elevated bilirubin levels during the study.

All 42 ECG findings, 18 at screening and 24 at PK visits, were normal. Of the 24 ECGs performed 4 hours after administration of the 4-in-1, the median (range) heart rate, QT
interval, and QTcF calculations were 143 (111–167) beats/minute, 260 (220–280) msec, and 344 (309–376) msec, respectively. HIV NATs showed negative results for all neonates throughout the study.

Acceptability and Tolerability

Seventeen capsule contents were administered with breast milk and 7 with formula milk. Swallowing of the 4-in-1 when mixed with milk was reported to be easy by all caregivers for all 24 administrations. No neonate refused or vomited the 4-in-1.

DISCUSSION

This is the first study to generate PK and safety data on a solid antiretroviral FDC formulation in neonates exposed to HIV. Administration of a single dose of the 4-in-1 in formula milk or breast milk was safe and well tolerated. ABC and 3TC exposures during the first 4 weeks of life were relatively high compared with those in infants and older children, but LPV and RTV exposures were very low. Unfortunately, while no safety concerns were observed, these interim PK results of the PETITE study do not support the use of the 4-in-1 FDC granule formulation in neonates for HIV prevention or treatment.

Few antiretroviral drugs are available for neonates, most being liquid formulations (eg, ABC, ZDV, 3TC, NVP, and LPV/r), and there are no appropriate FDCs. Liquids can be costly, require cold chain facility, require accurate measurement for administration, be extremely unpalatable, and may contain harmful excipients. The WHO advocates for individual and FDC solid pediatric antiretroviral formulations. Weight-band dosing is also recommended by the WHO, rather than mg/kg or mg/m², for the multiple challenges related to the LPV/r liquid formulation in young children. Owing to the lack of antiretroviral options for neonates, there was consensus at the WHO Pediatric Antiretroviral Drug Optimization meeting that the 4-in-1, although designed for infants older than 4 weeks, should be studied in neonates.

ABC is approved at a dose of 8 mg/kg twice daily in children older than 3 months. In the PETITE study, after a single dose of the 4-in-1 (median ABC dose of 8.6 mg/kg), ABC exposure was 36.12 µg.h/mL, consistent with another ABC single-dose study (median dose 8.1 mg/kg) using the liquid formulation in neonates where the median ABC AUC₀–₄₈₆ was 39.12 µg.h/mL. Owing to the slow maturation of the enzymes responsible for ABC metabolism in neonates,
these ABC exposures are substantially higher than those reported in young children and adults at equivalent twice-daily dosages. Indeed, in the PENTA-15 study assessing the steady-state PK and safety of the ABC and 3TC liquid formulations in children aged 3 months to younger than 36 months, the GM ABC AUC_{0-12} was 5.43 μg.h/mL (median dose 8.0 mg/kg; 45% of children on LPV/r-base ART), comparable with that reported in adults. Thus, the ABC exposures with the 4-in-1 in neonates were 6-fold to 7-fold higher than those in children at equivalent doses.

FIGURE 1. Concentration time curves for (A) abacavir, (B) lamivudine, and (C) lopinavir for each pharmacokinetic visit.
TABLE 2. Summary of Pharmacokinetic Parameters for Abacavir, Lamivudine, and Lopinavir

| Drug  | Cohort | PK Parameter         | Median (Min to Max) | Geometric Mean | 90% CI       |
|-------|--------|----------------------|---------------------|----------------|--------------|
| ABC*  | 1A + 1B| AUC0-12 (µg.h/mL)    | 31.12 (13.85–63.35) | 29.87          | 26.29 to 33.93 |
|       |        | AUC0-inf (µg.h/mL)   | 36.12 (16.37–89.91) | 34.81          | 29.90 to 40.53 |
|       |        | AUC0-12/AUC0-inf ratio | 0.87 (0.70–0.98)   | 0.86           | 0.83 to 0.89  |
|       |        | Cmax (µg/mL)         | 4.93 (2.55–7.24)   | 4.79           | 4.38 to 5.23  |
|       |        | Tmax (h)             | 2.0 (0.9–4.0)      | —             | —            |
|       |        | CL12 (µg/mL)         | 0.93 (0.12–2.95)   | 0.757          | 0.57 to 1.01  |
|       |        | CL/F (L/h/kg)        | 0.23 (0.13–0.51)   | 0.25           | 0.22 to 0.29  |
|       |        | Dose (mg/kg)         | 8.61 (6.63–11.36)  | —             | —            |
| 3TC*  | 1A + 1B| AUC0-12 (µg.h/mL)    | 13.83 (8.20–22.14) | 12.61          | 10.72 to 14.83 |
|       |        | AUC0-inf (µg.h/mL)   | 16.00 (3.26–26.47) | 14.28          | 12.06 to 16.92 |
|       |        | AUC0-12/AUC0-inf ratio | 0.90 (0.75–0.95) | 0.88           | 0.86 to 0.90  |
|       |        | Cmax (µg/mL)         | 2.09 (0.57–3.18)   | 2.00           | 1.75 to 2.29  |
|       |        | Tmax (h)             | 3.1 (2.0–4.1)      | —             | —            |
|       |        | CL12 (µg/mL)         | 0.39 (0.09–0.75)   | 0.33           | 0.26 to 0.41  |
|       |        | CL/F (L/h/kg)        | 0.27 (0.16–1.23)   | 0.31           | 0.26 to 0.35  |
|       |        | Dose (mg/kg)         | 4.30 (3.31–5.68)   | —             | —            |
| LPV*  | 1A + 1B| AUC0-12 (µg.h/mL)    | 4.89 (0–26.33)     | 3.49           | 2.13 to 5.72  |
|       |        | AUC0-inf (µg.h/mL)   | NC                 | NC             | NC           |
|       |        | AUC0-12/AUC0-inf ratio | NC                | NC             | NC           |
|       |        | Cmax (µg/mL)         | 0.75 (<0.05 to 4.06) | 0.58       | 0.38 to 0.90  |
|       |        | Tmax (h)             | 4.1 (1.1–8.1)      | —             | —            |
|       |        | CL12 (µg/mL)         | 0.11 (<0.05 to 2.31) | 0.21   | 0.12 to 0.37  |
|       |        | CL/F (L/h/kg)        | NC                 | NC             | NC           |
|       |        | Dose (mg/kg)         | 11.48 (8.84–15.15) | —             | —            |
|       |        | Dose (mg/m²)         | 181 (154–215)      | —             | —            |

3TC, lamivudine; ABC, abacavir; C12, 12-hours post-dose; CL/F, apparent clearance; inf, infinity; LPV, lopinavir; NC, cannot calculate; PK, pharmacokinetic.

*Reference data for comparison with PETITE study AUC0-inf: PENTA-15 children, ABC and 3TC steady state, AUC0-12SS were 5.43 µg.h/mL (95% CI 4.45 to 6.62) at 8.0 mg/kg twice daily and 4.74 µg.h/mL (95% CI 3.95 to 5.70) at 4.0 mg/kg twice daily, respectively.†††In the study conducted by Foisac et al, infants aged 6 weeks, with median (range) LPV steady-state AUC0-12SS 54.5 µg.h/mL (33.9–85.8), received LPV/r 40/10 mg twice daily.[27]

The liquid formulation of 3TC is approved at a dose of 4 mg/kg twice daily in children older than 3 months.[21] Although no dose is licensed for use in neonates, the PK and safety of 3TC liquid has been extensively studied and is recommended by the WHO for term neonates at a weight-band dose of 1.7–2.7 mg/kg twice a day. Moodley et al studied 3TC doses of 4.0 and 2.0 mg/kg twice daily in neonates with both doses well tolerated. The steady-state 3TC exposure was 16.88 µg.h/mL with 4 mg/kg twice daily, which is comparable with our study using a single dose of the 4-in-1 solid granule formulation. The 3TC exposures in neonates receiving 2.0 mg/kg twice daily after the first dose (within 12 hours of birth) and at steady state 7 days later were 12.08 and 5.78 µg.h/mL, respectively. High exposures of 3TC were also predicted in neonates when using the WHO weight-band dosing for children older than 4 weeks.[22] In the PENTA-15 trial, the steady-state 3TC AUC0-12 in children was 4.74 µg.h/mL (median dose 4.0 mg/kg), indicating the 3TC exposures were 3-fold higher in neonates given the 4-in-1 at equivalent doses. Of note, 3TC exposures in children are lower for the liquid formulation than for the tablets (approximately 40% lower relative bioavailability) despite no difference in adults, but this interaction has not been evaluated in neonates.

The LPV and RTV exposures observed in neonates after single dose(s) of the 4-in-1 formulation were extremely low. Limited PK data are available in neonates with the liquid LPV/r formulation.[25,26] The ANRS 12174 trial assessed infant LPV/r versus 3TC for the prevention of mother-to-child transmission of HIV during breastfeeding (NCT00640263). Neonates weighing 2.0–3.9 kg at birth were randomized to receive 40/10 mg LPV/r liquid twice daily starting at day 7 of life. Using a population PK model, the median (range) steady-state LPV exposures were estimated at 54.5 (33.9–85.8) µg.h/mL in 69 infants at 6 weeks of age. Although almost 2-fold lower than those reported in adults using the LPV/r meltrex tablet formulation, these steady-state exposures were comparable with those reported in children aged 14 days or older to younger than 6 weeks receiving liquid LPV/r formulation for HIV treatment in the IMPAACT P1030 trial.[14] There may be several contributing factors to the very low LPV and RTV plasma concentrations with the 4-in-1 formulation in neonates. First, the LPV dose with a single 4-in-1 capsule in neonates weighing 2.0 kg at birth was 11.5 mg/kg.26 The median LPV dose administered to the 16 neonates with the 4-in-1 was 11.5 mg/kg (or 181 mg/m²), but this lower dose was insufficient to explain the very low LPV exposures observed in the PETITE...
study. Second, all neonates received NVP perinatal prophylaxis (15 mg, once daily) per standard of care, and LPV exposure (at steady state) was reduced by approximately 30% when coadministered with NVP because of induction of cytochrome P450 CYP3A.28,29 Thus, a drug–drug interaction (DDI) with the background NVP prophylaxis regimen may have contributed to the low LPV exposures observed; however, extrapolation of this DDI to neonates is difficult because CYP3A4 activity is very immature during the first weeks of life (reaching 50% of adult levels between ages of 6 and 12 months).30 It is not expected that this DDI fully explains the low LPV exposures, but it cannot be ignored, and assessment of the 4-in-1 in the absence of NVP prophylaxis could be considered. A third potential factor is related to the 4-in-1 formulation. Eudragit E-PO cationic copolymer, commonly used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble when used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble and used as an excipient in the pharmaceutical industry, was used to taste-mask both LPV and RTV.31 This polymer is insoluble.
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