

Comparison of total and unbound lopinavir (LPV) pharmacokinetics (PK) in HIV-infected pregnant women receiving lopinavir/ritonavir (LPV/r) soft-gel capsules (SGC) or tablets.



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BACKGROUND

- Pregnant women experience physiological changes during pregnancy resulting in clinically significant alterations in antiretroviral pharmacokinetics (PK).
- Previous studies have reported a significant reduction in total LPV exposure during the later stages of pregnancy (third trimester) in patients receiving standard dosing of the LPV/r soft gel capsule (SGC; 400/100 mg bd)^{1,2}. However, LPV plasma concentrations equivalent to non-pregnant values were achieved with 533/133mg bd dosing³.
- PK data on the LPV/r tablet formulation (introduced June 2006) are limited⁴⁻⁶.
- PK studies are required for clarification of the optimum dose of the LPV/r tablet in pregnancy; based on the tablet's improved oral bioavailability⁷ standard dosing (2 tablets; 400/100 mg bd) should provide adequate exposure.

OBJECTIVES

- To determine total and unbound LPV PK during the second (T2) and third (T3) trimester(s) in HIV-infected pregnant women receiving 400/100mg bd of LPV/r SGC or tablet.

METHODS

Subjects

- HIV-infected pregnant women were recruited at St Mary's Hospital, London, UK, between September 2005 and January 2010. Pregnant women were enrolled in whom LPV/r had been selected as part of effective combination antiretroviral therapy
- Patients received triple-drug ART therapy containing either oral LPV/r SGC at the standard dose of 400/100 mg (3 SGC) bd; or (post June 2006) 2 tablets (400/100 mg) bd.

Study design

- Blood samples were collected 0-12h post-dose and LPV plasma and ultrafiltrate (unbound) concentrations determined by HPLC-MS/MS.
- LPV trough concentrations (C_{trough}) were also monitored in real-time, and LPV/r doses adjusted based on the LPV pre-determined minimum effective concentration (MEC; 1000 ng/ml)⁸.

Analytical and pharmacokinetic methods

- Total plasma LPV and RTV concentrations were determined in at the Liverpool Pharmacology Research Laboratories using a validated HPLC-MS/MS methodology⁹. [LLQ = 16 ng/ml (LPV); 5 ng/ml (RTV)].
- Ultrafiltration was used to separate total and unbound LPV (Centrifree[®] Micro-partition filter device filters). Unbound (ultrafiltrate) LPV concentrations (C_u) were quantified using spiked ultrafiltrate calibration curve (concentration range 5.4-421 ng/ml).

Data analysis

- PK parameters were calculated using noncompartmental analysis (WinNonlin).
- The fraction of unbound (fu) LPV exposure in plasma (AUC_{fu}) was determined by: AUC_{fu} (%) = (unbound AUC₀₋₁₂/total AUC₀₋₁₂)*100.

	LPV/r SGC		LPV/r Tablet	
	T2 (n=3)	T3 (n=6)	T2 (n=6)	T3 (n=10)
LPV AUC ₀₋₁₂ , ng.h/mL	76102 (33617-141773)	50391(36493-75276)	76873 (69890-84853)	58300 (49963-72261)
LPV C _{trough} , ng/mL	4220 (2013-7551)	2364 (1570-4092)	4320 (3717-5071)	2505 (2008-3488)
LPV C _{max} , ng/mL	8193 (3174-15811)	6031 (4595-8362)	9016 (7984-10247)	7663 (6826-8937)
LPV AUC _{cu} , ng.h/mL	693 (144-1664)	492 (329-800)	1116 (852-1482)	698 (547-956)
LPV AUC _{fu} , %	0.91 (0.61-1.27)	0.80 (0.53-1.25)	1.39 (1.05-1.86)	1.06 (0.88-1.33)
RTV AUC ₀₋₁₂ , ng.h/mL	2874 (1258-3915)	1918 (993-3708)	3227 (2772-3771)	3139 (2616-5339)
RTV C _{trough} , ng/mL	110 (26-197)	77 (17-207)	113 (102-126)	106 (80-184)
RTV C _{max} , ng/mL	394 (161-552)	298 (196-458)	0.53 (0.42-0.68)	546 (437-796)
Gestation, weeks [#] -at time of PK sampling	24 (15-26)	32.5 (28-34)	24.5 (19-26)	34.3 (30-38.4)

Values given as geometric mean (95% CI), [#]values given as median (range) (n = samples, patients).

Table 2. LPV and RTV PK parameters in HIV-infected pregnant women receiving standard dosing of the LPV/r SGC or tablet.

Baseline demographics (n=19)	
Age, years ^a	32.0 (17.4-41.6; 19)
CD4 count, cells/μl ^b	460 (40-1020; 19)
pVL, copies/ml ^b	2469 (<50-83856;19)
Ethnicity ^b	
Black	13 (68%)
Caucasian	4 (21%)
Other	2 (10%)
Naive to ART at baseline ^b	Yes 12 (63), no 7 (37)
Gestational age at ART initiation, weeks ^{a#}	26.6 (14.9-29.9; 12)
Gestational age at first PK sampling, weeks ^a	28.6 (13-35.9; 19)
LPV dosing ^b 400/100 mg, bd	19 (100)
Co-ART ^b	
Combivir	11 (58)
Kivexa	5 (26)
Truvada	1 (5)
Trizivir	1 (5)
Tenofovir + zidovudine	1 (5)

Table 1. Baseline demographic and clinical characteristics. ^avalues given as median (range; n/19); ^bvalues given as n (%); [#]in patients initiating ART during pregnancy; bd, twice daily.

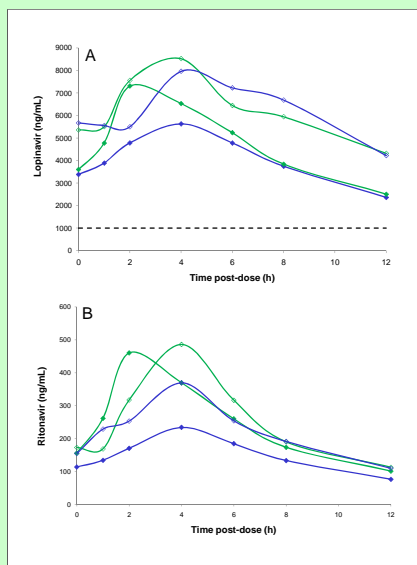


Figure 1. Geometric mean A) LPV and B) RTV PK profiles from HIV-infected pregnant women receiving standard dosing of the LPV/r tablet (green lines) or SGC (blue lines) during the second (open diamonds) and third (solid diamonds) trimesters of pregnancy. Dotted line indicates LPV MEC (1000 ng/ml)

RESULTS

Study population

- 19 of 21 patients enrolled were included in the final analysis: 8 (42%) received the LPV/r SGC and 11 (58%) the tablet. Of the 2 excluded patients: one was receiving LPV/r liquid formulation and one received the higher (600/150 mg bd) dose. The patient baseline characteristics are summarised in Table 1.
- 12/19 were antiretroviral naive and initiated LPV/r in pregnancy; median (range) gestation at initiation in these patients was 27 weeks (15-30). Baseline plasma viral load (pVL) was 2469 copies/ml (<50-83856).
- 17/19 patients had a pVL <50 copies/ml at the time nearest delivery.
- 6 (32%) delivered vaginally and 11 (68%) by caesarean section (5 elective, 6 emergency). Median (range) gestation at delivery was 39 weeks (32 - 41), there were no HIV-infected infants. 14 women stopped treatment.

LPV/r (total and unbound) pharmacokinetics

- Total LPV exposure was lower in T3 compared with T2 for women receiving both the LPV/r SGC and tablet formulations (Table 2).
- In T3 (median gestation 34 weeks) LPV AUC₀₋₁₂ was ~16% higher with tablet versus SGC.
- One patient receiving the SGC had T3 LPV plasma concentrations <1000ng/ml (later dose adjusted to 533/133mg bd), all on the tablet were >1000ng/ml.
- LPV %AUC_{fu} in T3 (SGC & tablet) was on average 0.95% and consistent with previous reports².

CONCLUSIONS

- Although LPV (tablet) exposure was reduced in the third trimester of pregnancy, the 'therapeutic' concentrations achieved in the majority of women (which were higher compared with those receiving SGC) and similarities in the f_u (%) suggest standard dosing of LPV/r tablet is appropriate during pregnancy.
- However, reduced LPV concentrations in the second/third trimesters highlights the need for TDM-guided dose adjustment in certain circumstances.

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