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ACTG Study A5283: Pharmacokinetic Study of Depot Medroxyprogesterone Acetate in HIV-Infected Women on Lopinavir/ritonavir

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ABSTRACT

Background: Little is known about use of depot medroxyprogesterone acetate (MPA) with boosted-protease inhibitors (PIs), a commonly used antiretroviral treatment regimen. Interactions with boosted PIs could lead to changes in efficacy or toxicity of any of these drugs.

Methods: We prospectively determined the effect of twice daily co-formulated lopinavir (LPV) 400mg/ritonavir (RTV) 100 mg along with 2 or more nucleoside reverse transcriptase inhibitors (NRTIs) on the PK exposure of MPA through every 2 week sampling from baseline (day 0) to week 12 (AUC_{0-12wk}) (Wilcoxon rank-sum test). We also determined the effect of MPA on the PK of LPV and RTV using AUC for LPV and RTV at baseline and after 4 weeks of depot MPA using intensive PK sampling at pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, and 10 hours post-LPV/r dosing (Wilcoxon signed-rank test). Safety and toxicity of depot MPA and ovulation suppression (using progesterone levels of <5ng/mL) were assessed biweekly during the 12-week study; HIV+ subjects on LPV/RTV were compared with 14 HIV+ control subjects not on HIV meds or only NRTIs, previously enrolled in A5093, who received depot MPA with identical assessments. All MPA assays were performed by PPD, Inc.

Results: 24 evaluable women on LVP/RTV were enrolled; 58% were black, 25% Hispanic and 13% white; median age 32 years; median CD4 622 cells/mm3; all had HIV RNA<400 copies/mL and negative pregnancy tests. Of the 14 historical controls, 79% were black, 14% Hispanic, and 7% white; median age 33 years. No women appeared to ovulate during the study and there were no pregnancies. MPA concentrations (median AUC_{12wk} 18.08 ng*week/mL) were higher than the 14 A5093 controls (median AUC_{12wk} 12.38 ng*week/mL) ($p<0.001$). There were no changes in the LPV and RTV levels after depot MPA (see table below). In this study, possibly treatment-related toxicities occurred in 8 (33%) subjects, the most frequent being vaginal bleeding (8), and irritability (2). These side effects were not significantly different compared to historical controls (ACTG 5093) or compared to those described with use of DMPA in the general population.

Conclusions: MPA levels were significantly higher in HIV-infected women taking BID ritonavir-boosted lopinavir compared to HIV-infected women on no HIV medications or NRTIs alone. Levels of LPV and RTV were not altered by depot MPA and there was no evidence of ovulation through week 12. Depot MPA was well-tolerated despite having AUC levels 46% higher compared to historical controls, and side effects were similar to those reported in HIV-uninfected women on depot MPA.

HYPOTHESES

- LPV/r may affect the PK profile of MPA through induction and/or inhibition of the cytochrome p450 3A4 (CYP3A4) enzyme.
- MPA may induce the CYP3A4 activity and affect the PK of LPV and RTV.

BACKGROUND

- Depot medroxyprogesterone Acetate (DMPA) is an injectable depot formulation of MPA, a synthetic progestin, providing effective contraception for 3 months after IM injection, and used by millions of women around the world.
- Little is known about the potential drug-drug interactions between DMPA and RTV- boosted PIs which are also metabolized through CYP 3A4

METHODS

- Open-label, multicenter, non-randomized PK study of DMPA and LPV/r in HIV+ women

Primary objectives:

- Evaluate effect of twice daily LPV/r on PK exposure of MPA by comparing MPA AUC_{0-12wk} with that from historical controls
- Evaluate effect of MPA on PK of LPV by estimating changes in LPV AUC from before and 4 weeks after DMPA (AUC_{0-4wk})

Secondary objectives:

- Determine suppression of ovulation by determining progesterone level >5 ng/mL at weeks 0, 2, 4, 6, 8, 10, and 12
- Evaluate effect of LPV/r on other MPA PK parameters, minimum plasma concentration (Cmin), maximum plasma concentration (Cmax), time to Cmax (Tmax), half-life (T1/2), and clearance (Cl/F), and compare with historical controls
- Evaluate effect of MPA on other LPV or RTV PK parameters Cmin, Cmax, Tmax, T1/2, and Cl/F, comparing baseline to week 4 after DMPA
- Evaluate toxicity and safety of twice daily LPV/r administered with MPA

Statistical Considerations:

- To detect a 40% difference in MPA AUC and a 30% change in LPV AUC with 80% power using two-tailed t-test at α=0.05, using the nonparametric Wilcoxon test as primary analysis method
- MPA PK parameters were compared when administered alone (historical controls) and when co-administered with LPV/r, using nonparametric Wilcoxon rank-sum test
- Compared changes in LPV and RTV PK parameters from baseline and 4 weeks after DMPA administration, using nonparametric Wilcoxon signed-rank test

Inclusion Criteria

- HIV+ women >13 years of age, able to give consent
- On LPV 400mg/RTV 100mg twice daily for 30 days if postpartum or for >14 days if on a previously stable antiretroviral regimen
- HIV-1 RNA < 400 copies/mL and CD4+ cell count ≥200 cells/mm3 within 30 days prior to entry
- Last menstrual period <35 days prior to entry or if >35 days, follicle-stimulating hormone (FSH) <40 MIU/mL
- Negative serum or urine-HCG pregnancy test at entry
- All women agree not to participate in a conception process for the 12 week study

LPV and RTV Pharmacokinetics:

Blood (plasma) for LPV and RTV levels before LPV/r dosing and at 30 minutes and 1, 2, 3, 4, 5, 6, 8, and 10 hours after LPV/r dosing at entry/day 0 and at week 4.

MPA Pharmacokinetics:

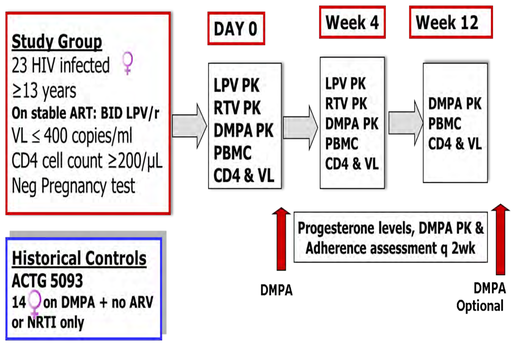
Blood samples taken for MPA levels every 2 weeks during the 12-week period after a single-dose of DMPA 150mg was administered intramuscularly (IM) at entry after all 10-hour LPV and RTV blood samples had been drawn.

Safety and tolerability:

- Safety and tolerability of DMPA was monitored with emphasis on grade 2 or higher adverse events
- Weight, mood changes, changes in menses were monitored.
- Provision to monitor pregnancies for safety and outcomes were in place but no pregnancies occurred.

METHODS

ACTG A5283 Schematic Study design



RESULTS

- 25 women enrolled, 1 was not evaluable due to protocol violation (use of prohibited medication)
- HIV VLs were unchanged throughout the study
- All women tolerated DMPA. Grade 2 or higher adverse events are shown in Table 2.

Table 1. Characteristics of A5283 study participants and A5093 historical controls

Characteristic	LPV/r (n=25)	Controls (n=14)
Race/Ethnicity		
Black	15 (60%)	11 (79%)
White	3 (12%)	1 (7%)
American Indian	1(4%)	0
Hispanic	6 (24%)	2 (14%)
Median age (years)	32	33
Median CD4$^+$ (Cells/mm^3)	622	704

RESULTS

Figure 1. Median (IQR) MPA Concentration-time curve over the 12 weeks from A5283 study compared to A5093 historical controls

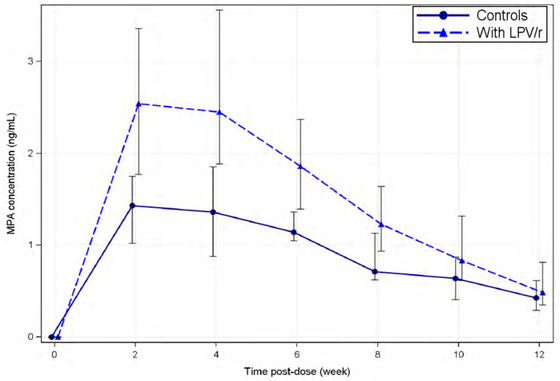


Table 2. Possibly or Probably Treatment Related Adverse Events of Grade 2 and higher

	A5283 (N=24) Number (%)	A5093 (N=14) Number (%)
Menstrual ABN.	1(4)	3 (21)
Mood Disorders	0 (0)	0 (0)
Weight Gain	0 (0)	0 (0)
Headache	0 (0)	2 (14)
Other[1]	0 (0)	2 (14)

[1] a grade 2 Creatine Kinase and a grade 2 Dry Skin

Table 3. Summary of MPA PK Parameters in A5283 participants and A5093 historical controls

Analyte	Parameter	Treatment	N	Median	IQR (Q1, Q3)	p-value[1]
MPA	AUC_{12wk} (ng*wk/mL)	Controls	14	12.38	(8.88, 13.88)	<0.001
		With LPV/r	24	18.08	(16.22, 24.10)	
	C_{min} (ng/mL)	Controls	14	0.43	(0.29, 0.60)	0.565
		With LPV/r	24	0.47	(0.35, 0.74)	
	C_{max} (ng/mL)	Controls	14	1.74	(1.02, 2.09)	<0.001
		With LPV/r	24	2.88	(2.28, 4.04)	
	CL/F (L/week)	Controls	14	12117.08	(10808.03, 16890.53)	<0.001
		With LPV/r	24	8297.35	(6223.57, 9250.23)	
	$T_{1/2}$ (week)	Controls	14	5.37	(3.04, 12.15)	0.088
		With LPV/r	22	3.37	(2.05, 5.42)	

[1] p-value of Wilcoxon rank-sum test

Table 4. LPV and RTV PK parameters from A5283 study before and 4 weeks after administration of DMPA

Parameter	Tx	N	LPV			RTV		
			Median	IQR (Q1, Q3)	p-value[1]	Median	IQR (Q1,Q3)	p-value[1]
AUC_{0-12h} (ng*hr/mL)	W/O DMPA	24	97607	(81425, 105776)	0.761	5080	(3981, 7380)	0.523
	W/ DMPA	24	96374	(83792, 111719)		4968	(3590, 6681)	
C_{min} (ng/mL)	W/O DMPA	24	5630	(4645, 6700)	0.708	181	(122, 281)	1.000
	W/ DMPA	24	5700	(4585, 6810)		195	(112, 283)	
C_{max} (ng/mL)	W/O DMPA	24	10750	(9220, 12350)	0.857	884	(957, 1080)	0.541
	W/ DMPA	24	10950	(9300, 12300)		729	(587, 1089)	
$T_{1/2}$ (hour)	W/O DMPA	24	10	(7, 16)	0.868	4	(3, 6)	0.956
	W/ DMPA	24	12	(9, 13)		4	(3, 7)	

[1] Wilcoxon rank-sum test of changes from period without DMPA to period with DMPA

LIMITATIONS

- The short follow-up period limits our ability to assess long term adverse events.
- We are unable to extrapolate these results to other protease inhibitors (PIs) based regimens as other PIs may affect the P450 system differently and other PIs are typically used with lower doses of ritonavir.

CONCLUSIONS

- MPA levels were significantly higher in HIV-infected women taking LPV/r compared to those on no HIV medications or NRTIs alone
- LPV and RTV levels were not altered by DMPA
- Ovulation did not occur among study participants or controls who received DMPA 150 mg through week 12
- Adverse events were similar in study participants and controls despite higher levels of MPA in the women on LPV/r
- Although MPA AUC was higher with LPV/r, MPA levels were similar in LPV/r and control arms at week 12, suggesting that DMPA dosing interval does not need to be adjusted.

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