INTERACTION BETWEEN ETONOGESTREL-RELEASING IMPLANT AND 3 ANTIRETROVIRAL REGIMENS

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Background

- High unplanned pregnancy rates are a public health problem because they negatively influence several indicators of women's and child's health and in HIV infected women may result in vertical transmission.

- Long acting reversible contraceptives (LARCs), such as etonogestrel (ENG)-releasing implants have the highest efficacy and continuations rates among all reversible contraceptives.

- World Health Organization (WHO) classifies ENG implant as category 2 for HAART users (the advantages of using the method generally outweigh the theoretical or proven risks).[1]

- There are limited data on pharmacokinetic (PK) interactions between the etonogestrel releasing implant (ENG) and antiretroviral therapy.[2] Case reports of pregnancy in HIV women under HAART and using ENG implants and efavirenz have been published.[3]

- The ENG implant package insert states that significant interactions have been noted with the co-administration with protease inhibitors or non-nucleoside reverse transcriptase inhibitors.

- We evaluated both the effect of ENG on the PK parameters of 3 highly active antiretroviral (ARV) regimens including: ritonavir boosted atazanavir (ATV/r), ritonavir boosted lopinavir (LPV/r) or efavirenz (EFV) and the effect of these ARVs on ENG levels in HIV infected postpartum women.

References

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3. Pregnancy rates in HIV-positive women using contraceptives and efavirenz-based or nevirapine-based antiretroviral therapy in Kenya: a retrospective cohort study.Patel RC, Onono M, Gandhi M, Blat C, Hagey J, Shade SB, Vittinghoff E, Bukusi EA, Newmann SJ, Cohen CR.Lancet HIV. 2015 Nov;2(11):e474-82

Methods

- International Maternal Pediatric Adolescent AIDS Clinical Trial (IMPAACT) Protocol P1026s is an ongoing, non-blinded international study of ARV PK in pregnancy and postpartum.

- We enrolled postpartum women who desired to use ENG implants and were taking ATV/r, LPV/r, or EFV-based regimens for at least 2 weeks.

- Women on medicines known to interfere with absorption, metabolism, or clearance of the drugs being evaluated and those with clinical or laboratory toxicity that would like to require a change in the medicine regimen during the study were excluded.

- ENG implant is an off-white, non-biodegradable, single sterile rod implant for subdermal use. Each rod contains 68 mg of the synthetic progestin etonogestrel (ENG). It is expected to provide contraception for up to three years when it should be removed.

- ENG implant was inserted between 2 and 12 weeks postpartum.

- ARV PK sampling was performed before and 6 to 7 weeks after implant insertion. ENG sample was obtained once at 6-7 weeks after insertion.

- Plasma samples collected at 0, 1, 2, 6, 8, 12 hours post-dose for LPV and a 24 hours post-dose sample was obtained in women under EFV or ATV.

- ARV and ENG concentrations were measured using liquid chromatography-mass spectrometry.

- Target minimum AUC for ATV, LPV and EFV were 29.4, 52 and 40 µg*hr/mL (10^{th} percentile in non-pregnant historical controls), respectively.

- PK parameters were calculated with standard non-compartmental methods. Two-tailed Wilcoxon signed rank tests compared within-subject PK parameters with a two sided–value <0.1.

- Median (range) ENG concentration within the first few weeks of use in women not receiving ARV's is 400 pg/mL (250-500 pg/mL). ENG concentration >90 pg/mL is believed to reliably suppress ovulation.

Results

- PK data are available for 62 postpartum women: 22 were using ATV/r, 26 on LPV/r and 12 on EFV.

Table 1. Participants Characteristics

	N (%) or Median (Range)
- Age (years)	26.9 (15.8-41.1)
- Weight (kg)	62.5 (38.7-157.9)
- Race/Ethnicity	
Black Non-Hispanic	6 (9.7)
Hispanic	49 (79.0)
Asian, Pacific Islander	7 (11.3)
- Country	
Argentina	5 (8.1)
Brazil	41 (66.1)
Thailand	7 (11.3)
USA	9 (14.5)
- CD4 (cells/mm^3)	584 (79 – 1578)
- Viral Load before ENG insertion (copies/ML)	
< 400	40 (74.1)
< 50	30 (55.6)

- Table 2 presents ENG concentrations and ARV AUCs among these three arms. Median ENG concentration of EFV arm was <10% of the other two arms.

Table 2. ENG Concentration and ARV AUC Comparisons between Different Arms

		Study arm			
Characteristic		**ATV/r/TFV+ENG (N=24)**	**EFV+ENG (N=12)**	**LPV/r+ENG (N=26)**	**P-Value**
ENG Concentration	N	22	9	23	
(pg/mL)	Median (Q1, Q3)	604 (436, 838)	41.5 (26.7, 136.0)	469 (366, 565)	<.001*
	Min, Max	260, 2,400	2.0, 280.0	225, 3,680	
ENG Conc < 90 pg/mL	Yes	0 (0%)	6 (67%)	0 (0%)	<.001**
	No	22 (100%)	3 (33%)	23 (100%)	
ARV AUC (mcg*hr/mL)	N***	21	11	26	
Pre-ENG AUC	Median (Q1, Q3)	53.9 (29.6, 80.9)	62.6 (48.4, 93.5)	116.0 (97.3, 129.1)	
Post-ENG AUC	Median (Q1, Q3)	52.3 (26.4, 65.4)	57.6 (43.6, 113.9)	100.2 (72.9, 131.5)	
Pre/Post-ENG AUC Ratio	GMR (90% CI)	1.11 (0.83, 1.47)	1.08 (0.85, 1.37)	1.24 (0.97, 1.59)	

Abbreviations: N: Number with PK result available; ARV: Either ATV, EFV, or LPV, respectively; AUC: Area under the Curve; GMR (90% CI): Geometric Mean Ratio (90% confidence interval)
*Kruskal-Wallis Test
**Fisher's Exact Test
***Excludes 4 women (3 ATV and 1 EFV) who had a pre-ENG AUC but not a post-ENG AUC.

- ARV AUCs before and after ENG insertion did not differ significantly. Fig 1, 2 and 3

Figure 1: Summary of the Median ATV Concentrations

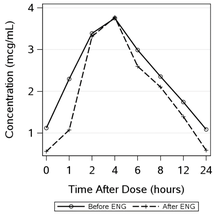


Figure 2: Summary of the Median LPV Concentrations

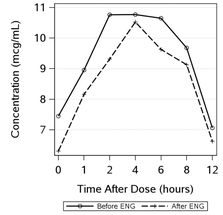
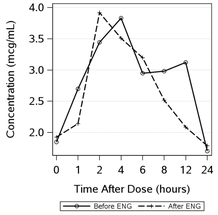


Figure 3: Summary of the Median EFV Concentrations



- Proportions of women meeting ARV PK targets before and after ENG insertion were: 77% and 66% for ATV/r, 84% and 84% for LPV/r and 90% and 81% for EFV (p=0.73).

A twin pregnancy occurred in EFV arm 16 months after ENG implant insertion, the implant was removed and pregnancy is ongoing. ENG levels 6-7 weeks after implant insertion is this patient was 88.7 pg/mL.

Conclusions

- No significant change in ATV/r, LPV/r and EFV exposure was seen after ENG insertion.

- EFV use was associated with greatly decreased ENG concentration to levels that may impair contraceptive efficacy.

- Women receiving EFV should be counseled about the increased risks of implant failure and advice to use alternative or additional contraceptive method. Implant substitution before three years or ARV regimen change may be considered.

- Co-administration of LPV/r and ATV/r with ENG resulted in adequate ENG concentration, suggesting that these combinations should have no impact on implant efficacy.

- Further clinical and pharmacokinetics studies need to evaluate newer ART regimens in combination with implants.

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