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Pharmacokinetics and Pharmacodynamics of a Combined Oral Contraceptive and a Generic Combined Formulation Antiretroviral in Malawi

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INTRODUCTION

Over 16 million reproductive age women are HIV+ [1]. Access to ARVs for HIV treatment is expanding, and like the HIV epidemic more than half of all ARV users are women [2]. The fusion of contraceptives to antiretrovirals (ARV's) for HIV treatment and Pre-Exposure Prophylaxis (PrEP) is on the horizon, because similar to ARVs, effective contraception, such as combined oral contraceptives (COCs), saves lives and lowers the burden of HIV on individuals and society [3]. The COC is the second most popular contraceptive worldwide, is inexpensive, and easy to store and dispense [4]. However, HIV+ women on common ARV regimens are advised to avoid COCs by guidelines and monographs [5–7]. Decreased serum concentrations of contraceptive steroids are reported when ARVs such as nevirapine and lopinavir/ritonavir (LPV/r) are taken concomitantly [8–11]. However, whether the decrease in steroid concentration truly results in failure of COC effectiveness is unknown because data on clinical outcomes such as pregnancy or ovulation are limited [12–13].

Understanding interactions between ARV and oral contraceptives has recently become an even more urgent matter for research. First, the preliminary reported results from FEM PrEP (Study to Assess the Role of Truvada® in Preventing HIV Acquisition in Women) indicate that women taking oral contraceptives and a daily fixed dose tenofovir/emtricitabine combination had the highest proportion of pregnancies (9%) [14]. Although investigations are ongoing to understand the basis for this finding, there are no data describing the effect of these drugs on ovulation in women taking oral contraceptives. Second, the promising findings from HPTN 052 (Preventing Sexual Transmission of HIV with Anti-HIV Drugs)

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[15] highlight the need to ensure HIV+ women on antiretrovirals have equal opportunities for fertility control. The objective of our study was to assess the feasibility of measuring anovulation in a PK study of COCs and ARVs in women in Malawi.

METHODS

The Malawi National Health Sciences Research Committee (NHSRC) and the Institutional Review Board at the University of North Carolina at Chapel Hill approved the study protocol. The trial was registered at ClinicalTrials.gov (NCT00998725). Women with documented HIV status who chose the Malawi Ministry of Health (MOH) supplied COC (30mcg ethinyl estradiol/300mg norgestrel) for birth control, were recruited into three groups; HIV+ taking ARVs (a generic formulation of nevirapine 200 mg+stavudine 30 mg +lamivudine 150 mg taken twice daily), HIV+ women not requiring ARVs (Group 2), and HIV negative (Group 3).

Women were invited to enroll if they met the following eligibility criteria; 21 – 35 years old, known HIV status, able to attend all study visits, desired to prevent pregnancy for at least six months, had no known history of infertility, a hemoglobin greater than 10 mg/dL, body mass index (BMI) greater than 18.5 kg/m^2, no use of medications known to interfere with the cytochrome P450 system, no use of hormonal contraception in the previous six months, menses every 21–35 days lasting at least four days, and known last menstrual period. Group 1 women must have used ARVs for at least 48 consecutive days prior to enrollment with reported adherence to treatment and non-hormonal contraception for the duration of the study.

Women in Group 1 (HIV+ on ARVs) returned for serum progesterone sampling between Days 20 and 22 of their first menstrual cycle after enrollment and then started COC's immediately afterwards. Women in Groups 2 (HIV+ not taking ARVs) and 3 (HIV negative) started COC immediately upon enrollment. Follow-up visits were performed on day 14 of COC cycle 1, and the PK visit occurred on day 14 of COC cycle 2.

We used an abbreviated, 8-hour sampling strategy due to logistical issues for patients travelling long distances on public transportation. Adherence to medications for three days prior to arrival was recorded. Women were rescheduled if non-adherence was reported for more than 10% of doses. Reimbursement for transportation and snacks and breakfast were provided to all participants. Blood sampling occurred immediately before observed ingestion of morning medications ($Time_0$), with subsequent sampling 0.5, 2, 4, 6 and 8 hours later. The 8-hour truncated sampling scheme included the terminal elimination phase for all drugs examined, even though the dosing intervals for ARVs and COCs are 12 and 24 hours respectively [16,17]. At the conclusion of the PK visit all women were referred to a local family planning clinic to continue their health care.

Validated assays for nevirapine (NVP), stavudine (d4T) and lamivudine were used [18]. Because norgestrel is a racemic mixture of levonorgestrel (LNG) and dextronorgestrel, assays for LNG were used and those results reported. Assays for LNG and ethinyl estradiol (EE) were determined by validated radioimmunoassays [19,20]. Genotyping was performed for cytochrome P450 2B6 516.

Pharmacokinetic measurements were calculated using noncompartmental methods. The log-linear trapezoidal method was used to calculate the values for $AUC_{0–8hr.}$ Values for $AUC_{0–24hrs}$ were derived using λ_z extrapolations.

RESULTS

Nine women enrolled, three in each group, and all attended all study visits. Age and BMI were similar between the three groups. The women in Group 1 (HIV+ on ARVs) had been on ARVs for 121 days prior to starting COCs (range 95–147). In the pre-COC cycle two of the three women had serum progesterone levels greater than 3.0 ng/mL (8.0, 21 ng/mL), indicating ovulation and one woman had serum progesterone of 1.0 ng/mL.

Contraceptive steroid measurements were higher in both groups of HIV+ women than in the HIV negative women (Table 1). The median C_{0hr} for levonorgestrel in the three Groups were higher than the reported minimal concentration of 0.3 ng/mL required to maintain contraceptive effectiveness. The LNG Area Under the Curve (AUC) measurements, and all EE PK parameters, were also higher in both groups of HIV+ women than the HIV negative women. The progesterone measurements in COC cycle 2 in the women in Group 1 were <0.2ng/mL (indicating anovulation) [21,22]. Two women had NVP levels 2–4 fold higher than the third. Cytochrome P450 2B6 516 genotypic analysis revealed that these two women were heterozygous for the T-allele (GT), and the third woman had a wild-type (GG) genotype.

DISCUSSION

We found a number of surprising results among the HIV+ and HIV negative Malawian women in our study. The EE and LNG levels were higher in all the HIV+ women, including those taking ARVs, than in HIV negative women. This important finding challenges current dogma that COCs will not be effective when used concomitantly with nevirapine. Additionally, we confirmed that the COCs maintained effectiveness in these women by demonstrating anovulation. Despite the small sample size, and our truncated PK sampling scheme, we believe our findings justify further PK/PD investigations of HIV+ women using ARVs and COCs, in multiple, real-life settings.

Two factors may contribute to our findings of higher contraceptive steroid concentrations than expected. First, women were dosed to steady state conditions when they presented for PK/PD blood sampling. In contrast, previous PK data collection for contraceptive steroids have often focused only on EE, occurred before steady state was reached, or were collected from healthy volunteers [6–11,23]. Second, there may be metabolic or pharmacogenetic differences in metabolism of contraceptive steroids in Malawian women compared to women previously investigated in the United States.

As we expected, concentrations of all antiretrovirals were similar to previous PK studies in Malawi despite the addition of LNG and EE [17]. The presence of the CYP450 2B6 516 T allele in this small cohort likely explains the higher NVP concentrations in two of the women [24].

An important strength of our methods was measuring LNG in addition to EE. The progestin component of COCs is primarily responsible for the anovulation effect COCs, whereas the EE stabilizes the endometrium and potentiates the progestin effects [25]. Progestin does also exert additional contraceptive effects by thickening cervical mucus, decreasing tubal motility, or making the endometrium inhospitable to a fertilized egg [25]. However, a definitive, and validated, measure for COC efficacy is to use serum progesterone of < 3 ng/mL as presumptive evidence of anovulation [21].

Our study is limited by small sample size, but the methods reported are important and justify further investigation of women taking COCs and ARVs concomitantly in real life clinical settings. The findings reported can be used to inform future investigations. The focus on

COCs deserves special mention because although COCs are not the most effective contraceptive available, they are the second most popular method worldwide [4,26,27]. Therefore, understanding clinical outcomes of COCs in women taking ARVs should be a priority, especially in settings where HIV prevalence is greater than 10%. HIV+ women are currently precluded from use of COC primarily because PK data are interpreted without PD data, in small subsets of women. Investigations should determine whether COCs represent an appropriate option for HIV+ women taking ARVs, and for HIV negative women who may use ARV-containing PrEP.

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Table 1

Baseline characteristics and pharmacokinetic measurements of levonorgestrel, ethinyl estradiol, nevirapine, lamivudine and stavudine

Drug	PK	Group 1 (HIV+ ARV+) N=3	Group 2 (HIV+ ARV−) N=3	Group 3 (HIV Negative) N=3
	C_{0hr}	6.11 [3.50–7.02]	4.72 [4.03–7.36]	1.41[1.04–4.03]
LNG	$AUC_{0–8hr}$	78.3 [5.37–83.8]	52.4 [49.2–79.9]	24.0 [23.4–58.7]
	$AUC_{0–24hr}$	147 [112–177]	114 [105–139]	37.9 [36.9–107]
	C_{0hr}	57.3 [40.8–60.7]	82.2 [67.1–98.2]	47.0 [39.3–81.7]
EE	$AUC_{0–8hr}$	817 [611–820]	816 [765–1,019]	670 [664–837]
	$AUC_{0–24hr}$	1,384 [1,130–1,425]	1,457 [1,371–1,610]	1,144 [1,111–1,583]
	C_{0hr}	8,456 [6,542–12,229]		
NVP	$AUC_{0–8hr}$	77,791 [60,989–108,395]		
	$AUC_{0–24hr}$	111,596 [86,761–149,259]		
	C_{0hr}	146 [125–137]		
3TC	$AUC_{0–8hr}$	7,393 [7,010–9,381]		
	$AUC_{0–24hr}$	8,278 [7,946–10,668]		
	C_{0hr}	0		
d4T	$AUC_{0–8hr}$	1,974 [1,647–2,204]		
	$AUC_{0–24hr}$	2,029 [1,889–2,273]		

Data presented as Median [interquartile range]; LNG, levonorgestrel; EE, ethinyl estradiol; NVP, nevirapine; 3TC, lamivudine; d4T, stavudine. All C_{0hr} represented as ng/mL except EE (pg/mL). All Area Under the Curve (AUC) represented as ng*mL/hr except EE (pg*mL/hr).