Published in final edited form as:

AIDS. 2015 November ; 29(17): 2353–2359. doi:10.1097/QAD.0000000000000827.

Effectiveness of Hormonal Contraception in HIV-Infected Women using Antiretroviral Therapy: A Prospective Study

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Data were presented at the 8th IAS Conference on HIV Pathogenesis, Treatment & Prevention in Vancouver, Canada.

Authors' Contributions: JMB and RH conceived of the research question; MP conducted the data analysis. MP & JMB drafted the paper. NRM, KN, KKT, CC and APK assisted in refining the research question and analysis. EW, HR, and EB assisted in data collection. All authors contributed to editing the text and approved the final version.

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Data management was provided by DF/Net Research, Inc. (Seattle, USA) and site laboratory oversight was provided by Contract Lab Services (University of the Witwatersrand, Johannesburg, South Africa).

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Abstract

Objective—To assess whether antiretroviral therapy (ART) may diminish the effectiveness of hormonal contraceptive methods.

Methods—Using data from 5,153 HIV-infected women followed prospectively one to three years in three HIV prevention studies in Africa, we compared incident pregnancy rates by contraceptive method (implant, injectable, oral, or none) and ART use. Multivariable Cox regression models were used to determine adjusted hazard ratios (aHR) and test interactions between each method and ART use.

Results—During follow-up, 9% of women ever used implants, 40% used injectables, and 14% used oral contraceptives; 31% of women ever used ART, mostly nevirapine (75% of ART users) or efavirenz-based (15%). Among women not using contraception, pregnancy rates were 13.2 and 22.5 per 100 women-years for those on and not on ART, respectively. Implants greatly reduced the incidence of pregnancy among both women on ART (aHR 0.06, 95% CI 0.01-0.45) and not on ART (aHR 0.05, 95% CI 0.02-0.11). Injectables (aHR 0.18 on ART and aHR 0.20 not on ART) and oral contraceptives (aHR 0.37 on ART and aHR 0.36 not on ART) also reduced pregnancy risk, though by lesser degrees. ART use did not significantly diminish contraceptive effectiveness, although all methods showed non-statistically significant reduced effectiveness when concurrently using efavirenz.

Conclusion—Hormonal contraceptive methods are highly effective in reducing pregnancy risk in HIV-infected women, including those concurrently using ART. Studies of potential interactions between ART and contraceptives should evaluate real-world effectiveness of contraceptive methods; in this study, implants were the most effective method to prevent pregnancy, even during ART use.

Keywords

hormonal contraception; women; antiretroviral agents

Introduction

Worldwide, a substantial unmet need for safe, effective contraception remains, particularly in areas with a high HIV prevalence [1]. For HIV-infected women, contraception is

important for their own health, for preventing mother-to-child HIV transmission, and to control their fertility. For women using antiretroviral therapy (ART), concerns have been raised that some progestin-based contraceptive methods may be less effective when used with certain ART agents. Specifically, it has been suggested that the non-nucleoside reverse-transcriptase inhibitors (NNRTIs), nevirapine (NVP) and efavirenz (EFV), may accelerate the progestin metabolism through the cytochrome p450 pathway [2]. Studies of interactions between ART and contraceptive methods have been limited by short follow-up times, HIV-uninfected populations, and/or surrogate endpoints [3]. We sought to understand the effect of ART on contraceptive effectiveness, measured by the clinical endpoint of pregnancy, using prospectively collected data from over 5,000 women with chronic HIV infection from East and Southern Africa.

Methods

Study Population

Data contributed by women in three prospective studies (Partners in Prevention HSV/HIV Transmission Study, Couples Observation Study, and Partners PrEP Study) were combined for this analysis. Enrollment for these studies has previously been described [4–6]. In brief, 8,640 HIV serodiscordant heterosexual couples from seven African countries (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia) were enrolled and followed between 2004 and 2013; overall, in 63% of couples the seropositive partner was female. At enrollment, HIV-infected partners were not using ART; clinical and immunologic status was monitored during follow-up and ART was recommended according to national guidelines.

Demographic information was collected at enrollment; data on sexual behavior, including contraceptive use and ART use were collected quarterly. Tests for *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* were performed at baseline for all studies and annually in the Partners PrEP Study. CD4 counts were measured every six months; viral load was measured every six months in the Partners in Prevention HSV/HIV Prevention Study and Couples Observational Study and annually in the Partners PrEP Study. Condoms, hormonal, and non-hormonal contraception were offered in all studies and contraceptive method use was self-reported at each visit; however, information regarding specific brands was not recorded. Pregnancy status was ascertained at each study visit; urine pregnancy tests were done as clinically indicated and quarterly in Partners in Prevention HSV/HIV Transmission Study. All women gave informed, written consent; these studies were approved by the University of Washington Human Subjects Review Committee and local ethics review boards associated with each study site.

Statistical Analysis

For this analysis, only women who were HIV infected, ≤49 years of age, and who contributed ≥1 follow-up visit were included. Months during which women reported diaphragms, IUDs, tubal ligation, or hysterectomies for contraception were excluded; this included 5 person-years on diaphragm, 120 person-years on IUD, and 520 person-years on tubal ligation/hysterectomy, with only one pregnancy (on IUD). The primary endpoint was incident pregnancy. The first visit at which a woman was pregnant, determined by positive

pregnancy test and the date of her last menstrual period, was classified as the incident event; visits while pregnant were censored and women returned to the risk set at the first visit after each pregnancy ended. The primary exposure was hormonal contraceptive use, defined as implant, injectable, oral contraceptives (OCs), or none. ART use at each study visit was analyzed as an effect modifier and the rate of incident pregnancy was calculated for each contraceptive-ART use stratum. Thus, when a pregnancy was first detected at a study visit, contraceptive and ART exposure were reported at that same visit, since data collection for those exposures referred to the period when the pregnancy began. Interaction terms between each of the three contraceptive methods and ART use were included in multivariable Cox proportional hazards models, with an Andersen-Gill extension allowing for repeated events [7]. P-values for these interactions were determined by likelihood ratio tests, with no hormonal contraception and no ART use as the reference category. Age, CD4 count, site, and study were included *a priori*; other potential covariates were tested and only sexual frequency and condomless sex were added to the model. Subgroup analyses were done, restricted to women using NVP or EFV (with no ART use as the reference group). All analyses were conducted in SAS 9.4 (Cary, NC).

Results

Among the 5,153 women included in this analysis, 54% were under 30 years old at baseline and 51% had CD4 counts ≥500 cells/mm^3 at enrollment (Table 1). A total of 9,266 person-years were accrued and median follow-up time was 1.8 years (IQR 1.2-2.3). During follow-up, 24% of women became pregnant and 31% ever used ART, including 23% who used NVP and 5% who used EFV. Also during follow-up, 9% of women ever used implants, 40% ever used injectable contraception, and 14% ever used OCs; for women who used implants at baseline, 82% of subsequent visits had continued use, while for injectables continuation was 70% and OCs 58%.

The overall pregnancy rate was 14.8 per 100 person-years. Women not using contraception but using ART had a lower pregnancy rate compared to those not using contraception and not using ART (13.2 vs 22.5 per 100 person-years; aHR 0.62, 95% CI 0.51-0.75, p<0.001.)In a sensitivity analysis that excluded the first six months after each pregnancy, this association between ART use and pregnancy was attenuated (aHR 0.80, 95% CI 0.63-0.99, p=0.03), potentially indicating that this difference was due to a post-partum effect for women who had initiated ART during pregnancy.

Implants were highly effective in reducing incident pregnancy, with rates less than 1.5 per 100 person-years among those both on and not on ART (Table 2); pregnancy incidences among implant users were >90% lower when compared to women not using contraception. There was no statistical difference between the effects of implants on pregnancy prevention for women using versus not using ART (interaction p=0.73). Both injectables and OCs also significantly reduced pregnancy risk compared to women not using contraception, although to a lesser extent than implants. For women using injectables, the reduction in pregnancy incidence was approximately 80%, and for OCs the relative reduction was approximately 60%; neither of these effects differed significantly for women on ART versus not on ART.

Nevirapine was the most common ART agent reported, with 1000 person-years of follow-up. The results among women using NVP were very similar to the overall analysis. Injectables reduced pregnancy by approximately 80% and OCs reduced pregnancy by approximately 60%; for both methods, the pregnancy prevention effects were not different when using versus not using NVP (interaction term p=0.80 for injectables and p=0.95 for OCs). There were no pregnancies among women using NVP and implants.

Approximately 200 person-years accrued from women using EFV. The pregnancy prevention point estimates for women using EFV were lower for all types of progestin-based contraception: implants reduced pregnancy incidence by approximately 60%, injectables by 70%, and OCs by only 15%. None of these reductions in incidence were statistically significant, in part likely because of the small sample size; there were also no statistically significant interactions for EFV use with any contraceptive method compared to women not using ART. For women using OCs with EFV, the point estimate for the pregnancy rate was double that of those using NVP. For women using implant, a single pregnancy occurred during 16.7 person-years of concurrent use with EFV, at eleven months post-insertion of the implant.

Discussion

In this analysis of a large, prospective database from African women living with HIV, we found that hormonal contraceptives were effective in reducing pregnancy, including for women using ART. Implants were the most effective at reducing pregnancy incidence, by >90%, and we found no evidence that ART use in general diminished implant effectiveness. Injectable and oral methods were also effective, and their effectiveness did not differ significantly by ART use. All hormonal methods had point estimates suggesting lesser effectiveness among EFV users, although the sample size for analyses limited to EFV users was small.

Our analysis is consistent with the existing literature. Most pharmacokinetic and observational studies of NVP have found no difference in progesterone levels nor contraceptive effectiveness with progestin-based contraception [8–15]. The literature regarding EFV is more mixed. Studies have found no effect of EFV on progesterone levels when using DMPA [8,10,16], but significantly lower progesterone levels among implant users [17–19,15], along with contraceptive failure rates up to 15% among levonorgestrel implant users [20–22]. Evidence regarding EFV and OCs is very limited, suggesting lower progesterone levels but not necessarily increased ovulation on EFV [13,23,24]. The existing evidence has led at least one national health department in Africa to recommend against implant use for women on EFV [25]. However, a recent retrospective analysis found that implants were more effective at pregnancy prevention than injectables for women using NVP or EFV [26]. Likewise, in the present analysis contraceptive failures were seen on all methods, although they were rare for women using implants.

Among women not using contraception, we found ART use was associated with lower pregnancy incidence; other studies have found that ART use was associated with either an increase or no difference in pregnancy [27,28]. However this difference would not affect the

significance of the interaction terms presented, since the primary comparison was pregnancy incidence for women using versus not using contraception, separately for those on and not on ART. In a sensitivity analysis that excluded six-months after each pregnancy, the association between ART use and pregnancy was attenuated, suggesting potential confounding with PMTCT and reduced fertility in the post-partum period. Furthermore, the estimated hazard ratios and significance of the interaction terms were not changed. In addition, there may have been residual confounding due to behavioral and health differences between women who initiate ART versus those not yet starting ART.

Limitations of this study include that ascertainment of ART use, contraceptive use, and important potential confounders, such as sexual behavior, were based on self-report. We are unable to further distinguish specific progestin-based contraceptive methods, although DMPA was the predominant form of injectable, levonorgestrel was the most common implant, and combined pills were the most common OCs available at the study sites. Duration of ART and hormonal contraception use were not examined and may be of interest. This study benefits from a large sample size from 2004 to 2013, with over 9000 person-years of follow-up; however time on EFV was limited. Detailed information was collected to date the beginning of each pregnancy.

This longitudinal study of incident pregnancies suggests that hormonal contraceptive methods remain effective for HIV-infected women who are using ART, including NNRTIs. Implants, which have the lowest adherence requirements out of these three methods, showed the greatest reduction on pregnancy rates, including for women concurrently using ART. Pregnancy incidence was highest for women using OCs, followed by injectables, with failure rates considerably higher than in ideal use settings, possibly relating to inconsistent or incorrect use. As national policies evaluate the potential pharmacokinetic interactions between ART and hormonal contraception, prospective studies such as this, which comparatively evaluate the real-world effectiveness of contraceptive methods, are essential.

Acknowledgments

We thank the women who participated in these studies.

Sources of grant support: Health Promotion and Disease Prevention Research Center supported by Cooperative Agreement from the Centers for Disease Control and Prevention (U48 DP 005013 SIP 14-023), the Eunice Kennedy Shriver National Institute of Child Health and Development of the US National Institutes of Health (R21 HD074439), and the Bill & Melinda Gates Foundation (OPP1056051, 26469, and 41185). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC, NIH, or the United States Government.

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Table 1
Baseline & Follow-up Characteristics of the Study Population

AT BASELINE (n=5,153 women)	% (n) or median (IQR)
Age, years	29 (24, 34)
17-24	26.1 (1344)
25-29	27.8 (1430)
30-34	23.8 (1224)
35-39	13.8 (713)
40-44	5.8 (297)
45-49	2.8 (144)
Education >8yrs	32.3 (1664)
Any monthly income	41.4 (2131)
Married	88.1 (4542)
Years living with study partner	4.5 (1.8, 9.2)
Number of children with study partner	1 (0, 2)
Pregnant	3.5 (179)
Number of sex acts in last month	4 (2, 8)
Number of condomless sex acts in last month	0 (0, 1)
Any condomless sex acts in last month	28.7 (1477)
Other sexual partner	1.2 (61)
Any gonorrhea, chlamydia or trichomonas	14.0 (723)
missing	7.6 (393)
Any gonorrhea, chlamydia or trichomonas among male study partner	7.3 (377)
missing	1.4 (74)
CD4 count, cells/mm^3	
<200	0.7 (34)
201-349	19.8 (1019)
350-499	28.4 (1464)
>=500	51.2 (2636)
HIV viral load (log $_{10}$), copies/ml	3.85 (3.14, 4.45)
Hormonal Contraceptive use	
Implant	2.3 (118)
Injectable	17.4 (896)
Oral	4.3 (221)
None	75.7 (3900)
On ART	0 (0)
Study	
Partners PrEP Study	54.1 (2790)
Partners in Prevention HSV/HIV Transmission Study	41.3 (2129)

AT BASELINE (n=5,153 women)	% (n) or median (IQR)
Couples Observation Study	4.5 (234)
DURING FOLLOW-UP VISITS	% (n)
Ever became pregnant	24.1 (1240)
Contraceptive use	
Ever used implant	9.0 (466)
Ever used injectable	39.6 (2039)
Ever used oral contraception	14.2 (732)
Ever on ART	31.0 (1596)
Ever on NVP	23.1 (1191)
Ever on EFV	4.8 (247)
PROPORTION OF FOLLOW-UP TIME (n=9266.3 person-years)	% (n)
Pregnant	3.5 (327.9)
Hormonal contraceptive use	
Implant	6.5 (606.7)
Injectable	26.3 (2433.2)
Oral	7.1 (654.3)
None	60.2 (5577.1)
On ART	14.6 (1351.7)
NVP	10.8 (1000.4)
EFV	2.2 (204.1)
3TC	12.3 (1140.4)
AZT	7.8 (723.8)
TDF	2.4 (224.4)
FTC	0.2 (19.7)
D4T	2.8 (259.4)
Lopinavir/Ritonavir	0.3 (27.5)
Atazanavir/Ritonavir	0.0 (0.23)
Nelfinavir	0.0 (0.76)

Table 2

Contraceptive Effectiveness, By ART Status and Type of Contraception

ART Use	Hormonal Contraception Use	# Pregnancies	Person-Years	Pregnancy Incidence Rate (per 100 person-years)	aHR* (95% CI), p-value versus no contraception and same ART use	p-value for interaction term**
None	**None**	1067	4733.6	22.5	ref	--
	Implant	7	507.5	1.4	0.05 (0.02, 0.11), p<0.001	ref
	Injectable	111	2100.5	5.3	0.20 (0.16, 0.24), p<0.001	ref
	Oral Pills	63	573.1	11.0	0.36 (0.28, 0.47), p<0.001	ref
Any ART	**None**	111	843.5	13.2	ref	--
	Implant	1	94.1	1.1	0.06 (0.01, 0.45), p=0.005	0.73
	Injectable	11	332.8	3.3	0.18 (0.10, 0.35), p<0.001	0.79
	Oral Pills	5	81.2	6.2	0.37 (0.15, 0.91), p=0.03	0.97
NVP	**None**	86	624.7	13.8	ref	--
	Implant‡	0	67.7	0	--	--
	Injectable	8	245.6	3.3	0.18 (0.09, 0.38), p<0.001	0.80
	Oral Pills	4	62.4	6.4	0.35 (0.13, 0.97), p=0.04	0.95
EFV	**None**	16	127.5	12.6	ref	--
	Implant	1	16.7	6.0	0.43 (0.07, 2.50), p=0.34	0.12
	Injectable	2	52.2	3.8	0.29 (0.07, 1.22), p=0.09	0.63
	Oral Pills	1	7.7	12.9	0.86 (0.11, 6.76), p=0.88	0.46

*Adjusted for site, study, age (categorical), any unsafe sex, total sex, CD4 (categorical). Any ART, NVP and EFV are each separate models.

**p-values for interactions are from LR tests.

‡Due to small sample size, estimates are not included from the Cox model.