Hormonal contraception and the risk of HIV acquisition among women in South Africa

Charles S. Morrison[a], Stephanie Skoler-Karpoff[b,c], Cynthia Kwok[a], Pai-Lien Chen[a], Janneke van de Wijgert[c,d], Marlena Gehret-Plagianos[c], Smruti Patel[e], Khatija Ahmed[f], Gita Ramjee[g], Barbara Friedland[c] and Pekka Lahteenmaki[c,h]

Objectives: To evaluate the effect of hormonal contraception including combined oral contraceptives (COCs), and the injectable progestins depo-medroxyprogesterone acetate (DMPA) and norethisterone enanthate (Net-En) on the risk of HIV acquisition among women in South Africa.

Design/methods: We analyzed data from 5567 women aged 16–49 years participating in the Carraguard Phase 3 Efficacy Trial. Participants were interviewed about contraceptive use and sexual behaviors and underwent pelvic examinations and HIV testing quarterly. We used marginal structural Cox regression models to estimate the effect of hormonal contraception exposure on HIV acquisition risk among women overall and among young women (16–24 years) in particular.

Results: Two hundred and seventy participants became HIV-infected (3.7 per 100 woman-years); HIV incidence was 2.8, 4.6, 3.5 and 3.4 per 100 woman-years in the COC, DMPA, Net-En and nonhormonal contraceptive groups, respectively ($P = 0.09$). The adjusted hazard ratios (AHRs) were 0.84 [95% confidence interval (CI) 0.51–1.39], 1.28 (95% CI 0.92–1.78) and 0.92 (95% CI 0.64–1.32) among COC, DMPA and Net-En users, respectively, compared with the nonhormonal group controlling for covariates. Age modified the effect of hormonal contraception on HIV acquisition risk; among young women, the AHRs were 1.02 (95% CI 0.46–2.28) for COCs, 1.68 (95% CI 0.96–2.94) for DMPA and 1.36 (95% CI0.78–2.35) for Net-En users.

Conclusions: In this study conducted among South African women, hormonal contraception did not significantly increase the risk of HIV acquisition. However, the effect estimate does not rule out a moderate increase in HIV risk associated with DMPA use found in some other recent studies.

AIDS 2012, **26**:497–504

Keywords: Africa, depo-provera, heterosexual transmission, HIV acquisition, hormonal contraception, oral contraceptives, women

Introduction

Hormonal contraception is used by over 150 million women worldwide including over 100 million women who use combined oral contraceptives (COCs) and over 50 million who use the injectable progestin depo-medroxyprogesterone acetate (DMPA) [1]; [2]. Injectable progestin use [DMPA and norethisterone enanthate

[a]FHI 360, Durham, North Carolina, [b]Memorial Sloan-Kettering Cancer Center, New York, [c]Population Council, New York, USA, [d]Academic Medical Center of the University of Amsterdam and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands, [e]University of Cape Town, [f]University of Limpopo Medunsa Campus, [g]Medical Research Council, Durban, South Africa, and [h]University of Helsinki, Helsinki, Finland.

Correspondence to Charles S. Morrison, PhD, FHI 360, Durham, NC 27713, USA.

Tel: +1 919 544 7040/11472; fax: +1 919 544 7261; e-mail: cmorrison@fhi360.org
Received: 13 July 2011; revised: 14 November 2011; accepted: 23 November 2011.

DOI:10.1097/QAD.0b013e32834fa13d

(Net-En)] is increasing especially among young women and among women in South Africa [3]. In much of sub-Saharan Africa, condom use remains low within marriage and among women using highly effective contraception [4].

Studies from macaques and some (but not all) studies conducted among high-risk women (e.g. sex workers) suggest that hormonal contraceptive use, and in particular DMPA use, may increase women's risk of HIV acquisition [5–9]. Studies among women from general population groups have been inconsistent, although a reanalysis of the Hormonal Contraception and Risk of HIV Acquisition (HC-HIV) study, the largest and most rigorous study of the issue to date, found a 50% increase in HIV acquisition risk among women using DMPA, but no statistically significant increased risk among women using COCs [7]. Importantly, young women (<24 years) who used either DMPA or COC in the HC-HIV study appeared to be at increased risk of HIV acquisition [7].

We used data from a randomized trial of the candidate microbicide Carraguard to evaluate the effect of hormonal contraceptive use on HIV acquisition among women at three research sites in South Africa [10]. The Carraguard study collected high-quality contraceptive data on women using DMPA, Net-En, COCs and women not using hormonal contraception. The dataset also contained important covariates (e.g. sexual practices) of contraceptive use and large numbers of well timed incident HIV infections.

Methods

The analysis used a subset of data from a randomized, double-blinded, placebo-controlled trial which investigated whether Carraguard gel prevented HIV infection when used vaginally by women in South Africa. The study was conducted by the Population Council between March 2004 and March 2007 in collaboration with the Medical Research Council (MRC) of South Africa, the University of Limpopo/Medunsa Campus (Medunsa), and the University of Cape Town (UCT) at sites in Isipingo (Kwa-Zulu Natal), Soshanguve (Gauteng), and Gugulethu (Western Cape), respectively. All study participants provided written informed consent; the study was reviewed and approved by the Population Council Institutional Review Board, by institutional review boards at each of the three participating South African sites and by the South African Medicines Control Council. Results showed an HIV incidence of 3.6 per 100 woman-years, with an incidence of 3.3 in the Carraguard group and 3.8 in the placebo group, although the difference in arms was not statistically significant. Detailed methods and results have been reported previously [10].

Study population and procedures

Participants in the main study were sexually active, nonpregnant, HIV-negative females, aged 16 years and older. Sexual activity was defined as having had at least one sex act in the past 3 months. Women with active sexually transmitted infections (STIs) were enrolled following effective treatment provided by the study clinic. Participants were provided with Carraguard or placebo (methylcellulose gel) depending on randomization. Both groups received male latex condoms, nonlubricated, or lubricated with a nonspermicidal lubricant. Female condoms were also available upon request.

All participants were instructed to use both the gel and condoms throughout the study during each act of vaginal intercourse. Following enrollment, participants completed study visits at month 1, month 3, and quarterly thereafter for a minimum of nine months and a maximum of 24 months. At all visits, participants had a pelvic exam, testing for HIV and pregnancy, counseling on HIV risk reduction and family planning and a staff-administered interview which included questions about recent sexual activity, gel use, and current contraceptive use. At months 3, 6, 12, 18 and 24 and when clinically indicated, women were tested for chlamydia, gonorrhea, syphilis and trichomoniasis; women were tested for bacterial vaginosis and yeast when symptomatic. Study clinics provided treatment to all women with curable sexually transmitted or vaginal infections.

Study staff specifically encouraged the use of contraceptives throughout the trial. UCT provided hormonal contraception throughout the study, whereas Medunsa and MRC began providing hormonal contraception on site in October 2005 to reduce high pregnancy rates and maximize participant follow-up [11]. Hormonal contraceptives available at the sites included some or all of the following: oral contraceptives (Biphasil, Microval, Nordette, Ovral and Triphasis) and injectables (DMPA, Net-En). Women who became pregnant or HIV-infected during the main study were discontinued from the study and referred to local services in the trial communities for further care.

Analysis population and variable definition

A detailed description of the HIV testing algorithm has been described elsewhere [10]. Briefly, two rapid blood tests were used at each visit; positive results were confirmed by enzyme immunoassay or RNA PCR. For participants who seroconverted at month 1 or 3, baseline samples were tested to determine their HIV infection status at enrollment using HIV PCR. The date of HIV infection was estimated to be the midpoint between the date of the participant's first positive HIV result and the most recent previous HIV-negative result. Time to infection was computed as the difference (in days) between the estimated infection date and the enrollment date plus one. Participants who completed the

study without HIV seroconversion, those who discontinued early and those who were lost to follow-up, were censored at the date of their last HIV test.

Participants included in this analysis consisted of all participants eligible for the main study who were 16–49 years of age and provided contraceptive use data at enrollment. Contraceptive use was divided into four groups: DMPA, COC, Net-En and no use of hormonal contraception. The nonhormonal group excluded women using intrauterine devices (IUDs) or who had had a hysterectomy because these women may be at differential HIV risk than other women not using hormonal contraception [8].

We defined contraceptive exposure for our primary analysis as time-varying contraceptive use at each study visit – that is, if a woman used any of the four methods (i.e. COC, DMPA, NET-EN, and no use of hormonal contraception) since the previous visit she was coded as 1 for that contraceptive variable for that visit; otherwise she was coded as 0. We also performed a sensitivity analysis on only those participants reporting consistent contraceptive use since the baseline visit (i.e. the woman was censored at first contraceptive switch). A composite participant behavioral risk variable was used in the analysis. This variable was defined as having a new steady sex partner, multiple sex partners, a nonsteady sex partner or exchanging sex for money. We defined condom use as any use of a male or female condom during the period since the last study visit (used either with or without another family planning method).

Statistical methods

Baseline categorical variables or continuous variables that were categorized were summarized by frequencies and percentages and analyzed using the Cochran–Mantel–Haenszel test across the four contraceptive exposure groups. Data recorded for continuous variables were summarized by medians and ranges and analyzed using the Kruskal–Wallis test across the contraceptive use groups.

Cox proportional hazard regressions and logistic regressions adjusted for repeated observations were used to evaluate bivariable associations between baseline and time-varying characteristics and HIV acquisition. All suspected confounders were prespecified either by study researchers or were suggested by the literature. We evaluated the following baseline variables: site, age, race, education, living with partner, gel treatment group, and time-varying variables: coital frequency, unexpected genital discomfort, participant behavioral risk (new partner, concurrent partners, sex for money), any condom use, condom use at last sex, abnormal epithelial findings, abnormal vaginal discharge, STIs. If a time-dependent covariate was associated ($P < 0.05$) with HIV acquisition and predicted subsequent hormonal contraception exposure and was also predicted by past hormonal contraception exposure, it was considered a time-dependent confounder [12]. We used a marginal structural Cox survival model (MSCSM) to provide consistent estimates of the hormonal contraception exposure effect on HIV acquisition [13].

This approach first generates stabilized inverse-probability-treatment weights (IPTW) for hormonal contraception exposure using multinomial logistic regressions of hormonal contraception exposure vs. identified time-dependent confounders and time-independent covariates (e.g. site, age, living with partner) as well as other potential time-varying confounders. Similarly, we used logistic regressions adjusted for the same set of covariates to estimate the probability of remaining uncensored by either the end of the study, pregnancy occurrence or by dropout to obtain estimates of the censoring weights. A weighted Cox proportional hazard model with stabilized weights (IPTW $\times$ censoring weights) was further used to estimate the effect of hormonal contraception exposure on HIV acquisition. We calculated 95% confidence intervals (CIs) for estimated hazard ratios using the robust sandwich estimate of the covariance matrix [14].

We also tested several baselines variables including age, condom use, participant behavioral risk, and STIs (prevalent chlamydia or gonorrhea) for effect modification of the hormonal contraception–HIV relationship. These variables were prespecified in our analysis plan because age and (high) risk group have modified the hormonal contraception and HIV acquisition relationship in previous studies. If the interaction term for the variable was statistically significant ($P \leq 0.05$), we report strata-specific results.

Data analyses were conducted using SUDAAN version 8.0.1 (RTI International, Research Triangle Park, North Carolina, USA) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Of 6004 women eligible at enrollment with valid HIV results, 5567 (93%) were included in the primary analysis population. A total of 437 women were excluded including two who did not have consistent contraceptive data at enrollment or screening, eight who did not have contraceptive use data during follow-up, 72 who used nonstudy methods (IUD or hysterectomy) at enrollment or their first follow-up visit, and 355 aged 50 years or older.

Participant characteristics at enrollment

Of the 5567 women in the primary analysis population, 1995 (36%) were from UCT, 2185 (39%) from Medunsa and 1387 (25%) from the MRC site (Table 1). Study

Table 1. Characteristics of South African women at enrollment by contraceptive use group.

Characteristic	COC ($n=501$) n (%) or median (Q1–Q3)	DMPA ($n=1618$) n (%) or median (Q1–Q3)	NET-EN ($n=1163$) n (%) or median Q1–Q3)	NH ($n=2285$) n (%) or median (Q1–Q3)	Total ($N=5567$) n (%) or median (Q1–Q3)	*P* value[a]
Site						
UCT (Gugulethu)	128 (25.55)	819 (50.62)	494 (42.48)	554 (24.25)	1995 (35.84)	<0.001
Medunsa (Soshanguve)	292 (58.28)	365 (22.56)	537 (46.17)	991 (43.37)	2185 (39.25)	
MRC (Durban)	81 (16.17)	434 (26.82)	132 (11.35)	740 (32.39)	1387 (24.91)	
Gel treatment group						
Placebo	247 (49.30)	794 (49.07)	575 (49.44)	1146 (50.15)	2762 (49.61)	0.921
Carraguard gel	254 (50.70)	824 (50.93)	588 (50.56)	1139 (49.85)	2805 (50.39)	
Sociodemographic[b]						
Age group						
16–21	73 (14.57)	324 (20.02)	399 (34.31)	454 (19.87)	1250 (22.45)	<0.001
22–24	65 (12.97)	255 (15.76)	268 (23.04)	231 (10.11)	819 (14.71)	
25–49	363 (72.46)	1039 (64.22)	496 (42.65)	1600 (70.02)	3498 (62.83)	
Race: Black	488 (97.41)	1602 (99.01)	1160 (99.74)	2244 (98.21)	5494 (98.69)	<0.001
Living with partner	162 (32.34)	505 (31.21)	197 (16.94)	752 (32.91)	1616 (29.03)	<0.001
Reproductive health and STI history						
Number of lifetime pregnancies	2 (1–3)	2 (1–3)	1 (0–2)	2 (1–4)	2 (1–3)	<0.001
Unexpected genital discomfort	9 (1.80)	20 (1.24)	12 (1.03)	61 (2.67)	102 (1.83)	0.001
Participant's sexual risk behavior						
Sexual partner:						
Steady partner only	463 (92.42)	1561 (96.48)	1113 (95.70)	2083 (91.16)	5220 (93.77)	<0.001
Any nonsteady partner	37 (7.39)	54 (3.34)	50 (4.30)	196 (8.57)	337 (6.05)	
Participant behavioral risk[c]	40 (7.98)	57 (3.52)	55 (4.73)	208 (9.10)	360 (6.47)	<0.001
Number of coital acts (last 2 weeks)	4 (2–6)	3 (2–6)	3 (2–6)	3 (1–5)	3 (2–6)	<0.001
Any condom used[d]	103 (20.56)	185 (11.43)	177 (15.22)	808 (35.36)	1273 (22.87)	<0.001
Steady partner's sexual behavior						
Steady partner had other partner(s)	50 (9.98)	267 (16.50)	108 (9.29)	401 (17.55)	826 (14.84)	<0.001
Clinical/laboratory data						
Prevalent chlamydia[b]	41 (8.18)	191 (11.80)	174 (14.96)	170 (7.44)	576 (10.35)	<0.001
Prevalent gonorrhea[b]	9 (1.80)	53 (3.28)	43 (3.70)	65 (2.84)	170 (3.05)	0.181
Prevalent trichomonas[b]	66 (13.17)	188 (11.62)	97 (8.34)	350 (15.32)	701 (12.59)	<0.001
Abnormal epithelial finding	25 (4.99)	85 (5.25)	44 (3.78)	146 (6.39)	300 (5.39)	0.014
Abnormal vaginal discharge	17 (3.39)	56 (3.46)	28 (2.41)	99 (4.33)	200 (3.59)	0.037

COC, combined oral contraceptive; DMPA, depo-medroxyprogesterone acetate; MRC, Medical Research Council; Net-En, norethisterone enanthate; NH, nonhormonal; STI, sexually transmitted diseases; UCT, University of Cape Town.
[a]Cochran–Mantel–Haenszel test for categorical variables; Kruskal–Wallis test for continuous variables.
[b]At screening visit.
[c]Includes new steady partner, or multiple partners, or nonsteady partner, or sex for money.
[d]Current male or female condom use.

participants contributed 33 108 visit segments to the analysis including 630 visit segments when women were found to be pregnant. At baseline, 1618 (29%) of participants used DMPA, 1163 (21%) used Net-En, 501 (9%) used COCs, and 2285 (41%) were in the nonhormonal group (a combination of women using condoms, female and male sterilization, diaphragm, traditional methods, or not using any contraceptive method) (Table 1). Median age was 28 years, and most women were single, never married. Over 90% of women had a steady sexual partner only, and about one-quarter reported any male or female condom use. About 12% of women had either a chlamydial or gonococcal infection at baseline and 13% had trichmoniasis.

A higher proportion of DMPA and Net-En users were from the UCT site, a higher proportion of the COC users was from the Medunsa site, and a higher proportion of the nonhormonal group was from the MRC site (Table 1). Net-En users tended to be younger (16–24 years), whereas COC and nonhormonal groups were older (25–49 years). A lower proportion of Net-En users lived with a partner and Net-En users had the fewest lifetime pregnancies. In terms of sexual behavior, more nonhormonal and COC users had nonsteady sex partners and high participant behavioral risk than DMPA or Net-En users. Nonhormonal users had the highest (35%) and DMPA users the lowest (11%) reported condom use. More nonhormonal and DMPA users than COC or Net-En users reported a partner who had other sex partners. At enrollment, chlamydia was most prevalent among Net-En users (15%), whereas trichomoniasis was most prevalent in the nonhormonal group (15%). No differences occurred among the contraceptive groups in treatment arm (Carraguard gel vs. placebo) or prevalent gonorrhea.

Pregnancy and contraceptive switching

We recorded 627 pregnancies during the study. As expected, pregnancies occurred unequally between the

Table 2. HIV infection incidence rates among South African women by contraceptive use group.[a]

Characteristic	COC N/wy (incidence rate per 100 wy)	DMPA N/wy (incidence rate per 100 wy)	NET-EN N/wy (incidence rate per 100 wy)	NH N/wy (incidence rate per 100 wy)	Total N/wy (incidence rate per 100 wy)
Study sites					
UCT (Gugulethu)	6/194 (3.1)	32/1124 (2.8)	21/610 (3.4)	18/754 (2.4)	77/2683 (2.9)
Medunsa (Soshanguve)	10/421 (2.4)	23/526 (4.4)	23/766 (3)	32/1138 (2.8)	88/2852 (3.1)
MRC (Durban)	5/140 (3.6)	48/583 (8.2)	11/189 (5.8)	41/784 (5.2)	105/1695 (6.2)
Age group at screening					
16–21	7/123 (5.7)	30/382 (7.9)	27/533 (5.1)	21/380 (5.5)	85/1417 (6)
22–24	3/101 (3)	22/320 (6.9)	16/327 (4.9)	7/211 (3.3)	48/960 (5)
25–49	11/531 (2.1)	51/1532 (3.3)	12/705 (1.7)	63/2085 (3)	137/4853 (2.8)
Total	21/755 (2.8)	103/2234 (4.6)	55/1565 (3.5)	91/2676 (3.4)	270/7230 (3.7)

COC, combined oral contraceptive; DMPA, depo-medroxyprogesterone acetate; MRC, Medical Research Council; Net-En, norethisterone enanthate; NH, nonhormonal; UCT, University of Cape Town; wy, woman-years.
[a]Test for homogeneity among the contraceptive groups: $P = 0.059$.

contraceptive groups with 356 (57%) occurring among the nonhormonal group, 119 (19%) among the COC group, whereas users of Net-En and DMPA had lower numbers of pregnancies [96 (15%) and 56 (9%), respectively].

Approximately one-third of women (35.6%) ever switched their contraceptive method during the study. Contraceptive switching occurred among 31% of DMPA users, 35% of nonhormonal users, 40% of Net-En users and 41% of COC users.

HIV incidence by contraceptive group

A total of 270 incident HIV infections were included in this analysis (Table 2). HIV incidence rates were highest among the DMPA users (4.6 per 100 woman-years) and lowest among the COC users (2.8 per 100 woman-years) (test for homogeneity: $P = 0.06$). Incidence rates were considerably higher at the MRC site than either the UCT or Medunsa sites (6.2 vs. 2.9 and 3.1 per 100 woman-years, respectively). HIV incidence was highest for women 16–21 years of age (6.0 per 100 woman-years) followed by 22–24 year old (5.0 per 100 woman-years) and woman 25 years and older (2.8 per 100 woman-years). HIV incidence rates were highest among DMPA users at the MRC (Durban) and Medunsa sites but not at the UCT sites (where HIV incidence was highest among the Net-En group).

In bivariable analysis, DMPA was associated with an increased risk of HIV acquisition (hazard ratio 1.43; 95% CI 1.07–1.92), whereas no significant associations occurred between Net-En (hazard ratio 1.09; 95% CI 0.77–1.53) or COC use (hazard ratio 0.89; 95% CI 0.55–1.44) and HIV acquisition (Table 3). In the regular multivariable Cox hazard model, none of the hormonal contraceptives were significantly associated with HIV acquisition. We also found that unexpected genital discomfort, participant sexual behavioral risk, any condom use, abnormal epithelial findings, and abnormal vaginal discharge were significant time-dependent confounders of the hormonal contraception and HIV acquisition relationship, and were included into the IPTW and IPCW estimation modeling. In multivariable analysis using marginal structural modeling neither DMPA [adjusted hazard ratio (AHR) 1.28; 95% CI 0.92–1.78] nor Net-En (AHR 0.92; 95% CI 0.64–1.32) or COC use (AHR 0.84; 95% CI 0.51–1.39) was significantly associated with HIV acquisition controlling for site, treatment group, age, living with partner, baseline genital discomfort, baseline participant behavioral risk, baseline condom use and baseline epithelial findings and abnormal vaginal discharge.

Secondary analyses

We conducted several secondary analyses. First, we considered the relationship between consistent hormonal contraceptive use and HIV acquisition when data were censored at the time of a woman's first contraceptive switch from her baseline contraceptive method. Whereas limited to 158 outcomes, we found that neither DMPA (AHR 1.18; 95% CI 0.80–1.76) nor Net-En (AHR 0.92; 95% CI 0.57–1.47) or COC use (AHR 0.76; 95% CI 0.36–1.60) were associated with HIV acquisition adjusting for covariates.

Effect modification of the hormonal contraception and HIV infection relationship

We specified several analyses *a priori* to consider possible effect modification of the hormonal contraception and HIV infection relationship by age, participant behavioral risk, condom use, and STIs. We found no evidence of an interaction between hormonal contraception and either participant behavioral risk, condom use or STIs. However, we found a significant interaction between age and the effect of hormonal contraception on HIV acquisition. For example, the interaction between age and Net-En use is associated with HIV acquisition ($P = 0.03$). In stratified analysis, we found that young women (16–24 years) who used DMPA (AHR 1.68; 95% CI 0.96–2.94) had a marginally increased risk of HIV acquisition, whereas young women who used either

Table 3. Hormonal contraceptive use and incident HIV infection among women in South Africa.

Characteristic	Bivariable associations (HR; 95 CI) Cox hazards model	Multivariable associations (AHR; 95 CI) Cox hazards model[a]	Marginal structural Cox model[b]
Time-varying variables any contraceptive use:			
COC	0.89 (0.55, 1.44)	0.88 (0.49, 1.30)	0.84 (0.51, 1.39)
DMPA	1.43 (1.07, 1.92)	1.27 (0.93, 1.73)	1.28 (0.92, 1.78)
Net-En	1.09 (0.77, 1.53)	0.87 (0.60, 1.25)	0.92 (0.64, 1.32)
NH	Reference	Reference	Reference

AHR, adjusted hazard ratio; CI, confidence interval; COC, combined oral contraceptive; DMPA, depo-medroxyprogesterone acetate; HR, hazard ratio; Net-En, norethisterone enanthate; NH, nonhormonal.
[a]AHR taken from Cox hazards model including time-varying (TV) COC, DMPA and Net-En use, site, gel treatment group, age, living with partner and the following time-varying variables: unexpected genital discomfort, participant behavioral risk, any condom use, abnormal epithelial finding, and abnormal vaginal discharge.
[b]Weights computing included baseline covariates (site, gel treatment group, age, living with partner) and time-varying confounders; unexpected genital discomfort, participant behavioral risk (having a new partner, or multiple sex partners, a nonsteady sex partner, or exchanging sex for money), any condom use, abnormal epithelial finding, and abnormal vaginal discharge. AHR for COC, DMPA and Net-En taken from marginal structural Cox model which includes time-varying COC, DMPA and Net-En use, baseline covariates and baseline measures of unexpected genital discomfort, participant behavioral risk, any condom use, abnormal epithelial finding, and abnormal vaginal discharge.

Net-En or COCs had no significant increased HIV acquisition risk (Table 4). Among older women, those who used Net-En (AHR 0.54; 95% CI 0.28–1.04) had a marginally decreased risk of HIV acquisition, whereas there was no association between DMPA and COC use and HIV acquisition risk.

Discussion

We found no increased risk of HIV acquisition overall among women using DMPA, COCs or Net-En among South African women participating in the Carraguard Microbicide Trial. However, we found modest evidence of an increased HIV acquisition risk among young women who used DMPA, whereas there was no statistically significant increased risk among young women using COCs or Net-En. We also found modest evidence of decreased HIV acquisition risk among older women who used Net-En but not among older women who used DMPA or COCs.

Table 4. Adjusted hazard ratios for incident HIV infection among South African women by age and contraceptive exposure group using marginal structural modeling.[a]

	Adjusted hazard ratio (95% confidence interval)
Age group: ≤24	
COC	1.02 (0.46–2.28)
DMPA	1.68 (0.96–2.94)
NET-EN	1.36 (0.78–2.35)
No HC use	Reference
Age group: >24	
COC	0.78 (0.40–1.50)
DMPA	1.14 (0.76–1.71)
NET-EN	0.54 (0.28, 1.04)
No HC use	Reference

COC, combined oral contraceptive; DMPA, depo-medroxyprogesterone acetate; HC, hormonal contraception; Net-En, norethisterone enanthate; NH, nonhormonal.
[a]Adjusted hazard ratio for COC, DMPA and Net-En taken from marginal structural Cox model which includes time-varying COC, DMPA and Net-En use, site, gel treatment group, age, living with partner, and the following baseline variables: unexpected genital discomfort, participant behavioral risk (having a new partner, or multiple sex partners, a nonsteady sex partner, or exchanging sex for money), any condom use, abnormal epithelial finding, and abnormal vaginal discharge.

The results from previous prospective studies reporting on the relationship between use of hormonal contraceptives and HIV acquisition have been inconsistent [8]. A reanalysis of the HC-HIV study using marginal structural modeling found an increased HIV acquisition risk for DMPA users (AHR 1.48; 95% CI 1.02–2.15) but not for COC users (AHR 1.19; 95% CI 0.80–1.76) [7]. A recent publication from a secondary analysis of almost 3800 HIV-1-serodiscordant couples from seven African countries found that women using hormonal contraception, primarily DMPA, were at a two-fold increased risk of acquiring HIV. Women who were HIV-infected at the beginning of the study and using injectable contraception were also twice as likely to transmit the infection to their uninfected male partners [15]. Whereas we found no statistically significant association overall between DMPA use and HIV acquisition in this analysis, our effect estimate for DMPA (AHR 1.28; 95% CI 0.92–1.78) is relatively similar to that from the HC-HIV study and not inconsistent with a moderate increase in HIV risk associated with DMPA use reported in other recent studies [15]. Differences in the results of these studies may be partially due to differences in the study populations. In the serodiscordant couples study all women were presumably exposed to HIV during each coital act in which a condom was not used. In contrast, women participating in this study and the HC-HIV study were from the general population and it is likely that many were never exposed to HIV during the study period.

Our finding of no increased HIV risk associated with Net-En use is in agreement with previous research. Only

two previous studies, both from South Africa, have examined this relationship and both found no significant association between Net-En use and HIV acquisition [16,17] though the power of these prior studies to detect a Net-En-HIV association was somewhat limited. Although the differences between the effect estimates for DMPA and Net-En are not great in this study, they are in the expected direction with somewhat higher risk estimates for DMPA than for Net-En use. Whereas the effects of dosage or serum levels should not be directly compared between different progestins, DMPA appears to suppress ovulation more profoundly than Net-En (3 vs. 2 months for a single dose) and with longer carryover in terms of resumption of ovulation. Also, medroxyprogesterone (the active component of DMPA) in contrast to progesterone (and perhaps other progestins) binds to the glucocorticoid receptor expressed by many cells of the immune system and thus may exert stronger immunosuppressive effects than progesterone [18].

The analysis found modest evidence of an increased HIV acquisition risk among young women who used DMPA but not COCs or Net-En. This finding is similar to the results from the HC-HIV study reanalysis in relation to DMPA use but not COC use. The HC-HIV study found an almost three-fold and a two-fold increased HIV risk for young women who used DMPA and COCs, respectively [7]. The Mombasa sex worker study did not find an interaction between hormonal contraceptive use and age although there were relatively few young women participating in the study [5].

This analysis of hormonal contraception and HIV acquisition among women participating in the Carraguard Microbicide trial has a number of strengths. First, there were a large number of incident HIV infections and also large numbers of women using the different hormonal methods. Thus the study had enough statistical power to detect differences between contraceptive groups. Large numbers of young women allowed us to analyze the HIV risk associated with hormonal contraceptive use among young (<25 years) women – an important objective of this analysis. HIV infection was measured often (every 3 months) using a standardized testing algorithm that allowed accurate timing of infection. Finally, we used a marginal structural modeling approach to analyze the longitudinal effect of hormonal contraception on HIV acquisition. The marginal structural modeling approach has become increasingly recognized as a preferred method to analyze longitudinal data subject to time-dependent confounding, especially in cohort studies of HIV infection and the effect of highly active antiretroviral therapy (HAART) on HIV disease progression [5,7,13,19–22].

Our analysis also had limitations. First, hormonal contraception was not provided by the study at all sites throughout the study. Therefore we could not compare self-reported contraceptive use data with records of contraceptive provision by study staff. Second, herpes simplex virus type 2 (HSV-2) data were not available for study participants and thus no analysis of the relationship between hormonal contraceptive use and HIV acquisition among HSV-2-negative women was possible. Finally, data on condom use, sexual risk behavior by male partners and other important covariates were self-reported by the study participants and the validity of these data are unclear.

In summary, we found no statistically significant increased risk of HIV acquisition associated with either DMPA, Net-En or COC use overall and modest evidence of an increased HIV acquisition risk among young women who used DMPA but not Net-En or COCs. Women in areas of high HIV incidence should be counseled about the need for condom use and maintaining a monogamous relationship. This may be especially important for younger women and particularly those who use DMPA as their contraceptive method. Efforts should also be made to expand women's access to highly effective nonhormonal (e.g. IUDs) and low-dose hormonal (e.g. implants) methods. Moreover, to resolve this important public health question, we need to conduct a randomized trial to clarify the relationship between hormonal contraception and HIV acquisition, particularly among young women.

Acknowledgements

S.S.K., J.W., B.F., and P.L. were involved in the overall study design and protocol development. S.P., K.A. and G.R. were responsible for implementation at the study sites. M.G.P. was responsible for data management, and P.C. and C.K. oversaw data analysis. C.M., S.S.K., B.F., P.C., M.G.P., and P.L. participated in writing the manuscript, which all authors reviewed and approved.

This project is made possible by the generous support of the American people through USAID, Bureau for Global Health, Office of Population and Reproductive Health, under the terms of Award Nos. GPO-A-00–04–00019 (Population Council) and GPO-A-00–05–00022–00 (FHI 360).

Disclaimer: The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, the United States Agency for International Development (USAID), or FHI 360, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Conflicts of interest

There are no conflicts of interest.

References

1. Population Reference Bureau. *Family Planning Worldwide 2008 Data Sheet*. Washington, DC: Population Reference Bureau; 2008.
2. World Contraceptive Use 2003. New York, New York: United Nations, Department of Economic and Social Affairs Population Division; 2003.
3. South Africa Demographic and Health Survey 2003. Pretoria, South Africa: Department of Health, Medical Research Council, OrcMacro; 2007.
4. Morrison CS, Richardson BA, Mmiro F, Chipato T, Celentano DD, Luoto J, *et al*. **Hormonal contraception and the risk of HIV acquisition.** *AIDS* 2007; **21**:85–95.
5. Baeten JM, Benki S, Chohan V, Lavreys L, McClelland RS, Mandaliya K, *et al*. **Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women.** *AIDS* 2007; **21**:1771–1777.
6. Marx PA, Spira AI, Gettie A, Dailey PJ, Veazey RS, Lackner AA, *et al*. **Progesterone implants enhance SIV vaginal transmission and early virus load.** *Nat Med* 1996; **2**:1084–1089.
7. Morrison CS, Chen PL, Kwok C, Richardson BA, Chipato T, Mugerwa R, *et al*. **Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling.** *AIDS* 2010; **24**:1778–1781.
8. Morrison CS, Turner AN, Jones LB. **Highly effective contraception and acquisition of HIV and other sexually transmitted infections.** *Best Pract Res Clin Obstet Gynaecol* 2009; **23**:263–284.
9. Trunova N, Tsai L, Tung S, Schneider E, Harouse J, Gettie A, *et al*. **Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques.** *Virology* 2006; **352**:169–177.
10. Skoler-Karpoff S, Ramjee G, Ahmed K, Altini L, Plagianos MG, Friedland B, *et al*. **Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial.** *Lancet* 2008; **372**:1977–1987.
11. Cele N, Palanee T, Myeni N, Mnyandu N, Langa Z, Shange E, *et al*. *Impact of provision of hormonal contraception on pregnancy incidence in women enrolled in the Phase 3 Carraguard clinical trial at three sites in South Africa*. New Delhi, India: Poster presentation at Microbicides Conference; 2008.
12. Robins JM, Hernan MA, Brumback B. **Marginal structural models and causal inference in epidemiology.** *Epidemiology* 2000; **11**:550–560.
13. Hernan MA, Brumback B, Robins JM. **Marginal structural models to estimate the joint causal effect of nonrandomized treatments.** *J Am Stat Assoc* 2001; **96**:440–448.
14. Lin DY, Wei LJ. **The robust inference for the Cox proportional hazards model.** *J Am Stat Assoc* 1989; **84**:1074–1078.
15. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, *et al*. **Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study**. *Lancet Infect Dis* 2011. [Epub ahead of print]
16. Kleinschmidt I, Rees H, Delany S, Smith D, Dinat N, Nkala B, *et al*. **Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort.** *Contraception* 2007; **75**:461–467.
17. Myer L, Denny L, Wright TC, Kuhn L. **Prospective study of hormonal contraception and women's risk of HIV infection in South Africa.** *Int J Epidemiol* 2007; **36**:166–174.
18. Hel Z, Stringer E, Mestecky J. **Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection.** *Endocrine Rev* 2010; **31**: 79–97.
19. Sterne JA, Hernan MA, Ledergerber B, Tilling K, Weber R, Sendi P, *et al*. **Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study.** *Lancet* 2005; **366**:378–384.
20. Brotman RM, Klebanoff MA, Nansel TR, Andrews WW, Schwebke JR, Zhang J, *et al*. **A longitudinal study of vaginal douching and bacterial vaginosis–a marginal structural modeling analysis.** *Am J Epidemiol* 2008; **168**:188–196.
21. Palella FJ Jr, Armon C, Buchacz K, Cole SR, Chmiel JS, Novak RM, *et al*. **The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study.** *Ann Intern Med* 2009; **151**:73–84.
22. Hernan MA, Brumback B, Robins JM. **Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men.** *Epidemiology* 2000; **11**:561–570.