The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections

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Objectives: To investigate the association between hormonal contraceptives and risk of HIV-1 seroconversion and prevalence of other sexually transmitted infections.

Design: Prospective cohort.

Methods: The study population was 2 236 HIV-negative women who were screened in a biomedical intervention trial in Durban, South Africa. The association between the use of hormonal contraceptives and risk of HIV-1 seroconversion was modeled using Cox proportional hazards regression analysis. Prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections were assessed using logistic regression models.

Results: Hormonal injectables were the most common method of contraceptives (46.47%) followed by condom use (28.04%). Overall, compared with women who reported using condoms or other methods as their preferred form of contraceptive, those who reported using hormonal contraceptives (injectables and oral pills) were less likely to use condoms in their last sexual act. Using hormonal injectables during the study was significantly associated with increased risk for HIV-1 infection [adjusted hazard ratio 1.72, 95% confidence interval (CI) 1.19–2.49, $P = 0.005$]; hormonal injectables were also significantly associated with higher prevalent of *C. trachomatis* infections (adjusted odds ratio 2.46, 95% CI 1.52–3.97, $P < 0.001$).

Conclusion: Hormonal injectables are highly effective and well tolerated family planning methods and have played an important role in reducing unplanned pregnancies and maternal and infant mortality. However, they do not protect against HIV-1 and other sexually transmitted infections. This study reinforces the importance of comprehensive contraceptive counseling to women about the importance of dual protection, such as male condoms and hormonal contraceptives use.

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Introduction

Women continue to be one of the populations at highest risk for HIV infection [1,2]; developing an effective female-controlled biomedical intervention such as a microbicide is, therefore, a high priority [3,4]. HIV prevention trials on safety and efficacy of biomedical interventions recruit young women at reproductive age and encourage them to use a highly effective birth control methods, since safety of the interventions during pregnancy usually has not been established. Lower pregnancy rates are also desirable for the purpose of retention of women in these trials.

Barrier methods, particularly the male condom, have well established effectiveness in reducing the risk of pregnancy, HIV-1 and other sexually transmitted infections (STIs) [5–7]. Hormonal contraceptives have been reported to be one of the most common forms of method used by women in South Africa [8]. They are preferred because of their high efficacy (>99%) and safety compared with the other methods [9]. These female-controlled effective methods have a key role in reducing important physical, emotional and social consequences for individuals and society owing to unintended pregnancies [10].

An epidemiologic relationship between hormonal contraception use and HIV-1 infection has been discussed in several studies [11–13]. Although it has not been consistently shown, studies have suggested that the use of hormonal contraceptives, especially injectables, may have an association with HIV-1 infection [11–17]. According to the results from the most recent study, women who use hormonal contraceptives may be twice as likely to become infected with HIV as women who do not use hormonal contraceptions [18].

In this study, we investigated the association between the use of hormonal contraceptives and risk of HIV-1 seroconversion and prevalence of other STIs among women who were screened for a large biomedical intervention trial.

Methods

Participants and design

A total of 2236 HIV-negative women included in this analysis where more than 90% of them enrolled and followed-up at biomedical intervention trial at the sites in Durban, South Africa [19]. Women were counseled to use condoms during all sex acts and given options to access contraceptives; they also received unrestricted supplies of free condoms at the research clinics. Self-reports of contraceptive use were recorded at the enrollment and every quarterly visits. The study received local scientific and ethical approval from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal. HIV-1 infection was confirmed by the central reference laboratory; presence of *Neisseria gonorrhoeae* or *Chlamydia trachomatis* was established by a positive nucleic acid amplification assay at week 24 only.

Statistical analyses

The primary outcome measures were incidence of HIV-1 seroconversion and prevalence of *N. gonorrhoeae* and *C. trachomatis*. Women were categorized according to their self-reported contraceptive methods: hormonal injectables (Depo-Provera injection or generic alternative medroxyprogesterone acetate), oral pills and male condoms or other forms of contraceptives (including female condoms, tubal ligation, vasectomy, intrauterine device and traditional methods). Hormonal injectables also included three participants who reported using implants such as Norplant. Age at baseline was calculated using self-reported date of birth and was treated as a continuous covariate. Self-reported highest level of education at baseline was dichotomized as secondary school completed (reference) versus secondary school not completed. The number of sexual partners in last 3 months was categorized as 1 and 2 or more. The number of sexual acts in last 2 weeks was categorized as 1 or less, 2, 3 or more.

Frequency distribution and percentages were used to describe the demographic and socioeconomic characteristics of women by their patterns of contraception use at enrollment. Groups were formally tested using the χ^2-test. Participants' ages were described using summary statistics and formally tested using analysis of variance methods.

Time-dependent Cox proportional hazard regression models were used to assess the impact of contraceptive methods on risk of HIV-1 seroconversion. Variety of covariates were considered in adjusted analyses: except demographic data (age, education level and religion), all other factors (method of contraceptive, number of sexual partners in last 3 months, number of sex acts in last 2 weeks, condom used at last sex and pregnancy) were considered as time varying (i.e. they were updated at each visit). As presence of *C. trachomatis* and *N. gonorrhoeae* were only tested at week 24, they were treated as cross-sectional study endpoints and analyzed using logistic regression.

All analyses were conducted using STATA 10.0 (College Station, Texas, USA).

Results

Out of the 2236 women included in this study, 2051 (92%) reported using at least one contraceptive method at baseline. Table 1 presents baseline characteristics of women by the patterns of contraception use. At baseline, hormonal injectables were the most commonly used method compared to oral pills (46.47 versus 7.02%).

Table 1. Pattern of contraceptive use at enrollment by selected characteristics of enrolled women.

Characteristics	Total	None	Injectables	Oral pills	Condoms/others[a]	*P* value
All participants	2236	185 (8.27)	1039 (46.47)	157 (7.02)	855 (38.24)	
Age, median (IQR)	27 (22–37)	37 (23–43)	25 (21–32)	26 (23–36)	31 (22–39)	<0.001
Employment status						0.172
Employed/regular income	394 (17.62)	38 (20.54)	172 (16.55)	36 (22.93)	148 (17.31)	
Not Employed	1842 (82.38)	147 (79.46)	867 (83.45)	121 (77.07)	707 (82.69)	
Education level						0.171
Less than secondary school	1550 (69.32)	140 (75.68)	703 (67.66)	109 (69.43)	598 (69.94)	
At least secondary school	686 (30.68)	45 (24.32)	336 (32.34)	48 (30.57)	257 (30.06)	
Religion						0.068
Christian	890 (39.80)	72 (38.92)	385 (37.05)	68 (43.31)	365 (42.69)	
Other	1346 (60.20)	113 (61.08)	654 (62.95)	89 (56.69)	490 (57.31)	
Age at first sex[b]						0.198
<15 years	113 (5.06)	13 (7.07)	58 (5.58)	9 (5.73)	33 (3.86)	
15–19 years	1730 (77.40)	134 (72.83)	816 (78.54)	120 (76.43)	660 (77.19)	
≥20 years	392 (17.54)	37 (20.10)	165 (15.88)	28 (17.83)	162 (18.95)	
Number of sex acts in last 2 weeks before the enrollment						0.005
1	657 (29.38)	71 (38.38)	278 (26.76)	42 (26.75)	266 (31.11)	
2	625 (27.95)	56 (30.27)	307 (29.55)	40 (25.48)	222 (25.96)	
3 or more	954 (42.67)	58 (31.35)	454 (43.70)	75 (47.77)	367 (42.92)	
Number of sexual partners in last 3 months						0.449
1	606 (27.10)	54 (29.19)	265 (25.51)	43 (27.39)	244 (28.54)	
2 or more	1630 (72.90)	131 (70.81)	774 (74.49)	114 (72.61)	611 (71.46)	
Condom used at last sex, *n* (%)						<0.001
No	896 (40.09)	132 (71.35)	454 (43.70)	65 (41.40)	245 (28.69)	
Yes	1339 (59.91)	53 (28.65)	585 (56.30)	92 (58.60)	609 (71.31)	
STI diagnosis[c]	492 (22.00)	45 (24.32)	236 (22.71)	33 (21.02)	178 (20.82)	0.643

Other variables considered in the analyses but not included were as follows: having a regular sexual partner (99%), anal sex (<1%) in last 4 weeks and condom used with anal sex. IQR, inter-quartile range; STI, sexually transmitted infection.
[a]Also includes female condoms, tubal ligation, vasectomy, intrauterine device and traditional methods.
[b]Excludes one participants who declined to report her age at first sexual debut.
[c]At least one positive test for *Neisseria gonorrhea*, *Chlamydia trachomatis*, *Trichomonas vaginalis* or syphilis at screening.

Women who reported using hormonal contraceptives (injectables or oral pills) were significantly younger than those who reported using none or other contraceptive methods. Employment status, level of education, religion, age at sexual debut and number of sexual partners in last 3 months were not significantly different across the contraceptive groups. Groups did not differ in terms of the frequency of diagnoses of an STI at baseline. However, proportion of women who reported using a condom in their last sexual act was highest among those who reported using the male condoms or other forms of contraceptives as their preferred method (71.31%) compared with those who reported using either injectables or oral pills (58.60 and 56.30%, respectively, $P < 0.001$).

HIV incidence and injectable hormonal contraceptives

In univariate analysis, there was an increased HIV-1 incidence with the use of injectable hormonal contraceptives compared with the condom and other contraceptive methods [hazard ratio 1.45, 95% confidence interval (CI) 1.04–2.03, $P = 0.028$]; this association was stronger when the analysis was adjusted for age, average number of sexual acts per week, condom used in last sexual act and incidence of pregnancy (hazard ratio 1.72, 95% CI 1.19–2.49, $P = 0.005$). When hormonal contraceptives were considered during the study follow-up, risk of HIV acquisition became stronger in both unadjusted and adjusted analyses (unadjusted hazard ratio 1.82, 95% CI 1.24–2.65, $P = 0.001$ and adjusted hazard ratio 2.02, 95% CI 1.37–3.00, $P < 0.001$). There were no statistically significant associations between the oral pills users and risk of HIV-1 seroconversion in unadjusted and adjusted analysis.

Prevalence of *Chlamydia trachomatis* and injectable hormonal contraceptives

In unadjusted analysis, the estimated odds ratio of *C. trachomatis* infection for women who were using injectables at the enrollment was 1.41 (95% CI 0.99–2.02, $P = 0.060$). This borderline association was not sustained when the model was adjusted for age, average number of sexual acts per week and condom use in last sex act. However, when the forms of contraceptives were considered during the study follow-up injectables were significantly associated with prevalence of *C. trachomatis* infection in both unadjusted and adjusted analyses.

Prevalence of *Neisseria gonorrhoeae* and injectable hormonal contraceptives

Forms of contraceptive use at enrollment or during the study were not determined to be the predictor of *N. gonorrhoeae* in unadjusted and adjusted analyses.

Discussion

In this study, we found that injectable hormonal contraceptive use was significantly associated with increased risk of HIV-1 and *C. trachomatis* infections among women in Durban, South Africa. At the enrollment, women were encouraged to use at least one form of effective contraceptive; however, they were not excluded if they chose not to use them. Nevertheless, the majority (92%) of the women were using at least one form of contraceptive, particularly injectables. This is consistent with the pattern of contraceptive use in sub-Saharan Africa [8,20]. Women using effective forms of nonbarrier methods, such as injectables and pills, may be less likely to use condoms [21] and this was supported by this study. Compared with women who reported using condoms as their preferred form of contraceptive, those who reported using injectables were less likely to use condoms in their sexual acts.

The most recent study has indicated that users of hormonal contraceptives (oral or injectable) were more likely to both acquire and transmit HIV [18]. The increased likelihood of transmission was thought to be a result of elevated genital HIV viral loads in hormonal contraceptive users. This effect was driven by users of injectable hormonal methods, who had 67% increased odds of having a detectable genital viral load [18].

Decisions about contraceptives should reflect both the need to prevent unplanned pregnancies and the need to prevent HIV and other STIs. Condoms, which are currently the most widely available and most effective method for prevention of HIV and STIs, may not necessarily be the most effective contraceptive under typical conditions [7]. The combination of a barrier method with a more effective contraceptive could potentially maximize the dual protective effect. Yet not all participants may be empowered to use dual protective methods, as cultural proscriptions on the use of barrier contraceptives may exist [22,23], and women may not be able to insist upon their use [24]. Two potentially woman-controlled barrier methods currently exist: the female condom and the vaginal diaphragm. Although the vaginal diaphragm could potentially be used independently of the cooperation of a male partner, it has not conclusively been shown to prevent the acquisition of HIV [25]. The female condom, although probably effective as an anti-HIV measure [26,27], has been somewhat limited in use and uptake owing to cost and policy factors [28,29]. Although, they do not protect against HIV and other STIs, intrauterine contraceptive devices are also

Table 2. Incidence of HIV-1 infection, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

	HIV incidence			
	Unadjusted HR (95% CI)	*P* value	Adjusted[a] HR (95% CI)	*P* value
HIV incidence				
At enrollment				
Condom/others[b]	1		1	
Oral pills	0.86 (0.51–1.45)	0.573	0.93 (0.54–1.58)	0.779
Injectables	1.45 (1.04–2.03)	0.028	1.72 (1.19–2.49)	0.005
On study[c]				
Condom/others[b]	1		1	
Oral pills	0.94 (0.61–1.43)	0.760	0.95 (0.62–1.46)	0.822
Injectables	1.82 (1.24–2.65)	0.001	2.02 (1.37–3.00)	<0.001
*Chlamydia trachomatis**				
At enrollment				
Condom/others[b]	1		1	
Oral pills	1.29 (0.69–2.41)	0.429	1.28 (0.68–2.40)	0.441
Injectables	1.41 (0.99–2.02)	0.060	1.46 (1.01–2.10)	0.430
On study[d]				
Condom/others[b]	1		1	
Oral pills	1.74 (0.93–3.23)	0.082	1.74 (0.94–3.25)	0.080
Injectables	2.22 (1.39–3.52)	0.001	2.46 (1.52–3.97)	<0.001
*Neisseria gonorrhea**				
At enrollment				
Condom/others[b]	1		1	
Oral pills	0.34 (0.08–1.45)	0.147	0.35 (0.10–1.46)	0.150
Injectables	0.80 (0.47–1.37)	0.422	0.80 (0.47–1.38)	0.428
On study[d]				
Condom/others[b]	1		1	
Oral pills	0.73 (0.26–2.04)	0.549	0.74 (0.26–2.07)	0.566
Injectables	1.28 (0.69–2.40)	0.437	1.31 (0.69–2.50)	0.413

CI, confidence interval; HR, hazard ratio.
*Values presented for *Chlamydia trachomatis* and *Neisseria gonorrhea* are odds ratios.
[a]Age, religion, number of sexual partners in last 3 months, condom used in last sex and pregnancy.
[b]Includes male and female condoms, tubal ligation, vasectomy, intrauterine device and traditional methods.
[c]Included in the model as a time-varying covariate.
[d]Last method reported.

considered to be one of the most effective female-controlled contraceptive methods and may play important role in dual protection if woman does not want to use hormonal injectables or pills. New research efforts are being made toward the development of dual protective woman-controlled technologies, such as intravaginal rings, in which both contraceptive and microbicidal agents are combined [30], although wide availability of such methods is likely to be several years distant.

Our findings add to the current body of knowledge surrounding the relationship between hormonal contraception and risk of HIV-1 [18]. However, some caution should be exercised in the interpretation of the data, as the women involved were participants in a clinical trial and were considered to be at particularly high risk for acquisition of HIV-1. Contraception use was also self-reported; thus, data may have been subject to recall bias. Like previously published studies, these findings were derived from observational data, which may be biased by self-selection. Therefore, results may not be widely generalizable but, at the least, may inform local healthcare guidelines.

Conclusion

Hormonal contraceptives, particularly injectables, play important role in improving maternal and child health by reducing unplanned pregnancies. Although these woman-controlled methods empower women and increase reproductive health, they do not protect against HIV-1 and other STIs. Results from this study reinforce the importance of comprehensive contraceptive counseling of women regarding increased risk of HIV-1 and other STIs and importance of dual protection, such as dual condom and hormonal contraceptive use Table 2.

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H.W. proposed and conducted the analysis; G.R. was the principal investigator of the MDP 301 study in Durban and was involved in implementation of the study. Both authors interpreted, drafted and reviewed the results.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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