

Hormonal contraceptive use and HIV-1 infection in a population-based cohort in Rakai, Uganda

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Background: Hormonal contraceptives have been associated with increased risk of HIV acquisition.

Methods: The association between hormonal contraception use and HIV acquisition was assessed in a rural community-based cohort in Rakai District, Uganda. A group of 5117 sexually active HIV-negative women were surveyed at 10 month intervals between 1994 and 1999. Information on demographic and sociobehavioral characteristics, use of hormonal contraception (pill and injectable methods), condoms and the number of sexual partners was obtained by home-based interview. HIV incidence rate ratios (IRR) and 95% confidence intervals (CI) associated with hormonal contraception were estimated by multivariate Poisson regression after adjustment for age, condom use, number of sexual partners, marital status, education and history of genital ulcer disease.

Results: At one or more interviews, 16.6% of women reported use of hormonal contraceptives and 23.0% reported condom use. HIV incidence was 2.3/100 person-years in hormonal contraceptive users compared with 1.5/100 person-years in non-hormonal contraceptive users (unadjusted IRR, 1.56; 95% CI, 1.00–2.33). After multivariate adjustment, the IRR associated with hormonal contraceptives was reduced to 0.94 (95% CI, 0.53–1.64). The adjusted IRR was 1.12 (95% CI, 0.48–2.56) with oral contraceptive use and 0.84 (95%CI, 0.41–1.72) with injectable methods.

Conclusion: Use of hormonal contraception is not associated with HIV acquisition after adjustment for behavioral confounding. © 2003 Lippincott Williams & Wilkins

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Introduction

Sub-Saharan Africa will have 28.1 million people living with HIV by the end of 2001 [1]. Uganda was the first

country in the region to acknowledge the HIV/AIDS epidemic as a serious problem, and is the first country in the region to show a decline in HIV prevalence [1,2]. Currently, it is estimated that 820 000 people are

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living with HIV in Uganda, of whom 51.2% are women aged 15–49 years. The vast majority of new infections (84%) in Uganda occur as a result of heterosexual transmission [3]. Women are particularly vulnerable because of their status in this society, with lower education, higher unemployment and weaker negotiating skills within relationships [4,5].

In addition to the HIV epidemic, sub-Saharan Africa has one of the fastest growing populations. Uganda's population was estimated to be 22.2 million in 2000 with an annual growth rate of 2.5% and is expected to double in the next 25 years [6,7]. Population control has become a public health priority, and methods offered by family planning programs include hormonal contraceptives. However, some studies suggest that hormonal contraceptives may increase susceptibility to, and infectiousness of, HIV [8]. Prospective studies of commercial sex workers in Thailand found that use of injectable contraceptives was associated with an increased risk of HIV acquisition, but no association was observed with oral contraceptives [9], whereas a prospective study of commercial sex workers in Kenya, reported that both injectable and oral contraceptives were associated with HIV risk [10]. However, other prospective studies did not find statistically significant increased risks of HIV associated with hormonal contraceptives [11–15]. The results from cross-sectional studies are also contradictory; several failed to show an association between hormonal contraceptive use and HIV prevalence [16–18], while others reported an increased risk [19,20]. Hormonal contraceptives, especially those containing progestins, cause thinning of the vaginal and cervical mucosa, possibly increasing the likelihood of trauma and increasing the density of HIV target cells [21,22]. Hormonal contraceptives are also associated with cervical ectopy, which is thought to be a risk factor for HIV and other sexually transmitted infections (STD) [23]. In HIV-infected women, hormonal contraceptive use is associated with increased shedding of HIV into the genital tract, suggesting that hormonal contraceptive users maybe more infectious [24,25]. An association between hormonal contraceptives and increased HIV acquisition or transmission is of public health concern, particularly given the need for HIV-infected women to prevent unwanted pregnancy in order to avoid transmission of HIV to their infants [26]. The purpose of this study was to examine the association between hormonal contraception and HIV acquisition in a rural population-based cohort in Rakai District, Uganda.

Methods

This observational study used data from an on-going community-based cohort established in November

1994 for the Rakai STD Control for AIDS Prevention Trial [27]. Rakai is a rural district in southwestern Uganda. This analysis utilizes data from six surveys conducted between November, 1994 and December, 1999. All consenting adults aged 15–59 years, resident in 56 communities on secondary roads were enrolled and followed-up at intervals of 10 months. At each survey, participants were interviewed in their homes and asked to provide biological samples for HIV and STD diagnoses. HIV status was determined by two different enzyme immunoassays (EIA) (Vironostika HIV-1, Organon Teknika, Charlotte, North Carolina, and Cambridge Biotech, Worcester, Massachusetts, USA) with Western blot confirmation of discordant EIA tests and seroconverters (HIV-1 Western Blot, Bio-Merieux-Vitek, St Louis, Missouri, USA).

At each survey visit, respondents who reported ever being sexually active were asked whether, at the time of the visit, they or their partners were currently using any of the following family planning methods: pills, injections (mainly Depo-Provera), spermicides, condoms, or an intrauterine device. Information was obtained on sexual abstinence, use of natural family planning (mainly periodic abstinence or calendar method), and lactational amenorrhea. In addition, information was gathered on sociodemographic characteristics (age, marital status, education, occupation and religion), and sexual behaviors (number of sexual partners in the preceding year, condom use in the 6 months prior to the interview and whether this condom use was consistent or inconsistent.) Study subjects were asked whether they had experienced symptoms suggestive of an STD including genital ulcer, discharge or dysuria, during the preceding intersurvey period. Free condoms were made available by the Project and other methods of contraception were available via government clinics, from private pharmacies and drug shops, and from non-governmental organizations. The Project also provided health education on HIV prevention, STD recognition and prevention, and family planning. Confidential voluntary HIV counseling and testing were provided free of charge by 20 community counselors in the client's home or other selected venues.

This analysis was restricted to sexually active, initially HIV-negative women aged 15–49 years, who were followed up at two or more study visits in order to ascertain HIV seroconversion. There were 8092 sexually active women of whom 7283 (90.0%) provided blood for HIV testing, and 6053 (83.1%) were initially HIV negative. Of the 6053 HIV-negative women, one or more follow-up blood sample to detect seroconversion was available for 5117 (84.5%). The exposures of interest were use of hormonal contraceptives (pills and injections) during each 10-months follow-up interval, ascertained by self-report at the interview following each interval of observation. Condom users were

treated as a separate exposure group. If a respondent reported a different contraceptive method at a subsequent visit, she was assumed to have changed methods at mid-interval and ascribed 5 months of exposure during the interval. For this analysis, the reference group was defined as women who reported neither use of hormonal contraceptives nor use of condoms. The person-years of exposure were determined from the intervals during which respondents either used or did not use hormonal contraceptives or condoms. A study subject who seroconverted was assigned an exposure of the last method reported during the interval at which seroconversion was detected. HIV incidence per 100 person-years were estimated for each contraceptive exposure group, using the person time of use or non-use as the denominator.

Statistical analysis

Statistical analysis used STATA software package version 7.0 (Stata Corporation, College Station, Texas, USA). Differences in exposed and non-exposed groups were analyzed using Mantel–Haenszel chi-square method for univariate and bivariate stratification. Poisson multivariate regression was used to estimate adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI) of HIV seroconversion associated with hormonal contraceptive use, relative to non-users of hormonal contraception or condoms, after adjustment for covariates. Potential confounders included in the models were age, marital status, education, reported number of sexual partners in the preceding 12 months, and reported genital ulcer disease in the intersurvey period. The number of sex partners and genital ulcer disease were considered as time-dependent covariates that could change from one survey interval to another, while age, marital status, and education level were assumed as fixed covariates at baseline. Reported condom use in the 6 months prior to a follow-up visit was used in the analysis as a time-dependent measure of condom use for STD/HIV prevention. To assess which covariates might affect the IRR values associated with hormonal contraception, models were constructed with individual variables and stepwise regression models. Since each individual woman could provide more than one observation in these analyses, the Huber–White sandwich estimator of variance was used to adjust for the clustering at individual level in the estimation of the 95% CI in all the models [28].

Results

Over the duration of the study, 5117 HIV-negative eligible women (3714 recruited in 1994–1995 and the remainder in subsequent survey visits), provided 13 654 person years of observation. The median duration of follow-up was 2.6 years (mean \pm SD, 2.8 \pm

1.4). The median age was 25.0 years (mean, 27.8 \pm 9.0). Table 1 shows the characteristics of the study population and use of hormonal contraception. Exclusive use of oral contraception was reported by 325 women (6.3%), and exclusive use of injectable contraception was reported by 539 women (10.5%), with 96 women (1.9%) reporting use of both hormonal methods at different times during observation. Therefore, a total of 960 women (18.8%) used some hormonal contraception during observation, of whom 8.3% used oral contraception and 12.4% used injectable contraception at some time during observation.

Hormonal contraceptive use was highest in the 20–24 and 25–34 age groups (19.9% and 23.5%, respectively) and was lowest in adolescents and older women (approximately 10% each). Married women were more likely to report current use of hormonal contraceptives (19.1%) than the divorced, separated, widowed (7.5%) or the never-married women (11.5%) ($P < 0.001$). The proportion of women using hormonal contraceptives increased with higher levels of education ($P < 0.001$), and those reporting multiple sex partners were more likely to use hormonal contraception (21.6%) than women with one partner (16.3%) ($P < 0.05$). Hormonal contraception was more frequently reported by women who reported using condoms during at least one study visit (22.8%) compared with women who reported no condom use (14.7%) ($P < 0.001$). There was no statistically significant difference in hormonal contraceptive use among women who did or did not report genital ulcer disease.

There were 202 HIV incident cases, of whom 159 (78.7%) were not using any hormonal contraception or condoms at time of seroconversion, 12 (5.9%) were using the pill, 16 (7.9%) injectable contraception and 15 (7.4%) used condoms. Table 2 shows HIV incidence rates and unadjusted IRR values for hormonal contraceptive users relative to non-users of hormonal contraceptives or condoms. The overall HIV incidence was 1.5/100 person-years (95% CI, 1.3–1.70). HIV incidence in non-hormonal contraceptive users was 1.5/100 person-years, while incidence in hormonal contraceptive users was 2.3/100 person-years (unadjusted IRR, 1.56; 95% CI, 1.00–2.33). HIV incidence was higher in the younger age groups; in women who were divorced/separated or widowed; and in those reporting multiple sex partners, condom use or genital ulcer disease. The IRR values for hormonal contraceptive users relative to non-users were elevated for those under age 24 years, but this was not statistically significant and was not observed among older women. The HIV IRR values associated with hormonal contraceptive use were also elevated, but not significantly, in all the women assessed, in the group of women who reported one or more sex partners, and among condom users. The IRR of HIV seroconversion associated with

Table 1. Prevalence of hormonal contraceptive use in the study population stratified by age, marital status, education, number of sex partners, condom use and genital ulcer disease.

Characteristic	Total (proportion)	Period prevalence of hormonal contraceptive use (%) ^a	<i>P</i> value ^b
All women	5117	18.8	
Age (years)			
15–19	1073 (0.21)	10.2	< 0.001
20–24	1256 (0.25)	19.9	
25–34	1480 (0.29)	23.5	
35–49	1308 (0.26)	10.8	
Marital status			
Never married	911 (0.18)	11.5	< 0.001
Currently married	3687 (0.72)	19.1	
Divorced/separated/widowed	517 (0.10)	7.5	
Education			
None	649 (0.13)	6.9	< 0.01
Primary	3418 (0.67)	14.8	
Secondary	922 (0.18)	27.4	
Tertiary	120 (0.02)	33.3	
Sex partners ^c			
1	4858 (0.95)	16.3	0.02
2+	259 (0.05)	21.6	
Reported ever use of condoms during the study period ^d			
Yes	1161 (0.23)	22.8	< 0.001
No	3956 (0.77)	14.7	
Genital ulcer disease ^e			
Yes	792 (0.15)	18.2	0.20
No	4325 (0.85)	16.3	

^aEver used hormonal contraceptives during observation period (1994–1998) as a percentage of total study population.

^bFor age, marital status: *P* value for a test of independence among the categories; for sex partners, condom use and genital ulcer disease: *P* value tests that prevalence of hormonal contraceptive use is the same in the two categories; for education: *P* value is for a chi-square trend test of hormonal contraceptive use with increasing education.

^cEver reported two or more sex partners in the 12 months prior to any survey period.

^dEver reported condom use in the 6 months prior to a survey visit.

^eReported genital ulcer disease episode in the intersurvey period.

hormonal contraceptive use were increased in respondents who reported genital ulcer disease in the preceding 12 months.

Use of oral contraceptive pills was associated with an HIV IRR of 1.70 (95% CI, 0.85–3.04) while use of injectable contraception was associated with an IRR of 1.47 (95% CI, 0.82–2.45).

The Poisson multivariate regression adjusted IRR for any hormonal contraceptive use was 0.94 (95% CI, 0.53–1.64), and the adjusted IRR for oral contraceptive use and injectable contraception were 1.12 and 0.84, respectively (Table 3). None of these estimates was statistically significant. Age, education and condom use were not significantly associated with incident HIV after adjustment. However, HIV risks were significantly increased in women who reported marital disruption (IRR, 2.17; 95% CI, 1.06–4.43), multiple sex partners (IRR, 3.11; 95% CI, 1.50–6.43) and genital ulcer disease (IRR, 3.00; 95% CI, 1.94–4.65). The IRR was reduced from a crude estimate of 1.56 to 0.94 after adjustment (Tables 2 and 3), suggesting substantial confounding. Therefore, separate models including

each of these potential confounding variables were constructed to assess which covariates were most likely to have confounded the estimates for hormonal contraception. The IRR for hormonal contraception was reduced to 1.35 (95% CI, 0.86–2.11) in a model that included only marital status, to 0.95 (95% CI, 0.56–1.62) in a model with number of sex partners, and to 1.05 (94% CI, 0.62–1.79) in a model that only included genital ulcer disease. Using a stepwise regression, the only variables retained were marital disruption (IRR, 2.00; 95% CI, 1.24–3.21), number of sex partners (IRR, 3.16; 95% CI, 1.71–5.85), genital ulcer disease (IRR, 3.19; 95% CI, 2.12–4.81) and age group 35–49 (IRR, 0.67; 95% CI, 0.44–1.00). Assessment of potential interaction between hormonal contraceptive use and any of the other variables did not show any statistically significant results.

Over the duration of the study, 22.8% (1161/5102) of respondents reported using condoms at one or more surveys. Inconsistent condom use was reported by 15.9% of respondents (811/5102), and consistent use was reported by 6.8% (350/5102). Those who reported condom use were more likely to be young (15–24

Table 2. HIV incidence and crude incidence rate ratios in hormonal contraceptive users and non-users.

Characteristic	Hormonal contraceptive use			Non-use of hormonal contraception			Incidence rate ratios ^a
	Seroconversions/number of hormone users	Person-years of hormonal use	Crude incidence rate (per 100 person-years)	Seroconversions/number of non-hormonal users	Person-years of non-hormonal use	Crude incidence rate (per 100 person-years)	HIV incidence in hormone users versus non-users (95% CI)
All women	28/850	1222.8	2.3	173/4267	11774.2	1.5	1.5 (1.01–2.33)
Age (years)							
15–19	3/109	118.3	2.5	33/964	2324.9	1.4	1.79 (0.35–5.70)
20–24	10/251	306.5	3.3	47/1005	2709.6	1.7	1.88 (0.85–3.77)
25–34	12/348	560.3	2.1	58/1132	3391.4	1.8	1.21 (0.59–2.27)
35–49	3/142	237.3	1.3	36/1166	3348.0	1.1	1.18 (0.23–3.72)
Marital status							
Never married	3/105	115.0	2.6	24/809	1646.2	1.5	1.79 (0.34–5.89)
Currently married	22/703	1057.4	2.1	119/2984	8745.1	1.4	1.53 (0.92–2.42)
Divorced/widowed	3/039	48.9	6.1	25/478	1376.8	1.8	3.37 (0.65–11.05)
Education							
None/primary	19/553	783.8	2.4	138/3514	9772.0	1.4	1.72 (1.00–2.78)
Secondary/tertiary	9/294	434.1	2.1	36/748	1984.0	1.8	1.14 (0.48–2.41)
Sex partners							
1	24/794	1149.0	2.1	154/4064	11245.1	1.4	1.53 (0.95–2.35)
2+	4/56	73.4	5.4	20/203	528.8	3.8	1.44 (0.36–4.30)
Condom use							
No	17/584	870.9	1.9	118/3372	9621.2	1.2	1.59 (0.90–2.66)
Yes	11/266	351.5	3.1	56/895	2152.7	2.6	1.20 (0.57–2.32)
Genital ulcer disease							
Yes	10/144	225.7	4.4	52/648	1929.1	2.7	1.64 (0.74–3.27)
No	18/706	996.7	1.8	107/3619	9844.8	1.1	1.66 (0.95–2.75)
Method of hormonal contraception							
Pills	12/421	481.5	2.5	173/4267	11774.2	1.5	1.70 (0.85–3.04)
Injections	16/635	740.9	2.2	173/4267	11774.2	1.5	1.47 (0.82–2.45)

^aThe reference groups are women who use neither hormonal contraceptives nor condoms for contraception but may report occasional condom use for HIV/sexually transmitted disease prevention.

Table 3. Results of Poisson regression analysis showing the adjusted HIV incidence rate ratios.

Variable	Adjusted incidence rate ratio (95% CI) ^a
Age (years)	
15–19 (ref.)	1.00 (–)
20–24	1.13 (0.69–1.85)
25–34	1.04 (0.64–1.70)
35–49	0.67 (0.38–1.17)
Marital status	
Never married (ref.)	1.00 (–)
Married	1.08 (0.62–1.88)
Separated/divorced/widowed	2.17 (1.06–4.43)*
Education	
None/primary (ref.)	1.00 (–)
Secondary/tertiary	0.94 (0.61–1.47)
Sex partners in past year	
1 (ref.)	1.00 (–)
2+	3.11 (1.50–6.43)*
Condom use in past 6 months ^b	
No condom use (ref.)	1.00 (–)
Used condoms	1.21 (0.67–2.17)
Genital ulcer disease in past 12 months	
None (ref.)	1.00 (–)
Yes	3.00 (1.94–4.65)*
Contraceptive method	
No hormonal contraceptive use and no condom use (ref.)	1.00 (–)
All hormonal contraceptive use aggregated	0.94 (0.53–1.64)
Oral contraceptive pills ^c	1.12 (0.48–2.56)
Injectable contraception ^c	0.84 (0.41–1.72)

CI, confidence interval; ref., reference variable.

^aAdjusted for hormonal contraceptive use, number of sex partners in past year, age group, education level, marital status, genital ulcer disease, condom use in the past 6 months.

^bUsed condoms for either contraception or HIV/sexually transmitted disease prevention.

^cIndividual hormonal contraceptives were fitted in a separate model that did not include all hormone combined into one group but had all the other covariates as listed in the table.

*Statistically significant difference in incidence rate ratio.

years), unmarried, more educated and have two or more sex partners in the past year. There were 657.4 person-years of observation accrued for condom use and 15 seroconversions, giving an incidence rate of 2.3/100 person-years, and an unadjusted IRR of 1.52 (95% CI, 0.83–2.57) relative to respondents who reported neither condom nor hormonal contraception use. There were no seroconversions among the 350 women who reported consistent condom use. The incidence rate for inconsistent condom users was 4.6/100 person-years (15/328.2) giving an IRR of 3.6 (95% CI, 1.97–6.23) compared with the reference group of women who reported neither condom nor hormonal contraception use.

Discussion

This is the first prospective study to examine the association between hormonal contraceptives and HIV acquisition in a general population; no significant

association was observed between hormonal contraceptive use and the risk of HIV acquisition in either unadjusted or adjusted analyses (Tables 2 and 3). It is noteworthy that the unadjusted IRR was 1.56, and that this was reduced to 0.94 after adjustment (39.7% decrease), suggesting substantial behavioral confounding between hormonal contraception and higher risk behaviors.

No increased risk of HIV was found to be associated with oral contraception (IRR, 1.12; 95% CI, 0.48–2.56). Previous prospective studies that had reported increased risks of HIV among oral contraceptive users were conducted among commercial sex workers [8,10], who have a higher frequency of contraceptive use, high turnover of sexual partners and more frequent contacts with high-risk sexual partners than the general population. However, one prospective study in Kenyan prostitutes found no statistically significant association between use of oral contraceptives and HIV acquisition [29] and a prospective study of family planning attendees in Tanzania reported similar findings [13]. Case-control studies in prostitutes have shown similar results [30]. Although these observational studies have limitations, the majority suggest that oral contraceptives are not associated with an increased risk of HIV acquisition.

Use of injectable contraception was not associated with HIV seroconversion (adjusted IRR, 0.84; 95% CI, 0.41–1.72) in the present study, which is consistent with a prospective study of family planning attendees in Tanzania [13] and a cross-sectional study in Kenya [31]. Two studies that found a statistically significant increase in risk of HIV acquisition associated with use of injectable contraception were conducted among commercial sex workers in Thailand [9] and Kenya [29]. It is likely that these investigations of high-risk women may have been affected by uncontrolled confounding. Our data also suggest confounding between injectable contraception and higher risk behaviors. For example, the unadjusted IRR was 1.47, but after multivariate adjustment the IRR was 0.84 (a 43.2% reduction), suggesting that the model controlled for differential risk behaviors.

We found no overall protective effect against HIV acquisition in women who reported condom use, largely because of the inconsistent nature of condom use. This is supported by other studies, which suggested that only consistent condom use is protective against HIV and STD [32].

This observational study is subject to limitations. The women self-selected to use hormonal contraceptives and these women may have different risk behaviors to those in women who chose not to use hormonal contraceptives. For example, hormonal contraception

was significantly more common in currently married women, and in women reporting multiple partners (Table 1), and hormonal contraceptive users reported higher rates of genital ulcer disease. The regressions that included only hormonal contraception and each potentially confounding covariate, as well as the stepwise regression, suggest that marital status, multiple sex partners and genital ulcer disease are associated with HIV risk (with IRR values greater than twofold), and confounded the estimates for hormonal contraception. The multivariate adjustment in the Poisson models (Table 3) appears to have compensated for such differentials and resulted in non-significant estimates of risk associated with hormonal contraception. Ascertainment of hormonal contraceptive exposure was based on self-reported use and could not be verified from medical records. However, our findings with respect to HIV risk were in agreement with a Kenyan study that used clinic records to assess contraceptive exposure [31], which suggests that self-reported exposure ascertainment was unlikely to have resulted in misclassification bias. In addition, no seroconversions were observed among women who reported consistent condom use at each survey visit, which suggests that respondents reliably reported condom practice. Another problem related to exposure assignment is the assumption that there was no carry-over effect of hormonal contraceptives after the cessation of use. The hormonal exposure was assigned by current contraceptive use at the last visit at which respondent was confirmed to be HIV negative. If the effects of hormones persisted for some time after the cessation of use, then our exposure assignment may underestimate the effect of the hormonal contraceptives.

In conclusion, our data and those of other investigations suggest that hormonal contraceptive use is not associated with increased HIV acquisition, and that these methods of family planning can be promoted as effective contraception even in areas with high HIV prevalence. In Rakai, the prevalence of hormonal contraceptive use, particularly injectables, has increased over time [33]. Family planning providers should be trained to provide HIV/AIDS counseling to clients and should consider promotion of both hormonal methods in conjunction with condoms. Also, HIV counselors should be encouraged to provide family planning services or referral.

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Appendix

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