Hormonal contraception and risk of cervical infections among HIV-1-seropositive Kenyan women

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**Objective:** To evaluate the relationship between hormonal contraceptive use and the acquisition of cervical sexually transmitted infections (STI) among HIV-1-infected women.

**Design:** A prospective cohort study of 242 commercial sex workers in Mombasa, Kenya, followed from the time of HIV-1 infection.

**Methods:** At monthly follow-up visits, sexual behavior and contraceptive use were recorded, and laboratory screening for STI was performed. Multivariate Andersen–Gill proportional hazards models were constructed to examine the association between the use of hormonal contraception and the occurrence of cervical STI.

**Results:** The median duration of follow-up after HIV-1 acquisition was 35 months, and 799 person-years of follow-up were accrued. After adjustment for demographic factors and sexual behavior, women using the injectable contraceptive depot medroxyprogesterone acetate were at increased risk of *Chlamydia trachomatis* infection [hazard ratio (HR) 3.1, 95% confidence interval (CI) 1.0–9.4, \( P = 0.05 \)] and cervicitis (HR 1.6, 95% CI 1.0–2.3, \( P = 0.03 \)) compared with women using no contraception. The use of oral contraceptive pills was associated with an increased risk of cervicitis (HR 2.3, 95% CI 1.4–3.8, \( P = 0.001 \)). Hormonal contraception was not associated with an increased risk of infection with *Neisseria gonorrhoeae*.

**Conclusion:** The use of hormonal contraception by HIV-1-infected women was associated with an increased risk of cervicitis and cervical chlamydia infection. HIV-1-seropositive women using hormonal contraception should be counseled about the importance of consistent condom use to prevent both STI and HIV-1 transmission.

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**Keywords:** cervicitis, chlamydia, HIV-1, hormonal contraception, sexually transmitted infections

**Introduction**

Genital tract infections of the cervix caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae* account for half of the curable sexually transmitted infections (STI) worldwide [1], and are a cause of significant morbidity among women of reproductive age living in developing countries [2]. There is substantial overlap between areas with a high prevalence of STI and HIV-1, especially in sub-Saharan Africa, and studies have

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suggested important synergy between the global STI and HIV-1 epidemics [3]. The identification of modifiable risk factors for STI acquisition may suggest interventions to reduce morbidity and mortality, especially from HIV-1.

The use of hormonal contraception by HIV-1-seronegative women has been associated with an increased risk of the acquisition of cervical STI, including chlamydial infection, gonorrhea, and non-specific cervicitis [4–6]. It is unknown whether hormonal contraception also increases the risk of STI for HIV-1-seropositive women. If such an effect exists, it could have important public health implications, especially in populations in which HIV-1 and STI are common, because cervical STI increase genital tract shedding of HIV-1, probably indicating enhanced infectivity [7,8].

In 1993, we established an open cohort study of HIV-1-seronegative female sex workers in Mombasa, Kenya [9]. One of the principal aims of the study has been to examine the role of hormonal contraception in HIV-1 and STI transmission. Here, we examine the relationship between hormonal contraception and cervical STI among women who seroconverted to HIV-1 during follow-up.

Methods

Population and procedures

The study procedures have been detailed previously [4,9]. Briefly, female sex workers attending a municipal STI clinic were offered confidential HIV-1 testing, and if seronegative, enrollment in the cohort. At monthly visits, standardized questionnaires were administered, addressing recent sexual behavior and contraceptive practices, and serological testing for HIV-1 and pelvic examination for STI screening were performed. Women who seroconverted to HIV-1 were invited to continue their regular monthly clinic visits as part of a study of HIV-1 natural history [10]. At all visits, individualized risk-reduction counseling, the provision of condoms, and general outpatient medical care were provided, including treatment of STI, malaria, and other common ailments. Antiretroviral therapy was not used by any study participants. Prophylactic antimicrobial therapy for opportunistic infections was provided to HIV-1-seropositive individuals, including isoniazid for those without evidence of active pulmonary tuberculosis and cotrimoxazole for those with CD4 cell counts of less than 200 cells/μL. Participants who developed active tuberculosis received free medications through an adjacent public tuberculosis clinic. The study was approved by the institutional review boards of the University of Washington and the University of Nairobi, and all participants provided informed consent.

Laboratory methods

HIV-1 infection was diagnosed using enzyme-linked immunosorbent assay (ELISA; Detect-HIV; Biochem ImmunoSystem, Montreal, Canada). Positive samples underwent confirmatory testing with a second ELISA (Recombigen; Cambridge Biotech, Worcester, MA, USA). Endocervical secretions were cultured on modified Thayer–Martin media for the detection of *N. gonorrhoeae* and were tested for *C. trachomatis* antigen by ELISA (Microtrak; Syva, San Jose, CA, USA). Cervicitis was defined by a mean of more than 30 polymorphonuclear cells in three oil-immersion fields of Gram-stained cervical secretions.

Data analysis

Statistical analysis was performed using SPSS version 10.0 (SPSS, Chicago, IL, USA) and SPLUS 2000 (MathSoft, Seattle, WA, USA). Women who seroconverted to HIV-1 during follow-up were included in this analysis. HIV-1 infection was estimated to have occurred at the midpoint between the last HIV-1-seronegative visit and the first HIV-1-seropositive visit. Data were collected between February 1993 and January 2003; however, testing for chlamydia infection was discontinued in 1999 because of the low incidence in the cohort and thus data for this outcome were from the period February 1993 to April 1999.

Women using the injectable hormonal contraceptive depot medroxyprogesterone acetate (DMPA) or oral contraceptive pills were compared with women reporting no contraceptive method or who had undergone tubal ligation. Visits at which other contraceptive methods were reported were excluded because of small numbers. As many women in the cohort used condoms for STI protection, often in addition to a hormonal method for contraception, condom use was analysed as a separate covariate.

For women who changed their contraceptive method during follow-up, we estimated that the effect of hormonal contraception would persist for 70 days after discontinuation, as we have done previously [4,9]. STI were assumed to have been acquired at the midpoint between clinic visits. As visits occurred monthly, the time from STI acquisition to detection was estimated at 15 days. The total interval of effect on STI acquisition after the discontinuation of hormonal contraceptive use was thus set at 85 days.

Andersen–Gill proportional hazards models were used to assess the effect of hormonal contraception on the acquisition of cervical infections after HIV-1 infection. Multivariate models were adjusted for the following potential confounders: age, years of education, years of...
prostitution, parity, workplace, number of sexual partners per week, and condom use. Age, duration of prostitution, and sexual behavior were analysed as time-dependent variables. Sexual behavior variables were calculated using the mean of reported behavior for each 6-month block of HIV-1 seropositive follow-up time, in order to capture average behavior. Continuous variables were dichotomized at the median.

**Results**

**Study population**

Between February 1993 and January 2003, 1498 HIV-1-seronegative women were enrolled in the cohort, of whom 248 seroconverted to HIV-1 during follow-up (seroincidence of 8.5 per 100 person-years). Six women used a contraceptive method other than DMPA, oral contraceptive pills, or tubal ligation throughout their seropositive follow-up and were excluded from this analysis. The remaining 242 women accumulated 3176 visits after HIV-1 infection, for a total of 799 person-years of follow-up. The median duration of follow-up after HIV-1 infection was 35 months [interquartile range (IQR) 11–62 months], the median number of follow-up visits was eight (IQR 7–9), and the median interval between visits was 40 days (IQR 28–81). Demographic and behavioral characteristics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR) or N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29 (25–34)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8 (7–9)</td>
</tr>
<tr>
<td>Duration of prostitution (years)</td>
<td>4 (2–6)</td>
</tr>
<tr>
<td>Place of work</td>
<td></td>
</tr>
<tr>
<td>Bar</td>
<td>198 (82%)</td>
</tr>
<tr>
<td>Nightclub</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (8%)</td>
</tr>
<tr>
<td>Number of sex partners per week</td>
<td>1 (0–1)</td>
</tr>
<tr>
<td>Condom use (% sex acts)</td>
<td>100 (0–100)</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Contraceptive method</td>
<td></td>
</tr>
<tr>
<td>None/tubal ligation</td>
<td>124 (51%)</td>
</tr>
<tr>
<td>DMPA</td>
<td>79 (33%)</td>
</tr>
<tr>
<td>Oral contraceptive pills</td>
<td>37 (15%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cervical ectopy present</td>
<td>57 (24%)</td>
</tr>
</tbody>
</table>

DMPA, depot medroxyprogesterone acetate; IQR, interquartile range.

Table 1. Population characteristics at the time of HIV-1 seroconversion (N=242).

At the time of HIV-1 seroconversion, there were no statistically significant differences between the women who reported no contraceptive method or who had undergone tubal ligation compared with those who used DMPA or oral contraceptive pills with regard to age, education, duration of prostitution, parity, workplace, number of sex partners per week, or condom use (data not shown). At some point during follow-up after HIV-1 acquisition, 104 women (43%) used DMPA and 54 (22%) used oral contraceptive pills.

**Hormonal contraception and cervical incidence of sexually transmitted infections**

During follow-up, there were 26 cases of infection with *C. trachomatis* (incidence 7.7 cases/100 person-years), 119 cases of infection with *N. gonorrhoeae* (14.9 cases/100 person-years), and 193 cases of cervicitis (24.2 cases/100 person-years). Compared with women who used no contraceptive method, those using DMPA had a significantly increased incidence of cervical chlamydial infection and cervicitis, and those using oral contraceptive pills had a significantly increased incidence of cervicitis (Table 2). Neither DMPA nor oral contraceptive pill use was associated with cervical infection with *N. gonorrhoeae*. Univariate associations between demographic and behavioral factors and cervical STI are also presented in Table 2.

Multivariate models were used to assess the relationship between hormonal contraceptive use and cervical STI incidence, in order to adjust for potential confounding by demographic characteristics or sexual behavior during follow-up (Table 3). In multivariate analysis, DMPA was significantly associated with an approximately threefold increased risk of chlamydia infection and a 1.6-fold increased risk of cervicitis. Oral contraceptive pills were significantly associated with a more than twofold increased risk of cervicitis and were also associated with a more than twofold increased risk of chlamydia infection, although this did not achieve statistical significance. Multivariate analysis demonstrated no significant association between either DMPA or oral contraceptive pill use and cervical gonorrhea.

In these multivariate models, several covariates retained associations with cervical infections. Chlamydial infection was less common among women reporting 100% condom use [hazard ratio (HR) 0.4, 95% confidence interval (CI) 0.1–1.1, *P* = 0.08]. Gonorrhea was more frequent among women who had had more than two pregnancies (HR 1.7, 95% CI 1.0–3.0, *P* = 0.04) and was less frequent among those with more than 4 years of commercial sex work (HR 0.5, 95% CI 0.3–1.0, *P* = 0.04). Cervicitis was more common among women with 8 years of education or less (HR 1.5, 95% CI 1.0–2.3, *P* = 0.06) and with more than one sex partner per week (HR 1.6, 95% CI 0.9–2.7, *P* = 0.09), and was less common among those with...
more than 4 years of sex work (HR 0.6, 95% CI 0.4–0.9, \( P = 0.006 \)).

Earlier studies have argued that cervical ectopy, which has been associated with hormonal contraceptive use, may increase the rate of detection of *C. trachomatis*. Therefore, the presence of cervical ectopy may bias studies of hormonal contraceptive use and chlamydia infection [5,11]. To account for this, we further adjusted the multivariate models in Table 2 for the presence of cervical ectopy as a time-dependent variable. There was essentially no change in the relationship between hormonal contraception and chlamydia (for DMPA, HR 3.0, 95% CI 1.0–9.6 and for oral contraceptive pills, HR 2.3, 95% CI 0.7–7.2).

To exclude any effect of changing contraceptive method during HIV-1-seropositive follow-up, additional multivariate models were created, right-censoring at the point at which women switched their contraceptive method from that reported at the time of HIV-1 seroconversion. For these analyses, three women who were using other methods of contraception at seroconversion and one woman who had used both DMPA and oral contraceptive pills during the 85 days before HIV-1 seroconversion were excluded. The risk

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### Table 2. Univariate associations between incident cervical sexually transmitted infections and contraceptive method, demographic characteristics, and sexual behavior

<table>
<thead>
<tr>
<th></th>
<th>Chlamydia trachomatis</th>
<th>Neisseria gonorrhoeae</th>
<th>Cervicitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>DMPAb</td>
<td>3.1 (1.2–8.4)</td>
<td>0.02</td>
<td>1.2 (0.7–1.9)</td>
</tr>
<tr>
<td>Oral contraceptive pillsb</td>
<td>1.7 (0.4–7.3)</td>
<td>0.5</td>
<td>0.6 (0.3–1.5)</td>
</tr>
<tr>
<td>Age &gt; 29 years</td>
<td>0.4 (0.2–1.1)</td>
<td>0.09</td>
<td>0.7 (0.4–1.1)</td>
</tr>
<tr>
<td>Education &gt; 8 years</td>
<td>1.2 (0.4–4.0)</td>
<td>0.8</td>
<td>1.4 (0.8–2.2)</td>
</tr>
<tr>
<td>Sex work &gt; 4 years</td>
<td>0.7 (0.2–2.5)</td>
<td>0.6</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>Parity &gt; 2</td>
<td>0.8 (0.3–2.3)</td>
<td>0.7</td>
<td>1.4 (0.8–2.2)</td>
</tr>
<tr>
<td>Bar/other versus nightclub N/A</td>
<td>1.3 (0.6–2.5)</td>
<td>0.5</td>
<td>1.0 (0.4–2.4)</td>
</tr>
<tr>
<td>Sex partners &gt; 1/week</td>
<td>1.1 (0.3–3.8)</td>
<td>0.9</td>
<td>2.0 (1.1–3.9)</td>
</tr>
<tr>
<td>100% condom use</td>
<td>0.5 (0.2–1.3)</td>
<td>0.2</td>
<td>0.7 (0.4–1.1)</td>
</tr>
</tbody>
</table>

CI, Confidence interval; DMPA, depot medroxyprogesterone acetate; HR, hazard ratio.

bWomen who used DMPA or oral contraceptive pills were compared with those using no contraception or who had had a tubal ligation.

cAll cases of *C. trachomatis* occurred among women who worked in bars and thus this coefficient could not be calculated.

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### Table 3. Incidence of cervical sexually transmitted infections and multivariate associations by contraceptive method

<table>
<thead>
<tr>
<th></th>
<th>No contraceptive method or tubal ligation</th>
<th>DMPA</th>
<th>Oral contraceptive pills</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence (no. cases)</td>
<td>Incidence (no. cases)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatisb,c</td>
<td>4.1 (8)</td>
<td>14.4 (13)</td>
<td>3.1 (1.0–9.4)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>14.2 (65)</td>
<td>17.7 (44)</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>Cervicitisd,e</td>
<td>16.6 (76)</td>
<td>29.8 (74)</td>
<td>1.6 (1.0–2.3)</td>
</tr>
</tbody>
</table>

CI, Confidence interval; DMPA, depot medroxyprogesterone acetate; HR, hazard ratio.

bTesting for *C. trachomatis* was discontinued in April 1999. A total of 339 person-years of follow-up were accumulated, contributed by 182 women.

cBecause all cases of *C. trachomatis* infection occurred among women who worked in bars, multivariate models for this outcome did not include workplace as a covariate. Stratified multivariate analyses limited to women who worked in bars demonstrated generally similar results to those for the entire study population: DMPA HR 3.0, 95% CI 1.0–9.1 and oral contraceptive pills HR 2.1, 95% CI 0.7–6.3.

dOne case of gonorrhea and one case of cervicitis were exposed to both DMPA and oral contraceptive pills.

eThirty-two cases of cervicitis also had a laboratory diagnosis of *N. gonorrhoeae* or *C. trachomatis* infection.
of chlamydia remained elevated for both DMPA (HR 5.1, 95% CI 1.4–19.2) and oral contraceptive pills (HR 2.8, 95% CI 0.6–15.0), as did the risk of cervicitis (for DMPA, HR 1.7, 95% CI 1.1–2.7 and for oral contraceptive pills, HR 2.5, 95% CI 1.3–4.6).

**Discussion**

In this 10-year prospective study of HIV-1-infected Kenyan female sex workers, hormonal contraceptive use was associated with significantly increased risks of cervical chlamydia infection and cervicitis, after controlling for demographic factors and sexual behavior. Hormonal contraception was not associated with cervical gonorrhea.

There is biological and epidemiological support for our results. Animal model studies have suggested that progesterone enhances susceptibility and the persistence of genital chlamydia infections [12]. A meta-analysis of cross-sectional studies of the relationship between oral contraceptive pill use and chlamydia infection found a summary odds ratio of 1.93 (95% CI 1.77–2.11) [11], and three prospective studies have also found an increased risk [4,6,13]. Two studies found an increased risk of infection with *C. trachomatis* among DMPA users [4,14]. We previously reported 1.6 and 1.8-fold increased risks of chlamydia, respectively, among HIV-1-seronegative DMPA and oral contraceptive pill users in this cohort [4]. To our knowledge, this is the first study to examine the question of contraceptive method and STI risk for HIV-1-seropositive women. Although our results did not show a statistically significant association between the use of oral contraceptive pills and chlamydia infection, our risk estimate was in line with results of previous studies, suggesting that small numbers may have limited statistical significance in our study. Our cervicitis results are in agreement with our earlier study among HIV-1-seronegative women that found 1.5 and 1.8-fold increased risks of DMPA and oral contraceptive pills, respectively [4].

We did not observe an increased risk of gonorrhea among users of hormonal contraception. Previous studies have had conflicting results on this issue [4,6,15]. Among HIV-1-seronegative women in this cohort, we found only a marginal increased risk of gonorrhea among oral contraceptive pill users (HR 1.4, *P* = 0.1), with no effect for DMPA users (HR 1.1, *P* = 0.5) [4]. Laboratory studies have suggested that the relationship between hormone effects on the genital tract and infection risk is less profound for *N. gonorrhoeae* compared with *C. trachomatis* [16]. Importantly, the lack of association between hormonal contraceptive use and gonorrhea suggests that our findings for chlamydial infection and cervicitis are not a result of confounding by sexual behavior, because this would be expected to increase the risk of all STI.

Cervical STI, including chlamydia and non-specific cervicitis, increase HIV-1 shedding in cervical secretions, suggesting that women with these infections are at an increased risk of transmitting HIV-1 to sexual partners [8]. Other studies have shown that STI also increase the plasma HIV-1 viral load, which could predict a more rapid course of HIV-1 disease [17]. Our results thus suggest that hormonal contraceptive use, by enhancing STI susceptibility, could place HIV-1-seropositive women at risk of greater infectivity and faster disease progression. Moreover, cervical STI themselves are associated with significant morbidity as etiologies of pelvic inflammatory disease, which may be especially severe among HIV-1-infected women [18].

There are several strengths to our study. First, prospective evaluation and frequent follow-up permitted an accurate measurement of the timing of contraceptive exposure relative to incident STI. Second, multivariate analysis controlled for demographic and behavioral variables, including condom use, thus minimizing confounding. Third, the large sample size and long duration of follow-up provided good statistical power.

One limitation of this study is that the laboratory methods used for the detection of *C. trachomatis* and *N. gonorrhoeae* are relatively insensitive. It is likely that many of the cases of cervicitis detected were caused by one or both of these infections. In particular, the antigen detection system used in this study for the diagnosis of chlamydial infection has been shown to have only modest sensitivity [19,20]. However, it is unlikely that our testing methodology introduced bias, because missed cases of gonorrhea and chlamydia would have occurred equally in women using and not using hormonal contraception. A second limitation is that the high incidence of STI among the sex workers in this study may not reflect the STI risk for women in all populations and may limit the generalizability of our results. However, similarly high rates of cervical STI have been documented among HIV-1-infected populations from a variety of settings [21,22]. Finally, as women in our study were followed from the time of HIV-1 seroconversion, and no participant was infected for more than 10 years, few patients developed severe immunosuppression during follow-up. The interaction between immunosuppression, contraception, and STI acquisition should be explored, as well as the effect of contraception on STI incidence in the context of antiretroviral therapy.

Safe and effective contraceptive methods are essential for women with HIV-1. Our results suggest that HIV-1-seropositive women using hormonal contraception may be at increased risk of cervical infections. This
may translate into increased infectiousness and excess morbidity. HIV-1-seropositive women should be counseled about the importance of consistent condom use to prevent STI acquisition, especially those using hormonal contraception.

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