Complications of use of intrauterine devices among HIV-1-infected women

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Summary

Background A WHO expert group and the International Planned Parenthood Federation recommend against use of intrauterine devices (IUDs) in HIV-1-infected women based on theoretical concerns about pelvic infection and increased blood loss. We investigated whether the risk of complications after IUD insertion is higher in HIV-1-infected women than in non-infected women.

Methods 649 (156 HIV-1 infected 493 non-infected) women in Nairobi, Kenya, who requested and met local eligibility criteria for insertion of an IUD were enrolled. We gathered information on IUD-related complications, including pelvic inflammatory disease, removals due to infection, pain, or bleeding, expulsions, and pregnancies at 1 and 4 months after insertion. Patients' HIV-1 status was masked from physicians.

Findings Complications were identified in 48 of 615 women (11 [7·6%] HIV-1-infected women, 37 [7·9%] non-infected). Incident pelvic inflammatory disease (two [1·4%] HIV-1 infected, one [0·2%] non-infected) and infection-related complications (any tenderness, removal of IUD for infection or pain; ten [6·9%] HIV-1 infected, 27 [5·7%] non-infected) were also rare and similar in the two groups. Complication rates were similar by CD4 (immune) status. Multivariate analyses suggested no association between HIV-1 infection and increased risks for overall complications (odds ratio 0·8 [95% CI 0·4–1·7]) or infection-related complications (1·0 [0·5–2·3]), adjusted for marital status, study site, previous IUD use, ethnic origin, and frequency of sexual intercourse, but a slight increase cannot be ruled out.

Interpretation Our data suggest that IUDs may be a safe contraceptive method for appropriately selected HIV-1-infected women with continuing access to medical services.

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Introduction

12 million women worldwide are infected with HIV-1,[1] and many have a critical need for safe and effective contraception. Studies suggest that 13–40% of children born to HIV-1-infected mothers will be infected; the proportions are generally high in sub-Saharan Africa, where most HIV-1-infected women live.[2] Nevertheless, few data exist on appropriate contraceptive methods for these women. The use of combined oral contraceptives by HIV-1-infected women may result in increased cervical shedding of HIV-1, with possible increased infectiousness to sexual partners.[3,4] However, complications associated with contraceptive use and the effectiveness of contraceptive methods among HIV-1-infected women have not been studied.

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Intrauterine devices (IUDs) are used by about 100 million women worldwide[5] and are a highly effective, safe, inexpensive, and long-lasting contraceptive method for women not infected with HIV-1. A serious potential complication of IUD use is pelvic inflammatory disease; research suggests that the risk of pelvic inflammatory disease among IUD users is significantly increased immediately after insertion and is subsequently low for up to 8 years.[6]

A WHO expert group and the International Planned Parenthood Federation recommend against IUD use by HIV-1-infected women based on theoretical concerns about pelvic infection and increased blood loss.[7,8] No published studies have, however, investigated the risk of complications among this group of women. We therefore investigated whether HIV-1-infected women have an higher risk of short-term complications with IUD use than women not infected with HIV-1.

Methods

The study was approved by the ethical review committee of Kenyatta National Hospital and by the Protection of Human Subjects Committee of Family Health International.

We recruited participants from two public family-planning clinics in Nairobi (Kenyatta National Hospital and Riruta City Clinic). Women who started family planning in 1994–95 were counselled on contraceptive options by clinic staff and were referred to the study if they asked for an IUD to be fitted. In accordance with local eligibility criteria, women were eligible for IUD insertion if they had no evidence of: history of ectopic pregnancy; pregnancy within the previous 42 days; leiomyomata of the uterus; active pelvic inflammatory disease (Hager criteria[9]); malignant disease in the reproductive tract; an abnormality of the vagina, cervix, or endometrial cavity; a known copper allergy; mucopurulent cervicitis; unexplained abnormal vaginal bleeding; or high risk for sexually transmitted diseases. Additional study eligibility criteria included no antibiotic use within 14 days of insertion, an address adequate for contact, willingness to return for follow-up, and acceptance of HIV-1 testing.

Clinic staff referred 1702 women to the study. After consultation with study staff, five women declined IUD insertion and 11 women were assessed but found to be ineligible on medical grounds. Therefore, 1686 women had IUDs inserted and were tested for HIV-1 infection at the baseline visit. All HIV-1-infected women were invited to participate in the 4-month cohort study. For each HIV-1-infected woman selected, we randomly selected about three non-infected women from those recruited at the same clinic (within 1 week). 649 (156 HIV-1 infected and 493 non-infected) women were enrolled into the longitudinal study. The others were scheduled for normal IUD follow-up care.

Upon referral, the study nurse explained to patients in Kiswahili or English all study procedures and the risks and benefits of IUD insertion. Women were counselled about HIV-1 transmission and prevention and were offered condoms. Written informed consent was then obtained from each woman. The nurse provided counselling before HIV-1 testing and asked in a short interview for information on sociodemographic characteristics, sexual behaviour, and contraceptive use. The study physician made physical assessments, and if the participant was eligible, inserted a copper T380A IUD. Blood samples were collected for HIV-1-antibody testing. Participants were scheduled to make a follow-up visit 1 month after insertion and were advised to return earlier if they experienced any discomfort.

Characteristics	% HIV-1-infected (n=156)	% HIV-1-non-infected (n=493)
Sociodemographic factors		
Age 20–30 years	77	67
⩾2 live births	70	71
Education ⩾secondary level	60	61
Marital status (married/monogamous)*	67	85
Ethnic origin*		
Kikuyu	40	59
Luo	28	8
Occupation		
No occupation or housewife	44	50
Domestic/labourer	19	9
STD history		
STD in the previous year	8	4
Partner with possible STD in previous year*	24	15
Sexual/contraceptive behaviour†		
⩾2 sexual partners*	3	1
Frequency of sexual intercourse (<1 time/week)*	29	18
Previous IUD use	31	38
Physical assessment data		
Abnormal vaginal discharge	4	4
Cervical oedema*	8	3
Cervical friability*	25	17
Cervical discharge (after swabbing)*	19	10
IUD insertion difficulties	5	3

STD=sexually transmitted disease. *p<0·05 for HIV-1-infected *vs* non-infected study participants. †In 3 months before baseline interview.

Table 1: **Characteristics of HIV-1-infected and non-infected women at baseline visit**

Study physicians were masked to participants' HIV-1 status throughout the study. At 1 month, participants were given a pelvic examination and received their HIV-1 test results and counselling from study nurses. Participants answered in an interview questions about their health and sexual and contraceptive behaviour. Cervical samples were taken for diagnosis of chlamydia and gonorrhoea and serum samples were collected to measure CD4 lymphocytes. At 4-month and unscheduled visits, similar clinical and data collection procedures were used. Since gonorrhoea and chlamydia testing is not normally done at these sites (and because of study funding), we collected samples only from women with symptoms at 4 months. Study participation was complete at 4 months or earlier if women developed complications or had their IUDs removed. Women diagnosed with pelvic inflammatory disease had their IUDs removed and received antibiotic treatment. Women with cervical infections received antibiotic treatment and remained in the study.

The primary outcome was overall complications associated with IUD use: pelvic inflammatory disease, full or partial IUD expulsion, pregnancy, or IUD removal because of infection, pain, or bleeding. Diagnosis of pelvic inflammatory disease was based on criteria of the US Infectious Disease Society of Obstetrics and Gynaecology[9] by identification of three tenderness criteria (abdominal, cervical motion, and adnexal tenderness) and at least one objective criterion of: laboratory evidence of gonococcal or chlamydial infection; pyrexia (>38°C); leucocytosis (>10 000 white blood cells/mL); or pelvic abscess or inflammatory complex on bimanual investigation.

We used two secondary measures. Infection-related complications was defined as identification of any pelvic-tenderness criterion upon physical assessment or IUD removal for infection or pain. We used this measure because our criteria for pelvic inflammatory disease were strict and may have had low sensitivity. The second variable, IUD complaint, was used to reflect women's reports of an IUD-related disorder since the previous visit.

Serum samples were tested for HIV-1 antibody with a screening ELISA kit (Organon Vironostika HIV-1 Microelisa, Organon Teknika, Durham, NC, USA).[10] We took samples with negative results to be HIV-1-negative. We retested positive samples or those with no results with a confirmatory ELISA based on a different antigen preparation (HIV-I Recombigen, Cambridge Bioscience, Worcester, MA, USA). Women with positive results from both tests were taken to be HIV-1-positive. We did lymphocyte phenotyping at 1 month with the FACScan system (Becton-Dickinson, San Jose, CA, USA).

We tested for *Chlamydia trachomatis* antigen with an EIA (MicroTrak II, Syva, Belgium). The endocervical samples were cultured for *Neisseria gonorrhoeae*. Samples were inoculated directly on to Thayer-Martin medium, and stored at 4°C until used. Plates were kept in jars containing carbon dioxide at room temperature until they were transported to the laboratory where they were incubated in carbon dioxide for 48 h and read as positive or negative.

We used χ^2 and Fisher's exact tests to compare the two groups. Comparisons of complications were limited to the 615 women (144 HIV-1 infected, 471 non-infected) with follow-up data. We used the cumulative incidence ratios or risk ratios to find the relative effects of HIV-1 infection on IUD complications because the observation period was short and outcomes were expected to develop within a fixed duration.[11] Taylor-series CIs for risk ratios were computed on Epi Info, version 6.

We used adjusted odds ratios to estimate the risk ratio in multivariate logistic models. We tested as confounders age, marital status, ethnic origin, parity, site, previous IUD use, IUD difficulties at insertion, frequency of sexual intercourse, and condom use. We included confounders in multivariate models if covariate inclusion changed the variable estimate for HIV-1-infection status by at least 10%.[12] Models were tested for goodness of fit with the Hosmer-Lemeshow statistic.[13]

We computed statistical power with Epi-Center Power, version 1.31 and used SAS, version 6.11 for all other analyses. The type I error rate was set at 0·05, two-tailed, unadjusted for multiple comparison for all analyses.

Results

We enrolled mainly parous, married women, aged 20–30 years, with at least a secondary-school education (table 1). Few participants reported more than one sexual partner or use of condoms in the previous 3 months, or a sexually transmitted disease in the year before the baseline visit. 48 (31%) of 156 HIV-1-infected and 187 (38%) of 493 non-infected women had previously used IUDs.

The 493 non-infected women selected for follow-up were representative of the 1530 non-infected women enrolled at baseline for demographic, behavioural, and

Outcome type	HIV-1 infected (n=144)	Non-infected (n=471)	Crude risk ratio (95% CI)	Adjusted odds ratio (95% CI)
Complications				
Overall	11 (7·6%)	37 (7·9%)	0·97 (0·51–1·86)	0·80 (0·38–1·68)*
Pelvic inflammatory disease	2 (1·4%)	1 (0·2%)		
IUD removals	6 (4·2%)	18 (3·8%)		
IUD expulsions	3 (2·1%)	17 (3·6%)		
Pregnancies	0	1 (0·2%)		
Infection-related complications†	10 (6·9%)	27 (5·7%)	1·21 (0·60–2·44)	1·02 (0·46–2·27)‡
IUD complaints	37 (25·7%)	90 (19·1%)	1·34 (0·96–1·88)	1·41 (0·88–2·25)§

*Adjusted for previous IUD use, study site, marital status, and ethnic origin, p=0·33 (goodness-of-fit test). †Includes women with IUD removals for infection or pain and women with a sign of pelvic, cervical motion, or adnexal tenderness during physical examination. ‡Adjusted for previous IUD use, study site, marital status, ethnic origin, and coital frequency, p=0·06 (goodness-of-fit test). §Adjusted for previous IUD use, study site, marital status, ethnic origin, and coital frequency, p=0·60 (goodness-of-fit test).

Table 2: **Crude risk ratios and adjusted odds ratios for study outcomes in HIV-1-infected and non-infected women**

physical-assessment variables. HIV-1-infected women were more likely to be single or in a polygamous marriage, to be of Luo ethnic origin, to be a domestic worker or labourer, to have had a partner with a possible sexually transmitted disease, to have had more than one sexual partner, and to have had sex less frequently in the previous 3 months than non-infected women. At baseline, HIV-1-infected women were more likely than non-infected women to have cervical abnormalities, including oedema, friability, and cervical discharge (table 1). The two groups had similar proportions of women with complete data at 1 month (79% HIV-1 infected *vs* 82% non-infected) and 4 months (82% HIV-1 infected *vs* 80% non-infected), and similar median follow-up (126 days and 125 days, respectively).

Of the 615 women with follow-up data, we gathered information from 15 in home interviews, of whom three (one HIV-1 infected, two non-infected) reported complications. Rates of short-term complications were low in the two groups. Overall complications were diagnosed in 11 (7·6%) of HIV-1-infected women and in 37 (7·9%) of non-infected women (table 2). HIV-1-infected women had a higher frequency than non-infected women of pelvic inflammatory disease (1·4% *vs* 0·2%), but both rates were low. Likewise, rates of IUD removals for medical reasons and IUD expulsions were low among HIV-1-infected women and similar to those among non-infected women. Multivariate analysis adjusted for previous IUD use, study site, marital status, and ethnic origin confirmed that HIV-1-infected women had no increased risk compared with non-infected women of overall complications or of infection-related complications (adjusted odds ratio 0·80 [95% CI 0·38–1·68] and 1·02 [0·46–2·27], respectively; table 2).

More HIV-1-infected women than non-infected women reported IUD-related complaints (25·7% *vs* 19·1%; 1·41 [95% CI 0·88–2·25]). The most common complaints in the two groups were heavy bleeding or bleeding for longer than normal, abdominal pain, backaches, itching, and yellowish discharge. We compared IUD-related complaints among women before and after they received HIV-1 test results. HIV-1-infected and non-infected women reported more complaints after they received their test results; the proportion of complaints in the two groups remained similar (risk ratio before receiving test results 1·40; risk ratio after, 1·47).

We found no increase in overall complications in HIV-1-infected women by CD4 (immune) status. In severely, moderately, and mildly immunocompromised women, rates were similar for overall complications (9%, 8%, 8%), infection-related complications (0%, 8%, 8%), and IUD complaints (27%, 32%, 23%).

At 1 month, 32 (5·5%) of the 580 women tested had confirmed chlamydial or gonococcal infections. Cervical infections were more common among HIV-1-infected than non-infected women (7·8% *vs* 4·8%, p=0·17) and were significantly associated with overall complications (risk ratio 2·85 [95% CI 1·30–6·27]) and infection-related complications (2·76 [1·15–6·62]).

We also investigated HIV-1-infection status and IUD complications among women confirmed to be free of cervical infections. After control for potential confounding factors, HIV-1-infected and non-infected women were at similar risk for overall complications (adjusted odds ratio 0·89 [95% CI 0·39–2·02]) and infection-related complications (1·14 [0·48–2·68]), HIV-1-infected women free of cervical infections were more likely to report an IUD-related complaint than non-infected women (1·58 [0·96–2·59]).

Discussion

The low rates of overall and infection-related complications among HIV-1-infected women during the 4 months after insertion suggest that IUDs may be appropriate for women in countries with high prevalences of HIV-1.

Although rates of pelvic inflammatory disease were low and not significantly different in the two groups, our study did not have adequate power to detect differences in these rates between the two groups. We cannot rule out, therefore, that pelvic inflammatory disease may be more frequent or more severe among HIV-1-infected women, especially those who are severely immunocompromised. Some hospital studies suggest that HIV-1-infected women are admitted with a more severe clinical presentation (fever, high leucocytosis, tubo-ovarian abscesses) than women without HIV-1 infection.[14–17] Studies of pelvic inflammatory disease and HIV-1 in Nairobi[18,19] have found little difference in clinical presentation of pelvic inflammatory disease among HIV-1-infected and non-infected women, but more tubo-ovarian abscesses and pelvic masses were diagnosed among HIV-1-infected women. However, most studies reported satisfactory resolution of pelvic inflammatory disease with antimicrobial regimens in both groups. Nevertheless, while rates of pelvic inflammatory disease were low in our study and were similar to those reported in previous African studies,[20,21] HIV-1-positive women given IUDs should have continuing access to medical services.

We found similar risk of overall and infection-related complications in the two groups among women without cervical infections. This finding suggests that in developed countries, in which women are commonly free of cervical infections before IUD insertion, HIV-1 infected women who are confirmed to be free of cervical infections are not at increased risk of short-term complications of IUD use.

In our study, HIV-1-infected women reported more IUD-related complaints than non-infected women, for which there are several explanations. First, a woman who knows she is HIV-1 infected might report more health problems. We found, however, no difference in reporting rates with or without knowledge of HIV-1 status. Second, some HIV-1-infected women may have known their infection status before entering the study, but limited availability of HIV-1 screening in Nairobi makes this likelihood small. Third, HIV-1-infected women may have had more health problems and may have attributed them to IUD use, despite no increase in diagnosed complications.

We investigated only complications arising in the 4 months after IUD insertion. The length of follow-up, therefore, may have been too short to differentiate between the experiences of HIV-1-infected and non-infected IUD users. For example, only 9% of HIV-1-infected women were severely immunocompromised (CD4 <200). As more HIV-1-infected women become severely immunocompromised, IUD-associated complications may increase. Nevertheless, because pelvic inflammatory disease and IUD expulsions and removals are common during the first 4 months after insertion,[6] data focusing on this period are important.

In addition to IUD-related complications, other important factors related to the appropriateness of IUD use in countries with high prevalences of HIV-1, include the contraceptive efficacy of IUDs in HIV-1-infected women; the impact of IUD use on progression of HIV-1

disease; the effect of IUD use on HIV-1 acquisition by non-infected women; and the impact of IUD use on HIV-1 transmission from an infected woman to a non-infected sexual partner. Few data exist on the first two factors. We found no decrease in contraceptive efficacy among HIV-1-infected women, but the power of our study to detect such a difference was poor. Cross-sectional studies exploring IUD use and HIV-1 acquisition by women have reported inconsistent results,[22–27] and the only longitudinal study found no association (relative risk 0·8 [95% CI 0·4–1·7]).[28] The only study that investigated the impact of IUD use on female-to-male HIV-1 transmission found no association.[29] Therefore, although more information is needed, current data do not support the prohibition of HIV-1-infected women from using an IUD.[7,8]

Strengths of our study include its prospective nature and its control for confounders. The power to detect a risk ratio of 2·0 (80% for one-tailed and 72% for two-tailed tests) was sufficient for overall complications in HIV-1-infected women compared with non-infected women. The masking of women's HIV-1 status from physicians limited ascertainment bias and the matching of women in the two groups by site and enrolment date limited bias introduced by different IUD insertion conditions and differences in ascertainment of outcomes by site. The high and similar follow-up rates in the two groups suggests limited bias due to differences in follow-up. Limitations of our study include possible selection bias, since we were unable to randomise the women, and non-confirmation of pelvic inflammatory disease by laparoscopy or endometrial biopsy.

Our study did not have sufficient power to detect differences between the two groups for specific IUD-related complications such as pelvic inflammatory disease. As expected, event rates were low among HIV-1-infected and non-infected women. Because the rates were low, we cannot rule out a slight increase in overall or infection-related complications in HIV-1-infected women. Our data suggest, however, that any such increase is unlikely to be large.

Few studies have assessed the safety and efficacy of contraceptive methods for HIV-1-infected women. Our data suggest that the IUD may be a safe contraceptive method for appropriately selected HIV-1-infected women with continuing access to medical services and support continued IUD use in areas with high prevalences of HIV-1.

Contributors

Samuel Sinei helped to design the study, supervised the field site, and edited the manuscript. Charles Morrison helped design the study, coordinated the overall project, including statistical analysis, and drafted and edited the manuscript. Christine Sekadde-Kigondu helped design the study, supervised daily field activities, including all laboratory work, and helped draft and edit the manuscript. Melissa Allen monitored data collection and edited the manuscript. Donald Kokonya supervised clinical activities and edited the manuscript.

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