Population-based study of fertility in women with HIV-1 infection in Uganda

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Summary

Background To assess the effects of HIV-1 and other sexually transmitted infections on pregnancy, we undertook cross-sectional and prospective studies of a rural population in Rakai district, Uganda.

Methods 4813 sexually active women aged 15–49 years were surveyed to find out the prevalence of pregnancy by interview and selective urinary human chorionic gonadotropin tests. The incidence of recognised conception and frequency of pregnancy loss were assessed by follow-up. Samples were taken to test for HIV-1 infection, syphilis, and other sexually transmitted diseases.

Findings At time of survey, 757 (21·4%) of 3544 women without HIV-1 infection or syphilis were pregnant, compared with 46 (14·6%) of 316 HIV-1-negative women with active syphilis, 117 (14·2%) of 823 HIV-1-positive women with no concurrent syphilis, and 11 (8·5%) of 130 women with both syphilis and HIV-1 infection. The multivariate adjusted odds ratio of pregnancy in HIV-1-infected women was 0·45 (95% CI 0·35–0·57); the odds of pregnancy were low both in HIV-1-infected women without symptoms (0·49 [0·39–0·62]) and in women with symptoms of HIV-1-associated disease (0·23 [0·11–0·48]). In women with concurrent HIV-1 infection and syphilis the odds ratio was 0·28 (0·14–0·55). The incidence rate of recognised pregnancy during the prospective follow-up study was lower in HIV-1-positive than in HIV-1-negative women (23·5 *vs* 30·1 per 100 woman-years; adjusted risk ratio 0·73 [0·57–0·93]). Rates of pregnancy loss were higher among HIV-1-infected than uninfected women (18·5 *vs* 12·2%; odds ratio 1·50 [1·01–2·27]). The prevalence of HIV-1 infection was significantly lower in pregnant than in non-pregnant women (13·9 *vs* 21·3%).

Interpretation Pregnancy prevalence is greatly reduced in HIV-1-infected women, owing to lower rates of conception and increased rates of pregnancy loss. HIV-1 surveillance confined to pregnant women underestimates the magnitude of the HIV-1 epidemic in the general population.

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Introduction

The prevalence of HIV-1 infection among women of reproductive age is increasing worldwide.[1–5] In sub-Saharan Africa, serological surveys have shown an earlier age of onset and higher HIV-1 prevalence in women than in men, with peak female prevalence generally observed in the 20–29-year age-group.[4–6] The high rate of HIV-1 infection in women is a major public-health concern because of the direct impact on the women themselves and the risk of vertical transmission to children. Although there have been extensive studies of vertical transmission of HIV-1,[1,2] the effects of infection on pregnancy outcome,[7,8] and the effect of pregnancy on the course of maternal infection,[9–11] there is little information on the fertility of HIV-1-infected women.[12,13] Surveillance of HIV-1 prevalence in pregnant women attending antenatal clinics, or at time of delivery, is commonly used to monitor the course of the epidemic in women of reproductive age.[1,3,5] However, if pregnancy rates are low in HIV-1-infected women, such surveillance could underestimate the magnitude of the epidemic in the general female population.

Between 1989 and 1992, we carried out a cohort study of HIV-1 dynamics in rural Uganda.[6] We noted that birth rates were lower among women positive for HIV-1 than among HIV-1-negative women.[4] We have since collected more detailed data on prevalence of pregnancy and its determinants, as well as prospective data on pregnancy rates and pregnancy loss in women with and without HIV-1 infection.

Methods

We are carrying out a randomised, community-based trial of control of sexually transmitted diseases for AIDS prevention in 56 communities of rural Rakai District, southwestern Uganda. At the baseline survey round, completed between November, 1994, and June, 1995, all consenting adult residents aged 15–59 years were enrolled. This survey provided data on the prevalence of pregnancy. A follow-up survey between August, 1995, and April, 1996, provided prospective data on the incidence of recognised conception and pregnancy loss.

A signed informed consent form was obtained from all participants, and the project was approved by Institutional Review Boards at Johns Hopkins and Columbia Universities, the Office for Protection from Research Risks of the National Institutes of Health, and the AIDS Research Sub-Committee of the Ugandan Council on Research and Technology. All data collection was done within participants' homes to maximise recruitment and compliance, and to reduce self-selection. The women enrolled were representative of the general population of this rural district, in which agriculture and vending/clerical work are the predominant occupations, reported by 73·9% and 10·7% of women, respectively. Only 1·8% of women reported working in bars or other occupations at high risk of HIV-1 infection. 92% of adults present in the communities agreed to participate. Of those enrolled, 99% completed an interview providing information on sociodemographic characteristics, reproductive history, contraceptive and sexual behaviours, and symptoms of current or recent illness. 91% of women enrolled provided blood samples for HIV-1 serology. Women did not know their HIV-1 status at baseline and, in accordance with the policy of the Ugandan Ministry of Health, confidential results and counselling were made

available to women on request. About 20% of women requested and received their HIV-1 results between the baseline and follow-up surveys. Because the treatment regimens to be used in the randomised trial were modified for pregnant women, each woman of reproductive age (15–49 years) was asked detailed questions to ascertain whether she was currently pregnant. If the respondent or the interviewer was unsure about the woman's pregnancy status (no reported menstrual period within the previous month), a urine sample was obtained for measurement of human chorionic gonadotropin (HCG).

We report on prevalence of pregnancy in sexually active women aged 15–49 years who had at least one sexual partner in the previous year and provided a blood sample for HIV-1 serology (n=4813). All households were revisited 9–10 months after the baseline survey. We obtained data on the incidence of recognised conceptions as current or completed pregnancies reported by the women or detected by a single measurement of HCG, and the outcome of pregnancies, for events that occurred during a follow-up interval of about 9 months. Follow-up data were available for 4020 women (83·5% of those seen at the baseline survey).

During home visits, respondents were asked to provide samples for laboratory diagnosis of sexually transmitted diseases. All samples were tested for HIV-1 by two EIAs (Recombigen, Cambridge Biotech, Worcester, MA; and Organon, Organon Teknika, Durham, NC, USA). Samples with conflicting EIA results were subjected to western-blot confirmation (Cambridge Biotech). Serological screening for syphilis used the toluidine red unheated serum test (New Horizons, Columbia, MD, USA), and all positive samples were subjected to a qualitative *Treponema pallidum* haemagglutination test (Sera-Tek, Miles Inc Diagnostics, Elkhart, IN, USA). Women positive in both tests were classified as having active syphilis. Serological results on HIV-1 and syphilis were available for 4813 women. Screening for chancroid used an adsorption EIA for *Haemophilus ducreyi*.[15] This is a labour-intensive, non-commercial research assay and results are available for only 385 women of reproductive age. Urine samples collected from 94% of participants were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* by ligase chain reaction (Abbott Laboratories, Abbott Park, IL, USA). These assays have sensitivity of about 94% and specificity of more than 98%.[16,17] Because of assay cost, the tests were done on a representative, age-stratified, random sample of 1945 participants. Women were also asked to take two vaginal swabs for culture of *Trichomonas vaginalis* by the InPouch TV culture system (Biomed Diagnostics, San Jose, CA, USA) and for diagnosis of bacterial vaginosis by quantitative morphology of a gram-stained slide.[18] Vaginal swabs were provided by 94% of women, trichomonas cultures were available for 4671, and because of laboratory constraints, results for bacterial vaginosis were available for a random sample of 3543 women.

The prevalence of pregnancy associated with HIV-1 infection, syphilis, and other sexually transmitted diseases was assessed with women who had no serological evidence of HIV-1 infection or syphilis as the reference group (controls). The sociodemographic and behavioural covariates potentially associated with pregnancy prevalence included age; marital status (married or in consensual union *vs* single, widowed, and divorced); gravidity; a history suggesting subfertility (defined as an inability to achieve pregnancy during a period of $\geq$2 years); use of contraception, divided into use of modern contraceptive methods (mainly oral contraceptives, injection, or condom use) or sexual abstinence; and current breastfeeding. We asked respondents about the number of sexual partners they had had during the previous year and the time since they had last had intercourse, which is recognised as a proxy measure for frequency of intercourse.[19] We also asked all women about symptoms suggestive of clinical HIV-1 disease including chronic cough, fever, and diarrhoea (lasting more than 1 month), weight loss, herpes zoster, Kaposi's sarcoma, and oral candidosis. HIV-1-infected women with one or more of these symptoms were classified as symptomatic. Although we had information on amenorrhoea, we did not include this feature as a symptom of HIV-1-associated disease because it could be a consequence of pregnancy (the outcome variable of interest), or of cofactors such as breastfeeding. Among non-pregnant, non-lactating women, the prevalence of amenorrhoea was 9·1% in those positive and 8·0% in those negative for HIV-1.

We assessed HIV-1 status and symptomatic illness in male partners of women in stable partnerships who provided information at the baseline survey. Individually linked data were available for 2179 couples, 75·3% of the 2894 women who stated that they were in stable partnerships. These couple-based data allow assessment of the effects of female HIV-1 status, with control for illness in the male partner.

Among the 4020 women with prospective follow-up information, the occurrence of conceptions during follow-up was ascertained by interview and HCG testing. The prospectively determined pregnancy rates per 100 woman-years were calculated for 3257 women who were not pregnant at baseline. These women contributed 2443·7 woman-years of observation. The frequency of pregnancy loss (miscarriages and stillbirths) was ascertained among 1043 women who reported a pregnancy outcome during follow-up.

The main analysis assessed the pregnancy prevalence and the prevalence ratio or risk ratio of pregnancy in HIV-1-infected and HIV-1-uninfected women. We also assessed pregnancy rate in relation to syphilis because of the known deleterious effects of this disease during pregnancy.[20] The reference or control women used for these analyses were those with no evidence of HIV-1 infection or syphilis. Tests of statistical inference used 95% CI of the rate ratio and χ^2 tests. To adjust for differences in characteristics and behaviours between women positive and negative for HIV-1, we used odds ratios estimated by multiple logistic regression,[21] incorporating known or suspected potential confounding variables. These confounders included age (as a continuous variable), marital status, gravidity, subfertility history, contraceptive use, lactation, number of sexual partners, and time since last intercourse, all of which were significantly associated with HIV-1 infection or with pregnancy in bivariate analyses. Goodness-of-fit was assessed by the log-likelihood ratio.[21] Models were also fitted for interaction between HIV-1 infection and syphilis and for symptomatic and asymptomatic HIV-1 infections. We also estimated pregnancy rates per 100 woman-years and rates of pregnancy loss during follow-up per 100 pregnancies among women infected and not infected with HIV-1.

Results

Prevalence study

4813 sexually active women at risk of pregnancy were enrolled at baseline. 931 (19·3%) of these women were pregnant; 83·7% of the pregnancies were reported by the women and 16·3% were detected by urinary HCG testing. 953 women (19·8%) were infected with HIV-1. The prevalence of HIV-1 infection varied with age (7·3% in women aged 15–19, 26·5% in women aged 20–29, 21·7% in women aged 30–39, and 9·7% in women aged 40–49). Active syphilis was detected in 446 (9·3%), and the point prevalence of current cervical or vaginal infections was 1·9% for gonorrhoea, 2·8% for chlamydia, and 25·3% for trichomonas. The prevalence of bacterial vaginosis, defined as gram-stain scores of 7–10, was 52·9%.

The pregnancy rate was significantly higher among women with no serological evidence of HIV-1 infection or syphilis than among HIV-1-negative women with active syphilis or HIV-1-positive women with or without syphilis (table 1). The age-specific pregnancy rates were lower in HIV-1-infected than control women in all age-groups (figure 1). By contrast, among the HIV-1-negative women with active syphilis, the lower proportion pregnant was seen only in the youngest age-group, who are likely to have had recent infections.

Among the 953 HIV-1-infected women, 833 (87·4%) had no symptoms or signs suggesting clinical HIV-1 disease, and 120 had such disorders. The pregnancy rate was significantly higher among the symptom-free

	Number pregnant/ total with diagnosis	Pregnancy rate (%)	Risk ratio of pregnancy (95% CI)*
No HIV-1 or syphilis	757/3544	21·4	1·0
HIV-1-positive women			
All	128/953	13·4	0·63 (0·53–0·75)
No syphilis	117/823	14·2	0·67 (0·58–0·80)
With syphilis	11/130	8·5	0·40 (0·22–0·70)
HIV-1-negative with other STDs			
Syphilis	46/316	14·6	0·68 (0·52–0·90)
Bacterial vaginosis	280/1475	19·0	0·89 (0·79–1·01)
Trichomonas	166/823	20·2	0·94 (0·81–1·10)
Chlamydia	11/47	23	1·10 (0·65–1·84)
Gonorrhoea	4/20	20	0·94 (0·39–2·25)
Chancroid	12/ 51	24	1·10 (0·67–1·81)

*Relative to women with no HIV-1 infection or syphilis.
†Results available for HIV-1 and syphilis in all 4813 women. The following numbers of HIV-1-negative women were tested: trichomonas 3744, bacterial vaginosis 2840, chlamydia 1945, gonorrhoea 1944, chancroid 385.

Table 1: **Pregnancy prevalence rates associated with HIV-1 infection and other sexually transmitted diseases (STDs)**

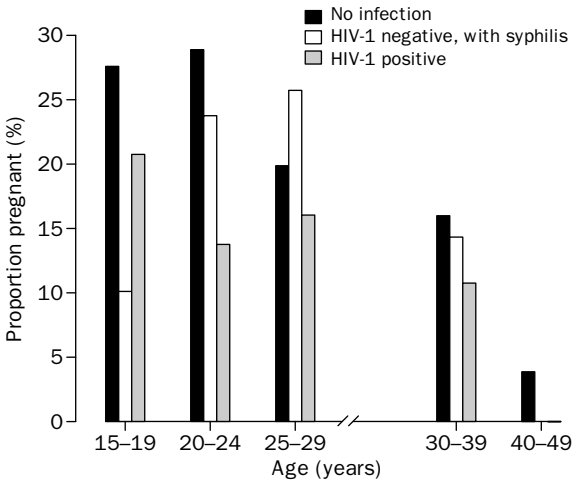

Figure 1: **Age-specific prevalence of pregnancy**

seropositive women than among those with HIV-1-associated clinical signs (119 [14·3%] *vs* nine [7·5%], p=0·05). Among the HIV-1-positive women with symptoms, none of five with herpes zoster, two of 34 who had chronic cough, two of 31 with oral candidosis, and seven of 80 who reported weight loss were pregnant (some of these women had several symptoms).

Data were available on HIV-1 status and symptoms suggesting HIV-1-associated illness for both partners in 2179 couples. The pregnancy rate was significantly lower among 369 couples in which the woman was the HIV-1-infected partner than among 1810 couples in which the woman was HIV-1-negative (53 [14·4%] *vs* 472 [26·1%], p<0·001). We also examined couples with concordant and discordant HIV-1 status. The pregnancy rate was 26·5% (438 of 1653) among concordant HIV-1-negative couples and 21·7% (34 of 157) among couples in which only the man was infected (p=0·22). However, the pregnancy rate was significantly lower among discordant couples with an HIV-1-positive woman and an HIV-1-negative man (20 [16·7%] of 120; p=0·02) and among concordant HIV-1-positive couples (33 [13·3%] of 249; p=0·0002). These findings suggest that the woman's HIV-1 status is the predominant factor affecting pregnancy prevalence, even after control for male HIV-1 status.

The 249 concordant HIV-1-positive couples were examined further to assess whether symptomatic HIV-1 infection in women or their partners was associated with a low pregnancy rate. Among 177 HIV-1-positive couples in which neither partner reported symptoms, 26 (14·7%) women were pregnant, and among 30 couples in which the man had symptoms but the woman did not, five (17%) women were pregnant. By contrast, there were only two (5%) pregnancies among 42 symptomatic HIV-1-infected women. With these concordant positive couples used to control for HIV-1 infection in both partners, the Mantel-Haenszel weighted rate ratio of pregnancy associated with symptomatic AIDS compared with asymptomatic HIV-1-infection reported by the women was 0·31 (95% CI 0·11–0·88; p=0·029), irrespective of male symptom status. We also examined whether the health status of male partners of HIV-1-infected women might affect sexual activity. The proportions of HIV-1-positive men reporting sexual intercourse during the month preceding interview were 91·6% in those with symptoms and 96·2% in those without. These findings suggest that symptomatic HIV-1 infection in male partners does not account for the lower pregnancy rate in HIV-1-infected women.

The rates of pregnancy among HIV-1-negative women with other current sexually transmitted diseases (table 1) were similar to the rate of 21·4% among HIV-1-negative women with no current sexually transmitted infection or serological evidence of syphilis.

Many characteristics or behaviours could affect the probability of pregnancy and potentially confound the observed associations with HIV-1 and syphilis. The pregnancy rate decreased with age (figure 1) and was lower among single than among married women (10·7 *vs* 21·5%). Rates were much lower among women who were currently breastfeeding (6·0%), and those using modern contraceptive methods (3·5%) or periodic sexual abstinence for family planning (6·0%). Pregnancy rates were also lower among women with a history suggesting subfertility than among those without such a history (12·3 *vs* 20·0%). Among women who reported that their last intercourse was more than 1 month before the interview, the proportion pregnant was 11·9% compared with 20·6% among women who reported intercourse within the previous month. However, we observed no significant difference in pregnancy rate associated with multiple sexual partners in the previous year or other characteristics, such as education.

Stratified analyses were done to assess whether the low pregnancy rate associated with HIV-1 infection might result from confounding by cofactors described above. Analyses focused on comparisons between HIV-1-negative women without syphilis and HIV-1-positive women. There were several significant differences between the groups in the proportions with various characteristics (table 2). However, the pregnancy rate was consistently lower in the HIV-1-infected women than in the HIV-1-negative women irrespective of age, marital status, gravidity, no history of subfertility, lack of contraceptive precautions, non-breastfeeding, number of sexual partners during the previous year, and the recency of last intercourse. Other sociodemographic characteristics, such as religion or education, did not affect these differences.

Multiple logistic regression was used to estimate the reduction of pregnancy rate associated with HIV-1 infection and syphilis after adjustment for potential confounding due to age, marital status, gravidity, contraceptive use, lactation, subfertility, and time since last intercourse. With HIV-1-negative women who had no evidence of syphilis as the reference group, the adjusted odds ratio of pregnancy among all HIV-1-positive women

	Number with characteristic		Pregnancy rate (%)		Risk ratio of pregnancy HIV-1-positive/ HIV-1-negative (95% CI)
	No HIV-1 or syphilis	HIV-1 positive	No HIV-1 or syphilis	HIV-1 positive	
All women	3544	953	21·4	13·4	0·63 (0·53–0·75)
Age (years)					
15–19	847 (23·9%)	68 (7·1%)*	27·5	20·6	0·75 (0·46–1·21)
20–24	938 (26·5%)	293 (30·7%)	28·7	13·7	0·48 (0·35–0·65)
25–29	578 (16·3%)	292 (30·6%)	19·9	16·1	0·81 (0·59–1·10)
30–39	775 (21·9%)	249 (26·1%)	16·0	10·8	0·68 (0·46–1·00)
⩾40	406 (11·5%)	51 (5·4%)	3·9	0	. .
Marital status					
Married/in union	2894 (81·7%)	682 (71·6%)*	23·7	14·5	0·61 (0·51–0·74)
Single	650 (18·3%)	271 (28·4%)	11·1	10·7	0·97 (0·64–1·45)
Pregnancy history					
Nulligravid	499 (14·1%)	74 (7·8%)*	31·1	18·9	0·61 (0·37–0·99)
Gravid	3045 (85·9%)	879 (92·2%)	19·8	13·0	0·66 (0·54–0·79)
No subfertility	3268 (92·2%)	817 (85·7%)*	22·0	13·6	0·62 (0·51–0·74)
Subfertility	275 (7·8%)	135 (14·2%)	13·5	12·6	0·94 (0·55–1·60)
Contraception					
None	2821 (79·6%)	717 (75·2%)†	25·5	16·6	0·65 (0·47–0·72)
Modern methods	379 (10·7%)	136 (14·3%)	3·5	3·7	1·07 (0·39–2·95)
Abstinence	203 (5·7%)	64 (6·7%)	5·9	6·3	1·06 (0·35–3·16)
Lactation					
Not breastfeeding	2150 (60·7%)	655 (68·7%)*	31·1	17·6	0·57 (0·47–0·69)
Breastfeeding	1394 (39·3%)	298 (31·3%)	6·4	4·4	0·68 (0·39–1·21)
Sexual partners during previous year					
One	3392 (95·7%)	879 (92·2%)‡	21·5	13·4	0·62 (0·52–0·75)
Two or more	152 (4·3%)	74 (7·8%)	18·4	13·5	0·73 (0·38–1·43)
Last intercourse					
<1 month	3070 (86·6%)	773 (81·1%)*	22·6	14·6	0·65 (0·54–0·78)
⩾1 month	474 (13·4%)	180 (18·9%)	13·5	8·3	0·62 (0·36–1·05)

*p<0·001; †p<0·05; ‡p<0·01.

Table 2: **Distribution of characteristics, pregnancy rate, and rate ratio of pregnancy among women with neither HIV-1 infection nor syphilis and women with HIV-1 infection**

was 0·45 (95% CI 0·35–0·57). The adjusted odds ratio was 0·49 (0·39–0·62) for symptom-free HIV-1-positive women, whereas risk of pregnancy was greatly reduced in symptomatic HIV-1-infected women (0·23 [0·11–0·48]). The odds ratios for pregnancy among women with syphilis were 0·28 (0·14–0·5) for HIV-1-positive and 0·70 (0·49–1·00) for HIV-1-negative women. HIV-1-positive women without syphilis had an odds ratio for pregnancy of 0·48 (0·37–0·61). In the subgroup of HIV-1-negative women aged 15–19 with active syphilis, the adjusted odds ratio for pregnancy was 0·32 (0·23–0·44) compared with control women in the same age-group.

As a consequence of the lower frequency of pregnancy associated with HIV-1 infection, the rate of HIV-1 infection was lower among pregnant than among non-pregnant women (128 [13·8%] of 931 *vs* 825 [21·3%] of 3882; p<0·0001). The difference in HIV-1 prevalence between pregnant and non-pregnant women was greatest among the 20–29-year age-group (figure 2), the age-group with the highest pregnancy rates.

Prospective study

Follow-up data were available for 3340 (86·0%) of the 3882 women who were not pregnant at baseline. The follow-up rate was similar for HIV-1-positive and HIV-1-negative women (85·0 *vs* 86·2%). The 692 HIV-1-positive, initially non-pregnant women contributed 519 woman-years of follow-up; 122 (17·6%) reported a recognised conception during follow-up. The 2382 HIV-1-negative women without active syphilis who were not pregnant at baseline contributed 1787 woman-years of follow-up; 537 (22·5%) reported pregnancies during follow-up. The pregnancy rate during follow-up was significantly lower among HIV-1-positive women than among those without HIV-1 infection or syphilis (23·5 *vs* 30·1 per 100 woman-years; p=0·007). The multivariate adjusted risk of recognised pregnancy associated with HIV-1 infection was 0·73 (95% CI 0·57–0·93) after control for age, contraceptive use, and breastfeeding. The pregnancy rates were similar for women who had been informed of their HIV-1 status and for those who had not requested or received their serological results (23·4 *vs* 23·7 per 100 woman-years).

Prospective data were also available on outcomes of pregnancies ascertained at baseline or during follow-up that were completed during follow-up. Of 130 such pregnancies in HIV-1-infected women, 24 (18·5%) ended in a recognised pregnancy loss, compared with 105 (12·2%) losses among 861 pregnancies in women with neither HIV-1 infection nor syphilis. The age-adjusted odds ratio of pregnancy loss in HIV-1-infected versus uninfected women was 1·50 (1·01–2·27; p=0·048).

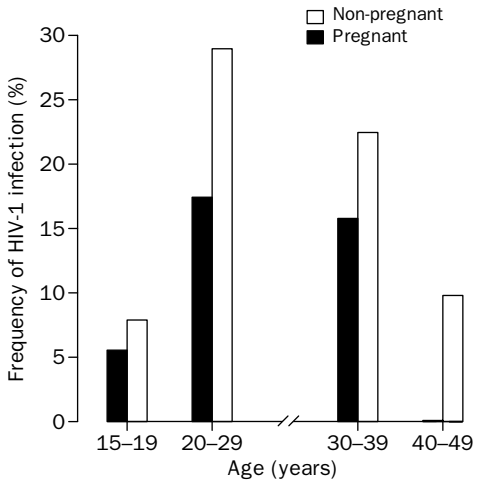

Figure 2: **Age-specific prevalence of HIV-1 infection**

Discussion

Our main finding was a 55% reduction in the adjusted odds of pregnancy among women with HIV-1 infection compared with women who had no evidence of HIV-1 infection or syphilis. The reduction in the odds of pregnancy was greater for women with symptoms of HIV-1-associated clinical disease than for those with asymptomatic HIV-1 infection (77 *vs* 51%). These findings could not be explained by confounding due to differentials in sociodemographic characteristics or behaviours, and these women did not know their HIV-1 status at the baseline survey. No interaction on pregnancy was observed between HIV-1 infection and the presence of other sexually transmitted diseases. Among HIV-1-negative women with syphilis, the pregnancy rate was low in the youngest age-group, but not in older women, which probably reflects the increased risk of pregnancy loss in early syphilis.[20] There was no evidence of an effect of other sexually transmitted infections on pregnancy rate, but we could not ascertain the effects of previous infection on tubal infertility. Follow-up showed lower rates of recognised pregnancies in HIV-1-positive than in HIV-1-negative women, and prospectively determined rates of pregnancy loss were higher in the HIV-1-infected than in the uninfected women. Thus, the lower prevalence of pregnancy among the HIV-1-infected women at the baseline survey probably reflects the combined effects of a lower rate of clinically recognised pregnancy and a higher rate or pregnancy loss.

The high prevalence of HIV-1 infection, particularly among women aged 20–29, is similar to the results of other East African population-based studies.[4–6] Our findings on pregnancy rates are compatible with other smaller African investigations of urban, clinic-based populations.[12,13] In our previous cohort study in Rakai district, we found that age-adjusted annual birth rates were lower among HIV-1-positive than among HIV-1-negative women, and a 6-year cohort study in the adjacent district of Masaka had similar findings.[22]

The lower frequency of pregnancy in HIV-1-positive women has important implications for HIV-1 surveillance programmes. The significantly lower frequency of HIV-1 infection in pregnant than in non-pregnant women was most pronounced in the younger age-groups (figure 2), in which the incidence of HIV-1 infection and fertility rates are likely to be greatest.[6,14] Thus, if HIV-1 surveillance is confined to pregnant women, the prevalence of HIV-1 among women of reproductive age will be seriously underestimated.[1,3,5,23] In addition, time trends in the prevalence of HIV-1 among pregnant women may be difficult to interpret if HIV-1-infected women are less likely to conceive or carry a pregnancy to term.[1,3,23] Reduced pregnancy or birth rates could also affect estimates of the numbers requiring zidovudine treatment in pregnancy and projections of the future burden of childhood AIDS.[1,2] A reduction in births to HIV-1-infected mothers will affect demographic projections of the future numbers of AIDS orphans, as well as projections of the impact of HIV-1 on population growth.[24]

What mechanisms could explain these findings? If women knew their serostatus, those positive for HIV-1 might be motivated to prevent pregnancy to avoid vertical transmission of infection to the infants.[7] However, in our study, participants did not know their HIV-1 results at the time of baseline survey because access to testing and counselling was not available in these rural areas before this project. Intentional prevention of conception or voluntary termination of pregnancy is therefore an unlikely explanation of the low pregnancy rate. Use of contraception or sexual abstinence was infrequent in this population (table 2), and induced abortion is illegal and probably rare in this rural area. Similarly, the differences in pregnancy incidence during follow-up are unlikely to be due to voluntary fertility regulation, since we controlled for contraceptive use and abstinence in these analyses. Only a minority of women requested and received their HIV-1 results between baseline and the follow-up surveys, and knowledge of HIV-1 status did not affect prospectively determined pregnancy rates. Studies in other African settings have found that counselling of HIV-1-positive women does not substantially increase contraceptive use, probably because the great importance placed on childbearing outweighs concerns over transmission from mother to child.[7,12,13]

Low pregnancy rates in women with clinical manifestations of HIV-1 disease are to be expected, since debilitating illness is likely to reduce the frequency of intercourse, results in anovulation and amenorrhoea, and possibly to cause spontaneous abortion. Other studies have shown that HIV-1-positive women with symptoms or signs compatible with AIDS have lower birth rates than symptom-free HIV-1-infected women.[12,25] However, we also observed a low pregnancy rate among symptom-free HIV-1-infected women, so clinical AIDS cannot explain our findings. HIV-1-associated illness in the male partner might affect sexual activity. To avoid bias in sexual exposure, only women who reported sexual activity during the previous year were included in this analysis. More than 80% of HIV-1-infected and uninfected women reported having had sex within the month before interview, which suggests high exposure to the risk of pregnancy. Among these women, there was a pronounced reduction in pregnancy rate in the HIV-1-infected (table 2).

We do not think that concurrent HIV-1 infection or AIDS symptoms in the male partners can explain the observed effects. Among 2179 linked couples, the pregnancy rate was significantly reduced if the woman was HIV-1-positive, but not if she was HIV-1-negative, irrespective of the man's HIV-1 status. Moreover, among concordant HIV-1 infected couples, symptomatic AIDS in the woman, but not in the man, was associated with a very low pregnancy rate. More than 90% of HIV-1 infected men reported coitus within the previous month, irrespective of AIDS symptoms. Abnormal semen variables have been reported in men with clinical AIDS, but not among symptom-free HIV-1-infected men.[26] A direct effect of HIV-1 on semen quality is an unlikely explanation for our findings, since the majority (84·7%) of HIV-1-positive men in this population did not have AIDS.

Another possibility is that the HIV-1-infected women had had sexually transmitted diseases or pelvic inflammatory disease and were more prone to tubal infertility or other sequelae of upper-genital-tract infection. Several studies have shown that the prevalence of sexually transmitted disease is higher and the clinical course of pelvic inflammatory disease more severe in women with HIV-1 infection than in those without.[27,28] Compared with non-infected women, those with HIV-1-infection were more likely to have a history of subfertility. We could not undertake clinical investigations needed to diagnose tubal infertility and we have no reliable measure of previous sexually transmitted or pelvic inflammatory disease.

However, we observed a lowered pregnancy rate in the majority of HIV-1-infected women who did not have a history of subfertility, or who had no laboratory evidence of another sexually transmitted infection. Therefore, although we cannot exclude the possibility of undiagnosed tubal disease in HIV-1-infected women, this seems an unlikely explanation for the majority of women. Moreover, tubal infertility could not explain the observed excess rates of pregnancy loss.

HIV-1-infected pregnant women experience higher rates of miscarriage and stillbirth.[29–32] HIV-1 can be detected in aborted fetuses,[31–33] and in-situ hybrisation studies identified the virus in fetal tissues from 60% of spontaneous fetal losses in HIV-1-seropositive women.[31] Early in-utero HIV-1 transmission may be common and may have deleterious effects on pregnancy survival.[31] Therefore, the low prevalence and incidence of pregnancy could reflect clinical and subclinical fetal loss resulting from HIV-1 infection per se. We were, however, unable to detect early subclinical loss with the tests available for field use.

We cannot directly ascertain the mechanisms through which HIV-1 affects reproduction. Whatever the mechanisms, the lower fecundity in HIV-1-infected women has important consequences for HIV-1 surveillance in obstetric populations, and for projections of the future impact on health-care needs for pregnant women and their offspring.

Contributors

Ronald Gray helped to design and implement the study, and was responsible for the analysis and preparation of the paper. Maria Wawer, the US principal investigator, designed and supervised the study and contributed to analysis, writing of the paper, and interpretation of results. David Serwadda contributed to study design, monitoring and implementation in Uganda, and analysis and report preparation. Nelson Sewenkambo, the Ugandan principal investigator, was responsible for study design, supervision, and preparation of reports. Chuanjun Li was responsible for programming and analyses. Fred Wabwire-Mangen supervised field activities and was responsible for prospective data on pregnancy outcome. Lynn Paxton was responsible for conduct of the study and contributed to analysis and preparation of reports. Noah Kiwanuka and Godfrey Kigozi were responsible for day-to-day management of the study, and contributed to data collection and preparation of reports. Joseph Konde-Lule helped oversee fieldwork. Thomas Quinn and Charlotte Gaydos were responsible for laboratory testing for chlamydia and gonorrhoea, and quality control for other tests, and contributed to preparation of the paper. Denise McNairn was responsible for laboratory testing in Uganda and contributed to data and this report.

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