Should screening of genital infections be part of antenatal care in areas of high HIV prevalence? A prospective cohort study from Kigali, Rwanda, 1992-1993

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Abstract

Objective—To study the prevalence and incidence of genital infections and their association with HIV-1 infection among pregnant women in Kigali, Rwanda.

Subjects and methods—HIV+ and HIV- pregnant women were followed prospectively during the last three months of pregnancy. At enrolment, syphilis test (RPR) on blood sample, *Chlamydiae trachomatis* ELISA test on cervical smear, laboratory gonococcal culture, trichomonas and candida direct examination, CD4 lymphocyte count were performed. At each monthly follow-up clinic visit until delivery, genital infections were screened in the presence of clinical signs and symptoms.

Results—The HIV seroprevalence rate was 34.4% (N = 1233), 384 HIV+ women and 381 HIV- women of same parity and age were enrolled. Prevalence of genital infections at enrolment was generally higher in HIV+ women than in HIV- women: syphilis, 6.3% versus 3.7% ($p = 0.13$); *Neisseria gonorrhoea*, 7.0% versus 2.4% ($p = 0.005$); *Trichomonas vaginalis*, 20.2% versus 10.9% ($p = 0.0007$); *Chlamydia trachomatis*, 3.4% versus 5.5% ($p = 0.21$); *Candida vaginalis*, 22.3% versus 20.1% ($p = 0.49$). Until delivery, the relative risk of acquiring genital infections was also higher in HIV+ women than in HIV- women: 1.0 for syphilis (95% CI: 0.5-2.2), 3.7 for *Neisseria gonorrhoea* (1.0-13.3), 2.6 for *Trichomonas vaginalis* (1.5-4.6) and 1.6 for *Candida vaginalis* (1.1-2.4).

Conclusion—In the context of high HIV-1 seroprevalence among pregnant women, prenatal care should include at least once screening for genital infections by clinical examination with speculum and a syphilis testing in Africa.

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Keywords: STDs; genital infections; HIV-1 infection; Africa; pregnant women

Introduction

Human immunodeficiency virus type-1 (HIV) infection is a major public health problem in

sub-Saharan Africa.¹ In Rwanda, a national serosurvey estimated in December 1986 that the HIV seroprevalence was 18% among urban dwellers, reaching 30% among those aged 26-40 years and 21% specifically among adult women, all ages combined.² Heterosexual transmission accounts for most of the cases of HIV infection in sub-Saharan Africa and there are more women of reproductive age and children infected on this continent than in any other part of the world.^{1,3} HIV infection has therefore common epidemiological features with other sexually transmitted diseases (STDs).⁴ Because STDs are a major cause of chorioamnionitis which is itself a risk factor for mother-to-child transmission of HIV infection,⁵ their association during pregnancy could modify the rate of mother-to-child transmission of HIV. A prospective cohort study on the impact of HIV-1 infection on pregnancy was launched in July 1992, in Kigali, the capital city of Rwanda.⁶ The main objectives were: 1) to document the pregnancy outcomes after screening for common genital infections and treating them and 2) to study the maternal post-partum complications in HIV-positive (HIV+) women in comparison to HIV-negative (HIV-) women.

The aim of the present report is to provide background prevalence figures of maternal genital infections, to estimate the incidence of genital infections until delivery and to study the relation between HIV and other genital infections, in this prospective cohort study, in order ultimately to improve STDs and HIV prenatal control programmes in this African environment.

Subjects and methods

A prospective cohort has been enrolled at the Centre Hospitalier de Kigali (CHK) between July 1992 and August 1993.⁷ All pregnant women attending the prenatal clinic of the CHK, living in the Kigali area and wishing to deliver at the CHK were informed by a trained social worker about HIV infection as well as objectives, constraints and benefits of the study. Eligible women were examined by echography. Those between 21 and 28 weeks of gestation and consenting to participate to the study were systematically offered HIV antibody screening by two commercial enzyme-linked immuno-sorbent assays (ELISA) (Vironostika HIV Mixt and

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Vironostika Uniform, Organon Teknika, Boxtel, the Netherlands). Discordant samples by ELISA were confirmed by a commercial Western Blot technique (Du Pont de Nemours, Delaware, USA) using the Centers for Disease Control criteria of interpretation.⁸ Pre and post-test counselling were systematically offered.

Two weeks after the HIV screening test, we enrolled formally all HIV+ women and an equivalent number of HIV- women. The two groups were selected to be comparable in terms of maternal age and parity. At inclusion, data on the socio-economic status and on gynaecological and medical history were collected on standardised questionnaires. History of treated leucorrhoea and genital ulcers during the two years preceding inclusion was recorded. A clinical examination was performed by a physician, looking for HIV-related signs and symptoms and particularly those included in the WHO clinical AIDS case definition.⁹ A pelvic examination was also performed. Physicians, nurses and social workers were blinded to the HIV serostatus. CD4 and CD8 lymphocyte absolute counts were performed using a commercial immunomagnetic method (Biosys, France). A Rapid Plasma Reagin (RPR, Syphacard, Wellcome, USA) serum test was used for the diagnosis of syphilis.¹⁰ It was considered positive when serum was reactive at dilution 1:2.¹¹ *Chlamydiae trachomatis* was detected on cervical smear by an enzyme immunoassay (EIA Chlamydiazyme, Syva, USA). Gonococcal laboratory culture as well as direct microscopic examination by saline wet mount for trichomonas and candida (yeast) were also performed. Standardised treatment was systematically offered in case of genital infection to women and their partners. (Treatment modalities: in case of syphilis: benzathine-penicillin, 2-4 million units, one injection each week during three weeks; *Neisseria gonorrhoea*: spectinomycine, 2 g in one injection; *Chlamydiae trachomatis* and chancroid ulcers: erythromycin, 1.5 g daily per os during 7 days; trichomoniasis: metronidazole, 2 g single dose per os (only during second and third trimester); candidiasis: myconazole, one vaginal suppository of 400 mg daily during three days.) Until delivery, each woman enrolled had a monthly follow-up including a systematic pelvic examination. Screening of genital infections was repeated, except for chlamydiae, in the following situations: (1) if control was required at the end of the treatment, (2) if symptoms or abnormal physical signs at pelvic examination were found (leucorrhea, genital ulcer, cervical inflammation), or (3) if women complained of genital symptoms. Treatment procedures were repeated if needed.

HIV+ and HIV- women were compared at inclusion for socio-economic and clinical characteristics and prevalence of genital infections using the chi square, Fisher's and Student's *t* tests with a significance level of 5%. In each group of women, we estimated the incidence density rate (incidence) of individual genital infections until delivery except

for *Chlamydia trachomatis*. Women who presented with syphilis at inclusion were excluded from this longitudinal analysis because of the persistence of positive markers during six months or more after treatment.

Relative Risks (RR) and prevalence odds ratios (OR) were computed with their 95% confidence interval (CI). Adjustment was performed with the Mantel-Haenszel method and their 95% CI computed with the Miettinen method.

Results

From 1 July 1992 to 13 August 1993, 1233 pregnant women attending the antenatal clinic of the CHK and fulfilling the inclusion criteria were tested for HIV-1 antibodies. Among them, 424 (34.4%) were found to be HIV+ (CI: 31.7%-37.1%). Forty HIV+ women (9.4%) could not be enrolled in the cohort, mainly because of husband refusal or change of residence. When looking, for comparable HIV- women, 25 could not be enrolled for the same reasons.

In total, 15 days after the first interview, 384 HIV+ women and 381 HIV- women were enrolled in the cohort (92.2% of eligible women). The mean maternal age was 26.0 years (standard deviation (SD): 4.8, range: 15-43). The average number of pregnancies, including the current one, was 2.5 (SD: 1.7, range: 1-11). The proportion of women living in a stable relationship (legal marriage or common law union) was not different between the HIV+ and HIV- groups (93.4% versus 91.2%, chi square test; *p* = 0.23). HIV+ women did not differ from HIV- women in terms of occupation, 56.9% being housewives overall. The HIV+ women enrolled had a lower educational level than HIV- women: 42.4% of the HIV+ women had a primary school level only versus 29.3% (chi square test; *p* = 0.0001). Socio-economic characteristics will be described in detail elsewhere.

When comparing clinical signs and symptoms of the AIDS clinical definition at inclusion, the only differences between HIV+ and HIV- women were for generalised lymphadenopathy (10.7% versus 1.1% respectively; chi square test; *p* = 0.0001) and recurrent herpes zoster infection (3.6% versus 0.3%; Fisher's exact test; *p* = 0.0007). At enrolment in the cohort, three HIV+ women only fulfilled the WHO definition for clinical AIDS and none of the HIV- women. Profound immunosuppression defined by a CD4 count lower than 200/mm³ was observed in 7.5% of the HIV+ women (*n* = 360) and in 0.3% of the HIV- women (*n* = 362), (chi square test; *p* < 0.0001).

A history of leucorrhoea and genital ulcers was more frequently reported by HIV+ women than by HIV- women (table 1). The same difference was observed with clinical signs at pelvic examination (table 1). Among the genital infections screened, candidiasis excluded and both groups combined, 25.2% of the women presented with at least one

Table 1 Gynaecological history and clinical signs among HIV-1 infected (HIV+) and uninfected (HIV-) pregnant women at inclusion in the cohort (results are percentages). Kigali, Rwanda, 1992-1993

	HIV+ (n = 384)	HIV- (n = 381)	p value†
History of treated leucorrhoea*	14.3	5.3	0.0001
History of genital ulcers*	22.3	8.4	0.0001
Leucorrhoea at pelvic examination	48.2	36.1	0.0007
Genital ulcers	7.6	3.7	0.032
Cervical inflammation	34.4	15.7	0.0001
Cervical contact bleeding	49.5	29.2	0.0001

*In the two years preceding inclusion.

†Chi square test.

Table 2 Prevalence of genital infections among HIV-1 infected (HIV+) and uninfected (HIV-) pregnant women at inclusion in the cohort (results are percentages). Kigali, Rwanda, 1992-1993

Genital infections	HIV+ (n = 384)	HIV- (n = 381)	p value*
Syphilis	6.3	3.7	0.13
<i>Neisseria gonorrhoea</i>	7.0	2.4	0.0056
<i>Trichomonas vaginalis</i>	20.2	10.9	0.0007
<i>Chlamydia trachomatis</i>	3.4	5.5	0.21
<i>Candida albicans</i>	22.3	20.1	0.49
At least one of the above genital infections, candidiasis excepted	30.2	20.2	0.0019

*Chi square test.

genital infection. Prevalence of individual genital infections at enrolment in relation with HIV infection is described in table 2. The prevalence of active syphilis was not significantly different in the two groups. *Neisseria gonorrhoea* infection and trichomoniasis were statistically associated with HIV infection (table 2). The prevalence of vaginal candidiasis was not significantly different between HIV+ and HIV- women (table 2). *Chlamydia trachomatis* infection was less frequent in HIV+ women than in HIV- women although this difference did not reach statistical significance (table 2). The risk of at least one genital infection (candidiasis excluded) was 1.7 for HIV+ women in comparison to HIV- women (OR = 1.7; CI: 1.2-2.4). Among the 316 women who had at least one genital infection diagnosed through systematic screening at inclusion, only 74.1% had at least one abnormal

physical sign or symptom at pelvic examination (leucorrhoea or genital ulcer or cervical inflammation) (table 3). Among the 67 women who had syphilis or *Neisseria gonorrhoea* infection, 70% presented at least one abnormal physical sign or symptom. Thus, the positive predictive value of the clinical examination was 88% and the negative predictive value was 94% for these two major STDs.

At inclusion, regardless of HIV status, there was no significant difference in the average number of CD4 lymphocytes among women presenting at least one genital infection and the others (628 and 670 CD4 cells/mm³, respectively, Student's *t* test, *p* = 0.12). When adjusting for HIV serostatus, there was no significant association between immunodeficiency (CD4 cell count lower than 200/mm³) and the presence of genital infections (adjusted OR: 1.14; CI: 0.53-2.45).

Over the study period, the mean follow-up of the cohort was 70 days until delivery (SD: 8 days; range: 0-128) without difference between the two groups. There was no significant difference between HIV+ and HIV- women for the incidence of active syphilis, excluding those who were diagnosed at inclusion (table 4). There also was no significant difference between the two groups for the incidence of gonorrhoea (table 4). There was a significantly higher risk of trichomoniasis and candidiasis among HIV+ women than HIV- women (table 4).

In our study, only one of the 26 HIV+ women versus one of the nine HIV- women had repeated gonorrhoea infection after a standardised treatment (Fisher's exact test, *p* = 0.41); among those who presented with a vaginal trichomoniasis infection at inclusion, 22.4% of the 76 HIV+ women were found positive during follow-up versus 7.3% of the 41 HIV- women (chi square test, *p* = 0.03); finally, 22.6% of the 84 HIV+ women who had a vaginal candidiasis at inclusion had a new episode versus 25.3% of the 75 HIV- women (chi square test, *p* = 0.68).

Table 3 Prevalence of clinical signs* among the 316 pregnant women presenting at least one genital infection at inclusion in the cohort. Kigali, Rwanda, 1992-1993

Genital infections	Number of events	Leucorrhoea (%)	Genital ulcers (%)	Cervical inflammation (%)	At least one clinical sign (%)
Syphilis	38 (100%)	60.5	13.1	28.9	71.1
<i>Neisseria gonorrhoea</i>	35 (100%)	60.0	14.3	35.2	68.6
<i>Trichomonas vaginalis</i>	117 (100%)	76.1	9.4	38.4	82.1
<i>Chlamydia trachomatis</i>	34 (100%)	50.0	5.8	20.6	58.8
<i>Candida albicans</i>	159 (100%)	72.6	6.4	28.5	76.7

*Sums of percentages may exceed 100, several clinical signs may coexist.

Table 4 Incidences of genital infections per 100 women-months among HIV-1 infected (HIV+) and uninfected (HIV-) pregnant women during the last three months of pregnancy. Kigali, Rwanda, 1992-1993

Genital infections	HIV+* (n = 360)	HIV-* (n = 367)	Relative risk	95% Confidence interval
Syphilis	1.62	1.58	1.0	0.5-2.2
<i>Neisseria gonorrhoea</i>	1.24	0.34	3.7	1.0-13.3
<i>Trichomonas vaginalis</i>	4.98	1.92	2.6	1.5-4.6
<i>Candida albicans</i>	6.97	4.59	1.6	1.1-2.4
At least one of the above genital infections, candidiasis excepted	6.59	3.50	1.9	1.2-2.9

*Incidence were computed per 100 women-months, excluding women with syphilis at inclusion.

Discussion

In Kigali, women attending prenatal clinics are considered to be representative of women of reproductive age: 92% of urban pregnant women seek prenatal medical services during the last trimester of pregnancy,¹² only 2% of Rwandan women are sterile,¹³ less than 14% of Rwandan women use a modern contraceptive method¹² and the fertility rate is one of the highest in the world (8.6 children per woman at the end of her childbearing years).¹² In addition, only 8% of the eligible women refused to participate to this study and the CHK is the only hospital of the city. Overall, our sample is considered to be representative of adult urban Rwandan women, allowing us to estimate the prevalence of HIV and genital infections in this population.

The HIV seroprevalence observed was the highest figure ever reported since the beginning of the HIV epidemic in Rwanda and in Africa. Bearing in mind the seroprevalence rate of 21% in 1986 among urban women,² the HIV seroprevalence rate of 34% in 1993 among urban pregnant women suggests the continuing progression of the HIV epidemic in this population. Furthermore, the Rwandese serosurveillance system has also shown that HIV seroprevalence among urban adults has increased in recent years in Kigali.¹⁴ Finally, a seroincidence study in HIV – women of reproductive age has found in the same population an annual incidence around 3 to 5%.¹⁵

Regardless of HIV infection, the prevalence at inclusion of genital infections was high in pregnant women. Genital infections are clearly a public health problem in this population. The prevalence of syphilis is high as it is in numerous countries of Africa, such as Kenya,¹⁶ Mozambique,¹⁷ Cameroon¹⁸ and Uganda.¹⁹ This figure was 4.4% in the same population in 1980.²⁰ The prevalence of gonorrhoea seemed to be lower than the rate of 13% estimated in 1988 among HIV+ women from the same population.²¹ These high prevalence figures confirm, first, the weakness of prevention programmes against genital infections and may explain the explosive AIDS epidemic in many developing countries including Rwanda.^{22 23} Second, we know that adverse neonatal and maternal complications may be associated with maternal syphilis, gonorrhoea or *Chlamydia trachomatis* infections during pregnancy. *Chlamydia trachomatis* seemed to be less important than anticipated in our population. In front of this heavy public health burden, our findings suggest that prenatal care should include in Kigali at least once a systematic screening for syphilis and clinical genital examination with speculum and in the presence of signs or symptoms, a laboratory work-up looking for syphilis, gonorrhoea, trichomoniasis or candidiasis.

We consider that our estimation of incidence of genital infections was a minimum estimate because laboratory screening was not systematically repeated for cost reasons. However, the two groups of HIV+ and HIV – women being similar in terms of age, parity,

marital status and follow-up procedures, our comparison group of HIV – women allowed us to study prospectively the association between genital infections and HIV infection and more specifically the impact of HIV infection on the occurrence of genital infections.

HIV+ women had more genital infections at inclusion (*Neisseria gonorrhoea* and *Trichomonas vaginalis*) than HIV – women. However, this cross-sectional analysis does not allow us to establish a causal relationship between STDs and occurrence of HIV infection. Several studies have already proven that in Africa, STDs and particularly genital ulcers have the most consistent and strongest association with HIV infection.^{24–28} Heterosexual transmission accounts for most HIV infections in Africa and other STDs play the role of co-factors in spreading HIV infection with the same risk behaviour.^{4 16 25 26 29 30}

The longitudinal part of our study, controlling the temporal sequence of events, showed that HIV infection was associated with an increased occurrence of certain genital infections. We did not find any impact of HIV infection on syphilis incidence, contrary to several epidemiological studies.²⁵ This may be explained by a decrease of the reliability of the RPR reaction with the degree of immunodeficiency.^{10 31} or the lack of power because of the low number of events in our study. HIV infection tended to be associated with an increased occurrence of gonorrhoea. This is in agreement with other observations in Africa where the incidence of gonorrhoea ranged between 1% and 23%.^{21 25 32} HIV infection had a strong impact on the incidence of *Trichomonas vaginalis* infection in our study, even if the figures reported here are lower than those obtained in Kinshasa, Zaire.³² In addition, we found that HIV infection seemed to facilitate relapse of trichomoniasis after treatment. This could be due to reinfection or a failure of treatment. For *Chlamydia trachomatis*, our observations were discordant with those reported in other populations in which the prevalence and also incidence were associated with HIV infection.^{17 19 29} The reason for this difference remains unclear but diagnostic techniques vary from one study to the other.

When controlling for the HIV serostatus, a profound immunodeficiency was not a risk factor for developing genital infection. However, our findings suggest several hypotheses for increased incidence of genital infections among HIV+ women in comparison to HIV – women: more frequent at risk sexual practices, poor compliance to treatment or increased susceptibility to infectious agents.

We documented clearly in our sample high HIV seroprevalence and high prevalence of other genital infections. These results suggest the limited effectiveness of prevention programmes against AIDS and STDs in this population and the usefulness of serosurveillance among pregnant women. Controlling the spread of HIV infection in women is of utmost importance because a large number of HIV+ women of reproductive age will result

in a higher number of children with perinatally acquired HIV infection.³ Integration of STDs and HIV control programmes into maternal and child health care and family planning services should be useful in the aim of prevention and control of STDs and HIV transmission in Africa.³³ Furthermore, pregnancy may be a unique opportunity for the treatment of STDs among women. STDs management may be integrated into prenatal care in Africa, using simple algorithms based on a syndromic case management without the systematic need of laboratory tests when they are not available on a large scale.^{33,34} However, syphilis screening should be systematically offered to every pregnant woman as already demonstrated elsewhere.¹⁶ This study underlines once more the necessity for quick, inexpensive and reliable diagnostic tests for STDs. Further studies are in progress in this cohort, to measure the impact of HIV infection on pregnancy outcome, after treatment of other STDs.

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