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Cervical dysplasia and HIV type 1 infection in African pregnant women: a cross sectional study, Kigali, Rwanda

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Objective: To study the prevalence of cervical squamous intraepithelial lesions (SILs) and their association with HIV-1 infection and immunodeficiency among pregnant women in Kigali, Rwanda.

Methods: As part of a cohort study on the impact of HIV-1 infection on pregnancy outcome, HIV-1 seropositive (HIV+) and seronegative (HIV-) pregnant women were enrolled during the last trimester of pregnancy at the maternity ward of the Centre Hospitalier de Kigali from July 1992 to August 1993. At inclusion, women were screened for sexually transmitted diseases (STDs)—syphilis, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*. CD4+ lymphocyte counts were measured and a Papanicolaou smear performed.

Results: Papanicolaou smear was interpretable in 103 HIV+ women and 107 HIV- women. Prevalence of SILs was significantly higher in HIV+ women than in HIV- women: 24.3% v 6.5% (odds ratio=4.6; 95%CI: 1.8–12.3). SIL+ women (n=32) tended to have more STDs than SIL- women (n=178), but this did not reach a statistical difference: 37.5% and 24.7% respectively (p=0.13). They also had a mean CD4 count significantly lower than SIL- women (623 and 784 CD4+ cells $\times 10^6/l$, respectively; p=0.02).

Conclusion: SILs were HIV related and the association with immunosuppression was statistically significant. Prevalence of SILs was high in this population of pregnant women with high HIV/STDs prevalence. Screening policy for STDs and SILs in African women should be assessed in prenatal care.

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Keywords: STDs; cervical dysplasia; HIV-1 infection; Africa; pregnant women

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Introduction

There are currently more HIV infected women of reproductive age in sub-Saharan Africa than in any other part of the world. Cervical carcinoma is another public health problem in Africa¹ but risk factors for squamous intraepithelial lesions (SILs), precursor for invasive cervical carcinoma, are still poorly understood in Africa. Cervical carcinoma has been demonstrated to be HIV related and, since 1993, this disease is considered as an AIDS defining event.² The role of human papillomavirus (HPV) infection, more frequent in HIV infected women, is also clearly established.^{2,3} Previous reports suggested that HIV induced immunosuppression predisposes to increased HPV mediated cervical cytological abnormalities.^{4–8} In Africa, few studies have estimated the prevalence of SILs and stressed its association with HIV infection.^{5–11}

In Kigali, Rwanda, a prospective cohort study on the effect of maternal HIV-1 infection on pregnancy outcome was initiated in 1992.¹² This provides an opportunity to estimate the prevalence of SILs among pregnant women and to clarify their association with HIV in relation to immunological status and other risk factors.

Subjects and methods

A prospective cohort was enrolled at the Centre Hospitalier de Kigali (CHK) between July

1992 and August 1993. Detailed enrolment procedures have been published elsewhere.^{12,13} Briefly, all pregnant women attending the antenatal clinic between 21 and 28 weeks of pregnancy were given information by a trained social worker about HIV infection and the objectives, constraints, and benefits of the study. Eligible pregnant women who gave consent to participate in the study were offered HIV antibody screening using two enzyme linked immunosorbent assays (ELISA). Discordant samples by ELISA were confirmed by a western blot technique.

Two weeks after the HIV screening test, all HIV positive (HIV+) women were enrolled with an equivalent number of frequency matched negative (HIV-) women similar in age and parity. Physicians, nurses, and social workers were blinded to the HIV serostatus. A Papanicolaou smear, CD4 lymphocyte absolute count using an immunomagnetic method (Biosys, Compiègne, France), and a systematic STD screening were performed. A rapid plasma reagin (RPR, Syphacard, Wellcome, USA) serum test was used for the diagnosis of syphilis. *Chlamydia trachomatis* was detected on cervical swab by an enzyme immunoassay (EIA Chlamydiazyme, Syva, USA). Gonococcal culture as well as direct microscopic examination by saline wet mount for screening of *Trichomonas vaginalis* were performed. Standard treatments were systematically offered in case

of genital infection to women and their partners.¹³

Papanicolaou smears were analysed at the cytopathology laboratory, Centre for Prevention of Cancer, University of Antwerp, Belgium, in the light of relevant clinical information, but without knowledge of HIV serostatus. We report only the results for the first 210 consecutive specimens, as further samples were lost during the Rwandan war in 1994. Papanicolaou smears were interpreted according to the 1988 Bethesda system¹⁴ using two presumptive diagnoses of SILs—low grade (CIN1) and high grade (CIN2-CIN3) SILs.

HIV+ and HIV- women with a Papanicolaou smear were compared at inclusion for socioeconomic, clinical, and immunological characteristics. Women who presented with SILs (SIL+) were compared with those who did not (SIL-) for associated factors using prevalence odds ratios (OR) with a 95% confidence interval (CI). Adjusted analysis on HIV status was performed using the Mantel-Haenszel method.

Results

From July 1992 to August 1993, of the 1233 pregnant women attending the antenatal clinic of the CHK who were tested for HIV-1 antibodies, 424 (34.4%) were found to be HIV+ (CI: 31.7%–37.1%). In total, 384 HIV+

women and 381 HIV- controls, were enrolled in the cohort (92% of those eligible).

Papanicolaou smear results were available and interpretable for cytological diagnosis for the first 103 HIV+ (26.8% of all HIV+ women enrolled) and 107 HIV- women (30.2%). There was no difference between the study sample with a Papanicolaou smear and the other women enrolled in the cohort. In the study sample, the mean maternal age was 25.7 years (SD 4.7 years, range 15–40 years). The average number of pregnancies, including the current one, was 2.5 (SD 1.7, range 1–9 pregnancies). The proportion of women living in a stable relationship did not differ between the HIV+ and HIV- groups (94.2% versus 92.1%; $p=0.53$). HIV+ women did not differ from HIV- women in terms of occupation, and a total of 58.9% were housewives ($p=0.12$). HIV+ women had achieved a lower educational level than HIV- women, with no more than primary school in 44.6% versus 30.4% ($p=0.02$). When comparing gynaecological signs and STD diagnoses at inclusion, a significant difference was observed between HIV+ and HIV- women for clinical cervical inflammation (35.5% versus 16.5%, respectively; $p=0.0009$). HIV+ women tended to present more frequently at least one STD (including syphilis, *N gonorrhoeae*, *T vaginalis*, or *C trachomatis*) than HIV- women but this did not reach statistical significance (30.6% versus 22.6%; $p=0.16$). At inclusion, none of the HIV+ women had been diagnosed with clinical AIDS. CD4 cell count lower than $200 \times 10^6/l$ was observed in four (4.3%) of the HIV+ women and in none of the HIV- women.

Prevalence of SILs was significantly higher in HIV+ women ($n=103$) than in HIV- women ($n=107$), 24.3% and 6.5%, respectively (table 1), (OR=4.6; CI: 1.8–12.3). Comparisons of baseline variables in relation to presence or absence of SILs (low and high grade lesions grouped) are presented in table 2. SIL+ women ($n=32$) and SIL- women ($n=178$) were comparable for age, number of pregnancies, marital status, and educational level. SIL+ women tended to present more clinical cervical inflammation and STDs than SIL- women, but this difference was not statistically significant. The mean CD4+ lymphocyte count was 160 cells in SIL+ women, significantly lower than in SIL- women ($p=0.02$), (table 2). After stratification and adjustment for HIV serostatus, there was no significant difference between SIL+ and SIL- women for presence of cervical inflammation (adjusted OR=0.9; CI=0.4–2.4), presence of STDs (adjusted OR=1.6; CI=0.7–3.9), and immunodeficiency defined as a CD4 cell count lower than $500 \times 10^6/l$ (adjusted OR=1.2; CI=0.5–3.1). Data on age at first intercourse and number of sexual partners were only available for 96 women overall, 15 SIL+ and 81 SIL-. Age at first intercourse was significantly lower for SIL+ women than for SIL- women, 19 years *v* 21 years, respectively ($p=0.04$). Five of 15 SIL+ women had more than one partner in the past year compared with 18 out of the 81 SIL- ($p=0.28$).

Table 1 Prevalence of cervical cytological diagnoses according to the 1988 Bethesda system in HIV infected (HIV+) and HIV uninfected (HIV-) pregnant women, Kigali, Rwanda, 1992–3

Cytological diagnosis	HIV+ women ($n=103$)		HIV- women ($n=107$)		<i>p</i> Value*
	No	%	No	%	
Normal	18	17.5	22	20.6	0.56
Abnormal†	85	82.5	85	79.4	
Infection suggested‡	68	66.1	77	72.2	0.31
Inflammation suggested§	45	43.7	38	35.5	0.23
Squamous intraepithelial lesions	25	24.3	7	6.5	0.0004
Low grade lesions	15	14.6	5	4.6	
High grade lesions	10	9.7	2	1.9	

* χ^2 test.

†One specimen may have several abnormalities.

‡Reference group: no infection.

§Reference group: no inflammation.

Table 2 Comparison of baseline characteristics in 210 pregnant women with diagnosis of squamous intraepithelial lesions (SIL+) and without (SIL-), Kigali, Rwanda, 1992–3. Univariate analysis

Variable	SIL+ women ($n=32$)	SIL- women ($n=178$)	<i>p</i> Value*
HIV-1 infection (%)	78.1	43.8	0.0004
Mean age (years) (SD)	25.5 (5.1)	25.7 (4.6)	0.38
Mean number of pregnancies (SD)	2.4 (1.7)	2.5 (1.7)	0.42
Marital status (%)			0.25
Single, divorced or widowed	9.3	4.5	
Common union or married	90.7	95.5	
Low educational level (%)	34.8	43.8	0.33
Cervical inflammation (%)	25.0	21.9	0.70
HIV+	7/25	23/78	0.88
HIV-	1/7	16/100	0.90
At least one STD† (%)	37.5	24.7	0.13
HIV+	10/25	22/78	0.26
HIV-	2/7	22/100	0.68
CD4 cell count $<500 \times 10^6/l$ (%)	37.5	23.8	0.11
HIV+	11/25	31/78	0.71
HIV-	1/7	10/100	0.54
Mean CD4+ cell count $\times 10^6/l$ (SD)	623.3 (325.8)	784.0 (413.7)	0.02

* χ^2 , Fisher's exact test, or Student's *t* test.

†Includes syphilis, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, *Chlamydia trachomatis*.

Discussion

This comparative study of HIV+ and HIV– pregnant women provides prevalence data of SILs allowing for the presence of STDs and HIV related immunodeficiency. In this population with a high HIV seroprevalence, we documented a high prevalence of SILs, five times greater in HIV+ than in HIV– pregnant women. Because only 8% of the eligible women attending antenatal care refused to participate in the study, in a setting where 92% of urban women seek antenatal care during the last trimester of pregnancy,¹⁵ our findings are fairly representative for pregnant women in Kigali.

The overall prevalence of SILs was 2.0% in a large population attending family planning clinics in Kenya¹⁰ and 7.5% among 67 HIV-1 infected women in Senegal.⁷ This figure is much lower than in our population of pregnant women. Our prevalence of SILs was lower than those reported in previous studies carried out in Africa which involved only a small number of women: 43% in 14 HIV-1 infected women in Senegal (95%CI: 17–69%),¹¹ and 27% in 41 HIV+ women in Zaire (95%CI: 13–41%).⁵ However, our data are consistent with those reported on the relation between HIV and cervical dysplasia in developed¹⁶ and developing countries.^{5–10}

Although the inclusion of HIV– women allowed us to confirm that SILs were HIV related, this cross sectional analysis cannot establish a causal relation between HIV infection and SILs. Other factors such as age, age at first intercourse, parity, STDs, and number of sexual partners may be confounding factors in the analysis of this association.¹⁶ As the two groups of SIL+ and SIL– women were similar in terms of age, number of pregnancies, marital status, and educational level, no confounding was likely to take place for these factors. Information on age at first intercourse and number of sexual partners was not reported for a sufficient number of women and could not be taken into account in our analysis. We have no data on smoking behaviour in our cohort, but smoking is known to be rare in Rwandan women.¹⁷ Surprisingly, no clear association appeared in our sample between STDs and SILs, although this association has been reported by others.^{5–9,16} Thus, HIV infection was the variable most strongly associated with SILs. SILs tended to be associated with HIV related immunodeficiency but only few HIV+ women were immunosuppressed. We were not able to collect information about HPV infection, limiting our ability to study their association with cervical abnormalities in HIV infected women.

In the 1980s, the crude incidence rate of cervical cancer in east Africa was already high—21/100 000 inhabitants, which is three to four times higher than in the United States or Europe.¹ With an increased incidence of cervical dysplasia observed among HIV infected women in these countries and considering the fact that cervical dysplasia may develop, cervical cancer could become an increasing problem in these populations.² However, AIDS has a shorter incubation time than cervical

cancer and therefore this latter disease may be a problem more important among HIV– women than among HIV+ women in Africa.

The Papanicolaou smear remains the routine method in gynaecological care of HIV infected women in a large part of the world, especially in developing countries.¹⁸ However, in Africa, the feasibility of a systematic Papanicolaou smear screening in prenatal or gynaecological clinics remains to be assessed.¹⁰

The EGE Study Group

The EGE Study Group comprises the following: *epidemiology*: F Dabis*, C Gazille*, J Ladner*†, V Leroy*, P Msellati‡, R Salamon*; *gynaecology and obstetrics*: A De Clercq (principal investigator), A Cyimana, M Mudaheranwa (now deceased), C Munyangabe, M Nyiraziraje, C Zilimwabagabo (all at Department of Gynaecology and Obstetrics, Centre Hospitalier de Kigali); *microbiology*: J Bogaerts§, E Karita¶, A Simonon¶, P Van de Perre¶.

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Contributors: V Leroy contributed to monitoring the cohort in Kigali, was in charge of statistical analysis, and co-wrote the report; J Ladner was the epidemiologist responsible for the project in Kigali and co-wrote the report; A De Clercq was the obstetrician principal investigator of the project in Kigali; F Dabis was the project coordinator and co-wrote the report; A Meheus supervised Papanicolaou smear analysis; M Nyiraziraje was one of the obstetricians on the project in Kigali; and E Karita was in charge of HIV related laboratory activities in Kigali and co-wrote the report.

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