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Differences in fertility by HIV serostatus and adjusted HIV prevalence data from an antenatal clinic in northern Uganda

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Summary

OBJECTIVES To estimate differences in fertility by HIV serostatus and to validate an adjustment method for estimating the HIV prevalence in the general female population using data from an antenatal clinic.

METHODS We used Cox regression models to retrospectively estimate the age-specific relative fertility (RF) of HIV-positive compared to HIV-negative women among 3314 antenatal clinic attenders in northern Uganda. RF and the age distribution of women in the general female population were used to extrapolate the antenatal clinic-based HIV prevalence. This procedure was indirectly validated by comparing the adjusted estimate with those based on standard adjustment factors derived from general female populations in Uganda and Tanzania.

RESULTS HIV-positive women reported a lower fertility than HIV-negative women [age-adjusted RF = 0.83, 95% confidence interval (CI): 0.75–0.93]. Except for girls aged 15–19 (RF = 0.96, 95% CI: 0.74–1.24) HIV-positive women in all age groups were less fertile (20–24 year: RF = 0.83, 95% CI: 0.67–1.01; 25–29 years: RF = 0.79, 95% CI: 0.62–1.00; 30–49 year: RF = 0.79, 95% CI: 0.65–0.96]. Adjusting the antenatal clinic-based HIV prevalence (11.6%) for these differences yields a higher estimate (13.8%) that is lower than those based on standard adjustment factors derived from general female populations (from 14.6% to 17.7%).

CONCLUSIONS The age-specific pattern of differential fertility by HIV serostatus derived from antenatal clinic data is consistent with findings from population-based studies conducted in Africa. However, differences in fertility between HIV positive and HIV-negative clients underestimate those in the general female population yielding inaccurate estimates when used to extrapolate the HIV prevalence.

keywords HIV, fertility, surveillance, Africa

Introduction

In sub-Saharan Africa, the HIV epidemic is commonly monitored by conducting sentinel surveillance among pregnant women attending antenatal clinics (ANC). In this region, where heterosexual intercourse is the main mode of HIV transmission (Schmid *et al.* 2004), the prevalence of infection among attendees of ANCs is sometimes assumed to be representative of that among the general population (males and females combined) and is thus used as input to estimate national prevalence (Walker *et al.* 2003). However, comparative studies conducted in Africa have shown that the HIV prevalence among pregnant women tends to represent an underestimate with respect to the prevalence among the general female population of reproductive age (GFP), especially in areas where the epidemic is mature and there is a low rate of contraception use (Kwesigabo *et al.* 1996; Carpenter *et al.* 1997; Gray *et al.* 1998; Kilian *et al.* 1999; Fylkesnes *et al.* 2001; Glynn *et al.* 2001). This is mainly because HIV-positive women are less represented in ANCs than HIV-negative women, as a result of the lower fertility among HIV-positive women (Zaba & Gregson 1998), which is associated with social, behavioural and biological factors (Brocklehurst & French 1998; Ross *et al.* 1999).

To address this issue, a method that adjusts for differences in fertility by HIV serostatus has been proposed for estimating the HIV prevalence in the GFP using prevalence data from pregnant women (Fabiani *et al.* 2001,2003). This method is mainly based on standard adjustment factors derived from the GFP of the Masaka district in South-west Uganda (Carpenter *et al.* 1997), which, however, may be not representative of those in other African countries with different epidemic stage, rate of contraceptive use and mean age at sexual debut. On the other hand, updated country-specific data on fertility by HIV serostatus in the GFP are not widely available and are costly to collect, while these estimates could be easily obtained from ANC sites where anonymous HIV surveillance is routinely conducted.

The objectives of this study are to estimate the differences in fertility by HIV serostatus among pregnant women attending an ANC in northern Uganda and to indirectly validate an adjustment method for estimating the HIV prevalence in the GFP that is based on these differences (Desgrees du Lou *et al.* 1999).

Materials and methods

During the period 2001–2003, a total of 3314 women attending the antenatal clinic of St. Mary's Hospital Lacor (Gulu district, North Uganda) were anonymously tested for HIV infection in the context of the Ugandan HIV-1 surveillance system. Information on age, parity, age at sexual debut and time since last birth was used to retrospectively estimate the overall and age-specific differences in fertility between HIV-positive and HIV-negative women. These differences were estimated through Cox regression models comparing time since initiation of sexual activity and time since last birth by HIV serostatus for primipara and multipara pregnant women, respectively. For each age group, the Cox regression model was run including only HIV-serostatus as independent variable, while, in the overall analysis, age group was also included as potential confounder. Differences in the age-specific relative fertility rates (RF) of HIV-positive women compared with HIV-negative women were evaluated testing the interaction term between HIV serostatus and age group in the overall model (likelihood ratio test). The age-specific RFs of HIV-positive women compared with HIV-negative women, together with the age distribution of women in the GFP, were then used to adjust the HIV prevalence among the GFP, based on the age-specific prevalence observed among pregnant women (see appendix – first method). This procedure was indirectly validated by comparing the adjusted estimate with those obtained by applying: 1) the same method, but using the age-specific differences in fertility by HIV serostatus estimated in the GFP of the Masaka district (south-west Uganda) as standard reference; 2) a second method, which is primarily based on the parity-specific differences in HIV prevalence between sexually active fecund women (assumed to be represented by pregnant women) and the other fertility risk-groups in the GFPs of Kisesa (Tanzania) and Masaka (Uganda) as standard reference (see appendix – second method). A more detailed description of both the methods of adjustment and the standard reference data on which they are based is given in appendix and elsewhere (Zaba *et al.* 2000; Fabiani *et al.* 2003).

This study is based on data derived from the HIV-1 sentinel surveillance activity at the antenatal clinic of the St. Mary's Hospital Lacor, which was approved and authorised by the STD/AIDS Control Programme of the Ugandan Ministry of Health.

Results

HIV-positive women reported a lower fertility than HIV-negative women [age-adjusted RF = 0.83, 95% confidence interval (CI): 0.75–0.93]. Although the interaction between HIV serostatus and age group was not statistically significant (likelihood ratio test, $P = 0.725$), fertility associated with HIV infection was reduced among older women (20–24 years: RF = 0.83, 95% CI: 0.67–1.01; 25–29 years: RF = 0.79, 95% CI: 0.62–1.00; 30–49 years: RF = 0.79, 95% CI: 0.65–0.96), whereas, among women aged 15–19 years, HIV-positive women reported a fertility similar to that of HIV-negative women (RF = 0.96, 95% CI: 0.74–1.24). Adjusting the HIV prevalence among ANC attendees (11.6%) for these differences yields an increased estimate (13.8%) that is lower than those obtained by applying the methods based on standard reference data from GFPs (Table 1). In fact, adjusting the ANC prevalence for the standard differences in fertility from the GFP of Masaka yields a HIV prevalence equal to 17.7%. The second adjustment method, based on standard reference data from the GFPs of Kisesa and Masaka, yields a prevalence equal to 14.6%, increased to 16.7% when also sub-fertility among HIV-positive fecund women in the GFP is taken into consideration (HIV prevalence for multipara ANC attendees weighted by time since last birth).

Discussion

The pattern of age-specific differences in fertility by HIV serostatus derived from these antenatal clinic data is consistent with findings from population-based studies conducted in sub-Saharan African countries with mature epidemics (Zaba & Gregson 1998). In fact, although of borderline significance, a reduced fertility among HIV-positive women was observed for all the age groups, with the exception of younger women aged 15–19 years, among whom the infection is likely to be so recent to have not yet caused fertility-related problems.

Overall, the reduced fertility associated with HIV infection is likely to be mainly due to biological factors (e.g., foetal wastage, menstrual dysfunctions, severe weight loss leading to amenorrhoea, decreased production of spermatozoa and reduced coital frequency of infected

Table 1 Adjusted HIV prevalence for the general female population compared to that observed among antenatal clinic attendees

		HIV-1 prevalence (%)				
Age group	*RF (95% CI)*	ANC (no. tested)	Adjusted (RD)†	Adjusted (RD)‡	Adjusted (RD)¶	Adjusted (RD)§
<20 years	0.96 (0.74–1.24)	6.4 (966)	6.7 (4.1)	4.8 (−24.7)	–	–
20–24 years	0.83 (0.67–1.01)	10.3 (1021)	12.2 (18.5)	15.4 (49.9)	–	–
25–29 years	0.79 (0.62–1.00)	15.7 (509)	19.1 (21.6)	23.1 (46.9)	–	–
≥30 years	0.79 (0.65–0.96)	13.9 (818)	17.0 (22.3)	25.5 (82.9)	–	–
Overall	0.83 (0.75–0.93)	11.6 (3314)#	13.8 (18.9)	17.7 (53.1)#	14.6 (25.5)	16.7 (45.6)#

RF, relative fertility of HIV-positive women compared with HIV negative women estimated through Cox regression analysis of antenatal clinic data; CI, confidence interval; ANC, antenatal clinic; RD, relative difference (percentage difference in prevalence with respect to that among antenatal clinic attendees).
HIV-1 prevalence directly standardized by age using the age distribution of the general female population of the Gulu district as a reference.
† First adjustment method based on the age-specific differences in fertility by HIV-status estimated through the Cox regression analysis of the antenatal clinic data.
‡ First adjustment method based on age-specific differences in fertility by HIV-status derived from the general female population of Masaka district (south-west Uganda).
¶ Second adjustment method based on relative HIV prevalence and population distribution by fertility-risk category and parity derived from the general female population of Masaka (south-west Uganda) and Kisesa (Tanzania).
§ Second adjustment method modified to account for sub-fertility of HIV-positive fecund women (prevalence among multipara women weighted by time since last birth).

regular partner, premature mortality of infected regular partner, etc.) rather than to voluntary behavioural mechanisms (e.g., avoiding pregnancy because of the fear of leaving orphans, break-up of partnerships because of disclosure of HIV status, use of contraceptive methods, etc.) (Zaba & Gregson 1998; Ross *et al.* 1999; Zaba *et al.* 2003). In fact, a low proportion of women in sub-Saharan Africa are likely to be aware of their HIV-status, thus limiting the possibility that HIV-positive women voluntarily reduced their fertility. However, the increasing diffusion of voluntary counselling and testing for HIV infection, which is the first step to accede to programmes for the prevention of mother-to-child transmission and to antiretroviral therapy programmes, is expected to increase the number of women aware of their HIV serostatus and thus the importance of behavioural mechanisms in regulating fertility of HIV-positive women. Research in areas where voluntary counselling and testing is already widely implemented and accepted would help in better understanding the potential impact of HIV status knowledge on fertility regulation. Moreover, prospective studies aimed at investigating the reverse causal relationship between HIV status and fertility (i.e., effect of fertility problems on risky sexual behaviour, such as unprotected extramarital sex aimed at conceiving a child) would also be needed to confirm findings from previous studies that support this hypothesis (Favot *et al.* 1997; Ikechebelu *et al.* 2002).

As suggested by the comparison of the age-specific differences in fertility by HIV serostatus derived from these ANC data with those derived from the GFP of the Masaka district (Carpenter *et al.* 1997), although the age-specific patterns are consistent, the differences derived from ANC data probably underestimate those in the GFP (Figure 1). This is for three main reasons: (1) ANC data do not represent young women in the GFP who have never had sex, thus leading to overestimate the fertility of HIV-negative women and to underestimate the absolute difference in fertility among women aged 15–19 years; (2) ANC data only reflect sub-fertility, but not infertility, which is likely to account for most of the differences in fertility between HIV-positive and HIV-negative women in the older age groups of the GFP. This leads to overestimate

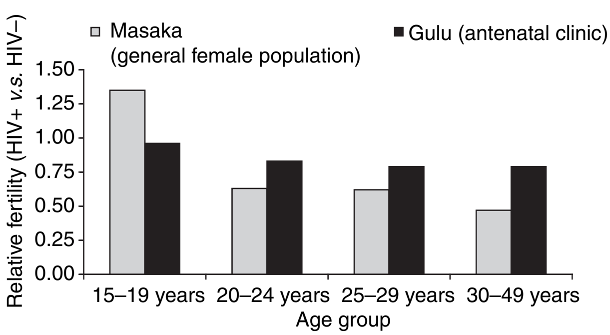

Figure 1 Age-specific relative fertility of pregnant women in the Gulu district (northern Uganda) compared with that of the general female population in the Masaka district (south-west Uganda).

the fertility of HIV-positive women and to underestimate the differences in fertility among older women; (3) ANC data do not represent women who are current users of contraceptive methods, which, although there are no strong evidences in literature, are likely to be more frequently used by HIV-positive and older women in settings where the overall rate of contraception use is low (Lewis *et al.* 2004). This is partly supported by unpublished data from the ANC of St. Mary's Hospital Lacor, which show a higher proportion of past users of contraception among HIV–positive pregnant women compared with HIV-negative pregnant women (26.8% *vs.* 18.7%, $P < 0.001$). Although in Uganda there is a relatively low rate of contraception use (20.1% in 2000–2001; Uganda Bureau of Statistics and ORC Macro 2001), this bias could also lead to overestimate the fertility of HIV-positive women and to underestimate the differences in fertility among older women.

In estimating differences in fertility between HIV-positive women and HIV-negative women, we only considered the recent reproductive history of multipara ANC attendees (i.e., time since last birth). Although these differences could be estimated accounting for all the reproductive history of multipara women (i.e., number of pregnancies since initiation of sexual activity), this would introduce a further bias because part of the fertility reported by HIV-positive multipara women was probably experienced before their seroconversion.

Adjusting the HIV prevalence for differences in fertility by HIV serostatus derived from ANC data yields a HIV prevalence estimate for the GFP that is 19% higher than the crude prevalence among ANC attendees. By contrast, the methods based on adjustment factors derived from GFPs data yield estimates that are from 26% to 53% higher. These estimates are consistent with data from comparative studies conducted in sub-Saharan Africa that show HIV prevalence rates in the GFPs from 26% to 47% higher than those observed in the corresponding ANCs (Fabiani *et al.* 2003).

In general, differences in prevalence between ANC attendees and women in the GFP could also be affected by factors other than differential fertility by HIV serostatus and age distribution in the GFP, which are both accounted for in the first adjustment method. In fact, although differential fertility by HIV serostatus indirectly reflects and then accounts for other possible biases (e.g., use of contraceptives and being not sexually active), other factor could still play a role. For example, independently on differential fertility, differences in antenatal clinic attendance between HIV-positive and HIV-negative pregnant women could bias the HIV prevalence estimates derived from antenatal clinic data. However, in many countries of sub-Saharan Africa, a very high proportion of pregnant women have been reported to attend antenatal clinic for a first visit (e.g., 94% in Uganda; Uganda Bureau of Statistics and ORC Macro 2001), thus becoming eligible for anonymous HIV surveillance and reducing to a minimum the selection bias due to assuming antenatal clinic attendees as representative of all pregnant women. This conclusion is supported by the close correspondence between the HIV prevalence observed in GFPs and those obtained adjusting antenatal clinic data only for age and differential fertility (Fabiani *et al.* 2003), which suggests that differences in antenatal clinic attendance between HIV-positive and HIV-negative pregnant women, as well as other possible biases that are not mediated by fertility, probably play a minor role.

In conclusion, ANC data provides useful information on the pattern of age-specific differences in fertility by HIV serostatus. However, differences in fertility between HIV positive and HIV-negative antenatal clinic clients underestimate those in the GFP, thus leading to inaccurate estimates when used to extrapolate the HIV prevalence from pregnant women to the GFP.

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Différences dans la fertilité selon le statut VIH et données de prévalence VIH ajustées dans une clinique anténatale du nord de L'Ouganda

objectifs Estimer les différences dans la fertilité selon le statut sérologique VIH et valider une méthode ajustée pour l'estimation de la prévalence VIH dans la population féminine générale, en utilisant les données d'une clinique anténatale.
méthodes Nous avons utilisé le modèle de régression de Cox pour estimer rétrospectivement, la fertilité selon l'âge chez les femmes VIH positives comparées aux femmes VIH négatives sur 3314 femmes consultant une clinique du nord de l'Ouganda. Les fertilités selon la distribution d'âge des femmes dans la population générale ont été utilisées pour extrapoler la prévalence VIH basée sur la clinique anténatale. Cette méthode a été validée indirectement, en comparant l'estimation ajustée à celles basées sur les facteurs d'ajustement standards provenant des populations féminines générales de l'Ouganda et de la Tanzanie.
résultats Les femmes VIH positives rapportaient une fertilité plus faible que les femmes VIH négatives (ajustement de l'âge RF = 0,83, IC95%: 0,75–0,93). A l'exception des femmes âgées de 15 à 19 ans (RF = 0,96, IC95%: 0,74–1,24), tous les groupes d'âge étaient moins fertiles (chez les 20–24 ans: RF = 0,83 ; IC95%: 0,67–1,01, chez les 25–29 ans: RF = 0.79, IC95%: 0,62–1,00, chez les 30–49 ans: RF = 0.79, IC95%: 0,65–0,96). L'ajustement de la prévalence VIH basée sur les données de la clinique anténatale (11,6%) pour ces différences a révélé une estimation plus haute (13,8%) qui est pourtant moins élevée que celle basée sur les facteurs d'ajustement standards provenant des populations féminines generales (17,7%).
conclusions Le profil âge-spécifique de la fertilité selon le statut VIH provenant des données de la clinique anténatale est consistant avec ceux observés dans les études de population menées en Afrique. Cependant, les différences dans la fertilité entre VIH positives et VIH négatives sous estiment celles de la population féminine générale.

mots clés VIH, fertilité, surveillance, Afrique

Diferencias en fertilidad según el seroestatus de VIH y datos de prevalencia de VIH ajustados de clínicas antenatales en Uganda del norte

OBJETIVOS Calcular las diferencias en fertilidad según el seroestatus de VIH y validar un método de ajuste para estimar la prevalencia de VIH en la población femenina en general, utilizando datos de una clínica antenatal.

MÉTODOS Utilizamos modelos de regresión de Cox para estimar retrospectivamente la fertilidad relativa especifica por edad en 3,314 mujeres que consultaron una clínica antenatal en el norte de Uganda de mujeres VIH positivas comparadas con aquellas VIH negativas. La fertilidad relativa y la distribución por edad de las mujeres en la población general fueron utilizadas para extrapolar la prevalencia de VIH a partir de los datos de clínicas antenatales. Este procedimiento fue validado indirectamente comparando el las estimaciones ajustadas con aquellas basadas en los factores de ajuste estándar derivados de la población general femenina en Uganda y Tanzania.

RESULTADOS Las mujeres VIH positivas reportaron una menor fertilidad que las VIH negativas [ajustado por edad RF = 0.83, 95% intervalo de confianza (IC): 0.75–0.93]. Excepto en el caso de niñas entre 15–19 años (RF = 0.96, 95% CI: 0.74–1.24) todos los grupos de edad fueron menos fértiles (20-24 años: RF = 0.83, 95% CI: 0.67–1.01; 25-29 años: RF = 0.79, 95% CI: 0.62–1.00; 30–49 años: RF = 0.79, 95% CI: 0.65–0.96]. La prevalencia de VIH basada en las clínicas antenatales (11.6%) ajustada por estas diferencias resulta en una estimación más alta (13.8%), que es más baja que la basada en los factores de ajuste estándar derivados de la población general femenina (de 14.6% a 17.7%).

CONCLUSIONES El patrón específico por edad de la fertilidad diferenciada por seroestatus VIH derivado de las clínicas antenatales es consistente con los hallados en los estudios basados en población general en África. Sin embargo, las diferencias de fertilidad entre mujeres VIH positivas y VIH negativas entre las usuarias de clínicas antenatales, subestiman aquellas de la población general femenina.

palabras clave VIH, fertilidad, vigilancia, África

Appendix

First adjustment method

The first method consists of adjusting the age-specific HIV prevalence rates observed among ANC attendees accounting for differences in fertility between HIV-positive women and HIV-negative women, and then directly standardising the overall prevalence using the age structure of the GFP derived from census data as reference. In detail, the adjusted HIV prevalence for the GFP (P_{GFP}) was calculated according to the following formula:

$$\mathrm{P_{GFP}} = \sum_{\mathrm{ageclass}} \mathrm{F_{GFP}} \left(\frac{\mathrm{P_{ANC}}}{\mathrm{RF} - \mathrm{RF} \times \mathrm{P_{ANC}} + \mathrm{P_{ANC}}} \right)$$

where, for each age class, F_{GFP} indicates the proportion of women among the GFP; P_{ANC} indicates the HIV prevalence observed among ANC attendees; *RF* indicates the relative fertility of HIV-positive women compared with HIV-negative women.

Second adjustment method

The second method requires data from the GFP on both the relative HIV prevalence and the population distribution by fertility risk-category (i.e., never had sex; had sex, no currently sexually active; sexually active, using contraception; sexually active, infecund; sexually active, fecund) and parity (i.e., mothers versus women who have never born a child). Specifically, the relative HIV prevalence were used for extrapolating HIV prevalence from ANC attendees (assumed to be representative of the group of sexually active fecund women) to the other fertility risk-categories of the GFP, whereas the population distribution was used as reference for directly standardising by fertility risk-category and parity the overall adjusted HIV prevalence for the GFP. To account for sub-fertility among HIV-positive fecund women in the GFP, the HIV prevalence for multipara ANC attendees should be weighted by time since last birth. In detail, the adjusted HIV prevalence for the GFP (P_{GFP}) was calculated according to the following formula:

$$P_{GFP} = \sum_{\mathrm{parity}} P_{ANC} \times \left(\sum_{\mathrm{fertility\ risk-category}} F_{GFP} \times RP_{ANC} \right),$$

where for each stratum of parity by fertility risk-category, F_{GFP} and RP_{ANC} indicate the proportion of women among the GFP and the relative HIV prevalence with respect to that among ANC attendees, respectively, and, for each parity stratum, P_{ANC} indicates the HIV prevalence observed among ANC attendees.