Original
articleSeroprevalence and incidence of genital ulcer
infections in a rural Ugandan population

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Objectives: To determine age-sex specific seroprevalence and incidence rates of *Treponema pallidum*, *Haemophilus ducreyi*, and HSV-2; to assess the association between HIV-1 status and incidence of these STIs; and HSV-2 serostatus with number of lifetime sexual partners.

Methods: Antibodies against HIV-1, *T pallidum*, *H ducreyi*, and HSV-2 infections were tested using approximately 1000 paired (2 year interval) sera collected from a rural adult (15–54 years) population cohort in south west Uganda.

Results: Overall HIV-1 prevalence was 4.9%. Prevalence for *T pallidum* was 12.9% among males and 12.6% among females. The corresponding rates for *H ducreyi* were 9.8% and 7.3% respectively. HSV-2 prevalence rates were considerably lower in males (36.0%) than in females (71.5%), $p < 0.001$. Incidence rates for *T pallidum* per 1000 person years of observation were 8.4 for males and 12.3 for females. The corresponding rates for *H ducreyi* were 24.6 and 20.0 and for HSV-2 were 73.2 and 122.9 per 1000 person years of observation, respectively. The RR of HSV-2 incidence was 3.69 in HIV seropositive cases versus HIV seronegative after adjusting for age and sex. The corresponding RR for *H ducreyi* was 3.50 among female HIV positive cases versus negatives with no effect seen in males. Association between HIV-1 prevalence and prevalence of other STIs was significant (Mantel–Haenszel test) for *H ducreyi* ($p = 0.01$) and for HSV-2 ($p = 0.004$) but not for *T pallidum* ($p > 0.4$). HSV-2 prevalence was associated with number of lifetime sexual partners (females, $p = 0.003$; males, $p = 0.08$).

Conclusions: The results have provided a reliable estimate of the magnitude of the STI problem and demonstrated an association between HIV-1 status and serology of other STIs in a general rural population in sub-Saharan Africa. The study has also highlighted a correlation between HSV-2 seropositivity and number of reported lifetime sexual partners.

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Keywords: genital ulcer infections; HIV-1; rural population

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Introduction

Although it is generally recognised that sexually transmitted infections (STIs) contribute a major public health problem, little information exists on the burden of STIs in general populations of sub-Saharan countries.^{1,2} Studies done on STIs have been mainly on selected populations such as females attending gynaecological, obstetric, and family planning clinics, STI clinic attenders, and among female sex workers.^{3–5} Findings from such studies cannot be generalised to general populations in whom most STIs are either unrecognised or asymptomatic. The scarcity of accurate data is consequently a handicap in designing appropriate control measures. Yet such measures are particularly important in the context of the HIV epidemic since it is now well established that STIs, particularly those causing genital ulceration, facilitate HIV transmission and HIV infection may simultaneously prolong or augment the infectiousness of individuals with STIs.^{6–9} A more meaningful source of data would be from large population serological surveys using the current assays now available for most STIs. Such population surveys done on longitudinal serological studies would also provide data on recent exposures and be useful for surveillance and evaluation of interventions.

In 1994 we published results from an exploratory STD serological study of the adult

population of two villages in south west Uganda.¹⁰ Paired blood samples with an interval of one year from a total of 294 adults were tested. The results indicated that the STIs studied—*Treponema pallidum*, *Haemophilus ducreyi*, *Chlamydia trachomatis*, and herpes simplex virus types 1 and 2—were common. Because of the small numbers the precision of the study was low, particularly for age and sex subgroups. To contribute further to the understanding of the descriptive epidemiology of STIs in rural sub-Saharan populations, we conducted a larger study from adult members of a general population cohort. The specific objectives were to determine the age and sex specific prevalence and incidence rates of serological reactivity to *T pallidum*, *H ducreyi*, and herpes simplex virus type 2 (HSV-2); to assess the association between HIV-1 status and incidence of other STIs; and to assess HSV-2 serostatus with number of lifetime sexual partners, as it has been suggested that HSV-2 serology could be a useful indicator in monitoring sexual behaviour changes.¹⁰

Methods

In 1989 the Medical Research Council Programme on AIDS in Uganda enrolled a rural population cohort from 15 neighbouring villages in south west Uganda to study the population dynamics of HIV-1 transmission and associated risk factors. The cohort has been

Table 1 Age-sex seroprevalence* and incidence of *T pallidum*

Age (years)	Prevalence			Incidence		
	N	Pos	%	Pyof†	Inc	Rate
Males:						
15-19	101	1	1.0	183.4	0	0.0
20-24	50	6	12.0	128.8	1	7.8
25-34	88	13	14.8	165.1	1	6.1
35-44	64	18	28.1	120.1	1	8.3
45+	54	8	14.9	114.9	3	26.1
Total	357	46	12.9	712.3	6	8.4
95% CI			(9.6-16.8)			(3.8-18.7)
Females:						
15-19	96	3	3.1	181.8	1	5.5
20-24	85	9	10.6	181.3	2	11.0
25-34	154	27	17.5	333.5	3	9.0
35-44	121	18	14.9	234.2	4	17.1
45+	82	11	13.4	211.0	4	19.0
Total	538	68	12.6	1141.8	14	12.3
95% CI			(10.0-15.7)			(7.3-20.7)

*Both RPR and TPHA positive.
†Person years of observation.
Seroincidence rates per 1000 person years of observation.

followed annually through annual demographic and serological surveys.¹¹ The sampling and follow up rate have been described elsewhere¹² but, briefly, all resident adults (about 5000) in the study area were selected for the main study. Compliance rates were approximately 80% at baseline survey, 66% and 60% for 1990-1 and 1992-3 annual survey rounds respectively. Non-compliance was not, however, cumulative and 88% of the last round resident population had complied at some time. The present study utilised sera from the main surveys with the objective of selecting and testing a random sample of 1000 adults aged 15-54 years with paired sera from 1990-1 and 1992-3 surveys. Sufficient stored sera were available for testing at least one sample from 924 adults.

In addition to the selected paired samples from the whole population we also tested paired samples from HIV incident subjects at two different time points. In order to increase the number of available subjects we included pre- and post seroconversion samples for the incident cases identified during annual surveys between 1990 and 1994. Sufficient serum samples were available for 42 incident cases.

Testing for HIV-1 antibody was carried out at the Uganda Virus Research Institute, Entebbe, Uganda, using two independent ELISA systems (Recombigen HIV-1 EIA, Cambridge Bioscience, USA, and Wellcozyme HIV-1 Recombinant, Wellcome Diagnostics, UK) and confirmed with western blot using Novopath HIV Immunoblot (Bio-Rad Laboratories, USA) if the ELISA results were discordant or weakly concordant. The quality control procedures and test algorithm are described in detail elsewhere.^{13 14} Samples were tested for *T pallidum* and *H ducreyi* at the Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium. For syphilis serology a rapid plasma reagin card test (Macro-Vue RPR Card Test, Becton-Dickinson, USA) and a *T pallidum* micro-haemagglutination assay (TPHA, Fujirebio Inc, Japan) were used. Both tests were performed qualitatively and repeated in a quantitative assay if the qualitative test showed

reactivity. Serum immunoglobulin G antibodies to *H ducreyi* were assayed in an ELISA system using an ultrasonicated whole cell antigen.¹⁵ HSV-2 samples were tested at the Viral Immunology Section, Centers for Disease Control and Prevention, Atlanta, USA. The reactivity against HSV-2 type specific glycoproteins was assessed by western blot technique.¹⁶ All laboratories received samples blind to subject characteristics. In interpreting reactivity, we followed the manufactures' instructions or, for non-commercial assays, the criteria provided by the laboratory performing the test.

The prevalence estimates have been obtained from serological findings of the first blood sample while incidence rates are based on seroconversions for the specified STIs that occurred in those seronegative at the first assessment. Estimates of incidence rates were obtained using the person years between the first and second serum sample; Poisson regression analyses were used to correct for age and sex differences. Seroincidence was assumed to have occurred midway between the dates of the seronegative and the seropositive samples.

Reported number of life sexual partners from the ongoing medical questionnaire based interviews were obtained only during the 1992-3 annual survey and the data have been linked to HSV-2 serostatus at the time of the second assessment.

Results

The HIV-1 seroprevalence in the population studied was 4.9% (95% CI 3.6-6.5%), 45 of 924 people assessed.

T PALLIDUM PREVALENCE

The age-sex prevalence (both RPR and TPHA positive) rates are shown in table 1. Results for both RPR and TPHA were available for a total of 895 people (357 men, 538 women). The overall rates for males (95% CI) were 12.9% (9.6-16.8) and for females 12.6% (10.0-15.7). The rates increased steeply between the 15-19 and 20-24 age groups from 1% to 12% for males and from 3% to 11% for females. The overall increase with age was significant ($\chi^2_{trend}=16.53$, $p<0.001$ for males, $\chi^2_{trend}=5.67$, $p=0.02$ for females). After adjusting for age there was no difference in prevalence rates between males and females.

T PALLIDUM INCIDENCE

Of 735 people initially negative for active syphilis (RPR and/or TPHA negative), and with a serum sample available, 20 (six men, 14 women) seroconverted for both RPR/TPHA. Incidence rates were 8.4 (95% CI 3.8-18.7) for males and for females 12.3 (95% CI 7.3-20.7) per 1000 person years of observation. The rates were higher in females than in males for all ages except in those aged 45 or more. The female:male rate ratio was not significant (1.32, 95% CI 0.51-3.45).

H DUCREYI PREVALENCE

A total of 893 samples had results for *H ducreyi* serology. Seroprevalence in males was 9.8%

Table 2 Age-sex seroprevalence and incidence of *H ducreyi*

Age (years)	Prevalence			Incidence		
	N	Pos	%	P _{yo} *	Inc	Rate
Males:						
15–19	101	5	5.0	172.4	4	23.2
20–24	50	3	6.0	129.7	1	7.7
25–34	87	11	12.6	170.5	6	35.2
35–44	64	7	10.9	143.7	1	7.0
45+	54	9	16.7	114.0	6	52.6
Total	356	35	9.8	730.3	18	24.6
95% CI			(6.9–13.4)			(11.3–28.6)
Females:						
15–19	96	2	2.1	179.6	2	6.7
20–24	85	1	1.2	201.2	4	19.9
25–34	153	9	5.9	354.0	9	25.4
35–44	121	14	11.6	250.4	4	16.0
45+	82	13	15.9	211.9	5	23.6
Total	537	39	7.3	1197.1	24	20.0
95% CI			(5.2–9.8)			(13.4–29.8)

*Person years of observation.

Table 3 Age-sex seroprevalence and incidence of HSV-2

Age (years)	Prevalence			Incidence		
	N	Pos	%	P _{yo} *	N	Rate
Males:						
15–19	101	10	9.9	163.0	5	30.6
20–24	52	14	26.9	115.8	12	103.6
25–34	89	42	47.2	105.1	8	76.1
35–44	66	32	48.5	68.7	6	87.3
45+	59	34	57.6	66.4	7	105.4
Total	367	132	36.0	519.1	38	73.2
95% CI			(31.2–41.1)			(53.4–100.3)
Females:						
15–19	96	34	35.4	116.3	11	94.6
20–24	88	65	73.9	55.2	12	217.4
25–34	155	120	77.4	75.2	7	93.1
35–44	121	106	87.6	33.3	3	90.1
45+	81	62	76.5	45.5	7	153.8
Total	541	387	71.5	325.5	40	122.9
95% CI			(67.5–75.3)			(90.4–167.1)

*Person years of observation.

(6.9–13.4) and in females, 7.3% (5.2–9.8). The rates were higher in males than females across all age groups except in those aged 35–44 years (table 2). There was a highly significant increase in prevalence by age group in both sexes; in males, $\chi^2_{\text{trend}} = 6.20$, $p = 0.01$ and in females, $\chi^2_{\text{trend}} = 19.13$, $p < 0.001$. There was a suggestion that males had slightly higher rates than females after adjusting for age ($p = 0.06$).

H. DUCREYI INCIDENCE

Of 775 people initially negative for *H ducreyi* and with a serum sample available, 42 seroconverted. Incidence rates were 24.6 (95% CI 11.3–28.6) in males and 20.0 per 1000 person years of observation (95% CI 13.4–29.8) in females. The age adjusted rate ratio was not significant (0.79, 95% CI 0.43–1.46).

Table 4 Association between HIV status and incidence of other STIs

HIV status	STI incidence rates/1000 p _{yo} *								
	<i>T pallidum</i>			HSV-2			<i>H ducreyi</i>		
	p _{yo}	inc	rate	p _{yo}	inc	rate	p _{yo}	inc	rate
Negative	1760.6	19	10.8	813.3	69	84.8	1838.2	37	20.1
Prevalent	77.7	1	12.9	15.0	5	333.3	70.5	4	56.7
Incident	55.5	1	18.0	29.6	9	304.1	59.3	2	33.7

*Person years of observation.
Rate per 1000 person years.

Figure 1 HSV-2 prevalence rates by age and sex (for those aged 15–30 years).

HSV-2 PREVALENCE

Results were available for 908 adults; the overall prevalence rates were 36.0% (31.2–41.1) in males and 71.5% (67.5–75.3) in females. Rates increased with age in both males and females to approximately 60% ($\chi^2_{\text{trend}} = 48.34$; $p < 0.001$) and over 80% ($\chi^2_{\text{trend}} = 48.10$; $p < 0.001$) respectively (table 3). The gradual increase with age is clearly seen in figure 1 which shows the prevalence by age and sex for those aged 15–30 years. Across all age groups the rates in males are significantly lower than in females. The peak prevalence rates are reached at about 21 years in females and much later in males, about 27 years.

HERPES SIMPLEX VIRUS TYPE 2 INCIDENCE

Of 373 people initially seronegative for HSV-2 and with sample available, 78 seroconverted, incidence rates were 73.2 (95% CI 53.4–100.3) for males and 122.9 (95% CI 90.4–167.1) per 1000 person years of observation in females. The age adjusted rate ratio was 1.70 (95% CI 1.09–2.65), $p = 0.02$.

ASSOCIATION BETWEEN HIV-1 SEROPOSITIVITY AND THE SEROINCIDENCE AND PREVALENCE OF OTHER STIs

Table 4 shows the association between HIV status and incidence of other STIs studied, it includes data from all the HIV incident cases studied. The rate ratio of HSV-2 incidence was 3.69 (95% CI 2.06–6.61) in HIV seropositive cases versus HIV seronegative after adjusting for age and sex. The corresponding rate ratio for *H ducreyi* was 3.50 (95% CI 1.29–9.46) among female HIV positive cases versus negatives with no effect seen in males. For *T pallidum* there were too few incident cases to make any meaningful comparison.

Association between HIV-1 seroprevalence and prevalence of other STIs was significant (Mantel-Haenszel test) for *H ducreyi* ($p=0.01$) and for HSV-2 ($p=0.004$) but not significant for syphilis ($p>0.4$).

HSV-2 SEROSTATUS BY AGE AND NUMBER OF LIFETIME SEXUAL PARTNERS

A total of 778 adults (289 men, 489 women) had information on reported lifetime sexual partners and HSV-2 serology available at the time of the second assessment. There was a significant association between HSV-2 seropositivity and the reported number of lifetime sexual partners after adjusting for age and sex, $p = 0.001$, although the effect was stronger among females than males, $p=0.003$ and $p=0.08$ respectively. In females, rates of infection were high, over 60%, for all numbers of reported lifetime sexual partners and increased to over 80% among those reporting two to four partners with no major increase thereafter. In males HSV-2 prevalence rose from 23% to slightly over 60% among those with 0–1 and 10+ lifetime sexual partners respectively.

Discussion

The results of this study have confirmed our earlier data on the descriptive epidemiology of STIs which indicated that STIs are common in this rural population. We have observed overall prevalence rates of about 13% for syphilis and about 8% for *H ducreyi* with no differences between sexes. HSV-2 prevalence rates were very high, and in females were approximately twice those in males. These prevalence rates are against a background of stable HIV-1 prevalence of 8% in adults in the general population with an annual incidence rate of approximately 0.6%.¹⁷ The rate in the sample population studied was however lower (4.9%), the most probable reason being that the blood from HIV positives would be more likely to have been used up in other ongoing studies. The observed finding that peak prevalence rates in females are reached by 20 years for HSV-2 and by 25 years for syphilis, while the corresponding ages in males are 25 and 35 years respectively, indicates earlier sexual activity in females compared with males in this population.

Data on STI prevalence and particularly on incidence in general populations are generally scarce owing to difficulties associated with conducting population based longitudinal studies. This study has relied on serological testing rather than symptom recognition since we know that most STIs particularly HSV-2 do not cause easily recognisable symptoms. Our findings are based on a sample size of approximately 1000 subjects enrolled from ongoing studies of population dynamics of HIV-1 infection. Incident analysis was, however, based on slightly smaller numbers than would have otherwise been owing to a lack of sufficient volumes of samples at the different times for all individuals. The antibody assays and test algorithms were performed under rigorous quality control procedures to ensure reliable results. We are aware that the sensitivity and specificity

of the *H ducreyi* ELISA test used are not optimal. However, this test has been successfully used by several groups and has proved to be a useful tool for epidemiological studies and for definition of existing (current and past) levels of exposure.¹⁸ For *T pallidum* and HSV-2 we used the most reliable tests available which are considered to be the gold standards. Those giving a blood sample in our surveys are more likely to be compliant than those not doing so and some were more willing to give larger samples than others. We do not think, however, that compliant people have significant differences in sexual exposure and antibody test results from those who do not. In conclusion, the results of this study, in our opinion, provide a reliable estimate of the magnitude of the STI problem in the population under study.

Most available data on STI prevalence and incidence rates are STI clinic based and there are virtually none from general populations. Similarly, systematic surveillance of STI epidemiology with the exception of HIV does not exist in sub-Saharan Africa.¹⁹ This is a handicap and makes comparison of our findings with others rather difficult. There is limited literature on syphilis data in general populations; baseline survey results from a community trial in rural Tanzania showed prevalence of active syphilis in the range of 8–9%.²⁰ In another community based trial of STD control for HIV-1 infection in rural south west Uganda, 10.2% of women had active or recent syphilis infection.²¹ Another comparable population based study, in Kagera region, Tanzania, found an overall prevalence of 5.9% for active syphilis among adults, and 13.5% for past syphilis with an overall incidence of 11.6 per 1000 person years at risk.²² In the same study a highly significant association between HIV-1 infection and syphilis was found, a finding that we did not observe in this study possibly because of smaller numbers. There is now available evidence that genital ulcerative diseases facilitate transmission and acquisition of HIV-1^{23–24} but we are not aware of any study that has looked at the association between HIV-1 status and incidence of other STIs. We have found that the risk of incidence for HSV-2 and *H ducreyi* is much higher among HIV prevalent and incident cases than in HIV negative individuals. Similar associations have been found in other studies with the prevalence of HSV-2 shedding in HIV seropositive women being up to four times greater than in HIV seronegative women.²⁵

The observed female-male differences for HSV-2 prevalence and incidence rates have been documented by other studies.^{26–28} The difference is believed to be due to the greater mucosal surface of the female genital tract, which results in higher risk of transmission to women. Males are also thought to have higher rate of disease recurrence which is likely to make them more infectious²⁹; the estimated risk of a susceptible female contracting HSV from an infected male is 80% following a single contact.³⁰ It has also been suggested that there is a more vigorous immune response by women

which may also partly explain their higher seroprevalence.³¹

There are difficulties in obtaining reliable population based sexual behaviour data. We have assessed the association between HSV-2 seropositivity and reported number of lifetime sexual partners to see whether this could be used as a marker of past sexual behaviour since it is a chronic and persistent infection primarily transmitted sexually. The correlation of seropositivity with number of reported lifetime sexual partners is better and significant for females, a finding that has been observed in other studies.³¹ In sexual behavioural intervention trials HSV-2 incidence could be used as an objective marker of sexual behaviour.

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Contributors: Anatoli Kamali was involved in the study design, directly supervised the field data collection, and was highly involved in data analysis and writing the paper. Andrew Nunn, programme statistician, instrumental in designing the study, did most of statistical analysis and assisted greatly in writing the paper. Daan W Mulder, head of the Medical Research Council Programme at the time the study was conducted, was responsible for the overall direction of the study. He was the key person in the study design and gave tremendous support in writing the paper. Eddy Van Dyck was responsible for testing sera for *H. ducreyi* and *T. pallidum* in Antwerp and interpretation of test results. In addition, he contributed to the writing of the paper. Jim G Dobbins was responsible for testing sera for HSV-2 at CDC Atlanta and interpretation of the test results. James AG Whitworth took over from Daan Mulder as the head of the programme. He was a key person in the whole process of data analysis and writing the paper from the initial draft up to the time of submission.

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