

Declining HIV-1 incidence and associated prevalence over 10 years in a rural population in south-west Uganda: a cohort study

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Summary

Background In Uganda, there have been encouraging reports of reductions in HIV-1 prevalence but not in incidence, which is the most reliable measure of epidemic trends. We describe HIV-1 incidence and prevalence trends in a rural population-based cohort between 1989 and 1999.

Methods We surveyed the adult population of 15 neighbouring villages for HIV-1 infection using annual censuses, questionnaires, and serological surveys. We report crude annual incidence rates by calendar year and prevalence by survey round.

Findings 6566 HIV-1 seronegative adults were bled two or more times between January, 1990, and December, 1999, contributing 31 984 person years at risk (PYAR) and 190 seroconversions. HIV-1 incidence fell from 8.0 to 5.2 per 1000 PYAR between 1990 and 1999 ($p=0.002$, χ^2 for trend). Significant sex-specific and age-group-specific reductions in incidence were evident. Incidence was 37% lower for 1995–99 than for 1990–94 ($p=0.002$, t -test). On average, 4642 adult residents had a definite HIV-1 serostatus at each yearly survey round. HIV-1 prevalence fell significantly between the first and tenth annual survey rounds ($p=0.03$, χ^2 for trend), especially among men aged 20–24 years (6.5% to 2.2%) and 25–29 years (15.2% to 10.9%) and women aged 13–19 years (2.8% to 0.9%) and 20–24 years (19.3% to 10.1%) (all $p<0.001$, χ^2 for trend).

Interpretation Our findings of a significant drop in adult HIV-1 incidence in rural Ugandans give hope to AIDS control programmes elsewhere in sub-Saharan Africa where rates of HIV-1 infection remain high.

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Introduction

As the HIV/AIDS epidemic starts its third decade, the spread continues at a frightening pace in sub-Saharan Africa. In southern Africa, for example, where presence of a severe epidemic has only lately been officially recognised, evidence points to a fast expanding epidemic.^{1,2} Uganda, one of the countries in Africa where the epidemic was first reported, has noted encouraging downward trends in HIV-1 prevalence in rural and urban populations since the late 1990s, from about 28% to 8%.^{3–7} Similar reductions or stabilisation in HIV-1 prevalence have been described in Senegal⁸ and Zambia,⁹ and for particular groups in Democratic Republic of Congo^{10,11} and Kenya.¹² These reductions have been attributed in part to successful intensive behaviour change campaigns, such as reduction in number of sexual partners and encouragement of use of condoms.^{3,6–14}

Reductions in HIV-1 prevalence, especially those in young adults, probably indicate concomitant falls in HIV-1 incidence. However, other factors, such as mortality rates, migration, and survey coverage,^{4,15,16} also contribute to prevalence trends. Thus incidence trends cannot be estimated directly from prevalence trends. Reductions in HIV-1 incidence trends would provide the most convincing evidence of a decrease in epidemic size, but large, long-term, longitudinal studies are needed to obtain such evidence. We describe the direction of the AIDS epidemic by analysing rates and trends in incidence and prevalence among a population-based cohort located in rural southwest Uganda who were followed up between 1989 and 1999.

Population and methods

Survey methods

The study population has been described previously,^{3,5,17} but in brief it consisted of all adults (aged 13 years and above) who were resident in a cluster of 15 neighbouring villages in rural southwest Uganda. This open cohort had been under epidemiological surveillance for HIV-1 infection by the Medical Research Council Programme on AIDS in Uganda (MRC), who had used annual censuses, questionnaires, and serological surveys since 1989.

Survey rounds began in November and ended in October (first round in 1989–90 and tenth round in 1998–99). Trained interviewers obtained sociodemographic census data (residence, migration, and vital status of all registered residents) through household visits. A monthly birth and death register maintained by local registrars has been used to supplement census data since the third survey round (1991–92). We visited the community and household yearly to explain study aims and benefits of participation. We explained how to access HIV-1 test results, answered questions, and clarified any misconceptions in the community. After obtaining

informed consent, trained survey staff administered standard risk factor questionnaires to individuals in private, after which blood was taken for HIV-1 serological tests. Questionnaires and serum samples were transported to Entebbe (about 160 km away) for further processing.

Laboratory methods

We used two independent enzyme immunoassays to establish HIV-1 status (Wellcozyme HIV-1 recombinant VK 56/57, Murex Biotech, Dartford, UK; and Recombigen HIV-1/2, Trinity Biotech, Galway, Ireland) with set algorithms. Samples discordant on enzyme immunoassay and all first time positive samples were tested by western blot (Cambridge Biotech HIV-1 western blot, Calypte Biomedical, Rockville, MA, USA).¹⁸ Reproducibility of results from this laboratory was achieved by rigorous internal quality assurance, by use of several positive and negative control samples on each enzyme immunoassay plate, and by a computerised assessment of coefficient of variance of these samples' optical densities with a cutoff of 20%.¹⁹ Additional external quality assurance was provided through the US Centers for Disease Control and Prevention model performance evaluation program (CDC-MPEP).

Ethical issues

Survey staff encouraged participants to request their HIV-1 test results from trained counsellors who worked within the study area.²⁰ In line with Uganda national guidelines for HIV testing, results were only issued to respondents in person after pre-test and post-test counselling (Uganda AIDS Commission policy statement). Residents had access to free medical care from a purpose-built study clinic, stocked according to the Uganda Essential Drug List, since 1995. The HIV-1 status of participants was masked to local survey and clinical staff for reasons of confidentiality. The Uganda National Council for Science and Technology gave ethical approval for the study.

Statistical methods

Census, questionnaire, and laboratory data were double entered with Foxpro 2.6 for Windows (Microsoft Corp, USA) and checked for consistency before statistical analysis was done with Stata version 6.0.

We calculated incidence rates for adult residents with an initial HIV-1 seronegative result who were bled two or more times. Follow-up began at the date an individual was first bled and ended at the estimated date of seroconversion (endpoint) or date last bled if still HIV-1 seronegative (censoring). We calculated date of seroconversion as the midpoint between the last negative and first positive HIV-1 result. HIV-1 incidence rate was estimated for 10 calendar years (1990–99). The numerator was the total number of seroconversions occurring during the calendar year and the denominator was the total number of person years at risk (PYAR) accrued in the calendar year. To find out whether HIV incidence varied between the early and late periods (1990–94 and 1995–99, respectively), we compared the average HIV-1 incidence in those periods using a *t*-test. We used χ^2 test for linear trends to assess the significance of incidence rate trends across calendar years. We also assessed incidence rates by sex and by age group separately. Because of limited power due to small numbers, we used a single, arbitrarily chosen cutpoint of age 35 years. Age-sex standardisation of incidence rates was not necessary because the population distribution,

the median age, and the age distribution for each sex stayed roughly the same throughout the 10 years of the survey. A least-squares linear regression was computed to assess the yearly average change in incidence.

We estimated prevalence for ten survey rounds (1989–99) using all definitive HIV-1 serological results for each round. Adult residents censused but not bled at a particular round were classified as HIV-1 seronegative if they tested seronegative at a later round and seropositive if they had tested seropositive at an earlier round. With this method of imputation (interpolation and extrapolation) we could assess HIV-1 status for some individuals who were censused but not bled at particular rounds, and thereby improved coverage by making use of the longitudinal nature of this cohort study. One possible bias of this method is to underestimate the prevalence of HIV-1 at the earliest rounds and to overestimate the prevalence at the later rounds. However, prevalence measured this way compared with cross-sectional measures showed no noticeable systematic bias apart from survey rounds one and ten (figure 1).

The numerator for the prevalence rate was the number of adults with an HIV-1 seropositive status and the denominator was the total number of adult residents with a definite HIV-1 serostatus at the round. Coverage was defined as the proportion of adult residents with known HIV-1 status divided by the total number of adults censused at that round. To assess trends in HIV-1 prevalence, the prevalences for different age-sex groups were computed. The population was split into seven age categories (13–19, 20–24, 25–29, 30–34, 35–39, 40–44, and ≥ 45) for this purpose. We used the Wilcoxon sign test to compare differences in HIV-1 prevalence between men and women at each yearly survey round. We examined differences in average HIV-1 prevalence over the entire study period among people who migrated into the cohort (joiners) and among those who migrated out of the cohort (leavers) with the Wilcoxon matched-pair test.

To relate epidemiological findings to degree of HIV-1 awareness in the population, we did a descriptive analysis of questions about sources of information and counselling asked at the tenth yearly survey round.

Role of funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

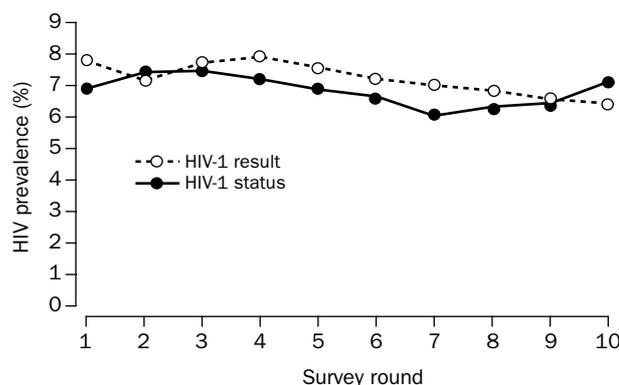


Figure 1: Comparison of imputation* and repeated cross-sectional† methods to calculate HIV-1 prevalence over ten survey rounds

*imputed HIV status $p=0.03$, †HIV test result $p<0.001$, both χ^2 test for trend.

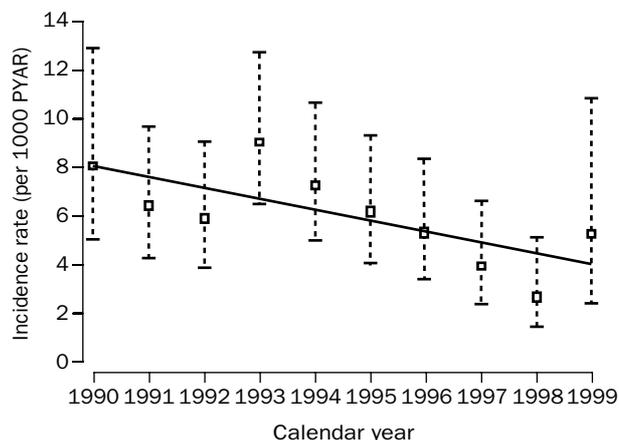


Figure 2: **Changes in HIV-1 incidence rate during 10 calendar years of follow-up**

Bold line=least squares regression estimated from incidence rates ($p=0.002$, χ^2 test for trend). Horizontal bars=95% CI.

Results

A total of 5238 women and 4589 men were censused and bled between January, 1990, and December, 1999. Of these, 463 women and 283 men were positive for HIV-1 on their first sample and were excluded from incidence analysis. Of the remaining 9081 HIV-1 seronegative adults, 3408 women and 3158 men were bled two or more times. 97 women and 93 men seroconverted in 31 984 PYAR. The median age at seroconversion was 27.0 years (IQR 21.1–37.7) and was lower for women (23.2 years) than for men (29.8 years). The median interval between the last HIV-1 seronegative and first seropositive result was 1.1 years (IQR 1.0–2.3). The overall incidence for 10 calendar years (1990–99) was 5.9 per 1000 PYAR (95% CI 5.2–6.8).

Figure 2 shows the HIV-1 incidence rate by calendar year. The confidence intervals of the first and last year's incidence rates are wide because most participants did not contribute to a full year of observation (only 2122 PYAR in 1990 and 1358 PYAR in 1999 compared with greater than 3400 PYAR for all intervening years). HIV-1 incidence declined steadily from 8.0 per 1000 PYAR in 1990 to 5.2 per 1000 PYAR in 1999 ($p=0.002$, χ^2 for trend), apart from in 1993 when we noted a spike. 37% of the decrease in incidence took place between 1990–94 (7.3 per 1000 PYAR) and 1995–99 (4.6 per 1000 PYAR, $p=0.002$, t test). With regression analysis based on these 10 years of incidence rates, the average yearly reduction in incidence was about 0.45 per 1000 PYAR. There were significant falling trends from 1990 to 1999 by sex

Survey round	Population censused	Known HIV-1 status (n)	Coverage (%)	HIV-1+ (n)	Prevalence (%)	
					Rate	95% CI
1	4997	4913	98.7	340	6.92	[6.22–7.70]
2	5233	4782	91.4	353	7.38	[6.65–8.19]
3	5447	4788	87.9	360	7.52	[6.78–8.34]
4	5340	4581	85.8	332	7.25	[6.51–8.07]
5	5364	4637	86.5	321	6.92	[6.21–7.72]
6	5256	4534	86.3	298	6.57	[5.87–7.36]
7	5223	4521	86.6	278	6.15	[5.47–6.92]
8	5436	4669	85.9	294	6.30	[5.62–7.06]
9	5633	4727	83.9	303	6.41	[5.73–7.17]
10	5772	4271	74.0	305	7.14	[6.38–7.90]

Coverage is ratio of people with known HIV-1 status divided by total number of people censused during the round.

Table 1: **Adult crude HIV-1 prevalence rate (%) by round**

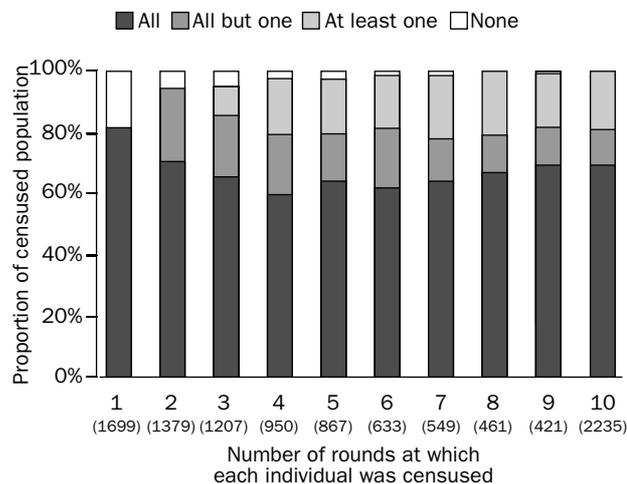


Figure 3: **Longitudinal coverage in the cohort**

Number of participants for each round is shown in parentheses.

(women from 6.4 per 1000 PYAR to 4.4, $p=0.03$; men from 9.7 to 6.0, $p=0.045$) and by age group (age ≤ 35 from 7.2 to 7.0, $p=0.04$; age >35 from 9.2 to 2.0, $p=0.008$).

For ease of comparison with rates published by UNAIDS, webfigure1 (<http://image.thelancet.com/extras/01art10410webfigure1.pdf>) shows HIV-1 incidence rate by calendar year, for adults aged 15–49 years. Again, HIV-1 incidence fell steadily from 8.0 per 1000 PYAR in 1990 to 5.2 in 1999, apart from in 1993 when we noted a spike. The downward trend for this subset was of lower significance than for the entire study cohort ($p=0.009$, χ^2 for trend).

Adult HIV-1 prevalence declined from round one to round ten. ($p=0.03$, χ^2 test for trend; table 1). The high prevalence rate at round ten can probably be attributed to the apparent low coverage because we could not use round 11 HIV-1 results to impute HIV-1 status among the HIV-1 seronegative non-responders at round ten. Otherwise, coverage was good, and at least 80% of individuals censused had known HIV-1 status at each round. Longitudinal coverage was also good, with about 80% of participants having an HIV-1 status for all, or all but one, of the rounds at which they had been censused (figure 3). By comparison, prevalence rates based on HIV-1 test results from the yearly cross-sectional surveys fell significantly from 7.8% at round one to 6.4% at round ten ($p<0.001$, χ^2 test for trend).

Changes in prevalence by age and sex group are shown in figure 4. Women had higher HIV-1 prevalence than men throughout the period of observation (7.7% vs 6.3%; $p=0.002$, Wilcoxon sign test). However, HIV-1 prevalence fell significantly during the study period in young women: from 2.8% to 0.9% in those aged 13–19 years and from 19.3% to 10.1% in those aged 20–24 years. For men, a significant decline was seen during the study period in 20–24 year olds (from 6.5% to 2.2%) and 25–29 year olds (from 15.2% to 10.9%). Increasing prevalence was recorded in women aged 30–34 years (from 10.7% to 20.6%) and 35–39 years (from 8.3% to 14.7%). In other age groups prevalence stayed roughly constant.

For direct comparison with rates published by UNAIDS, webfigure2 (<http://image.thelancet.com/extras/01art10410webfigure2.pdf>) provides the HIV-1 prevalence rates for each survey round by sex, for adults aged 15–49 years. HIV-1 prevalence fell from 9.8% at round

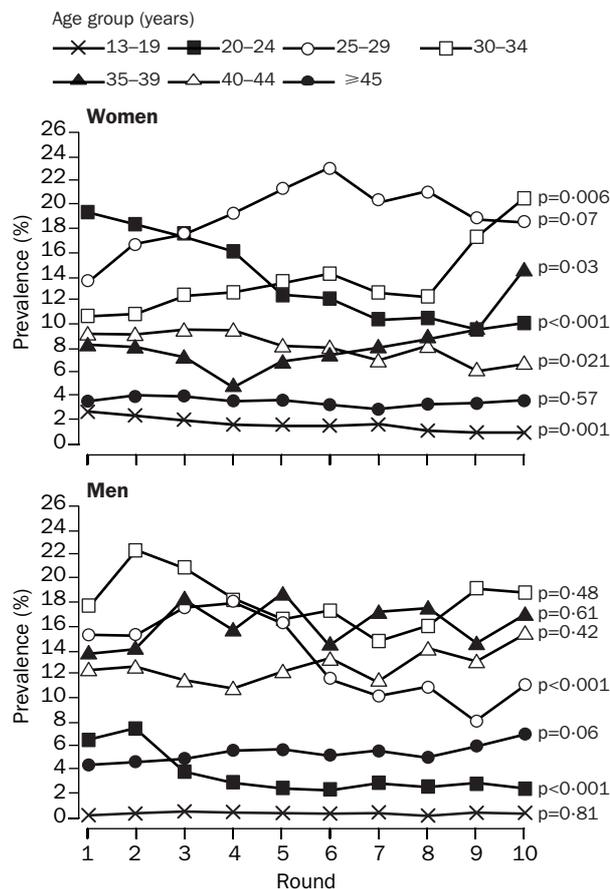


Figure 4: HIV-1 prevalence by age group according to sex
p values are for χ^2 test for trend.

one to 7.8% at round ten ($p < 0.001$), with consistently higher rates in women than in men. As expected the prevalence for people aged 15–49 years was higher than for the overall study population.

As expected, HIV-1 prevalence rates were consistently higher in migrants than in the general population (table 2). Mean HIV-1 prevalence over the entire study period was consistently higher (apart from round 5) in joiners than in leavers (13.6% vs 10.2%, respectively, $p = 0.04$, Wilcoxon matched-pair test).

Data from round ten showed high awareness about HIV-1 infection: 59% of respondents had heard an

Survey round	Prevalence rate (%)	Prevalence rates for migration			
		Joiners		Leavers	
		n	Rate	n	Rate*
1	6.92	820	10.2
2	7.38	689	13.0	712	8.4
3	7.52	727	13.0	820	10.3
4	7.25	613	13.8	546	11.8
5	6.92	602	11.4	691	11.6
6	6.57	588	14.4	576	11.8
7	6.15	563	14.2	579	8.7
8	6.30	727	12.1	664	7.6
9	6.41	722	11.5	977	5.2
10	7.14	521	9.1
Overall	7.15	..	13.6	..	10.2

For each round, this table also shows HIV-1 prevalence rates (%) within joiners and leavers. *Leavers' prevalence rates (%) are calculated for people who will leave the cohort by the next survey round and they thus should be compared with the prevalence rate among joiners at the next round.

Table 2: Adult crude HIV-1 prevalence rate by survey round and migration status

HIV-related message in the past month. Their sources included radio or newspaper (90%), friends or relatives (86%), and information disseminated by MRC survey staff about HIV-1 and AIDS when visiting the population for yearly surveys (79%). Only 8% of respondents reported having received counselling and HIV-1 test results in the past 12 months. We showed no difference in reporting frequency by HIV-1 status.

Discussion

We have shown a significant reduction in HIV-1 incidence in a rural adult general population in sub-Saharan Africa. The incidence fell significantly throughout the 1990s in all population groups: men, women, young adults, and older adults. We also noted significant reductions in HIV-1 prevalence in young adults (13–24 years), as shown in our previous reports.^{3,17} Our findings are also consistent with previous reports from Uganda of a 40% reduction in HIV-1 seroprevalence in women attending antenatal clinics over 6 years,⁹ of a fall in HIV-1 prevalence from 32% in 1991 to 10.3% in 1997 in such women aged 15–19 years,⁷ and of a reduction in HIV-1 prevalence from 21% to 16% during 3 years in young adults aged 15–24 years.⁴ Investigators in Zambia have also reported a significant reduction in HIV-1 prevalence in women aged 15–24, from 16% to 12% during 4 years.⁹ In Uganda, falls in HIV-1 prevalence have been associated with decreases in pregnancy rates in teenagers, and increases in safer sexual behaviour practices, reported age at first sex, age at first marriage among women, and reported condom use.^{3,6,7} We recorded a significant rise in prevalence of HIV-1 in women aged 30–34 and 35–39 years, which is probably a cohort effect caused by infected women ageing into these age groups. Over the course of the study the median age of HIV-1 seropositive men had risen from 32 years to 35 years, and of women from 26 years to 30 years.

Our report highlights the need for long-term follow-up before reliable incidence trends can be detected. Even in a study of this size we noted only seven to 33 incident cases per year. Results of the two previous studies published from our cohort at 5 and 7 years showed conflicting trends in HIV-1 incidence. In one we concluded at 5 years that although HIV-1 prevalence was stable, incidence among women seemed to increase. In retrospect, the spike seen in 1993 probably influenced our conclusions.¹⁷ Similarly, assessment at 7 years failed to show a significant fall in HIV-1 incidence.³ Study results of HIV-1 incidence in neighbouring Rakai district also showed stable incidence at 3 years of observation.⁴ Short follow-up most likely limited the power of these studies. However, because the results of these studies showed that HIV-1 prevalence was falling in young adults, a group in which infection time is short and mortality low,^{5–7} concomitant falls in HIV-1 incidence were suspected.

By contrast with our previous analyses in which we used serial cross-sectional data to monitor prevalence trends, for this analysis we used the longitudinal property of the data to describe prevalence trends. This approach allowed us to make use of all available longitudinal data from the cohort and to achieve a high coverage of HIV-1 status for the resident population at any particular survey round. Since the probabilities of participation by a specific individual at different rounds are intrinsically correlated, to determine the magnitude or the direction of bias in trends derived from cross-sectional data is difficult. Strickler and others¹⁶ have done a detailed review of potential bias due to serial cross-sectional surveys. By use of the current method of analysis we constrained the

direction of bias and could estimate its magnitude with greater certainty and take it into account. The systematic bias caused by the use of HIV-1 serostatus from another survey round if a particular person was not bled at that round was small, and served to diminish the magnitude of reductions in HIV-1 prevalence trends that we report here. An analysis of the prevalence trend truncated to remove the first and last survey rounds (which are the most biased) shows a highly significant fall in prevalence (8.6% at round two and 7.0% at round nine; $p < 0.001$).

Our results are from a large, long-term, well characterised cohort with excellent follow-up. However, several potential biases need to be considered. HIV-1 incidence trends are sensitive to case ascertainment, prevalence, migration, mortality, and completeness of follow-up.^{4,15} This was an open cohort in which people moved freely both into and out of the group, but the demographic distribution of the population was largely unchanged during the study, and we did not find a group of consistent non-responders from our comparison of cross-sectional and imputed data. Variability in coverage at different rounds may have introduced some uncertainty in estimates of dates of seroconversion, and affected estimation of rates of HIV-1 infection by calendar year. Although almost all individuals who seroconverted early in the study were identified and contributed to HIV-1 incidence rates, some recent seroconverters will not have been identified because they have not yet had a positive test result and so do not contribute to incidence rates. Consequently, we expect estimates for the early time points to be robust and those for the later time points to change upwards in future. However, because the median period between last negative and first positive tests was 1.1 years, and 64% of individuals had an estimated date of seroconversion within 24 months of their last HIV-1 negative result, we do not think that the direction and strength of the falling trends will change much in future. It is theoretically possible, but unlikely, that a few seroconversions were not detected by our testing algorithms. Our HIV-1 test results showed high sensitivity and specificity (98.4% and 100%, respectively) in the study period,¹⁹ and quality and reproducibility of results from our laboratory were confirmed through external quality assurance and computerisation. Indeed, with experience, our results are likely to have improved.

Migration could take place differentially among individuals with different risk characteristics for seroconversion, and this explanation, although unlikely, is being explored. Previous analyses failed to attribute HIV-1 prevalence trends to selective out-migration of HIV-1 seropositive individuals.²¹ We noted that, overall, in-migrants had higher HIV-1 prevalence than did out-migrants. Therefore declines in HIV-1 prevalence are unlikely to be due to selective migration.

Interventions to treat or prevent sexually transmitted disease (STD) are generally accepted to result in reduced rates of new HIV-1 infections.^{22,23} No specific STD interventions were applied to this population, although participants received free treatment from the study clinic. Our casual observation suggests that prevalence of reported STD signs and symptoms have changed little in the population. Delays in seeking medical help and use of inappropriate treatment continue to characterise STD treatment-seeking behaviour in this population.²⁴ A carefully designed comparative study would be required to assess effect of interventions such as STD treatment provided by the clinic or the educational messages provided through mobilisation activities. Falling HIV-1 incidence and prevalence in Uganda, where AIDS

programmes have had political commitment since the late 1980s, are quite possibly due to vigorous and continuous countrywide AIDS education and condom promotion activities.^{25,26} However, in this cohort, a Hawthorne effect (change of behaviour induced by study activities) should be considered as part explanation for the recorded trends. Knowledge of HIV-1 status among individuals negative for HIV-1 might be a powerful motivation to change behaviour. However, rates of uptake of counselling and requests for HIV-1 results were low and did not differ by HIV-1 status. Similar disappointing rates have been described by others.^{27,28} Therefore, decisions based on knowledge of HIV-1 status are unlikely to have determined the trends we report.

These trends are consistent with the risk-lowering behaviour changes previously recorded for a 4-year period in this population, such as an increase in median age at first sex in boys from 17.5 to 18.2 years, an increase in median age at first marriage for girls from 18.5 to 19.5 years, a halving of the unmarried teenager pregnancy rate, and a trebling of the ever use of condoms.³ Programme activities generated a high level of awareness as demonstrated at the tenth survey round. Although programme activities were designed to be similar in content to those disseminated by the National AIDS Control Programme, they were probably more intensive. Further analyses of the characteristics of seroconverters, their potential risk factors, and any changes over time might elucidate the underlying reasons for these epidemic trends.

More than half a million people have died from AIDS in Uganda since the start of the epidemic, which still rages at unacceptably high rates throughout sub-Saharan Africa. However, our findings lend support to evidence from earlier studies of declines in HIV-1 prevalence and increases in risk-lowering sexual behaviour,^{2,6,7} and give hope that AIDS control programmes can control the AIDS epidemic with messages about changes in behaviour.

Contributors

S M Mbulaiteye was study coordinator and oversaw field data collection 1997–2000, interpreted data, and drafted the manuscript. C Mahe did most of the data analysis, contributed to interpretation of data, and helped to draft the report. J Whitworth led protocol design, contributed to interpretation of data, and edited the paper. T Ruberantwari and J Nakiyingi contributed to data analysis. A Ojwiya oversaw laboratory data collection. A Kamali was study coordinator and oversaw field data collection 1990–97. All authors commented on and contributed to the final draft of the manuscript.

Conflict of interest statement

None declared.

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