The epidemiology of HIV-1 in a rural Ugandan population

(De epidemiologie van HIV-1 in a rurale populatie in Oeganda)

PROEFSCHRIFT

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To the population of Kyamulibwa
and the staff of the MRC/ODA/UVRI
Programme on AIDS in Uganda

Contents

Chapter 1

Introduction: The Masaka Cohort Study

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HIV infection and AIDS are currently among the most pressing global public health issues (1). The World Health Organization estimates that since the beginning of the pandemic in the late 1970s to the end of 1994 a total of 18 million adults and 1.5 million children had become infected with HIV, 11 million cases in Africa alone (2).

In Uganda, the first cases of clinical AIDS were recognised in 1982 in the Rakai district situated in the South-West of the country (3). By the end of 1988 a cumulative total of about 6,750 AIDS cases had been reported to the Ministry of Health; the majority of cases were residents of Kampala, the capital, and Rakai and neighbouring Masaka districts. There is little doubt that the reported number is a considerable underestimate of the actual figure. Available data on the HIV seroprevalence in adults living in Kampala suggested that the level increased from about 10% in 1985 to 18% in 1988 (4). In 1988 adult seroprevalence levels were of the order of 1% in some rural villages in Northern Uganda and 30% or more in some villages in South-West Uganda. Thus, a major HIV epidemic was emerging.

In 1987, the Government of Uganda requested the help of the British Medical Research Council (MRC) to deal with the AIDS epidemic. This request resulted in the development of a multidisciplinary research programme, the MRC Programme of Research on AIDS in Uganda. The Programme, based at the Uganda Virus Research Institute in Entebbe, was developed in close collaboration with the Ugandan counterparts following discussions with the Ugandan scientific community, and was directed by the author from its start in 1988 until September 1994. The work described in this thesis was carried out as an integral part of the MRC Programme activities.

The aims of the programme were to investigate the epidemiology of HIV-1 infection and the natural history of HIV-1 associated disease in rural Uganda, and to contribute to the development of AIDS control strategies. More specifically, the aims were to quantify the role of biological and behavioural risk factors for the transmission of HIV-1; to determine the rate of progression from HIV infection to disease and from disease to death, and risk factors for such progression; and, to evaluate community interventions aiming at a reduction in the transmission of HIV. As to date HIV-2 has not been identified in Uganda, and this thesis will deal with HIV-1 only.

Background

In 1988 knowledge of the epidemiology of HIV-1 in Africa was largely based on studies of patients attending urban hospitals and on selected urban populations, as comprehensively reviewed by Francis and Quinn (5), Piot and Carael (6), Piot et al (7,8) and Quinn et al (9).

Limited information was available on the prevalence of HIV-1 among rural populations but no data existed on the incidence of HIV-1 infection or on the HIV-associated mortality in such populations. There was strong evidence that among African adults heterosexual contact was the predominant mode of HIV-1 transmission: the highest prevalence of infection was among those sexually active, the male:female ratio among AIDS patients was 1:1, and the risk of being infected with HIV was strongly associated with the reported number of (hetero)sexual partners (10), contact with a female prostitute (11), and with the presence of other sexually transmitted diseases (STDs) (11). Mother-to-child transmission had been identified as the most important infection route in children. Transmission through transfusion of contaminated blood was at the time considered to be important in both adults and children. The relative importance of these transmission routes or the importance of contaminated needles or sharp instruments was not known. There were some indications that transmission by other means such as intimate non-sexual contact or insect vectors was much less important (12). Homosexuality and intravenous drug abuse were not reported.

The results of studies on heterosexual transmission suggested that both male-to-female and female-to-male sexual transmission occured but in most studies no relationship was found between the risk of transmission and length of relationship or number of acts of sexual intercourse. This suggested the possibility of a marked heterogeniety between individuals in infectivity and possibly in susceptibility, and also within individuals in infectivity during the long incubation period from HIV infection to disease (13). The risk of heterosexual transmission appeared to be similar to that observed in studies in industrialised countries, with a suggestion that female-to-male transmission might be less efficient than male-to-female (13).

There was mounting evidence that STDs could be important cofactors for enhancing HIV transmission (14). While the evidence for an association between HIV infection and the presence of other STDs was consistent in many studies, STDs could just be a marker for sexual behaviour and prospective studies were required to determine if STDs were an independent risk factor for HIV infection. Two such studies conducted in Nairobi by Plummer et al among female prostitutes and among their male clients showed an increased susceptibility for HIV-1 infection in prostitutes with genital ulcers (15) and increased infectivity of these women (16). Holmberg et al showed a temporal association between HSV-2 infection and increased risk for the acquisition of HIV-1 in a study of homosexual men (17). In addition, it was shown that infections with C. trachomatis may increase the susceptibility for HIV infection in women, possibly due to increased friability of the cervix (17). No temporal associations between other STDs and the risk of HIV infection had been observed. HIV antigens had, however, been identified in lymphocytes from vaginal and cervical secretions, but not in genital epithelial cells (11). This suggested that conditions which increase the number of lymphocytes in the female genital tract may potentiate the risk of HIV transmission by increasing the pool of infected cells in

a seropositive person or the pool of target cells in a seronegative person (14). It was plausible, therefore, that all STD pathogens which elicit an inflammatory response could potentiate the risk of HIV transmission. There was some indication that oral contraceptive use might increase the susceptibility for HIV infection in women (15). Explanations for such an effect include an increase in the area of cervical ectopy and an increased risk of infection with C. trachomatis caused by oral contraceptives (18). Finally, the studies from Nairobi suggested that circumcised men were at a lower risk of HIV infection than men who were not circumcised (19).

Available data from sub-Saharan Africa on the rates of disease progression from HIV infection to symptomatic disease and from disease to death suggested a progression rate from infection to disease similar to that observed for cohorts of homosexual men in the USA and Europe but a much faster progression from disease to death (6,20).

In Uganda, as in most parts of Africa, the majority of people live in rural areas. While it was considered plausible that the modes of HIV transmission and risk factors would be similar in urban and rural populations (21), the relative risks and population attributable risks could well be distinctly different in the two settings. Similarly, the natural history of disease following HIV infection observed during studies of rural populations might differ from such observations made during studies of patients in urban hospitals as a result of different exposures to infectious agents which could act as risk factors for disease progression. Finally, it was considered that the most pressing need was for research directed towards the development of effective control measures, including studies of cultural practices contributing to the spread of HIV (22), patterns of sexual behaviour, and the evaluation of the efficacy of health education interventions designed to encourage the use of condoms and to reduce the number of sexual partners (23).

Study objectives and design

The specific objectives for the first phase (1989-93) of the programme were to determine for a rural and semi-urban area

1. the age- and sex- specific prevalence of HIV-1 infection and HIV-1-associated disease;
2. the age-specific population attributable risks for HIV-1 infection through heterosexual contact, blood transfusions and other potential modes (e.g. injections, scarification, household contact, etc.), except vertical transmission, in view of the difficulty of diagnosing HIV-1 infection in infants;
3. the biological risk factors which influence heterosexual transmission of HIV-1, the relative risks associated with each of these risk factors, and their distribution in the population;
4. the behavioural risk factors which influence the heterosexual transmission of HIV-1, the relative risks

associated with each of these risk factors, and their distribution in the population.

It was further planned to initiate during this period prospective studies of a rural population

1. to ascertain the efficiency of male-to-female and female-to-male transmission of HIV-1 and the effect of risk factors, in particular STDs, on this efficiency;
2. to determine the rate of progression from HIV-1 infection to disease and from disease to death, and risk factors for such progression;
3. to evaluate the effectiveness of interventions in reducing the transmission of HIV-1.

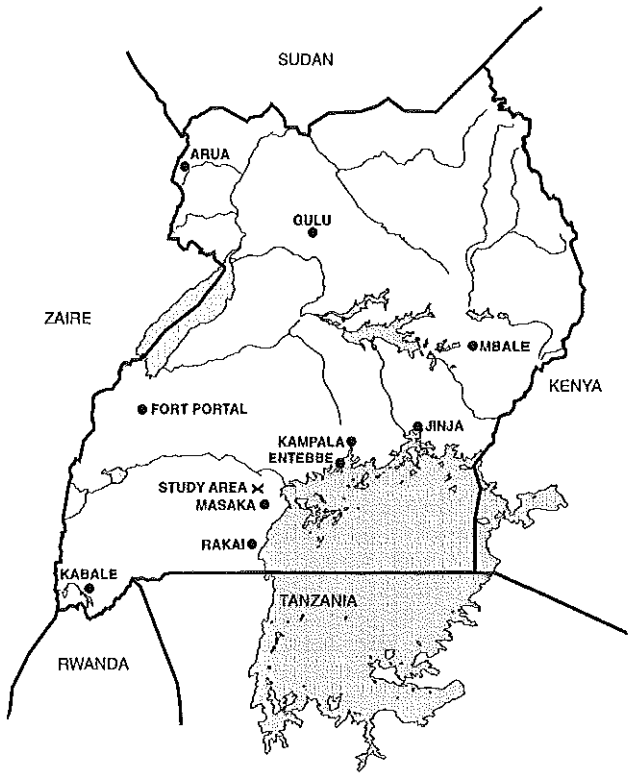
While cross-sectional surveys and case-control studies are of some value to explore possible associations between exposure factors and HIV-status, and to generate hypotheses, these designs are prone to bias due to recall and measurement errors. In general, a prospective design is preferred to ascertain causal relationships and to study the incidence of HIV-1, the HIV-1-associated mortality and the natural history of HIV-1-associated disease. The approach adopted was, therefore, to combine the follow-up of a large population cohort for study of the epidemiology of HIV-1 with the follow-up of a smaller sub-cohort for clinical studies. The population cohort would include a cluster of neighbouring villages with a total population of approximately 10,000, half of them adults. Assuming an annual incidence rate of HIV-1 infection among adults between 1% and 2%, a cohort of this size would yield 50-100 new infections annually. This was considered adequate for the planned studies. This cohort was kept under surveillance through annual repeat surveys. Members of the population cohort who were of special interest would be enrolled into the clinical cohort for detailed study during quarterly visits to the study clinic.

Ethnographic and anthropological studies, in particular of aspects of sexual, treatment seeking and coping behaviour would be carried out in both cohorts. Of particular concern was the development of methods for the collection of valid sexual histories from the majority of adults in the general population cohort and it was envisaged that initial qualitative studies would be followed by a combination of quantitative and qualitative studies.

Study area and population

Selection of the area

We intended to establish the population cohort in a rural area with a HIV-1 prevalence in adults of the order of 5% to 10%. The area was to have a stable population, be within reasonable travelling distance from Entebbe, accessible during all seasons of the year and havea medical facility of acceptable quality in the vicinity. Also, there had to be good prospects for cooperation by the population. During discussions at central level the Masaka district in South-West Uganda was identified as



Map of Uganda

the district of choice. In Masaka district extensive discussions were held with medical and administrative authorities, a number of potentially suitable areas were visited, and the Kyamulibwa sub-county was selected for the study. The area was rural, about 100 miles from Entebbe and had a mission health center and two government dispensaries. To obtain an approximate estimate of the prevalence of HIV-1 infection among adults in the area we collected 140 sera from local residents who attended the health center for various complaints but did not have symptomatic HIV-associated disease. These were tested anonymously and 24 (17%) were HIV-1 positive by ELISA and Western Blot. As it had been observed that the HIV-1 prevalence among hospital outpatients in Uganda was higher than in the general adult population we estimated that the HIV-1 prevalence among adults in the sub-county would be close to 10%.

Area and population

The total population of the Kyamulibwa sub-county was approximately 29,000 (census 1991). The average household size was 5.5 persons. In- and out- migration was relatively low with an annual rate of the order of 6%-7%. The majority of the population (70%) were Baganda, but there was a large representation (20%) of immigrants from Rwanda and Burundi who had settled, over the last 70 years, on land on the outskirts of established villages. The remainder belonged to a variety of ethnic groups. The community was predominantly Roman Catholic

(65%). Approximately 25% were Muslims and about 10% Protestants. The area was relatively fertile and mainly inhabitated by farmers who cultivate coffee as a cash crop and bananas for cooking. Compounds were scattered and normally there was only one family living on a compound. The smallest administrative unit was the "village", though there are no villages in terms of a concentration of a large number of houses except to some degree in the trading center which was situated in the middle of the sub-county.

As in the rest of Uganda, there were two political systems operating. In 1986-87 the Government established a five tier system of administration based on elected councils and committees of citizens. The village council, the Resistance Council I (RC I), was made up of all adult residents, with an executive committee of nine members. The parish council, the RC II, included the RC I executive committee members from all villages in the parish, and also had an executive committee with nine members. Similar councils and committees existed at sub-county (RC III), county (RC IV) and district (RC V) levels. Alongside this structure chiefs were appointed who acted as administrators. At times there was uncertainty about which system had the jurisdiction in a particular situation. As far as the Government was concerned the RC system was the more important one. For the purpose of the study a village was defined as the households belonging to a certain RC I council.

The area was connected to Masaka town, the district capital, by an all-weather murram (earth) road. Villages in the area were reached by the research teams using dirt tracks and a 4-wheel-drive vehicle was sometimes required during the rainy season.

As mentioned, there were a health center and two dispensaries in the area. The programme established a clinic for research purposes. Treatment was provided for patients presenting with complaints of a STD and those referred by staff of the health units in the area. Drugs were freely sold in many of the little shops in the area and in markets. The nearest hospital was approximately 20 km away.

About 15 km from the area, and linked to it by tracks used by bicycles but rarely by other vehicles, there was a busy trading center on the trans-African highway, Lukaya. The center was frequented by lorries travelling from Kenya to Rwanda, Burundi and Zaire. The HIV prevalence in places like Lukaya was high (4). There was a busy trade between Kyamulibwa and Lukaya, particularly young men from Kyamulibwa who brought bananas by bicycle to Lukaya to generate cash.

Organisational aspects of the programme

The programme had its main base at the Uganda Virus Research Institute, Entebbe (UVRI), where the administration and statistical unit were accommodated. The HIV serology work for the programme was done at the Institute and a test algorithm and

quality control procedures were developed in collaboration with the UVRI virologists (24,25).

In Kyamulibwa a field station was established which included offices, a study clinic and laboratory. A temporary clinic and laboratory was run in Lukaya. Support services of the programme in the Kyamulibwa area included a counselling service which provided counselling both to communities and to individuals who wanted to know their HIV status (26), assistance for the health facilities in the area, a community based health care service, health education activities and a water source protection scheme. Various community development activities were initiated with the long term aim of developing the community capacity, in particular to deal with the effects of the AIDS epidemic (27-29). Needless to say, the interaction between programme and community were intense. Of particular relevance for the implementation of programme activities were regular meetings with the RC III, the highest administrative and political authority in the area, and with a Health Advisory Committee which included political, religious and medical leaders of the area (27).

Under an umbrella agreement with Makerere University, Kampala, the programme collaborated with the Faculty of Social Science, the Medical School, the Institute of Statistics and Applied Economics, and the Institute of Public Health. Close liaison was maintained with the AIDS Control Programme, Ministry of Health, and with the AIDS Commission. The programme was guided by a General Advisory Committee which consisted of leading authorities of the Ministry of Health, the AIDS Control Programme, the Faculties of Medicine and of Social Sciences, Makerere University, and the UVRI.

Research implementation, 1989-94

The plans for the first years of field research were to determine the distribution of HIV-infection and of biological and behavioural risk factors for HIV infection using enrolment data of the general population cohort. HIV-positive cases and HIV-negative controls matched by age, sex and village, would then be selected for a case-control study. Using identical procedures a comparative study would be carried out in the semi-urban (trading) center. In this thesis results are presented of studies of the general population cohort on the epidemiology of HIV-1.

An ethno-demographic and medical/sero survey of a cluster of 15 villages with a total population of about 10,000 people was carried out during the period November 1989 - September 1990. Baseline data allowed us to examine risk factors for HIV-1 infection in adults (**Chapter 2.1**) and, among other things, the general and HIV-1 associated morbidity in adults (30) and the spatial distribution of HIV-1 infection (31). Additional data were collected to assess the population attributable risks for various modes of transmission (32,33). HIV-positive cases and matched negative controls identified during the baseline survey were selected for a detailed case-control study of possible risk

factors (**Chapter 2.2**). Using a survey approach, but identical interview and examination procedures, a comparative risk factor study was carried out in Lukaya (34). Baseline data served also as the basis for simulation modelling exercises of the association of HIV-1 and other STDs, and its relevance to intervention programmes in rural Uganda (**Chapter 3.2**; 35,36). The demographic and medical surveys of the general population cohort were repeated annually. This made it possible to study the seroincidence of STDs (**Chapter 3.1**), the incidence of HIV-1 infection in children and the relative importance of various transmission routes (**Chapter 4**), and the incidence of HIV-1 infection in adults (**Chapter 5**). Detailed information was obtained on HIV-1 associated mortality so that it was possible to quantify the relative risk of death among those infected with HIV-1 relative to those not infected as well as the HIV-1-associated excess mortality in the study population (**Chapter 5**). In addition, trends in the prevalence and incidence of HIV-1 in adults could be monitored (**Chapter 6**). Finally, cohort data were used to model the impact of various intervention strategies on the transmission of HIV-1 (**Chapter 7**).

Other studies were on migration and HIV-1 infection (37) and on the impact of the HIV epidemic on the magnitude of the orphan problem (38). A continuous registration of births and deaths was introduced in July 1991 to assist in obtaining a more complete assessment of all births and deaths. Reported deaths were included in a study of the use of verbal autopsy as a tool for ascertaining the HIV-attributable mortality fraction in a rural population (39).

Studies of some risk factors for the heterosexual transmission of HIV, notably the role of STDs, circumcision and sexual behaviour, were successful only in part. As regarding STDs, valuable descriptive data were collected (Chapter 3, section 1; 40,41) but as few patients with STDs attended the study clinic (40-43) it was not possible to quantify the effect of STDs on the efficiency of HIV transmission. In a study of the role of circumcision, this factor was completely confounded with being Muslim since among males only Muslims were circumcised and life-style factors (other than those we measured and controled for) associated with being Muslim may have been responsible for any difference found (44). Data on sexual behaviour was collected through quantitative and qualitative studies (45-52); much of this material is important for the design of intervention strategies but its use for epidemiological purposes is limited as it was not possible to obtain precise information on recent sexual partners for the majority of adults in the cohort. Crude male-to-female and female-to-male transmission rates were calculated using cohort data on discordant couples (53). It follows from the above that it was not possible to obtain precise estimates of the transmission efficiency in the absence of risk factors and to quantify the effect of various risk factors on the transmission efficiency; modelling approaches are, however, being used to obtain approximations. In addition, the collection of relatively detailed sexual behaviour data from participants in the clinical studies is ongoing.

During the period 1992-94 blood samples were collected from all consenting HIV-positive adults in the general cohort and from matched controls for a case-control study of the association between HLA alleles and the risk of HIV-1 infection (54). It is anticipated that the results of this study will be available in 1996. Data from this study will be used later to assess a possible association between HLA alleles and the rate of disease progression in HIV-1 infected adults.

Beginning in late 1990, a random sample of HIV-1 positive cases and matched controls were enrolled in a natural history (clinical) cohort study with the aim of determining the rate of progression of HIV-1 infection to disease, and risk factors for such progression. Incident cases of HIV-1 infection identified during annual surveys of the population cohort and matched controls are added to the study as are HIV-1 negative subjects at high risk of acquiring HIV-1 infection. Participants are examined quarterly at the study clinic. A detailed medical history is taken, questions on sexual behaviour are asked and a full medical examination is followed by extensive laboratory investigations including tests for STDs, six monthly T-cell subset counts, and the isolation and characterization of HIV strains.

In the original plan of investigation high priority was given to the implementation of a STD/HIV intervention trial. A village based randomisation scheme was foreseen. However, the mobility between villages turned out to be high and concerns were raised about possible dilution effects. Subsequently a large controlled trial was designed with parishes, scattered over Masaka district, as units of randomisation. This trial, which started in mid 1994, has three arms: in one arm behaviour change interventions only, in a second arm behaviour change interventions together with improved STD management and a comparison arm.

In the absence of a cure or vaccine AIDS control depends primarily on behaviour change strategies. Studies were carried out to ascertain cultural factors determining sexual behaviour and obstacles to behaviour change (46-50,52). Further studies examined how households were coping with illness and crisis as a consequence of the AIDS epidemic (28,29,55-57) and how the community capacity to deal with an increased morbidity and dependency burden can be enhanced (58-59). Disease perceptions and treatment seeking behaviour for malaria and STDs were studied in order to contribute to the design of interventions (40-43,60).

Finally, various methodological contributions were made (45,61-65).

In mid 1994 a pilot study started for a double-blind placebo controlled trial of pneumococcal vaccine in HIV-infected individuals. A study of sexual networks in Lukaya was being planned as were studies of cytotoxic T-lymphocyte responses. The cohort studies, the behaviour change and STD trial, and HLA and virological studies are ongoing.

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Chapter 2.1

Risk factors for HIV-1 infection in adults in a rural Ugandan community: a population study.

Nunn AJ, Kengeya-Kayondo JF, Malamba SS, Seeley JA, Mulder DW.

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Risk factors for HIV-1 infection in adults in a rural Ugandan community: a population study

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Objective: To determine sociodemographic risk factors associated with HIV-1 infection in a rural Ugandan population.

Design: A population-based survey.

Methods: All adult residents (aged ≥13 years) in a cluster of 15 neighbouring villages of the Masaka District of south-west Uganda were invited to participate in a sociodemographic and serological survey. Questions relating to sexual behaviour were asked separately in an accompanying case–control study. Socioeconomic data and an unambiguous HIV-1 serostatus were obtained by house-to-house survey for 3809 (72%) of the adult population. The association between serostatus and the following variables were analysed: age, sex, marital status, tribe, religion, education, occupational group, place and frequency of travel and recent history of sexually transmitted disease.

Results: Women aged 13–21 years were at a much higher risk than men of the same age [odds ratio (OR), 8.6; 95% confidence interval (CI), 3.0–24.5]. Married people aged <25 years were twice as likely to be infected as those who were not currently married (OR, 2.3; 95% CI, 1.5–3.7). In contrast, in those aged ≥25 years, women were at a lower risk than men (OR, 0.72; 95% CI, 0.52–0.98) as were those who were currently married compared with those who were not (OR, 0.47; 95% CI, 0.34–0.64). In both age groups those with a history of a recent genital ulcer were approximately three times more likely to be infected. Muslims had lower risks than non-Muslims (OR, 0.58 for both age groups).

Conclusions: The people most at risk of HIV-1 infection in this rural Ugandan population are young married women who had, presumably, commenced sexual activity recently.

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Keywords: Rural population, risk factors, HIV-1 infection, Uganda.

Introduction

Risk factors for HIV infection are well documented for population groups such as homosexuals, intravenous drug users and commercial sex workers. In sub-Saharan Africa, where the majority of the people live in a rural environment, the AIDS epidemic affects whole communities. It could be hypothesized that such people are at lower risk than those living in an urban environment because they are away from recognized risk arenas with their bars, nightclubs and commercial sex workers. Poor rural health services, such as absence of blood transfusion facilities, paradoxically reduces the likelihood of infection by such routes [1]. However, inadequate treatment for sexually transmitted diseases (STD) is likely to enhance the spread of HIV infection. It is clearly important to identify risk behaviour in rural populations in order to assist in the development of prevention programmes.

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Studies on risks factors in rural or mixed urban/rural sub-Saharan populations have been reported from the Bukoba District of Tanzanzia [2], the Rakai District of Uganda [3], Rwanda [4] and The Gambia [5]. This paper reports on the results of surveys conducted in a rural population in the Masaka District of Uganda. The study was undertaken as part of a broader research programme on the population dynamics of HIV-1 infection. A case–control study that specifically addresses questions of sexual behaviour is reported separately [6].

Background

The area of study is a subcounty of Masaka District in south-west Uganda situated approximately 32 km from Masaka town and 16 km from the trans-African highway at its nearest point. A cluster of 15 neighbouring villages, approximately one-third of the total subcounty population, were selected for study. The area was chosen because of its accessibility, the anticipated stability of the population and likely compliance of the local administration.

The inhabitants are mainly peasants who grow bananas as a subsistence crop and cultivate coffee for sale; the population also raises livestock, usually chickens and goats and, occasionally, cows. Households are scattered, although some are concentrated around the trading village at the centre of the study area. The predominant tribal group, the Baganda, constitute approximately 70% of the population. Substantial numbers of Rwandese immigrants have settled in the area. Medical facilities are limited to two government dispensaries and a mission health centre. The nearest hospital is 16 km from the study area.

Methods

Subjects

Beginning in late-1989, the study villages were mapped and a census and socioeconomic questionnaire administered to all consenting heads of household. Following the census, all adults (defined as those aged ≥ 13 years) were interviewed to obtain information on occupation, education, ethnicity, religion and travel. Occupation has been grouped under six categories: (1) cultivators (including cash and subsistence farmers, household staff and craftspersons); (2) traders (including shopkeepers and health practitioners); (3) teachers (and religious teachers); (4) other salaried workers (including police, drivers and office staff); (5) other occupation; and (6) no employment. No individual appears in more than one category. Professional categories take preference, so a teacher who is also a subsistence farmer and a shopkeeper appears in group 3.

Within 2–3 weeks of socioeconomic data collection data a medical team visited each of the households. All adults were invited to participate in the medical survey, which involved a brief medical history, a physical examination and the collection of a blood sample. A counselling service was available for those who wished to know their serostatus. Additional information on the study methods and the procedures adopted to improve compliance have been described in more detail elsewhere [7].

Laboratory methods

Blood specimens were transported at weekly intervals to the laboratory of the Uganda Virus Research Institute in Entebbe, where they were tested for antibodies to HIV-1. The quality control procedures and test algorithm have been described in detail elsewhere [8,9]. In brief, all sera were tested using two enzyme immunoassay (EIA) systems: Recombigen HIV-1 EIA (Cambridge Biotech Corporation, Worcester, Massachusetts, USA) and Wellcozyme HIV-1 Recombinant (Wellcome Diagnostics, Dartford, England, UK) with Western blot (WB) when indicated (Novopath HIV Immunoblot, Bio-Rad Laboratories, Watford, England, UK).

All data processing was performed in Entebbe and data entered on to databases. Data entry was performed by double entry and verification using IBM personal computers and Dbase III plus software. Data were checked for consistency and completeness.

Statistical analysis

Logistic regression analyses using EGRET were used to obtain estimates of odds ratios (OR) for each of the factors of interest, adjusted for age, sex and the age-sex interaction. Multivariate analyses were performed separately according to age (< 25 and ≥ 25 years). Factors included in the analysis were age group, sex, current marital status, tribe, religion (Muslim or non-Muslim), having an occupation, leaving the village for work, frequency of leaving the village, county or district, frequency of visiting Masaka and Kampala, history of genital ulcer and history of pain when passing urine in the previous 6 months. Level of education attained was included for those aged ≥ 25 years. Age groupings were 13–21 and 22–24 years in the younger population, and 25–34, 35 to 44 and 45 ≥ years in older people. Circumcision is a practice restricted to Muslims in this population and no additional data were collected on it. All variables associated with seropositivity at the 10% level of significance were included in the model using a stepwise procedure until no further reduction in the likelihood ratio statistic at the 5% significance level was observed.

The study was approved by the Ugandan Ministry of Health and National Council of Science and Technology.

Results

A total of 1981 inhabited households were identified and census information obtained from 1806 (91%). Of the remainder, 60 (3%) refused to cooperate and in 56 (3%) the occupants were found to be repeatedly absent. A *de jure* population of 9820 was enumerated, residence being defined as having stayed in the study area for at least the last 3 months or having recently moved to the area with the intention of staying. Adults, defined as those aged ≥ 13 years, comprised 5278 (53.7%) of the population.

The individual socioeconomic questionnaire was administered to 4494 (85%) of adults. Rates of compliance increased with age from 77% in those aged < 25 years to 91% in older people. Seventy-nine per cent agreed to give a blood sample. Both socioeconomic data and an unambiguous serostatus was available for 3809 (72%).

Seroprevalence by age and sex

Of 4175 adults with assessable serostatus, 342 (8.2%) were seropositive. Rates by sex and 5-year age group are shown in Table 1. Highest rates occurred in women aged 20–24 years (21.4%) and in men aged 25–34 years (18.1%).

Table 1. Prevalence of HIV-1 infection by age and sex.

Age (years)	Men			Women		
		Seropositive			Seropositive	
	No.	No.	%	No.	No.	%
13–14	231	0	0.0	222	2	0.9
15–19	386	2	0.5	374	25	6.7
20–24	239	27	11.3	281	60	21.4
25–29	193	35	18.1	259	36	13.9
30–34	156	28	17.9	170	21	12.4
35–39	112	17	15.2	148	12	8.1
40–44	110	13	11.8	145	14	9.7
45–49	102	10	9.8	111	8	7.2
50–54	112	5	4.5	127	6	4.7
55–59	64	2	3.1	90	3	3.3
60–64	97	1	1.0	103	3	2.9
≥65	186	9	4.8	157	3	1.9
Total	1988	149	7.5	2187	193	8.8

Marital status

Data by age and sex on the association of marital status with seroprevalence are shown in Table 2. In the 13–24-year age group rates are lowest among those who are single in contrast to the older age group, where the lowest rates are among those who are currently married or those who have been widowed, the majority of whom are aged ≥ 45 years. The rate in young single women considerably exceeds the rate in young single men. Fewer men reported themselves as divorced and many fewer as being widowed (28 men versus to 222 women).

Table 2. HIV-1 seropositivity by marital status.

Age (years)	Current marital status	Men			Women		
			Seropositive			Seropostive	
		No.	No.	%	No.	No.	%
13–24	Single	644	13	2.0	468	24	5.1
	Married	72	14	19.4	266	46	17.3
	Widowed	0	–	–	2	1	50.0*
	Divorced	2	0	0.0*	17	4	23.5*
≥25	Single	175	28	16.0	128	18	14.1
	Married	778	68	8.7	658	48	7.3
	Widowed	28	2	7.1	220	12	5.5
	Divorced	89	12	13.5	155	18	11.6

*Percentages based on less than 25 observations.

In logistic regression analyses those currently married were compared to the unmarried (single, widowed or divorced). In the 13–24-year age group there was a highly significant risk attached to being married [OR for married versus unmarried, 4.7; 95% confidence interval (CI), 3.0–7.3; $P < 0.001$], after allowing for differences in rates between sexes. However, there was also a significant sex–marriage interaction and the OR for men and women were 11.8 and 3.3, respectively. In the analysis of those aged ≥ 25 years there were significant differences between the sexes and between the age groups but no significant interactions; marriage had an apparently protective effect (OR, 0.48; 95% CI, 0.36–0.65; $P < 0.001$).

Tribe, religion and education

An analysis by tribal group (Table 3) showed no significant variation between the major groups living in the area, although there is a suggestion that rates among the Baganda are lower than those in other Ugandan tribes ($P = 0.1$) and the Rwandese ($P = 0.07$).

Seroprevalence rates by religious affiliation are shown in Table 3. The majority of the population are Roman Catholics and rates in this group do not differ significantly from those in the Church of Uganda and 'other' groups. Muslims, however, have significantly lower rates (OR, 0.61; 95% CI, 0.45–0.83; $P < 0.001$).

Analysis by education level is restricted to those aged ≥ 25 years since many younger people would be unlikely to have completed their education. Percentage seroprevalence rates suggest an increased risk for those achieving higher levels of education, i.e., completing primary level or higher. After adjusting for the effect of age, however, these differences become much smaller since many more of the younger population had attained higher educa-

Table 3. HIV-1 seropositivity by tribe, religion and educational level attained.

	Total	Seropositive No.	Seropositive %	Odds ratio* (95% CI)
Tribe				
Buganda	2569	196	7.6	1
Other Ugandan	219	24	11.0	1.4 (0.90–1.2)
Rwandese	729	68	9.3	1.3 (0.98–1.8)
Other nationalities	292	20	6.8	0.90 (0.55–1.5)
Religion				
Roman Catholic	2277	197	8.7	1
Church of Uganda	416	41	9.9	1.1 (0.76–1.6)
Muslim	1022	62	6.1	0.61 (0.45–0.83)
Other	91	8	8.8	1.1 (0.53–2.4)
Education†				
None	826	61	7.4	1
Incomplete primary	1077	82	7.6	0.67 (0.46–0.97)
Incomplete junior	242	38	15.7	1.1 (0.70–1.8)
Complete junior	186	25	13.4	1.0 (0.40–2.5)

*Corrected for age, sex and the age–sex interaction; †adults aged ≥ 25 years. CI, confidence interval.

tion levels than the more elderly, who have much lower rates of infection (Table 1).

Occupation

Since few people in the area are able to subsist on any one form of employment, most of those questioned, including those in full-time education, gave two or more occupations. Some form of occupation was mentioned by 3675 (96.5%); 58 of the remaining 134 were attending school and 46 were over the age of 55 years. OR for the effect of each occupational group have been compared with the cultivator group (Table 4).

The occupational group associated with a significantly higher risk compared with those in the baseline group includes army personnel, police, drivers and office workers. The lowest rates were among teachers and the unemployed (OR, 0.53 for both); however, these differences were not statistically significant.

Travel within the subcounty and beyond

Each respondent was asked to name up to six places to which he or she travelled regularly; three within the subcounty and three beyond.

The results have been analysed by travel beyond the village, the county and the district; travel to the district town, Masaka, and the capital city, Kampala, was also analysed. There is evidence that seropositive status is associated with frequency of travel and destination, the most significant findings being in the analysis of travel beyond the county and the district. Seropositivity rates among those who never left the county were 6.4% compared with 14.6% among those who left weekly or more frequently, and for leaving the district 7.2 and 16.0%, respectively ($P < 0.03$ for trend with increasing frequency of travel for both comparisons). The trends in seropositivity by frequency of travel to Masaka or to Kampala were not significant.

History of STD

Respondents were asked about the occurrence of STD symptoms within the previous 6 months; 134 (3.5%) reported having had a genital ulcer and 246 (6.5%) pain when passing urine. For both, there was a significant association with HIV serostatus, the strongest being a history of genital ulcers (OR, 3.4; 95% CI, 2.2–5.3).

Table 4. Seropositivity by occupation.

Occupation category	No.	Seropositive No.	Seropositive %	Odds ratio (95% CI)
Cultivator	2902	241	8.3	1
Trader	615	43	7.0	0.81 (0.58–1.2)
Teacher	79	4	5.1	0.53 (0.19–1.5)
Other salaried	52	13	25.0	3.4 (1.7–6.8)
Other occupation	27	2	7.4	1.1 (0.25–4.8)
No employment	134	5	3.7	0.53 (0.21–1.33)

See Methods for definition of categories. CI, confidence interval.

Table 5. Results of multivariate logistic regression analysis.

Sex and age group/ significant factors	Odds ratios (95% CI)
13–24-year age group	
Men aged 13–21 years	1.0
22–24 years	22.4 (7.3–68.5)
Women aged 13–21 years	8.6 (3.0–24.5)
22–24 years	21.1 (6.9–64.6)
Currently married	2.3 (1.5–3.7)
History of genital ulcer	3.6 (1.7–7.7)
Muslim	0.58 (0.35–0.95)
≥ 25-year age group	
25–34 years	1.0
35–44 years	0.64 (0.44–0.92)
≥ 45 years	0.22 (0.15–0.32)
Female	0.72 (0.52–0.98)
History of genital ulcer	2.8 (1.6–5.0)
Currently married	0.47 (0.34–0.64)
Muslim	0.58 (0.39–0.85)
Works outside the village	1.8 (1.2–2.6)

Factors are shown according to the order in which they were added to the model. In the older age group education level attained contributed siginificantly to the reduction in the likelihood ratio statistic; however, none of the four levels differed significantly from the base level of no formal education. CI, confidence interval.

Multivariate analysis

Results of the multivariate analyses are shown in Table 5 by the two selected age groups. Differences between men and women is greatest in those aged 13–21 years (OR, 8.6 for comparison of women with men of this age group). As noted previously,

marriage is associated with a higher seroprevalence in those aged < 25 years but a lower seroprevalence in the older age group. OR for an increased risk in those with a genital ulcer and a decreased risk in Muslims were almost identical for both age groups. Two additional factors were of significance in the older age group, namely working outside the village and the level of education attained, although none of the individual differences between education levels and the base level were significant.

Discussion

This study reports on risk factors associated with HIV-1 infection in a rural Ugandan population. Up to 99% of transmission in adults in this population is estimated to be a consequence of heterosexual encounters, the remainder being through blood transfusion [1]. In the absence of population data on sexual history and sexual practices an assessment of risk factors in a population must concentrate on likely surrogate markers for sexual activity. The baseline socioeconomic and medical surveys conducted at the outset of this longitudinal study provided an excellent opportunity to assess the relative roles of a number of possible such markers.

Efforts were made to include all adult members of the study population. Inevitably, some were absent from the study area at the time of one or both surveys. These absentees are likely to have been the more mobile individuals who have been shown to have higher risks of infection. Reasons for refusal to comply were rarely given; some may have refused on account of known seropositivity. On the other hand, ill people might have been more inclined to comply in the expectation of receiving treatment [10]. Seroprevalence rates may therefore have been under or overestimated, but the net effect on OR estimates is likely to have been small.

Population coverage was high: 72% of the adult *de jure* population consented to an interview by a member of the social science team and the drawing of a venous blood sample to assess HIV-1 serostatus. Compliance rates were highest in the older members of the population: 82% of those aged ≥ 25 years compared with 63% of those aged 13–24 years. Many of the younger age group were away at school at the time of interview.

Many of the findings from this study are not unexpected. Rates in women are somewhat higher than those in men, and the highest rates in women occur at an earlier age than in men. Those who travel beyond their own village are at greater risk than those who stay at home. Frequency of travel is also associated with risk of infection.

The results of the analysis by current marital status are particularly interesting. In the youngest age group (< 25 years) marriage represents a substantial risk factor, particularly in women. We have analysed provisional data from the general population on sexual histories from young adults aged 13–24 years. Only one in five single people aged 13–19 years report that they have begun sexual activity. In contrast, most single people aged ≥ 20 years report having begun sexual activity. In both age groups the reported number of sexual partners in sexually active single people is very similar to that of married people of the same age. It is therefore probable that marriage in younger people equates with having recently begun sexual activity. The protective effect of marriage in the older age group (≥ 25 years) suggests that, in contrast to older single people, married people may have changed partners less frequently in recent years, i.e., since the start of the AIDS epidemic. Data from the case–control study on a subgroup of this population confirms that those with larger numbers of lifetime partners are more likely to be infected. Thus, OR of 1.8–3.7 were observed when those with between four and 10 and ≥ 11 lifetime sexual partners, respectively were compared with those reporting between one and three partners [6].

The findings that Muslims are at decreased risk compared with non-Muslims (OR, 0.58 in multivariate analyses for both age groups) is consistent with those from other studies including another Ugandan population [3]. Two studies of African countries have assessed the correlation between estimates of the proportion of the male population who have been circumcised and seroprevalence rates of HIV-1; both studies support the hypothesis that lack of circumcision is a risk factor [11,12]. In our study population this difference does not appear to be a result of the number of sexual partners, either lifetime or recent, as a detailed analysis in the case–control study shows [6]. Since male circumcision in this population is not practised outside the Muslim community, it is possible that this difference, which is found not only in men but also in women, may be due to the possible protective effect of circumcision to both men and their partners. However, undetected differences in the sexual practices of Muslims and fundamental differences in the characteristics of their sexual networks cannot be excluded. Considerable caution needs to be exercised in the interpretation of these data, as demonstrated recently in a comprehensive literature review [13]. Further studies are needed, preferably in populations where circumcision is not associated with important confounding lifestyle differences.

An important factor not included in the current analysis is socioeconomic status. In an earlier publication [14] we have shown a significant association between the socioeconomic status of the head of the household and his/her serostatus. Three indices

of economic status: type of house, land size and a household item index were inversely associated with seropositivity, without any sign of sex differences in this relationship. This finding extended to the spouses and daughters of the household head but not to the sons.

Sexual behaviour and risk exposure are determined by many factors. Women may be at risk because of poverty, offering sex to men in exchange for goods or money. Those with the opportunity to travel are exposed on account of moving frequently into risk arenas.

The level of education received does not appear to substantially increase or reduce the risk of infection. This finding is in accordance with other studies in Tanzania and Abidjan [15,16]. Reasons for this are likely to be complex and may include aspects of mobility and wealth as well as accessibility to treatment of STD and practice of safe sex.

A highly significant risk factor in both age groups was a history of a genital ulcer in the previous 6 months. Other workers have found a similar association [17]. The weakness of cross-sectional analysis is that causality cannot be established; it remains to be determined whether the presence of an STD enhances the likelihood of HIV-1 infection, whether STD occur as a consequence of HIV infection, or whether a history of STD is only a proxy for frequent partner change.

At the time of this study we did not know how to ask the general population sensitive questions or whether the inclusions of sensitive questions would jeopardize compliance in other parts of the survey. For this reason, we invited a subsample of this study population to participate in a more detailed enquiry on sexual behaviour, which is reported separately [6].

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Chapter 2.2

Risk factors for HIV-1 infection in adults in a rural Ugandan community: a case-control study.

Malamba SS, Wagner HU, Maude G, Okongo M, Nunn AJ, Kengeya-Kayondo JF, Mulder DW.

AIDS 1994, **8**:253-257.

SHORT COMMUNICATION

Risk factors for HIV-1 infection in adults in a rural Ugandan community: a case–control study

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Objective: To study in depth sexual history and sexual behaviour variables as risk factors for HIV-1 infection in a rural Ugandan population.

Methods: Following a socioeconomic and serological survey of a rural population in Masaka District, south-west Uganda, 233 randomly selected HIV-1-positive cases and 233 negative controls matched on age and village of residence, were invited in October 1990 to participate in a case–control study. A total of 132 cases and 161 controls attended for in-depth investigation including an interview about sexual behaviour.

Results: The factor most strongly associated with increased risk of infection was a greater number of lifetime sexual partners, with odds ratios (OR) of 2.1 and 4.9 for those reporting 4–10 and 11 or more partners, respectively, compared with those reporting less than four partners. Having only one sexual partner did not provide complete protection, a total of seven (one male, six female) subjects reporting only one sexual partner were HIV-1-positive. Other significant factors were a history of genital ulcers [OR, 2.9; 95% confidence intervals (CI), 1.0–9.1) and not being a Muslim (OR, 5.4; 95% CI, 1.8–16.5) suggesting a possible protective effect of circumcision. There was a suggestion that those who married within the last 7 years (OR, 2.4; 95% CI, 0.9–6.1) and men exposed to menstrual blood (OR, 5.7; 95% CI, 0.7–49.8) were at an increased risk of HIV-1 infection.

Conclusions: These results confirm the predominant role of sexual behaviour in the HIV-1 epidemic. Of particular concern is the observation of HIV-1 infection among those reporting only one partner. Where HIV-1 infection is widely distributed in the general population, risk reduction strategies should, in addition to the promotion of partner reduction, place strong emphasis on safe-sex techniques.

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Keywords: HIV-1, risk factors, case–control study, sexual history, rural population, Uganda.

Introduction

AIDS has been spreading rapidly into rural areas in parts of sub-Saharan Africa [1]. Studies to obtain data on sensitive questions regarding sexual history and behaviour have been reported from several African countries, usually from selected populations, but few have investigated rural communities. Rural

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studies in Ghana [2], Tanzania [3], Rwanda [4] and Uganda [5] identified sexual intercourse with prostitutes, history of sexually transmitted diseases (STD), sexual behaviour and traditional practices as risk factors in adults.

In 1989–1990, a rural population cohort was established in an area of south-west Uganda in order to study the population dynamics and the role of risk factors for HIV infection with the aim of assisting the development of appropriate intervention programmes. When the study began, knowledge on how to ask questions about sensitive issues such as sexual behaviour was limited and it was decided to conduct a case–control study based on a random sample of seropositive cases and matched controls to address these questions. The results of this case–control study are reported here.

Methods

From November 1989 to September 1990, a survey was carried out in a subcounty of Masaka District to establish a population cohort of approximately 10000 people in a cluster of 15 neighbouring villages with scattered households [6]. Sera were assayed for HIV-1 antibodies and an unambiguous serostatus obtained from 7802 people (4175 adults defined as ≥13 years of age). In all, 4.8% (377) of the general population and 8.2% (342) of adults were HIV-1-positive. A sample of two out of every three HIV-1-positive adults were randomly selected as cases. Because of small numbers, it was not possible to match on more than two factors and, since knowledge on the possible confounders was limited at the time of selection, an HIV-1-negative control matched by village and age groups was randomly selected for each case. Ages were matched to within 1 year for those under 25 years of age and to within 5 years for those aged 25 years or more. HIV status was determined using an indirect and a competitive enzyme immunoassay (EIA) system, Recombigen HIV-1 EIA (Cambridge Biotech, Corporation, Worcester, Massachusetts, USA) and Wellcozyme HIV-1 Recombinant (Wellcome Diagnostics, Dartford, England, UK), and Western blot using Novapath HIV Immunoblot (Bio-Rad Laboratories, Watford, England, UK) when appropriate [7]. The HIV status of participants was known only to the project statistician.

Informed written consent was sought during visits to the homes of all selected subjects, at which stage each subject was asked to attend a clinical interview and examination conducted by a physician at the study clinic. In addition to medical events, the questionnaire included sections on sexual histories with varying recall periods of 7 days, 4 weeks, 6 months, 12 months and lifetime. To assess consistency of responses on sexual history questions and the possible interviewer effects, semi-structured interviews were conducted by a female social scientist on a random subsample of respondents. Interviews were conducted in private, in a local dialect. For logistical reasons they took place immediately after the physician's interview; the interviewer was unaware of the physician's results.

Of the 233 HIV-seropositive cases and 233 HIV-seronegative controls selected, 132 cases and 161 controls attended for enrolment. Forty-one individuals (27 cases, 14 controls) had moved away and 22 died before enrolment (20 of whom were HIV-positive), possibly on account of the 11-month interval between the population survey and study enrolment. Rates of refusal and failure to attend were similar in the two groups; 55 cases (29.6%) and 56 controls (25.8%). No seroconversions were observed between the survey and enrolment.

Statistical analysis

Since a substantial number of the originally selected cases (44%) and controls (31%) did not present for enrolment to the study, the number of observations available for analysis reduced to 95 matched pairs. To improve statistical power and precision, a modification was made in the analysis to create extended matched sets that preserved all available matched pairs but also included additional cases or controls from the same village and age group if these were otherwise unmatched. Thus, it was possible to match all except 36 of the 293 enrolled subjects, leaving 257 subjects (119 cases, 138 controls) in 106 matched sets. All odds ratios (OR) were estimated by conditional logistic regression using the EGRET package (Statistics and Epidemiology Research Corporation, Seattle, Washington, USA). Significance was assessed by the likelihood ratio statistic (LRS). When interactions were investigated, ages were grouped as 13–24, 25–34 and ≥35 years.

Results

The age of the cases ranged from 16 to 76 years; 46.2% (55) of the cases and 52.9% (73) of the controls were women. Table 1 shows the general sociodemographic variables. There was no evidence of risk of HIV-1 infection because of tribe, education, history of blood transfusion, previous admission to hospital or scarification. Those who had married within the previous 7 years had an increased risk of infection compared with those who had married earlier [OR, 2.4; 95% confidence interval (CI), 0.9–6.1, adjusted for sex]. There was a fivefold increased risk of infection in non-Muslims compared with Muslims after adjusting for sex, marital status, number of lifetime sexual partners and their interac-

tions with age (adjusted OR, 5.0; 95% CI, 1.4–16.7; $P=0.04$).

Table 1. Risk of HIV-1 infection for 132 cases and 161 controls by selected variables.

Variable	Distribution (%)		OR*	95% CI	P
	Cases	Controls			
Tribe					
Baganda	70	64	1.0		
Banyarwanda	20	24	1.5	0.7–3.1	
Other	10	12	1.4	0.6–3.6	0.5 (2 d.f.)
Education†					
None/primary (1)	20	17	1.0		
Primary (2/3)	46	58	1.1	0.5–2.6	
Primary (≥4)	34	25	1.6	0.6–4.4	0.4 (2 d.f.)
Current marital status					
Not married	33	33	1.0		
Married	67	67	1.0	0.6–1.9	0.9
Year of marriage					
1984	37	63	1.0		
1985–1991	63	37	2.4	0.9–6.1	0.06
Travelling					
Outside District	42	44	1.0		
Not beyond District	29	24	1.0	0.5–2.0	
Not beyond county	27	30	1.5	0.7–3.0	
Not beyond village	2	2	0.4	0.1–4.0	0.5 (3 d.f.)
Religion					
Muslim	16	29	1.0		
Non-Muslim (Christian, other)	84	71	5.4	1.8–16.5	0.02
Ever had a blood transfusion					
No	97	96	1.0		
Yes	3	4	0.9	0.2–3.5	0.8
Admitted to hospital (past 5 years)					
No	86	88	1.0		
Yes	14	12	1.3	0.6–2.7	0.5
Scarification or ear piercing					
No	56	49	1.0		
Yes	44	51	0.8	0.5–1.4	0.4
Genital ulcers or sores‡					
No	7	14	1.0		
Yes	93	86	2.9	1.0–9.1	0.05
Abnormal vaginal discharge‡					
No	15	35	1.0		
Yes	85	65	5.7	0.7–50.0	0.1
Urethral discharge (men)‡					
No	3	3	1.0		
Yes	97	97	0.9	0.2–4.2	0.9

Denominators vary by variable due to missing information. *Odds ratios (OR) adjusted for sex and age/sex interaction terms except for abnormal vaginal and urethral discharge. †Years of formal education given in parentheses. ‡In the 6 months prior to the interview. CI, confidence interval.

Sexually transmitted diseases

Participants reporting a history of genital ulcers in the 6 months prior to interview had a three-fold increased risk of infection compared to those without (OR, 2.9; 95% CI, 1.0–9.1; $P=0.05$, adjusted for sex and the age/sex interaction). There was also an increased risk of HIV-1 infection in women reporting a history of unusual vaginal discharge although this increase was not statistically significant (OR, 5.7; 95% CI, 0.7–50.0; $P=0.1$). In contrast, there was no suggestion that a history of urethral discharge in men was associated with increased risk of HIV-1 infection (OR, 0.9; 95% CI, 0.2–4.2; $P=0.9$).

Number of sexual partners

There was no relationship between HIV-1 infection and number of partners reported in periods less than 12 months (OR of 1.0, 0.8 and 0.9 for those reporting 1–3, 4–10 and ≥11 partners, respectively). However, the risk of HIV-1 infection increased with increasing numbers of lifetime sexual partners with OR of 2.1 and 4.9 for those reporting 4–10 and ≥11 partners, respectively, compared with those reporting 1–3 partners (χ^2 for trend across sexual partner groups adjusted for age and sex = 12.3, 1 d.f.; $P<0.001$).

The risk of infection by the number of reported lifetime partners and age group is shown in Table 2. There was a significant interaction between reported numbers of sexual partners and age group ($P=0.03$), indicating a greater effect of a large number of partners in those aged under 25 years. Of the cases, 36 men reported more than 10 sexual partners compared with only one woman; one man and six women reported only one lifetime sexual partner.

Other sexual behaviour

Factors relating to sexual history in both men and women are shown in Table 3. Those who reported receiving or giving gifts or money in exchange for sex and those who had experienced abrasions as a result of sexual intercourse showed no significant increased risk of HIV-1 infection. There was no evidence that age at first sexual contact was associated with an increased risk of infection. Approximately 40% of the respondents reported first sexual contact at the age of 15 or 16 years (median age, 15 years for women and 17 years for men). In women, neither intercourse before or age at first menstruation, nor use of intravaginal herbs were associated with an increased risk of infection.

Sexual intercourse during menstruation in the past 12 months was reported to the physician by only five (three cases, two controls) out of 128 women; compared with nine (three cases, six controls) of the 59 randomly selected women seen by the social scientist. Twelve men (nine cases, three controls) reported having intercourse while their partner was menstruating (data not shown) (OR, 5.7; 95% CI, 0.7–49.8; $P=0.06$). Four (three cases, one control) out of 128 women (55 cases, 73 controls) reported to the physician that they had been forced to have sexual intercourse against their will in the past 12 months.

AIDS 1994, Vol 8 No 2

Table 2. Odds ratios for HIV-1 infection in men and women for reported numbers of sexual partners, shown within each age group.

Number of sexual partners	Distribution (%)		Age groups (years)			All ages combined (95% confidence interval)
	Cases	Controls	13–24	25–34	≥35	
Lifetime						
1–3	50	31	1.0	1.0	1.0	1.0
4–10	36	37	4.5	0.8	3.7	2.1 (1.0–4.4)
≥11	14	32	12.8	8.6	2.5	4.9 (1.9–12.4)

$\chi^2 = 12.3$, 1 d.f.; $P < 0.001$, trend across lifetime sexual partner groups adjusted for age and sex.

Table 3. Risk of HIV-1 infection by sexual history variables for 132 cases and 161 controls.

Variable	Percentage		OR	95% CI	P
	Cases	Controls			
Received or gave gift/money in exchange for sex					
No	82	83	1.0		
Yes	18	17	1.3	0.6–2.5	0.5*
History of abrasions resulting from sexual intercourse					
No	95	96	1.0		
Yes	5	4	1.1	0.3–3.4	0.9*
Median age at first sexual contact					
<15	56	59	1.0		
15 and 16	19	21	0.9	0.4–2.1	
≥17	25	20	1.7	0.8–4.1	0.1 (2 d.f.)
Women only					
First sexual intercourse before menstruation					
No	85	88	1.0		
Yes	15	12	0.9	0.2–5.0	0.5
Age at first menstruation (years)					
11–13	24	27	1.0		
14	47	38	0.4	0.1–1.7	
≥15	29	35	1.4	0.4–4.9	0.5
Ever insert herbs (or other) into vagina					
No	86	89	1.0		
Yes	14	11	0.6	0.1–2.3	0.4
Had sexual intercourse while menstruating in past 12 months					
No	94	97	1.0		
Yes	6	3	0.5	0.1–5.5	0.6
Men only					
Had sexual intercourse in past 12 months while partner was menstruating					
No	86	93	1.0		
Yes	14	7	5.7	0.7–49.8	0.06

*Odds ratios (OR) adjusted for sex and age/sex interaction. CI, confidence interval.

In contrast, 13 (seven cases, six controls) of the 59 women (30 cases, 29 controls) interviewed by the social scientist said that they had sex against their will. A paired analysis of responses to the social scientist and to the physician showed that significantly more women reported rape and sex during menstruation to the social scientist ($P < 0.01$ for both comparisons).

Discussion

In contrast to many previous studies that have taken their cases from selected subgroups of the population, the cases and controls in the current study were drawn randomly from the general population. Lack of matching by sex restricted the scope of the analysis, since it was often desirable to consider the results for men and women separately, thus reducing the number of discordant sets available. The modification of the analysis that created extended matched sets and therefore an increased number of discordant sets, produced similar but more precise results compared with those obtained when analysis was restricted to the matched pairs selected at the design stage.

As with all case–control studies, the method of selection of cases and controls is crucial to the interpretation of the findings and bias may have been introduced by the selection process used in this study. If, for example, non-compliance was associated with high-risk behaviour, differences between cases and controls will have been diluted. Compliance rates of seropositive and seronegative subjects in the population survey were, however, very similar and the refusal rates for the case–control study were similar for both groups.

The main findings of this study were an increased risk of HIV-1 infection associated with a greater number of lifetime sexual partners, a history of genital ulcers, recent marriage and not being a Muslim. That the risk of infection rises with increasing number of lifetime sexual partners has been shown elsewhere [3,8]. However, having only one sexual partner does not guarantee protection from infection; six of the 55 female cases and one of the 64 male cases reported only one sexual partner. Of the six female cases, three had HIV-positive husbands, one was a widow, one was separated and one had an HIV-negative husband. The only male case reporting one sexual partner had a seronegative wife.

In those aged < 25 years who reported a high number of lifetime sexual partners, the risk of infection is considerably increased compared with those aged ≥35 years reporting the same number of partners. It is likely that the majority of partners reported by those aged ≥35 years concern sexual relationships

in the more distant past before the advent of the present epidemic.

The absence of a relationship between the reported number of sexual partners in the past 12 months and HIV-1 infection suggests that recent behaviour does not necessarily reflect behaviour in the period prior to infections. Data currently being collected from newly infected individuals should help to determine such associations more precisely.

Since all 23 Muslim men and only three (3.3%) non-Muslims had been circumcised, it was not possible to study directly the effect of male circumcision on HIV-1 infection because of the confounding factor of Islamic religion. However, adjustment for other behaviour variables did not alter the effect of religion. The reduction in risk of HIV infection amongst Muslims in comparison with non-Muslims suggests a protective effect of male circumcision. There could, however, be other factors that may account for this finding and differences in lifestyle should not be ruled out. A review of currently available evidence on lack of male circumcision as a risk factor for STD including HIV infection concludes that there is a need for more studies before firm conclusions can be drawn [9].

The collection of sensitive data such as sexual histories continues to be a problem [10]. Comparison of the interviews by the social scientist with those conducted by the physician showed good agreement for quantitative questions such as numbers of sexual partners, although this might have been due to the closeness of the two interviews. There was, however, significant under-reporting by the physician on questions regarding rape and sexual intercourse during menstruation. Men reporting sex with a menstruating partner were found to be at an increased risk of infection.

In Uganda, and Africa in general, where AIDS affects the general heterosexual population [11], a very high proportion of adult transmission of HIV-1 infection is likely to be through heterosexual contact. There was no suggestion of risk due to non-sexual factors in this study.

Elsewhere, we have shown a high risk of infection in recently married women and we suggested that marriage in younger people equates with having recently begun sexual activity [6]. In this paper we have shown that having only one sexual partner does not guarantee protection from infection. These observations fit the dynamics of an STD widely distributed in the general population, where individuals are at risk of becoming infected through their first or only partner. In such settings risk reduction strategies should, in addition to the promotion of partner reduction, place strong emphasis on the promotion of safe-sex techniques.

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Chapter 2.3

Socio economic status, gender and risk of HIV-1 infection in a rural community in South West Uganda.

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Socioeconomic Status, Gender, and Risk of HIV-1 Infection in a Rural Community in South West Uganda

This report explores the hypothesis that the presence of HIV infection in rural south west Uganda is associated with socioeconomic status and gender. As part of an ethnographic, medical, and serological survey in 15 villages in Masaka district, population 9,950 persons, data were collected on a series of possible socioeconomic indicators. Serological specimens were collected from all consenting individuals for the determination of HIV serostatus. In five selected study villages, there was a good correlation between wealth rankings made by selected local residents and four socioeconomic indices, namely, type of dwelling, available land size, ownership of cattle, and an index of household items. These indices were applied to the full data set to rank the households in all villages. The resulting ranking was matched against HIV-1 status of household heads and, subsequently, their first-degree relatives. Analyzing the data from the 15 villages combined, there was evidence from all four indicators that both male and female heads of the poorest households were most likely to be HIV positive. The increased risk of HIV infection of the poor may be due in part to the income-generating strategies they adopt to survive.
[Uganda, HIV infection, socioeconomic status, gender, rural population]

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Introduction

Comparatively little is known about the dynamics of HIV-1 transmission in rural populations in developing countries. Much of the research in Africa has focused on urban populations, but there is, as yet, little understanding of the occurrence and distribution of risk factors in rural populations in the region. Various urban studies have advanced hypotheses on risk groups. Some have argued that it is the well-educated professional classes who are particularly at risk (Ryder et al. 1990). Others (for example: Aden et al. 1987; Alderman 1988; Brokensha et al. 1988; Carswell 1987; De Zalduondo 1991; Okware 1987; Pickering et al. 1992; Piot et al. 1987; Saimot et al. 1987) have identified specific occupational groups in East and Central Africa as being at high risk of infection, notably prostitutes, truck drivers, and migrant workers in mines. This tendency to associate HIV's modes of transmission with "risk groups" rather than "risk behaviors" has arisen because of the difficulties in observing individual behavior. Social groups who share certain characteristics are often easier to study than individuals (Frankenberg 1989:35), and when considering risk modification strategies, "groups" provide an attractive target for interventions and education messages. Individuals may only follow certain behavior patterns for brief periods, which would not qualify them for inclusion in an occupational or social "risk group." In a country such as Uganda, where HIV-1 infection has spread well beyond the "traditional" high-risk occupational groups, such as truck drivers, bar girls, and soldiers, into the general population, it is important to look at risk behavior and the social and economic circumstances that determine behavior patterns. Under what circumstances may a person be at risk?

A number of commentators have characterized AIDS as a "disease of poverty," implying that the circumstances associated with poverty may make a person vulnerable to HIV infection. Some studies in the United States have shown a link between poverty and HIV transmission for both males and females (for example, Conway et al. 1991; Krueger et al. 1990). These studies conclude that the impoverished are at increased risk for HIV infection because of their social and physical circumstances, which include poor access to risk-reduction information and less support for change to safer behaviors. Garrison (1988) attributes the increasing numbers of urban poor (both male and female) affected by AIDS in Brazil to their lack of access to public health services.

The particular vulnerability of women to HIV infection has been the subject of a number of studies (for example, Bassett and Mhloyi 1991; Carovano 1991; Kisekka 1990; Schoepf 1988). In 1989, the Society for Women and AIDS in Africa used the phrase "triple jeopardy" to describe the dangers women face as individuals, mothers, and caretakers in the face of the AIDS pandemic (Panos Institute 1990). Ankrah comments that the "low status and powerlessness of the African woman have been identified as leading contributors toward their vulnerability to HIV infection" (1991:971). Rwabukwali et al. (1991), in a study of women in Kampala, Uganda, found that the income of women was a significant predictor of HIV status in their study population of 65 HIV-infected and 65 HIV-uninfected females between the ages of 15 and 30 years. Women with incomes regarded as high, ranging from $12 to $20 a month, had the lowest chance of being HIV infected.

Two-thirds of the women stated that women have boyfriends for economic reasons. Men were thus characterized as the "rich" providers.

This report describes research carried out by the Medical Research Council (UK) Programme on AIDS in Uganda (MRPA). The primary aims of the Programme are to study the dynamics of HIV-1 transmission, the natural history of HIV-associated disease, and strategies for AIDS control in a rural population. The study area is a rural subcounty in Masaka District, two hours' drive southwest of Kampala. Most of the population are Baganda, living in dispersed settlements and small trading centers and farming bananas and coffee. The study population is made up of the inhabitants of a cluster of 15 neighboring villages with a total population of approximately 9,950, about half of whom are over 13 years of age.

There is a popular belief in this area that poor women, especially those who are separated, divorced, or widowed, are at particular risk (as well as being *a* particular cause of risk) for HIV-1 infection. It is recognized that they must shoulder the responsibilities for providing food and other household necessities without the help of husband and lineage members. One of the common survival strategies is believed to be providing sexual services in return for cash or goods to support themselves and the family. In the study area, women without husbands who make a living from petty trade, hiring out their labor, and beer brewing or selling are called *nakyeyombekedde*, which can be literally translated as "I built my own house" (a similar category of women is described by Mandeville [1979] and Obbo [1976, n.d.]). The term *nakyeyombekedde* is also considered by local people to be synonymous with "prostitute." If such women supply sexual services, the implication is that there are men in the villages who can afford to pay them or have "favors" in the form of goods to spare.

The aim of this study, in the light of this local belief, is to test the hypothesis that HIV-1 infection in south west Uganda is associated with socioeconomic status and gender, with poor women and rich men being particularly at risk.

Methods

As part of an ethnographic, medical, and serological baseline survey in the 15 villages, information was collected from a total of 1,806 households (household is taken to mean people who share cooking and eating facilities; members may be temporarily resident elsewhere). The aim of the survey was to provide a profile of the study population and data to assist in generating hypotheses. Two social questionnaires were administered, one to household heads on household socioeconomic status and one to all adults (13 years or more) on individual socioeconomic characteristics, followed two to three weeks later by a medical history and examination that included collection of a blood sample for the determination of HIV-1 serostatus. Sera were examined in the Uganda Virus Research Institute laboratory in Entebbe and serostatus was determined by two independent ELISA assays and, where necessary, confirmation by Western blot. Qualitative data on sexual behavior were provided by focus group discussion groups of women and men in the survey villages.

Although a considerable amount of general data on the socioeconomic circumstances of households were obtained, the interpretation of these data was difficult. This was partly because reliability of answers to questions on landholdings

and crop production was poor as people prefer to hide this information because of fear of taxation. Many people had only a general idea of harvests and the buying and selling of farm products over a year or were reluctant to disclose the details for the benefit of the survey. Neither education nor employment status was found to be a reliable indicator of economic status because in present day Uganda most salaries are so low that purchasing power is very limited.

The problem of determining which survey indices of wealth are valid indicators of the economic status can be overcome in part by using a community's own criteria for assessing wealth rather than referring to external standards of wealth or income. This method, called "wealth ranking," was adapted from Grandin (1986) and was used to identify appropriate economic indicators.

Informant wealth ranking is based on a card-sorting technique in which the name of the household head is written on a small card, and informants are asked to sort the cards according to the wealth of each household. The method is detailed in the appendix.

For this study, five of the 15 villages in the study area were randomly selected. One or two local residents were chosen based on previous contacts from these five villages. These informants then ranked households in their villages into four or five levels. This ranking was then used to select the best-fitting variables included in the socioeconomic baseline survey.

The following variables were selected as socioeconomic indicators: (1) materials used in house construction—grass only, mud and wattle with grass roof, baked bricks with grass roof, mud and wattle with iron sheet roof, baked bricks with iron sheet roof or tiled roof; (2) the total land acreage available for cultivation (the *kibanja*); (3) a household item index—the ownership of each item (a jerry can for carrying and storing water, a pot for boiled water, a dish-drying rack, bed(s), a radio or radio cassette, a bicycle, and a motorized vehicle) being one point on the index with a total score of 7, with the few owners of motorized vehicles automatically given a score of 7 because the ownership of the vehicle was a clear indication of wealth; and (4) ownership of cows.

Heads of household were classified by each of the four selected indices and by HIV-1 serostatus. The data were analyzed to investigate associations between each index and serostatus separately for male- and female-headed households.[1] Subsequently, similar analyses were performed for first-degree relatives of household heads. The analysis of first-degree relatives was performed separately for spouses of heads of household, usually female, and male and female adult children (13 years or more) of heads of household (recognizing that associations might well be different for spouses and children of different age groups). There were too few parents of heads of household in this category to analyze.

Tests for association (using the EPIINFO statistical package) were performed using a chi-square trend test. Subsequently, the data were analyzed using a multivariate logistic model (EGRET package), with seropositivity as the dependent variable. Significance was assessed by the Likelihood Ratio Statistics test (LRS). In addition to the selected socioeconomic index, the independent variables included were age, sex, an age-sex interaction term, and a wealth-sex interaction term. Additional explanatory variables included the number of persons living on the kibanja, the available acreage per person, and as a measure of mobility, the presence of a bicycle or motorized vehicle in the household.

Results

Survey data were obtained from 1,806 households in five villages including 9,950 people. A total of 5,278 (53.7 percent) were adults, and of these 4,494 (85.1 percent) answered the individual socioeconomic questions. Information on both socioeconomic data and an unambiguous serostatus is available for 3,809 (72.2 percent) of the *de jure* adult population, including 1,543 heads of household. The overall prevalence of HIV-1 infection in the adult population was 8.2 percent and in heads of household was 9.8 percent (10.2 percent for males, 8.9 percent for females).

In each village, wealth-ranking scores correlated with most, if not all, the socioeconomic indices (Table 1). Thus in village E, the proportions of households with an iron sheet or tiled roof were 95 percent, 80 percent, 38 percent, and 27 percent by decreasing wealth rank ($p < .001$ for trend).

Heads of Households

The results of the univariate analysis of associations between each of the four selected indices and the serostatus of male and female heads of households are shown in Table 2. The direction of the association between each index and seropositivity is the same for both males and females; the poorer the household, the more likely it is that the head of the household is seropositive. Thus for male heads of households living in houses with household item indices less than 4, prevalence rates were greater than 10 percent. For those with higher indices, the rates were 9.4 percent, 7.5 percent, and 6.7 percent, respectively. A similar trend was observed among the female heads of households. For three of the four socioeconomic indicators, the inverse association between wealth and seropositivity is statistically significant (range $0.02 < p < 0.002$, both genders combined); the exception is for ownership of cows ($p < .2$).

In further analysis, each of the three indices was inversely related to seropositivity even after adjusting rates for age, gender, and the age-gender interaction. Since no interaction was detected between gender and household item index, there was no evidence to suggest that the relationship between seropositivity and the household item index is different for female and male household heads.

The presence of a bicycle (or motorized vehicle) in the household was inversely associated with HIV-1 seropositivity, an effect independent of the value of the household item index, suggesting that mobility did not confound the relationship of economic status to seropositivity.

In contrast to the findings on land available per household, there is no suggestion that the amount of land available *per person* is associated with seropositivity.

First-Degree Relatives

Female Spouses of Heads of Households The trends in seropositivity with socioeconomic indices observed in first-named wives (that is the first one to be listed by the head of household when the census was being taken, often but not

TABLE 1

Four socioeconomic indices and wealth ranking by local residents for five villages.

Village	Index[a]	Wealth ranking[b]				
		1	2	3	4	5
A	Iron or tiled roof (%)	18	42	51	76	83
	Kibanja size (median)	2	3	2	3	5.5
	Household item index (mean)	1.9	2.5	3	4.2	4.7
	Ownership of cows (%)	6	8	3	16	33
	Number of households	(17)	(12)	(37)	(25)	(6)
B	Iron or tiled roof (%)	19	17	44	65	53
	Kibanja size (median)	2	2	2	4	2
	Household item index (mean)	2.5	2.8	3.3	3.4	4.5
	Ownership of cows (%)	12	3	9	24	5
	Number of households	(26)	(30)	(34)	(17)	(19)
C	Iron or tiled roof (%)	21	17	50	71	62
	Kibanja size (median)	1	1.5	5.5	4	4.5
	Household item index (mean)	2.4	2.8	2.6	3.9	4.7
	Ownership of cows (%)	0	0	0	19	44
	Number of households	(19)	(12)	(8)	(21)	(34)
D	Iron or tiled roof (%)	5	94	71	80	
	Kibanja size (median)	2	3	10	10	
	Household item index (mean)	2.8	4	4.4	5.4	
	Ownership of cows (%)	3	13	50	40	
	Number of households	(40)	(47)	(14)	(5)	
E	Iron or tiled roof (%)	27	38	80	95	
	Kibanja size (median)	1	2	4	6	
	Household item index (mean)	2.9	3.7	4.4	5.2	
	Ownership of cows (%)	0	9	20	35	
	Number of households	(30)	(45)	(25)	(20)	

[a]Index items correlated significantly with wealth ranking ($0.05 < p < 0.001$) except for ownership of cows in villages A and B, and land size in village B.

[b]Wealth ranking ranges from 5, wealthiest, to 1, poorest, except for villages D and E, which were ranked on a 4-point scale so that 4 was the wealthiest and 1 the poorest.

always, the favorite wife) were in the same direction and were similar to those of their husbands.

Adult Male Offspring of Heads of Households Staying with Their Parents
Data were available for 516 adult sons of heads of households living with their parents. There were no seropositive males under the age of 20 years in this group; thus only the 129 males aged 20 or more were included in the analysis. Of those males, 17 (13.2 percent) were seropositive; there was no suggestion of an association between seropositivity and any of the socioeconomic indices.

TABLE 2

Socioeconomic indices of household wealth and serostatus of head of household.

Index	Male household head			Female household head		
	Total	Seropositive		Total	Seropositive	
	N	*N*	(%)	*N*	*N*	(%)
Type of house						
Grass or mud, wattle and grass	514	68	13.2	158	17	10.8
Mud, wattle and grass with iron or bricks	402	29	7.2	194	14	7.2
Brick with iron or tile roof	149	15	10.1	55	4	7.3
Kibanja size (acres)						
≤1	298	32	10.7	138	12	8.7
2	249	36	14.5	107	14	13.1
3	156	18	11.5	60	4	6.7
4	118	8	6.8	31	4	12.9
5–9	179	10	5.6	39	1	2.6
≥10	86	4	4.7	27	1	3.7
Household item index						
0 or 1	100	10	10	58	10	17.2
2	218	27	12.4	114	8	7
3	282	35	12.4	128	11	8.6
4	244	23	9.4	75	6	8
5	159	12	7.5	28	1	3.6
6 or 7	105	7	6.7	17	1	5.9
Ownership of cows						
No	951	102	10.7	394	36	9.1
Yes	157	12	7.6	26	1	3.8

Total number of household heads per index varies because of incomplete data.

Adult Female Offspring of Heads of Households Staying with Their Parents

There were 481 daughters of heads of household living with their parents and with serological results available. One of the 193 aged 13 to 15 years was seropositive as were 5 (4.3 percent) of the 116 aged 16 to 19 years. The positivity rate in those aged 20 years or more was 18.8 percent (30 of 160). In this age group, the highest rates, 27.5 percent of 40, were in those from the poorest households as measured by the household item index. This compares with 18.9 percent of 74 and 10.9 percent of 46 in the comparatively wealthier groups ($p < .05$ for trend).

Villagers' Views

In addition to the quantitative data, complementary qualitative data were obtained from two sources, namely, comments on the wealth ranking provided by the villagers who carried it out and data from focus group discussions dealing with

sexual behavior in the villages. These findings shed some light on the quantitative findings of this study.

The following comments are typical of those made about household heads of lower economic status by the villagers who participated in the wealth-ranking exercise:

> Her land is very small, and she has no source of income except the men who come to love her.

> She has no land: she looks for jobs in the village and runs up and down for men to help her financially.

> He doesn't cultivate his land: he spends all his time brewing beer and moving round the villages.

Brewing alcohol (particularly *waragi*, a distilled spirit that keeps and can be stored for sale, unlike beer which has to be consumed rapidly before it spoils) is a popular local income-generating activity for persons without enough land or in need of extra cash. Brewing is especially common as an income earner for separated or widowed women, and members of the study community see it as a common form of income-generating activity for the nakyeyombekedde. Places where beer and waragi are drunk are associated in peoples' minds with places of sexual license.

Alcohol was frequently mentioned in the focus group discussions as a cause of people engaging in careless sex. In the discussions, women criticized men who drink heavily for wasting their money, money that could have contributed to the household budget and, hence in the context of this study, improved their socioeconomic status.

When discussing why certain people had not changed their behavior, one middle-aged woman observed that sex is often part of an exchange relationship:

> In this village there are some people who do not have enough food, and there is a youth who has plenty of food but no wife . . . so people go to him for food and give him sex. When you see that youth, he is not fit to be loved by those women, but because of food he loves them.

Both married and unmarried women cited the risky behavior of adolescent girls who live with their parents and want dresses and cosmetics but have no access to the household cash; therefore, they seek lovers to supply them with the fancy goods they want. One woman explained:

> Some parents make their adolescent children work with them in their farms. When it comes to selling produce, they claim all the money leaving nothing for the children. . . . This forces them [the children] to look for alternative means of survival.

Another said, "men go with young girls; they entice them with money, and the poor girl gives in."

The desire for material gain from sex, according to the discussants, operated on two levels: the adolescents giving sex in exchange for fancy goods, and the women with families who use sex to get necessities for day-to-day living.

86

Discussion

The wealth-ranking technique proved to be a relatively simple method of data collection for assessing households and for providing useful data on community stratification within the setting of the study. There are, however, a number of limitations to the method. First, the wealth-ranking exercise was not independent of the indices selected from the survey data. The criteria most frequently mentioned by the wealth-ranking respondents themselves were also indices collected in the socioeconomic questionnaire. Second, the selected indices are relatively insensitive to changes in the socioeconomic status of the households. The permanent brick or block house, for example, may not necessarily demonstrate current prosperity; it may be the legacy of a wealthier past. The household-item index is probably the index most likely to reflect current wealth: the more items a household had accumulated, the wealthier it appeared to be; no record, however, was made in the survey of whether the items were functional. The question on ownership of cows required a simple yes or no answer. A loss of wealth could not be measured if, for example, the number of cows owned had been drastically reduced. Likewise, for ownership of land, no account was taken of how productive the land in use was. Third, the method measures household wealth, not individual wealth. In our analysis, we have assumed that heads of household will be more likely than other members to reflect the "wealth" of a household and that first degree relatives, spouses and children, will also reflect household wealth but to a lesser extent. This may not be the case.

The results of this study suggest that poverty leads to a greater risk of HIV-1 infection for both male and female heads of household. The infection of males and females is obviously interrelated, and the vulnerability to infection of the poor men may be linked to the risk of infection in their partners. Such a situation would occur when a woman adopts an income-generating strategy such as brewing and selling alcohol coupled with the provision of sexual services to provide a cash income. Our qualitative data suggest that alcohol manufacture is one means by which the poor seek to increase their incomes, and alcohol consumption may keep some men and women in poverty and at increased risk of "careless" sex.

Among first-degree relatives, adult daughters belonging to poor households appear to be at increased risk of HIV-1 infection. The apparent greater risk of the female offspring of heads of household staying with their parents would seem to support part of the original hypothesis that suggested that poor women, because of the strategies they adopt to survive, are at an increased risk of infection. Analysis of the data on the male offspring of heads of household, who often engage in petty trade to earn some cash income, did not reveal an association between seropositivity and any of the socioeconomic indices.

A possible means of infection for the poor men would be through travel. Studies of mobility in the study population have shown that seropositivity is associated with distance travelled (Malamba et al. 1991). Our data indicate, however, that this does not hold for the poorest men or women.

The current seroprevalence rates are the accumulation of ten years or more of exposure of the population to HIV-1, an exposure that has only in the most recent years begun to make its mark. We cannot exclude the possibility that, to some

extent, HIV-1 infection has been the cause of the observed association between poverty and HIV-1 infection.

The results of this rural study suggest that both women and men of low socioeconomic status in the study area are at greater risk of HIV-1 infection than people of higher status. There is probably no simple association between any one factor of poverty and risk of HIV-1 infection. It is likely, however, that there is a link between an individual's lack of access to resources and the economic strategies adopted to survive and to support a family.

NOTES

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1. The headship of the household usually belongs to the person who has either inherited, bought, or been given the land. Thus female heads of household may have inherited land from their father or been given land by their fathers or brothers on the breakup of their marriages, or when they became widows. The woman is often sent away from her dead husband's land, the land passes to his clan members, which may include the woman's children, who are members of the father's not the mother's clan.

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Appendix

The Wealth-Ranking Technique

1. The chosen community needs to be of such a size that the local informant can identify the majority, if not all, of the named households. For this, a community of 100 to 150 households is the best size, which for this study coincided with village size.
2. The local concept of wealth is discussed with selected members of the community. Does "property," for example, mean more than wealth? The local vernacular terms need to be identified so that one can check that all informants use the same criteria and terms are translated in the same way.
3. The village census list should be checked to ensure completeness and to note recent changes; the death of a household head, for example, may mark the transition of a household from one wealth category to another.
4. The confirmed list of household names is transferred to cards and numbered.
5. Informants are then chosen, preferably two or more per community, who know the community well. It is an advantage if they are from different sections of the community so that the knowledge can be complementary.
6. The cards are given to the informants to sort in private. Each informant should be left to decide the number of categories to be used. If, however, one category (usually the middle one) has many more cards than the others (say, over 40 percent of all cards), the informant can be asked if it is possible to divide that category into two. The households not known to the informant should be put in a separate category. In this study, the informants (who were all literate in Luganda, the main local language) found it useful to note for each householder why they had put them in a particular category. Notes are a considerable benefit since the next stage is to go through the ranking with the informant and to discuss the differences within each category.

Chapter 3.1

Seroprevalence and Incidence of Sexually Transmitted Diseases in a Rural Ugandan Population.

Wagner HU, Van Dyck E, Roggen E, Nunn AJ, Kamali A, Scott Schmid D, Dobbins JG, Mulder DW.

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ORIGINAL ARTICLE

Seroprevalence and incidence of sexually transmitted diseases in a rural Ugandan population

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Summary: The aim of the study was to determine in a rural population the age- and sex-specific prevalence and incidence rates of serological reactivity of 5 common sexually transmitted diseases (STDs) and their association with HIV-1 antibody status.

Of the adult population of two villages (529 adults aged 15 years or more) 294 provided an adequate blood specimen both on enrolment and at 12 months. The sera were tested at 3 collaborating laboratories for antibodies against HIV-1, *Treponema pallidum, Haemophilus ducreyi, Chlamydia trachomatis* and herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). A sample of 45 children were tested for HSV-1 and HSV-2.

Seroprevalence rates in adults on enrolment were 7.8% for HIV-1, 10.8% for active syphilis, 10.4% for *H. ducreyi*, 66.0% for *C. trachomatis*, 91.2% for HSV-1 and 67.9% for HSV-2. Males were significantly more likely than females to be seropositive for *H. ducreyi* (15.6% versus 6.6%), but less likely to be HSV-2 antibody positive (57.0% versus 74.4%). Reactivity to *H. ducreyi*, *C. trachomatis* and HSV-2 rose with increasing age. In contrast, active syphilis showed no age trend. All STDs tended to be more common in those HIV-1 seropositive. Incidence rates over the 12 months were nil for HIV-1, 0.5% for syphilis, 1.2% for *H. ducreyi*, 11.3% for *C. trachomatis*, and 16.7% for HSV-2.

The results of this exploratory study indicate that all STDs included are common in this rural population. The high HSV-2 prevalence rate among adolescents suggests that HSV-2 may be an important risk factor for HIV-1 infection. HSV-2 serology may be a useful tool to monitor sexual behaviour interventions in young people.

Keywords: Sexually transmitted diseases, HIV-1, serology, rural population, Uganda

INTRODUCTION

It has been shown among groups with high risk behaviour, such as commercial sex workers and their clients, that the risk of HIV transmission can be enhanced in the presence of other sexually transmitted diseases (STDs)[1–6]. It is not known, however, how important this interaction is in facilitating HIV transmission in general populations where there may be no discernable core groups. This issue is particularly relevant to the design of AIDS control strategies in countries where HIV infection is predominantly transmitted through heterosexual contact and where, in some areas, the infection is widely spread in the general population.

It is difficult to measure how common STDs are in general populations. Since large surveys usually preclude the possibility of genital examinations, investigators often rely on reported STD symptoms. However, the reporting of STDs tends to be affected by biases which, in most cases, lead to an underestimation of the true prevalence and incidence rates, and the determination of serum antibodies against some common STDs would thus help to understand the epidemiology of these diseases (syphilis, chancroid, *Chlamydia* infection and HSV-2). While cross-sectional serological surveys

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are relatively cheap and easy to conduct, the value of such studies is limited because seroprevalence rates represent a cumulative record of past exposure. Moreover, the duration of detectable antibody production after primary infection may vary. Longitudinal serological studies, on the other hand, are more expensive and cumbersome but allow the collection of precise data on recent exposure. This is, among other things, useful for monitoring the impact of interventions.

This paper presents the results of a prospective serological study of reactivity to common STDs among the adult residents of 2 Ugandan villages. The study was undertaken as part of a research programme on the population dynamics of HIV-1 transmission in a large rural cohort. The specific objectives of the serological study were to determine the age- and sex-specific prevalence and incidence rates of serological reactivity to *Treponema pallidum, Haemophilus ducreyi, Chlamydia trachomatis,* herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), and to assess their associations with HIV-1 antibody status.

METHODS

The general population of 15 neighbouring villages in Masaka district, Southwestern Uganda, has been followed since November 1989 through annual demographic and seroepidemiological house to house surveys. All residents of the 15 villages were eligible for study. Details of the survey procedures have been described elsewhere[7,8]. For the purposes of the present serological study, 2 groups of subjects were selected. Of 529 adult (i.e. those aged 15 years or more) residents of 2 neighbouring villages who had been enrolled at baseline and were present one year later (Group A): 294 (56%) provided an adequate venous blood specimen during both surveys. To obtain information on HSV-1 and HSV-2 infection in children, 31 children aged 10–14 years with unequivocal HIV-1 serostatus at both surveys, and a random sample of 14 children aged 0–9 years resident in the same 2 villages, were included (Group B).

Following consent, venous blood samples were drawn and separated into aliquots. Sera were stored at −20°C until dispatch to 3 collaborating laboratories. Testing for HIV-1 was performed at the Uganda Virus Research Institute, Entebbe, Uganda, for *T. pallidum, H. ducreyi* and *C. trachomatis* at the Department of Microbiology, Institute of Tropical Medicine, Antwerp, Belgium, and for HSV-1 and HSV-2 at the Viral Exanthema and Herpesvirus Branch, Centers for Disease Control and Prevention, Atlanta, USA.

HIV-1 antibody status was determined using two independent ELISA systems (*Recombigen HIV-1 EIA*, Cambridge Biotech Corporation, Worcester, Massachusetts, USA, and *Wellcozyme HIV-1 Recombinant*, Wellcome Diagnostics, Dartford, England, UK), and confirmed with Western blot using *Novopath HIV Immunoblot* (Bio-Rad Laboratories, Watford, England, UK) if the ELISA results were discordant or weakly concordant[9]. For syphilis serology a Rapid Plasma Reagin card test (*Macro-Vue RPR Card Test*, Becton-Dickinson, Cooheysville, USA) and a *T. pallidum* microhaemagglutination assay (TPHA, Fujirebio Inc., Tokyo, Japan) were used.

Both tests were performed qualitatively and repeated in a quantitative assay if the qualitative test showed reactivity. Reactivity to *C. trachomatis* was determined with a commercial indirect fluorescent antibody technique (*C. trachomatis Spot IF*, Biomérieux, Mercy l'Etoile, France). Serum immunoglobulin G antibodies to *H. ducreyi* were assayed in an ELISA system using an ultrasonicated whole cell antigen[9,10]. Reactivities against HSV-1 and HSV-2 type-specific glycoproteins were assessed by Western blot technique[11]. The laboratories received unpaired samples and were not informed about subject characteristics.

To interpret reactivity, we followed the manufacturers' instructions or, for non-commercial assays, the criteria provided by the laboratory performing the test. Data analysis was performed with the packages *Epiinfo* version 5 and EGRET. The strengths of associations were calculated as odds ratios with 95% confidence limits (OR, 95% CL) after

Table 1. Seroprevalence rates (%) of antibodies against HIV-1, T. pallidum, H. ducreyi, C. trachomatis, *HSV-1 and HSV-2 by age in 294 adults*

Age group	No. of subjects	HIV-1 294	T. pall.[a] 279	H.d.[b] 288	C.t.[c] 288	HSV-1 215	HSV-2 212
15–19	48	2.1 (1)	4.2 (2)	2.1 (1)	31.2 (15)	94.9 (39)	34.2 (13)
20–24	42	11.9 (5)	12.5 (5)	9.5 (4)	57.1 (24)	93.5 (31)	78.2 (23)
25–29	40	15.0 (6)	8.1 (3)	13.5 (5)	75.7 (28)	96.6 (29)	82.1 (23)
30–34	22	9.1 (2)	9.5 (2)	9.5 (2)	71.4 (15)	100.0 (17)	82.4 (14)
35–39	24	4.2 (1)	21.7 (5)	4.3 (1)	78.3 (18)	93.8 (16)	81.2 (13)
40+	118	6.8 (8)	11.8 (13)	14.5 (17)	76.9 (90)	84.3 (83)	70.7 (58)
Total	294	7.8 (23)	10.8 (30)	10.4 (30)	66.0 (190)	91.2 (196)	67.9 (144)

In brackets = number of seropositive subjects

[a]Both RPR & TPHA reactive, [b]*H. ducreyi*, [c]*C. trachomatis*

adjustment for age and sex. The chi-squared test (χ^2) for linear trend was applied to assess whether seroprevalence rates showed a significant trend with age.

RESULTS

Paired samples were available from 294 adults (group A) and 45 children (group B). Of the adults 126 (42.9%) were male. Table 1 shows the adult age distribution.

HIV-1

At baseline, 23 out of 294 adults (7.8%) were HIV-1 antibody positive (Table 1). Five out of 12 female seropositives and one out of 11 male seropositives were younger than 25 years. At follow-up 12 months later, none of the initially seronegative individuals had seroconverted.

T. pallidum

Unequivocal results were available from 279 adults. Of these, 11.5% were reactive for RPR and 32.6% for TPHA. All but 2 of those with a positive RPR test were also reactive in the TPHA test (10.8%) and thus could be classified as having active syphilis (Table 1). Rates of reactivity with TPHA and RPR in males (30.5% and 13.6%, respectively) were similar to those in females (34.2% and 9.9%, respectively). TPHA prevalence rates tended to rise with age: 12.5% (6 of 48) in the age group 15–19 years, 20.0% (8 of 40) in those aged 20–24, 35.1% (13 of 37) in those aged 25–29, and 41.6% (64 of 154) in those 30 years and older (χ^2 for trend 15.2; $P<0.001$). In contrast, co-reactivity to both tests (Table 1) did not show a significant age trend (χ^2 for trend 2.2; $P=0.14$). Of women aged 15–34 years 23.9% were positive by TPHA, and 6.8% were reactive in both tests. Three out of 19 HIV-1 seropositive subjects (15.8%) and 27 out of 260 HIV-1 seronegatives (10.4%) were RPR/TPHA positive (OR 1.6, 95% CL 0.4–5.9).

Of 183 subjects who were initially negative for RPR and TPHA, 4 (2.2%) seroconverted for RPR, but only one also became positive for TPHA and could thus be classified as a certain incident case of syphilis (Table 2). An additional 5 cases had low TPHA-titres (1 : 80–1 : 320) but remained RPR-negative.

Table 2. Seroprevalence and incidence rates of selected STDs, and associations between the STD and HIV-1 prevalence rates

	HIV-1	T. pall.[a]	H.d.[b]	C.t.[c]	HSV-2
Prevalence (%)	7.8	10.8	10.4	66.0	67.9
Odds ratio for assoc. with HIV-1	—	1.6	2.7	1.5	1.2
95% CI		0.4–5.9	0.9–8.3	0.5–4.4	0.2–6.2
Incidence (%)	0.0	0.6	1.2	11.3	16.7

[a]Both RPR & TPHA reactive, [b]*H. ducreyi*, [c]*C. trachomatis*

H. ducreyi

A total of 288 serum specimens were available for *H. ducreyi* serology from adults at baseline. Of these 30 were positive (10.4%), 212 negative (73.6%) and 46 (16%) indeterminate. The age-specific seroprevalence rates varied between 2.1% and 14.5% (Table 1). Males were more likely to be reactive (19 out of 122, 15.6%) than females (11 out of 166, 6.6%), with an odds ratio of 2.5 (95% CL 1.1–5.0). Of 254 subjects with negative or borderline results at baseline three (1.2%) seroconverted. All 3 incident cases (2 women aged 25 and 39, and one man aged 50) remained HIV-1 negative. Five out of 21 HIV-1 positive cases (23.8%) and 25 out of the 267 who were HIV-1 negative (9.4%) showed definitive reactivity in the *H. ducreyi* ELISA (OR 2.7, 95% CL 0.9–8.3).

C. trachomatis

In adults a total of 190 out of 288 serum samples (66.0%) were reactive for *C. trachomatis*. The positivity rates were similar in males (77 out of 122; 63.1%) and in females (113 out of 166; 68.1%). The age-specific rates rose from 31.2% in the age group 15–19 to 75.7% in those aged 25–29 (Table 1; χ^2 for linear trend 16.7; $P<0.001$). In the age groups 15–19 and 20–24 years, rates in females tended to be higher than in males: 34.5% versus 26.3%, and 66.7% versus 40.0% respectively (OR 2.1, 95% CL 0.8–5.6). Sixteen out of 21 HIV-1 positive subjects (76.2%) and 174 out of the 267 who were HIV-1 negative (65.2%) showed reactivity against *C. trachomatis*, corresponding to an odds ratio of 1.5 (95% CL 0.5–4.4).

Incident cases were defined as those whose titres were increased by 3 or more dilutions on repeat testing. Twenty-two fulfilled this criterion out of 194 cases who did not show reactivity or had low titres at baseline (11.3%). The incidence rates were similar in males and females, and did not show a trend with age. Three out of 11 HIV-1 positive subjects (27.3%) and 19 out of the 183 who were HIV-1 negative (10.4%) became *C. trachomatis* antibody positive (OR 4.3, 95% CL 0.9–19.8).

Herpes simplex type 2

HSV-2 Western blot results at baseline were available for 212 adults aged 15 years and older (group A) and for 45 children (group B). In all, 144 adults (67.9%) and one child (2.2%; an 11 year old female) were reactive. The HSV-2 seroprevalence rates among adult females and males were 74.4% and 57.0% respectively (OR 2.4, 95% CL 1.3–4.6). The age-specific rates rose steeply between 15 and 29 years of age (χ^2 for linear trend 16.5; $P<0.001$) and remained at high levels in older age groups (Table 1). The rates in female adolescents increased more steeply and to higher levels than in young males. In the age-group 15–19, 43.4% of females and 20.0% of males were reactive. In the age group 20–24

Table 3. Relationship between HIV-1 serostatus and the number of STDs (syphilis, H. ducreyi, C. trachomatis and HSV-2) to which serological reactivity was demonstrated

Number of STDs	Number assessed	HIV+ve No.	HIV+ve %
None	32	0	0.0
1–2	151	4	2.6
3–4	25	5	20.0

Based on 208 subjects with complete range of test results
χ^2 for linear trend 11.9, $P<0.001$

the rates were 85.0% and 54.5% respectively (OR 3.7, 95% CL 1.2–11.7). Eight of 10 HIV-1 seropositive adults and 136 of the 202 who were HIV-1 negative (67.3%) were reactive for HSV-2 (OR 1.2; 95% CL 0.2–6.2).

A total of 99 HSV-2 results were available for adults at one year follow-up. Of 36 subjects who were HSV-2 seronegative at baseline 6 (16.7%) seroconverted (Table 2); all 6 remained HIV-1 negative. There was a suggestion that females were at a higher risk of HSV-2 infection than males: 4 (21.1%) out of 19 women and 2 (11.8%) out of 17 men acquired HSV-2 antibodies. Two (4.5%) of the 44 children who were initially HSV-2 negative seroconverted (girls aged 12 and 14 respectively). In contrast to HSV-2, HSV-1 seroprevalence rates were high in all age groups and the sex specific rates were similar. In children 11 (78.6%) of those aged 0–9 years and 28 (90.3%) of those aged 10–14 years were positive.

There was a significant association between HIV-1 infection and the number of STDs (syphilis, *H. ducreyi*, *C. trachomatis* and HSV-2) for which a subject showed serological reactivity (Table 3). HIV-1 prevalence rates were 0.0% among subjects without serological evidence of previous STD, 2.6% among those with markers of one or two STDs, and 20.0% among those with serological evidence of three or four STDs. This trend was significant (χ^2 for linear trend 11.9, $P<0.001$).

DISCUSSION

The HIV-1 seroprevalence rate of 7.8% observed in the adult population of 2 villages was similar to the overall rate of 8.2% in the total cohort of 15 villages[8]. Typically for sub-Saharan Africa, females under 25 years showed higher infection rates than males in the same age group. No HIV-1 seroconversion was observed in this group. This is not surprising, since the annual incidence in the total population cohort was only 1%[8].

Most reports on STDs in Africa refer to selected groups such as blood donors, antenatal clinic attenders, and STD patients. This makes meaningful comparisons difficult[12]. Among the STDs investigated in the present study syphilis has been studied most extensively in Africa[13]. Non-treponemal tests (e.g. RPR) confirmed by a treponemal test (e.g. TPHA) are believed to provide a reasonably accurate measure of active syphilis in areas where non-venereal treponematoses are rare*. Among rural women attending antenatal and family planning services in Swaziland in 1981, 10.0% were found positive for RPR, and 33.3% positive for TPHA[14]. Evidence of active syphilis was found in 6.3% of pregnant women from rural and urban areas of Mozambique[15] and in 12.8% of rural and urban antenatal clinic attenders in Zambia[16]. These rates are similar to those observed by us among women aged 15–34 years: 7.8% of these women were positive by both RPR and TPHA, and 24.4% by TPHA alone. In contrast to data on prevalence rates of syphilis, data on the incidence of syphilis in Africa is scarce. Two studies in Uganda (1976) employed numbers of sexually acquired syphilis cases diagnosed at STD clinics to estimate annual incidence rates in the clinic catchment populations, and the estimated rates were 0.2% in a general semi-urban population[17] and 0.6% in an urban population[18]. These rates are of the same order as suggested by our data, i.e. 0.5% in the adult population which would correspond to about 0.3% in the general population. We consider this estimate to be conservative because it disregards the 3 subjects seroconverting for RPR without converting for TPHA and 5 subjects who seroconverted for TPHA but not for RPR. It cannot be ruled out that these 8 cases included some true incident cases, i.e. those with early syphilis who had not yet become positive by TPHA or those treated soon after infection who had already lost RPR reactivity.

The observation that those who were reactive in both syphilis tests had a HIV-1 seroprevalence rate which was higher than the rate in those not reactive (OR = 1.6), was similar to findings elsewhere in Africa, e.g. among Cameroonian STD patients[19]. There are various possible explanations for this association between HIV-1 seroprevalence and syphilis, explanations which would equally apply to the association between HIV-1 and other STDs. The association could be true and result from an enhancing effect of syphilis on the risk of acquiring HIV-1 infection. It could, however, be spurious and result from a confounding effect of sexual behaviour, or alternatively concurrent HIV-1 infection could affect the serological response to syphilis which may be either enhanced or decreased[20]. The pronounced trend of an increased rate of TPHA reactivity with age possibly reflects the cumulative lifetime exposure to venereal syphilis. In the older segments of the population it may, however, in part be explained by an exposure to yaws, a non-venereal treponematosis which was eradicated in the 1950s.

The seroprevalence rate of 10% of antibodies against *H. ducreyi* was similar to the rate of active syphilis (11%). Comparisons with other African populations cannot be made due to lack of data.

*To the best of our knowledge, yaws was eradicated in Uganda in the 1950s and no cases have been recorded recently in the study area

The estimated annual *incidence of infection with H. ducreyi* of 1.2% appears high when compared with the rate of 3% to 4% observed in a cohort of prostitutes from Kinshasa[6].

High seroprevalence and incidence rates were found for *C. trachomatis*. Extra-genital infections may have contributed to the high observed prevalence[21] but the age- and sex-specific distribution suggests that sexual transmission is predominant. The same argument applies to anti-HSV-2 reactivity with sharply increasing rates with age among adolescents, with highest rates of 85% among females aged 20–24 years and 82% in males aged 25–29 years. By comparison, in a study of 3533 pregnant women in the UK HSV-2 prevalence rates among black women born in Africa increased from 0% at age 16 to 40% at age 35[22].

The estimated one year incidence rate of infection with HSV-2 (16.7%) was similar to an estimated rate of 10% per annum reported from a prospective study of 29 couples discordant for HSV-2 infection in the USA[23]. Also in line with that study are our observations that women and HSV-1 sero-negative persons tended to have an increased risk of acquiring HSV-2 infection. In both studies, however, the numbers were small. The results strongly suggest that in this population HSV-1 infection is acquired mainly non-sexually, probably in early childhood. A potentially protective effect against HSV-2 afforded by prior HSV-1 infection does not appear to be relevant on a population basis but may reduce the severity of HSV-2 infection.

Although we observed no seroconversions for HIV-1 and only a moderately strong association between HIV-1 and HSV-2 seroprevalence rates, the high HSV-2 infection rates do suggest a high potential of interaction between these 2 viral infections. An increased risk of HSV-2 seropositive persons for subsequent infection with HIV-1 has been demonstrated, e.g. in the San Francisco cohort study of homosexual men[24]. In view of the lifelong persistence of HSV-2 infection in the majority of the sexually active population and of the increased rate of recurrence of genital ulcers due to HIV-1 associated immunodeficiency, HSV-2 appears from an AIDS control perspective the most important and problematic STD in this Ugandan population.

Finally, the age-specific HSV-2 seroprevalence rates seem to provide a sensitive measure of sexual behaviour in adolescents. It can offer a more objective measure of sexual behaviour change than self-reporting and thus may be a useful tool for evaluating behavioural interventions against the AIDS epidemic.

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Chapter 3.2

Estimating the proportion of HIV infections attributable to other STDs in a rural Ugandan population.

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(submitted)

For details of the model, see Chapter 7

Estimating the proportion of HIV infections attributable to other STDs in a rural Ugandan population

Short title: HIV infections attributable to STDs

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Summary

Background. The proportion of HIV infections attributable to the enhancing effect of other sexually transmitted diseases (STDs) on transmission of HIV is unknown. The primary objective of this study was to estimate the proportion of HIV infections attributable to the presence of ulcerative and non-ulcerative STDs in a rural population cohort of 10 000 in south-west Uganda.

Methods: This was addressed by application of a simulation model of the transmission dynamics of HIV infection and of STDs.

Results: In simulations of the first 10 years (1980-1990) of the HIV epidemic, over 90% of HIV infections were attributed to STDs. Even given conservative assumptions concerning the prevalence of STDs, and their enhancing effects on HIV transmission, STDs played a critical role in the rapid and widespread transmission of HIV infection. The role of STDs decreases with progression of the epidemic.

Conclusions: In developing countries, HIV control may benefit substantially from successful STD intervention programmes, especially where HIV infection is not already well established.

Keywords: HIV, STDs, STD cofactor effect, mathematical model, intervention, Uganda, sub-Saharan Africa

Introduction

Why does HIV spread so much more rapidly and extensively by heterosexual transmission in some populations than others? This question is fundamental to our understanding of the dynamics of HIV transmission, and to the control of the HIV epidemic. Many characteristics of populations are likely to play some part in the way HIV spreads, but are there important overriding factors? The importance of sexual behaviour mixing patterns and sexual practises in determining the spread of HIV infection have been demonstrated in theoretical exercises.[1,2] In sub-Saharan Africa, high prevalences of other sexually transmitted diseases (STDs) have been documented,[3-5] and it is believed this may also contribute to the spread of HIV, by enhancing sexual transmission of the virus.[6-10] If this is so then interventions aimed at diagnosing and treating STDs may provide an important opportunity to reduce HIV incidence in the population.[11-13] The extent to which STDs may be contributing to the spread of HIV infection, and thus the potential impact of STD interventions is, however, unknown.

Direct estimation of the proportion of HIV infections attributable to STDs through empirical studies is difficult, since this would require eliminating STDs altogether from a study population, and comparing the incidence of HIV with a comparable control population. Indirect estimation of the proportion of HIV infections attributable to STDs at a specific point in time is possible if we have both an estimate of the prevalence of STDs at that time and a measure of the relative risk of HIV infection per sexual contact in the presence and absence of STDs (ie STD cofactor effect). Estimation of the STD cofactor effect per sexual contact is rather difficult from epidemiological studies of associations between HIV and STDs since: (1) these studies tend to measure associations based on a history of STDs over a prolonged time period (often 6 months or 1 year), which serves to dilute the actual STD cofactor effect, as the STD will usually be present for only part of this period; and (2) it is difficult to fully adjust for the confounding effect of sexual behaviour in such studies. Furthermore indirect estimation only accounts for primary infections and not those arising from secondary infections.[10]

Fitting of a detailed simulation model to a specific rural population in Uganda (*NJ Robinson et al, Modelling the dynamics of HIV infection and other STDs in rural Uganda, submitted*), studied by the MRC/ODA/UVRI Programme on AIDS in Uganda, has provided an opportunity to develop HIV-1 transmission models around one of the most complete and extensive data sets generated from prospective follow-up of an entire population cohort in a rural community in sub-Saharan Africa.[14,15] This paper investigates the role that STDs may have played in the spread of HIV infection in this population. Under different assumptions about STD cofactor effects, simulated scenarios of this rural population in south-west Uganda have been employed to address three questions of particular interest. Firstly, if there were no STDs circulating in this population, how would HIV have spread during the years immediately following its introduction? Secondly, given that an epidemic is already established and widespread, what role are STDs likely to play in the future transmission of HIV? And thirdly, and related to the first two, how does the proportion of new HIV infections attributable to STDs depend on the phase of the epidemic?

Methods

A simulation model (Simul-AIDS)[16] was extended and employed to model the transmission dynamics of HIV infection and STDs in this rural population in south-west Uganda (*NJ Robinson et al, Modelling the dynamics of HIV infection and other STDs in rural Uganda, submitted*).

Simul-AIDS is an age-structured stochastic (Monte Carlo) simulation model. Every individual in the simulated population (of 10 000) is represented by a set of characteristics, including age, sex, STD and HIV status, type of sexual relationships and the identity of all sexual partners. At each time step (in this exercise 5-days), events occur with given probabilities and the status of the entire population is updated.

The models developed for the study population incorporate fertility, mortality, migration, dynamically-modelled ulcerative and non-ulcerative STDs (that is with representations of natural history and probability of transmission of the STDs), and HIV transmission dynamics. Sexual behaviour is represented by three types of sexual partnerships: one-off sexual contacts, and short- and long-term partnerships. Men have all possible combinations of these types of partnerships. Women either have only one-off sexual contacts, or have a combination of short- and long-term partnerships. Model and parameter assumptions are described elsewhere (*NJ Robinson et al, Modelling the dynamics of HIV infection and other STDs in rural Uganda, submitted*).

The model was used to simulate the spread of HIV infection in the Ugandan cohort, from its assumed introduction in 1980, in just a few individuals, up until the first survey of the cohort in 1990. Values for parameter inputs were chosen on the basis of data from the cohort and, where necessary, from other sources. Input parameters were specified so as to achieve a reasonable fit to recorded characteristics of the study population in 1990, including: age structure; profile of HIV prevalence by age and sex; HIV prevalence among adults of about 9%, and a female-to-male HIV prevalence ratio of about 1.1.

Results are given for two modelling scenarios, defined by assuming different enhancing effects of STDs on HIV transmission (STD cofactor effects). For one, transmission of HIV infection per sexual contact was assumed to be enhanced 10-fold during all episodes of ulcerative STDs, and 2-fold during episodes of non-ulcerative STDs in women. This has been referred to as the "low cofactor scenario". A second scenario employed STD cofactor effects of 100 and 5 respectively. This has been referred to as the "high cofactor scenario".

For each scenario, small adjustments to the sexual behaviour assumptions and to the probability of transmission of HIV were necessary to preserve the fit of the model to the study population in 1990. Simulated prevalence levels of ulcerative and non-ulcerative STDs in 1990 were about 0.5% and 2.5% respectively among both men and women for the low cofactor scenario, and 0.4% and 1.5% for the high cofactor scenario. The difference in simulated STD prevalences between the two scenarios resulted from employing slightly different sexual behaviour assumptions while maintaining identical parameter values for STD transmission dynamics.

To estimate the proportion of HIV infections attributable to STDs in the first 10 years of the epidemic (1980-1990), simulations were re-run from introduction of HIV in 1980 without STDs in the population, but with all other factors remaining unchanged. The proportion of adult HIV infections attributable to STDs was then assessed by comparing the cumulative number of adult HIV incident cases in the presence and absence of STDs. The proportions of infections attributable to ulcerative and non-ulcerative STDs were similarly assessed by running simulations from 1980 in the absence of ulcerative and non-ulcerative STDs respectively.

To estimate the proportion of HIV infections attributable to STDs between 1990 and 2000, the further spread of HIV infection from the recorded population in 1990 was simulated both in the presence and absence of STDs, and the number of cumulative HIV infections compared 10 years later.

To investigate the proportion of new infections attributable to STDs at different stages of the epidemic, simulations were run for a one year period, in the presence and absence of STDs, from introduction of HIV in 1980, and from populations recorded 10 and 20 years after introduction of HIV. In each case, STDs were assumed present up to the beginning of these one year periods.

All simulations were replicated ten times. The proportion of HIV infections attributable to STDs was calculated as $1 - \bar{x} / \bar{y}$, where $\bar{y}$ represents the mean cumulative number of HIV infections assuming presence of STDs, and $\bar{x}$ represents the mean cumulative number of infections assuming absence of STDs. A confidence interval for this proportion was derived using the log(-log) transformation [17]. In this way limits for confidence intervals were bounded by 0% and 100%.

Results

Table 1 gives the proportion of adult HIV infections attributed to STDs for the low and high cofactor scenarios during the first and second decades of the HIV epidemic. During the initial 10 years (1980-1990), over 90% of HIV infections were attributed to STDs, for both low and high cofactor scenarios. Ulcerative STDs accounted for the majority of these infections. As illustrated in figures 1 and 2 for the low and high cofactor scenarios respectively, the simulated HIV prevalence in 1990 was considerably reduced in the absence of ulcerative STDs, but there was little reduction when only non-ulcerative STDs were eliminated. HIV infection spreads more rapidly and levels off earlier for the high cofactor scenario.

In the 10 years from 1990, about 40% and 80% of HIV infections were attributed to STDs for the low and high cofactor scenarios respectively (table 1).

Table 2 gives the proportion of new HIV infections attributed to STDs during one year periods, at various time points after the introduction of HIV. The declining proportion of infections attributed to STDs with time since introduction of HIV is striking. During 1980, the proportion of HIV infections attributed to STDs for the low cofactor scenario was 86%. This declined to 17% by the year 2000. At all times the proportion of infections attributed to non-ulcerative STDs was less than that for ulcerative STDs.

Table 1: **Percentage (95% confidence interval) of adult HIV infections attributed to STDs in the intervals 1980-1990 and 1990-2000 for low and high STD cofactor scenarios**

	Ulcerative STDs	Non-ulcerative STDs	Both STDs
Low cofactor scenario			
1980-1990	83 (77-88)	9 (3-24)	93 (91-95)
1990-2000	28 (24-33)	6 (2-16)	38 (34-42)
High cofactor scenario			
1980-1990	97 (95-99)	2 (0-87)	99 (99-100)
1990-2000	77 (75-79)	6 (1-25)	83 (81-85)

Table 2: **Percentage (95% confidence interval) of adult HIV infections attributed to STDs during 1980, 1990 and 2000 for low and high STD cofactor scenarios**

	Ulcerative STDs	Non-ulcerative STDs	Both STDs
Low cofactor scenario			
1980	68 (52-83)	17 (1-99)	86 (78-92)
1990	22 (16-31)	10 (4-20)	29 (23-36)
2000	16 (13-20)	3 (1-12)	17 (12-23)
High cofactor scenario			
1980	95 (92-98)	4 (0-100)	100 (98-100)
1990	71 (66-75)	15 (4-50)	81 (77-85)
2000	51 (47-55)	4 (0-57)	58 (55-62)

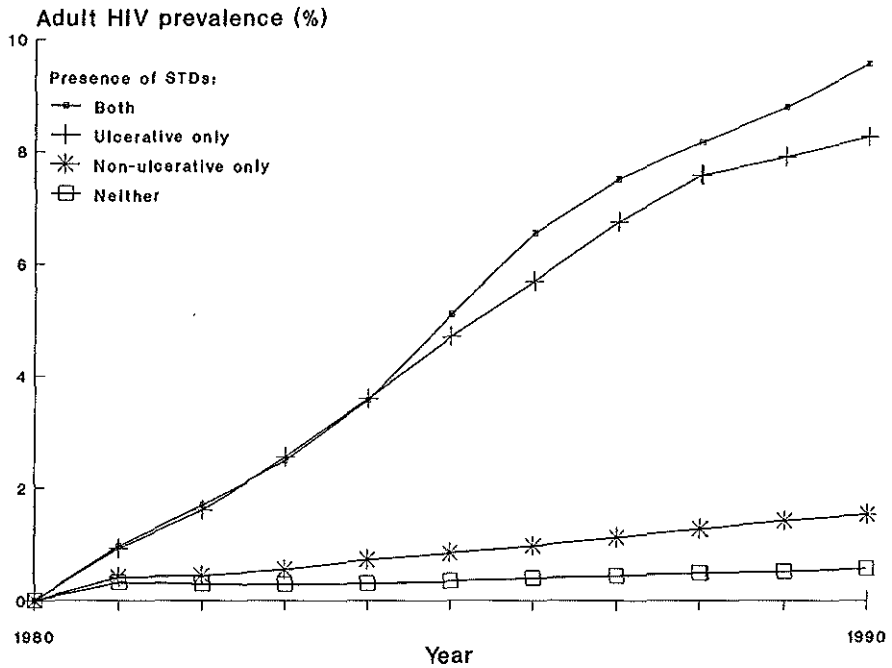

Figure 1: Mean adult HIV prevalence (10 replications) in the presence and absence of STDs for the low cofactor scenario

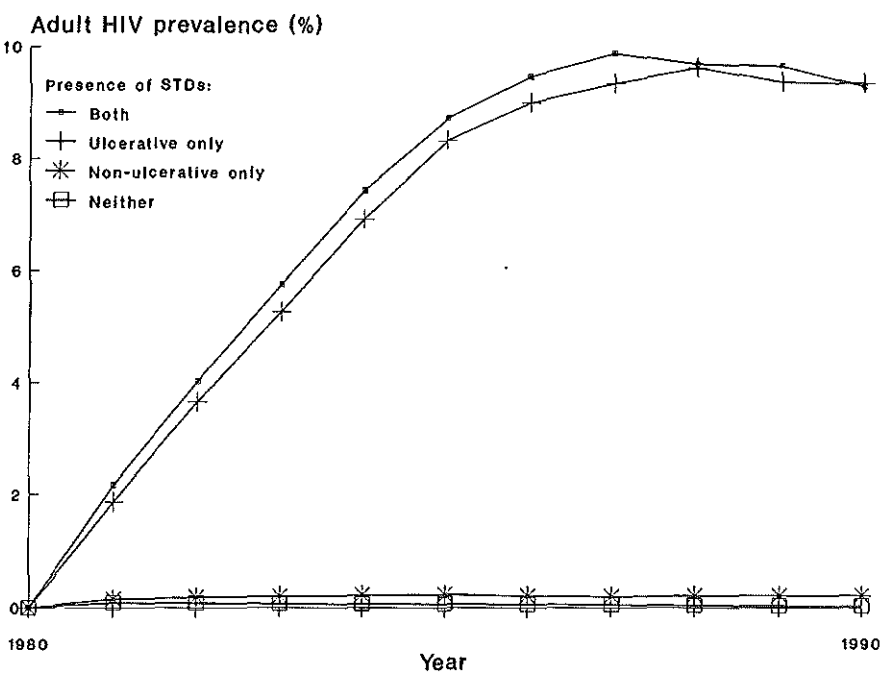

Figure 2: Mean adult HIV prevalence (10 replications) in the presence and absence of STDs for the high cofactor scenario

Discussion

Simul-AIDS was developed to facilitate simulation of the transmission dynamics both of HIV infection and of STDs in populations in developing countries. The motivation for this came from epidemiological data which, by the late 1980s, suggested that STDs may be enhancing transmission of HIV and thus possibly playing an important role in the spread of HIV infection. In many developing countries, where lack of treatment for STDs over many years has resulted in high prevalence levels of STDs, it has been hypothesised that this may be an important factor in explaining the often rapid spread of HIV infection.

By application of Simul-AIDS we have developed a means to explore the possible impact of STDs on the spread of HIV. Without use of simulation models, this is very difficult to study because the proportion of HIV infections attributable to other STDs depends not only on the STD cofactor effect and the prevalence of STDs, but also on the way in which HIV and STDs are clustered among the more sexually active individuals in the population.

The uniqueness of this project, however, results not only from the concurrent modelling of HIV and STDs, but in its focus on a specific African population, defined by one of the most complete and extensive data sets generated from prospective follow-up of an entire population cohort in sub-Saharan Africa (*NJ Robinson et al, Modelling the dynamics of HIV infection and other STDs in rural Uganda, submitted*). Data from the first survey in 1989-90 were used to guide input parameter values. Data from subsequent follow-up of the study population has been used to further assess the fit of the different scenarios.

Even for this well-defined population there were many unknowns relating to demographic features, sexual behaviour characteristics and dynamics of both HIV and of STDs. It is therefore difficult to conclude that a particular modelling representation truly reflects reality. At best, we can report that particular modelling representations replicate a range of documented characteristics from the study population very well. Continued surveillance of the study population will allow for further evaluation in due course.

Since STD cofactor effects per sexual contact are unknown, three scenarios were developed, defined by assuming different enhancing effects of STDs on HIV transmission. The two scenarios discussed here were both able to replicate recorded characteristics of the study population in 1990. However, the high cofactor scenario was more consistent with our current understanding of input parameter values.[10,18] For a third scenario assuming no enhancing effects of STDs on HIV transmission, empirical results from the study population could not be replicated for reasonable input parameter values (*NJ Robinson et al, Modelling the dynamics of HIV infection and other STDs in rural Uganda, submitted*). Only the high cofactor scenario could replicate evolution of the HIV epidemic in the study population during subsequent years of follow-up.[19]

In these simulated scenarios STDs played a critical role in initiating the spread of HIV infection, even though prevalence levels of STDs in 1990 among adults were not assumed to be particularly high. These results are consistent with other modelling exercises that have incorporated the dynamics of STDs as well as of HIV infection.[20,21] The role played by STDs in the spread of HIV infection decreases with progression of the HIV epidemic, a consequence of the spread of HIV into the less sexually active population, where STDs are less prevalent.

In these simulations, non-ulcerative STDs played a minor role compared with ulcerative STDs, even though the prevalence of non-ulcerative STDs was 3-5 times higher. This resulted from the low cofactor effect assumed for these STDs. If either the cofactor effect or the prevalence of non-

ulcerative STDs are increased, and both may be reasonable, the proportion of HIV infections attributable to non-ulcerative STDs increases.[22]

When both STDs were removed from the population prior to introduction of HIV, the size of the epidemic was substantially reduced. For the high cofactor scenario, there was no sustained epidemic in four of the ten repetitions. HIV was maintained in the population in all repetitions for the low cofactor scenario.

These results emphasise the potential value of STD control measures, especially if taken at the earliest stages of the epidemic, even before HIV infection is acknowledged in a community. The likely impact of such measures in limiting the scale of HIV epidemics should strengthen the resolve of the international community to find resources to undertake and implement STD control programmes in all populations where STDs are prevalent, and not only those in which HIV infection is already established and widespread.

Sadly, in many parts of sub-Saharan Africa, the opportunity for early intervention is passing. In many parts of Asia, however, the early implementation of rigorous STD control programmes is still possible. This may help control the potentially explosive HIV epidemics that are forecast for this region.

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Chapter 4

Post-natal incidence of HIV-1 infection among children in a rural Ugandan population: no evidence for transmission other than mother-to-child.

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POST-NATAL INCIDENCE OF HIV-1 INFECTION AMONG CHILDREN IN A RURAL UGANDAN POPULATION: NO EVIDENCE FOR TRANSMISSION OTHER THAN MOTHER-TO-CHILD

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ABSTRACT
We conducted a prospective cohort study to determine the post-natal incidence of and possible transmission routes for HIV-1 infection in rural Ugandan children. The cohort consisted of the population of a cluster of 15 villages in Masaka District, south-west Uganda, and was enrolled in 1989-90 through a demographic and serological survey. During the period 1991-93 the population was re-surveyed annually. A total of 5,492 children aged 0-12 years were enrolled; of these, 41 (0.7%) were seropositive infants. A total of 3,941 (72%) children were HIV-negative on enrolment and had at least one follow-up specimen. During 8596 person years of observation only 1 seroconversion was observed, an incidence rate of 0.12 (95% CI 0.00-0.35) per 1,000 years of observation. The transmission of HIV was most probably through breast milk. The case corresponds to a rate of 1.1 per 1,000 in households with one or more HIV-positive adults (874 years of observation); no incident case was observed in households with only seronegative adults (6,423 years of observation). Thus, HIV infection among children aged 0-12 years in this population is virtually exclusively the result of mother-to-child transmission. No infections were observed attributable to parenteral exposure, non-sexual casual or household contact, or insects.

Keywords: HIV-1, incidence, children, prospective cohort, mother-to-child, household contact, scarification, vectors, rural population, Uganda

INTRODUCTION

It only took a few years after the initial recognition of AIDS to document the three main routes of HIV-transmission, namely sexual contact with an infected person, parenteral or mucous membrane exposure to infected blood and from infected mother to infant (Melbye 1986; Friedland and Klein 1987; Quinn *et al.* 1986). However, the possibility that HIV might be transmitted by other routes, notably non-sexual 'casual' or household contact (for example through skin contact, through saliva by sharing kitchen utensils, or through body fluids by sharing toilet facilities) and through insects, has remained an issue of widespread concern. HIV transmission through casual contact is rare in industrialised countries but occasional cases have been reported (Gershon *et al.* 1990; Simonds and Chanock 1993; Dunn and Newell 1994; Wahn *et al.* 1986; Anonymous 1992; Fitzgibbon *et al.* 1993).

The living conditions in many households in sub-Saharan countries, with poor sanitary facilities, overcrowding and large numbers of mosquitos and other arthropods, are very different from those in most households in industrialised countries. Therefore, if casual or household contact and insect vectors do play a role in the transmission of HIV, this is more likely to be observed in sub-Saharan than in industrialised countries. In addition, in sub-Saharan Africa many injections are administered by informal health-care providers and it has been suggested that they may contribute to the transmission of HIV in Africa (Berkley 1991).

We are aware of 7 reports from sub-Saharan Africa which dealt with the relative importance of HIV transmission through casual or household contact and parenteral exposure through injections (Mann *et al.* 1986a; Mann *et al.* 1986b; Sewankambo *et al.* 1987; Monny-Lobe *et al.* 1989; Hira *et al.* 1990; Hitimana *et al.* 1993; Kengeya-Kayondo *et al.* 1995). Transmission through these routes was reported for 4 studies (Mann *et al.* 1986a; Mann *et al.* 1986b; Hitimana *et al.* 1993; Kengeya-Kayondo *et al.* 1995) while no cases were reported from the remaining studies. All these studies were cross-sectional thus making it difficult to ascertain with reasonable certainty past exposure. This is particularly true when older children are studied and when no information is available on the mothers through which vertical transmission can be ruled out.

In late 1989 we began a descriptive cohort study of a rural population in Uganda with the aim of studying the population dynamics of HIV-1 transmission (Mulder *et al.* 1994). We recently reported the prevalence of HIV-1 infection among children enrolled into the cohort and discussed the relative importance of various routes of HIV-1 transmission among these children (Kengeya-Kayondo *et al.* 1995). In the present paper we report the incidence of HIV-1 infection over a three year period among children aged less than 13 years.

Study area and population
The area of study is a cluster of 15 neighbouring villages, approximately one third of the total population of a sub-county in Masaka District in south-west Uganda, situated 32km from Masaka town and 16km from the trans-African highway at its nearest point. There are two dispensaries and a health centre in the area. The nearest hospital is 20km away.

The area is inhabited mainly by farmers who cultivate coffee and bananas. Compounds are scattered and usually only one family lives on a compound. The majority of the population are Baganda (70%).

Methods
Full detail of the study procedures are given elsewhere (Mulder *et al.* 1994). In brief, beginning in late-1989, after mapping the study villages a census and socioeconomic questionnaire were administered to all consenting heads of household. All residents were included. After 2-3 weeks a medical team visited each of the households. All adults were invited to participate in the medical survey while blood specimens were collected from all consenting adults and children aged 0-12 years. The specimens were transported weekly to the laboratory of the Uganda Virus Research Institute in Entebbe where they were tested following rigorous quality control procedures and an algorithm using two different enzyme immunoassay (EIA) systems on all specimens (Recombigen HIV-1 EIA, Cambridge Biotech Corporation, Worcester, Massachusetts, USA; and Wellcozyme HIV-1 Recombinant, Wellcome Diagnostics, Dartford, England, UK). Supplementary testing with Western blot (WB; Novopath HIV Immunoblot, Bio-Rad Laboratories, Watford, England, UK) was performed when the EIA results were discordant or weakly concordant (Nunn *et al.* 1993; Nunn *et al.* 1994).

During the period 1991-93 re-surveys of the population were undertaken annually using procedures similar to those at baseline, and newborns and immigrants to the area were enrolled together with a number of those who were resident at baseline but absent or refused to comply. To obtain information on possible ways of exposure to HIV-1 in seropositive children a semi-structured interview was conducted with their parents or guardians; the details of the interview procedures have been described elsewhere (Kengeya-Kayondo *et al.* 1995). A counselling service was available for those participants who wanted to know their HIV status (Seeley *et al.* 1991). All staff except the programme statisticians were kept unaware of the HIV serostatus of study participants.

Existing software packages were used for statistical analysis. In calculating person years of observation, subjects were included from the time they were enrolled with a negative HIV-1 test result until they seroconverted or until the last sero-negative result before their 13th birthday. Confidence intervals on incidence rates were calculated using exact poisson inference.

Results

At the initial survey there were 1981 households in the 15 study villages; 1806 (91.2%) of households agreed to be censused with a total population of 9,780. This baseline population included 4574 children aged 0-12 years (Table) and of these 4161 (91%) were enrolled. Of 751 births recorded during the first 2 years of follow up 496 (66%) were added to the cohort as were 835 (75%) of 1111 children who moved into the study area. In all, 5492 children with unequivocal serology results were enrolled; 41 (0.7%) of these were HIV-positive infants who were excluded from further analysis. Of the children present at baseline 17% left the area within the following three years.

Table: **Enrolment of children aged 0-12 years, 1989-92**

Group	Year	Total	Enrolled	%
Baseline population	1989-90	4574	4161*	91*
Newborns	1990-92	751	496	66
Joined area	1990-92	1111	835	75
Total	1989-92	6436	5492	85

* 3623 (79%) of children were enrolled during the initial survey and 538 (12%) during re-surveys

At the time of the initial survey the overall HIV-1 seroprevalence was 4.8%; the prevalence among adults (aged 13 years or more) was 8.2%. Among children the age-specific prevalence for the age groups 0-18 months, 19-60 months and 5-12 years was 4.0% (12/298), 1.1% (12/1080), and 0.4% (10/2245) respectively.

Information on HIV-1 incidence is available for 3941 children who had a seronegative test result on enrolment and at least one follow up result. Only one seroconversion was observed during a total of 8,596 person years of observation. This corresponds to an incidence of 0.12 (95% CI 0.00-0.35) per 1,000 years of observation.

At the time of the initial survey the father of the incident case was HIV-1 positive while both the mother and the case, a girl, then one month old, were seronegative. At the first re-survey both mother and then one year old daughter were negative. A year later both had unambiguous positive results. Six months earlier, when still breast feeding, the mother was EIA positive and had an indeterminate Western Blot (strong p24; trace gp160, gp41, p51) test result. Interview of the parents did not elicit any risk factor other than breast milk; specifically, the child had not received a blood transfusion, scarifications or injections other than those included in the Expanded Programme on Immunization.

For an analysis of intra household transmission complete follow up data on the serostatus of both adults and children in study households include 7,297 child years of observation: 874 child years in households with one or more positive adults and 6423 years in households with only seronegative adults. The one observed seroconversion corresponds to an incidence rate of 1.1 (95% CI 0.0 - 3.4) per 1,000 years of observation in households with a seropositive adult. No incident case was observed in households with only seronegative adults.

Discussion

During up to 4 years of follow-up of 3941 children who were HIV-negative on enrolment we observed only 1 seroconversion. This very low incidence implies that parenteral transmission of HIV-1 to children in this population must be very rare and confirms that the risk of transmission through non-sexual casual contact and through insect vectors is remote.

The HIV-1 testing algorithm had a sensitivity and specificity close to 100% (Nunn *et al.* 1993). While we cannot rule out errors in ascertainment it is very improbable that such errors can explain the observed low incidence rate. It is also improbable that selective enrolment introduced bias since 91% of the children resident at the time of the initial census were enrolled. Among adults there was no difference in compliance with re-surveys between those HIV-1-positive and negative, suggesting that bias due to differential compliance by children is unlikely. Thus, it seems improbable that bias can invalidate the main finding of the study, namely a very low incidence rate of HIV-1 infection among children.

The complete absence of transmission to children living in households with only seronegative adults shows that parenteral transmission is uncommon in this population. As far as transmission through blood is concerned this is not surprising since residents of this area rarely receive a blood transfusion (Kengeya-Kayondo *et al.* 1995, Malamba *et al.* 1994). More than half of the children in this population completed the immunization schedule of the Expanded Programme on Immunization and it is reassuring that there was no evidence of transmission through injections. The risk of using unsterilised syringes and needles by formal and informal health workers has, however, been well documented and our observation should on no account serve as an argument in favour of relaxing sterilisation practices. Moreover, in urban areas with a higher prevalence of HIV-1 among adults and better access to medical care the risk of parenteral HIV-1 transmission may well be higher than observed in this study.

In this population breast feeding is universal. Transmission of HIV-1 from mother-to-child through breast feeding has been well documented (Dunn *et al.* 1992; Datta *et al.* 1994) in particular in mothers who seroconvert while breast feeding (Van de Perre *et al.* 1991). Infection of the only incident case observed in this

study can, in our opinion, with virtual certainty be attributed to breast feeding. Excluding this case, no transmission was observed in households with one or more seropositive adults. This provides strong evidence to suggest that HIV-1 is very difficult to transmit through casual contact in conditions of overcrowding and poor sanitary facilities. Moreover, since mosquitos and other arthropods are common in this area the study provides evidence that the risk of vector borne transmission is minute if not zero. During the 4-year period of this study a total of 41 seropositive infants were enrolled. Our study was not designed to quantify the rate of mother-to-child transmission and since these seropositive newborns were excluded from the analysis it is probable that we have underestimated the postnatal transmission through breast-milk. Thus, apart from mother-to-child transmission HIV-1 infection of children in this population is extremely rare.

Effective risk communication may help to dispell misconceptions as well as reduce fear and discrimination. Understandably, for many people it is hard to believe that a virus that is spreading rapidly is not easily transmitted. Much fear stems from lack of knowledge about the actual, exclusive routes of transmission. Moreover, misconceptions may seriously hamper intervention approaches aiming at a reduction of sexual risk behaviour. The results of this large prospective population study should help in making prevention efforts more effective by reinforcing that the main focus of these efforts should be the prevention of sexual HIV transmission.

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Chapter 5.1

HIV-1 incidence and HIV-1 associated mortality in a rural Ugandan population cohort.

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AIDS 1994, **8**:87-92.

HIV-1 incidence and HIV-1-associated mortality in a rural Ugandan population cohort

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Objective: To determine the incidence of HIV-1 infection and HIV-1-associated mortality in a rural Ugandan population.

Design: A prospective cohort study.

Methods: A cohort consisting of the population (*de jure* census 9820) of a cluster of 15 villages in Masaka District, south-west Uganda was enrolled between 1989 and 1990 through a demographic and medical survey. The HIV-1 seroprevalence rate was 4.8% for all ages combined and 8.2% for those aged 13 years or more. The survey was repeated after 1 year.

Results: The 1-year HIV-1 incidence rate among adults was 1% [9.2 per 1000 person-years of observation; 95% confidence interval (CI), 5.5–12.9). A total of 84 deaths were observed. In adults, half of all deaths (31 out of 60) were in HIV-1-seropositive individuals. The age-adjusted overall mortality rate ratio for HIV-positive adults compared with HIV-negatives was 20.8 (95% CI, 12.0–35.7). In the 13–44 age group the corresponding rate ratios for men, women and both sexes combined were 16.3, 108.9 and 58.7, respectively. The HIV-attributable mortality fractions, i.e., the proportion of deaths that would have been avoided in the absence of HIV, were 44, 50 and 89% for adult men, adult women and adults aged 25–34 years (both sexes combined), respectively. The 1-year progression to death among HIV-1-seropositive adults was 10.3%.

Conclusion: These results demonstrate the profound impact that the HIV-1 epidemic has on adult mortality in a rural area of Uganda where the HIV-1 prevalence and incidence rates in adults are 8 and 1%, respectively.

AIDS 1994, 8:87–92

Keywords: Rural population, HIV-1 incidence, HIV-1-specific mortality, Uganda, prospective cohort.

[For editorial comment, see pp 127–128]

Introduction

While there is an extensive literature on prevalence rates of HIV-1 infection in urban and rural populations in sub-Saharan Africa [1,2], few reports document studies of the incidence of HIV-1 infection in sub-Saharan Africa [3,4] and the impact of the epidemic in terms of mortality [5,6], presumably because of a lack of well established cohorts [2]. Information on HIV-1 incidence and mortality is important for understanding the population dynamics of HIV transmission and the impact of the HIV pandemic, and data on rural populations are of particular interest since the majority of the population in sub-Saharan Africa is rural.

The objective of this study was to determine the incidence of HIV-1 infection and HIV-1-associated mor-

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tality in rural Uganda. This work is part of a broader study on the dynamics of HIV-1 transmission in a general rural population.

Study area and population

The study area, a subcounty of Masaka District, south-west Uganda was selected based on the expectation that HIV-1 seroprevalence in adults would be of the order of 5–10% and that the population would be relatively stable. It is a relatively fertile area, which is inhabited mainly by farmers, most of whom cultivate coffee and bananas. Compounds are scattered and usually only one family lives on a compound. Villages consist of households belonging to one administrative unit. The majority of the population are Baganda (approximately 70%), but there is a substantial number of immigrants from Rwanda (20%). The area is connected with Masaka, the main town of the district, through an all-weather road on which taxis, and occasionally a bus, travel. There are two government dispensaries and a health centre. A field station, which includes a clinic and laboratories, has been established for research purposes. Counselling services are provided for individuals who want to know their HIV status [7].

Methods

The core of the study is a demographic, medical and serological surveillance of members of approximately 2000 households in a cluster of 15 villages. The design is longitudinal. Between 1989 and 1990, when the study started, all consenting residents were enrolled. Newborns and immigrants are entered into the study continuously.

Subjects

Community mobilization began in November 1988, 1 year before the cohort's enrolment. Questionnaires and forms were pre-tested, translated from English into Luganda and translated back into English by professional translators. Each house in the study villages was mapped and assigned a number. Medical and technical personnel received appropriate training and a pilot study was carried out in November 1989. The procedures for the baseline survey of a village were as follows. Following a community meeting, all households were visited by interviewers, accompanied where possible by a community leader, and all *de jure* residents censused. For study purposes, a *de jure* resident was defined as a subject who belonged to any of the following categories: (1) having lived in the area for more than 3 months, (2) having lived in the area for less than 3 months but intending to stay, and (3) considered to belong to a study household but normally living elsewhere (for example, children at boarding school). In addition, interviewers administered socioeconomic interviews. A 10% random sample of respondents was re-interviewed to enable assessment of repeatability. Interviewers were debriefed by survey facilitators for each questionnaire. Data entry took place at the Entebbe office where census lists for use by the medical field team and identity cards for study participants were also produced.

Approximately 2 weeks after the census, households were informed by community leaders about the intended visit of the medical team. Upon arrival, the team explained the purpose of the study and the visit, issued identity cards and requested written consent. Consenting adults (≥13 years) were examined after a brief medical history. A blood sample was taken from consenting adults and children. Subjects with ailments were treated when possible by members of the survey team or referred to the study clinic if appropriate. A 10% random sample of participants was re-examined. Questionnaires were taken to Entebbe and discrepancies in census information obtained by social and medical teams reported to the field for investigation by programme staff.

Communities were debriefed following the survey and a counselling service was available for those individuals who wanted to know their HIV status.

Laboratory methods

Blood specimens were drawn by technicians, stored in a cool box while field work was in progress and taken to the field laboratory at the end of each day for separation, aliquoting and storage at 4°C. Specimens were transported weekly to the reference laboratory in Entebbe, where they were tested for antibodies to HIV-1 using two different enzyme immunoassay (EIA) systems (Recombigen HIV-1 EIA, Cambridge Biotech Corporation, Worcester, Massachusetts, USA; and Wellcozyme HIV-1 Recombinant, Wellcome Diagnostics, Dartford, England, UK). An EIA was repeated if the result was borderline and both EIA were repeated if the results were discordant. Supplementary testing with Western blot (WB; Novopath HIV Immunoblot, Bio-Rad Laboratories, Watford, England, UK) was performed if results were discordant between or within screening assays or if either repeat EIA result was borderline [8]. Rigorous quality control procedures were applied [9].

Follow-up

After 1 year, during the period November 1990 to September 1991, the cohort was re-surveyed and the follow-up status of individuals censused during the baseline survey was obtained on an individual basis. Thus, deaths were ascertained through re-census. Procedures for the re-survey were similar to those used at baseline. All staff except the programme statistician were kept unaware of the HIV serostatus of study participants.

Statistical analysis

Personal computers were used for data entry, both in the laboratory and in the data-processing office. Software programmes were written in Dbase III plus. Questionnaires were checked for completeness and consistency. Data were entered by two independent operators onto temporary databases, which were verified and corrected if necessary prior to updating the main database. Existing software packages (EPI info and EGRET) were used for statistical analyses. In calculating person-years of observation, those who died or left the area were included in the denominator up to the time of actual death or leaving the area.

The study was approved by the Ugandan Ministry of Health and National Council of Science and Technology.

Results

At baseline, there were 1981 households in the 15 study villages. Of these, the inhabitants were repeatedly absent in 56 households (2.8%), 60 (3%) households refused to participate and 59 (3%) households did not comply for other reasons. Overall, the census was administered to 1806 (91.2%) households with a total *de jure* population of 9820. Age distribution of the census population and the compliance in the baseline survey is shown in Table 1. A total of 8105 individuals (83%) agreed to give a blood sample. Reasons for non-compliance were absence on three occasions in 9%, refusal in 6% and miscellaneous, including those with unknown reasons, in 2%. The lowest compliance (74%) was among those aged 13–24 years.

Table 1. *De jure* census population and compliance in baseline survey, Masaka cohort, 1989–1990.

Age (years)	*De jure* census			Gave blood	
	Men	Women	Total	No.	%
0–4	970	943	1913	1665	87
5–12	1338	1291	2629	2251	86
13–24	1159	1198	2357	1737	74
25–34	467	501	968	781	81
35–44	273	332	605	516	85
45–54	263	268	531	452	85
55–64	192	214	406	356	88
≥65	219	192	419	347	82
Total	4881	4959	9820	8105	82

Unequivocal serology results at baseline are available for 7802 subjects, the 303 missing values resulting mainly from insufficient serum in children. A total of 377 (4.8%) were positive. Overall seroprevalence in women was 5.3%, compared with 4.4% in men. Seroprevalence in adults aged ≥13 years was 8.2%. The age- and sex-specific seroprevalence rates (Fig. 1) show a typical distribution, with highest rates in women aged 15–34 and in men aged 25–34 years.

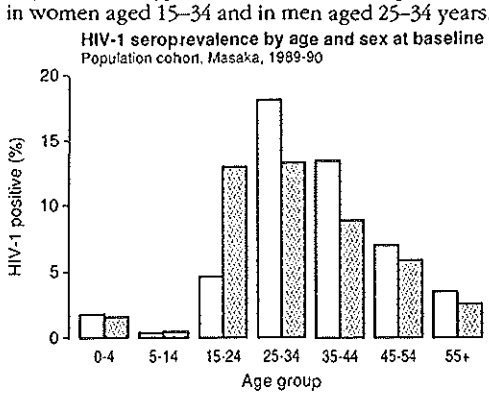

Fig. 1. HIV-1 seroprevalence by age and sex at baseline in the Masaka population group, 1989–1990 (n=7802). □, men; ▨, women.

Of the 7802 enrolled individuals with available serostatus, 569 (7.3%) had left the area at 1 year follow-up, 84 (1.1%) had died and 37 (0.5%) refused re-census (Table 2). Of the 7112 individuals known to be remaining in the area, 5478 (77%) were seen and gave a blood sample. Reasons for loss to follow-up are shown in Table 2. Information on the incidence of HIV-1 infection is based on 5251 subjects who were seronegative on enrolment and who had unequivocal serology results in the repeat survey, and includes a total of 5389 person-years of observation. A total of 24 seroconversions were observed, corresponding to an overall incidence of HIV-1 infection of 4.4 [95% confidence interval (CI), 2.6–6.4] per 1000 person-years. The age-specific incidence rates are shown in Table 3. All seroconversions were in adults (aged ≥13 years), corresponding to a rate in adults of 9.4 (95% CI, 5.5–12.9) per 1000 person-years. The age-specific rates in men were relatively constant for those aged 13–54 years, with slightly lower rates in those aged ≥55 years. The overall rate in adult men was 10.7 (95% CI, 4.9–16.5). The highest rates in women were observed in those aged 13–24 and ≥55 years, with an overall rate in adult women of 7.9 (95% CI, 3.2–12.6) per 1000 person-years. The difference between the overall incidence rates in adult men and women was not statistically significant; moreover, there was no significant interaction between age and sex ($P>0.2$).

Data on mortality, available from re-census at 1 year follow-up, is based on a total of 7570 person-years of observation (Table 4). A total of 45 deaths occurred in seronegative individuals, corresponding to a rate of 6.2 (95% CI, 4.4–8.0) per 1000 person-years. This compares with 39 deaths in seropositive individ-

AIDS 1994, Vol 8 No 1

Table 2 Follow-up status 1 year after enrolment, Masaka cohort, 1990–1991.

	No.	%
Unambiguous serostatus at baseline	7802	100.0
Left area by round 2	569	7.3
Died	84	1.1
Refused re-census	37	0.5
Remaining for assessment	7112	100.0
Seen and gave blood sample	5478	77.0
Absent	708	10.0
Refused all investigations	416	5.8
Refused to give a blood sample	367	5.2
Reason not known	143	2.0

uals and a corresponding rate of 118.2 (95% CI, 80.7–155.7) per 1000. The mortality rates were 11.4 and 421.1 per 1000 in seronegative and seropositive children aged 0–4 years, respectively; the corresponding rates in children aged 5–12 years were 0.5 and 0, respectively.

Half of all deaths in adults were in seropositive subjects. Mortality rates in HIV-negative adult men and women were 7.2 (95% CI, 3.2–11.2) and 8.2 (95% CI, 4.1–12.3), and 87.6 (95% CI, 37.5–137.7) and 116.6 (95% CI, 63.7–169.5) per 1000 among HIV-positive adult men and women, respectively. Age-specific adult rates varied from 81.6 per 1000 person-years in those aged 35–44 years to 263.2 in those aged ≥55 years. The age-adjusted overall mortality rate ratio in adults, i.e., the ratio of the rate in seropositive adults to the rate in those seronegative, was 20.8 (95% CI, 12.0–35.7). Similarly, the rate ratio for adults aged 13–44 years was 58.7 (95% CI, 22.3–154.6); the sex-specific rate ratios for men and women in this age-group were 16.3 (95% CI, 4.0–67.3) and 108.9 (95% CI, 25.2–471.0), respectively.

Assuming that the excess mortality in HIV-positive subjects was largely due to HIV infection, the HIV-associated excess mortality in the population can be calculated by deducting the mortality rate in the

Table 3. Age-specific incidence of HIV-1 infection after approximately 1 year of follow-up in 5251 participants who were seronegative at baseline.

Age (years)	Men			Women			Total		
	Person-years	No.	Rate	Person-years	No.	Rate	Person-years	No.	Rate
0–4	554	0	0.0	493	0	0.0	1047	0	0.0
5–12	894	0	0.0	845	0	0.0	1739	0	0.0
13–24	467	6	12.8	471	5	10.6	938	11	11.7
25–34	195	2	10.2	276	1	3.6	471	3	6.4
35–44	139	2	14.4	213	1	4.7	352	3	8.5
45–54	154	2	13.0	179	0	0.0	333	2	6.0
≥55	260	1	3.8	248	4	16.1	508	5	9.8
Total	2664	13	4.8	2725	11	4.0	5389	24	4.4
Adults	1216	13	10.7	1387	11	7.9	2603	24	9.2

Rates per 1000 person-years of observation.

Table 4. Age-specific mortality at 1-year of follow-up by HIV-1 baseline serostatus for 7765 subjects.

Age (years)	HIV−			HIV+			Total			
		Deaths			Deaths			Deaths		Excess mortality
	Person-years	No.	Rate	Person-years	No.	Rate	Person-years	No.	Rate	
0–4	1317	15	11.4	19	8	421.1	1336	23	17.2	5.8
5–12	2185	1	0.5	11	0	0.0	2196	1	0.5	0.0
13–24	1549	3	1.9	100	9	90.0	1649	12	7.3	5.4
25–34	644	1	1.6	108	10	92.6	752	11	14.6	13.0
35–44	457	0	0.0	49	4	81.6	506	4	7.9	7.9
45–54	422	1	2.4	24	3	125.0	446	4	9.0	6.6
≥55	666	24	36.0	19	5	263.2	685	29	42.3	6.3
Total	7240	45	6.2	330	39	118.2	7570	84	11.1	4.9
Adults										
Men	1798	13	7.2	137	12	87.6	1935	25	12.9	5.7
Women	1940	16	8.2	163	19	116.6	2103	35	16.7	8.4
Total	3738	29	7.8	300	31	103.3	4038	60	14.9	7.1

Rates per 1000 person-years of observations.

HIV-negative population from the overall crude rate. Thus, the total excess mortality was 4.9 (11.1–6.2) per 1000. In adult men the excess mortality was 5.7 per 1000, which compares with 8.4 per 1000 in adult women. The excess mortality was highest (13 per 1000) among adults aged 25–34. Corresponding HIV-attributable mortality fractions, i.e., the proportion of deaths that would have been avoided in the absence of HIV, were 44% for the total population, 48% for adults (44% for men, 50% for women) and 89% for adults aged 25–34 years.

Of the 31 seropositive adults who died during the 1-year period only five (16%) had clinically defined AIDS on enrolment, while 20 (65%) did not show any of the major symptoms included in the World Health Organization's clinical AIDS case definition [10,11].

Discussion

From this study of a general rural population in Uganda, it is estimated that the 1-year incidence of HIV-1 infection for adults was 1%, the age-adjusted mortality rate ratio 20.8, and the HIV-attributable mortality fraction 48%.

Of the *de jure* population of the 15 villages included in this study, 83% gave a blood sample at baseline and of those remaining in the area with known baseline serostatus 77% gave a blood sample after 1 year.

Non-compliance would bias the study outcome if numbers of absentees and refusals differed according to serostatus, age or sex. Our data suggest that the mortality rates among refusals and absentees are slightly higher in all age groups than in those with available HIV serology (not shown), implying an underascertainment of HIV-positive subjects. We may, therefore, have underestimated the HIV-associated mortality, particularly among those aged 13–24 years, the age group with the lowest compliance rate.

Specimen collection and HIV serology were carried out using strict quality assurance procedures [9]. A testing algorithm with sensitivity and specificity close to 100% was used [8]. It is improbable, therefore, that false-negative results on enrolment could have contributed to the observed HIV incidence. Conversely, all 12 incident cases with an available follow-up specimen were confirmed positive. There were, however, three subjects who showed evidence of transient antibody response who have not been classified as incident cases. One case is a 69-year-old man who had strong positive results on both EIA assays 1 year after enrolment. Four follow-up sera, collected over 15 months, suggest progressive loss of reactivity, the last two specimens being unambiguously negative. The second case, a 20 year-old man, had some EIA reactivity but was WB-negative on enrolment with strong positive EIA results after 1 year. Two follow-up sera, collected in the following year, also suggest gradual loss of reactivity. The third case is a 6-year-old boy, who was unambiguously seronegative on enrolment and whose father is among the classified incident cases. During the year the father was joined by a new spouse who was seropositive. At 1 year the boy had some EIA reactivity and positive WB. A follow-up specimen 1 year later was unambiguously negative. Thus, all three cases showed a possible transient antibody response suggesting exposure to HIV-1, possibly without established infection. We anticipate that these cases will be given a definitive classification in due course, following the outcome of ongoing investigations.

Our studies of seroprevalent cases of HIV-1 infection in this population suggest that approximately 99% of all HIV-1 infections in adults are due to heterosexual contact, the remaining 1% being probably due to blood transfusions [12]. Risk factors for HIV-1 infection in seroprevalent and incident cases are described elsewhere [13,14].

The observed number of new HIV infections was relatively small, resulting in a rather wide confidence interval for the estimated rate. The observed incidence rate of approximately 1% among adults in this rural cohort is similar to those reported for mixed urban/rural cohorts in the Kagera region in Tanzania [3] and the Rakai District in Uganda [4]. In absolute numbers the incidence of HIV-1 was similar to the HIV-1-associated mortality suggesting little change in overall seroprevalence.

For death ascertainment, at 1-year follow-up experienced interviewers administered individual questionnaires on which personal identifiers obtained at baseline had been entered. The questionnaire included explicit questions related to death. Notwithstanding this procedure, the mortality rates for HIV-negative adults and children suggest an underascertainment of deaths, which is also likely to apply to HIV-positive subjects. A continuous death registration was introduced in mid-1991 and comparison of death ascertainments through the continuous registration system with the annual re-census shows that the results are very similar. A higher mortality rate among seronegative subjects would result in a lower estimate of the mortality rate ratio and HIV-attributable mortality fraction; it would not, however, affect the observed extremely high mortality among HIV-positive subjects. It is customary in the area that people who become seriously ill return to their natal home to die. If such patients were to have been included in this population there would have been an overestimation of the HIV-associated mortality. However, none of the six HIV-positive deaths resident for less than 1 year on enrolment had clinical AIDS at that time.

AIDS 1994, Vol 8 No 1

Clearly, the HIV-related excess mortality depends on both the prevalence of HIV-1 infection and the mortality rate among HIV-positives. The excess mortality was 4.9 per 1000 for the general population with a seroprevalence of 4.8%, and 7.1 per 1000 in adults with a seroprevalence of 8.2%. The high rate of 13 per 1000 in the 25–34-year age group is particularly striking, and is due to high seroprevalence rates in both men (18.1%) and women (13.3%). The excess mortality in adult women (8.4 per 1000) is considerably higher than the excess mortality in men (5.7 per 1000), which is the result of both a higher seroprevalence rate in women than in men (female : male ratio, 1.2 : 1) and a higher mortality rate among positives women (117 versus 88 per 1000).

The annual HIV-related mortality rates between 1985–1987 in Kinshasa, Zaïre, were estimated to be of the order of 0.7–1 per 1000 in studies of hospital patients and selected groups [5,15]. Based on a study of adult cadavers in the two largest morgues in Abidjan, Côte d'Ivoire, De Cock *et al.* [6] estimated the 1988–1989 adult mortality due to HIV in that city to be 0.49 per 1000. They also estimated that 15% of adult men and 13% of adult women deaths were due to AIDS. The results from our study of a rural population suggest considerably higher mortality rates and HIV-attributable fractions. This difference may in part be explained by a more complete death ascertainment in our study since it was community based. The observed HIV-attributable mortality fraction of 89% for adults aged 25–34 years is similar to the results by Lindan *et al.* [16] in a study of a cohort of pregnant women in Kigali.

We observed a mortality rate of 10.3% in HIV-positive adults during a 1-year follow-up. This compares with a 2-year mortality rate of 15% observed in Kinshasa [17] and with annual progression rates from asymptomatic seropositivity to symptomatic disease of 5–6% for cohorts in Europe and the United States [18–20]. Since the majority of the 31 seropositive adults who died during the 1-year period did not show any of the major symptoms included in the clinical AIDS case definition, our data suggest that the progression from infection to symptomatic disease and from symptomatic disease to death in this population is extremely rapid.

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Chapter 5.2

Two-year HIV-1 associated mortality in a Ugandan rural population.

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Public health

Two-year HIV-1-associated mortality in a Ugandan rural population

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Summary

The mortality in 15 villages in South-West Uganda was studied in relation to HIV infection. After a population census, serum samples were tested for antibodies to HIV-1. Deaths were ascertained over 2 years. Unequivocal HIV-1 serology results were available for 9389 individuals.

The prevalence of infection was 4·8% for all ages and 8·2% for adults (aged 13 or more). 198 deaths were recorded during 15 725 person years of observation. Mortality among seronegative adults was 7·7 per 1000 and among seropositive adults 115·9 per 1000. The excess annual death rate associated with HIV-1 infection was 5·3 per 1000 and in adults 7·9 per 1000. Highest excess mortality was 16·9 per 1000 in the age group 25–34. Among adults, half of all deaths and among those aged 13–44 over 80% of deaths were attributable to HIV-1 infection.

These results show the strong impact that HIV-1 infection is having on mortality in a rural area of Uganda where the overall HIV-1 adult prevalence rate is below 10%—a rate lower than in many other parts of East Africa.

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Introduction

The World Health Organization predicts that, by the year 2000, 30–40 million people will have been infected with HIV-1,[1] about half of them in sub-Saharan Africa. Between and within sub-Saharan countries the prevalence of infection is not uniform;[2] in urban areas as many as 30% of adults may be infected[3] and seroprevalence rates of around 10% have been reported in rural districts.[4]

Some mathematical models predict that in the worst-affected areas AIDS is likely to lead to negative population growth,[5] others suggest that negative growth is improbable.[6,7] Inconsistent predictions are due, in part, to lack of information on HIV-1 transmission efficiency, the effect of risk-factors, sexual behaviour patterns, disease progression, and fatality rates. There have been few studies of the impact of HIV-1 infection on mortality in Africa,[8–11] and none for a general rural population. Information on disease progression and on survival following diagnosis of AIDS is also scarce.[11–14] We did a prospective study of a rural population in Uganda,[15] and report here on HIV-related mortality.

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Methods

The population studied was the inhabitants of 15 neighbouring villages, approximately one-third of the population of a sub-county of the Masaka District in South-West Uganda. The inhabitants are mainly subsistence farmers, and the Baganda ethnic group constitutes about 70%. In November 1989 to August 1990 a census was conducted. Those selected for follow-up were all who consented to participate and who had been resident in the area for 3 months or more, or for less than 3 months but stated they intended to stay. Newborns and those new to the area since the initial survey were enrolled subsequently.

Census clerks visited and recorded the composition of all households, and 2–4 weeks later, households were visited by a medical team. Consenting adults (aged 13 years or more) were examined and a brief medical history was taken. Blood samples were taken from both adults and children. Subjects with ailments were treated by members of the survey team or referred to the study clinic, and a counselling service was available. In 1991 and 1992, re-surveys of the population were undertaken. Field staff were not aware of the HIV status of study participants. In mid-1991 continuous death registration was introduced.

Blood samples were tested for HIV-1 antibodies at the Uganda Virus Research Institute. Quality control procedures and the test algorithm are described elsewhere.[16,17] Children < 18 months who were seropositive were assumed to be HIV-infected unless subsequent specimens showed loss of reactivity.

Statistics

In calculating person years of observation, subjects were included from the time they were enrolled until they died, migrated, or were seen at the second annual re-survey. Standardised mortality rates are included in the text and are calculated by the direct method with the total population as a standard. Age-adjusted mortality-rate ratios were calculated by Poisson regression methods. Non-standardised total rates are shown in the tables, since adjustment for the strong age-serostatus interaction makes any adjusted rate of little interest.

Results

At the initial survey there were 1981 households in the study villages. Inhabitants were repeatedly absent in 56 (2·8%), 60 (3·0%) refused to participate, and 59 (3·0%) households did not comply for other reasons. The remaining 1806 (91·2%) households had a population of 9820.

Age group (years)	Census population			Compliance	HIV-1 prevalence (%)	
	Males	Females	Total	%	Males	Females
0–4	970	943	1913	87	1·8	1·6
5–12	1338	1291	2629	86	0·5	0·5
13–24	1159	1198	2357	74	3·4	9·9
25–34	467	501	968	81	18·1	13·3
35–44	273	332	605	85	13·5	8·9
45–54	263	268	531	85	7·0	5·9
55+	411	406	817	86	3·5	2·6
Total	4881	4939	9820	83	4·4	5·3

Table 1: **Compliance and HIV-1 seroprevalence by age and sex or enrolment**

Age group (years)	HIV negative			HIV positive			Total		
	PYO	Deaths	Rate	PYO	Deaths	Rate	PYO	Deaths	Rate
0–4	2316	43	18 6	41	14	342 4	2357	57	24·2
5–12	4675	4	0 9	29	2	70 1	4704	6	1·3
13–24	3488	3	0 9	187	14	74 7	3676	17	4 6
25–34	1386	3	2 2	240	28	116 5	1627	31	19·1
35–44	926	12	2·2	107	9	84 2	1033	11	10 7
45–54	867	10	11 5	48	6	125 4	915	16	17 5
55+	1367	44	32 2	47	16	338 3	1414	60	42 4
Total	15 026	109	7·3	699	89	127 3	15 725	198	12 6
Adults	8034	62	7 7	630	73	115 9	8664	135	15 6

PYO = person years of observation. Rate is per 1000 PYO.

Table 2: **Mortality by HIV-status and age at 2-year follow-up**

83% (8105) people agreed to give a blood sample (table 1). Unequivocal serology results were available for 7802 (the 303 missing were mainly due to insufficient serum from children); 377 (4·8%) were HIV-1 positive. The seroprevalence in adults aged 13 years or more was 8·2%.

At re-survey 1 year after enrolment, unequivocal serology results were obtained for an additional 707 individuals (7%) from the baseline census and 880 (60%) of 1456 newborns and people who had moved into the area. In all, 9389 individuals with unequivocal serology results were enrolled. 2 years after the start of the survey, 2% had died, 13% had left the area, and 84% had remained. 29 individuals refused follow-up and are excluded from the analysis. The analysis is based on 9360 persons and 15 725 person years of observation.

There were 198 deaths (table 2); 109 in seronegative individuals (7·3 per 1000 person years) and 89 in seropositive individuals (127·3 per 1000). The standardised death rates among seronegative and seropositive adults were 7·5 (95% confidence intervals [CI] 5·6–9·4) per 1000 and 132·1 (97·0–167·1) per 1000, respectively.

HIV-1 negative males and females had similar death rates. HIV-1-positive males and females had mortality rates of 109·3 per 1000 and 143·4 per 1000, respectively. The highest mortality among those HIV-positive was in males aged 25–34 and in females aged 13–24 and 25–34. The ratio of the mortality rates in seropositive and seronegative individuals are shown in table 3. The highest age-specific ratio was 87 (CI 25–302) in the age-group 13–24. In the age-group 13–44 the overall age-adjusted ratio was 60 (28–129). The adjusted ratio for males was 33 (10–98) compared with 79 (28–224) for females (p for male-female difference = 0·18).

Excess mortality in the population due to HIV-1 infection can be estimated by subtracting the mortality rate in those HIV-negative from that in the total population (table 4). Overall age-standardised excess mortality was 5·4 (4·4–6·5) per 1000. Age-standardised excess mortality among adult males was 6·8 (3·7–10·0) per 1000 compared with 9·2 (7·4–10·9) per 1000 in adult females. Excess mortality was considerable among all age groups and highest, at 16·9 (10·5–23·3) per 1000, amongst males and females aged 25–34.

Age group	Mortality rates (per 1000 PYO)		Rate-ratio* (95% CI)
	HIV-pos	HIV-neg	
0–12	229	6 7	34
13–24	75	0 3	87
25–34	116	2 2	54
35–44	84	2 2	39
45+	232	24 2	10
13–44			
Males	79	1 4	331 (10–98)
Females	108	1 3	791 (28–224)
Total	95	1 4	601 (28–129)

*Rate-ratio: Rate in HIV-positives divided by the rate in those HIV-negative.
†HIV-negative. Age-adjusted ratio. PYO = person years of observation.

Table 3: **Mortality by HIV-1 status and mortality rate ratios by age and sex**

Age group	Excess mortality per 1000			HIV-1 attributable mortality fraction (%)		
	Males	Females	Both	Males	Females	Both
0–4	4 5	6 8	5 6	19	28	23
5–12	0·0	0 8	0 4	0	40	33
13–24	0 5	6 9	3 8	49	86	81
25–34	17 3	16·5	16 9	84	93	89
35–44	10 6	6 8	8 5	81	78	80
45–54	1 1	10 2	6 0	6	61	34
55+	13 5	7 0	10 2	34	16	24
Total	4 4	6·3	5 3	38	46	42
Adults	6 7	8 9	7·9	47	53	50

Table 4: **HIV-1-specific excess mortality and HIV-1 attributable mortality fractions by age and sex**

Discussion

This prospective study shows a high HIV-1-associated mortality; more than 50% of all deaths in adults, and more than 80% in young adults, were HIV-1-associated (table 4). Might the results be biased by factors such as selective enrolment to the study, non-compliance or out-migration during follow-up, and errors in the ascertainment of HIV-1 or vital status?

Unequivocal serology results were available for 87% of the population. Available data suggest that the mortality among those who were included in the census but did not participate was higher: among those aged 13–44 the death rate in those who were absent or refused was 12·9 per 1000 compared with 9·1 per 1000 among those participating. Thus, selective enrolment and non-compliance are likely to have underestimated mortality rates.

At 1 year 60% of newborns and those new to the area were enrolled. Of these, 3% had died and 19% had left the area 1 year later. These rates are higher than the 2-year rates for the baseline population. Higher mortality can be explained partly by a relatively high proportion of infants in this group (44%) and partly by a higher HIV-1 seroprevalence among adults (16·0%); the reason for the increase over baseline (8·2%) was presumably that some adults returned to their villages from urban areas with high prevalence rates. While bias may have been caused by this mobile group, they accounted for only 5% of the person-years of observation. 13% of those enrolled left the area during the 2-year period. While similar rates of out-migration were recorded in HIV-1-seronegative and HIV-1-seropositive,

some bias due to different trial mortality among those leaving is possible.

The HIV testing algorithm had a sensitivity and specificity of close to 100% (16). Errors in the ascertainment of serostatus cannot be ruled out, but any such misclassification would result in underestimation of HIV-1-associated excess mortality. Finally, it is customary in this area for seriously ill persons to return to their natal homes to die and this may have resulted in an under ascertainment of adult deaths.

The sources of bias considered above are either small or affect equally both seronegative and seropositive people. If similar levels of under ascertainment occurred in the two groups, the mortality rate ratio and attributable fraction would be unaffected, while the absolute level of mortality among those HIV-1 seropositive would be underestimated. It therefore seems unlikely that any biases have materially distorted the main finding of the study, that of a high mortality in HIV-1 seropositive people in this population. Except in 25 participants who seroconverted during the first year of follow-up,[15] dates of seroconversion in the present study were unknown. The mortality rate of 11·6% among seroprevalent adults was, however, much higher than those in industrialised countries where annual progression from asymptomatic seropositivity to symptomatic disease is in the range of 5% to 6%.[18,19] The rate is, however, consistent with a study of female prostitutes in Nairobi in whom the median interval from seroconversion to AIDS was 45 months.[13]

We observed rapid progression from asymptomatic infection or mild disease to death. Medical assessment 1 year or less prior to death was available for 64 of 73 of the HIV-1-positive adults. Of these, 5 (8%) had AIDS as defined by the Bangui case definition,[20] 31 (48%) one or more major symptoms, and 28 (44%) no major symptoms. Thus, a substantial proportion of these patients progressed within 6 months, on average, from asymptomatic infection or mild disease to death. The rapid progression and high mortality rate suggest that both the interval from infection to symptomatic disease and the symptomatic survival period may be shorter than those in developed countries, and it is plausible that both are affected by lack of medical care.[21]

Although the highest mortality rates were in seropositive children under 5 and in adults over 55 years, mortality among seronegative people was also higher in these groups. The highest mortality rate ratios—indicating relative risk—were seen in the middle years of adulthood (60 in those aged 13–44). A finding of this magnitude, in an age-group which typically has low mortality, is difficult to explain other than as a direct causal effect of HIV-1 infection on mortality. The results indicate an HIV-1 attributable mortality fraction of 50% for all adults (47% and 53% for adult males and females, respectively). These results compare with estimates of 15% and 13% in Abidjan in 1988–89,[10] and 20–24% among employees in Kinshasa in 1987–88.[22] The attributable fraction among females aged 25–34 was 90%, a result similar to that of a prospective study of childbearing women in Kigali, Rwanda.[11]

This is the largest prospective study of its kind in sub-Saharan Africa. While possible biases cannot be ruled out, they are unlikely to invalidate the main findings, namely the rapid rate of progression to death in HIV-1 positive individuals, a relative mortality risk in seropositive people of 60, and the attribution to HIV-1 infection of more than 50% of deaths among adults and 80% of deaths among those aged 13–44 years. These findings, in a population which has a lower HIV-1 prevalence than some urban African centres, highlight the severe impact of the HIV-1 epidemic on the sub-Saharan population.

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Chapter 6

Decreasing HIV-1 seroprevalence in young adults in a rural Ugandan cohort.

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PAPERS

Decreasing HIV-1 seroprevalence in young adults in a rural Ugandan cohort

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Abstract

Objective—To assess the trend in HIV-1 seroprevalence in an adult population in Uganda.

Design—An observational cohort study with four year follow up.

Setting—A cluster of 15 villages in rural Uganda.

Subjects—All residents of the 15 villages—about 10 000 people.

Main outcome measure—Prevalence of HIV-1 infection as assessed by enzyme immunoassay.

Results—During the five year period the overall standardised seroprevalence of HIV-1 showed little change; 8·2% in 1990, 7·6% in 1994. Among males aged 13-24 years the prevalence decreased from 3·4% to 1·0% (P for trend <0·001); among females of the same age the corresponding values were 9·9% and 7·3%. The decrease was greatest in males aged 20-24 years and females aged 13-19 years.

Conclusion—This is the first report of a decline in HIV-1 prevalence among young adults in a general population in sub-Saharan Africa with high overall HIV-1 prevalence. It is too early to conclude that the epidemic in this population is in decline, but the results of this study should be reason for some cautious optimism and encourage the vigorous pursuit of AIDS control measures.

Introduction

The HIV-1 epidemic continues to spread in Africa,[1] but some studies have reported unchanging HIV-1 prevalence among adult populations in different regions in Burundi, Rwanda, and Zaire.[2-4] In some of the major towns of Uganda the prevalence of HIV-1 among women attending antenatal clinics included in the national sentinel surveillance programme has declined since 1992; for example, the reported rates from the two main hospitals in Kampala, the capital city, fell from 29% to 22% in one hospital and to 17% in the other.[5]

The population dynamics which underlie the course of the HIV-1 epidemic are complex.[6] Sociodemographic, cultural, and biological factors play an important part, as does the effect of specific interventions, including behaviour change and promotion of condom use, counselling, and control of sexually transmitted diseases. In recent years encouraging results have been reported from sub-Saharan Africa on successful interventions in cohorts of women attending antenatal clinics,[7] and prostitutes[8-10]; but only one successful intervention has to date been reported for general populations in sub-Saharan Africa.[11-13]

In 1989-90 we began a descriptive study of the population dynamics of HIV-1 by enrolling a rural population cohort in Uganda.[11-14] We report here the age and sex specific trends in HIV-1 prevalence during four years of follow up.

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BACKGROUND

The area of study is a cluster of 15 neighbouring villages containing about one third of the population of a subcounty of Masaka district in south west Uganda, situated about 32 km from Masaka town and 16 km from the trans-Africa highway at its nearest point. The inhabitants are mainly peasants who grow bananas as a subsistence crop and cultivate coffee for sale. Households are scattered, although some are concentrated around the trading village at the centre of the study area. The predominant tribal group, the Baganda, constitute approximately 70% of the population. Most people are Roman Catholics; about one quarter are Muslims. The area used to have two dispensaries and a health centre; in 1990 the research programme opened a study clinic.

The median age at first sexual contact is 15 years for women and 17 years for men.[15] Sexually transmitted diseases are common[11 14] and condoms are used relatively rarely.

As we set out to conduct an observational study, the AIDS control measures initiated by the programme were initially limited in scope and intensity and complemented general awareness campaigns of the national AIDS control programme. Measures initiated by the programme included health education efforts, a limited distribution of condoms, and improvement of control of sexually transmitted diseases.

Methods

Beginning in late 1989, after the study villages had been mapped, a census and socioeconomic questionnaire were administered to all consenting heads of household. All de jure residents were included. Two to three weeks later a medical team visited each of the households. All adults were invited to participate in the medical and serological survey, which involved a medical history and physical examination. A blood sample was taken from consenting adults and children. Details of the procedures have been described elsewhere.[12]

Blood specimens were transported at weekly intervals to the laboratory of the Uganda Virus Research Institute in Entebbe, where they were tested for antibodies to HIV-1 following a rigorous algorithm and quality control procedures.[17 18] In brief, all serum samples were tested by using two enzyme immunoassay systems: Recombigen HIV-1 enzyme immunoassay (Cambridge Biotech Corporation, Worcester, Massachusetts) and Wellcozyme HIV-1 Recombinant (Wellcome Diagnostics, Dartford) with western blot when indicated (this included all specimens from subjects positive for the first time; Novopath HIV Immunoblot, Bio-Rad Laboratories, Watford).

During 1990-4 the cohort was surveyed annually by using procedures similar to those at baseline. On each of these surveys newborns and those new to the area

were added to the cohort. A counselling service was available for those participants who wanted to know their HIV status.[11] Field staff were not aware of the HIV status of study participants.

Data were entered by double entry and verification, and data were checked for consistency. Existing software packages (EPI INFO and EGRET) were used for statistical analyses. In calculating significance of differences in prevalence or of trends in prevalence over time we used methods for non-matched data. As a consequence the reported P values underestimate true differences.

Results

At the initial survey there were 1981 households in the 15 study villages; 1806 (91·2%) of households agreed to take part in the census: a total population of 9777. Of 5226 adults (aged 13 years or more) 4167 (80%) were enrolled during the initial survey and had an unambiguous serostatus. After four years 89% of adults initially present had been enrolled. During the four year follow up period 28% of those present in the first survey left the area. Those remaining in the study area, leaving the study area, or joining from outside the area had 5·5%, 11·5%, and 16·3% progressively higher (standardised) rates of HIV-1 infection.[10] After four years the total adult population was 5649; 88% of these had had blood samples taken at some time and had an unambiguous serostatus.[11]

At the four follow up surveys the compliance rates among the resident population were 67%, 61%, 57%, and 62%. Non-compliance was not cumulative, however, and at four years 71% had an unambiguous serostatus at either the three year or the four year follow up. For young adults aged 13-24 the compliance rates were 62%, 56%, 52%, and 57% at the follow ups; of those resident at the fourth follow up, 88% had given a blood sample on one or more occasions.

Table I shows HIV-1 seroprevalence by survey round for the total adult population and by age and sex. During the five year period the overall age and sex standardised seroprevalence showed little change from 8·2% (95% confidence interval 7·4% to 9·1%) at round 1 to 7·6% (6·7 to 8·5) at round 5. There was, however, a considerable decrease in prevalence in males aged 13-24 years (from 3·4% to 1·0%; P for trend $<0·001$) and a suggestion of a corresponding decrease in females (from 9·9% to 7·3%; P for trend=0·08). Changes in other age groups were small.

The HIV-1 prevalence among those aged 13-24 years is more closely examined in table II. In the age group 13-19, seroprevalence in males was very low at both round 1 (0·2%) and round 5 (0·4%); in young adult females the rate fell from 4·5% (27/601) to 2·4% (13/531; P=0·09). In men aged 20-24 years rates declined from 11·8% (28/237) to 2·7% (5/187; $P<0·001$); there was little change among women of the same age.

TABLE I—*HIV-1 seroprevalence by age group, sex, and survey round rural cohort, Masaka, Uganda, 1989-94. Values are percentages (number positive/total) of subjects*

	Round 1	Round 2	Round 3	Round 4	Round 5
Males					
13-24	3·4 (29/846)	3·6 (26/716)	2·3 (15/657)	1·6 (10/637)	1·0 (7/688)
25-34	18·3 (64/350)	18·2 (54/296)	19·8 (57/288)	22·9 (63/275)	19·4 (61/314)
35-44	13·5 (30/223)	11·9 (23/194)	12·1 (24/199)	12·2 (22/181)	14·5 (29/200)
≥45	4·8 (27/561)	4·6 (22/483)	4·4 (20/452)	5·3 (22/419)	5·3 (23/435)
Females					
13-24	9·9 (87/883)	8·2 (68/833)	7·8 (61/778)	8·1 (56/691)	7·3 (54/742)
25-34	13·3 (57/429)	12·6 (50/396)	15·2 (57/374)	17·1 (63/369)	15·9 (60/377)
35-44	8·8 (26/294)	9·5 (23/243)	10·5 (25/238)	7·9 (17/215)	7·7 (18/234)
≥45	3·9 (23/586)	4·0 (20/501)	3·9 (17/439)	3·9 (16/406)	4·2 (14/452)
Total†	8·2 (343/4172)	7·8 (286/3662)	7·8 (276/3425)	8·1 (269/3193)	7·6 (271/3342)

†Percentages standardised for age and sex.

TABLE II—*HIV-1 prevalence in age groups 13-19 and 20-24 years, rural cohort, Masaka, Uganda, 1989-94. Values are percentages (number positive/total) of subjects*

	Round 1 (1989)	Round 5 (1994)	Difference in percentages (95% confidence interval)	P value
Males				
13-19	0·2 (1/609)	0·4 (2/501)	−0·2 (−0·1 to 0·4)	>0·5
20-24	11·8 (28/237)	2·7 (5/187)	9·1 (4·4 to 13·9)	<0·001
Total	3·4 (29/846)	1·0 (7/688)	2·4 (1·0 to 3·8)	<0·01
Females				
13-19	4·5 (27/601)	2·5 (13/531)	2·0 (−0·1 to 4·1)	0·09
20-24	21·3 (60/282)	19·4 (41/211)	1·9 (−5·3 to 9·0)	0·25
Total	9·9 (87/883)	7·3 (54/742)	2·6 (−0·2 to 5·3)	0·08

During the period 1989 to mid-1994 the incidence of HIV-1 infection among adults in the cohort remained at about 7/1000 person years (7·3 in 1989-91 and 7·1 in 1992-4; data not shown). There was a suggestion of a decrease in incidence among males aged 13-24 years from 6·4/1000 person years (7/1094) to 2·6/1000 (4/1530; P=0·14); however, among females of the same age the corresponding rates were 8·2/1000 (9/1100) and 9·7/1000 (14/1442; P=0·7).

At the initial survey there were 29 seropositive males and 87 seropositive females in the 13-24 year age group. In the following four years 75 (27 males, 48 females) moved into the next age group; 19 (all females) left the area and eight (1 male, 7 females) died. The remaining 14 (1 male, 13 females) were still present at the time of the fourth resurvey and aged less than 25 years.

Two (1 male, 1 female) seropositive children moved into the 13-24 year age group; 29 seropositive 13-24 year olds (3 male, 26 female) joined the cohort, 25 of these after moving into the area; and 19 (4 males and 15 females) seroconverted. Thus at the fourth follow up survey there were nine seropositive males and 55 seropositive females in the 13-24 year age group.

Discussion

During four year follow up of a rural Ugandan cohort we observed a significant decline in the prevalence of HIV-1 infection among males aged 13-24 and a non-significant reduction among young females but no such change in other age groups. This is the first time that a decline in HIV-1 prevalence is being reported for a sub-Saharan population.

POSSIBLE BIASES

Almost 90% of those aged 13-24 who were resident in the fourth year of follow up had given one or more blood samples, suggesting that enrolment bias was limited. The rates of non-compliance and of leaving the area were slightly higher for participants who were HIV-1 positive than for those who were negative, but there was no indication of an increase in these differences over time; only one seropositive man in the age group 13-24 left the area. Those aged 13-24 years who were included in the census but who did not give a blood sample had a higher mortality (16·8/1000 person years compared with 6·2/1000 among those participating), a finding in support of selective non-compliance; this group counted, however, for only 11% of the person years of observation.

The HIV testing algorithm and quality control procedures remained unchanged during the course of the study.[17,18] Errors in the ascertainment of serostatus cannot be totally excluded, but is is unlikely that they changed over time.

Thus, although selective enrolment and non-

compliance may well have resulted in an underestimate of the absolute prevalence of HIV, there is no indication that there have been major changes in these differentials over the five years of the study and it is improbable that any biases have distorted the main finding of the study—namely, the substantial decline in HIV prevalence among young males.

PREVALENCE PATTERNS

The transmission of HIV-1 among adults in this population is almost exclusively through heterosexual contact,[21] and virtually no cases of HIV-1 infection are found in males aged 17 years or less and females aged 13 years or less. The prevalence of HIV-1 infection in young adults should therefore closely reflect recent incidence rates of HIV infection and be sensitive to changes over time. Thus, assuming a non-differential reduction in the force of infection, we would expect to see the largest changes in prevalence in 20-24 year old males and 13-19 year old females. This is consistent with our observations.

When mortality, mobility, age effects, and incidence are taken into account, the decline in seroprevalence in 13-24 year old males seems to be explained largely by the effect of aging and a low incidence. In comparison, the pattern among young females is more mixed: a smaller aging effect, a substantial mortality (presumably since women are infected at a younger age), a higher incidence, and a high rate of joining and leaving the area. The resulting modest decrease in seroprevalence in females aged 13-24 years masks the substantial decline in prevalence among 13-19 year old females.

EXPLAINING THE DECLINE

Study and intervention effects, or a combination of these, may have contributed to the decline in HIV prevalence. At the start of the study the programme recruited about 50 people from the subcounty, and an additional 40 technical and support staff were brought in and accommodated on a permanent basis. A field office, clinic, and laboratories were set up, and there is little doubt that the presence of the programme had a high profile in this rural area. The taking of blood samples caused considerable anxiety among the study population and stimulated heated discussions. Moreover, the start of the study happened to coincide with a rapid increase of deaths associated with HIV infection among long term residents. It is probable, therefore, that a study effect did operate.

The observed decline cannot be explained by lack of replacement of subjects at high risk. In a closed cohort the incidence of HIV-1 infection, in the absence of other effects, may decrease rapidly with time as subjects at highest risk of HIV infection become infected and are not replaced[22]; however, the group of young adults who are just entering sexually active life are effectively an open cohort with a high rate of replacement.

Intervention efforts aiming at reducing the frequency of partner change, distribution and promotion of condoms, and the control of sexually transmitted diseases were gradually expanded. The effect of these efforts was not evaluated. Messages to reduce the frequency of partner change were initially delivered during community meetings, and AIDS awareness was promoted through song and drama competitions at schools. From 1992 onwards efforts to change behaviour became more intense and used community health workers, traditional birth attendants, and women and adolescent peer groups. Condoms were distributed on a limited scale. Community based condom promotion and distribution through peer networks started in 1993; by mid-1994 its scale was still very limited. Sexually transmitted diseases are common in this population.[15] Measures for control of sexually transmitted diseases, introduced in late 1990, included free treatment, notification of contacts, and efforts to influence the population's patterns of seeking treatment; even so, only a relatively small proportion of people with symptomatic sexually transmitted diseases sought treatment in the official health sector (H U Wagner *et al*, sixth international conference on AIDS in Africa, Dakar, 1991). On balance, though, it seems reasonable to assume that the intervention efforts initiated by the programme, together with the activities of the national AIDS control programme, will have had an impact.

Key messages

- Some reports suggest that the AIDS epidemic may be stabilising in some African countries
- This observational cohort study of a rural population in Uganda shows an overall stable prevalence
- A significant decline in the prevalence of HIV-1 among young adult males was observed; there was a suggestion of a corresponding decrease in young females
- These findings should encourage the vigorous pursuit of AIDS control measures

The most important result of this study is the observation that a decrease in infection rates among young adults is possible, even in populations with a relatively high force of HIV infection, with no more than a modest intensity of interventions. To determine if the transmission of HIV-1 has also decreased among older age groups will require a longer term cohort follow up. Even if there was no effect on the incidence in older age groups, a reduction in the prevalence of infection among young adults is undoubtedly a public health benefit.

Although in our study the decline in prevalence was less in women than in men, the observed decline is consistent with the recent results of the national antenatal surveillance system,[7] suggesting that the epidemic may be levelling off in at least some rural and urban areas in Uganda. It is too early to conclude that the epidemic is in decline, but the results of this study should be reason for cautious optimism and encourage the vigorous pursuit of AIDS control measures.

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Chapter 7

Modelling the impact of alternative HIV intervention strategies in rural Uganda.

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Modelling the impact of alternative HIV intervention strategies in rural Uganda

N. Jamie Robinson*†, Daan W. Mulder†‡, Bertran Auvert* and Richard J. Hayes†

Objective: To assess the likely impact on HIV incidence of increased condom use, a reduction in casual sexual partners, treatment programmes for other sexually transmitted diseases (STD) and combinations of these in rural Uganda.

Methods: A simulation model for the transmission dynamics of HIV infection and STD was employed, drawing on data from a rural population cohort in South-West Uganda with an HIV prevalence of 9% among adults in 1990.

Results: For the scenario most consistent with data from the study population, 39% of all adult HIV infections were averted, in the 10 years from 1990, when condoms were used consistently and effectively by 50% of men in their contacts with one-off sexual partners (such as bar girls and commercial sex workers). Reducing by 50% the frequency of men's sexual contacts with one-off partners averted 68% of infections. Reducing by 50% the duration of all STD episodes averted 43% of infections. Combining these three interventions averted 82% of all adult infections in the 10 years from 1990.

Conclusion: A substantial proportion of HIV infections may be averted in general populations through interventions targeted only on less regular sexual partnerships.

AIDS 1995, 9:1263–1270

Keywords: Simulation model, interventions, HIV incidence, Uganda

Introduction

The World Health Organization (WHO) estimated that by mid-1994 the cumulative number of adult HIV infections in sub-Saharan Africa was over 10 million. This is expected to more than double by the year 2000 [1]. In the absence of effective drugs and vaccines, WHO has called for vigorous efforts to prevent transmission of HIV infection.

The three main intervention strategies currently employed by national AIDS control programmes are promotion of condom use, promotion of a reduction in sexual partners and treatment programmes for other sexually transmitted diseases (STD). The relative efficacy of each of these interventions in general populations is unknown. Such knowledge is important for guiding intervention policy. One approach to this is by application of simulation modelling.

The UK Medical Research Council/UK Overseas Development Administration/Uganda Virus Research Institute (MRC) Programme on AIDS in Uganda has generated one of the most complete and extensive datasets from prospective follow-up of an entire population cohort in a rural community in sub-Saharan Africa [2–6]. Simulation modelling scenarios have attempted to replicate recorded characteristics of the study population in 1990, in order to try to improve our understanding of the transmission dynamics and spread of HIV infection and STD in rural Uganda ([7] and unpublished data).

In this paper we present results of running simulations from 1990 to explore the comparative effects of increas-

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AIDS 1995, Vol 9 No 11

ing use of condoms, reducing casual sexual contacts, improving STD treatments and combinations of these in an advanced epidemic in rural Uganda.

Methods

Description of the model

An earlier version of a simulation model (SimulAIDS) [8] was modified and extended (1) to allow simultaneous modelling of the transmission dynamics of HIV infection and of two STD, and (2) to enable reasonable replication of observed characteristics of the study population in rural Uganda in 1990. The motivation to model the transmission dynamics of STD as well as HIV came from epidemiological data which, by the late 1980s, suggested that STD were probably enhancing transmission of HIV and thus possibly playing an important role in the spread of HIV infection. The other main changes included the introduction of migration to enable a reasonable fit to the observed age structure of the rural population, and more flexibility in sexual behaviour to achieve a better representation of the observed profile of HIV prevalence by age and sex.

SimulAIDS is an age-structured simulation model with both deterministic and stochastic elements (based on Monte Carlo methods) elements. Every individual in the simulated population is represented by a set of characteristics, including age, sex, HIV and STD status, type of sexual relationships and identity of all sexual partners. At each time step (in this exercise 5 days), events occur with given probabilities, defined by input parameter values, and the status of the entire population is updated.

Modelling scenarios of the study population in rural Uganda have used selected features available in SimulAIDS, including demography (fertility, mortality, outmigration), sexual behaviour (represented by one-off, short-term and long-term partnerships), and transmission dynamics of two STD (ulcerative and non-ulcerative) and of HIV infection (i.e., with representations of the natural history and transmission probabilities per sexual contact). (See Appendix for descriptions of the main features of the model used in this exercise.)

Fitting models to data

The model was used to simulate the spread of HIV infection in the Ugandan cohort, from its assumed introduction in 1980, in just one or two individuals, up until the first survey of the cohort in 1990. At this time the characteristics for each individual in the entire population were recorded so that simulated interventions could then be run from the same initial population in 1990. Values for parameter inputs were chosen on the basis of data from the cohort and, where necessary, from other published sources. Input parameters were specified so as to achieve a reasonable fit to recorded characteristics of the study population in 1990, including age structure, HIV prevalence by age and sex, HIV prevalence among adults of 9% and a male-to-female HIV prevalence ratio of 0.9.

Results are given for two modelling scenarios, defined by assuming different enhancing effects of STD on HIV transmission (STD cofactor effects). For one, transmission of HIV infection per sexual contact was assumed to be enhanced 10-fold during all episodes of ulcerative STD, and two-fold during episodes of non-ulcerative STD in women. This was referred to as the 'low cofactor scenario'. A second scenario employed STD cofactor effects of 100 and 5, respectively. This was referred to as the 'high cofactor scenario'.

A full list of the specified input parameter values for sexual behaviour characteristics (prior to interventions) and for STD and HIV dynamics are given in Table 1. Input parameter values for sexual behaviour and for the probability of HIV transmission were adjusted, for the two scenarios, to preserve the fit of the model to the study population in 1990. Simulated prevalence levels of ulcerative and non-ulcerative STD in 1990 were approximately 0.5 and 2.5%, respectively, among both men and women for the low cofactor scenario, and 0.4 and 1.5% for the high cofactor scenario, respectively. The difference in simulated STD prevalences between the two scenarios resulted from employing slightly different sexual behaviour assumptions while maintaining identical parameter values for STD transmission dynamics.

Values for sexual behaviour parameters were modified from 1990 to simulate interventions (see below). Other input parameters related to condom use and STD treatments were ascribed non-zero values from 1990 to simulate interventions (see below). Additional details on the model, on fitting models to the data from the study population, and on choice of values for parameter inputs are given elsewhere (see Appendix, [7] and unpublished data).

Simulating interventions

To model the effect of interventions on HIV incidence, simulations were run for 10 years from recorded populations in 1990. The effect of interventions targeted both at the general population and at one-off sexual partnerships (such as those with bar girls and commercial sex workers) were examined. All simulated interventions were introduced at one time-point (namely 1990).

To assess model projections in the absence of interventions, simulations were run from 1990 without modifying input parameter values.

Condom interventions were simulated by assuming 50 or 100% of men always used condoms with their one-off partners. The efficiency of condoms in preventing transmission of both HIV and STD was assumed to be 100%. In practice the efficiency of condom use may be less than 100% [9]. In this exercise results, therefore, represent upper bounds for the impact of condom use.

Casual partner reduction was simulated by assuming (1) a reduction by 50% in the proportion of men with one-off

Table 1. Specified input parameter values for the two simulated scenarios. For most input parameters one value is given, which is used in both scenarios. For a few input parameters two values are given, representing the different values taken for the low and high sexually transmitted disease (STD) cofactor scenarios, respectively.

	STD cofactor scenarios		
	Both	Low	High
Sexual behaviour			
Long-term partnerships (LTP; marriage)			
Minimum age (years) of F/M in LTP	18.0/24.0		
Proportion of M with one/two LTP	0.65/0.10		
Minimum/maximum duration (years) of LTP	5.0/45.0		
Frequency of sexual contacts between LTP (weekly)	1.5		
Short-term partnerships (STP)			
Minimum age (years) of F/M in STP	13.0/16.0		
Maximum age (years) of F in STP		25.0	24.0
Maximum age (years) of M in STP	50.0		
Proportion of married/unmarried M with a STP	0.3/0.6		
Minimum/maximum duration (days) of STP	40/160		
Frequency of sexual contacts between STP for			
Married M (weekly)	0.5		
Unmarried M (weekly)		1.25	1.0
One-off sexual partnerships (OSP)			
Minimum/maximum age (years) of F in OSP	18.0/35.0		
Minimum age (years) of M in OSP		18.0	20.0
Maximum age (years) of M in OSP	69.0		
Proportion of married/unmarried M having contacts with OSP	0.3/0.4		
Frequency of OS contacts for married/unmarried M (monthly)	0.25/1.0		
Frequency of OS contacts for F (weekly)	2.0		
STD			
Ulcerative (UCL) STD			
Duration (days) of UCL STD in M/F	12/30		
Transmission probability of UCL STD per sexual contact M–F/F–M	0.30/0.25		
Among F having OS contacts, minimum proportion with UCL STD	0.1		
Non-ulcerative (non-UCL) STD			
Duration (days) of non-UCL STD in M/F	20/50		
Transmission probability of non-UCL STD per sexual contact M–F/F–M	0.35/0.20		
Among F having OS contacts, minimum proportion with non-UCL STD	0.1		
HIV infection			
Proportion of M–C/sexually transmitted infections developing AIDS	1.0/1.0		
Minimum/maximum AIDS incubation period (years) for M–C infections	0.0/2.5		
Minimum/maximum AIDS incubation period (years)			
for sexually transmitted infections	1.0/7.0		
Duration (days) of initial/final phase of incubation period	30/100		
Survival with AIDS (years) for M–C/sexually transmitted infections	0.5/0.5		
Probability of HIV transmission			
From M to C	0.3		
M–F per contact during standard phase of incubation period		0.004	0.0015
F–M per contact during standard phase of incubation period		0.00105	0.00029
Multiplying factor for probability of HIV transmission			
during initial and final phase of incubation period	10.0		
Enhancing effect of UCL STD either in M or F			
on HIV transmission per sexual contact		10	100
Enhancing effect of non-UCL STD in			
M on HIV transmission per sexual contact	1		
F on HIV transmission per sexual contact		2	5

Input values for demographic parameters were based on a total fertility rate of 8.6, age-specific background mortality rates taken from the South model life-table with mortality level 16 for females (F), and an annual net out-migration rate of 2%. These input parameter values were identical for the two scenarios. M, Male; M–C, mother–child.

sexual partners; (2) a reduction by 50% in the frequency of sexual contacts of men with one-off partners; and (3) the cessation of one-off sexual partnerships.

STD interventions were simulated by assuming 50 or 100% of all STD episodes had their duration reduced by 50%.

A package of interventions was simulated by assuming (1) 25% of men always used condoms with one-off partners, the frequency of sexual contacts of men with one-off partners was reduced by 25%, and 50% of all STD episodes had their duration reduced by 50%; and (2) 50% of men always used condoms with one-off partners,

AIDS 1995, Vol 9 No 11

the frequency of sexual contacts of men with one-off partners was reduced by 50%, and all STD episodes had their duration reduced by 50%. Scenarios were also set up to assess all combinations of the three components of the full package of interventions both at the 25 and 50% levels. The components of the full package were referred to as 'part package interventions'.

For each simulated intervention the mean annual adult HIV incidence from 10 replications is given with time, where HIV incidence is calculated as number of incident infections divided by total population. The proportion of HIV infections averted in the 10 years from 1990, i.e., the efficacy of a particular intervention, was calculated as: $1-(\bar{x}/\bar{y})$ where $\bar{y}$ represents the mean cumulative number of HIV infections in the absence of an intervention, and $\bar{x}$ represents the mean cumulative number of infections in the presence of an intervention. A confidence interval (CI) for this proportion was derived using the log(-log) transformation [10]. In this way, limits for CI were bounded by 0 and 100%.

Results

Figure 1 shows results for simulated HIV prevalence from 1980 to 2000, in the absence of interventions. For the high cofactor scenario HIV spreads more rapidly, peak prevalence is reached earlier, and subsequently HIV prevalence declines. Note that input parameter values were modified slightly for each scenario to give an HIV prevalence of 9% in adults in 1990, as observed in the study population.

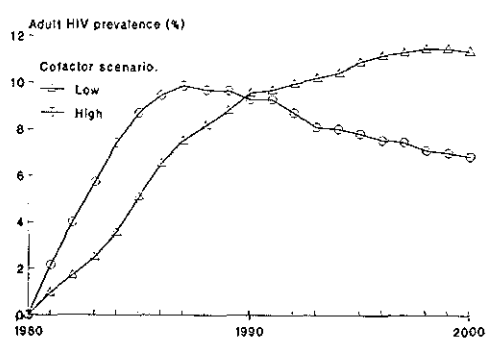

Fig. 1. Simulated projections for mean adult HIV prevalence assuming no interventions for the low and high cofactor scenarios.

Figures 2a and 2b show the impact on HIV incidence of introducing condom use in only one-off sexual contacts for the low and high cofactor scenarios respectively. They give results for no intervention, and also assuming 50 and 100% of men always use condoms for one-off sexual contacts. For 50% condom use, the 10-year cumulative proportions of HIV infections averted for the

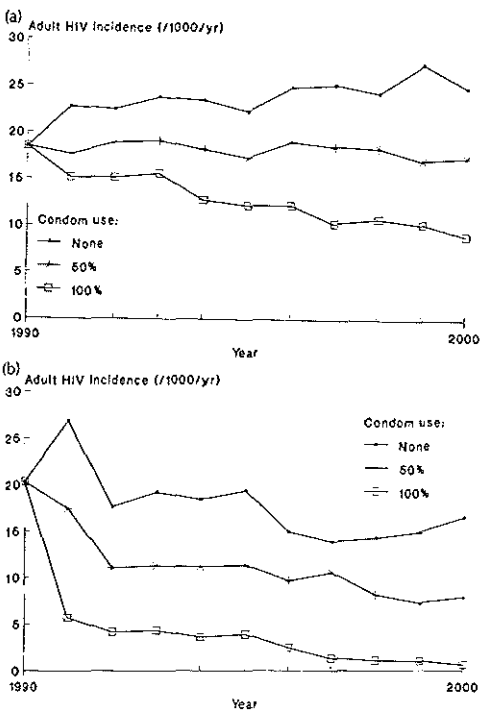

Fig. 2. Simulated projections for the (a) low and (b) high cofactor scenarios of mean adult HIV incidence, assuming a proportion of men always use condoms in one-off sexual contacts.

low and high cofactor scenarios were 24 and 39%, respectively (Table 2).

Figures 3a and 3b give results of reducing the proportion of men having one-off sexual contacts or reducing the frequency of men's one-off sexual contacts. Reducing the frequency of sexual contacts had a more striking effect. In just 2 years a 50% reduction in the frequency of sexual contacts with one-off partners led to a reduction in HIV incidence in adults of more than 50% to nine per 1000 per year, for the high cofactor scenario. The corresponding 10-year cumulative proportion of HIV infections averted was 68% (Table 2).

Figures 4a and 4b show results assuming, from 1990, that the duration of 50 or 100% of all STD episodes was reduced by 50%. Results for the hypothetical removal of all STD from the population are also included. Assuming the duration of all STD episodes was reduced by 50%, 18 and 43% of infections were averted by 2000 for the low and high cofactor scenarios respectively (Table 2). In the case of the high cofactor scenario the effect of removal of all STD reflects the role that STD play in maintaining HIV infection.

Figures 5a and 5b give results for the full package of interventions. Results are most striking for the high co-

Table 2. Percentage of cumulative adult HIV infections averted (95% confidence intervals) after 10-year simulated interventions*.

Intervention	Cofactor scenario†	
	Low	High
Condom use (Fig. 2)		
50%	24 (20–30)	39 (34–45)
100%	48 (45–52)	84 (82–85)
Partner reduction (Fig. 3)		
50% Proportion	8 (3–19)	28 (19–39)
50% Frequency	23 (18–29)	68 (62–74)
100%	45 (41–49)	83 (81–85)
STD treatment (Fig. 4)		
50%	10 (5–19)	27 (20–36)
100%	18 (13–25)	43 (34–53)
Remove	38 (34–42)	83 (81–85)
Full package (Fig. 5)		
25%	29 (25–35)	56 (48–64)
50%	43 (39–48)	82 (80–84)
Part package at 25% level		
Condom use	13 (8–19)	21 (12–34)
Partner reduction	4 (1–18)	33 (24–45)
STD treatment	10 (5–19)	27 (20–36)
Condom & partner	23 (18–29)	50 (40–61)
Condom & STD	22 (18–28)	37 (30–45)
Partner & STD	22 (17–28)	51 (42–61)
Part package at 50% level		
Condom use	24 (20–30)	39 (34–45)
Partner reduction	23 (18–29)	68 (62–74)
STD treatment	18 (13–25)	43 (34–53)
Condom & partner	39 (36–44)	78 (73–83)
Condom & STD	34 (29–40)	62 (57–68)
Partner & STD	39 (34–45)	80 (79–82)

*The mean number of cumulative adult HIV infections for the low and high cofactor scenarios in the absence of interventions were 1110 and 770, respectively. †See Simulating Interventions in Methods for details of simulated interventions. STD, Sexually transmitted diseases.

factor scenario (Fig. 5b), where even the package of interventions effective at the 25% level had an immediate and dramatic effect on reduction of HIV incidence after 1990. On average, HIV incidence was reduced by nearly 50% in the first year, and 56% of infections were averted by 2000 (Table 2).

Table 2 also gives results of part package interventions. For the low cofactor scenario the three interventions were roughly equally efficacious. For the high cofactor scenario, reducing the frequency of men's contacts with one-off partners was as effective as the combined effect of increased condom use and STD treatment.

Discussion

SimulAIDS was developed to facilitate simulation of the transmission dynamics both of HIV infection and STD in populations in developing countries. In many developing countries where prevalence levels of STD are

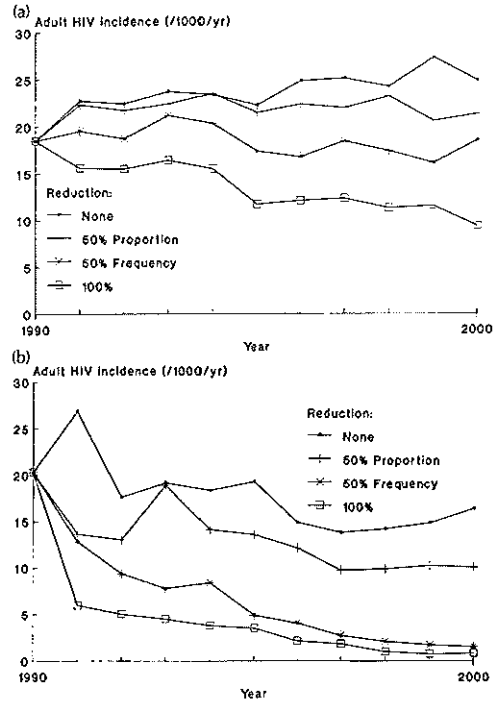

Fig. 3. Simulated projections for the (a) low and (b) high cofactors scenarios of mean adult HIV incidence assuming: no intervention, a 50% reduction in the proportion of men engaging in one-off sexual contacts, a 50% reduction in men's frequency of one-off sexual contacts, and a cessation in one-off sexual contacts.

high, their control is now considered an important intervention approach, supplementing increased use of condoms and casual partner reduction.

Information on the relative efficacy of different interventions is required for guiding policy. The gold standard for assessing this is the randomized controlled trial. With HIV incidence as the main endpoint, very large expensive trials are needed. Simulation models provide a useful alternative, and readily allow the comparison of many different combinations of interventions.

Conclusions based on modelling exercises, however, often depend on the detailed assumptions implicit in the model, and there are rarely adequate data to firmly establish these. Even though this model was based on one of the most complete and extensive data sets generated from prospective follow-up of an entire population cohort in sub-Saharan Africa, there are limitations in untested model assumptions and uncertain input parameter values. It is therefore difficult to conclude that a particular representation truly reflects reality. At best, we can report that particular modelling representations do replicate a range of documented characteristics from the study population reasonably well. Others fail to do so.

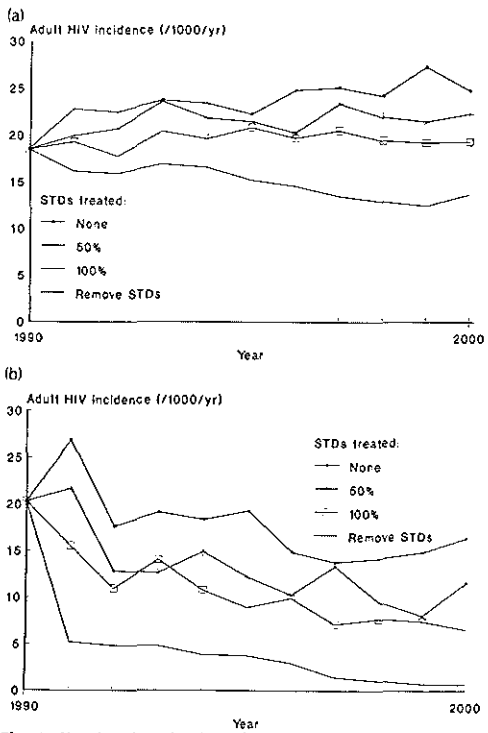

Fig. 4. Simulated projections for mean adult HIV incidence, assuming the duration of all sexually transmitted disease (STD) episodes is reduced by 50% in a specified proportion of cases for the (a) low and (b) high cofactor scenarios.

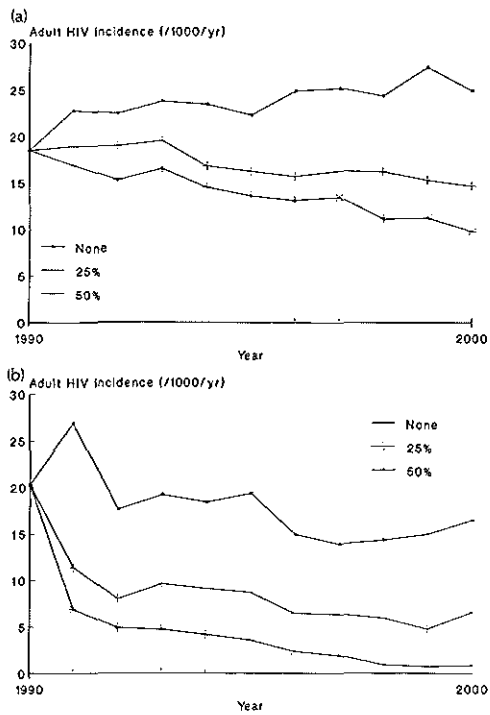

Fig. 5. Simulated projections for the (a) low and (b) high cofactor scenarios of mean adult HIV incidence, assuming a full package of interventions.

Since STD cofactor effects per sexual contact are unknown, three scenarios were developed, defined by assuming different enhancing effects of STD on HIV transmission. The two scenarios discussed here were both able to replicate recorded characteristics of the study population in 1990 [7, and unpublished data]. The high cofactor scenario, however, would appear more consistent with our current understanding of input parameter values [11,12]. Furthermore, as discussed below, only the high cofactor scenario could replicate evolution of the HIV epidemic in the study population during subsequent years of follow-up. For a third scenario, assuming no enhancing effects of STD on HIV transmission, empirical results from the study population in 1990 and during subsequent follow-up could not be replicated for reasonable input parameter values [7, and unpublished data].

It is clear, even without application of complex models, that the widespread and regular use of condoms would have a substantial effect on reducing HIV incidence levels. This, however, is not likely to be feasible at present, and thus we sought to explore the likely impact of condom use only in one-off sexual contacts on HIV incidence in the general population. This is unclear in a rural population where HIV infection is already established and widespread.

In this exercise HIV incidence was substantially reduced by promoting condom use, even if only in the less regular partnerships. Interventions were more effective for the high cofactor scenario since, in this case, more infections are attributed to one-off sexual contacts. This in turn is due to the larger differential in the probability of HIV transmission between one-off partners (where STD are clustered) and longer term partners. This is consistent with data from empirical studies [12].

Similar results were obtained whether condoms were used (i) for all one-off contacts of 50% of the men (Figs 2a and 2b); (ii) for 50% of one-off contacts of all the men; (iii) for all one-off contacts of 50% of the women; and (iv) for 50% of one-off contacts of all the women [data not shown for (ii)–(iv)]. Combining use of condoms by men and demand for condom use by women conferred substantial additional benefits (data not shown).

With respect to partner reduction, the more dramatic impact of reducing men's frequency of sexual contacts than the proportion of men having one-off contacts may be explained as follows. Reducing the frequency of men's sexual contacts with one-off partners results in a

reduction in HIV incidence among men that have one-off contacts, and thus also among women with one-off contacts. In contrast, as the proportion of men having one-off contacts is reduced (while retaining the same frequency of contacts), HIV incidence in this group remains roughly unchanged (although the group size diminishes). Consequently, in this case, HIV incidence among women in one-off sexual contacts also remains roughly unchanged (although the group size also diminishes).

For the high cofactor scenario especially, a substantial decline in HIV incidence resulted from successful STD intervention. Only treating STD in women with one-off sexual contacts resulted in a similar reduction in HIV incidence (data not shown). However, in rural populations this group of women is often not easily identifiable. For scenarios assuming higher STD prevalence levels, which are not uncommon, the impact of equivalent STD interventions would be even greater. As discussed elsewhere (unpublished data), treatment of STD early in an epidemic may confer substantial additional benefits [7,13,14].

The impact of STD control measures in a population will also depend on proportions of viral STD and asymptomatic STD, since these will be little affected by standard treatment policies. Although STD interventions should also be aimed at avoidance of sexual contact in the presence of symptomatic STD, in the case of asymptomatic STD more aggressive approaches, such as mass STD treatment programmes, are necessary.

The benefits associated with a combined approach to intervention may be substantial. Even a package of interventions, each effective at the 25% level led to a striking reduction in HIV incidence and averted a substantial proportion of infections.

In the actual study population, HIV incidence during the first year of follow-up yielded a rate of nine per 1000 per year in adults [15], and has decreased since [16]. This rate is considerably lower than incidence rates in 1990 generated from simulations. Corresponding to a prevalence of 9% in adults in 1990, both scenarios gave an HIV incidence of about 20 per 1000 per year. We believe that the observed incidence since 1990 represents a decrease in incidence, possibly as a result of the presence of the MRC Programme on AIDS in Uganda in the study area. Without a marked increase in condom use or STD treatment, it is believed that this reduction is due mainly to a reduction in the frequency of sexual contacts between irregular partners. Only simulated interventions for the high cofactor scenario were consistent with these empirical results.

Additional simulations, assuming that the effect of interventions was discontinued after 1995, suggest that HIV incidence would revert back to the pre-intervention levels of 1990 within 10 years (data not shown).

In conclusion, we believe that a substantial proportion of HIV infections in sub-Saharan Africa may be averted in the general population, even if interventions are focused only on less regular sexual partnerships. Interventions which reduce the frequency of men's sexual contacts with irregular partners were more effective in our simulations than those focused on reducing proportions of men engaging in irregular partnerships. Wider acceptance that women may demand the use of condoms by their irregular male partners should further increase the efficacy of condom interventions. Even in populations with relatively low prevalence of STD, treatment interventions aimed at STD should also provide a means to control HIV infection in an advanced epidemic. As also found elsewhere, perhaps greatest gains may be made by combinations of these interventions [17].

The knowledge that the implementation of these interventions may substantially reduce the incidence of HIV infection, as appears to be the case in the study population in South-West Uganda, should further strengthen the resolve of the international community to find the resources needed to implement and maintain focused intervention programmes in sub-Saharan Africa and elsewhere on a much wider scale.

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Appendix

Main features of SimulAIDS employed

Initial conditions

At the beginning of a simulation the computer creates an initial population. The size of the population is specified and the sex of an individual is randomly chosen. The date of birth of each individual is randomly chosen using the specified initial age pyramid as a probability function. Other individual characteristics are randomly attributed reflecting values of input parameters. Specified proportions of individuals may be randomly infected with HIV and STD independently.

Demography

At each time-step new individuals are created. The number is calculated using specified fertility rates and the number of women in the specified reproductive age bands. A newborn is equally likely to be male or female. To simulate natural death individuals are removed from the population. The probability that an individual is removed from the population at each time-step is calculated from the specified age-specific mortality rates. At each time-step each individual has a probability of migrating out of the study population. This probability is calculated from specified values for annual rate of out-migration, proportion of out-migrants in specified age-bands, and the ratio of male-to-female out-migrants.

Sexual behaviour

In SimulAIDS women are assumed to supply the demand for sex that is generated by the men. Women either have only one-off sexual contacts, or have a combination of short-term (casual) and long-term (regular/marriage) partnerships. Men have any combination of these three types of partnerships.

Men have a maximum of two regular partners at any one time. Women have no more than one regular partner. Specified proportions of men above a given age are randomly sampled to have one or two regular partners. Their spouses are randomly chosen from unmarried younger women, who are no more than 10 years younger and are above a specified minimum age. When necessary, new partnerships are created to re-establish the proportions. The duration of a regular relationship is randomly sampled from a uniform distribution bounded by specified upper and lower limits.

Men and women have no more than one short-term partner at any time. Specified proportions of men in a given age range are randomly sampled to have short-term partners, firstly from those with previous short-term relationships. Partners of the men are randomly chosen from younger women, in a specified age band, and again firstly from those with previous short-term partners. As with regular partnerships, when the proportions drop below their specified values, new partnerships are created to re-establish the proportions. The duration of a short-term partnership is also randomly sampled from a uniform distribution bounded by specified upper and lower limits.

When unmarried men reach a specified minimum age, a given proportion are randomly chosen to have regular one-off sexual contacts. This characteristic of a man remains constant until marriage, at which point it may change, depending on the specified proportions of married and unmarried men with one-off partners. The sampling process in this case differs from that used for long-term and short-term partnerships since the proportion of males with one-off partners at any time-step is not kept constant by monitoring and updating. Men choose one-off partners at random from the pool of women having one-off contacts. When there is a shortfall, further women are sampled from those without a regular partner in a specified age band. Having been recruited they continue to have only one-off partners at a specified frequency until they reach the specified maximum age, after which they cease all sexual activity.

Transmission dynamics of STD

An STD episode is specified to be of a fixed duration, during which the probability of transmission per sexual contact is specified. Each STD episode has a specified probability of being treated. When treated, the duration of an STD episode is reduced by a specified amount. To ensure that an STD is not removed from the population, a minimum prevalence level may be set. This is monitored at each time-step, and new STD infections are randomly created if necessary. Input parameters for the two STD are identical.

Transmission dynamics of HIV infection

HIV is assumed to be a single virus. Infected individuals are infectious to others at all times. A specified proportion of HIV-infected individuals develop AIDS, which is always fatal. An individual's AIDS incubation period is sampled from a uniform distribution with specified upper and lower bounds. A specified period with AIDS follows the incubation period. Sexual transmission of HIV is defined by a probability per sexual contact. This probability depends on whether infection is in an early, standard or late phase. The early phase starts immediately an individual becomes infected. The late phase of infection ends with the onset of AIDS. The standard phase represents that period not defined by the early and late phases. HIV transmission per contact is enhanced by a specified amount for the duration of an STD episode. For sexual contacts in the presence of any combination of STD, enhancing effects on HIV transmission were assumed to take the maximum value of the individual STD enhancing effects. All newborns have a specified probability of being infected with HIV at birth, which depends on the specified probability of HIV transmission from mother to child, and the proportion of HIV-infected women in the reproductive age band.

Chapter 8.1

Discussion: Study results

Discussion: Study Results

The studies presented in this thesis were planned with the aim of clarifying aspects of the epidemiology of HIV-1 through a longitudinal study of a rural Ugandan population. On enrolment of the cohort, data were collected on the prevalence and risk factors for HIV-1 infection in adults **(Chapter 2)**. Through demographic and medical surveillance of the cohort it was possible to determine the seroincidence of STDs **(Chapter 3)**, the postnatal incidence of HIV-1 infection in children **(Chapter 4)**, the incidence of HIV-1 and the HIV-1-associated mortality in adults **(Chapter 5)**, and trends over time in the prevalence and incidence of HIV-1 infection in adults **(Chapter 6)**. Using data from the cohort study, simulations were carried out of the potential impact of alternative intervention strategies **(Chapter 7)**. This discussion follows the order of the chapters.

HIV-1 prevalence

The overall HIV-1 *prevalence* at baseline was 4.8%. The prevalence among adults (aged 13 years or more) was 8.2%, a rate similar to that observed in 1990 among adults living in rural villages in the neighbouring district of Rakai (1). These rates are considerably higher than those reported for rural villages in Tanzania [1987 (2), 1990-91 (3)] and Rwanda [1986 (4)], suggesting that the prevalence of HIV-1 in rural South-West Uganda is higher than elsewhere in rural sub-Saharan Africa.

There is a marked *heterogeneity* in the geographical distribution of HIV-1. In general the prevalence of HIV-1 infection is higher in urban areas and roadside settlements than in rural areas (1-4), and we observed a prevalence of 40% among adults in a trading centre on the trans-African highway just 10 miles away from the study area (5). The high prevalence rates along the trucking routes in East and Central Africa suggest that it was along these routes that the infection spread and diffused into the surrounding countryside (2,3). Travel to areas of high infection is known to be associated with HIV seropositivity (6); we found a more general association of seropositivity with frequency of travel and destination (Chapter 2.1), and with change of residence (7). Within the study area too we found a marked heterogeneity in HIV-1 prevalence between villages; this variation was not, however, statistically significant (8).

The *age specific prevalence* rates (Chapter 5) show a bimodal distribution typical for sub-Saharan Africa (9): a relatively high prevalence among the age-group 0-4 years, consistent with mother-to-child transmission; a low prevalence of infection among those aged 5 to 12 years, indicating a low risk of infection in this age-group; and a high prevalence among adults, with highest rates in women aged 15-34 years and in men aged 25-34 years, consistent with heterosexual transmission. Transmission through blood transfusions is relatively rare (10) and there is no

evidence that homosexuality and intravenous drug abuse are risk factors in this population (11).

Risk factors for heterosexual transmission

The risk of becoming infected with HIV through heterosexual contact is the product of the following 3 probabilities: (i) of sexual contact; (ii) that this contact is with an HIV-infected individual; and (iii) that during this contact the virus is transmitted.

The probabilities of sexual contact and of contact with an HIV-infected individual

Following sexual debut, the main measure of sexual activity is the rate of sexual contact with one or more partners. Given such activity, the main factors which determine the risk of sexual exposure to an HIV-infected individual are the rate of partner change (12), the extent of concurrent partnerships (13) and the extent to which individuals in different classes of sexual activity and different age groups mix (12). For example, in populations where men have frequent contact with a small group of high-activity women, such as prostitutes, and some contacts with low- activity women, explosive epidemics can be expected (12).

We found it hard to obtain reliable information on contacts with prostitutes, and we did not observe an increased risk of HIV-1 infection among men or women who indicated that they had "sex in exchange for gifts or money" (**Chapter 2.2**). Similarly, it was difficult to obtain data on the age of recent partners, the number of concurrent partnerships and on recent partner changes. Arguably the most valid measure for the frequency of partner change in our studies is the reported number of lifetime sexual partners. Notwithstanding a considerable within subject variation on subsequent surveys, there is a strong association between the reported lifetime number of partners and the risk of HIV-1 infection (Chapter 2.2; 5,14). Moreover, the strength of the association is inversely related to the age of the respondents; this is what one would expect to observe in a relatively recent epidemic.

Cultural and socio-economic determinants of sexual behaviour

An understanding of cultural and socio-economic factors that determine sexual behaviour, and thus the risk of exposure to an HIV-infected individual, may help to explain mixing patterns and to guide behaviour change interventions. Our studies are consistent with the work of others (15) in showing that women aged 13-24 years are at a particularly high risk of acquiring HIV-1 infection because of both behavioural and biological mechanisms (16). Men tend to start their sexually active life a few years later than women; while the risk of HIV-1 infection is relatively low among men aged 13-21 years, among those aged 22-24 years the risk is very substantial indeed (**Chapter 2.1**). Regardless of age, change of residence is strongly associated with an increased risk of infection and is likely to be the

result of more risky sexual behaviour among those who move (7). Another important determinant of HIV-1 infection identified in our study is socioeconomic status (**Chapter 2.3**). It has often been assumed that poor women and rich men are particularly at risk of HIV-1 infection (17,18). The results of our study suggest, however, that poverty leads to a greater risk for both females and males, possibly due to reduced access to information, education and health care (19). Poverty can also induce damaging survival strategies as poor women may have to barter sex for material goods. For poor men the association between poverty and HIV-infection could be secondary to the rate of infection among women of the same income stratum.

The probability of HIV-1 transmission
The main (biological) determinants affecting the probability of HIV-1 transmission during heterosexual contact between a susceptible individual and an HIV-1 infected person include sexual practices, circumcision status, condom use, viral characteristics (including HIV-1 subtypes and strain virulence), disease stage, and STDs other than HIV (20,21).

In Chapter 2.2 the risk of HIV-1 infection is shown for various sexual practices. It is of interest to note that there is a suggestion that men exposed to *menstrual blood* are at an increased risk of HIV-1 infection, an observation consistent with the results of a large European study (22). In contrast, there is no indication of an increased risk for women who have sexual intercourse during menses.

It has been suggested that the use of *desiccating substances* in the vagina, a practice which is common in some parts of East, Central and Southern Africa, may increase the risk of infection in uninfected women (23,24). In our study we did not observe such an effect.

Circumcision possibly reduces the susceptibility of uninfected men to HIV infection (25). In the study population circumcision is exclusively practised by the Muslim community. The results of our studies show consistently that Muslims are at a decreased risk compared with non-Muslims. This association does not appear to be the result of differences in the number of sexual partners, and may be due to a protective effect of circumcision. Lifestyle factors cannot, however, be ruled out.

There is compelling evidence that *condoms*, when properly used, strongly reduce the risk of sexual transmission of HIV-1 (26-28). In the study population (reported) condom use was rare; of males in the age-groups 13-24 and 25-34 years only 25% and 20% respectively reported ever having used one.

In vitro some *viral isolates* replicate more efficiently than others, and there is strong evidence for a higher transmissibility of HIV-1 compared with HIV-2 (29). There is some epidemiological evidence of differences in transmissibility between different *HIV-1 subtypes*. The results from a study in Thailand suggest that HIV-1 subtype E is associated with a higher

risk of heterosexual transmission than subtype B (30). HIV-1 isolates of Ugandan origin belong predominantly to subtypes A and D (31). A study of HIV-1 subtypes and transmissibility has been planned, using DNA samples from cases identified in the Masaka cohort.

Several studies have shown that patients with advanced clinical *disease* or profound *immunodeficiency* are more infectious than those with early disease (32,33). Similarly, there is evidence that the infectiousness is higher during the initial viraemic stage following infection than during the long latent period (21,34). This being so, most HIV-infected people are healthy carriers and together they form the largest pool of HIV infection (35). The Masaka cohort will probably not yield sufficient transmission events to permit epidemiological study of the association between stage of disease and infectivity.

There is some evidence that *genetic factors* may influence the susceptibility to HIV and disease progression (36,37), and the common caucasian haplotype HLA-A1-B8-DR3 has been associated with more rapid disease progression (38,39). The results of various studies have not, however, shown a consistent pattern. This inconsistency may simply reflect the small sample size of most studies, or might be due to geographical variation in viral subtypes, ethnic group differences in susceptibility alleles or to another gene being the actual susceptibility locus, located within the major histocompatibility complex and closely linked to the HLA genes under study. Preliminary results of a case-control study of 117 cases and 374 controls from the Masaka cohort suggest a lower susceptibility to infection in subjects with the class II allele DR 1302 (40).

The *immune response* to HIV infection is characterised by vigorous HIV-specific cytotoxic T lymphocyte (CTL) activity. In a study of HIV-negative female sex-workers with HLA-B35 in The Gambia CTL activity was identified against HIV-1 and HIV-2 cross-reactive peptide epitopes, suggesting that the CTL activity may represent protective immunity against HIV infection (41). A study of cellular immune responses to HIV-1 among participants in the Masaka cohort began in 1995 (42).

Sexually transmitted diseases
There is strong evidence from epidemiological research and from studies on viral shedding in genital fluids that other sexually transmitted diseases facilitate HIV transmission (43). While early studies had documented that genital ulcer diseases (GUD; syphilis, chancroid and herpes simplex virus type 2) were a risk factor for infection with HIV, there is recent evidence that non-ulcerative sexually transmitted diseases, notably gonorrhoea and chlamydial infection, are risk factors for HIV-1 transmission in women (16). STDs are known to be highly prevalent in many parts of Africa (44,45).

To obtain information on the *seroprevalence and incidence* of some important STDs we conducted a study using paired sera from 294 adults enrolled in the general population cohort (**Chapter 3.1**).

The results of this exploratory study suggest that syphilis, chancroid, chlamydia and herpes simplex virus type 2 (HSV-2) are common in this population with prevalence rates of 10.8%, 10.4%, 66.0% and 67.9% respectively. We recently completed a similar but larger study of paired sera from a random sample of approximately 1000 adults (46). The prevalence of active syphilis in this sample was 13%, similar to the results of the first study and to rates reported for other population groups in sub-Saharan Africa (Chapter 3.1; 47); studies of pregnant women suggest, however, that the geographical variation in the prevalence of syphilis is considerable (48). The observed incidence of HSV-2 among males and females was 6.7 and 10.6 per 100 person years respectively (46). A comparison with other African populations is not possible as no results of other studies are available. In a study of homosexual men a temporal association was found between HSV-2 seropositivity and subsequent infection with HIV-1 (49). HSV-2 infection persists lifelong and the rate of recurrence of genital ulcers increases in immunodeficient persons. Since HSV-2 is so common in this population, and antiviral treatment not affordable, the disease is both important and problematic.

Estimates of the per-exposure *cofactor effect* of GUD on the risk of HIV transmission during a single heterosexual exposure suggest an effect of 10-50 for male-to-female transmission, and of 50-300 for female-to-male transmission (50). While these estimates are subject to wide margins of error, they indicate that GUD may be responsible for a high proportion of heterosexually acquired HIV infections in sub-Saharan Africa. Using a simulation model of the transmission dynamics of HIV and other STDs, and data from the Masaka cohort, we estimate that during the first 10 years of the epidemic (1980-90) over 90% of HIV infections in the cohort were attributable to STDs (**Chapter 3.2**). Even under conservative assumptions, in our simulations STDs played a critical role in the rapid and widespread transmission of HIV infection. The simulation suggests that with the progression of the epidemic, when HIV spreads into the less sexually active population where STDs are less prevalent, the proportion of adult HIV infections attributable to STDs decreases. The results of these simulations underscore the potential value of STD control measures, especially if such measures are introduced at the early stage of an epidemic.

Postnatal incidence and routes of HIV-1 transmission in children

The main routes of HIV transmission, namely sexual contact with an infected person, parenteral exposure to infected blood and mother-to-child, have been well documented. However, concern that HIV might also be transmitted through other routes, namely non-sexual 'casual' contact or insect vectors, has been commonly expressed. These 'alternative' transmission routes can best be studied in children and we are aware of 7 relevant reports from sub-Saharan Africa (51,52-58). All these studies were, however, cross-sectional, making ascertainment of past exposure difficult. Our cohort study provided a unique opportunity to determine

prospectively the relative importance of various transmission routes among children (**Chapter 4**). Among approximately 3,900 children aged 0-12 years, who were HIV-negative on enrolment and had at least one follow-up specimen, only 1 seroconversion was observed. The transmission of HIV was most probably through breast milk as the child was breast fed at the time the mother seroconverted. Postnatal mother-to-child transmission through breast milk has been well documented (59-61) and this risk is particularly substantial during the viraemic stage of primary HIV infection (34).

During the 4-year period of this study a total of 41 seropositive newborns were enrolled. These children were excluded from further analysis and it is not possible, therefore, to use our data for a quantification of the contribution of breast milk to mother-to-child transmission. The finding that HIV-1 is transmissible through breast feeding has complicated advice for infant feeding (62). Breast milk is the prime source of nutrition for most infants worldwide, and breast feeding should continue to be promoted in most settings in developing countries as it has many advantages for infants and mothers.

Apart from mother-to-child transmission, HIV-1 infection of children in this population is extremely rare. It is assuring that there was no evidence of transmission through injections. The study provides the most conclusive evidence to date that transmission through non-sexual 'casual' contact and insect vectors is extremely small. This evidence should help to dispel misconceptions.

Adult HIV-1 incidence

The incidence of HIV-1 infection among adults in the cohort was 9.2 per 1,000 person years of observation during the first year of follow-up (**Chapter 5.1**). Similar rates have been reported for the rural strata of cohorts in the Kagera region in Tanzania (63) and the Rakai district in Uganda (64), and for occupational cohorts in Zaire and Tanzania (65,66). Considerably higher rates, of the order of 3%, have been reported for urban and mixed urban/rural cohorts of women of childbearing age in Zambia and Rwanda (67-70), and still higher rates for high risk groups.

Reported risk factors for the acquisition of HIV-infection are similar to those reported for prevalent cases and include young age, being single or divorced, having multiple sexual partners and a history of STDs (64,70). In view of the relatively small number of newly infected participants we did not report risk factors after the first year of follow-up (Chapter 5.1). During a 4-year follow-up period a total of 90 adults seroconverted, corresponding to an incidence of 7.1 (95%CI=5.6-8.5) per 1000 person years. The incidence rates were highest in males and females aged 25-34 years (18.4 per 1000 and 12.6 per 1000 respectively). Other important socio-demographic characteristics associated with seroconversion included (i) belonging to a non-indigenous tribe and (ii) having a religion other than Islam

(71).

HIV-1-associated adult mortality

Arguably our most important study results are those on HIV-1-associated mortality (**Chapter 5**). While it was clear that the HIV epidemic in sub-Saharan Africa was the cause of serious illness and death of hundreds of thousands of adults and children, the extent of the excess mortality associated with HIV-1 had not been measured in a general population. Based on analysis of the Masaka data the substantial excess mortality associated with HIV-1 infection was quantified for the first time (72). Adults aged 13-44 years testing positive for HIV-1 antibody were 60 times as likely to die during the 2-year observation period as were otherwise similar persons who tested negative (Chapter 5.2). This extraordinary high *relative risk* provides strong evidence that HIV-1 is the cause of substantial excess mortality (72).

The overall non-standardised adult relative risk of death associated with HIV-1 in this study was 15.0. This compares with recent reports on relative risks of 9.5 (95%CI 6.0-14.9) in a general population in the Rakai District, Uganda (73), 12.9 (95%CI 5.4-30.7) in an occupational cohort in Mwanza, Tanzania (66), and 13.3 (95%CI 10.0-17.2) in the UK population of haemophiliacs (74). The relative risks, observed in different populations using different study methods, are remarkably similar thus adding further credibility to a causal association between HIV and excess mortality.

Various groups have reported estimates of the proportional contribution of HIV and AIDS to the adult mortality in urban populations (75,76). In chapter 5.2 the 2-year *excess mortality* due to HIV-1 infection in a rural population is quantified both in absolute and relative terms: half of all adult deaths and more than 80% of deaths among those aged 13-44 years were attributable to HIV-1. At 4 year follow up of the cohort these figures were 47% and 74% respectively (77). Similar HIV attributable mortality fractions have been reported for a cohort of women of childbearing age in Rwanda (78), an occupational cohort in Tanzania (66) and the rural stratum of a population study in the Rakai District, Uganda (73). The profound impact of the HIV-1 epidemic on mortality in rural Uganda is also reflected by an estimate of the *life expectancy* at birth based on data from the Masaka cohort suggesting that the life expectancy decreased from 51 years in 1980 to 32 years in 1990 (79).

At 2-year follow-up we reported a rapid progression from asymptomatic infection or mild disease to death (Chapter 5.2). Using 4-year follow-up data and the Kaplan-Meier method for survival analysis we estimate that the median *survival from infection to death* in the Masaka cohort is approximately 7 years for those aged 13-54 years and only 2.5 years for those aged 55 years or more (preliminary results; 77). This compares with results from studies of survival following infection with HIV-1 among haemophiliac and homosexual populations in North America

and Europe suggesting a median survival time from infection to death of 9-11 years (80-82). Relatively little is known about survival rates in developing countries. The results of some studies (78,83-85) suggest rates similar to those in industrialised countries but a recent study among prostitutes in Nairobi also documented a much faster rate of progression, corresponding to a median survival from infection to AIDS of 4.4 years (86). The observed increase in rate of progression with age is consistent with reports from industrialised countries (81,87-89). Similar rates were observed for males and females; this again is consistent with reports from industrialised countries (90-93).

It is clear that there is considerable *variation in survival rates* among HIV-infected individuals. Recently, much attention has been given to healthy long-term seropositives, or "non-progressors" (94). How might non-progression or, conversely, rapid progression as discussed above for sub-Saharan patients, be explained? Most probably by a complex interrelationship of several independent factors (94) including the pathogenicity of the infecting HIV strains (95,96), immune response (97,98), genetic factors (99,100), concomitant infections (101), nutritional status (102), socioeconomic status (103), and antiviral therapy and prophylactic treatment (104). Lack of general medical care may affect both the duration of the asymptomatic (incubation) period and the duration of symptomatic survival (101). In this context it is useful to distinguish between rapid disease progression, marked for example by a rapid loss of CD4 cells, and premature death as a result of intense exposure to or lack of treatment for high grade pathogens (105). It is conceivable that both mechanisms play a role and carefully conducted prospective studies of incident cases of HIV-infection are required to clarify this issue.

Trends in HIV-1 prevalence and incidence

During the 4 years of cohort follow-up the overall annual HIV-1 incidence rates were 8.1, 6.8, 5.9 and 8.9 per 1000 person years respectively, thus providing little evidence of real change over time (71). Similarly, during the 5-year period the overall standardised seroprevalence showed little change from 8.2% (95%CI = 7.4-9.1) at round 1 to 7.6% (6.7-8.5) at round 5. In contrast, there was a highly significant decrease in prevalence among males aged 20-24 years from 11.8% to 2.7% ($p<0.001$); in females aged 13-19 years the prevalence fell from 4.5% to 2.5% ($p=0.09$) (**Chapter 6**). Moreover, there was a suggestion of a decrease in incidence among males aged 13-24 years but not among females of the same age. Thus, during 4 year follow-up we observed little change in the overall incidence and prevalence of HIV-1 infection, but a highly significant decline in the prevalence among young males and a non-significant reduction among young females.

In some of the major towns of Uganda the prevalence of HIV-1

among women (median age 22 years) attending antenatal clinics included in the national sentinel surveillance programme has declined since 1992; for example, the reported rates from the two main hospitals in Kampala, the capital city, fell from 29% to 22% in one hospital and to 17% in the other (106). Outside Uganda, a decline in HIV-1 prevalence has recently been observed among young Thai men entering military service. The decrease was observed in men from all regions in the country and at all educational levels (107).

Unfortunately, no data are available on trends in HIV-1 incidence in other general populations. Decreasing incidence rates have recently been reported following successful interventions in cohorts of prenatal women in Kigali (108) and of prostitutes in Nairobi and Kinshasa (109,110). A decrease in incidence has also been observed in closed cohorts (111,112) as subjects at highest risk of HIV-1 infection become infected and are not replaced by new high risk subjects (113). Unchanging HIV-1 prevalence levels have been reported for various adult populations in Zaire, Burundi and Rwanda (114-118).

As discussed, the dynamics which underlay the course of the HIV-1 epidemic are complex: socio-demographic, cultural (notably mixing patterns and frequency of partner change) and biological factors, such as other STDs and circumcision, play a role as well as the effect of specific interventions (20). Our observation of a substantial risk of infection in people reporting a stable partnership or only few sexual partners fits the dynamics of an STD which is widely distributed in the general population (Chapter 2; 119). More HIV-1-associated deaths are observed than new HIV-1 infections, and the relatively high level of HIV-1 infection among joining adults (7) explains at least in part the stable overall prevalence and incidence. Thus, the observations suggest that in the general adult population under study the HIV epidemic is in a dynamic equilibrium.

How can the observed decline in prevalence among young adults best be explained? In the Masaka cohort area intervention efforts aiming at a reduction in the frequency of partner change, distribution and promotion of condoms, and the control of STDs, were gradually expanded during the period 1989-94 but by 1994 the people using condoms or seeking treatment for STDs in the official health sector were still relatively few (Chapter 6). It is probable, therefore, that study and intervention effects together resulted in a change in sexual behaviour. This change may have included: postponement of first sexual intercourse; a reduction in one-off or short-term sexual partnerships; and, changes in partner choice. It cannot, however, be ruled out that a modest increase in condom use, improved STD treatment or a change in the force of infection contributed to the decline.

HIV/AIDS control

Since there is at present no preventive HIV vaccine or cure for AIDS, prevention of infection is the only way to fight the

disease. Attempts to control the epidemic should start as early as possible since the cost-effectiveness of interventions drops sharply when infections cross from high-risk groups into the general population (120-122). The three main intervention strategies currently employed by national AIDS control programmes are the promotion of condom use (26), the promotion of a reduction of sexual partners (123,124) and treatment programmes for other sexually transmitted diseases (122,125,126). The relative effectiveness of these interventions in general populations is unknown and we used data from the Masaka cohort to explore through computer simulations the relative effects of each of the three strategies, alone and in different combinations (**Chapter 7**). For the scenario most consistent with data from the study population, 39% of all adult infections were averted when condoms were used consistently and effectively by 50% of men in their contact with one-off partners; 68% of infections were averted when men reduced by 50% the frequency of sexual contacts with one-off partners; and 43% of infections were averted when the duration of all STD episodes was reduced by 50%. When the 3 interventions were combined, 82% of all adult infections were averted. Our main finding is that the greatest gains may be made by a combination of interventions targeted on less regular sexual partnerships. This result is consistent with the outcome of other simulation exercises (127).

A review of intervention programmes aimed at changing HIV risk behaviour concluded that a substantial proportion of such programmes had produced long-term behaviour change. None of the reviewed community interventions for heterosexual adults had, however, a controlled design (124).

To date only one community-randomised trial has been completed. This study, in a rural area of Tanzania, showed a 42% reduction in the incidence of HIV-1 infection as the result of improved STD case-management (128). This result indicates that the concept of STD control for HIV prevention can work in general populations (129). In Thailand, successful HIV/STD control on a national scale is reflected by a decline in STD cases (130) and in HIV-1 prevalence among young men entering the army (107). Two large, randomised population-based intervention trials are currently ongoing. One is a trial of STD mass treatment conducted in the Rakai District, Uganda. The second trial, described in Chapter 1, is similar in design to the Tanzanian study but comparing behaviour change approaches and improved STD management

There are at present a number of HIV vaccine candidates but it is not known whether any of these offer protection, and it will be many years before a preventive vaccine of proven efficacy will be available for large scale use. Therefore, for many years HIV prevention will continue to depend on the promotion of condom use, promotion of a reduction of sexual partners, improved STD management, and counselling and testing. The implementation of these interventions, based on knowledge currently available, should not be delayed. For health policy purposes the results of further controlled efficacy and cost-effectiveness trials are, however, urgently required. To develop strategies for behaviour

change that are more effective and adapted to local circumstances, a clearer understanding is still needed of the mechanisms underlying the heterogeneity of the spread of HIV in sub-Saharan Africa, in particular of sexual behaviour patterns, and risk factors for the heterosexual transmission of HIV.

The development and implementation of primary prevention approaches is a daunting task, particularly for the resource-poor countries in sub-Saharan Africa. As daunting for these countries is the task to provide treatment and care for HIV-infected individuals (105,131). Recent trial results show that combination therapy is dramatically more effective than (AZT) monotherapy at preventing disease progression and prolonging life (132). The cost of these treatments are, however, prohibitively high and it is likely that only few patients in sub-Saharan Africa will benefit. The prospects for a cure at affordable cost being remote, treatment strategies should focus on the diagnoses and treatment of infectious complications which are easy to diagnose and treat, and which occur relatively early on in the evolution of HIV disease, for example diseases caused by *Streptococcus* pneumonia, *Salmonella* or *Mycobacterium tuberculosis* (133). Some HIV-associated diseases are preventable. Efficacy trials and cost-effectiveness studies of interventions for the prevention of these diseases should have a high priority.

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Chapter 8.2

Implementation of the study: methodological and operational aspects

Implementation of the study: methodological and organisational aspects

Methodological aspects

At the time we embarked on the study it was clear that a major HIV epidemic was emerging. Information on the epidemiology of HIV in rural populations and contributions to the development of AIDS control strategies were urgently required. While it was clear that it would be possible to meet some of our objectives through cross-sectional and case-control studies, the main objectives would require a longitudinal population-based study (Chapter 1).

Longitudinal population-based studies
Longitudinal population studies are expensive, difficult to organise and laborious (1). Relatively few such studies have been conducted in developing countries, and most of these focused on mother and child health issues (2-6). Recent population studies include one on the natural history of mycobacterial diseases in Malawi (7) and studies of the epidemiology of HIV-1, conducted in the Rakai District, Uganda (8) and the Kagera District, Tanzania (9). When we started it was not known whether it would be feasible to undertake an intense and sensitive study of HIV, STDs and sexual behaviour in a rural population. The preceding chapters show that the study has been productive and resulted in information relevant to those concerned with the epidemiology and control of HIV-1. To which extent have these results external validity, ie are representative for other areas or populations? The only objective way of establishing this would be by conducting similar studies in other areas. Clearly, resources do not permit this. To some extent it is reassuring that our findings regarding HIV-1-associated mortality are similar to those observed in the rural stratum of the Rakai study (10).

Among the above mentioned studies the intensity of surveillance varied considerably, from home visits every two weeks (2,3) to once annually (5,8) or even less frequently (7). We kept the cohort under surveillance through annual visits but would have preferred a greater intensity. This was, however, not feasible for financial and logistical reasons. Whether a less intense, and thus less expensive, effort would have produced results of similar value, we do not know.

Objectives
The original objectives of the programme, to clarify aspects of the epidemiology of HIV-1 infection and the natural history of HIV-1-associated disease in rural Uganda, and to contribute to the development of HIV prevention strategies, were rather broad and did not change during the course of the study. As mentioned in Chapter 1, study of some risk factors for the heterosexual transmission of HIV-1, notably the role of STDs, circumcision and sexual behaviour, were successful only in part. In retrospect we should conclude that we were perhaps over-ambitious and optimistic at the time the study started. During recent years the

difficulty of studying these risk factors has been well documented (11-13), and it is doubtful whether we could have done much better. The original study plan gave high priority to a STD/HIV intervention trial using a village-based randomisation scheme. It soon became apparent that the mobility of the population was high and that villages were administrative units rather than social entities. Since we anticipated substantial dilution effects, it was decided to use parishes, scattered over the Masaka District, as the units of randomisation. This trial, which started in early 1994, is in progress.

Inter-disciplinary and multi-disciplinary approaches
The objectives of studying risk factors for HIV-1 transmission and methods for HIV prevention, made an inter-disciplinary approach essential (this is an approach whereby different disciplines closely collaborate in the design, implementation and analysis of various studies). It took considerable time and effort from all members of the team of epidemiologists, clinicians, anthropologists and statisticians, to learn to understand each other and to manage to contribute effectively to each others' studies. The existence of this highly motivated inter-disciplinary team proved a key factor to success during the first three years of field research. In 1993-94 the programme was, for managerial reasons, re-organised from a strongly centralised single programme to a structure with semi-autonomous projects. During this period work on basic and clinical research issues became more prominent, and the programme was joined by a molecular virologist. An inter-disciplinary approach involving laboratory, clinic and field investigators was perceived as unmanageable, and in stead we opted for an multi-disciplinary approach whereby investigators from various disciplines were aware of each others work and interacted as and when appropriate. Both approaches have their advantages and problems. Research needs and organisational issues together should determine the preferred level of intensity in interaction and collaboration.

Study area and population
At the time the study area was selected, there was uncertainty concerning the extent to which three of the selection criteria would be met: an HIV-1 prevalence among adults of the order of 5% to 10%; a stable population; and, active support from the population (Chapter 1). The baseline prevalence of 8.2% in the adult population was well in the range specified by the first criterium. As elsewhere in East Africa, migration was, however, high. During the first year of follow up 13% of the baseline population changed residence: 7% left the study area, 5% moved within the village and 1% outside the village but within the study area. Losses to follow up due to people leaving the study area, were, however, not cumulative as a proportion of those leaving returned at a later stage. The interaction with the community and its leadership was complex. This is often the case in community-based research, and it is not surprising that intense problems have to be faced when a 'foreign' group endeavours to undertake research on a highly sensitive topic such as HIV/AIDS (14). Notwithstanding various problems the cooperation and support from the community was more than

satisfactory.

Aspects of the field work

Community mobilisation, approaches to enhance participation
The first members of the community to be involved were the political leaders, who took an active part in finding accommodation and in recruiting local staff (14). One of their number became a fulltime programme employee, working as Community Liaison Officer. He played an important role, with a non-local Ugandan mobiliser, in an intensive mobilisation campaign which began in mid 1989. This campaign aimed at informing the population about the programme and consisted of a series of village meetings.

Prior to any new research activity in a village, meetings were first held with the village leaders, followed by a general village meeting. After this, the plans were discussed with heads of household and, finally, with each adult member of a household. Leaflets in the local language described objectives and practical details of planned activities. We made it an issue to provide feed-back to the study participants but were not very successful in doing this in a systematic way. To plan optimal mobilisation approaches, we used village profiles which documented networks of key persons in a village and issues of the day. For the full duration of the study monthly meetings were held between programme staff and the highest administrative authority in the area, and with a local Health Advisory Committee which included political, religious and medical leaders.

In addition to direct treatment benefits, the study communities benefitted from a range of community activities including the development of a community based health care service, AIDS home care for bedridden patients, an HIV counselling service, a water spring protection scheme, health education and AIDS prevention efforts, and income generating activities. Recently, an eye clinic was opened after an ophthalmological survey component had been added to the surveillance of the population cohort. Further issues related to community benefits and compliance are discussed in Chapter 8.3.

Demographic surveillance
Village maps were drawn by field staff using enlarged contour sketches of existing maps. The maps had to be updated annually since new houses were built continuously and old one's abandoned. The maps, although lacking geographical accuracy, were adequate for survey purposes; at the start of the study aerial photography was prohibitively expensive and satellite assisted positioning techniques were in their infancy.

An accurate enumeration of the population was initially difficult and during the baseline survey double registrations and omissions of individual residents were not uncommon. This was in part due to the fact that some individuals considered themselves as belonging to more than one household; for others, in particular

children going to boarding schools, there was sometimes uncertainty whether an individual should be counted as a resident. The high mobility of the population added to the enumeration problem. Many of the errors were corrected during re-surveys and the error rate decreased substantially with time as the census and medical field teams got to know the population.

On enrolment in the study participants received a personal identification (ID) number; this number included village and household codes, and a check-digit to safeguard against transcription errors. Participants who moved house received a residence number in addition to their personal ID number. On enrolment, participants also received an identification card. Prior to the start of the baseline survey the community had not been in favour of ID cards with photographs. Without these the cards were of limited use.

Progress of the surveys was monitored on a daily basis by clerks based at the field station. In all surveys a 10% random sample of respondents was re-interviewed, on the same day but by a different interviewer, to assess repeatability. Interviewers were debriefed by survey facilitators for each single questionnaire. In general, questions were pre-coded and coding would be completed by the interviewers. The baseline survey included, however, some open questions and during this survey coding of some more complex questions was done at the field station. Data were then entered on to databases in Entebbe; checks for consistency were run and any queries sent back to the field station for follow up. One of the advantages of working in one geographical area is that the follow-up of queries is relatively easy; in studies conducted in a sample of clusters scattered over a large area (8,9) such follow-up is time consuming. In our experience, the feed-back of queries to the census team, together with regular supervision, contributed considerably to the reliability of the data collected.

To enhance our confidence that no, or only few, births or deaths were missed, a continuous birth and death registration was introduced in 1991 in all 15 study villages. The registers were maintained by trained village leaders who were supervised on a monthly basis. Fortunately, we found a good consistency between the data collected through the annual census and those obtained through the continuous registration.

Compliance with the demographic surveys was without exception good. Moreover, the local interviewers played an important role as intermediaries between the programme and the community, and provided feedback on the response to the medical surveys in the villages, for example on misgivings people had about giving blood (14).

Medical surveillance

During the baseline survey and three following repeat surveys all consenting persons aged 13 years and over were examined for HIV-associated signs after a brief medical history had been taken. A 10% random sample was re-examined. A blood sample was taken

from all individuals, regardless of age, for whom consent was obtained: from infants a capillary sample, and from children and adults a venous sample (of the adults who refused to give blood very few were willing to give a saliva sample instead).

The medical history included mainly questions on HIV-associated symptoms. In order to reduce the semantic discrepancies between Western medical terms and their nearest vernacular equivalents, lengthy definitions had sometimes to be used. Moreover, five of the nine criteria of the clinical AIDS case definition incorporate specific durations ('for longer than one month') or frequencies ('three or more times per day'). The validation of such reported data is difficult. In the baseline survey, the repeatability of positive responses given by 342 randomly selected participants was low, particularly for rare events. For example, for chronic fever four subjects gave concordant-positive, 322 concordant-negative and 14 discordant responses (15). Unfortunately, there is no obvious way of dealing with this methodological problem.

As in many other communities, people living in the study area are reluctant to give blood as long as they are healthy, and the HIV/AIDS epidemic has added to this. Notwithstanding the intense mobilisation approaches the medical team were often forced to spend a disproportionate amount of their time on discussions with participants who were reluctant to give blood. All too often the going of the medical team was tough: walking long distances through mud, heavy rains or under a baking sun, sometimes only to bleed a handful of participants during a working day, and, occasionally, to be abused. No wonder then that the team often tended to loose heart. A most important task of the supervisors was to encourage the team members by making them feel that there work was important and that they were not left on their own. In addition, numb routine often tended to take over. This made it necessary to organise regularly refresher sessions to keep the team members on their toes.

Data management and the role of statisticians
The entry and storage of the vast amount of data generated by a large longitudinal study used to cause formidable problems. During the last decade computer hard- and software developments have, however, changed the situation dramatically. In Entebbe, the senior programme statistician together with his staff developed a highly efficient data management system. Once a week forms and questionnaires were transported from the field to Entebbe. Data were entered by double entry and verification, and checked for consistency. Within two weeks following completion of the census of a certain village an updated census list for that village used to be ready as were working lists for the medical field team and diaries. Where appropriate, reminder and revisit schedules were produced. Thus, it is now possible to manage field data from large studies in such efficient way that the data set itself proves invaluable for the day to day execution of these studies.

The programme statisticians were directly involved in most of the

programme activities and weekly visits to the field were made by at least one of them. This direct involvement of the statisticians in the field work greatly contributed to the quality of the data collected.

Organisational aspects

The study started in 1988, two years after the end of the Ugandan civil war. At the time the economy of the country was in a sorry state. Government institutions, including Makerere University, the Uganda Virus Research Institute and health facilities were cash strapped and facing serious shortages of qualified staff, power failures were very common and communication lines were poor. Thus, a situation which is rather typical for the poorest of the low income developing countries. But there was an important difference with other countries, namely the presence of many well educated, motivated and highly skilled people. It is worth pointing out that during the years 1988-94 Uganda has gone through a period of remarkable recovery.

Programme location and organisation
It was agreed in 1988 that the UVRI would be the leading Ugandan partner for MRC and that the programme would be based at the Institute. The Memorandum of Understanding between the Governments of Great-Britain and Uganda specified that the Director of the UVRI would be the technical 'counterpart' of the head of the MRC programme, and the Head of the Department of Epidemiology the operational 'counterpart'. The word 'counterpart' has been used in the past for very different concepts, and it would have been helpful if tasks and responsibilities had been set out in some detail shortly after the start of the programme.

At the UVRI the programme had temporary office accommodation which housed the administration and statistical unit. New office and laboratory accommodation was opened in early 1993, as were a new field clinic and residential accommodation on both sites. HIV serology work was carried out at the Institute, and elaborate procedures for monitoring quality control of laboratory work were successfully developed in collaboration with the virologists (16); less successful, though, were attempts to improve the adherence to proper safety procedures in the serology and virology laboratories.

At the start of the programme it was agreed that the organisation of supplies, transport, finances and general administration would be independent from the Institute. This proved to be a sensible decision as it made it possible to avoid some of the rather bureaucratic Government procedures and to reduce competition for supplies. For the procurement of supplies MRC channels had to be used. This occasionally resulted in long delays and it was not unusual that goods were received a full year after an order was placed. MRC head office staff were without exception very supportive, but tedious bureaucratic procedures and a high turn-over of head office staff made the system by times painfully slow

and communication difficult.

It was well recognised in 1988 and following years that the Government salaries were well below the living minimum, and it was generally accepted that payment of topping-up allowances was essential for ensuring dedicated labour. Since no guidelines or standards were available on what constituted reasonable salary levels for various categories of staff, the doors were permanently open for new salary demands and staff action. By agreeing with the staff that salaries would be reviewed twice annually disruptions became uncommon. In 1992 salaries were pegged to the Ugandan salary scales used by the British Foreign Office. This measure removed the need for salary negotiations within the programme and, in retrospect, this line should have been pursued much earlier.

Another financial uncertainty during the first years of the programme was the high rate of inflation in Uganda. The inflation was often, but not always, offset by a devaluation of the Ugandan shilling. This made financial planning and budget control difficult. Serious budgetary constraints were also caused by devaluations of the pound sterling. Recently, after a long process of negotiation, a mechanism was put in place to correct on an annual basis the MRC programme grant so as to take into account changes in local salaries and the sterling-shilling exchange rate. The lesson to be learned is that for the implementation of a longitudinal study a strong commitment from the supporting organisation(s) and flexibility are essential.

Networks and collaborations
As mentioned, by 1988 the severity of the HIV epidemic in Uganda was becoming apparent. The Government of Uganda openly acknowledged the fact that it was facing a major problem and welcomed overseas donor support for research on AIDS. At the same time, however, there were both in Government and in the scientific community feelings of being exposed and of unease about how to deal with the influx of foreign investigators. This response was understandable in view of the enormous amount of publicity which had been given in the mid 1980's to the AIDS epidemic in sub-Saharan Africa by media in industrialised countries. How fast should one move in such delicate situation to rally a support network? We decided on a rather cautious approach, the more so since we did not know whether it would be possible to successfully implement the population-based study and wanted to avoid false expectations.

Government officials at national, district and local levels were extensively consulted at all stages of the implementation of the programme. A General Advisory Committee was established to advise on an informal basis on the research direction; members of this committee included leading authorities of the Ministry of Health, AIDS Commission and Control Programme, the University, and the Uganda Virus Research Institute. This committee functioned very well indeed and facilitated effective communication between the relevant authorities in the country and the programme. We also established a Technical Advisory Committee to bring together

leading Ugandan scientists in relevant fields for advice, when required, on specific technical and scientific aspects of the intended research. As a committee this group did not function, presumably since the interests of individual members of the committee were too diverse. After a few unproductive meetings we decided to consult individual members on an ad-hoc basis.

As has been pointed out, the programme is based at the Uganda Virus Research Institute, and there was extensive interaction between programme and Institute's staff. Under an umbrella agreement with Makerere University collaboration took place with various Faculties and Institutes, including the Faculty of Social Science, the Medical School, the Institute of Statistics and Applied Economics, and the Institute of Public Health. During the first years of the programme the University struggled, however, with understaffing in all disciplines and consequently, experienced academic staff members were already burdened with a heavy workload. Thus, time-wise only limited inputs in programme activities by experienced academic staff could be realised. Various members of staff of the programme contributed to teaching activities at the University and held honorary posts. It had been anticipated that postgraduate students of Makerere University would carry out their field work in the context of programme activities. This did not materialise due to communication problems and poor absorption capacity on the side of some academic departments. Even when high priority is given to institutional research capacity strengthening, the weakness of institutional infrastructure itself may act as an obstacle to improvement.

Initial overseas collaborative links included the Institute of Tropical Medicine in Antwerp, the Liverpool School of Tropical Medicine and the London School of Hygiene and Tropical Medicine. By mid 1994 more than 15 collaborative links with academic and research organisations in Europe and the United States had been formalised. Not surprisingly, some collaborations are more productive (and enjoyable!) than others. There is probably no simple recipe for how to develop a successful collaboration, but there are a number of clues. First, it is essential that the overseas collaborator has a good understanding of the local situation and is appreciative of the various problems that are inherent in field research in resource-poor countries. Second, the collaborator should be willing to spend a considerable amount of time and energy on solving logistical hurdles. Third, both sides should be diligent in their communication. Finally, in our experience, collaborations tend to work best when there is money involved; in other words, when the collaboration appears in the budget of a grant application rather than in a statement of intent annexed to the application.

Staff recruitment and training

As mentioned, it proved hard to attract experienced Ugandan academic staff. There are various explanations for this, including the scarcity of expertise and a reluctancy to work in a rural community. In contrast, during the initial phase of the programme we were very fortunate with the recruitment of

international scientific staff members. These, together with the senior UVRI scientists on the programme, formed a team of exceptional dedication and quality.

Recruitment of university graduates went generally well. Grooming staff can be time consuming, but it has been highly rewarding to watch some of them grow and mature into competent scientists. Notwithstanding the importance of in-service training, formal postgraduate training is often important to give young researchers the opportunity to reflect and to learn new skills, and in view of long-term career prospects. While on several occasions funds were secured to send graduates overseas for a short period, all attempts to obtain funding for one-year master courses were in vain.

While it was difficult to recruit experienced laboratory technologists, for all other technical and support staff there was an abundance of choice. To select technical and skilled support staff we relied on formal job interviews. In recruiting local field staff school performance may not be a useful selection criterium: the quality of the performance of a field-worker depends more on his motivation than on his intelligence (1). We used to invite approximately twice the number of those actually required for a certain task, and selected the required number based on performance during initial training. For example, from among a large number of local people who had indicated their interest in working as interviewers 50 were trained, and half of these were selected for actual field work. Six years on, many of them are still active in the programme and an invaluable resource.

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Chapter 8.3

Implementation of the study: socio-cultural and ethical aspects

Implementation of the study: socio-cultural and ethical aspects

Underdevelopment, communication problems, cross-cultural differences and the effects of the HIV epidemic, all cause special challenges when AIDS research is conducted in resource-poor countries. The challenges imposed by underdevelopment range from endemic poverty to the failure of public health systems. Important impediments to communication include language problems, illiteracy and cross-cultural differences in concepts. These differences pertain to different perceptions and explanations of the material and immaterial world, and to different scientific, linguistic or semantic notions (1,2). A special dimension is added by the socio-economic disruption, anxiety and stigma caused by AIDS.

The AIDS pandemic has provoked intense discussions on the rights, needs and responsibilities of individuals and populations; these issues are often complex and sometimes controversial. Research involving human subjects has to be in accordance with the ethical principles *respect, beneficence* and *justice* (3,4). *Respect* requires that individuals are treated with respect for their capacity for self-determination. *Beneficence* refers to the obligation to maximise benefit and to minimise harm and wrongs. *Justice* refers to the obligation to treat each person in accordance with what is morally right and proper, to give each person what is due to him or her. These ethical principles can be conflicting, and the major conflict is between the rights of the individual and the needs of the population (5). For example, in an epidemic this problem may be manifested as the conflict between the right of society to protect itself against the spread of infection and the 'civil' rights of the groups hit by the epidemic (6); in trials conflicts may arise between the interests of patients within the trial and the longer term interest of obtaining reliable conclusions on which appropriate treatment policies for future patients can be based (7). Ethical and moral decisions are often complex. This complexity is increased in cross-cultural settings where differences in norms and values may fundamentally affect value assessments.

Cross-cultural issues

Perceptions of physiological functions and of diseases and their causes affect how people think and talk about their health and their health needs. For example, among the Baganda in the Masaka District in Uganda, malaria is an unknown disease concept. Fever is called *omusujja* and a range of causes of *omusujja* are recognised, including the consumption of corn: in this area, where malaria is meso-endemic, the population is most severely affected by the disease at the end of the rainy season, that is, when the corn is ripe (8). This example may illustrate that indigenous perceptions, more often than not, are based on a

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This chapter is based on a manuscript submitted for publication.

coherent and logical construct. When conducting a study these perceptions will have a bearing on which questions can be asked, how questions should be asked, and what the best setting is for an interview. Furthermore, it may follow that an intervention, particularly a behavioural intervention, is likely to fail if not introduced or implemented in a way which is appropriate in the local context.

Conversely, Western investigators will often introduce into local communities disease or research concepts that are alien. How can, for example, the concepts of randomisation and of a random sample be made clear? Most participants in our studies are coffee farmers and we explained random sampling by referring to the practice of coffee traders who sample a bag with beans by picking a few at random; it proved difficult to explain how a computer could be used for drawing a random sample and members of the community much preferred to pick names or numbers from a hat.

The difficulty of finding appropriate expressions in the local language may even occur when this language is the mother tongue of senior members of the research team. Translation problems tend to increase with the sensitivity of the subject, and this particularly applies to sexual behaviour issues. Extensive training may be required before members of staff feel at ease in discussing such sensitive issues.

When cross-cultural differences are ignored it will often be difficult to bring a study to a good end; it will be impossible to do justice to the expectations and needs of the study participants. In the following section we will deal in some detail with cross-cultural issues related to informed consent, confidentiality, counselling, and compliance and coercion.

Consent

The notion of informed consent has been changing during the last 4 decades. For example, forty years ago informed consent with clinical research meant little more than agreeing with what your doctor told you; the current view is that a patient must *demonstrate* understanding of the implications of his or her decisions (9). How informed consent should be interpreted in the context of research in Africa has been fiercely debated (10-18). The predominant view is that individual informed consent as an absolute principle should be sought in a culturally-sensitive way. Clearly, the interpretation of 'informed' is fraught with difficulty, particularly when concepts that are unfamiliar in the local culture are involved.

In many traditional settings, the freedom of individuals tends to be limited as a result of the hierarchical organisation of society. This makes it often necessary to seek consent at each hierarchical level (19). In our studies, a three-tiered approach is used involving the community, household and individual levels. Prior to any new research activity, meetings are first held with community leaders. These are followed by general village meetings, to explain plans and to address concerns. Rarely, a community refuses to participate (this did happen on one occasion

shortly after we had started distributing condoms at the community level, upsetting the religious leadership; extensive discussions over a few week period were required to defuse the situation). After the village meetings, the plans are discussed with heads of households. Finally, each adult member of the household is met in private, and plans and procedures are explained. As a rule consent is obtained in writing, but occasionally people are reluctant to sign a consent form while willing to participate in the study and witnessed verbal consent is then accepted.

Confidentiality
Medical research often involves the collection and storage of data that, if disclosed to third parties, could cause harm or distress, and investigators should arrange to protect the confidentiality of such data (4). Particular attention should be given to information on forms that may lead to the identification of individual subjects and to limiting access to forms and stored data. In addition, research staff should be trained to respect the privacy of individuals and to protect the confidentiality of data (20). The risk of disclosure particularly exists in community-based longitudinal AIDS studies as local members of staff may sense rather rapidly the HIV-status of some of the participants.

In communities where the HIV-associated mortality is high, the AIDS epidemic is causing considerable anxiety and often there is the notion that "only promiscuous people get infected". This situation is compounded in traditional communities where sharing of personal information is common. In such a situation, it may be incomprehensible for a participant that volunteered information should **not** become widely known and that a team member would **not** have access to all information. This may be felt in particular when interviewers and HIV counsellors are recruited locally. In our studies, confidentiality issues are discussed with participants and staff members whenever there is a suitable opportunity and it is our impression that participants' concerns about confidentiality decreased over time (21).

Counselling and disclosure of HIV status
The aim of counselling is to assist people in dealing with the emotional consequences of disease. AIDS counselling approaches in industrialised and developing countries originally evolved around diseased individuals and their families. Counselling of healthy individuals who like to be informed about their HIV status has, however, increasingly gained importance.

Based on the argument that disclosure may help prevent HIV transmission to others, some investigators insist that study volunteers should always be informed about their HIV status. There is, however, no evidence that disclosure of HIV status alone will induce behaviour change. Good counselling may do so, but it is our experience and the experience of others that infected but asymptomatic individuals are often very reluctant to inform their sexual partners, even after repeated counselling (13,22). Moreover, disclosure of HIV status can have social

implications, including the risk of divorce or stigmatisation: in a study in Nairobi where women were routinely informed about their HIV-status staff members often heard "I wish you had never told me" (16). From a practical perspective, the position that all subjects should be informed about their HIV status implies that all potential volunteers for a study have to be counselled before informed consent can be given. This may often not be feasible.

In our view, participants in population-based AIDS studies have the **right** to know their HIV status as well as the right **not** to know. We developed a community-based counselling service which took into account the unique test circumstances and the cultural context (23), and actively encouraged the study participants to attend this service.

Mandatory testing without informed consent has no place in AIDS research and prevention programmes (24). In situations where the provision of counselling is not affordable nor practical it is sometimes possible to anonymise the HIV test results while preserving linkage to relevant variables; such methods have been developed and successfully used.

Compliance and Coercion
Individuals and communities should not be pressured to participate in a study. However, it can be hard to draw the line between exerting pressure by offering inappropriate inducements and providing legitimate reimbursement for efforts (25); local staff will usually be in the best position to determine the right balance. In resource-poor settings basic commodities like sugar or soap can be powerful incentives, and thus be coercive. A practical problem with material incentives is that demands tend to increase over time, and once such incentive has been given there may not be a way back. Another approach to enhancing motivation, as described below, is to offer support for long-term community initiatives.

While participation is being negotiated, investigators should spell out clearly what benefit is being offered and refrain from implicit promises. Once a person enters a study, particularly someone who is poor and lacks access to medical care, the investigator assumes some duty to safeguard that person's health and welfare (26). From an opportunistic perspective, researchers have an interest in maintaining the health and welfare of subjects, as those who are healthy and satisfied are more likely to be compliant than those who are not (26). Should non-participants, such as family members, also be treated? There is no ethical obligation to do so, unless participation in a study has direct implications for family members. While possibly a useful incentive, there is a risk that the treatment demand will be exceed available resources. Moreover, once services are introduced, investigators have some ongoing responsibility beyond the temporal limits of the study.

In our population-based studies the willingness to participate varied dramatically, both between villages and from year to year,

and depended on historical, religious, political and ethnic issues, as well as the perceived benefit from the study. For each village we used a village profile, drawn by an anthropologist and documenting the network of key persons and issues of the day, as a basis for planning an optimal mobilisation approach.

Benefits for communities and individuals

Part of the benefit that communities and individuals may reasonably expect from participating in medical research is that they will be told of findings that pertain to their health (25). The information should include both the relevant research findings and their public health implications, and should be presented to the participants in a way which is locally meaningful. In addition, the findings should be communicated without undue delay to the local and national health authorities, and the scientific community.

In addition to the provision of care to study participants discussed above, it is important that there is a service commitment to the local population (27). This could include efforts to improve general health services or non-medical community services. Communities will often have health priorities which differ from those held by visiting investigators: shortages of food, water, and shelter commonly present urgent needs, and measles and other childhood diseases tend to be important. Moreover, the absence of a cure for AIDS or a preventive vaccine may cause communities to put AIDS relatively low on their priority lists.

If a project is to contribute to the improvement of local medical or non-medical services, careful thought should be given to the avoidance of "donor dependency". In our studies we started with assistance to the existing government health facilities with the aim of helping them to improve their services. Community activities have been expanded gradually and include community-based health care, AIDS home care for bedridden patients, protection of water springs, health education and AIDS prevention efforts, and income generating activities. The project's role is to facilitate these efforts, and the resource inputs are relatively small. Unfortunately these activities have only partly satisfied community expectations. Restricted access to the study clinic has been a source of profound discontent. The community based health care service and most other developmental activities supported by the project gave only a few people a sense of benefit; this is understandable since most of these activities do not result in immediate tangible improvements.

In settings where AIDS is considered an important public health problem arrangements for the care of AIDS patients (28) and the introduction or improvement of HIV control approaches are likely to be perceived as valuable short-term benefits. Investigators have, moreover, a moral obligation to assist individuals in protecting themselves against HIV infection and to contribute to HIV prevention. Clearly, this moral obligation may clash with the

objectives of observational studies or intervention trials; for example, the obligation to educate and counsel study subjects may make it necessary to considerably increase the sample size of an efficacy trial of a candidate preventive HIV vaccine.

In areas where the prevalence of HIV is high, investigators will be confronted with the socio-economic consequences of the HIV epidemic, particularly when studies are long-term. As it is probable that the socio-economic effects on households and communities will be felt for decades to come, "emergency" aid, in the form of one-off material or financial support, will be of little help. Even if resources would permit such material support, this kind of aid is likely to damage the often already vulnerable social fabric (29) and enhance "donor dependency".

Community-based studies enhance their prospects of being successful when research, care, and prevention efforts build on existing social networks and structures. In our experience, this may require an intense interaction between the project and community members. Community participation in research activities is likely to instill a sense of co-ownership and thus enhance the prospects for success (2,21).

The importance of avoiding false expectations cannot be over-emphasized. Raising false expectations, possibly in the hope of improving compliance, is dishonest and may prevent successful completion of a study or prevent future studies. Thus, an investigator should explain to candidate study volunteers or communities in a clear and explicit way which immediate and long-term benefits can be expected. Even when this has been done it may, in our experience, still be difficult to prevent in a long-term study the build-up of false expectations. Particular attention should be given to the avoidance of false expectations in connection with studies of anti-retroviral drugs and preventive HIV vaccines. In recent years, scientific developments in these fields have had enormous news value. Regardless of whether investigators are dealing with the press, communities or individuals, drug- and vaccine- related research must be discussed with cautious realism.

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Chapter 9

Summary

HIV and AIDS are currently among the most pressing global public health issues, and it is estimated that more than half of all HIV infected adults and children live in sub-Saharan Africa. In Uganda, the first cases of clinical AIDS were recognised in 1982 and a few years later it was clear that a major HIV epidemic was emerging. In 1987, the Government of Uganda requested the help of the British Medical Research Council (MRC) in dealing with the AIDS epidemic. This request resulted in the development of a multidisciplinary research programme, the MRC (UK) Programme on AIDS in Uganda, which was directed by the author during the period 1988-94. The aims of the programme are to clarify aspects of the epidemiology of HIV-1 and the natural history of HIV-1-associated disease in rural Uganda, and to contribute to the development of AIDS control strategies. This thesis presents results of studies on the epidemiology of HIV-1 in a rural Ugandan population, carried out as part of the MRC Programme.

Chapter 1 gives background information on the state of knowledge in 1988 of the epidemiology of HIV-1 in Africa, study objectives and design, the study area and population, and a summary of the research carried out during the period 1989-94. In 1988 knowledge of the epidemiology of HIV-1 in Africa was largely based on studies of patients attending urban hospitals and on selected urban populations. Since the majority of people in Uganda and other African countries live in rural areas, it was considered that there was a pressing need for studies of rural populations. A prospective study design was required to ascertain causal relationships between risk factors and HIV-1 infection, to study the incidence of HIV-1, and the natural history of HIV-1-associated disease, and the adopted approach was to combine the follow-up of a large cohort of a rural population for study of the epidemiology of HIV-1 with the follow-up of a small sub-cohort for clinical studies. A cluster of 15 neighbouring villages was selected in the Masaka district in South-West Uganda. An ethno-demographic and medical baseline survey of the 15 villages was conducted in 1989-90. Since then the cohort has been kept under demographic and medical surveillance through annual repeat surveys.

In *Chapter 2* three studies are presented on risk factors for HIV-1 infection in adults. The results of these studies confirm the predominant role of sexual behaviour in the HIV-1 epidemic: the factor most strongly associated with increased risk of infection is the number of lifetime sexual partners. People most at risk of HIV-1 infection in this Ugandan population are women aged 13-24 years. Men tend to start their sexually active life a few years later than women; while the risk of HIV-1 infection is relatively low among men aged 13-21 years, among those aged 22-24 years the risk is substantial. An important determinant of HIV-1 infection is socio-economic status. It has often been assumed that poor women and rich men are particularly at risk of infection. The results of one of the studies suggest, however, that poverty leads to a greater risk for both males and females, possibly due to reduced access to information, education and health care.

In *Chapter 3* two studies are described on the seroprevalence and incidence of sexually transmitted diseases (STDs), and on the role of STDs as risk factors for HIV-1 infection. The results of the first study suggest that infections with syphilis, chancroid, chlamydia and herpes simplex virus type 2 (HSV-2) are common in the cohort population. HSV-2 is particularly common. HSV-2 infection persists lifelong causing recurrent genital ulcerations. In view of its high prevalence, HSV-2 may well be an important risk factor for HIV-1 infection in this population. Using a simulation model of the transmission of HIV-1 and other STDs, and data from the Masaka cohort, we estimate that during the first 10 years of the epidemic (1980-90) over 90% of HIV-1 infections in the cohort were attributable to STDs. Even under conservative assumptions STDs played in our simulations a critical role in the widespread transmission of HIV-1 infection. The results of these simulations underline the potential value of STD control measures, especially if such measures are introduced at the early stage of an epidemic.

Chapter 4 describes a study of the post-natal incidence of HIV-1 infection in children. The main routes of HIV-1 transmission, namely sexual contact with an infected person, parenteral exposure to infected blood and mother-to-child, have been well documented. Concern has, however, been commonly expressed that HIV might also be transmitted through other routes, for example non-sexual 'casual' contact or insect vectors. These 'alternative' transmission routes can best be studied in children. Among 3,900 children aged 0-12, who were HIV-negative on enrolment and had at least one follow-up specimen, we observed only one seroconversion. In this case the transmission was most probably through breast milk. Apart from mother-to-child transmission, HIV-1 infection of children in this population is extremely rare. The study provides the most conclusive evidence to date that the probability of transmission through non-sexual 'casual' contact and insect vectors is extremely small. This evidence should help to dispel misconceptions.

In *Chapter 5* a study is presented on the incidence of HIV-1 infection and two studies on HIV-1-associated mortality in adults. During the first year of follow-up the incidence of HIV-1 infection was 9.2 per 1,000 person years of observation, a rate similar to those reported for other rural areas in sub-Saharan Africa.

Arguably the most important study results are those on HIV-1-associated mortality. At 2-year follow-up the mortality among seronegative adults was 7.7 per 1000 person years and among those seropositive 115.9 per 1000. Adults testing positive for HIV-1 antibody were 15 times as likely to die during the 2-year observation period as were otherwise similar persons who tested negative. Among those aged 13-44 years the relative risk was 60. Half of all adult deaths and more than 80% of deaths among those aged 13-44 years were attributable to HIV-1. At 2-year follow-up we reported a rapid progression from asymptomatic infection or mild disease to death. Using 4-year follow-up data we estimate that the median survival from infection to death in the cohort population is approximately 7 years for those aged 13-54 years. This compares with a median survival of 11 years in

industrialised countries. These results show the strong impact that HIV-1 infection is having on mortality in a rural area of Uganda where the overall adult HIV-1 prevalence is below 10%, a rate lower than in many urban areas in sub-Saharan Africa.

Chapter 6 describes a study of the trend in HIV-1 prevalence and incidence among young adults. While the overall adult HIV-1 prevalence and incidence showed little change during 4-year follow-up, the prevalence among males aged 20-24 years showed a highly significant decrease from 11.8% to 2.7% ($p<0.001$); in females aged 13-19 years the prevalence fell from 4.5% to 2.5% ($p=0.09$). In addition, there was a suggestion of a decrease in incidence among males aged 13-24 years, but not among females of the same age. During the period 1989-94 intervention efforts aiming at a reduction in the frequency of partner change, distribution and promotion of condoms, and the control of STDs, were gradually expanded in the study area, but by 1994 the people using condoms or seeking treatment for STDs in the official health sector were still relatively few. It is probable, therefore, that study and intervention effects resulted in a change of sexual behaviour among young adults. The most important result of this study is the observation that a decrease in infection rates among young adults is possible, even in populations with a relatively high force of HIV-1 infection, with no more than a modest intensity of interventions. This should be reason for cautious optimism and encourage the vigorous pursuit of HIV prevention measures.

Chapter 7 describes the results of a simulation study, using data from the Masaka cohort, to assess the likely impact on HIV-1 incidence of increased condom use, a reduction in casual sexual partners, treatment of other STDs, and combinations of these interventions. For the scenario most consistent with data from the study population, 39% of all adult infections were averted when condoms were used consistently and effectively by 50% of men in their contact with one-off partners; 68% of infections were averted when men reduced by 50% the frequency of sexual contacts with one-off partners; and 43% of infections were averted when the duration of all STD episodes was reduced by 50%. When the 3 interventions were combined, 82% of all adult infections were averted. The main finding of this study is that the greatest gains may be made by a combination of interventions targeted at less regular sexual partnerships.

In *Chapter 8* the results of the studies are discussed and placed in a broader context. Methodological and operational aspects of the implementation of the population-based cohort study are discussed in some detail, as are socio-cultural and ethical aspects.

Samenvatting

HIV en AIDS behoren momenteel tot de ernstigste gezondheids problemen in de wereld en meer dan de helft van alle HIV-geinfecteerde volwassenen en kinderen leven in Afrika ten zuiden van de Sahara. De eerste gevallen van AIDS in Oeganda werden geconstateerd in 1982 en een paar jaar later werd duidelijk dat er een ernstige epidemie op komst was. De Oegandese overheid verzocht in 1987 de Engelse Medical Research Council (MRC) om steun bij het ontwikkelen van wetenschappelijk onderzoek op het gebied van HIV en AIDS. Dit verzoek resulteerde in de ontwikkeling van een multi-disciplinair onderzoeks programma, de MRC(UK) Programme on AIDS in Uganda, waarvan de auteur de leiding had gedurende de periode 1988-94. Het programma had als doel bij te dragen aan de kennis van de epidemiologie van HIV in ruraal Oeganda en van het natuurlijk beloop van aan HIV-1 gerelateerde ziekte, en een bijdrage te leveren aan de ontwikkeling van betere interventies voor het verminderen van heterosexuele HIV-transmissie. In dit proefschrift worden resultaten beschreven van onderzoek naar de epidemiologie van HIV-1 in een rurale Oegandese populatie.

In *Hoofdstuk 1* wordt beschreven wat er in 1988 bekend was over de epidemiologie van HIV-1 en wat de doelstellingen en opzet van het onderzoek waren. In dit hoofstuk wordt tevens achtergrond informatie gegeven over de studie populatie en worden de verschillende studies die werden uitgevoerd tijdens de periode 1988-94 samengevat. De epidemiologische kennis van HIV-1 in Afrika was in 1988 voornamelijk gebaseerd op studies onder patienten die ziekenhuizen in de grote steden hadden bezocht en van geselecteerde stedelijke populaties. In Oeganda en vele andere Afrikaanse landen wonen de meeste mensen evenwel op het platteland, en er was daarom dringend behoefte aan onderzoek onder rurale populaties. Het onderzoek diende prospectief te zijn teneinde causale relaties vast te kunnen stellen tussen risicofactoren en infectie met HIV en voor het bestuderen van de incidentie van HIV-1 en het natuurlijk beloop van de ziekte. Besloten werd tot een combinatie van een groot ruraal cohort voor epidemiologische studies en een aanzienlijk kleiner sub-cohort voor klinische studies. Een groep van 15 naburige dorpen in het Masaka distrikt in Zuid-West Oeganda werd geselecteerd voor de studie. Het eerste ethno-demografisch en medisch onderzoek van de bevolking in de 15 dorpen vond plaats in 1989-90. Sindsdien is de bevolking gevolgd door middel van jaarlijks herhalings onderzoek.

In *Hoofdstuk 2* worden drie studies naar risico factoren voor infectie met HIV-1 onder volwassenen beschreven. De resultaten van deze studies bevestigen het grote belang van sexueel gedrag voor de HIV-1 epidemie: de risico factor die het sterkst met HIV-infectie geassocieerd bleek is het aantal seksuele partners. Vrouwen in de leeftijds groep 13-24 hadden het hoogste infectie-risico. Mannen worden een paar jaar later sexueel actief dan vrouwen in de studie populatie, en het infectierisico is relatief laag onder mannen in de leeftijdsgroep 13-21; onder mannen van 20-24 jaar is het risico evenwel substantieel. Een belangrijke risicofactor is socio-economische status. Het werd algemeen aangenomen dat met name vrouwen met een lage sociaal- economische

status en rijke mannen het risico liepen om geinfecteerd te worden met HIV. Het resultaat van onze studie suggereert evenwel dat armoede leidt tot een groter risico voor zowel mannen als vrouwen; een mogelijke verklaring is dat voor de armen in de samenleving informatie, onderwijs en gezondheidszorg moeilijk toegankelijk zijn.

Hoofdstuk 3 beschrijft een studie naar de seroprevalentie en incidentie van sexueel overdraagbare aandoeningen (SOAs) en een studie naar het mogelijk belang van SOAs als risico factoren voor infectie met HIV-1. De resultaten van de eerste studie suggereren dat infecties met *T. pallidum* (de verwekker van syphilis), *H. ducreyi* (de verwekker van chancroid), *Chlamydia trachomatis* (een verwekker van urethritis) en herpes simplex virus type 2 (HSV-2) veelvuldig voorkomen in de studiepopulatie. Infecties met HSV-2 persisteren gedurende het hele leven en veroorzaken terugkerende genitale ulceraties. Aangezien HSV-2 zeer veel voorkomt in deze populatie is het denkbaar dat het een belangrijke risico factor is voor HIV-1 infectie. Gebruik makend van een simulatie model voor de transmissie van HIV-1 en andere SOAs, en van gegevens van het Masaka cohort, werd een schatting gemaakt van het percentage HIV-1 infecties in het cohort die mogelijk het gevolg waren van co-infectie met SOAs. Het resultaat van deze studie gaf aan dat gedurende de eerste 10 jaar van de epidemie (1980-90) vermoedelijk meer dan 90% van de HIV-1 infecties in het cohort het gevolg waren van co-infectie. Ook onder conservatieve aannamen speelden SOAs in onze simulaties een kritische rol in het ontstaan van de HIV-1 epidemie. De resultaten van deze simulaties geven aan dat de preventie en bestrijding van SOAs waarschijnlijk van groot belang is teneinde een HIV epidemie te beperken, in het bijzonder wanneer dergelijke maatregelen in een vroeg stadium van een epidemie worden geintroduceerd.

Hoofdstuk 4 beschrijft een studie naar de post-natale incidentie van HIV-1 infectie in kinderen. De belangrijkste manieren waarop HIV-1 wordt overgedragen zijn bekend: sexueel contact met iemand die geinfecteerd is, parenterale blootstelling aan geinfecteerd bloed, en van moeder-op-kind. Herhaaldelijk is evenwel bezorgdheid geuit dat HIV ook op andere manieren overgedragen zou kunnen worden, bij voorbeeld door niet-sexueel "dagelijks" contact of door insecten. Deze 'alternatieve' transmissie mogelijkheden kunnen het beste bestudeerd worden in kinderen. We bestudeerden 5,490 kinderen in de leeftijd 0-12 jaar; 3,940 van deze kinderen waren HIV-negatief aan het begin van de studie en hadden ten minste een maal een vervolg onderzoek. In totaal werd slechts 1 seroconversie waargenomen. De transmissie van HIV vond hoogst waarschijnlijk plaats via moeder melk. De conclusie is dat afgezien van moeder-op-kind transmissie HIV-1 infectie in kinderen in deze populatie buitengewoon zeldzaam is en dat de kans of transmissie door niet-sexueel contact of door insecten zeer gering is. Het resultaat van deze studie zal hopelijk bijdragen aan meer effectieve preventie inspanningen door te onderstrepen dat deze inspanningen met name gericht moeten zijn op de preventie van sexuele transmissie.

Hoofdstuk 5 beschrijft een studie naar de incidentie van HIV-1 in volwassenen en twee studies naar HIV-1 geassocieerde mortaliteit onder volwassenen. De HIV-1 incidentie was 9.2 per

1,000 persoon-jaren (pj) in het eerste jaar dat het cohort werd gevolgd. Vergelijkbare resultaten zijn gerapporteerd voor andere rurale populaties in Afrika.

De belangrijkste studie resultaten zijn ons inziens de bevindingen betreffende de HIV-1 geassocieerde mortaliteit. Gedurende de eerste twee jaar dat het cohort werd vervolgd was de bruto jaarlijkse sterfte 7.7 per 1,000 pjr onder HIV-negatieve volwassenen en 115.9 per 1,000 pjr onder HIV-positieve volwassenen. Volwassenen met een HIV-positief testresultaat hadden een 15 maal groter sterfterisico dan vergelijkbare volwassenen met een negatief testresultaat. In de leeftijds groep 13-44 was het relatieve sterfterisico 60. De helft van alle sterfgevallen onder volwassenen was toe te schrijven aan HIV-1 infectie; in de leeftijds groep 13-44 was meer dan 80% van de sterfgevallen toe te schrijven aan HIV-1. De data die beschikbaar waren na twee jaar volgen van het cohort suggereerden een snelle progressie van asymptomatische infectie naar ernstige ziekte en dood. Gebruik makend van data voor een vervolgperiode van vier jaar schatten wij dat in de leeftijds groep 13-54 de mediane overlevingduur na infectie ongeveer 7 jaar bedraagt. Ter vergelijking, in geindustrialiseerde landen is de mediane overlevingsduur ongeveer 11 jaar. Deze resultaten laten zien hoe ernstig het effect is dat de HIV-1 epidemie heeft op de sterfte onder volwassenen in een ruraal gebied in Oeganda waar de HIV-1 prevalentie minder dan 10% bedraagt; in vele stedelijke gebieden in Afrika ten zuiden van de Sahara is de HIV-1 prevalentie belangrijk hoger.

Hoofdstuk 6 beschrijft het verloop in de tijd van de HIV-1 prevalentie en incidentie onder jonge volwassenen. Terwijl de totale prevalentie en incidentie onder volwassenen weinig verandering vertoonde gedurende de vijf studie jaren, nam de prevalentie onder mannen in de leeftijds groep 20-24 zeer sterk af van 11.8% tot 2.7% ($p<0.001$); onder vrouwen in de leeftijds groep 13-19 daalde de prevalentie van 4.5% tot 2.5% ($p=0.09$). Er was bovendien een geringe daling in de HIV-1 incidentie onder mannen van 13-24 jaar maar niet onder vrouwen van dezelfde leeftijd. Preventieve maatregelen in het studie-gebied met als doel het verminderen van het aantal partners, het bevorderen van condoomgebruik en het verbeteren van de behandeling van SOAs, namen gedurende de periode 1989-94 geleidelijk toe in intensiteit. Niettemin waren er in 1994 nog maar relatief weinig mensen die condooms gebruikten of die gebruik maakten van de officiele gezondheidszorgvoorzieningen voor de behandeling van SOAs. De meest waarschijnlijke verklaring voor de waargenomen daling in prevalentie onder jonge volwassen is daarom een verandering in sexueel gedrag mogelijk als gevolg van studie en interventie effecten. Het belang van deze studie is dat het resultaat aangeeft dat een afname in het infectie risico onder jonge volwassenen mogelijk is, ook in populaties met een relatief hoge infectiedruk, met relatief weinig intensieve interventies. Dit is een rede voor voorzichtig optimisme maar ook voor het zo krachtig mogelijk bevorderen van preventieve maatregelen.

Hoofdstuk 7 beschrijft de resultaten van een simulatie studie naar het waarschijnlijke effect op de incidentie van HIV-1 van verschillende interventies: toegenomen condoom gebruik, afname

van het aantal eenmalige sexuele contacten, behandeling van SOAs, en combinaties van deze drie interventies. Voor de simulaties werden data gebruikt van het Masaka cohort. Voor het scenario dat het meest consistent was met de cohort data, werd 39% van alle infecties onder volwassenen voorkomen wanneer condooms consistent en effectief werden gebruikt door 50% van de mannen tijdens sexueel contact met een eenmalige partner; werd 68% van de infecties voorkomen wanneer de frekwentie van sexueel contact dat mannen hadden met eenmalige partners werd gereduceerd met 50%; en werd 43% van de infecties voorkomen wanneer de duur van alle SOA gevallen met 50% werd gereduceerd. Wanneer in de simulatie de drie interventies werden gecombineerd, werden 82% van alle infecties onder volwassenen voorkomen. De conclusie van deze studie is dat de grootste winst, in termen van reductie van HIV-1 transmissie, kan worden geboekt door een combinatie van condoom promotie, vermindering van het aantal sexuele partners en SOA bestrijding.

In *Hoofdstuk 8* worden de onderzoeks resultaten bediscussieerd en in een bredere context geplaatst. Methodologische en operationele aspecten van de studie worden besproken, evenals socio-culturele en ethische aspecten.

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Curriculum vitae

The author of this thesis was born on August 26, 1949 in Heerde, The Netherlands. He completed his secondary education (HBS-B) in 1968 and graduated as a clinical doctor in 1974 (University of Groningen). Following his registration as a general practitioner and a 3-year period as Senior House Officer he went in 1978 to Tanzania as a general clinical officer. In 1979 the author became regional tuberculosis and leprosy coordinator in the Shinyanga Region, Tanzania. This was followed by a 2-year period in the tuberculosis and leprosy Central Unit of the Tanzanian Ministry of Health. In 1983-84 he attended the M.Sc. course in Epidemiology at the London School of Hygiene and Tropical Medicine. After obtaining his degree he joined the International Union Against Tuberculosis and assisted in the planning and implementation of tuberculosis control programmes in developing countries. In 1986 he joined the Royal Tropical Institute in Amsterdam, The Netherlands working on the control of mycobacterial infections, HIV, and health systems research. In 1988 the author joined the Medical Research Council (UK) and directed the MRC(UK)/ODA/UVRI Programme on AIDS in Uganda from its inception till late 1994. He is currently a Senior Lecturer at the London School of Hygiene and Tropical Medicine.

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