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Papers

# Mortality associated with HIV-1 infection over five years in a rural Ugandan population: cohort study

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## ▶ **Abstract**

**Objective:** To assess the impact of HIV-1 infection on mortality over five years in a rural Ugandan population.

**Design:** Longitudinal cohort study followed up annually by a house to house census and medical survey.

**Setting:** Rural population in south west Uganda.

**Subjects:** About 10 000 people from 15 villages who were enrolled in 1989-90 or later.

**Main outcome measures:** Number of deaths from all causes, death rates, mortality fraction attributable to HIV-1 infection.

**Results:** Of 9777 people resident in the study area in 1989-90, 8833 (90%) had an unambiguous result on testing for HIV-1 antibody; throughout the period of follow up adult seroprevalence was about 8%. During 35 083 person years of follow up, 459 deaths occurred, 273 in seronegative subjects and 186 in seropositive subjects,

corresponding to standardised death rates of 8.1 and 129.3 per 1000 person years. Standardised death rates for adults were 10.4 (95% confidence interval 9.0 to 11.8) and 114.0 (93.2 to 134.8) per 1000 person years respectively. The mortality fraction attributable to HIV-1 infection was 41% for adults and was in excess of 70% for men aged 25-44 and women aged 20-44 years. Median survival from time of enrolment was less than three years in subjects aged 55 years or more who were infected with HIV-1. Life expectancy from birth in the total population resident at any time was estimated to be 42.5 years (41.4 years in men; 43.5 years in women), which compares with 58.3 years (56.5 years in men; 60.5 years in women) in people known to be seronegative.

**Conclusions:** These data confirm that in a rural African population HIV-1 infection is associated with high death rates and a substantial reduction in life expectancy.

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**Key messages**

- Comparatively few data exist on mortality associated with HIV-1 in sub-Saharan Africa

- Adults positive for HIV-1 in a rural Ugandan population with a prevalence of infection of 8% were more than 10 times more likely to die over a 5 year period than those negative for HIV-1

- Over 40% of all deaths in adults were attributable to HIV-1 infection, the percentage in young adults aged 25-44 being in excess of 70%

- Life expectancy is estimated to have declined from 58.6 to 42.5 years as a consequence of the AIDS epidemic

# Introduction

Since the beginning of the HIV-1 pandemic 16 million people are estimated to have become infected in Africa, most of them in sub-Saharan countries.[1] Data on mortality associated with HIV in these countries remain comparatively scarce, and most of the

published studies have been in selected hospital or urban populations,[2] [3] [4] [5] [6] even though most people in sub-Saharan countries live in rural communities.

In 1994 we published the results of two years of follow up of a rural population cohort in southwest Uganda.[7] We showed the serious impact of HIV-1 infection on this population, in which about 8% of adults are positive for HIV-1. In this paper we report the data for five years of follow up.

## Subjects and methods

The area of study is a rural subcounty of Masaka district in southwest Uganda situated about 32 km from Masaka town and 16 km from the trans-African highway. A cluster of 15 villages with a population of about 10 000 was selected for study. The inhabitants are mainly peasant farmers who grow bananas as a subsistence crop and cultivate coffee for sale. The predominant tribal group, the Baganda, constitute about 70% of the population. Substantial numbers of immigrants from Rwanda settled in the area over 20 years ago; more recently some of them have begun to move back to Rwanda.

Late in 1989 the study villages were mapped and an adult member of the household, preferably the head, was asked how many people were in the household. This census included those who had been resident in the household for three months or more, those who had been resident for less than three months but stated that they intended to stay in the area, and those who were regarded as residents but were temporarily living elsewhere—for example, children at boarding school. A socioeconomic questionnaire was also administered.

Within four weeks of these interviews a medical team visited each household. All residents were invited to participate in a survey, which included a brief medical

history, a physical examination, and the collection of a blood sample. Absentees and those refusing were revisited to encourage them to participate.

Blood specimens were transported every week to the laboratory of the Uganda Virus Research Institute in Entebbe, where they were tested for antibodies to HIV-1. All serum samples were tested using two enzyme immunoassay systems, Recombigen HIV-1 EIA (Cambridge Biotech, Worcester, MA) and Wellcozyme HIV-1 Recombinant (Wellcome Diagnostics, Dartford, England), western blotting using Novopath HIV Immunoblot (Bio-Rad Laboratories, Watford, England) being used when indicated.[8] [9] None of the field workers were aware of the HIV status of study participants. Trained counsellors made results available to all those who requested them.[10]

Every year from 1990 to 1995, the second to sixth rounds of the survey, the census team returned to each household to ascertain the vital status of all those who were resident at the previous survey and to enumerate those who had joined the household through birth or migration. As in the first round of the survey, the medical team collected a blood sample from all those willing to provide one. After the fourth round blood samples were not taken from children (those aged <13 years).

Monthly birth and death registration was introduced from the beginning of the third round of the survey to supplement data obtained from the annual surveys. An additional question was asked at the time of the census about the vital status of all those who had left the area in the previous 12 months because it is not unusual for seriously ill people to return to their natal home to die.

### Statistical methods

Person years of observation were calculated from the time people were enrolled (the date of their first seropositive or seronegative specimen) until the date of the sixth round of the survey for those known to be alive; the date of death was recorded for those known to be dead, and the date of leaving was recorded for those who had left the study area. Those who seroconverted were counted as seronegative until the midpoint between the last known seronegative specimen and first seropositive specimen; thereafter they were counted as seropositive.

Standardised mortality rates were calculated by the direct method with the total population as the standard. Age adjusted mortality rate ratios were calculated by Poisson regression methods. Time to death analyses were performed by using Kaplan-Meier plots and log rank tests.

In the estimates of life expectancy one year intervals were used up to the age of 5 years and five year intervals thereafter, with those aged 75 years or more being combined into one group. In each instance the risk of dying during the first year of life was based on all births reported from the third round of the survey onwards, either through monthly birth and death registration or at the annual census. This is likely to overestimate the risk of dying for seronegative subjects, but inclusion of only those who were known to be seronegative underestimates the risk because the serological state of most of the children dying in the first few months of life was not known.

## ▶ Results

Of the 1981 households in the study area, 1806 agreed to participate at the initial survey. The total population of these households was 9777 people, of whom 8833 gave a blood sample for HIV-1 testing (either during the initial survey or subsequently) and had at least one unambiguous result. An additional 303 people gave a serum specimen but could not be classified serologically; they were mainly young children whose sample yielded insufficient serum for testing. At the first survey 377 out of 7802 people (4.8%) were HIV-1 positive, 343 (8.2%) of 4172 adults; in all, 412 (4.8%) of 8833 people who were resident at the first survey were found to be positive for HIV-1 at some time, 388 (8.3%) of 4685 adults.

During the five subsequent years a further 5130 people joined the population; 4475 of them were eligible to give a blood sample, and serological status was obtained for 3199 of them.

Of the 9777 people in the first round of the survey, 549 (5.6%) had died by the sixth round and 3090 (31.6%) had left the area and not returned.

A comparison of death rates among seropositive adults resident at the first round of the survey and those joining subsequently showed substantial differences in survival

rates (fig 1). Age and sex standardised death rates for those joining were significantly higher than those for members of the population in the first round (hazard ratio after correction for age 1.70 (95% confidence interval 1.24 to 2.32)). This difference was almost entirely on account of substantially higher death rates in the men who joined (age adjusted hazard ratio 3.31; 2.11 to 5.19); the difference in rates between female seropositive residents and those who joined was comparatively small (hazard ratio 1.11 (0.73 to 1.71)). Seropositive men who joined the study area seemed to be often in an advanced stage of their disease; hence many of them died soon after their arrival.
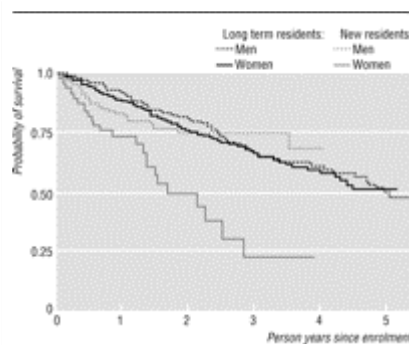


**Fig 1** Probability of survival of adults positive for HIV by sex and length of residence

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## Mortality in first round in residents with known HIV status

In the main analysis we compared death rates between seronegative and seropositive subjects in the cohort resident during the first round of the survey. A total of 459 deaths was reported in 35 083 person years of observation (table 1); 273 were seronegative subjects and 186 seropositive, corresponding to 8.1 and 129.3 per 1000 person years. Standardised death rates among seronegative and seropositive adults were 10.4 (9.0 to 11.8) and 114.0 (93.2 to 134.8) per 1000 person years respectively.

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**Table 1** Mortality by presence of antibody to HIV-1 in first round of survey in resident population

The excess mortality due to HIV-1 infection in adults (mortality in total adult population minus mortality in people negative for HIV-1) was 7.4 (7.5 when age standardised (6.4 to 8.7)) (table 2). The excess was highest (17.7 per 1000) in those aged 25-34. The mortality fraction attributable to HIV-1 infection was 41% for adults (those aged 13 and over) and 69% for those aged 13-44.
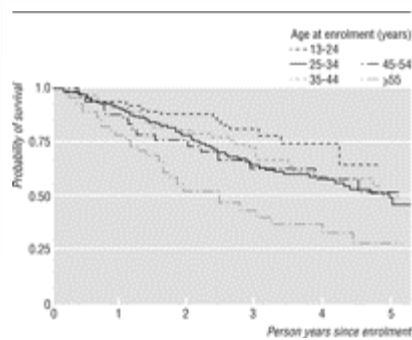
| View this table: [in this window] [in a new window] | **Table 2** Excess mortality and mortality fraction attributable to HIV-1 infection in adults by sex |
| --- | --- |

Standardised death rates in seropositive men and women were similar, being 104.0 and 118.1 per 1000 person years; excess mortality and attributable mortality fractions varied by sex and age (table 2), reflecting to a large extent differential rates of seropositivity. Thus, in those aged 20-24 the attributable mortality fraction was very high for women (76%) but much lower for men (9%). For all women combined the attributable mortality fraction was 42% compared with 40% in men.

The HIV-1 specific age adjusted mortality rate ratios (comparing HIV positive subjects with HIV negative subjects) were 11.9 (8.3 to 15.9) for men and 13.9 (10.3 to 18.8) for women; the corresponding ratios for those aged 13-44 years were 16.4 (9.9 to 27.4) and 28.0 (17.2 to 45.6)

Among adults who were positive for HIV-1 there was no difference in the rate of survival of men and women (fig 1) ($x^2$=0.29, 1 df, P=0.6, log rank test). When the data were analysed by age group (combining those aged 13-19 and 20-24) there were no differences between the four groups aged under 55 years of age ($x^2$=6.15, 3 df, P=0.14) (fig 2). However, those aged 55 years or more died considerably more rapidly than those aged 13-54 years ($x^2$=16.28, 1 df, P=0.0001).

**Fig 2** Probability of survival of adults positive for HIV-1 after five years of follow up

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Two years after enrolment the probabilities of survival for those aged 13-54 and 55 or more were 81.3% (77.4% to 84.7%) and 53.6% (37.7% to 67.2%) respectively. By five years the survival probabilities were 53.1% (45.4% to 60.2%) and 28.9% (14.1% to 45.6%) respectively. The hazard ratio comparing survival rates in these two age groups was 2.30 (1.52 to 3.47).

The crude death rate for the total resident population regardless of HIV positivity was 14.6 per 1000 person years overall and 19.3 per 1000 person years in adults. Standardised rates in adults without a defined serostatus were considerably higher than in those with: 39.0 and 17.9 respectively. The rate in the former group was particularly high during the first year of follow up (87.9 per 1000 person years) but declined thereafter to 26.6 per 1000 person years for the remainder of the follow up period.

### Life expectancy

Life expectancy in people resident in the study area at any time between the first and sixth rounds was estimated to be 42.5 years (41.4 for men and 43.5 for women). For those known to be seronegative, life expectancy was estimated as 58.6 years (56.5 years for men and 60.5 years for women); these estimates were based on 56 000 and 47 000 person years of observation respectively.

The probability of a 15 year old dying before reaching the age of 60 is 0.61 in the total population and 0.24 in people known to be seronegative; in men the probabilities are 0.66 and 0.30 and in women 0.57 and 0.19.

## Discussion

In 1994 we reported death rates associated with HIV-1 infection in a rural Ugandan population after a follow up of two years with about 16 000 person years of observation.[7] This report extends follow up to five years and is based on more than twice as many person years of observation.

We have confirmed our earlier findings of the impact of the HIV-1 epidemic on this rural population, whose underlying stable seroprevalence is about 5% and about 8% among adults. The mortality attributable to HIV-1 infection is estimated to be 41% in adults and over 70% in women aged 20-44 and men aged 25-44, which reflects the differences in age specific seroprevalence between the two sexes.

### Possible biases

Possible biases that should be considered when interpreting these results include selective enrolment and selective migration out of the area. Of the 9777 residents in the first round (in whom these estimates are based) 90% were enrolled and included in the analysis because they agreed to have blood samples taken and had an unambiguous result on testing for HIV-1 antibody. The age standardised mortality among the adults in the census who did not have blood samples taken was 39.0 per 1000 person years, considerably higher than the combined rates for seropositive and seronegative subjects for each age group. This could be due to a higher seropositivity rate in those who did not comply, but it may also reflect a high proportion of fatally ill people because 32 of the 62 adults who died in this group died within the first year of follow up.

Seriously ill patients often return to the village of their birth to die, and thus migration out of this closed cohort is likely to have resulted in an underestimate of the number of deaths and therefore of death rates. To minimise the number of deaths not ascertained, we inquired at each annual census from the third round onwards about whether those who had left the area in the previous 12 months were known to have died. The monthly death registration, introduced at the same time, did not identify any deaths that were not subsequently ascertained at the annual census.

We cannot rule out the possibility of errors in the ascertainment of HIV-1 antibody in the laboratory, but most participants had their blood assessed on more than one occasion. The HIV testing algorithm used had a sensitivity and specificity close to 100%.[6]

## Mortality associated with HIV

The extremely high mortality risk ratios associated with HIV-1 infection provide strong evidence that HIV-1 is the cause of substantial excess mortality.[11] The age adjusted risk ratio for adults in this study, 13.2 (10.6 to 16.4), compares with recent reports on relative risks of 9.5 (6.0 to 14.9) in a general population in the neighbouring Rakai district of Uganda[12]; of 12.9 (5.4 to 30.7) in an occupational cohort in Mwanza, Tanzania[6]; and of 13.3 (10.0 to 17.2) in people with haemophilia in Britain.[13] The relative risks observed in different populations using different study methods are remarkably similar, thus adding weight to the causal association between HIV and excess mortality.

It has been suggested that immunosuppressive foreign proteins contaminating commercial factor VIII and treatment with zidovudine may be causes of AIDS.[14] [15] Sabin et al, comparing HIV negative and HIV positive men with haemophilia A, recently rejected this hypothesis,[16] but the debate continues.[17] None of our subjects had received factor VIII or zidovudine; nor was there any evidence of misuse of injected drugs in the population.

The proportion of deaths attributable to HIV in this rural population was 42% among women and 40% among men. The proportions were even higher in those aged 13-44, 72% for women and 66% for men, peaking at close to 80% in both sexes in those aged 25-34. Similar mortality fractions attributable to HIV have been reported in a cohort of women of childbearing age in Rwanda[5]; in an occupational cohort in Mwanza, Tanzania[6]; and in the rural stratum of a population study in Rakai District, Uganda.[12] The profound impact of the HIV-1 epidemic on mortality in rural Uganda is also shown by estimates of life expectancy at birth, which is now only 42.5 years compared with 58.6 years in those who are uninfected. The probability of a 15 year old surviving to the age of 60 (0.39) is about half that of a seronegative person of the same age (0.76).

## Survival

We previously noted the rapid progression from asymptomatic infection or mild disease to death[7]; over half of the patients for whom data were available had one or more major symptoms of AIDS at the medical assessment one year or less before death. The five year follow up data show that infected people of 55 years or more progress to death much more rapidly than younger people (estimated median survival

<3 years $v$ >5 years). Increased rates of progression with age have been observed in several industrialised countries.[16] [17] [18] [19] [20] [21]

No clear trend in survival rate by age group emerged from the analysis of those aged 13-54 who were HIV antibody positive. Only as a larger cohort of those who have seroconverted is followed up for a longer time will possible differences in survival by age in this group become apparent.

Results from studies of survival after infection with HIV-1 among haemophilic and homosexual populations in North America and Europe suggest a median survival time from infection to death of 9-11 years.[22] [23] [24] Comparatively little is known about survival rates in developing countries. The results of some early studies suggested rates similar to those in industrialised countries,[5] [25] [26] [27] 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.[28] We found similar rates for men and women; this again is consistent with reports from industrialised countries.[29] [30] [31] [32]

A recent study describing progression to AIDS and survival after the diagnosis of AIDS in Africans living in London found that their survival was more similar to that of patients born in industrialised countries than to that of patients living in Africa.[33] However, the cohort studied was retrospective, the time of follow up was short, and a fifth of patients were lost to follow up for more than a year, including some who had returned to Africa. Although such studies are useful, large scale prospective studies are needed to understand better the survival experience of people of different ethnic origins living in different countries.

## ► Acknowledgements

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