

HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries?

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Objectives: To describe the progression times of HIV-1 infection from seroconversion to AIDS and to death, and time from first developing AIDS to death in rural Uganda. Also, to describe the proportion of individuals within the cohort dying with AIDS and the CD4 lymphocyte count before death.

Design: A prospective, longitudinal, population-based cohort.

Methods: Since 1990, 107 HIV-prevalent cases, 168 incident cases and 235 HIV-seronegative controls have been recruited into a cohort in rural Uganda. Participants are recruited from the general population and they are reviewed routinely every 3 months and at other times when ill.

Results: The median time from seroconversion to death was 9.8 years. Age over 40 years at seroconversion was associated with more rapid progression ($P < 0.001$, log rank test). For the first 4 years of the study, HIV contributed little to the death rates in the HIV incident cases, but after 5 years, the contribution of HIV became greater and was particularly marked in the oldest age group. Survival rates in the cohort were similar to those in the general population. The median time from seroconversion to AIDS was 9.4 years and from AIDS to death was 9.2 months. Of those infected with HIV-1, 80% died with AIDS and 20% had a CD4 count $< 10 \times 10^6$ cells/l.

Conclusions: Survival with HIV-1 infection is similar in Africa to industrialized countries before the use of antiretroviral therapy; when they do die, many of those in Africa are severely immunosuppressed and most have clinical features of AIDS.

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Introduction

More than 70% of the 30 million adults infected with HIV-1 in the world live in subSaharan Africa and prevalence rates of over 25% have been reported from several African countries [1], yet little is known about the progression of HIV disease on that continent. Although some studies have suggested that HIV-1 infection progresses more rapidly in Africans [2–4], others have found a similar disease progression to that in industrialized countries [5–8]. However, cohorts of individuals with documented negative and positive

HIV tests and hence an estimated date of seroconversion are rare. We are aware of only one study in Africa that has reported the median time from seroconversion to AIDS; this was in a cohort of sex workers in Kenya [9]. Otherwise all reports of survival and AIDS-free time from Africa are based on prevalent cohorts with unknown dates of seroconversion [4,7,10,11].

Uganda was the first government in Africa to acknowledge publicly that an HIV-1 epidemic was occurring in the general population. The political leaders took an active stance, and extensive HIV/AIDS prevention

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programmes were developed through governmental and non-governmental organizations. The high level of HIV/AIDS awareness, which is so obvious in the country today, has probably contributed to the decline in prevalence that has been reported from all over the country, both in sentinel sites and population-based studies [12,13]. The fall has been most pronounced in the younger age groups, a sector that gives a better measure of incidence. In our study area, the prevalence of HIV-1 infection in adults fell significantly from 8.2% in 1989–1990 to 6.9% in 1996–1997, with a non-significant reduction in incident rates from 7.7 to 4.6/1000 person-years of observation over the same period [14]. Despite these encouraging findings, the reality of coping for those who are infected with HIV and of providing treatment remains grim. Although Uganda recently became part of the UNAIDS drug access initiative to reduce the cost of antiretroviral therapy, the per capita GDP (gross domestic product) was around US\$100 in 1999–2000 [15], and so even the subsidized treatment cost is beyond the means of most people. This is particularly so in the rural areas where the majority of Ugandans reside, and where the main occupation is subsistence farming.

Knowledge of progression times and the main clinical problems associated with HIV infection is, therefore, important when trying to plan provision of health services to African populations. This information is also necessary for modelling estimates of the evolution of the epidemic, including the expected number of people living with HIV.

We report rates of progression to AIDS and death in adults with estimated dates of HIV-1 seroconversion enrolled in a clinical cohort in rural Uganda. We also examine the proportion of all participants with HIV infection who died with AIDS, the median survival from first being seen with AIDS and CD4 cell counts before death.

Methods

Selection of participants

Participants were recruited from a large general population study based in rural Uganda. The population study was established in 1989 to investigate the dynamics of HIV-1 infection in a population of around 4500 adults residing in 15 neighbouring villages [16]. This is done by annual HIV serosurveys. In 1990, a random selection of individuals found to be HIV positive at the first round of the population study were enrolled into a clinical cohort as prevalent cases of infection. All seroconverters detected during subsequent annual surveys of the population study were invited to enrol as incident cases, along with randomly

selected, age-stratified, HIV-negative controls for the HIV-infected subjects. The estimated date of seroconversion of the incident cases was taken as the mid-point between the dates of the last HIV-negative and the first HIV-positive test.

Study procedures

Home visitors contacted and explained the nature of the study to selected individuals and then, if they consented to attend the study clinic, the study was again explained by one of two clinicians. At the enrolment visit, all participants gave informed, written (signed or thumbprint) consent. Clinicians reviewed participants every 3 months and completed a detailed questionnaire about their medical and sexual history. At these routine visits, the participants also had a physical examination. After 1995, CD4 lymphocyte counts were routinely performed in the main laboratory 3 h drive away from the study area using FACS-COUNT (Becton Dickinson, San Jose, California, USA). Any complaints or medical findings were investigated and treated. Participants could also attend for free investigation and treatment of illnesses occurring between routine appointments. For each routine visit, HIV-seropositive participants were categorized according to the clinical and performance scale of the proposed WHO staging system [17] using a computer algorithm. AIDS is used synonymously with WHO stage 4. The study provided transport and cost of all hospital referrals for the participants and their families.

For reasons of confidentiality, the HIV status of participants in the cohort was unknown to any of the staff at the clinic. This also reduced reporting biases. All participants were strongly encouraged to attend HIV counselling and testing facilities provided by the project in the study villages.

Statistical analysis

Kaplan–Meier survival methods were used to estimate the median [and interquartile ranges (IQR)], cumulative and survival probabilities [and 95% confidence intervals (CI)] for times to the various endpoints. Log rank test was used to compare survival in different subgroups. All analyses were performed using STATA 6.0. statistical package (Stata Corporation, College Station, Texas, USA).

Analyses of time from seroconversion to AIDS included all incident cases. The endpoint was the date first seen with an AIDS-defining condition, whether at routine or interim visit, and follow-up of an individual was censored at his or her last routine appointment before 31 December 2000.

For time from seroconversion to death, the vital status of all but one of the incident cases of HIV infection was known at the end of 2000, and he was known to

be alive at the end of 1997. His follow-up was, therefore, censored at this date. All the living incident cases were censored at the end of 2000. The age-standardized mortality ratio was computed by linking data from the clinical cohort to the large population cohort from which participants are recruited. In order to take into account the increasing age of the population over the study period, a lexis transformation was performed (whereby each individual contributes to the different age groups as their age increases during follow-up).

A comparison of the incidence of death from seroconversion in different age groups is difficult to interpret because it combines HIV attributable deaths and deaths from other causes. Older age groups would be expected to have a greater proportion of deaths from natural causes; therefore, an HIV-attributable death cumulative incidence was computed by age group. For each year from enrolment, the death rate in the HIV-seronegative controls was subtracted from the death rate in the incident cases. A Nelson–Aalen-like cumulative incidence estimator was then obtained by adding these yearly HIV-attributable death rates.

All HIV-infected participants were used in the analysis of survival from developing AIDS. Participants with AIDS on enrolment were excluded. Time was estimated from first being seen with an AIDS-defining condition to death or last visit. Although most participants had only one AIDS-defining condition, if a participant presented with more than one at the same visit, he or she was included in the analyses for all presenting conditions.

Participants were classified as having died with AIDS if they were in WHO stage 4 at their last routine visit or, if they were not, from their medical records held at the clinic or information about the nature of their final illness from family and friends.

To compare survival of people in the cohort, who have regular follow-up and open-access to medical facilities, with those in the general population, who do not, all prevalent cases in the general population study who were infected with HIV-1 during the initial round of analysis in 1989–1990 were considered (cohort joiners and non-cohort). At the end of September 2000, the survival of prevalent cases who were randomly selected and joined the cohort between 1 October and 31 December 1990 was compared with the other prevalent cases not selected for enrolment (but still alive on 1 October 1990). People who were selected but did not enrol were excluded. As for participants in the cohort, home visitors contacted the family and friends of individuals who had moved out the study area to find out if they were still alive and, if they were not, when they died.

Results

By the end of 2000, 107 prevalent and 168 incident cases of HIV-1 infection and 235 HIV-seronegative controls had been enrolled into the cohort. Details of these participants are given in Table 1. The male incident cases were significantly older than the females ($P < 0.001$, Mann–Whitney), which reflects the transmission pattern of HIV in this rural community. At enrolment, 82 (77%) prevalent and 143 (85%) incident subjects were asymptomatic. Compliance rates have remained high throughout the study. During 2000, there were 1137 visits made out of 1230 scheduled visits for available participants, making the compliance rate 92.4%.

The 168 incident cases had a median of 12.3 months (IQR, 11.0–24.2) between the last negative and first positive HIV-1 test. The median period between the

Table 1. Numbers of participants in each age group on enrolment by gender and HIV category.

Age (years)	Prevalent	Incident	Negative	TOTAL
15–24	26	55	65	146
Males	9	13	26	48
Females	17	42	39	98
25–39	52	75	91	218
Males	36	47	51	134
Females	16	28	40	84
40–54	20	27	37	84
Males	11	16	23	50
Females	9	11	14	34
55 and over	9	11	42	62
Males	4	7	25	36
Females	5	4	17	26
Median age (IQR)	31.3 (25.3–41.0)	29.5 (23.6–38.2)	32.2 (24.3–45.3)	31.2 (24.4–42.4)
Males	31.7 (28.1–40.0)	31.4 (26.1–41.6)	35.4 (26.3–49.6)	32.4 (26.4–44.0)
Females	30.4 (23.4–42.8)	25.1 (22.0–35.1)	28.4 (23.3–41.9)	28.0 (22.4–38.9)
Total number	107	168	235	510

IQR, interquartile range.

estimated date of seroconversion and enrolment into the cohort was 12.9 months (IQR, 8.0–22.0). The median follow-up from seroconversion was 5.6 years (IQR, 3.6–7.3).

Of the incident cases, 44 developed AIDS. The median time from seroconversion to AIDS was 9.4 years (IQR, 5.5–10.1). The cumulative probability of AIDS was 22% (95% CI, 16–31), 36% (95% CI, 27–46) and 45% (95% CI, 34–57) at 5, 7 and 9 years, respectively, following seroconversion. Older age group (≥ 40 years) at seroconversion was associated with a faster progression to AIDS ($P < 0.001$, log rank test).

Among the incident cases, 47 died during 920.7 person-years of follow-up (age-standardized mortality rate 67.0/1000 person-years). The median survival from seroconversion was 9.8 years (IQR, 6.1 to > 10.3). The cumulative probability of death from seroconversion is shown in Fig. 1.

There were 10, 18 and 19 deaths among of 65, 68 and 35 participants in age groups 15–24, 25–39 and ≥ 40 years, respectively, at seroconversion. The cumulative probability of survival in each age group at 7 years was 79% (95% CI, 63–88), 72% (95% CI, 56–83) and 20% (95% CI, 6–40), respectively (Fig. 2). There was a lower probability of survival in the older age group compared with the younger age groups ($P < 0.0001$, log rank). Nineteen HIV-seronegative controls died during 1720.6 person-years of follow-up and the cumulative survival at 7 years was 92% (95% CI, 87–95). The age-standardized mortality rate was 8.5/1000 person-years. A significantly higher death rate was also seen in the HIV-seronegative controls aged ≥ 40 years on enrolment ($P < 0.0001$, log rank test). The HIV-attributable cumulative incidence of death is shown in Fig. 3. This shows that HIV-1 contributes little to the

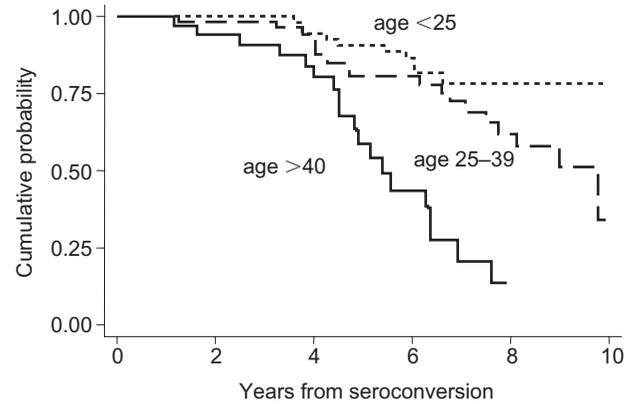


Fig. 2. Cumulative probability of survival by age group at seroconversion.

death rates in the HIV incident cases for the first few years in the cohort but then its contribution becomes greater; this is particularly marked in the oldest age group.

All together, 90 HIV-seropositive participants developed AIDS during follow-up. The median survival from developing AIDS to death was 9.2 months (IQR, 2.2–23.6). A CD4 lymphocyte count at, or within 3 months, of developing AIDS was available for 70 participants; the median count was 126×10^6 cells/l (IQR, 40–318). Survival was 3 to 4 months for those whose AIDS-defining conditions were wasting syndrome, candidiasis of the oesophagus and Kaposi's sarcoma. However, survival was over 20 months for participants with chronic herpes simplex virus infections and extrapulmonary tuberculosis as their AIDS-defining conditions. We have shown previously that survival depended on the initial AIDS-defining illness and there was little relationship between median

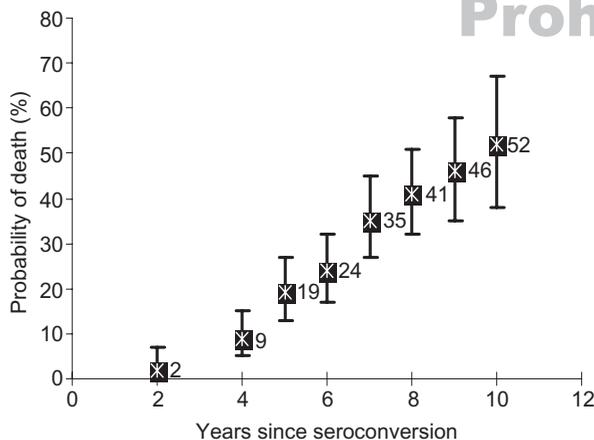


Fig. 1. The cumulative probability of death (95% confidence intervals) from seroconversion.

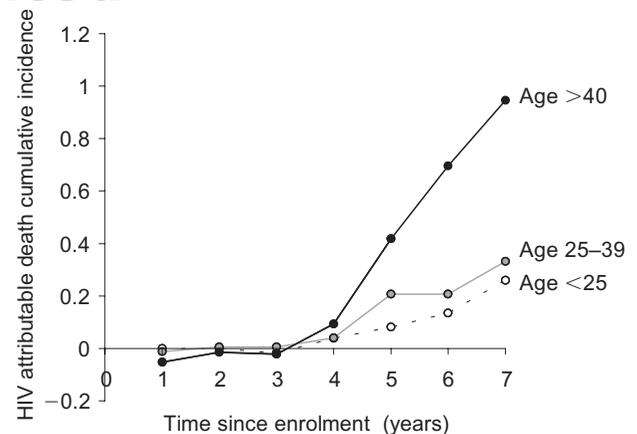


Fig. 3. HIV attributable incidence of death by age group.

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survival and the CD4 cell count of the AIDS-defining conditions [18].

Of the 121 HIV-seropositive participants who died, 74 (61%) had AIDS at their last routine clinic visit. A further 11 had a history from relatives of an AIDS-like illness before death; for 15 a cause of death could not be ascertained. Consequently, 80% (85/106) of HIV-infected participants were in WHO stage 4 at their last visit or were reported to have died with AIDS.

The last recorded CD4 cell counts within 6 months before death were available for 68 HIV-seropositive and 12 HIV-seronegative participants. The median CD4 cell count before death was 61×10^6 cells/l (IQR, 17–199) for the HIV-seropositive individuals and 716×10^6 cells/l (IQR, 581–1103) in the HIV-seronegative controls. The CD4 cell count was $< 10 \times 10^6$ cells/l prior to death in 22% of the HIV-infected participants.

A comparison of the survival of the 71 prevalent cases who joined the cohort between 1 October and 31 December 1990 and the 126 subjects who were not invited is shown in Fig. 4. There was no difference in survival times ($P = 0.63$, log rank test). Although there was a greater proportion of males in the cohort group ($P = 0.009$, chi-squared test) because of preferential selection aiming to recruit similar numbers of males and females, there was no difference in age group distribution ($P = 0.44$, chi-squared test). Many had moved away from the study area either permanently or for varying periods of time. Two individuals, one who joined the cohort and one who did not, were lost to follow-up. Another, not invited to join the cohort, was known to have died, but the date of death was not known. These three individuals were, therefore, excluded from the analysis.

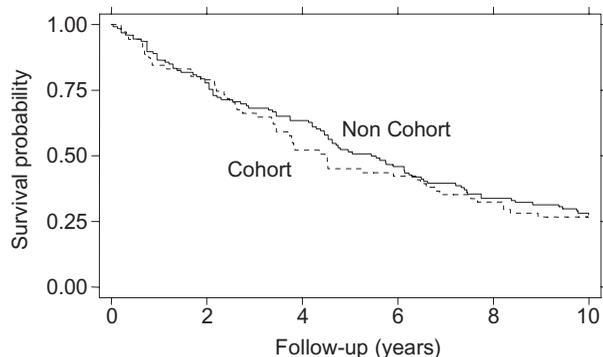


Fig. 4. A comparison of survival of prevalent cases of infection found to be infected in 1989–1990 and who joined the cohort with those who did not join.

Discussion

This is the first report of median survival with HIV-1 infection in an incident population-based cohort in Africa. The median survival from seroconversion was 9.8 years, which shows that HIV infection is not a more rapidly progressive disease in Africans. Once AIDS developed, the median survival was only 9.2 months, which is similar to that reported early in the epidemic in industrialized countries although much shorter than survival in these countries now. The majority of HIV-infected persons die with AIDS and they often have very low CD4 cell counts at the time of death.

This cohort has a number of strengths. It provides 10 years of longitudinal data on a rural population-based cohort. There are 168 incident cases with dates of seroconversion that have been followed for a median of over 5.5 years. There is an HIV-seronegative control group to measure background rates of morbidity and mortality in the population. Participants are seen routinely every 3 months and compliance is good, with over 90% of those available in the study area being seen at routine visits. There are data on 9334 routine visits, 4195 in HIV-seropositive participants. Follow-up is comprehensive; intensive, detailed clinical case notes are kept at the clinic and information about interim visits is recorded on the questionnaire. CD4 lymphocyte counts and microbiological diagnoses were also available for the last 5 years of the study. A network of home visitors followed people not seen at routine appointment. By the end of 2000, the vital status was known for all but two of the HIV-infected participants.

Comparing progression times in the cohort with those reported from industrialized countries is problematic since progression to AIDS and death depends on frequency of follow-up and mode of transmission, available treatment and chemoprophylaxis in the cohort being studied. Most cohort studies reporting from industrialized countries are from one exposure group or, if composed of several exposure groups, have few individuals with HIV-1 acquired by heterosexual transmission and, therefore, median survival for this group is not readily available. Some studies have reported a difference in survival between different transmission categories [19,20], but age at seroconversion is thought to be a major factor explaining these differences [21]. Comparing times to AIDS is further complicated by changes and different definitions of AIDS employed by each study. The median time to AIDS was 9.4 years in our Ugandan cohort. This is comparable with cohorts in industrialized countries before the better management of HIV infection, when the median survival to AIDS was around 9 or 10 years but ranged from 5.7 to over 12 years [19–25]. We found that the median survival from seroconversion to death was 9.8 years,

which is considerably longer than has been expected in African populations. This is also comparable to survival times of around 10 years (ranging from 8.3 to approximately 13 years) reported by cohort studies in industrialized countries prior to the widespread use of antiretroviral therapy [19,23–24,26]. Several studies have shown that age at seroconversion is a major factor in determining survival, with wide survival differences between younger and older age groups [22,26]. If survival by age group at seroconversion is considered in our cohort, there is no statistical difference in survival between the younger age groups, but those aged ≥ 40 years at seroconversion had a much lower survival. Older people are more likely to die irrespective of HIV disease; to remove this confounding factor, the HIV-attributable cumulative incidence was determined. This was minimal for the first 4 years in the study but increased thereafter, with the greatest effect in those aged ≥ 40 years at seroconversion.

The survival rates in the cohort were achieved by regular clinical review and prompt treatment of conditions diagnosed using basic laboratory facilities and standard drugs from the WHO essential drug list, which should be available in any health post throughout Africa. Participants also received intensive treatment even if it was suspected that they were in late-stage disease. Treatment was free because, in this very poor area, even a minimal charge for treatment would deter patients seeking care for frequent HIV-related events. It was, therefore, disappointing to find that survival was similar in the participants who formed the randomly selected prevalent HIV-seropositive cases of the cohort in 1989–1990 to that in prevalent cases who were not invited to join the cohort. Home visitors contacted friends and relatives of those who had enrolled in the cohort and had not been seen in the clinic, and so if they had died we would have heard about it shortly after the death. For those who did not enrol and were not living in the study area, home visitors made enquiries of family and friends during October 2000, so many of those who had died had done so several years before. Therefore, there may have been recall bias but this is unlikely for something as important as approximate date of death. Consequently, although considerable thought has been given to identifying possible biases, we do not have a good explanation of this lack of difference. However, it is a common and major assumption that medical care is very effective in reducing morbidity and mortality, whereas, on a population basis, social and economic interventions are more likely to produce changes in mortality [27]. It does mean, though, that our findings are likely to be representative of survival in the general population.

The median survival from developing AIDS in the cohort was 9.2 months. Although short, this is similar

to the average of 10 months reported in industrialized countries early in the HIV epidemic [28–30]. However, the course of AIDS in developed countries has changed with better management of HIV infection through the use of prophylaxis and antiretroviral drugs. Survival after an AIDS diagnosis in the United Kingdom increased from 10.6 months before 1987 to over 19 months in 1991 [31]. The survival of Africans attending a clinic in London was 22 months from attending with an AIDS-defining condition [32]. With highly active antiretroviral therapy, the incidence of AIDS has been reduced further and the survival with AIDS has been prolonged [33]. Of participants for whom a cause of death could be ascribed, 80% died with AIDS. This is in contrast to three other studies in Africa, where only 11% [34], 46% [7] and 66% [10] of deaths in HIV-positive subjects were reported to have been caused by AIDS, based on the WHO (Bangui) clinical case definition. In our study, we used the WHO staging system (which needs a positive HIV-1 test) [17]. This, plus the coverage and frequency of follow-up, probably accounts for the higher proportion of deaths from AIDS in our study. As we have seen, survival following AIDS is usually short in Africa; therefore the frequency and quality of follow-up will determine the proportion of deaths with AIDS that are identified

The median CD4 cell count within 6 months of death was 61×10^6 cells/l. However, a quarter of those who died had a count of $< 17 \times 10^6$ cells/l and some of these people survived many months with CD4 cell counts of this level. In a study of hospital admissions in Abidjan, the majority of persons with HIV had profound immunosuppression, as indicated by admission with a median CD4 cell count of 84×10^6 cells/l [35]. Therefore, again contrary to first thought, people in Africa do survive, and often for quite long periods, with very low CD4 cell counts.

In conclusion, our study shows that African adults infected with HIV-1 survive on average around 10 years after seroconversion; when they do die, many are severely immunosuppressed and most have clinical features of AIDS.

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