Survival of HIV-infected treatment-naive individuals with documented dates of seroconversion in Rakai, Uganda

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Objective: To estimate the survival time from HIV infection to death.

Methods: A community cohort in Rakai district, Uganda, identified 837 seroconverters followed annually between 1995 and 2003 until they died, were censored by out-migration or truncated on 31 December 2003 because antiretroviral treatment became available. HIV-1 subtype was determined by multiple hybridization assay for 396 seroconverters. The median interval from infection to death was estimated by Kaplan–Meier survival analyses and Weibull models. Hazard ratios (HR) and their 95% confidence intervals (CI) associated with survival were estimated using Cox proportional hazards modeling

Results: There were 122 deaths over 2330 person-years (py), an average mortality of 5.2/100 py. The median survival time was 8.7 years (95% CI 8.1–9.3), and did not differ by sex, place of residence or time period of seroconversion. Survival time decreased significantly with older age at infection ($P = 0.01$). Survival was shorter with subtypes D, AD recombinant or multiple infections compared with subtype A (log rank $P = 0.04$), but this was of borderline significance after adjustment (adjusted HR 3.47, 95% CI 0.89–15.44, $P = 0.07$). Non-A subtypes constituted 84.6% of all identifiable infections and had a median survival time of 7.5 years (95% CI 6.4–8.5), whereas over 90% of those infected with subtype A were still alive 7 years post-infection.

Conclusion: The median survival time in Rakai was shorter than reported in other African populations, and we hypothesize that this may be a result of the predominance of non-A subtypes with faster disease progression in this population.

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Introduction

Data on the survival of HIV-infected, treatment-naive individuals in sub-Saharan Africa are needed to provide guidance on the initiation of antiretroviral treatment (ART), to evaluate the effects of treatment on mortality and to project future needs for ART services. Such information is also needed for modeling the epidemic.

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Studies suggest that survival time from infection to death in sub-Saharan Africa [1–5] may be comparable to those observed in developed countries before the availability of ART [6], but shorter survival times have been reported among commercial sex workers in Kenya [7] and blood donors or military recruits in Thailand [8–10]. Older age is also associated with faster progression [6] and some data suggest that progression might differ by HIV subtype [11–15].

We previously reported on mortality rates by age and HIV status [16]. In this paper we describe survival among individuals with known dates of seroconversion between 1995 and 2003, and explore differentials by sex, age at seroconversion, place of residence, time period of infection and HIV subtype.

Methods

Since November 1994, the Rakai Community Cohort Study has conducted annual surveillance in an open cohort of individuals aged 15–49 years, resident in 50 communities in rural Rakai district of southwestern Uganda. The cohort has been described in detail elsewhere [17]. Eligible individuals were identified by annual censuses and consenting participants were administered a sociodemographic and behavioral questionnaire, and provided a venous blood sample for HIV testing. The population under annual surveillance varied from 10 000 to 14 000, because over time the cohort was adapted to specific studies and constrained by available financial resources in some years. The Rakai Health Sciences Program provided health education on HIV prevention, free voluntary HIV counseling and testing, free condoms and syndromic management of sexually transmitted diseases. ART became available in 2004, so analysis of deaths was truncated on 31 December 2003 to assess the survival of ART-naive HIV-infected individuals. Before 2004, the Program was only able to provide treatment for limited opportunistic infections and palliative care.

HIV seroconversion was determined by two separate enzyme immunoassays, with Western blot confirmation. Although the specific enzyme immunoassays and Western blot tests changed over time, the testing algorithm remained constant. In 396 individuals, whose serum samples had sufficient HIV RNA for reverse transcriptase polymerase chain reaction amplification, we were able to identify the viral subtype. These samples were obtained from seroconverters in HIV-discordant couples identified between 1995 and 1998 and for all seroconverters between 1999 and 2002, but costs of the multiple hybridization assay (MHA) precluded subtying of other samples. We determined HIV-1 subtype using MHA_{acd} [18,19]. Subtypes were classified as A, C, D, AD recombinants, and multiple infections. Earlier analyses of Rakai data suggested that subtypes D, AD recombinants and multiple infections have similar disease progression rates [11], and in this study population there were only two individuals with subtype C, so for analysis purposes we compared A with non-A virus subtypes.

The study was approved by four institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the National Council for Science and Technology (Kampala, Uganda), the Committee for Human Research at Johns Hopkins University, Bloomberg School of Public Health (Baltimore, MD, USA), and the Western Institutional Review Board (Olympia, WA, USA).

Statistical analyses

This analysis focuses on initially HIV-negative individuals who seroconverted between 1995 and 2002, and death among seroconverters between 1995 and 2003. The date of seroconversion was defined as the mid-interval between the last negative and the first positive HIV test. Age at seroconversion was calculated from the difference between the seroconversion date and the date of birth, and was categorized into 15–24, 25–29, 30–39 and 40+ year age groups. Residence was stratified into rural communities on secondary roads and urban communities on main roads.

Incident cases with no follow-up information after seroconversion ($n = 2$) and those with missing date of birth ($n = 2$) were excluded from this analysis. Individuals who outmigrated were censored at time of exit from the study, and follow-up time was truncated on 31 December 2003 just before ART became available to the population. Death from any cause was considered the outcome event of interest.

All analyses used Stata version 9 (Stata Corp., College Station, Texas, USA). Survival probabilities were estimated using Kaplan–Meier survival methods and the log-rank test was used to test for equality of survival functions between covariates of interest (e.g. sex, age, residence, time period and HIV subtype). Median survival times, interquartile ranges and 95% confidence intervals (CI) were estimated from the Kaplan–Meier analyses [20,21]. If the median survival could not be ascertained using a Kaplan–Meier analysis we used parametric regression to fit a Weibull distribution and extrapolate survival proportions to obtain an estimate of the median survival time and 95% confidence intervals [4]. Both the slope and shape parameters were considered for calculating the 95% confidence intervals for the median time of survival. Cox proportional hazards regression models were used to estimate hazard ratios (HR) of death associated with covariates of interest. Adjusted models included covariates found to be significant at $P < 0.15$ in univariate analyses, or covariates reported to be associated with survival in other studies.

Results

The distribution of seroconversions and deaths by year are shown in Table 1. The variation in the number of annual seroconversions partly reflects changes in the population under surveillance, as well as trends in HIV incidence. (HIV incidence declined from approximately 2.0 per 100 person-years in 1995–1996 to approximately 1.3 per 100 person-years in 2002, and prevalence declined from 17.7% in 1995 to 12.8% in 2003.) A total of 837 seroconverters were identified and these individuals provided 2330 person-years of observation, with a median follow-up time of 6.7 years (interquartile range 3.9–8.5 years). Of the 837 seroconverters, 480 (57.3%) were women and 357 (42.7%) were men (Table 2). As of data cutoff on 31 December 2003, 122 seroconverters had died (14.6%), with an average annual mortality rate of 5.2 per 100 person-years. The total number of HIV-negative individuals followed was 29 123.

Figure 1 shows the Kaplan–Meier and Weibull survival curves for the whole population. The median time from infection to death could not be ascertained using Kaplan–Meier analysis, but the first quartile (75% survival) was 5.5 years (95% CI 5.0–6.2). The Weibull estimated median survival time was 8.7 years (95% CI 8.1–9.3). There was no difference in survival between men and women ($P = 0.19$, Fig. 2). As shown in Fig. 2, the probability of survival decreased with older age at infection ($P = 0.01$). For individuals infected at the age of 40 years or more, the hazard ratio of death was 2.21 (95% CI 1.34–3.65), compared with individuals infected at ages 15–24 years. There was a significant trend towards lower survival with increasing age. There were no differences in survival by place of residence ($P = 0.36$), or time period of infection (1995–1998 versus 1999–2003, $P = 0.7$, results not shown).

Subtype information was available for 396 individuals, of whom 61 (15.4%) were subtype A, 231 (58.3%) were subtype D, 80 (20.2%) were AD recombinants, 22 (5.6%) were multiple infections (i.e. two or more viral strains) and two (0.5%) were subtype C. For the purpose of analysis we compared subtype A with all non-A subtypes combined, because the latter have similar disease progression rates [11]. As shown in Fig. 3, survival was significantly lower for non-A compared with A infections (log rank $P = 0.04$). There were only two deaths among the 61 subtype A infections (3.2%), compared with 42 deaths among the combined non-A infections (12.5%), and the unadjusted hazard ratio of death for D and AD versus A infections was 3.88 (95% CI 0.94–16.03, $P = 0.06$). The median survival time was 7.5 years (95% CI 6.4–8.5) for the combined non-A infections, whereas over 90% of subtype A seroconverters were still alive 7 years after infection, the latest estimate for which direct observations are available.

In a multivariable Cox model, applied to the 396 seroconverters with known viral subtypes, no individual covariates were significantly associated with death, but the adjusted hazards of mortality were of borderline significance for individuals aged 40 years or older at the time of infection (adjusted HR 2.27, 95% CI 0.94–5.48, $P = 0.07$), and for infections with non-A subtypes (adjusted HR 3.47, 95% CI 0.89–15.44, $P = 0.07$).

Table 1. Number of seroconverters, cumulative numbers of individuals at risk, deaths by year and sex plus general characteristics of individuals at risk.

Year of seroconversion	No. of seroconverters	Cumulative numbers at risk	Deaths	Numbers censored
1995	67	67	0	0
1996	134	201	0	3
1997	125	323	4	13
1998	119	425	12	50
1999	81	444	6	34
2000	118	521	16	22
2001	107	591	27	23
2002	86	627	30	59
2003	Na	538	27	511
Total	837	3738	122	715

Table 2. Characteristics of the individuals at risk.

Characteristics	*N*	%
Sex		
Women	480	57.4
Men	357	42.7
Age group (years)		
15–24	335	40.0
25–29	200	23.9
30–39	194	23.2
40+	108	12.9
Year of infection		
1994–1998	445	53.2
1999–2003	392	46.8

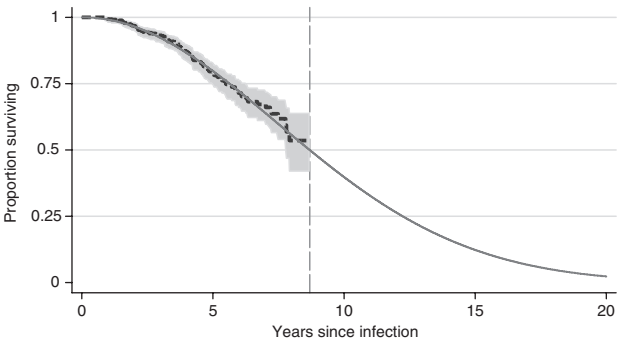

Fig. 1. Kaplan–Meier survival curves and Weibull model fit for the whole population of HIV seroconverters. 95% Confidence interval; ----- survivor function; —— Weibull model fit.

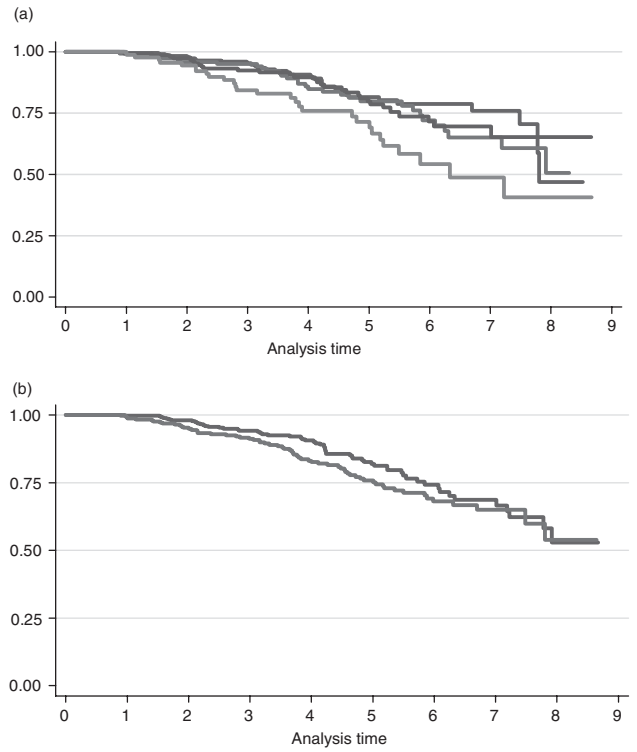

Fig. 2. Kaplan–Meier survival curves by age at infection and by sex. (a) Probability of survival by age group. —— 15–24 years; —— 25–29 years; —— 30–39 years; —— 40+ years. (b) Probability of survival by sex. —— Women; —— men.

Discussion

We found a median survival time of 8.7 years from infection to death among a large cohort of seroconverters with known dates of HIV infection. Survival time was reduced among individuals infected at older ages and in those infected with non-A viral subtypes (median survival of 7.5 years).

The median survival time in this rural population is very close to that observed in nearby Masaka district (9.1 years)

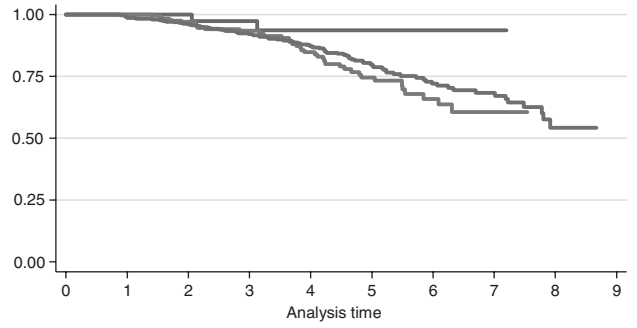

Fig. 3. Kaplan–Meier survival curves by A and non-A HIV-1 subtype infections. —— Subtype A; —— non-A subtype; —— unknown subtype.

[22], but is lower than that reported in the rural population of Kisesa, in Tanzania (11.5 years) [4]. Our estimates of survival times are also lower than those for mine workers in South Africa (11.6 years), and for high-income country populations in the pre-ART era [5,6]. The 8.7 year median survival time in Rakai was, however, higher than that observed among commercial sex workers in Kenya [7] and in Thai studies [8–10]. For the non-A subtypes, the 7.5 years (95% CI 6.4–8.5) survival time is less than the lower 95% confidence interval estimated for the other sub-Saharan African countries [1,4,5], and conversely, the upper 95% confidence interval for the non-A subtypes is lower than the point estimates for the other African population. The reasons for this diversity in estimated survival times between African populations is unclear. These differences might be partly the result of methodological considerations or insufficient follow-up time in some studies. We hypothesize that the predominant circulating viral subtypes in different populations might affect the course of HIV disease and thus overall survival. Studies in Uganda [11,13,14], Tanzania [12] and Kenya [15] consistently show faster disease progression with subtype D than subtype A. In Kenya, the median survival time with subtype D was 7.7 years [15], which is comparable to the 7.5 years median survival for non-A subtypes observed in the present study. The divergence of survival estimates between African populations could thus reflect differences in the predominant HIV-1 subtypes, because a higher prevalence of subtype A infections with slower disease progression would increase the estimated survival time for the population as a whole. There are major differences in the epidemiology of circulating HIV-1 subtypes. The Rakai epidemic has a unique predominance of non-A subtypes (84.6%), with only 15.4% subtype A infections. In Masaka, to the north of Rakai, subtype A constituted 36–40% of infections [13,14], in Dar es Salam, Tanzania, 27.3% of infections were subtype A [12], and in Kenya, 78% of infections were caused by subtype A [15]. Moreover, in the Tanzanian and Kenyan studies [12,15], subtypes A and C infections did not differ in rates of disease progression, suggesting that D or AD viruses may be uniquely pathogenic. It has been shown that subtype D and AD recombinant viruses preferentially utilize CXCR4 receptors, which are associated with more advanced disease, whereas subtype A viruses do not demonstrate CXCR4 receptor tropism [11]. There is a great diversity of viral subtypes in sub-Saharan Africa, with predominant C epidemics in southern Africa, A and D epidemics in east–central Africa and multiple subtypes in west Africa [23,24]. Survival from infection to death may thus vary between African populations, possibly depending on the predominant viral strains in each setting. In addition, differential viral subtype pathogenicity might also account for the shorter survival times in Thailand, where most infections are subtype E, which is also thought to be more pathogenic than other viruses [25].

In summary, we found lower survival times in rural Rakai than in other African and European populations. Non-A subtypes appear to have lower survival times compared with subtype A viruses, and it is possible that median survival time estimates differ depending on the predominant viral subtype in the population.

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Conflicts of interest: None.

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