Published in final edited form as:

AIDS. 2007 November ; 21(Suppl 6): S55–S63. doi:10.1097/01.aids.0000299411.75269.e8.

Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy

Jim Todd^a, Judith R. Glynn^b, Milly Marston^{b,c}, Tom Lutalo^d, Sam Biraro^a, Wambura Mwita^c, Vinai Suriyanon^e, Ram Rangsin^f, Kenrad E. Nelson^g, Pam Sonnenberg^{b,h}, Dan Fitzgeraldⁱ, Etienne Karita^j, and Basia aba^{b,c}

^aMRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda ^bLondon School of Hygiene and Tropical Medicine, London, UK ^cNIMR, Mwanza, Tanzania ^dRakai Health Sciences Program, Rakai, Uganda ^eResearch Institute for Health Sciences, Chiang Mai University, Chiang Mai, Thailand ^fPhramongkutklao College of Medicine, Phramongkutklao, Thailand ^gJohns Hopkins University Bloomberg School of Public Health, Baltimore, USA ^hUniversity College London, London, UK ⁱGroupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO), Haiti ^jProject San Francisco, Kigali, Rwanda

Abstract

Objectives—To estimate survival patterns after HIV infection in adults in low and middle-income countries.

Design—An analysis of pooled data from eight different studies in six countries.

Methods—HIV seroconverters were included from eight studies (three population-based, two occupational, and three clinic cohorts) if they were at least 15 years of age, and had no more than 4 years between the last HIV-negative and subsequent HIV-positive test. Four strata were defined: East African cohorts; South African miners cohort; Thai cohorts; Haitian clinic cohort. Kaplan–Meier functions were used to estimate survival patterns, and Weibull distributions were used to model and extend survival estimates. Analyses examined the effect of site, age, and sex on survival.

Results—From 3823 eligible seroconverters, 1079 deaths were observed in 19 671 person-years of follow-up. Survival times varied by age and by study site. Adjusting to age 25–29 years at seroconversion, the median survival was longer in South African miners: 11.6 years [95% confidence interval (CI) 9.8–13.7] and East African cohorts: 11.1 years (95% CI 8.7–14.2) than in Haiti: 8.3 years (95% CI 3.2–21.4) and Thailand: 7.5 years (95% CI 5.4–10.4). Survival was similar for men and women, after adjustment for age at seroconversion and site.

Conclusion—Without antiretroviral therapy, overall survival after HIV infection in African cohorts was similar to survival in high-income countries, with a similar pattern of faster

Correspondence to Jim Todd, Box 49, Entebbe, Uganda. jim.todd@mrcuganda.org.

Conflicts of interest: None.

progression at older ages at seroconversion. Survival appears to be significantly worse in Thailand where other, unmeasured factors may affect progression.

Keywords

HIV seroconversion; survival; Africa; resource-poor countries; pre-HAART

Introduction

HIV/AIDS is a major cause of death in many low and middle-income countries, and yet the natural history of the infection, and survival of people infected with HIV are not well defined in these countries [1]. Accurate estimates of the survival of HIV-infected individuals in resource-poor countries are needed for public health planning, including estimating the need for antiretroviral drugs, and as a baseline for assessing the effects of interventions.

The CASCADE collaboration compared survival patterns from 38 studies in HIV-infected individuals in high-income countries before the general availability of antiretroviral therapy (ART) [2]. The overall median survival time was 11.2 years. This showed that median survival after HIV seroconversion in 15 high-income countries varied considerably by age at seroconversion, but not by sex or by route of infection.

In 2000, Morgan *et al.* [3] reported a median survival time of 9.8 years in a representative population-based cohort of HIV seroconverters in rural Uganda. The dataset was, however, too small to make comparisons between ages, sex or other factors of interest. Two other African studies have estimated survival times from cohorts of seroprevalent cases [4,5]. A study in sero-incident South African miners recently showed a median time between seroconversion and death of 10.5 years [6], whereas two studies in Thailand, and one in Haiti, showed shorter survival times [7–9]. A further study in Kenyan sex workers showed that 75% survived 6.6 years, and 51% survived 8.7 years [10].

Two reviews of the natural history of HIV-1 in Africa, in 2001 and 2004, concluded that survival is comparable with survival in high-income countries before ART [11,12]. As a result of a lack of data, however, insufficient account may have been taken of different ages at infection. A review by Porter andaba [13] concluded that survival times for HIV-infected individuals in low and middle-income countries may be 10–20% lower than in high-income countries. There are many reasons for suspecting faster progression in low and middle-income countries: higher setpoint plasma viral loads [10,14], breastfeeding [15], micronutrient deficiency [16], virus subtype [17,18] and co-infections [19] may all affect survival and are associated with HIV infection in Africa. It is only by combining the data and carrying out common analyses that survival patterns can be explored in detail. In this paper, we use pooled data from eight (published and unpublished) studies to describe survival in large numbers of seroconverters from several low and middle-income countries, allowing exploration of the effects of age, sex and setting on survival.

Methods

As part of the ALPHA network (Analysis of Longitudinal Population-based HIV data in Africa), sites that could identify new HIV seroconverters from repeated cross-sectional surveys and had at least 2 years of follow-up were identified. In addition, researchers following seroconverter cohorts were identified from publications or conference presentations. From the 12 cohorts identified, we included eight studies: three community-based studies from the ALPHA network, two occupational cohorts and three clinic cohorts. The community studies, all in East Africa, had each conducted between five and 17 serological surveys involving a total of 107 464 cohort members (Table 1). Two of these studies (Masaka and Rakai) conducted demographic follow-up concurrent with the serosurveys [20,21], whereas the other (Kisesa) conducted separate demographic surveys of the population two or three times a year [22]. The two occupational cohorts (South African miners and Thai military) identified HIV seroconverters from records taken in the course of employment, and used employment data, national vital registration and active follow-up to determine the survival status of the seroconverters [6,7]. Three studies identified and followed up a cohort of seroconverters from clinic records: a Thai cohort of blood donors and their spouses [8], a cohort of women attending a maternal and child health (MCH) clinic in Rwanda [23], and a Haitian cohort of patients making repeated visits to an HIV testing centre and their partners [24]. Individual-level data from these eight studies were brought together for a pooled analysis using common criteria and methods. For the pooled analyses, the four East African studies (the three population based studies and the study in Rwanda) were grouped together and the two Thai studies were grouped together.

From each of the studies, the criteria for defining seroconversion and the date of seroconversion has been described in detail elsewhere [3,6–9,20–24]. Most studies defined the date of seroconversion as half way between the last negative and the first positive HIV test, and this was accepted for the pooled analysis. In the Thai blood donors study some cohort members were enrolled if a previous HIV-negative result from another clinic was able to be confirmed, and the study HIV-positive test result was within 2 years of the start of the HIV epidemic (taken as 1 December 1988 by the study investigators), or the start of sexual activity or of the husband's HIV-positive status [8].

Age at seroconversion was grouped into 5-year age groups. For the African studies four age groups were subsequently used: 15–24, 25–34, 35–44 and 45 years and above; but for the two Thai studies two age groups were used: 15–24 years, and 25 years and above. There was considerable variation in age across the sites. The analysis was adjusted to age 25–29 years, the age at which most infections occurred, to make comparisons between sites. For the African studies, in which seroconversions were observed over more than 5 years, the seroconversion period was split into two calendar periods, to represent earlier and later phases of the epidemic, and survival patterns were compared between the two periods.

Selection of individuals and right censoring

All HIV seroconverters identified in the eight studies were included in the analysis if they were at least 15 years of age at the estimated date of seroconversion and if the interval between the last HIV-negative test and the first HIV-positive test was less than 4 years.

Individuals were excluded if there was no follow-up information after their first HIV-positive test. All subjects were censored at the date of death, the end of the study, or when they were last known to be alive. Data on ART initiation were not recorded for individual subjects, but for all studies observation was limited to the period before ART became widely available, for example, at the beginning of 2004 for the studies in Uganda (Masaka, Rakai) and South Africa, at the beginning of 2005 for the study in Kisesa, Tanzania, and on 1 September 2003 for the Rwandan study.

Analysis methods

Detailed analysis of the individual study cohorts is described elsewhere [3,6–9,20–24]. Although the analysis calculated survival since the estimated date of seroconversion, individuals entered the analysis at the time of the first positive test (left truncation). For this analysis, Kaplan–Meier functions were used to calculate survival patterns, and the log-rank test was used to compare survival between groups. The Weibull distribution was fitted using parametric regression techniques and was used to model survival and to compare the effects of age at infection, sex and calendar time of infection. Crude and adjusted hazard rate ratios (HRR) are presented, with 95% confidence intervals (CI) and *P* values to compare differences between sites, age groups and sex. All analysis was undertaken using Stata 9.0 (Stata Corp., College Station, Texas, USA). Estimated survival times were taken from the model parameters.

Results

From all eight studies a total of 4110 individuals seroconverted, of whom 287 were excluded from the analysis; 64 because they were under 15 years of age at seroconversion, 230 because the seroconversion interval (time between the last negative HIV test and the first positive HIV test) was longer than 4 years, and one because no follow-up data had been obtained (Table 1).

A total of 3823 eligible seroconverters were included in the analysis (Table 2). The characteristics of the seroconverters differed between the studies, with the occupational cohorts being entirely male, the MCH cohort entirely female, and a younger median age at seroconversion in the Thai studies. Subsequent to seroconversion there was a total of 22 156 person-years of follow-up, of which 19 671 were observed after the date of the first HIV-positive test. In total, 1079 deaths were observed, with a median survival time across all studies of 10.2 years (95% CI 9.7–10.5 years).

The survival curves (Fig. 1a) differed between the sites (chi-squared 36.4, 7 df, $P < 0.001$), with a median survival of 10.3 years in the four East African studies, 10.5 years in South African miners, 7.9 years in the two Thai studies and 7.4 years in Haiti. These differences were mostly a result of the difference between African and non-African sites (chi-squared 18.5, 1 df, $P < 0.001$). Figure 1b shows the Kaplan–Meier survival curves for the pooled East African sites, the South African miners, the two Thai sites combined and the Haitian site, all adjusted to age 25–29 years at seroconversion. After adjusting to age 25–29 years at seroconversion, the difference between the African sites and the Thai sites becomes more apparent, with the adjusted median survival time of 11.1 years in East Africa (95% CI 8.7–

14.2), 11.6 years in South Africa (95% CI 9.8–13.7), 7.5 years in Thailand (95% CI 5.4–10.4) and 8.3 years in Haiti (95% CI 3.2–21.4).

The effect of age on survival was further explored. Using the age at infection in four groups, there was a significant difference ($P < 0.001$) in the East African cohorts: in the 15–24 year group the median survival was 12.8 years (95% CI 10.3–undefined), in the 25–34 year group the median survival was 10.6 years (95% CI 9.7–12.8), 7.5 years (95% CI 6.1–10.3) in the 35–44 year group and only 5.6 years (95% CI 5.0–7.2) in those aged 45 years or greater (Fig. 2a). The difference by age was also highly significant ($P < 0.001$) for the South African miners, the median survival times were 11.5 years (95% CI 10.8–undefined), 10.5 years (95% CI 10.1–undefined), 9.5 years (95% CI 8.4–10.0) and 6.3 years (95% CI 5.6–7.3) for the four age groups, respectively (Fig. 2b). In the Thai studies there were only 76 individuals aged 25 years or more at infection, and they had a median survival of 6.7 years (95% CI 5.8–9.2) although this was not significantly ($P = 0.2$) less than the 7.7 years (95% CI 7.2–undefined) for those aged less than 25 years at seroconversion (Fig. 2c).

Regression analysis showed significant differences in survival between the African sites and the Thai sites, which increased when adjusted for age (Table 3). Within the four East African sites, after adjusting for age the Ugandan subjects had lower survival than the Tanzanian site (HRR 1.64, 95% CI 1.12–2.42; $P = 0.01$), but the Rwandan site had similar survival to the Tanzanian site (HRR 1.14, 95% CI 0.73–1.80; $P = 0.56$). There was no significant difference between the two Ugandan sites ($P = 0.7$). Survival in the Haitian site was not significantly different from the African sites, although the numbers were small. In the Thai cohorts, there was no difference in survival between those recruited from the military, those recruited from blood donors, or in the sexual partners of the blood donors (chi-squared 0.24, 2 df, $P = 0.9$).

Excluding the three single sex studies (Thai military, South African miners and Rwandan MCH women), in univariate analysis there was a significant difference in survival by sex, with longer survival in women (HRR 0.78, 95% CI 0.62–0.98). After adjusting for age and site, the difference in survival by sex was no longer significant (HRR 0.91; $P = 0.4$), and was similar in African (HRR 0.90, 95% CI 0.68–1.18) and non-African cohorts (HRR 1.02, 95% CI 0.55–1.92). After adjusting for age, there was no significant difference between the mortality rates of women and men in the three East African studies when this could be assessed.

Survival was slightly longer in those who seroconverted in the later period in the East African studies (adjusted HRR 0.79, 95% CI 0.58–1.07; $P = 0.13$), but not in the South African miners. In the univariate analysis, there was some evidence that longer seroconversion intervals were associated with longer survival (HRR 0.86, 95% CI 0.73–1.02; $P = 0.08$), but this was not significant after adjusting for age and site (adjusted HRR 0.86, 95% CI 0.72–1.03; $P = 0.11$). This effect was mostly the result of a significant effect in Kisesa (adjusted HRR 0.40, 95% CI 0.18–0.89; $P = 0.025$) and Masaka (adjusted HRR 0.56, 95% CI 0.32–0.99; $P = 0.048$), which was not seen in Rakai or Rwanda. To compare with the CASCADE results, we excluded the 242 seroconversions, all in East African sites, with an interval between the last HIV-negative test and the first HIV-positive test greater than 3 years, which reduced the estimated age-adjusted median survival to 10.8 (95% CI 8.4–14.0).

in the East African sites. Further restricting the analysis to those with seroconversion intervals of less than 2 years, the estimated median survival, adjusted to age 25–29 years, in the East African sites was 10.9 years (95% CI 8.3–14.3), in the miners 11.8 years (95% CI 9.8–14.2), and in Thailand 7.5 years (95% CI 5.4–10.4).

Discussion

This paper reports survival from eight seroconverter cohorts in low and middle-income countries and highlights the different survival patterns seen in Africa and Thailand. All of the African studies, the East African population-based studies, the Rwandan MCH cohort, and the South African miners, had median survival times similar to those measured in the west before HAART became available. Adjusted to age 25–29 years, median survival in East Africa was 11.1 years and in South Africa 11.6 years, compared with 11.2 years (95% CI 10.9–11.6) in the west as measured by the CASCADE study [2]. The extent to which the small remaining differences can be explained by higher background mortality rates is explored separately [25]. In contrast, survival in the two Thai studies was considerably shorter (median 7.5 years), and the results from Haiti were intermediate (8.3 years), but were based on small numbers. The results from these pooled data agree with the findings from the separate sites, supporting the premise of a median survival post-HIV infection of approximately 11 years in Africa.

A strong influence of age at infection on survival was seen, as previously reported from high-income countries where increased adult mortality rates were observed as age increased [2,22,26]. In the African studies, median survival in the oldest age group was less than half that in the youngest adult age group. The accelerated mortality rates in the Thai studies meant that the survival patterns of newly infected 21-year-old conscripts were similar to those of individuals infected at age 35–44 years in Africa.

The reason for the shorter survival in the Thai studies is not known, but it is unlikely to be the result of bias as the seroconversion intervals were short and loss to follow-up was low. The results from the two studies were very similar to each other, despite differences in patient populations and procedures. Background mortality rates in both studies were low, and it is unlikely that nutrition or health services were worse than for the African population cohorts. Whereas host genetics and the range of co-infections differ, a possible explanation is the viral subtype: predominantly E in Thailand, A and D in East Africa, C in South Africa, and B in Haiti [8,27,28]. There is some evidence that subtype influences survival [17,18,29], although other studies have shown no difference in survival between African HIV subtypes [30]. It is not known whether subtype E progresses faster than other subtypes.

Median survival times in the Haitian cohort were between those observed in Africa and Thailand, although the numbers were very small. The higher mortality in Haiti could be a result of population factors, or viral strains, or the recruitment of the cohort from an HIV testing centre. As 22 of the 42 seroconverters from Haiti were symptomatic at the time of the first positive test, and seroconversion illness has been associated with more rapid progression [31], a greater number of fast progressors may have been included in the cohort.

There was weak evidence of longer survival in the later period of infection in East Africa and of the opposite trend in South Africa. We have truncated follow-up at the time that ART became generally available, but some subjects in the cohort may have accessed ART outside of the cohort, which, although unlikely, may have produced a small overestimate in the survival times in later periods. It is also likely that the treatment of opportunistic infections within the study clinics improved in the later periods, leading to better survival. In the later period, the national guidelines for the care of HIV-infected individuals included the use of cotrimoxazole as a prophylaxis against infection, which has been shown to reduce mortality in patients with advanced HIV disease [32]. Among the South African miners, the interpretation of survival by period of infection is complicated by other period effects such as changes in employment and access to medical care, and differential completeness of follow-up information.

There were some differences between the studies in the definition of seroconversion, the estimation of the seroconversion date, the methods of follow-up, and the determination of deaths. After adjusting for age, there were still significant differences in survival for the different strata (East Africa, South Africa, Thailand and Haiti), and it is important to take into account this variation when estimating the effect of covariates on survival. We did not, however, find it necessary to use a random effects model to allow for further unobserved differences between the sites. Approximately 15% of the eligible seroconverters in the African sites were lost to follow-up, or migrated out of the study area; the time between seroconversion and loss to follow-up has been included in the analysis. All cohorts maintained an active follow-up of recruited participants either through census activities, national vital registration, or active home follow-up.

The inclusion of individuals with seroconversion intervals up to 4 years is a potential bias. Fast progressors, some of whom may die before getting an HIV-positive test, could be missed, thus inflating the estimated survival. The majority of the individuals had a seroconversion interval of less than 2 years, except in the Kisesa site. In two East African studies, Kisesa and Masaka, there was significantly longer survival in those with a longer seroconversion interval. Excluding individuals with seroconversion intervals of more than 2 years reduced the median survival time in the East African population studies by 0.7 years, but made little difference to the results in other sites.

Three of the studies used representative, population-based, community cohorts. Two were occupational cohorts, one being workers in the mining industry, and the other drawing on a national, random selection of 21 year olds joining the military. Three studies recruited seroincident cases from clinic records, one from an HIV testing clinic, one from healthy subjects targeted for blood donation, and the third from women attending the MCH clinic. General population cohorts represent the whole spectrum of those infected, but may be subject to bias through migration into and out of the population. Such community cohorts may also report more deaths, as former residents return before death, and friends and relatives are more likely to report the deaths of loved ones, even if they are not living in the community. On the other hand, clinical cohorts may be affected by a recruitment bias, if patients are more likely to request an HIV test if they are sick, although this would not apply to blood donors or antenatal clinic attenders. Other studies have suggested that the

recruitment of clinical cohorts from hospital could overrepresent fast progressors [33]. Conversely, occupational cohorts may initially be healthier and if continuing in work, may have access to good medical care, and a higher economic status, and thus have a lower underlying rate of mortality. Both occupational cohorts continued follow-up after leaving employment, however, and are perhaps representative of the subsection of young, healthy men in the population from which they were drawn.

Overall, these results show that the survival of HIV-infected Africans before the advent of ART followed a similar pattern to survival in high-income country cohorts [2]. Shorter survival times were seen in Thailand, which may be the result of factors associated with the virus, the population, or the study design. This difference needs to be explored with further research, but the results are important for many people planning interventions to treat HIV-infected individuals in low and middle-income countries.

Acknowledgements

Without the Alpha network, which was funded by the Wellcome Trust, this topic would not have been explored. The Alpha network facilitated the workshop, supported individual attendance, and provided resources, training and support in the exploration of these data.

The authors would like to thank UNAIDS for supporting this special issue of AIDS.

The authors would also like to thank all study sites for contributing their data, and participating in the discussions leading to this analysis. They acknowledge the hard work of their staff, and the generosity of their funders in making the data available. Key individuals from each site include: Kisesa (Mark Urassa, Basia Mbabwa, Wambura Mwita, Milly Marston, Raphael Isingo, Milalu Ndege); Masaka (Sam Biraro, Heiner Grosskurth, Agnes Kasirye, Jessica Nakiyingi-Miiro, Lieve van der Paal, Leigh Anne Shafer, Duncan Ssematimba, Jim Todd); Rakai (Anthony Ndyababo, JohnBaptista Bwanika, Tom Lutalo); South African miners (Jill Murray, Gill Nelson, Andre Bester, Stuart Shearer, Pam Sonnenberg, Judith Glynn); Thai military cohort (Ram Rangsin, Kenrad Nelson, Phunlerd Piyanj, Narongrid Sirisopana, Thira Sirisanthana); Thai blood donors and partners (Ann Duerr, Kenrad Nelson, Caroline Costello, Vinai Suriyanon); Haiti GHESKIO cohort (Dan Fitzgerald); Projet San Francisco, Kigali (Philip Peters, Etienne Karita, Kayitesi Kayitenkore, Susan Allen).

References

1. UNAIDS. [Accessed: January 2007] AIDS epidemic update December 2006. Available at: http://data.unaids.org/pub/EpiReport/2006/2006_EpiUpdate_en.pdf
2. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU concerted action. Time from HIV-1 seroconversion to AIDS and death before the widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. *Lancet*. 2000; 355:1131–1137. [PubMed: 10791375]
3. Morgan D, Mahe C, Mayanja B, Okongo M, Lubega R, Whitworth J. HIV infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS*. 2002; 16:597–603. [PubMed: 11873003]
4. Leroy V, Msellati P, Lepage P, Batungwanayo J, Hitimana DG, Taelman H, et al. Four years of natural history of HIV-1 infection in African women: a prospective cohort study in Kigali (Rwanda), 1988–1993. *J Acquir Immune Defic Syndr*. 1995; 9:415–421.
5. Crampin AC, Floyd S, Glynn JR, Sibande F, Mulawa D, Nuondo A, et al. Long term follow-up of HIV-positive and HIV-negative individuals in rural Malawi. *AIDS*. 2002; 16:1545–1550. [PubMed: 12131193]
6. Glynn JR, Sonnenberg P, Nelson G, Bester A, Shearer S, Murray J. Survival from HIV-1 seroconversion in Southern Africa: a retrospective cohort study in nearly 2000 gold miners over 10 years of follow up. *AIDS*. 2007; 21:625–632. [PubMed: 17314525]

7. Rangsins R, Chui J, Khamboonruang C, Sirisopana N, Eiumtrakul S, Brown AE, et al. The natural history of HIV-1 infection in young Thai men after seroconversion. *J Acquir Immune Defic Syndr*. 2004; 36:622–629. [PubMed: 15097306]
8. Costello C, Nelson K, Suriyanon V, Sennun S, Tovanabutra S, Heilig CM, et al. HIV-1 subtype E progression among northern Thai couples: traditional and non-traditional predictors of survival. *Int J Epidemiol*. 2005; 34:577–584. [PubMed: 15737969]
9. Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD. HIV infection in Haiti: natural history and disease progression. *AIDS*. 2000; 14:2515–2521. [PubMed: 11101063]
10. Lavreys L, Baeten JM, Chohan V, McClelland S, Hassan WM, Richardson BA, et al. Higher set point plasma viral load and more severe HIV type 1 (HIV-1) illness predict mortality among high-risk HIV-1 infected African women. *Clin Infect Dis*. 2006; 42:1333–1339. [PubMed: 16586394]
11. Morgan D, Whitworth JAG. The natural history of HIV-1 infection in Africa. *Nat Med*. 2001; 7:143–145. [PubMed: 11175832]
12. Jaffar S, Grant AD, Whitworth J, Smith PG, Whittle H. The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review. *Bull WHO*. 2004; 82:462–469. [PubMed: 15356940]
13. Porter K, Zaba B. The empirical evidence for the impact of HIV on adult mortality in the developing world: data from serological studies. *AIDS*. 2004; 18(Suppl. 2):S9–S17.
14. Sterling TR, Vlahov D, Astemborski J, Hoover DR, Marqolick JB, Quin TC. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med*. 2001; 344:720–725. [PubMed: 11236775]
15. Nduati R, Richardson BA, John G, Mbori-Ngancha D, Mwatha A, Ndinya-Achola J, et al. Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. *Lancet*. 2001; 357:1651–1655. [PubMed: 11425369]
16. Semba RD, Tang AM. Micronutrients and the pathogenesis of human immunodeficiency virus. *Br J Nutr*. 1999; 81:181–189. [PubMed: 10434844]
17. Vasan A, Renfijo B, Hertzmark E, Chaplin B, Msamanga G, Essex M, et al. Different rates of disease progression of HIV type 1 infection in Tanzania based on infecting subtype. *Clin Infect Dis*. 2006; 42:843–852. [PubMed: 16477563]
18. Kaleebu P, French N, Mahe C, Yirell D, Watera C, Lyagoba F, et al. Effect of human immunodeficiency virus (HIV) type 1 envelope subtypes A and D on disease progression in a large cohort of HIV-1 positive persons in Uganda. *J Infect Dis*. 2002; 185:1244–1250. [PubMed: 12001041]
19. Shieh B, Chang MJ, Ko WC, Chen EJ, Wu JC, Lee CF, et al. Effects of multiple virus coinfections on disease progression in HIV-positive patients. *Intervirology*. 2003; 46:105–113. [PubMed: 12684549]
20. Wawer MJ, Gray RH, Sewankambo NK, Li CJ, Serwadda D, Konde-Lule JK. Trends in HIV prevalence may not reflect current HIV incidence in mature epidemics. *AIDS*. 1997; 11:1023–1030. [PubMed: 9223737]
21. Mulder DW, Nunn AJ, Wagner H-U, Kamali A, Kengeya-Kayondo JF. HIV-1 incidence and HIV-1-associated mortality in a rural Ugandan population cohort. *AIDS*. 1994; 8:87–92. [PubMed: 8011241]
22. Urassa M, Boerma JT, Isingo R, Ngalula J, Ng'weshemi J, Mwaluko G, Zaba B. The impact of HIV/AIDS on mortality and household mobility in rural Tanzania. *AIDS*. 2001; 15:2017–2023. [PubMed: 11600831]
23. Allen S, Lindan C, Serufilira A, Van de Perre P, Rundle AC, Nsengumuremyi F, et al. Human immunodeficiency virus infection in urban Rwanda. Demographic and behavioral correlates in a representative sample of childbearing women. *JAMA*. 1991; 266:1657–1663. [PubMed: 1886188]
24. Deschamps M-M, Pape JW, Hafner A, Johnson WD. Hetero-sexual transmission of HIV in Haiti. *Ann Intern Med*. 1996; 125:324–330. [PubMed: 8678397]
25. Marston M, Todd J, Glynn JR, Nelson K, Rangsins R, Lutalo T, et al. Estimating 'net' HIV-related mortality and the importance of background mortality rates. *AIDS*. 2007; 21(Suppl. 6):S65–S71.
26. Babiker A, Peto T, Porter K, Walker AS, Darbyshire JH. Age as a determinant of survival in HIV infection. *J Clin Epidemiol*. 2001; 54:S16–S21. [PubMed: 11750205]

27. Kilmarx PH, Limpakarnjanarat K, Kaewkungwal J, Srismith R, Saisorn S, Uthaivoravit W, et al. Disease progression and survival with human immunodeficiency virus type 1 subtype E infection among female sex workers in Thailand. *J Infect Dis.* 2000; 181:1598–1606. [PubMed: 10823759]
28. Costello C, Tang J, Rivers C, Karita E, Meizen-Derr J, Allen S, et al. HLA-B*5703 independently associated with slower HIV-1 disease progression in Rwandan women. *AIDS.* 1999; 13:1990–1991. [PubMed: 10513667]
29. Baeten JM, Chohan B, Lavreys L, Chohan V, Msclelland RS, Certain L, et al. HIV-1 subtype D infection is associated with faster disease progression than subtype A in spite of similar plasma HIV-1 loads. *J Infect Dis.* 2007; 195:1177–1180. [PubMed: 17357054]
30. DelAmo J, Petruckevitch A, Phillips A, Johnson AM, Stephenson J, Desmond N, et al. Disease progression and survival in HIV-1 infected Africans in London. *AIDS.* 1998; 10:1203–1209.
31. Tyrer F, Walker AS, Gillett J, Porter K. The relationship between HIV seroconversion illness. HIV test interval and time to AIDS in a seroconverter cohort. *Epidemiol Infect.* 2003; 131:1117–1123. [PubMed: 14959779]
32. Watera C, Todd J, Muwonge R, Whitworth J, Nakiyingi-Miiro J, Brink A, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1 infected adults attending an HIV/AIDS clinic in Uganda. *J Acquir Infect Dis Syndr.* 2006; 42:373–378.
33. Prins M, Brettle RP, Robertson JR, Aguado IH, Broers B, Carre N, et al. Geographical variation in disease progression in HIV-1 seroconverted injecting drug users in Europe. *Int J Epidemiol.* 1999; 28:541–549. [PubMed: 10405862]

Fig. 1. Survival curves for 3823 seroconverters from eight study sites.

(a) Unadjusted Kaplan–Meier survival curves by study site. (b) Kaplan–Meier survival curves adjusted to age 25–29 years at infection (seroconversion), grouped for studies from East Africa (population cohorts), South Africa (miners), Thailand and Haiti. BD+P, Blood donors and partners.

Fig. 2. Survival by age at infection: 15–24 years, 25–34 years, 35–44 years and 45+ years at seroconversion.

(a) In the four East African population cohorts (1449 seroconverters). (b) In the South African miners (1950 seroconverters). (c) In the two studies in Thailand (383 seroconverters).

Table 1
Description of the types and sizes of studies included in the analysis, the number of seroconverters and reasons for exclusion of seroconverters by study.

Study	Cohort	Size of cohort	No. of surveys ^a	Seroconverters		Reasons for exclusion		Seroconversion observed
				Total	Eligible	< 15 ^b	> 4-year gap ^c	
Kisesa, Tanzania	Community	46 130	5	405	281	53	71	1994–2003
Masaka, Uganda	Community	26 540	17	346	258	13	75	1990–2003
Rakai, Uganda	Community	34 794	11	837	763		74	1995–2003
South African miners	Occupational	N/A	–	1950	1950			1991–1997
Thailand blood donors	Clinic	N/A	–	150	150			1989–1996
Thailand military	Occupational	N/A	–	233	233			1991–1995
Haiti patients	Clinic	N/A	–	42	41 ^d			1985–1997
Rwanda MCH	Clinic	1057	–	147	147			1986–1993

MCH, Maternal and child health

^a Serological surveys with blood taken for HIV testing (population-based cohorts only).

^b Seroconverters excluded if estimated age of seroconversion was before 15th birthday.

^c Seroconverters excluded if there was greater than 4-year gap between last HIV-negative test and first HIV-positive test.

^d One subject with no follow-up data.

Table 2
Description of seroconverters in analysis and follow-up times at study sites.

Study	Eligible seroconverters	Proportion of seroconverters		Age at seroconversion (in years)		Date ART started ^a	Number migrated or lost to follow-up ^b	No of deaths	Period of follow-up	Follow-up time (years) ^c	
		< 2 Years between last negative and first positive test	Male	Median	Range					Total person-years	Maximum person-years
Kisesa, Tanzania	281	10%	44%	28	16–90	Jan 2005	47 (17%)	30	1994–2004	797	9.5
Masaka, Uganda	258	77%	50%	28	15–79	Jan 2004	25 (10%)	79	1990–2003	1202	13.4
Rakai, Uganda	763	77%	41%	27	15–61	Jan 2004	227 (30%)	110	1995–2003	2200	8.7
South African miners	1950	85%	100%	30	19–59	Jan 2004	298 (15%)	636	1991–2002	11 934	11.6
Thailand blood donors	150	97%	61%	24.5	15–44		0	61	1989–1999	811	9.7
Thailand military	233	100%	100%	21	20–27		0	77	1991–1999	1253	7.9
Haiti patients	41	100%	29%	27	17–66		0	16	1995–2000	221	12.5
Rwandan MCH	147	99%	0%	28	19–40	Sept 2003	37 (25%) ^d	70	1987–2003	1253	15.4

ART, Antiretroviral therapy.

^aFor this analysis follow-up was truncated at the date ART became generally available to cohort members.

^bLost to follow-up means those who were no longer followed by the study, and were censored at the date last seen.

^cFollow-up time from time of first HIV-positive test.

^dTwenty-five women died or were lost to follow-up during the genocide of 1994.

Table 3
Hazard ratios of survival from seven studies with observed survival of HIV seroconverters.

Characteristic	No. of subjects and person-years				Hazard rate ratios	
	Seroconverters	Deaths	Person-years	Rate per 100 person-years (95% CI)	Crude HR (95% CI)	Adjusted for age and site (95% CI) ^a
Study populations						
East Africa	1449	289	5451	5.30 (4.72–5.95)	1	1
South Africa	1950	636	11934	5.33 (4.93–5.76)	0.96 (0.84–1.11)	0.89 (0.77–1.03) ^a
Thailand	383	138	2065	6.68 (5.66–7.90)	1.49 (1.22–1.83)	1.91 (1.53–2.38) ^a
Haiti	41	16	221	7.24 (4.44–11.8)	1.35 (0.81–2.23)	1.24 (0.75–2.06) ^a
Sex (excluding single sex studies – South African, Thai military and Rwandan women)						
Male	675	167	2547	6.56 (5.63–7.63)	1	1
Female	818	129	2685	4.81 (4.04–5.71)	0.78 (0.62–0.98)	0.91 (0.71–1.16)
Calendar time of infection						
East Africa						
Early (1996)	536	205	3223	6.36 (5.55–7.29)	1	
Late (1997)	913	84	2228	3.77 (3.04–4.67)	0.85 (0.65–1.12)	0.79 (0.58, 1.07)
South African miners						
Early (1993)	891	347	6297	5.51 (4.96–6.12)	1	1
Late (1994)	1059	289	5637	5.12 (4.57–5.75)	1.22 (1.04–1.43)	1.17 (0.99–1.38) ^a
Seroconversion interval (time between last negative HIV test, and first positive HIV test)						
Under 2 years	3023	921	16 512	5.58 (5.23–5.95)	1	1
2–3.99 years	799	158	3159	5.00 (4.28–5.85)	0.86 (0.73–1.02)	0.86 (0.72–1.03)

CI, Confidence interval; HR, hazard ratio. Crude hazard ratios and adjusted for age in 5-year age bands.

^a Adjusted for age at infection only.