Determinants of time from HIV infection to linkage-to-care in rural KwaZulu-Natal, South Africa

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ABSTRACT

Objective: To estimate time from HIV infection to linkage-to-care and its determinants. Linkage-to-care is usually assessed using the date of HIV diagnosis as the starting point for exposure time. However, timing of diagnosis is likely endogenous to linkage, leading to bias in linkage estimation.

Design: We used longitudinal serosurveys from a large population-based HIV cohort in KwaZulu-Natal (2004-2013) to estimate time of HIV infection. We linked this data to patient records from a public-sector HIV treatment and care program to determine time from infection to linkage (defined using the date of the first CD4 count).

Methods: We used Cox proportional-hazards models to estimate time from infection to linkage and the effects of the following covariates on this time: gender, age, education, food security, socio-economic status, area of residence, distance to clinics, knowledge of HIV status, and whether other household members have initiated ART.

Results: We estimated that it would take an average of 4.9 years for 50% of seroconverters to be linked to care (95% confidence intervals (CI): 4.2-5.7). Among all cohort members that were linked to care, the median CD4 count at linkage was 350 cells/μL (95%CI: 330-380). Men and participants <30 years were found to have the slowest rates of linkage-to-care. Time to linkage became shorter over calendar time.

Conclusions: Average time from HIV infection to linkage-to-care is long and needs to be reduced to ensure that HIV treatment-as-prevention policies are effective. Targeted interventions for men and young individuals have the largest potential to improve linkage rates.

Keywords: HIV/AIDS; linkage to care; treatment cascade; care continuum; CD4 cell count; treatment-as-prevention; gender.

INTRODUCTION

Antiretroviral therapy (ART) improves patient outcomes, increases life expectancy, and reduces population-level transmission of HIV [1-3]. Timely linkage-to-care among the newly infected is important to maximize such individual and population-level benefits. The time from infection to linkage becomes especially relevant as HIV programs move from treatment to treatment-as-prevention. For treatment-as-prevention to achieve maximum success in reducing population-level incidence, linkage-to-care should ideally occur immediately following HIV infection for rapid ART initiation. In practice, however, several studies have found low linkage levels in sub-Saharan Africa [4-7]. A recent trial in rural KwaZulu-Natal (ANRS 12249) showed that low linkage-to-care was likely responsible for the failure to reduce population incidence through a community-based HIV treatment-as-prevention intervention [8, 9].

While earlier evidence demonstrated substantial losses to follow-up after ART initiation in several settings [4, 10, 11], it has recently become clear that the losses in the early phases of the HIV care continuum are even more severe [6, 7, 12-17]. Most of this research relied on data from provider-initiated counselling and testing and, to a lesser extent, individuals using voluntary counselling and testing (community-based or home-based) [5]. Few studies used population-based estimates of engagement in care [6-8]. Further, all the prior studies on linkage-to-care have in common that time to linkage was examined using the date of diagnosis, rather than the date of infection, as the starting point. Despite the urgency to improve early testing and treatment, substantial proportions of HIV-positive populations in sub-Saharan Africa still test late in the course of HIV disease [18]. Testing and treatment-seeking behaviors might be partly driven by perceived health status and examining the determinants of time to linkage-to-care from the date of infection, instead of date of HIV diagnosis (i.e., receipt of a first HIV positive test), can substantially advance our understanding of barriers to linkage – because the date of HIV diagnosis is likely endogenous to linkage rates. In other words, those who get diagnosed earlier are on average also more likely to link-to-care rapidly. Previous estimates of determinants of linkage-to-care are therefore potentially biased.

In this study, we aim to estimate the time from HIV infection to linkage, as well as the determinants of this time. We use data from one of the largest population-based HIV incidence cohorts in Africa and link this data to patient records from the local public-sector HIV treatment and care program. Improving our understanding of the factors influencing time from HIV infection to linkage-to-care can substantially improve our ability to design and target interventions aimed at addressing barriers to early linkage and treatment initiation. Such interventions will be especially important for the success of HIV treatment-and-prevention policies and the attainment of the UNAIDS 90-90-90 targets [19].

METHODOLOGY

Study population

Since 2000, the Africa Health Research Institute (AHRI) has operated longitudinal population health surveillance in rural KwaZulu-Natal (uMkanyakude district), South Africa [20]. Nested within the population health surveillance is one of Africa's largest HIV incidence cohorts. Surveillance covers an area approximately 440 km^2 in size, encompassing a population of 87,000 individuals (75,000 residents and 13,000 non-residents). It was designed to capture the complex and interwoven health, social, and demographic dynamics of a poor rural Southern

African population. In 2011, HIV prevalence in the adult population (15-50 years) was estimated at 29% and ART coverage of all HIV-positive adults was 31% [21].

The AHRI population health surveillance collects information on all individuals who live in the surveillance area. The surveillance is conducted in two separate data collection approaches. First, every four months, a household survey is administered to a key informant to gather data on attributes and events regarding physical structure, households, and individual household members [20]. Second, every year trained field workers collect data through individual interviews, during which confidential HIV testing is offered to each adult. Eligibility criteria for the HIV serosurveys from 2003 to 2007 were all women aged 15-49 years and men aged 15-54 years old. After 2007, HIV testing was administered to all individuals aged 15 years and over.

ART became available in the area shortly after the national roll-out in 2004 [22]. At that time, HIV-positive individuals could only get access to treatment from the surveillance area's hospital clinic. ART delivery has subsequently been scaled-up to 17 public-sector primary-care clinics in Hlabisa subdistrict; six of these clinics are located in the AHRI surveillance area [23]. The *Hlabisa HIV Treatment and Care Program* provides free HIV testing and counseling, condoms, and ART. In this study, linkage-to-care was operationalized as having a first CD4 count, the required diagnostic criterion to assess ART eligibility during the time of this study, in the local HIV treatment and care program [22]. Further details on both the AHRI population health surveillance, the data collection in the HIV treatment and care program, and the data linkage between these two databases can be found elsewhere [1, 20, 22, 24].

Procedures and variables

Seroconverters are identified among repeated-testers. Repeated-testers are defined as the subset of individuals aged 15 years and older who had more than one HIV test performed during annual serosurveys, for which the first test was negative. Slightly modifying the approach used by Vandormael and colleagues [25], the date of HIV infection was proxied by estimating the date of seroconversion. Given the time lag between subsequent serosurveys, we could not directly ascertain the date of HIV seroconversion but it must have occurred in the interval between the last negative HIV test and the first positive HIV test in the population-based HIV incidence cohort. For our main analysis, we randomly assigned the date of infection between the last HIV negative test and the first HIV positive test, or first CD4 count test, whichever occurred first. A total of ten datasets with random imputation of HIV infection dates were constructed in that way. Random imputation allows us to propagate the uncertainty associated with the unobserved HIV infection dates to our results. For presentation of baseline descriptive statistics, we used the midpoint date between the last negative HIV test and first positive HIV test (or between the last negative HIV test and the first CD4 count test) for simplicity (hereafter referred to as 'midpoint imputation'). Summary of the descriptive statistics of the ten imputed datasets can be found in supplemental materials (Table S1). Infections occurring before August 2004 were excluded since ART had not been rolled-out prior to that date and the individuals were hence not eligible for the outcome (i.e., linkage-to-care). Seroconverters in the AHRI population health surveillance and HIV incidence cohort were linked to the HIV treatment and care program database, using the South African identification number (or if missing, full names, sex, and birth date). Linkage-to-care is defined in this study as having a first CD4 count test performed following HIV infection, as per the *Hlabisa Treatment and Care Program*'s protocol.

Time to linkage-to-care was explored using time-varying covariates. The dynamic nature of the AHRI population cohort is captured through exposure episodes. Specifically, an exposure episode starts on the first day of the year and usually ends on the last day of that calendar year. If an individual changes residency or migrates inside or outside of the surveillance area, a new exposure episode is created for that period. Exposure episodes are thus of variable lengths and seroconverters can only live in one residence at a time (but multiple household memberships are allowed). All individuals who migrated out of the surveillance area, even temporarily, were censored on their emigration day. If an individual's infection date was estimated to have occurred while outside of the surveillance area, this person was excluded. Hence, the ten randomly imputed datasets may have slightly different sample sizes and person-time of follow-up. If seroconverters were not found to be linked to HIV care, they were censored on their last day of follow-up, the date they died, or January 2014 – whichever occurred first.

The main outcome of this study is time from HIV infection to linkage-to-care. The only time-invariant variables considered are gender, knowledge of HIV status at baseline (i.e., first positive test), and the calendar year of infection. Time-varying variables are: age, area of residence, socio-economic status (asset-based index categorized into quartiles, among seroconverters, using the first axis of a principal component analysis of 21 household assets), education level, whether one's household co-members are receiving ART, and the Euclidian distance to the closest health facility where ART is provided. Since some of the exposure episodes are retrospectively constructed (i.e., they are within two survey dates), we assigned them based on the closest survey date (but not more than one year after the beginning of the exposure episode). Household-level variables were attributed based on household residence and closest survey date. For missing education level values, if an individual was aged 19 years or above and had at least one observation with information on education level, we imputed that value using the previously reported education level.

Statistical analyses

Time from HIV infection to linkage-to-care was first explored using Kaplan-Meier estimates of the survival curve. CD4 counts at linkage, stratified by time to linkage-to-care, were also examined. Cox proportional hazards models were then used to estimate the effect of the different variables on time to linkage-to-care. Covariates with missing observations were retained in the analysis using the missing indicator method [26]. We present results for univariate and multivariable models. Because the question about knowledge of HIV status was not part of the questionnaire in 2004 and 2005, the multivariable model only included observations from individuals who seroconverted from 2006 onwards. The method of Grambsch and Therneau [27], based on the scaled Schoenfeld residuals, was used to test that all variables met the proportional hazards assumption. Because some covariates failed that test, we stratified the survival analyses using the calendar year of HIV infection. All analyses were performed individually on the 10 imputed datasets and results were combined with Rubin's rule [28] using the R statistical software [29]. The '*survival*' package [30] was used to fit the Cox proportional hazards models.

Ethics

All respondents provided informed consent. The *Biomedical Research Ethics Committee* of the University of KwaZulu-Natal granted ethical approval for data collection.

RESULTS

Among individuals that were believed to have seroconverted between August 2004 and December 2013, 10 were found to have been linked to care before their last negative test and were therefore excluded from our analyses. Since they were potentially outside of the *Hlabisa Treatment and Care Program*'s catchment area, individuals not recorded to be in the surveillance area at their estimated time of HIV infection were also excluded. Hence, and depending on the randomly imputed seroconversion dates, between 1,713 and 1,779 recent seroconverters contributed between 4,582 and 4,818 person-years of follow-up to our inferences. Results from the midpoint imputation and the randomly imputed datasets differed principally with regards to the uncertainty around the different estimates but not regarding the effect size estimates (see supplemental material Tables S2-S4 and Figures S1S2).

Baseline characteristics of recent seroconverters are presented in Table 1. The great majority (77%) of recent seroconverters were women and over 70% had some or completed secondary education. Mean age at HIV infection was 27 years. Most recent seroconverters did not have members of their household who had initiated ART. 63% of seroconverters responded that they were aware of their HIV status at the time of their first positive test. The median time between last negative test and first positive HIV test was 2.0 years (interquartile range (IQR): 1.1-3.2 years; with a maximum of 10 years).

Averaging over the imputed datasets, the median follow-up time was 2.2 years (IQR 1.1-3.9) and only 14% of those who were followed-up for a minimum of 12 months had a CD4 count test performed within that time-period (this rises to 29% two years after HIV infection). At linkage, the median CD4 count was 350 cells/μL (95%CI: 330 to 380) (Table 2). Seroconverters that were linked to care in less than one year had a higher median CD4 cell count (370 cells/μL; 95%CI: 320 to 410) than those that linked more than five years after infection (290 cells/μL; 95%CI: 160 to 430). A total of 40 recent seroconverters died before being linked to care after a median follow-up time of 3.0 years (IQR: 1.9-4.7) after infection. The pooled Kaplan-Meier estimates of time from HIV infection to linkage-to-care are presented in Figure 1. From this, we estimate that it would have taken an average of 4.9 years (95%CI: 4.2 to 5.7) for 50% of seroconverters to be linked to care (Table 3). Time to linkage-to-care differed by gender: it took about 1.7 years (95%CI: 1.5-2.0) for 25% of women to link to care versus 3.4 years (95%CI: 2.4-4.4) for men. Time to linkage-to-care also decreased with calendar time with 25% of seroconverters linking in 3.7 years (95%CI: 2.4-5.0) for those who acquired their infection in 2004 to 1.4 years (95%CI: 0.6-2.2) for those who did so in 2010.

In univariate analyses, the main determinants of time to linkage-to-care were gender, age, education level, and knowledge of HIV status from previous testing (Table 4). As compared with females, males had roughly half the hazards of being linked to care (adjusted Hazard Ratio [aHR]=0.49; 95%CI 0.37-0.64). Seroconverters in the 40-49 years of age category had hazards 54% higher (95%CI: 14-108%) of being linked to care as compared to seroconverters aged 15-29 years old. Individuals with some or completed secondary education had lower hazards of being linked to care than those with a year or less of education (aHR=0.63; 95%CI: 0.39-1.00). Household co-memberships with individuals who had previously initiated ART increased the hazards of being linked to care by 23% (95%CI: -2 to 55%) but the confidence intervals of this estimate crossed the null. Finally, the hazards of being linked to care for individuals that are aware of their HIV status from previous testing were 35% (95%CI: 9 to 68%) higher than those who were unaware of their status or who refused to answer the survey question.

DISCUSSION

We estimated that it has taken an average of 4.9 years for 50% of seroconverters to be linked to care during 2004-2013. Comparisons with other empirical data is difficult because time to linkage-to-care has been defined in the past using HIV diagnosis as the starting point. To the best of our knowledge, this study is the first to measure time to linkage-to-care using a direct estimate of the HIV infection date as a starting point. Our empirical estimate of time from HIV infection to linkage is highly policy-relevant because it is a minimum bound on the length of time during which HIV-positive individuals can transmit HIV before the transmission risk is potentially eliminated through HIV treatment [31]. Our results indicate that substantial linkage improvements will be needed to maximize population-level benefits of both HIV treatment and HIV treatment-as-prevention.

With close to a quarter of patients dying within their first year on ART [31], not only is earlier initiation required, but also earlier diagnosis. We estimated that the median CD4 counts at linkage-to-care were of 370 cells/μL for individuals linking within one year of HIV infection and 290 cells/μL for those linking five years or more after HIV infection. Several reasons could explain that the median CD4 count for individuals linking to care within one year was below 500 cells/μL. First, the observed time lag between the last negative and first positive HIV test had a median of 2 years. Non-differential misclassification of the date of HIV infection could have biased our results toward the overall median CD4 count of individuals linking to care. Second, rates of decline in CD4 counts follow an unobserved distribution that we can estimate only among those individuals who linked to care. If linkage is a function of health status, which has been shown in other studies [15, 32], those with rapid disease progression and lower CD4 cell counts will link to care faster. The resulting median CD4 count since time from HIV infection is thus likely lower among our sample of individuals that linked to care than the median CD4 count since time from HIV infection among all HIV-positive people.

In this mostly poor and rural population, rates of linkage-to-care were twice as high for females as those of males, substantiating previous research [5, 6, 33]. The same was true for age, with seroconverters in the 40-49 years old range having the highest rates of linkage-to-care. Having other household members who previously initiated ART tended to reduce time to linkage-to-care. This finding provides some limited evidence that family and social exposure HIV treatment can facilitate linkage and ART uptake.

Diagnosing HIV is the first, and necessary step, on the HIV treatment cascade. We estimated that 63% of individuals were aware of their HIV status at their first positive HIV test during the annual serosurveys and this was a predictor of linkage-to-care. Yet, linkage-to-care was low and delayed in this cohort of seroconverters. This finding could be partly due to the eligibility criteria for ART from 2004 to 2010. During those years, only individuals with CD4 count less than 200 cells/μL were eligible for ART initiation. Compounding this effect are the previously described low pre-ART retention rates [16] and high disengagement from care in this cohort [11]. These findings are corroborated by those from the first phase of the ANRS 12249 treatment-as-prevention trial, conducted in the same area as this study, which showed that the delays in linkage-to-care could compromise the population-level effectiveness of treatment-as-prevention [8, 9]. Preliminary results from the trial suggest that treatment-as-prevention did not substantially reduce HIV incidence because ART coverage in both arms of the trial were similar [8, 9]. That is, the intervention failed to link-to-care a substantial proportion of people in early HIV infection stages. Our estimates of time to linkage-to-care are nevertheless different than

those from this trial because the latter did not define time to linkage based on date of HIV infection but date of diagnosis (the trial was not powered to examined time from HIV infection to linkage-to-care).

Great challenges will need to be overcome to maximize the public health benefits of ART in settings such as the community in which this study took place. Several potential solutions have been proposed from point-of-care CD4 testing with home-based counseling and testing to health systems interventions and financial incentives [34, 35]. Yet, the quality of evidence for these proposed interventions is low and interventions often only target a single point in the HIV care continuum [34, 35][36]. More research is needed into multi-pronged approaches that would mitigate the individual, community, and structural barriers that delay linkage-to-care.

This study has some limitations. First, the exact date of HIV infection remains unknown and was estimated based on individuals who repeatedly participated in the annual population HIV surveillance surveys. Yet, random imputation of infection dates, resulting in non-differential measurement errors in time-to-event, generally introduces only small bias in the hazard ratio estimates [37, 38]. Further, we randomly imputed 10 datasets and the summary estimates we present included this uncertainty. Second, we cannot totally rule out that some individuals found to have seroconverted sought care outside of the *Hlabisa Treatment and Care Program*. Nevertheless, it is unlikely that the proportion of HIV positive individuals accessing ART outside of this public-sector program is higher than a few percent [24]. Low rates of health insurance makes private health care utilization, in particular for chronic diseases such as HIV, rare in this community [24].

An important strength of this research is the use of population-based data, from one of Africa's largest population-based HIV incidence cohorts, to estimate the time from HIV infection to linkage-to-care. Such estimates are likely more representative of the HIV-positive population than those derived from facility-based data. Other strengths include the definition of time to linkage-to-care based on date of HIV infection. To the best of our knowledge, this is the first study to use this definition, instead of the date of HIV diagnosis, which is likely to lead to substantial underestimates of time to linkage. Using a cohort of repeated testers to estimate infection date is more accurate than other approaches, such as back-calculation of seroconversion date based on CD4 cell counts at ART initiation or estimations based on tests for recent infections, which could introduce additional errors [39, 40]. Finally, we addressed a limitation of the extant literature on the determinants of linkage-to-care. Because HIV testing and diagnosis can, at least partly, be a function of health status and treatment-seeking behavior, using the date of diagnosis in survival analysis could lead to endogeneity biases. Our approach, based on the date of HIV infection rather than the diagnosis date, corrects for this potential bias.

In conclusion, large reductions in the time from HIV infection to linkage-to-care are required to realize the full potential of HIV treatment and HIV treatment-as-prevention in improving population health. Increasing HIV testing uptake and frequency, as well as interventions to improve linkage-to-care, in particular for men and young individuals, are likely good candidate interventions for shortening the time from infection to the first HIV clinic visit [41].

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: TB, FT, and DP. Performed the experiments: MMG. Analyzed the data: MMG MCB SAJ. Wrote the paper: MMG, TB, FT, SAJ, MCB, and DP.

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Table 1: Baseline characteristics of recent seroconverters (using midpoint imputation; N=1,733) residing in the demographic surveillance area, South Africa (2004-2013).

Variables	Mean (SD) or Total (%)
Gender	
Female	1,333 (76.9%)
Male	400 (23.1%)
Age (years)	26.8 (10.5)
Education level	
None or less than one year	103 (5.9%)
Some or completed primary	269 (15.5%)
Some or completed secondary	1,289 (74.4%)
Missing	*72 (4.2%)*
Socio-economic status	
Poorest	374 (21.6%)
Poor	435 (25.1%)
Rich	488 (28.2%)
Richest	435 (25.1%)
Missing	*1 (0.1%)*
Food security	
Never (or some months) missed meals	1,675 (96.7%)
Missing meals almost every month (financial reasons)	47 (2.7%)
Missing	*11 (0.6%)*
Uptake of ART by household members	
No household members on ART	1,463 (84.4%)
At least one household member on ART	270 (15.6%)
Knowledge of HIV Status*	
Aware	917 (63.3%)
Unaware / Refused	537 (36.7%)
Area of residence	
Urban	52 (3.1%)
Peri-urban	619 (35.7%)
Rural	1,061 (61.2%)
Distance to closest health facility (km)	6.0 (9.1)
Calendar year of HIV infection	
2004	81 (4.7%)
2005	198 (11.4%)
2006	240 (13.8%)
2007	259 (14.9%)
2008	262 (15.1%)
2009	207 (11.9%)
2010	180 (10.4%)
2011	153 (8.8%)
2012	129 (7.4%)
2013	24 (1.4%)

*The question about knowledge of HIV status from previous testing was not asked in 2004 and 2005 (279 seroconverters were excluded).

Table 2: Median CD4 cell count (cells/μL) at linkage, stratified by linkage time since HIV infection, with 95% bootstrapped confidence intervals.

Time from HIV infection to linkage-to-care	Median CD4 cells/μL (95%CI*)
Less than one year	370 (320, 410)
Between one and two years	380 (340, 420)
Between two and three years	360 (290, 430)
Between three and four years	310 (230, 390)
Between four and five years	320 (220, 410)
More than five years	290 (160, 430)
Overall	**350 (330, 380)**

*95%CI=95% confidence intervals. These are based on 9,999 bootstrap replicates.

Table 3: Time from HIV infection (years) to linkage to care stratified by gender and calendar year of HIV infection.

Characteristics	Time from HIV infection for 25% of seroconverters to link to care (95%CI*)	Time from HIV infection for 50% of seroconverters to link to care (95%CI*)
Gender		
Females	1.7 (1.5-2.0)	4.2 (3.7-4.6)
Males	3.4 (2.4-4.4)	NA†
Calendar year of HIV infection		
2004	3.7 (2.4-5.0)	6.1 (3.7-8.5)
2005	3.1 (2.4-3.8)	5.6 (4.2-7.1)
2006	2.3 (1.7-2.9)	4.6 (3.3-6.0)
2007	1.6 (1.0-2.3)	4.0 (2.7-5.4)
2008	1.5 (1.0-2.0)	NA†
2009	1.6 (1.0-2.2)	NA†
2010	1.4 (0.6-2.2)	NA†
Overall	**2.0 (1.8-2.2)**	**4.9 (4.2-5.7)**

*95%CI=95% confidence intervals. These are based on 9,999 bootstrap replicates.
†NA=not available (the follow-up time was not long enough to observe 50% of seroconverters linking to care).

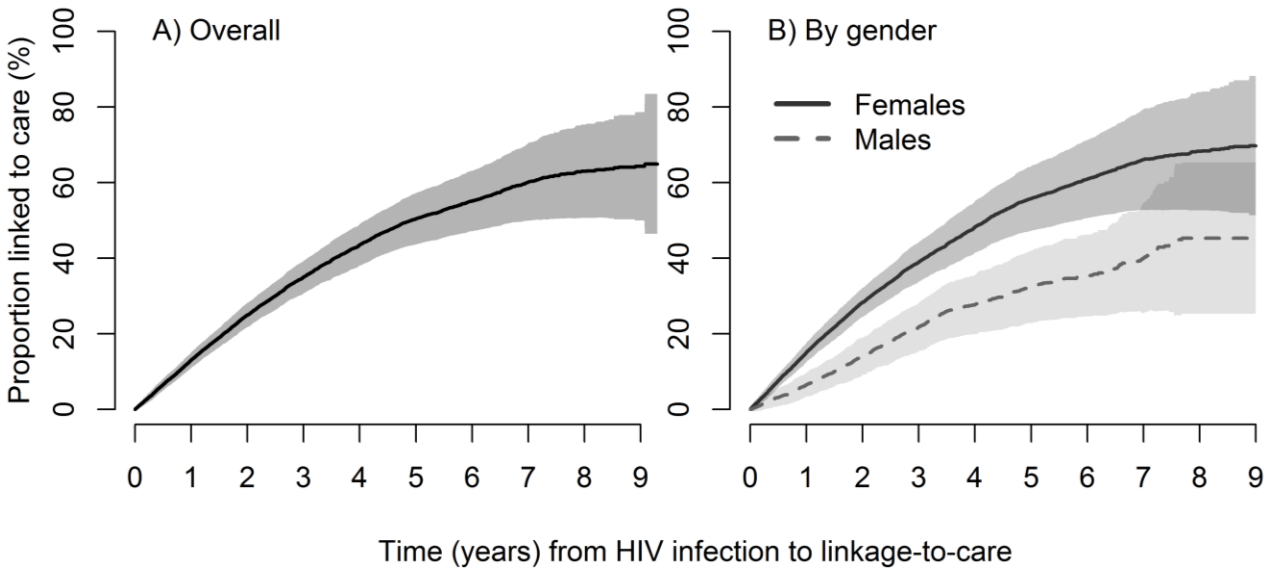


Figure 1. Pooled Kaplan-Meier estimates of time from HIV infection to linkage-to-care in rural Kwa-Zulu Natal South Africa (2004-2013) for A) all seroconverters and B) stratified by gender.

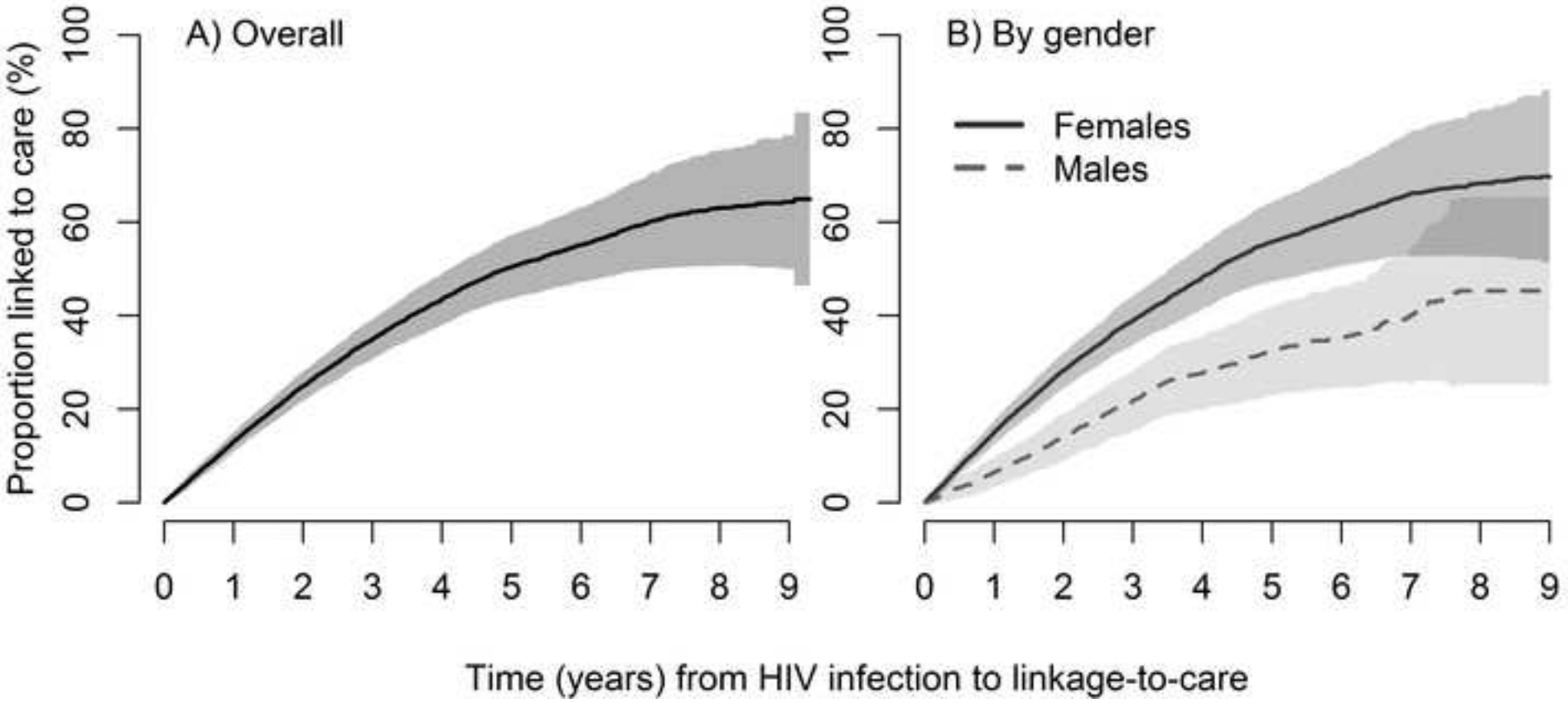
Table 4: Univariate and multivariable effect size estimates from Cox proportional hazard models of determinants of time from HIV infection to linkage-to-care in rural Kwa-Zulu Natal, South Africa. (Pooled results from the 10 imputed datasets.)

Variables	Univariate HR (95% CI)	Multivariable* aHR (95% CI)
GENDER		
Male	**0.49 (0.39-0.61)**	**0.49 (0.37-0.64)**
AGE		
15-29 years old	1.00	1.00
30-39 years old	1.22 (0.96-1.55)	1.16 (0.86-1.57)
40-49 years old	**1.92 (1.53-2.40)**	**1.54 (1.14-2.08)**
50+ years old	1.15 (0.80-1.64)	0.87 (0.53-1.44)
EDUCATION LEVEL		
None or less than one year	1.00	1.00
Some or completed primary	0.87 (0.61-1.25)	0.75 (0.46-1.22)
Some or completed secondary	**0.68 (0.50-0.93)**	0.63 (0.39-1.00)
FOOD SECURITY		
Missing meals almost every month (financial reasons)	1.56 (0.88-2.79)	1.37 (0.67-2.80)
SOCIO-ECONOMIC STATUS		
Poorest	1.00	1.00
Poor	1.15 (0.90-1.46)	1.21 (0.91-1.61)
Rich	1.14 (0.90-1.44)	1.19 (0.75-1.90)
Richest	1.00 (0.78-1.29)	1.05 (0.62-1.79)
OTHER HOUSEHOLD MEMBERS USING ART		
At least one (versus 'None')	1.16 (0.96-1.41)	1.23 (0.98-1.55)
KNOWLEDGE OF HIV STATUS*		
Yes (versus 'No / Refused')	**1.52 (1.24-1.87)**	**1.35 (1.09-1.68)**
AREA OF RESIDENCE		
Urban	1.00	1.00
Peri-Urban	0.65 (0.42-1.02)	0.73 (0.43-1.24)
Rural	0.77 (0.49-1.21)	0.76 (0.45-1.30)
DISTANCE TO HEALTH FACILITY		
<2 km	1.00	1.00
2 to 4 km	1.04 (0.86-1.25)	1.00 (0.79-1.26)
>4 km	1.16 (0.93-1.45)	1.10 (0.84-1.44)
CALENDAR YEAR OF HIV INFECTION	Included as strata	Included as strata

HR (95%CI)=Hazard Ratio (95% Confidence Interval); aHR=adjusted Hazard Ratio.
Results are presented after pooling the analyses of the 10 imputed datasets. All models were stratified using the calendar year of HIV infection to ensure that the proportional hazards assumption was met. The outcome variable was the time from HIV infection to linkage-to-care. We used the date of the first CD4 count test performed in the local HIV treatment and care program to identify the time from infection to linkage.
*The question about knowledge of HIV status from previous testing was not asked in 2004 and 2005, hence, observations from these years were not included in the multivariable model.

Figure 1

Click here to download Figure Figure 1.tiff



INTRODUCTION

Antiretroviral therapy (ART) improves patient outcomes, increases life expectancy, and reduces population-level transmission of HIV [1-3]. Timely linkage-to-care among the newly infected is important to maximize such individual and population-level benefits. The time from infection to linkage~~T~~inkage~~his~~ becomes especially relevant as HIV programs move from treatment ~~alone~~ to ~~a~~ treatment-as-prevention ~~approach~~. For treatment-as-prevention to achieve maximum success in reducing population-level incidence, linkage-to-care should ideally occur immediately following HIV infection for rapid ART initiation~~assessment of ART eligibility and enrolment in ART programs~~. In practice, however, several~~multiple~~ studies have found ~~inadequate~~ low linkage levels ~~and rates to and retention in care~~ in sub-Saharan Africa [4-7]~~,~~ ~~and a~~A recent trial in rural KwaZulu-Natal (ANRS 12249) showed that low linkage-to-care was likely responsible for the failure to reduce population incidence through a community-based HIV treatment-as-prevention intervention [8, 9].

While earlier evidence demonstrated substantial losses to follow-up ~~Loss-to-follow up~~ after ART initiation in several settings ~~has been well documented so far~~ [4, 10, 11], it has recently become clear that the losses in the ~~and recent studies have shifted their attention to the~~ early phases of the HIV care continuum are even more severe [6, 7, 12-17]. Most of this research relied on data from provider-initiated counselling and testing and, to a lesser extent, individuals using voluntary counselling and testing (community-based or home-based) [5]. Few studies used population-based estimates of engagement in care [6-8]. Further, all ~~of~~ the prior~~se~~ studies on linkage-to-care have in common that time to linkage ~~to care~~ was examined using the date of diagnosis, rather than the date of infection, as the starting point. Despite the urgency to improve early testing and treatment, substantial proportions of HIV-positive populations in sub-Saharan Africa still test ~~only~~ late in the course of HIV disease [18]. Testing and treatment-seeking behaviors might be partly driven by perceived health status and examining the determinants of time to linkage-to-care from the date of infection, instead of date of HIV diagnosis (i.e., receipt of a first HIV positive test), can substantially advance our understanding of ~~ould shed a different light on~~ barriers to linkage ~~–~~ ~~. Indeed, This is~~ because the date of HIV diagnosis is likely~~ould be~~ endogenous to linkage rates. In other words, those who get diagnosed earlier are on average ~~could~~ also ~~be~~ more likely to link-to-care rapidly. Previous estimates of determinants of linkage-to-care are therefore potentially biased.

In this ~~study~~study, we aim to estimate the time from HIV infection to linkage, as well as the determinants of this time. We use ~~Using~~ data from one of the largest population-based HIV incidence cohorts in Africa and link~~ing~~ thi~~ses~~e data to patient records from the local~~a~~ public-sector HIV treatment and care program~~ , the aim of this study is to explore determinants of time from HIV infection to linkage-to-care in a rural area of South Africa. By using population-based HIV surveillance data we are not only able to identify the time of HIV infection, but we are also avoiding the selection effects that commonly plague participation in voluntary counselling and testing and other facility-based HIV testing approaches., we are able to make inferences on all HIV-positive individuals in the surveillance area, not just those with access to HIV testing.~~ Improving our understanding of the factors influencing time from HIV infection to linkage-to-care can substantially improve our ability to design and target ~~is critical to inform proper~~ interventions aimed at addressing barriers to early linkage and ~~prompt~~ treatment initiation. Such interventions will be ~~This is~~ especially important for the success of HIV

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treatment-and-prevention policies and the attainment of ~~if~~ the UNAIDS 90-90-90 targets ~~is to be attained~~ [19].

METHODOLOGY

Study population

Since 2000, the Africa ~~Centre for Health and Population Studies~~Health Research Institute (AHRI~~Africa Centre~~) has operated~~established a~~ longitudinal population health~~demographic~~ surveillance ~~system~~ in rural KwaZulu-Natal (uMkanyakude district), South Africa [20]. Nested within the population health surveillance is one of Africa's largest HIV incidence cohorts. ~~The population health surveillance and HIV incidence cohort~~Surveillance ~~Africa Centre Demographic Information System (ACDIS)~~ covers ~~s~~ an area approximately 440 km^2 in size, encompassing a population of 87,000 individuals (75,000 residents and 13,000 non-residents). It was designed to capture the complex and interwoven health, social, and ~~dynamic~~ demographic dynamics of a poor rural Southern African population ~~with very high HIV prevalence~~. ~~realities of this population. The area is predominantly rural and poor with an urban township and informal peri-urban settlements.~~ In 2011, HIV prevalence in the adult population (15-50 years) was estimated at 29% and ART coverage of all HIV-positive adults was 31% [21].

The ~~ACDIS cohort~~AHRI population health surveillance collects information on all individuals ~~members of households or family units located~~who live in the surveillance area. ~~The surveillance longitudinally follows three units of observation: individuals, households (which are socially defined), and residences (which are geographically defined).~~ The surveillance~~ACDIS~~ is conducted in two separate data collection approaches~~cycles~~. First, ~~E~~every four~~six~~ months, a household survey is administered to a key informant to gather data on attributes and events regarding physical structure, households, and individual household members [20]. Second, ~~Conducted~~ every year trained field workers ~~collect through private interviews by trained field workers, the second type of survey~~ collect~~s~~ data through individual interviews, during which confidential ~~on individual members, including anonymous~~ HIV testing is offered to each adult~~(i.e., test results are not disclosed to participants)~~. Eligibility criteria for the HIV sero-surveys from 2003 to 2007 were all women aged 15-49 years and men aged 15-54 years old. After 2007, HIV testing was administered to all individuals aged 15 years and over.

ART became available in the area shortly after the national roll-out in 2004 ~~national roll-out~~ [22]. At that time, HIV-positive individuals could only get access to treatment from the surveillance area's hospital clinic. ART delivery has subsequently been scaled-up to 17 public-sector primary-care clinics in Hlabisa subdistrict; ~~(~~six~~6~~ of these clinics are ~~em being~~ located in the AHRI~~ACDIS~~ surveillance area~~)~~ [23]. The *Hlabisa HIV Treatment and Care Program* provides free HIV testing and counseling, condoms, and ART. ~~This highly decentralized program, run by nurses and counselors, enrolls those testing positive in pre-ART counselling and health monitoring to determine ART eligibility~~ [22, 23]. In this study, linkage-to-~~Enrollment in~~ care was~~is formally characterized by~~operationalized as having a first CD4 count, the required diagnostic criterion to assess ART eligibility during the time of this study, in the local HIV treatment and care program [22]. ~~During the time of this study, CD4 count was a required diagnostic criterion to assess ART eligibility. test performed. Patients' treatment status is recorded and updated in the ART evaluation and monitoring system (ARTemis) database~~. Further details on both the AHRI population health surveillance, the data collection in the HIV

treatment and care program, and the data linkage between these two databases ~~ACDIS and ARTemis~~ can be found elsewhere [1, 20, 22, 24].

Procedures and variables

Seroconverters are identified among repeated-testers. Repeated-testers are defined as the subset of individuals aged 15 years and older who had more than one HIV test performed during annual sero-surveys, for which the first test was negative. Slightly modifying the approach used by Vandormael and colleagues [25], the date of HIV infection was proxied by estimating the date of seroconversion. Given the time lag between subsequent sero-surveys, we could not directly ascertain the date of HIV seroconversion~~infection~~ but it ~~has to~~must have occurred in the interval between the last negative HIV test and the first positive HIV test in the population-based HIV incidence cohort. For our main analysis, we randomly assigned the date of infection between the last HIV negative test and the first HIV positive test, or first CD4 count test, whichever occurred first. A total of ten~~10~~ datasets with random imputation of HIV infection dates were constructed in that way. Random imputation allows us to propagate ~~to our results~~ the uncertainty associated with the unobserved HIV infection dates to our results. For presentation of baseline descriptive statistics, we used the midpoint date between the last negative HIV test and first positive HIV test (or between the last negative HIV test and the first CD4 count test) for simplicity (hereafter referred to as 'midpoint imputation'). Summary of the descriptive statistics of the ten~~10~~ imputed datasets can be found in supplemental materials (Table S1). Infections occurring before August 2004 were excluded since ART had not been rolled-out prior to that date and the individuals were hence not eligible for the outcome (i.e., linkage-to-care). Seroconverters in the AHRI population health surveillance and HIV incidence ~~based ACDIS~~ cohort were linked to the HIV treatment and care program database, using the~~ir~~ South African identification number (or if missing, full names, sex, and birth date)~~ to the local public sector treatment program database (ARTemis)~~. Linkage-to-care is defined in this study as having a first CD4 count test performed following HIV infection, as per the *Hlabisa Treatment and Care Program*'s protocol.

Time to linkage-to-care was explored using time--varying covariates. The dynamic nature of the AHRI population~~ACDIS~~ cohort is captured through exposure episodes. Specifically, an exposure episode starts on the first day of the year and usually ends on the last day of that calendar year. If an individual changes residency or migrates inside or outside of the surveillance area, a new exposure episode is created for that ~~time~~ period. Exposure episodes are thus of variable lengths and seroconverters can only live in one residence~~be a resident of one household~~ at a time (but multiple household memberships are allowed). ~~For each of these exposure episodes, we were able to assign seroconverters time-invariant and time-varying individual-level and household-level characteristics.~~ All individuals who migrated out of the surveillance area, even temporarily, were censored on their emigration day. If an individual's infection date was estimated to have occurred while outside of the surveillance area, this person was excluded. Hence, the ten~~10~~ randomly imputed datasets may have slightly different sample sizes and person-time of follow-up. ~~In the event that~~If seroconverters were not found to be linked to HIV~~ART~~ care, they were censored on their last day of follow-up, the date they died, or January 2014 – whichever occurred first.

The main outcome of this study is time from HIV infection to linkage-to-care. The only time-invariant variables considered are gender, knowledge of HIV status at baseline (i.e., first positive test), and the calendar year of infection. Time-varying variables are: age, area of residence ~~(urban, peri-urban, rural)~~, socio-economic status (asset-based index categorized into

quartiles, among seroconverters, using the first axis of a principal component analysis of 21 household assets), education level ~~(none or less than one year, some or completed primary, and some or completed secondary)~~, whether one's household co-members are receiving~~on~~ ART ~~(yes, no)~~, and the Euclidian distance to the closest health facility where ART is~~are~~ provided ~~(<2 km, between 2 and 4 km, and >4 km).~~ Since some of the exposure episodes are retrospectively constructed (i.e., they are within two survey dates), we assigned them based on the closest survey date (but not more than one year after the beginning of the exposure episode). Household-level variables were attributed based on household residence and closest survey date. For missing education level values, if an individual was aged 19 years or above and had at least one observation with information on education level, we imputed that value using the previously reported education level.

Statistical analyses

Time from HIV infection to linkage-to-care was first explored using Kaplan-Meier estimates of the survival curve. CD4 counts at linkage, stratified by time to linkage-to-care, were also examined. Cox proportional hazards models were then used to estimate the effect ~~size measure~~ of the different variables on time to linkage-to-care. Covariates with missing observations were retained in the analysis using the missing indicator method [26]. We present results for univariate and multivariable models. Because the question about knowledge of HIV status was not part of the questionnaire in 2004 and 2005, the multivariable model only included observations from individuals who seroconverted from 2006 onwards. The method of Grambsch and Therneau [27], based on the scaled Schoenfeld residuals, was used to test that all variables met the proportional hazards assumption. Because some covariates failed that test, we stratified ~~all~~ the survival analyses using the calendar year of HIV infection ~~to resolve the issue~~. ~~After stratification all covariates met the proportional hazards assumption.~~ All analyses were performed individually on the 10 imputed datasets and results were combined ~~using~~ with Rubin's rule [28] using ~~. All analyses were performed using~~ the R statistical software [29]. ~~and t~~The '*survival*' package [30] was used to fit the Cox proportional hazards models.

Ethics

All respondents provided informed consent. The *Biomedical Research Ethics Committee* of the University of KwaZulu-Natal granted ethical approval for data collection.

RESULTS

Among individuals that were believed to have seroconverted between August 2004 and December 2013, 10 were found to have been linked to care before their last negative test and were therefore excluded from our analyses. Since they were potentially outside of the *Hlabisa Treatment and Care Program*'s catchment area, individuals not recorded to be in the surveillance area at their estimated time of HIV infection were also excluded. Hence, and depending on the randomly imputed seroconversion dates, between 1,713 and 1,779 recent seroconverters contributed between 4,582 and 4,818 person-years of follow-up to our inferences. Results from the midpoint imputation and the ~~10 pooled~~ randomly imputed datasets differed principally with regards to the uncertainty around the different estimates but not ~~with regard to~~regarding the effect size estimates (see supplemental material Tables S2-S4 and Figures S1-S2).

Baseline characteristics of recent seroconverters are presented in Table 1 ~~(midpoint imputation)~~. The great majority (77%) of recent seroconverters were women~~, mean age at HIV infection was 27 years old,~~ and over 70% had some or completed secondary education. Mean age

at HIV infection was 27 years. Most recent seroconverters did not have members of their household who hadhaving initiated ART. and 63% of seroconverters responded that they were aware of their HIV status at the time of their first positive test. The highest numbers of seroconversions were observed in 2007 and 2008. The median time between last negative test and first positive HIV test was 2.0 years (interquartile range (IQR): 1.1-3.2 years; with a maximum of 10 years).

Averaging over the imputed datasets, the median follow-up time was 2.2 years (IQR 1.1-3.9) and only 314% of those who were followed-up for a minimum of six 12 months had a CD4 count test performed within that time-period (this rises to 14% for 12 months of follow-up and to 29% two years after HIV infection). Among those whothat had a CD4 count test performed, the median time to linkage-to-care was 1.6 years (95% confidence intervals (CI): 1.5 to 1.8). At linkage, the median CD4 count was 350 cells/μL (95% CI: 330 to 380) (Table 2). Seroconverters that were linked to care in less than one year had a higher median CD4 cell count higher (370 cells/μL; 95% CI: 320 to 410) than those that linked more than five years after infection (290 cells/μL; 95%CI: 160 to 430). A total of 40 recent seroconverters died before being linked to care after a median follow-up time of 3.0 years (IQR: 1.9-4.7) after infection. The pooled Kaplan-Meier estimates of time from HIV infection to linkage-to-care are presented in Figure 1. From this, we estimate that it would have taken an average of 4.9 years (95% CI: 4.2 to 5.7) for 50% of seroconverters to be linked to care (Table 3). After nine years of follow-up, the proportion of seroconverters linked to care reached a maximum of 64% (95%CI: 50-79%). Time to linkage-to-care differed by gender: it took about 1.7 years (95% CI: 1.5-2.0) for 25% of women to link to care versus 3.4 years (95% CI: 2.4-4.4) for men. Time to linkage-to-care also decreased with calendar time with 25% of seroconverters linking in 3.7 years (95% CI: 2.4-5.0) for those who acquired their infection in 2004 to 1.4 years (95% CI: 0.6-2.2) for those who did so in 2010.

In univariate analyses, the main determinants of time to linkage-to-care were gender, age, education level, and knowledge of HIV status from previous testing (Table 4). Of these variables, education level remained only marginally statistically significant in the full multivariable model. As compared with females, males had roughly half the hazards of being linked to care (adjusted Hazard Ratio [aHR]=0.49; 95%CI 0.37-0.64). Seroconverters in the 40-49 years of age category had hazards 54% higher (95%CI: 14 % to 108%) of being linked to care as compared to seroconverters aged 15-29 years old. Individuals with some or completed secondary education had lower hazards of being linked to care than those with a year or less of education, although this trend was only marginally significant (aHR=0.63; 95%CI: 0.39-1.00). Household co-memberships with individuals who had previously initiated ART increased the hazards of being linked to care by 23% (95%CI: -2 to % to 55%) but the confidence intervals of this estimate erossescrossed the nullis effect was marginally significant. Finally, the hazards of being linked to care for individuals that are aware of their HIV status from previous testing were 35% (95%CI: 9 to % to 68%) higher than those whothat were unaware of their status or whothat refused to answer the survey question.

DISCUSSION

We estimated that it has taken an average of 4.9 years for 50% of seroconverters to be linked to care during 2004-2013, period during which these individuals contributed to onward

HIV transmission. Among all recent seroconverters that had a CD4 count test performed, the median time to linkage-to-care was 1.6 years. CMeaningful comparisons with other empirical data settings is difficult because time to linkage-to-care has been defined in the past using HIV diagnosis as the starting point. To the best of our knowledge, this study is the first to measuredefine time to linkage-to-care using a direct n estimated of the HIV infection date as a starting point. The longitudinal HIV status data for this study was generated in one of Africa's largest population-based HIV incidence cohorts. Our empirical estimate of among a population-based cohort of repeated testers. This first directly measured empirical estimate of time from HIV infection to linkage is highly policy-relevant because it is a minimum bound on the length of time during which HIV-positive individuals can transmit HIV before the transmission risk is potentially eliminated through HIV treatment [31]. Our results indicate that substantial linkage improvements will be needed to maximize population-level benefits of both HIV treatment and HIV treatment-as-prevention.

With close to a quarter of patients dying within their first year on ART [31], not only is earlier initiation required, but also earlier diagnosis. We estimated that the median CD4 counts at linkage-to-care waswere of 370 cells/μL for individuals linking within one year of HIV infection and 290 cells/μL for those linking five years or more after HIV of infection, as opposed to 290 cells/μL for individuals linking five years or more after HIV infection. A number ofSeveral reasons could explain that the median CD4 count for individuals linking to care within one year was below 500 cells/μL. First, the observed time lag between the last negative and first positive HIV test had a median of 2 years. Non-differential misclassification of the date of HIV infection could have biased our results toward the overall median CD4 count of individuals linking to care. Second, rates of decline in CD4 counts follow an unobserved distribution that we are able tocan estimate only among those individuals who linked to care. If linkage is a function of health status, which has been shown in other studies [15, 32], those with rapid disease progression, and lower CD4 cell counts, will link to care faster. The resulting median CD4 cell count since time from HIV infection is thus likely lower among our sample of individuals that linked to care than the median CD4 cell count since time from HIV infection among all HIV-positive people.

This alternate definition provides more relevant data contributing to our understanding of HIV epidemiology and its transmission dynamics. Another limitation of the extant literature that our study is addressing is that HIV testing and diagnosis can, at least partly, be a function of health status and treatment-seeking behavior, leading to endogeneity biases when the date of diagnosis is used in survival analysis of the determinants of linkage-to-care. Our approach, which is based on the date of HIV infection rather than the diagnosis date, corrects for this potentially important bias. Moreover, time from HIV infection to linkage-to-care is important for policy making. The shorter this time, the higher are the chances of successful HIV treatment. Additionally, this time is an important determinant of the success of HIV treatment-as-prevention strategies, because it is the time during which an HIV-positive individual can contributes to transmissiontransmit the HIV virus. Our median estimate of a 5 years delay from HIV infection to linkage-to-care, results indicates that substantial linkage improvements will be needed to maximize population-level benefits of HIV treatment-as-prevention.

With close to a quarter of patients dying within their first year on ART treatment [31], not only is earlier initiation required, but also earlier diagnosis. We estimated that the median CD4 count at linkage-to-care was of 370 cells/μL for individuals linking within one year of infection, as opposed to 290 cells/μL for individuals linking five years or more after HIV

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~~infection. A number of reasons could explain that the median CD4 count for individuals linking to care within one year was below 500 cells/μL. First, the observed time lag between the last negative and first positive HIV test had a median of 2 years. Non-differential misclassification of the date of HIV infection could have biased our results toward the overall median CD4 cell count of individuals linking to care. Second, rates of decline in CD4 counts follow an unobserved distribution that we are able to estimate only among those individuals who linked to care. If linkage is a function of health status, which has been shown in other studies [15, 32], those with rapid disease progression, and lower CD4 cell counts, will link to care faster. The resulting median CD4 cell count since time from HIV infection is thus likely lower among our sample of individuals that linked to care than the median CD4 cell count since time from HIV infection among all HIV-positive people.~~

In this mostly poor and rural population, rates of linkage-to-care were twice as high for females as those of males, substantiating previous research [5, 6, 33]. The same was true for age, with seroconverters in the 40-49 years old range having the highest rates of linkage-to-care. ~~Individuals with more education were found to be less likely to link to HIV care, although this was only marginally significant.~~ Having other household members who previously initiated ART ~~also had a marginally significant effect on~~tended to reduce time to linkage-to-care. This finding provides some limited evidence that family and social exposure HIV treatment ~~to the *Hlabisa Treatment and Care Program* c~~an facilitate linkage and ~~ould bolster~~ ART uptake.

~~Not surprisingly, one's knowledge of his/her HIV status from previous testing was a strong predictor of linkage to HIV care.~~ Diagnosing HIV is the first, and necessary step, on the HIV treatment cascade. We estimated that 63% of individuals were aware of their HIV status at their first positive HIV test during the annual sero-surveys and this was a predictor of linkage-to-care. Yet, linkage-to-care was low and delayed in this cohort of seroconverters. This finding could be partly due to the eligibility criteria for ART from 2004 to 2010. During those years, only individuals with CD4 count less than 200 cells/μL were eligible for ART initiation. Compounding this effect are the previously described low pre-ART retention rates [16] and high disengagement from care in this cohort [11]. These findings are corroborated by those from the first phase of the ANRS 12249 treatment-as-prevention trial, conducted in the same area as this study, which showed that the delays in linkage-to-care could compromise the population-level effectiveness of treatment-as-prevention [8, 9]. Preliminary results from the trial suggest that treatment-as-prevention did not substantially reduce HIV incidence because ART coverage in both arms of the trial were similar [8, 9]. That is, the intervention failed to link-to-care a substantial proportion of people in early HIV infection stages. Our estimates of time to linkage-to-care are nevertheless different than those from this trial because the latter did not define time to linkage based on date of HIV infection but date of diagnosis (the trial was not powered to examined time from HIV infection to linkage-to-care). ~~Here, we provide direct evidence of important delays in time from HIV infection to linkage-to-care. Although these delays have tended to decrease with time, we estimated that the proportion of seroconverters linked to care would still be substantially lower than the UNAIDS target with a maximum proportion of 64% of seroconverters linked to care after the maximum observed follow-up of nine years.~~

Great challenges will need to be overcome to maximize the public health benefits of ART in ~~such~~ settings such as the community in which this study took place~~and to reach UNAIDS's 90-90-90 objective~~. ~~A number of~~Several potential solutions have been proposed from point-of-care CD4 testing with home-based counseling and testing to health systems interventions and

financial incentives [34, 35]. Yet, the quality of evidence for these proposed interventions is low and interventions often only target a single point in the HIV care continuum [34, 35]. It is also unlikely that a single intervention could efficiently address all barriers to timely linkage-to-care [36]. More research is needed into multi-pronged approaches that would mitigate the individual, community, and structural barriers that delay linkage-to-care.

This study has some limitations. First, the exact date of HIV infection remains unknown and was estimated based on individuals who repeatedly participated in the annual population HIV surveillance surveys. Yet, random imputation of infection dates, resulting in non-differential measurement errors in time-to-event, generally introduces only small bias in the hazard ratio estimates [37, 38]. Further, we randomly imputed 10 datasets and the summary estimates we present included this imputation uncertainty. Second, we cannot totally rule out that some individuals found to have seroconverted sought care outside of the *Hlabisa Treatment and Care Program*. Nevertheless, it is unlikely that the proportion of HIV positive individuals accessing ART outside of this public - sector program is higher than a few percent [24]. LMoreover, low rates of health insurance makes private health care utilization, in particular for chronic diseases such as HIV, of ART rare in this community [24].

An important strength of this research is the use of population-based data, from one of Africa's largest population-based HIV incidence cohorts, to estimates the time from HIV infection toof HIV linkage-to-care. Such estimates are likely potentially less biasedmore representative of the the full population of HIV-positive individualpopulations in a community than those derived from facility-based data. Other strengths include the definition of time to linkage-to-care based on date of HIV infection. To the best of our knowledge, this is the first study to use this definition, instead of the date of HIV diagnosis, which that is likely to could potentially lead to substantial underestimates of time to linkage.biased estimates. Using a cohort of repeated testers to estimate infection date is also more accurate than other approaches, such as back-calculation of seroconversion date based on CD4 cell counts at ART initiation or estimations based on tests for recent infections, which could introduce additional errors [39, 40]. Finally, we addressed a limitation of the extant literature on the determinants of linkage-to-care. Because HIV testing and diagnosis can, at least partly, be a function of health status and treatment-seeking behavior, using the date of diagnosis in survival analysis could lead to endogeneity biases. Our approach, based on the date of HIV infection rather than the diagnosis date, corrects for this potential bias.

In conclusion, large reductions in the time from HIV infection to linkage-to-care are required to realize the full potential of HIV treatment and HIV treatment-as-prevention in improving population health. iIncreasing HIV testing uptake and frequency, as well as targeted interventions to improve linkage-to-care, in particular for men and young individuals, couldare likely good candidate interventions for shortening the time from infection to the first HIV clinic visit be considered to facilitate earlier linkage to HIV care after infection [41]. Without timely linkage-to-care, the population-level impact of treatment-as-prevention is unlikely to significantly reduce HIV incidence in this population.

AUTHOR CONTRIBUTIONS

Conceived and designed the experiments: TB, FT, and DP. Performed the experiments: MMG. Analyzed the data: MMG MCB SAJ. Wrote the paper: MMG, TB, FT, SAJ, MCB, and DP.

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Table 1: Baseline characteristics of recent seroconverters (using midpoint imputation; N=1,733) residing in the demographic surveillance area, South Africa (2004-2013).

Variables	Mean (SD) or Total (%)
Gender	
Female	1,333 (76.9%)
Male	400 (23.1%)
Age (years)	26.8 (10.5)
Education level	
None or less than one year	103 (5.9%)
Some or completed primary	269 (15.5%)
Some or completed secondary	1,289 (74.4%)
Missing	*72 (4.2%)*
Socio-economic status	
Poorest	374 (21.6%)
Poor	435 (25.1%)
Rich	488 (28.2%)
Richest	435 (25.1%)
Missing	*1 (0.1%)*
Food security	
Never (or some months) missed meals	1,675 (96.7%)
Missing meals almost every month (financial reasons)	47 (2.7%)
Missing	*11 (0.6%)*
Uptake of ART by household members	
No household members on ART	1,463 (84.4%)
At least one household member on ART	270 (15.6%)
Knowledge of HIV Status*	
Aware	917 (63.3%)
Unaware / Refused	537 (36.7%)
Area of residence	
Urban	52 (3.1%)
Peri-urban	619 (35.7%)
Rural	1,061 (61.2%)
Distance to closest health facility (km)	6.0 (9.1)
Calendar year of HIV infection	
2004	81 (4.7%)
2005	198 (11.4%)
2006	240 (13.8%)
2007	259 (14.9%)
2008	262 (15.1%)
2009	207 (11.9%)
2010	180 (10.4%)
2011	153 (8.8%)
2012	129 (7.4%)
2013	24 (1.4%)

*The question about knowledge of HIV status from previous testing was not asked in 2004 and 2005 (279 seroconverters were excluded).

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Table 2: Median CD4 cell count (cells/μL) at linkage, stratified by linkage time since HIV infection, with 95% bootstrapped confidence intervals.

Time from HIV infection to linkage-to-care	Median CD4 cells/μL (95%-CI*)
Less than one year	370 (320, 410)
Between one and two years	380 (340, 420)
Between two and three years	360 (290, 430)
Between three and four years	310 (230, 390)
Between four and five years	320 (220, 410)
More than five years	290 (160, 430)
Overall	**350 (330, 380)**

*95%CI=95% confidence intervals. These are based on 9,999 bootstrap replicates.

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Table 3: Time from HIV infection (years) to linkage to care stratified by gender and calendar year of HIV infection.

Characteristics	Time from HIV infection for 25% of seroconverters to link to care (95%-CI*)	Time from HIV infection for 50% of seroconverters to link to care (95%-CI*)
Gender		
Females	1.7 (1.5-2.0)	4.2 (3.7-4.6)
Males	3.4 (2.4-4.4)	NA†
Calendar year of HIV infection		
2004	3.7 (2.4-5.0)	6.1 (3.7-8.5)
2005	3.1 (2.4-3.8)	5.6 (4.2-7.1)
2006	2.3 (1.7-2.9)	4.6 (3.3-6.0)
2007	1.6 (1.0-2.3)	4.0 (2.7-5.4)
2008	1.5 (1.0-2.0)	NA†
2009	1.6 (1.0-2.2)	NA†
2010	1.4 (0.6-2.2)	NA†
Overall	**2.0 (1.8-2.2)**	**4.9 (4.2-5.7)**

*95%CI=95% confidence intervals. These are based on 9,999 bootstrap replicates.
†NA=not available (the follow-up time was not long enough to observe 50% of seroconverters linking to care).

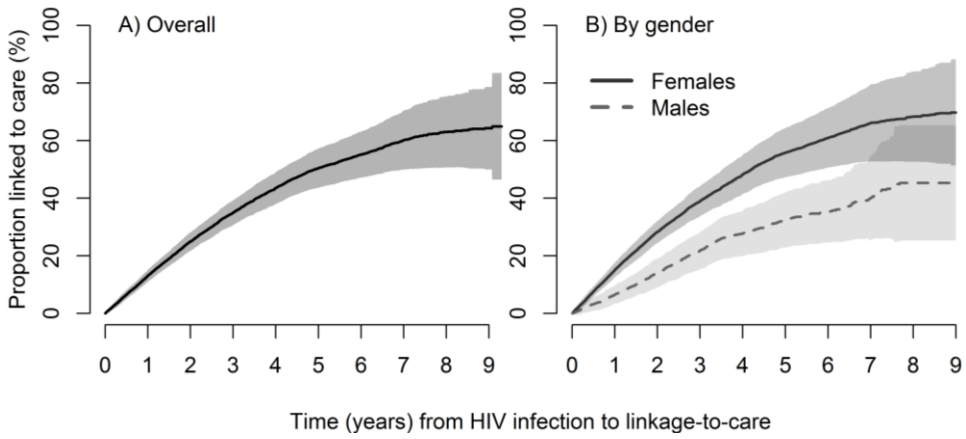

Figure 1. Pooled Kaplan-Meier estimates of time from HIV infection to linkage-to-care in rural Kwa-Zulu Natal South Africa (2004-2013) for A) all seroconverters and B) stratified by gender.

Table 4: Univariate and multivariable effect size estimates from Cox proportional hazard models of determinants of time from HIV infection to linkage-to-care in rural Kwa-Zulu Natal, South Africa. (Pooled results from the 10 imputed datasets.)

Variables	Univariate HR (95% CI)	Multivariable* aHR (95% CI)
GENDER		
Male	**0.49 (0.39-0.61)**	**0.49 (0.37-0.64)**
AGE		
15-29 years old	1.00	1.00
30-39 years old	1.22 (0.96-1.55)	1.16 (0.86-1.57)
40-49 years old	**1.92 (1.53-2.40)**	**1.54 (1.14-2.08)**
50+ years old	1.15 (0.80-1.64)	0.87 (0.53-1.44)
EDUCATION LEVEL		
None or less than one year	1.00	1.00
Some or completed primary	0.87 (0.61-1.25)	0.75 (0.46-1.22)
Some or completed secondary	**0.68 (0.50-0.93)**	0.63 (0.39-1.00)
FOOD SECURITY		
Missing meals almost every month (financial reasons)	1.56 (0.88-2.79)	1.37 (0.67-2.80)
SOCIO-ECONOMIC STATUS		
Poorest	1.00	1.00
Poor	1.15 (0.90-1.46)	1.21 (0.91-1.61)
Rich	1.14 (0.90-1.44)	1.19 (0.75-1.90)
Richest	1.00 (0.78-1.29)	1.05 (0.62-1.79)
OTHER HOUSEHOLD MEMBERS USING ART		
At least one (versus 'None')	1.16 (0.96-1.41)	1.23 (0.98-1.55)
KNOWLEDGE OF HIV STATUS*		
Yes (versus 'No / Refused')	**1.52 (1.24-1.87)**	**1.35 (1.09-1.68)**
AREA OF RESIDENCE		
Urban	1.00	1.00
Peri-Urban	0.65 (0.42-1.02)	0.73 (0.43-1.24)
Rural	0.77 (0.49-1.21)	0.76 (0.45-1.30)
DISTANCE TO HEALTH FACILITY		
<2 km	1.00	1.00
2 to 4 km	1.04 (0.86-1.25)	1.00 (0.79-1.26)
>4 km	1.16 (0.93-1.45)	1.10 (0.84-1.44)
CALENDAR YEAR OF HIV INFECTION	Included as strata	Included as strata

HR (95% CI)=Hazard Ratio (95% Confidence Interval); aHR=adjusted Hazard Ratio.
Results are presented after pooling the analyses of the 10 imputed datasets. All models were stratified using the calendar year of HIV infection to ensure that the proportional hazards assumption was met. The model's outcome variable was the time from HIV infection to linkage-to-care. We used ; the latter was defined using the date of the first CD4 count test was performed in the local HIV treatment and care program to identify the time from infection to linkage.
*The question about knowledge of HIV status from previous testing was not asked in 2004 and 2005, hence, observations from these years were not included in the multivariable model.

AIDS: Author's paper submission checklist

Title of paper:	►Determinants of time from HIV infection to linkage-to-care in rural KwaZulu-Natal, South Africa
Names of authors:	► Mathieu Maheu-Giroux, Frank Tanser, Marie-Claude Boily, Deenan Pillay, Serene A Joseph, and Till Bärnighausen

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1. DUPLICATE PUBLICATION is not acceptable and includes papers, or letters to the Editor reporting the same data previously published in any journal. Abstracts of papers presented at meetings and published in the proceedings of such meetings do not constitute duplicate publication, but should be disclosed by including a note at the beginning of the paper, i.e.. "Data presented previously at (state meeting) and published as abstract in (give reference)". Have you published these data previously?

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4. ETHICS All studies need to be approved by the local Ethical Committees. Was your study? Please provide the approval from your local Ethical Committees for any animal experimentation or human subject studies.

► Yes, the *Biomedical Research Ethics Committee* of the University of KwaZulu-Natal granted ethical approval for data collection

5. AUTHOR'S CONTRIBUTIONS AND APPROVAL OF TEXT Please state briefly how each of the authors contributed to the study, to data analysis and to the writing of your paper. Subject to your agreement, we will print this information, if the paper is accepted for publication. In addition, please confirm that all the authors have read and approved the text as submitted to AIDS. Justify individual's contributions when the author list exceeds 10.

► Conceived and designed the experiments: TB, FT, and DP. Performed the experiments: MMG. Analyzed the data: MMG MCB SAJ. Wrote the paper: MMG, TB, FT, SAJ, MCB, and DP.

6. STATISTICAL ANALYSIS Kindly please let me know who performed the statistical analysis of you data.

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