Adult life expectancy in the era of ART: evidence from four population-based HIV surveillance studies in Uganda, Malawi and South Africa.

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Abstract

Few studies directly measure the population-wide impact of antiretroviral therapy (ART) on HIV-related mortality in Africa, with existing estimates heavily relying on extrapolations of clinical data. We describe (i) trends in adult life expectancy (LE) at age 15, (ii) the LE gains directly attributable to ART, and (iii) the remaining LE deficit due to HIV in four population-based HIV surveillance sites. We fit a model of age-specific HIV incidence and natural survival to estimate counterfactual LE trends in the absence of ART and use that to derive the gains attributable to ART. Estimates are disaggregated by sex and span the years 1985 to 2017. Total or gross LE gains range between 6 and 17 years and are larger for women than men. LE gains are largest in eastern Africa, where HIV prevalence declined prior to ART availability, but the net effect of ART is largest in South African sites, where LE would have continued to decline without ART.

Introduction

The expansion of HIV care services is one of the largest public health interventions in sub-Saharan Africa of recent times, but it is difficult to directly measure its population-wide impact on HIV mortality because many of the countries that are most affected by the epidemic have poor registration of vital events. A number of studies from sub-Saharan Africa have described population-level trends in adult mortality following the scale-up of treatment for HIV, but they usually fall short of quantifying the net impact of ART on mortality.[1-3] A modeling study by Johnson and colleagues for South Africa is a notable exception.[4]

In this contribution, we use data from four demographic surveillance sites in three eastern and southern African countries to evaluate the impact of ART on adult life expectancy. In addition to the population perspective offered by these study sites, our analyses take advantage of their efforts to conduct repeated population-based HIV surveys, which allows us to estimate adult mortality trends by HIV status. We present three sets of estimates. First, we compute trends in population-wide adult LE and use these to estimate the *gross gains in adult LE* before and after the introduction of ART. Second, we estimate the counterfactual adult LE in the absence of treatment and subtract that from the gross LE gains to obtain a measure of the *net LE gains attributable to ART*. Third, we take the adult LE of HIV negative individuals as a benchmark, and compare it to the LE in the population as a whole. The difference between those is an estimate of the remaining *adult LE deficit associated with HIV*, or, the number of adult life-years that could be gained from further reductions in HIV-related mortality.

All estimates are disaggregated by sex. Gender equity in the uptake of ART has been a concern since the early days of the treatment scale-up; initially because of women's elevated HIV prevalence and men's privileged access to treatment, where it was offered under a patient co-pay scheme, [5,6] nowadays because program statistics are more favorable for women all along the cascade of HIV care and treatment. Nationally representative surveys from Africa consistently report higher female HIV Testing and Counseling (HTC) coverage rates, [7] and a disproportionately large number of women are on ART. [8,9] Women are also less likely to enroll with advanced disease, and tend to have lower attrition and mortality rates following treatment initiation. [10] [9,11-14]

Data

We use data from four rural study sites in Uganda, Malawi and South Africa with severe to very severe HIV epidemics (we will add more sites by the time of the conference, Figure 1). [15] The rollout of ART in the study sites started between 2004 and 2007, and by 2009 all residents had access to free ART at a local primary healthcare facility. All study sites use demographic surveillance to track the residency episodes and terminating events of residency episodes (death, migration and administrative censoring), and thus provides a measure of the events and person-time of exposure. HIV status information comes from community-based serological surveys, supplemented by self-reports, proxy reports in post-mortem interviews, and -in some settings- from individually-linked medical records. The data used in this analysis are described in greater detail in an ALPHA Network data resource profile. [16,17]

Figure 1: Location of the ALPHA Network study sites

Notes: ● = included in study; ● = not (yet) included in this abstract, but under consideration. We use location names to refer to the study sites. Other names are sometimes used to refer to the same study sites. This is the case for the study sites in Kisesa (Magu DSS), Kisumu (KEMRI/CDC Health and Demographic Surveillance System), Masaka (General Population Cohort in the Kyamulibwa sub-district), uMkhanyakude (AHRI Population Intervention Platform).

Methods

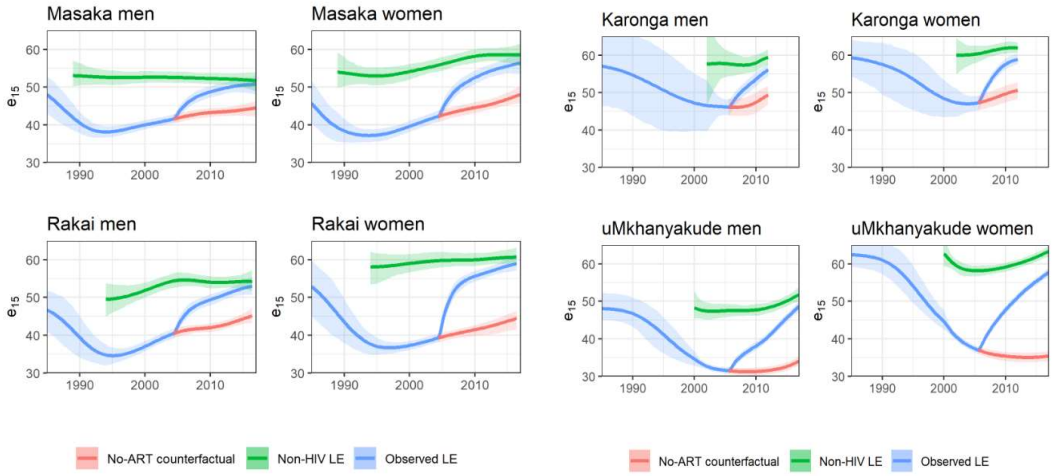
We define the adult LE as the number of additional years that a 15-year old can expect to live under the mortality rates that prevail in a particular year or period. These estimates are produced with a flexible continuous-time demographic model. The model incorporates natural (non-HIV) mortality, age-specific HIV incidence over time, natural HIV survival depending on age at infection, and reductions in HIV mortality during the period in which ART is available. This model is described in greater detail in Appendix 1.

We report on three derived LE measures (i) the population-wide gains in the adult LE before and after ART first became available (*gross LE gains*), (ii) the LE gains directly attributable to ART (*net LE gains due to ART*), and (iii) trends in the *remaining adult LE deficit* due to HIV. The gross LE gains are the difference in the overall LE between two points in time. These not only reflect the mortality reductions due to ART, but can also stem from historical reductions in the number of new infections (leading to contemporaneous declines in AIDS mortality), as well as changes in the background mortality from causes unrelated to HIV. To obtain the net LE gains due to ART, we first estimate the counterfactual LE in the absence of ART and subtract that from the observed adult LE. For computing the remaining LE deficit due to HIV, we treat the LE of HIV negatives as a benchmark of achievable LE and subtract the observed LE for the population as a whole. The adult LE deficit depends on the epidemic magnitude and maturity as well as the mitigating effects of ART. Mortality from non-HIV related causes will moderate the LE deficit because fewer life-years are lost to HIV in a population where the death rates from these competing causes are high (provided that they are uncorrelated HIV status). Younger ages at HIV infection and death will widen the LE gap.

Preliminary results

In Figure 2 we illustrate the outputs from our estimation model in terms of LE trends. Three estimates are shown in these plots, namely the observed adult LE trend (blue), the LE trend for HIV negative individuals, or, non-HIV LE (green) and the counterfactual LE trend under the assumption that no treatment for HIV exists (red). These estimates will later allow us to compute the derived measures discussed above (not shown here).

Figure 2: Trends in the adult LE at age 15, the adult LE of known HIV negative, and the no-ART counterfactual, by study site and sex (1985-2017)



All populations in this study have achieved (gross) adult LE gains in excess of one year per annum since the introduction of ART, and the total increase in the observed adult LE generally varies between 10 and 15 years. Treatment programs do not, however, deserve full credit for the mortality reductions because improvements in adult LE may also result from changes in background (non-HIV) mortality and, more importantly, earlier declines in the number of new infections. This is illustrated by the trend in the no-ART counterfactual, which shows that LE would have increased in in the three eastern African sites in the absence of ART. A decline in HIV-related deaths is thus the logical result of a reduction in the number of incident cases a decade earlier. The South African HIV epidemic is younger and in absence of treatment we would not have expected any substantial gains in adult LE. As a result, these preliminary results suggest that the net LE gains attributable to ART (the difference between the blue and red lines in Figure 2) (i) larger than the gross LE gains in the South African site, (ii) larger than the net LE gains in the eastern African study sites, and also (iii) larger than previously estimated.[1]

The expansion of treatment programs has not been gender-neutral. As we have shown elsewhere, women living with HIV now have significantly lower mortality rates than men in the majority of study sites.[3] This gender disparity in the mortality rates of PLHIV contribute to the larger female LE gains (both gross and net). Any assessment of gender inequities would be incomplete, however, without an evaluation of differences in the current adult LE deficit due to HIV (the difference between the green and blue lines in Figure 2). A comparison of the LE deficit between men and women suggests that the burden of HIV is still as large as, or even larger for women than it is for men. In other words, the expansion of ART seems to have benefited women more, but it has yet to fully rectify an existing gender imbalance in the burden of HIV on adult LE. Women's relatively large gains in adult LE are related to their more effective engagement with HIV diagnostic and treatment services as has been reported elsewhere, but it is also worth noting that the elasticity of women's LE with respect to HIV mortality is greater than that of men because women are generally infected at younger ages than men and also have lower mortality from causes other than HIV. These two phenomena imply that an HIV-related death induces a greater loss in life-years for a woman than it does for a man. Conversely, preventing a female HIV-related death will result in a larger gain in adult LE.

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Appendix I. Statistical model for estimating the counterfactual LE in the absence of ART

To estimate the adult LE in the absence of ART, we fit a flexible parametric Bayesian model to jointly estimate HIV incidence, HIV-related mortality including the effect of ART, and background (non-HIV) mortality from the cohort data. The model is estimated independently for each site and each sex. Then to calculate the counterfactual LE, we simulate the LE over time in the absence of any effect of ART.

The model is specified by three hazard functions: $\lambda(a,t)$ defining the HIV incidence rate at age a and time t, $\rho(a,t,u)$ defining the HIV-mortality rate for a person of age a, at time t, and duration of infection u, and $\mu(a,t)$ defining the background non-HIV mortality rate at age a and time t. The hazard functions are flexibly modeled using penalized b-splines ("p-splines") with knots every 5 years, penalizing first-order differences between spline coefficients.

The age-specific HIV incidence rate $\lambda(a,t)$ at age a and time t is modeled using independent smooth spline functions over age and time:

$$\lambda(a,t) = f(a) + f(t) + f(a,t)$$

where $f(a)$ and $f(t)$ specify average time trend and age pattern for incidence and $f(a,t)$ allows for an interaction between age and time, therefore allowing a change in the incidence age pattern over time, defined over the period $t \in (1970.0, 2017.0)$ and ages $a \in (10, 100)$.

Survival after HIV seroconversion in the absence of ART is modeled using a Weibull distribution with shape and scale parameter fitted to the data for age at seroconversion a_0, with priors derived from Bellan et al [20] based on data from HIV seroconverter cohorts in Europe.[21] After the introduction of ART at time t_{ART}, the effect of ART is incorporated by reducing the HIV-related mortality hazard as function of time $t > t_{\text{ART}}$. Thus $\rho(a,t,u)$ is defined as a product of a Weibull hazard function and a piecewise ART effect:

$$\rho(a,t,u) = \omega(a-u,u) \cdot g(t)$$

where $\omega(a_0 - u, u)$ is the Weibull hazard function for age at infection a_0, and $g(t)$ is the reduction in HIV mortality hazard after ART is available, defined as:

$$g(t) = \begin{cases} 1 & \text{if } t < t_{\text{ART}} \\ g_{\text{ART}}(t) & \text{if } t > t_{\text{ART}} \end{cases}$$

$g_{\text{ART}}(t)$ is a p-spline function with equally spaced knots.

Background (non-HIV) mortality was modeled additively for age and time. That is,

$$\mu(a,t) = h(a) + h(t)$$

where $h(a)$ and $h(t)$ are p-splines with knots every 5 years. The age pattern of non-HIV mortality is not allowed to change over time, though the overall magnitude changes over time.

Analyses are conducted separately for each study site and sex. Due to HIV testing results being available starting at age 15 in all study sites, incidence is treated as having occurred at age 10 or older, with the assumption that modeled incidence between ages 10 and 15 largely represents long-term survival of infant infections. Thus, taken together the data available for an individual i of a given sex in a given study site can be summarized as

$$Y_i = \{t_i^B, t_i^S, t_i^E, \delta_i, t_i^N, t_i^P, \gamma_i\}$$

where

t_i^B = date of birth
t_i^S = date of entry into cohort (first observed alive)
t_i^E = date of exit from cohort (death or censoring)
δ_i = indicator variable indicating death (=1) or censoring (=0) at t_i^E
t_i^N = start of potential seroconversion interval (either last HIV- test or age 10)
t_i^P = end of potential seroconversion interval (either first HIV+ test or t_i^E)
γ_i = indicator of known HIV+ (=1) or censoring (=0) at t_i^P.

It is possible that some individuals may not have any observed HIV serostatus data, in which case $t_i^N = 10, t_i^P = t_i^E, \gamma_i = 0$.

The likelihood for each individual Y_i is described as a function of the three hazard functions $\lambda(a,t)$, $\rho(a,t,u)$, and $\mu(a,t)$ accounting for the left truncation and right censoring of survival episodes and interval censoring of HIV serostatus observations. The model integrates over all possible seroconversion times $s \in (t_i^N, t_i^P)$. The total likelihood is the product of the likelihood for each individual, though individuals are aggregated into age/time cohorts to allow for computational efficiency. Additionally, for all sites, we incorporated additional estimates for the time-trend of HIV prevalence based on national estimates or regional antenatal clinic prevalence data to inform HIV trends prior to the establishment of population surveillance.

For computing the likelihood, time is discretized into 0.2-year time-steps and all event dates and ages are rounded to the nearest one-fifth of the year. The likelihood is programmed in Stan and R and estimated using Hamiltonian Monte Carlo, No U-Turn sampler (NUTS).

To calculate the counterfactual adult LE trend in the absence of ART, we fixed the function $g_{\text{ART}}(t) = 1$ and simulated the mortality rate from age 15 to 100 at time t at one fifth year intervals and calculated the period $e_{15}(t)$.