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Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment

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Abstract

The scale-up of antiretroviral therapy (ART) is expected to raise adult life expectancy in populations with high HIV prevalence. Using data from a population cohort of over 101,000 individuals in rural KwaZulu-Natal, South Africa, we measured changes in adult life expectancy for 2000–2011. In 2003, the year before ART became available in the public sector health system, adult life expectancy was 49.2 years; by 2011, adult life expectancy had increased to 60.5 years – an 11.3-year gain. Based on standard monetary valuation of life, the survival benefits of ART far outweigh the costs of providing treatment in this community. These gains in adult life expectancy signify the social value of ART and have implications for investment decisions of individuals, governments, and donors.

Main Text

For most of the twentieth century, life expectancy increased in nearly every part of the world (1). However, from the late 1980s, the HIV epidemic led to a reversal of this trend in southern Africa, with a large rise in mortality among working-age adults (1–3). In South Africa, life expectancy at age fifteen declined from 67.4 years in 1990 to 58.7 years in 2009; and in Swaziland, from 68.1 to 53.4 years (2). In addition to the direct loss of life, these declines in adult life expectancy had profound negative effects on households, communities, and governments, including declines in household wealth, large increases in the number of orphans, the loss of skilled workers, including teachers, doctors, and government officials, as well as the interruption of intergenerational transmission of knowledge and norms (4).

In the early 2000s, southern African nations began to disburse mass antiretroviral therapy (ART) for HIV through public sector treatment programs, often with support from international donors. Using a combination of three or more drugs, ART interrupts HIV replication, enables immune recovery, and improves survival among people with HIV (5). Population-level declines in HIV-related and all-cause mortality have been documented in South Africa (6–9), Malawi (10), and in other countries receiving financial assistance for HIV programs from the US government (11). However, the impact of ART on population-level adult life expectancy in highly-affected communities has not been quantified.

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Life expectancy summarizes age-patterns of mortality in a single statistic and is commonly used to compare differences in mortality across populations and over time (1–3). Since HIV predominantly affects working-age adults, adult life expectancy is of particular interest for governments and donors, as well as for individuals and households, whose plans for the future will be influenced by changes in the anticipated length of life. Adult life expectancy is defined as the mean age to which a fifteen-year old could expect to live if subjected to the full pattern of age-specific mortality rates observed for a population over a particular period of time. Since future mortality rates are unknown, adult life expectancy cannot be interpreted as the average age to which a cohort will live, except in the limited case in which age-specific mortality rates remain constant into the future. Adult life expectancy is best interpreted as a summary indicator of the mortality experience in a population at a given time.

This paper documents the impact of South Africa's public sector scale-up of ART on adult life expectancy in a large population cohort in rural KwaZulu-Natal, a setting with very high HIV prevalence (12). The life expectancy of HIV patients who initiate ART before they fall severely ill and who subsequently adhere to their ART regimens approaches the life expectancy of people who are HIV-negative (13). However, extrapolation to population level life expectancy is not straightforward, owing to the difficulties of measuring treatment coverage (14), adherence and retention (15), and survival for patients presenting at later stages of HIV disease (16). In addition, ART programs may have spillover effects on other aspects of health systems, which may in turn impact non-HIV mortality, although the direction and magnitude of such effects have yet to be established (17, 18). ART scale-up may also have other spillover effects on mortality, through changes in rates of depression and suicide, health care-seeking for other conditions, HIV risk compensation, and risk behaviors linked to survival expectations such as substance abuse and violence. By focusing on population-level life expectancy, we automatically account for any spillover effects on contemporaneous non-HIV mortality.

Existing estimates of population-level life expectancy in the era of ART are based on demographic models (1, 2, 19–21), which rely on a range of assumptions. For example, the South African government uses United Nations East Asia model life tables to infer age-specific mortality rates (20). In contrast to modeling approaches, we directly measured dates of death using individual-level data from a large community-based population surveillance system.

The study population included all adult resident and non-resident members of all households in a 434 km^2 surveillance area in rural KwaZulu-Natal. Data on births and deaths were collected from 2000 through 2011 via semi-annual household survey visits, with response rates >99% (22, 23). This Health and Demographic Surveillance System (HDSS) is maintained by the Africa Centre for Health and Population Studies (Africa Centre), a research center funded by the Wellcome Trust and affiliated with the University of KwaZulu-Natal. The Africa Centre's population surveillance is a dynamic (open) cohort (24), in which individuals are observed from the date when they join a household in the surveillance area. To account for complex patterns of cyclical migration, individuals are observed regardless of whether they reside in the surveillance area, provided that they are members of a household under surveillance. Individuals were included in this analysis so long as their death would have been observed had it occurred. The study included a total of 101,286 persons, of whom about 60,000 were aged 15 years or older and under surveillance in any given year.

The community is largely rural and is located in one of the poorest districts in South Africa (25). Rates of HIV infection are very high; 29% of adults are HIV-positive, with over half of

women ages 25–29 and over 40% of women and men 30–34 living with HIV (12). In the early 2000s, over half of all deaths in this community were attributable to HIV (7).

In 2004, South Africa began to provide ART for HIV-infected adults at government clinics and hospitals, with the goal of achieving universal coverage for all individuals meeting disease-stage eligibility criteria. The public sector HIV treatment program serving the Africa Centre surveillance area first enrolled patients in September 2004. The program is administered by the Department of Health, is led by nurses at community-based clinics, and is largely publicly financed. The Africa Centre has supported this program since its inception with funding from the US President's Emergency Plan for AIDS Relief (27).

By 1 July 2011, 12.6% of adults ages 15–49 residing in this community had sought care in the public sector HIV treatment program; 7.0% had initiated ART, representing about a quarter of all HIV-infected adults living in the community (fig. S1, Table S1). Due to the comparatively high cost of antiretroviral drugs, private sector utilization has always been very low in this community. The public sector scale-up of ART represented a clear shift in the therapeutic options available to people with HIV.

Trends in adult life expectancy both before (2000–2003) and after (2004–2011) ART became available in the public sector were analyzed using a continuous-time approach (28,29). Survival curves were estimated separately for each year using the Kaplan-Meier estimator (30). Adult life expectancy, or mean length of life, was calculated as the area under the estimated survival curve. For single-year estimates of adult life expectancy, data at ages >95 years were sparse. To avoid bias due to variation in the age of the oldest cohort member across years, we estimated life expectancy between ages 15 and 95 years. Ninety-five percent confidence intervals were calculated for each annual estimate (28). In the pooled 2000–2011 data, the difference between adult life expectancy to age 95 and adult life expectancy bounded by the age of the oldest cohort member was 0.12 years (0.04 years for men, 0.18 years for women), and these constants were added to all estimates to account for survival beyond age 95.

We also investigated changes in the median length of life (i.e. the fiftieth percentile of the survival distribution) and in the full distribution of survival times. Pointwise 95% confidence intervals on the survival curve were estimated (29). Confidence intervals for the median survival time were defined as the range of times for which the confidence bands on the survival function included the value 0.5. We constructed percentile-bootstrap confidence intervals (1001 samples) for the difference in adult life expectancy between 2003 and 2011 and similarly for the difference in median length of life (31).

Finally, to illustrate the source of life expectancy gains, we quantified the change in age-specific mortality rates from 2003 to 2011, for 10-year age intervals, and estimated rate ratios using Poisson regression, with log-exposure time as the offset.

Changes in adult life expectancy

Between 1 January 2000 and 31 December 2011, 13,060 deaths occurred among 101,286 individuals ages 15 years and older, contributing a total of 651,350 person-years of follow-up time.

Adult life expectancy declined from 52.3 years in 2000 (95% CI 50.9, 53.8) to 49.2 in 2003 (95% CI 48.2, 50.3) (Fig. 1). These life expectancies are substantially lower than the 2000 WHO adult life expectancy estimates for South Africa as a whole (61.4 years), but they are similar to the estimates for neighboring Swaziland (54.6) and Lesotho (51.2) (2). There is substantial geographic variation in HIV rates within South Africa, and adult HIV prevalence

in rural KwaZulu-Natal is more similar to Swaziland (23.6%) and Lesotho (24.5%) than to South Africa as a whole (17.1%) (32). From 2000 to 2003, adult life expectancy declined from 55.4 to 51.3 years for women and from 49.0 to 46.9 years for men (fig. S2).

In 2004, adult life expectancy started to increase, reaching 60.5 years in 2011 (95% CI 59.0, 62.0), an 11.3 year gain (95% CI 9.6, 12.9) in the mean length of life relative to 2003, the year before ART became available in the public sector health system (Fig. 1). Both men and women experienced large gains in adult life expectancy: 9.0 and 13.3 years, respectively (fig. S2). Sensitivity analyses using alternative definitions of the study population (e.g., excluding non-resident members of households located in the demographic surveillance area) yielded similar results (fig. S3). Annual estimates of adult life expectancy with 95% confidence intervals for men, women, and both sexes are reported in Table S2.

Comparing survival curves for 2003 and 2011 (Fig. 2), the median length of life rose from 42.6 years (95% CI 41.2, 44.3) in 2003 to 60.7 years (95% CI 58.8, 62.7) in 2011, an 18.1-year gain for a typical person in this population (95% CI 15.4, 20.6). The change in the median is larger than the mean, because prior to 2004 the distribution of survival times was skewed to the right, so that the median age at death was less than the mean age at death. Changes between 2003 and 2011 in the mean and median length of life were highly statistically significant ($p<.001$). Comparing the full distribution of ages at death for 2003 and 2011 (Fig. 3) reveals a reduction in the proportion of deaths occurring in young adulthood.

Between 2003 and 2011, all-cause mortality declined by over 50% for adults aged 25 to 44. Mortality reductions at older ages were much smaller and not statistically significant (Table 1 and fig. S4). These changes in age-specific mortality rates are consistent with the decline in HIV-related mortality reported in previous studies of this cohort (6, 7).

Economic valuation

As an extension of our analysis, we compared the observed changes in adult survival at the population level with the estimated costs of providing ART in this community between 2004 and 2011 to establish the cost-effectiveness of the past ART delivery. Our analysis complements previous studies that have used predictive models to project future costs and effects of ART (33–35).

Effects were assessed by comparing the total number of life years lived under the observed age- specific mortality rates between 2004 and 2011 with the number of life years that would have occurred during this period had the population been continuously exposed to mortality rates observed in 2003. Given that life expectancy probably would have continued to decline below 2003 levels in the absence of ART (Fig. 1), the 2003 mortality rates provide a conservative counterfactual. There were 436,135 life years lived between 2004 and 2011 based on observed mortality rates, and 427,993 life years in the counterfactual scenario without ART, a difference of 8142 life years (23) (Table 2 and table S3).

To estimate costs, we calculated the total number of person years on ART in the community in each year between 2004 and 2011 (fig. S1), and multiplied this by published costs of ART delivery for South Africa over this period, accounting for reductions in treatment costs over this period (36, 37). Person years in pre-ART care were included at one-sixth of ART costs (23). During the period 2004–2011, we observed 8609 person years on ART and 7857 person years in pre-ART care (tables S3 and S4). The total cost of ART in this population was estimated at $10.8 million over the study period. Discounting both costs and effects at 3%, the cost-effectiveness ratio (CER) was $1593 per life year saved, less than a quarter of South Africa's 2011 per-capita gross national income (GNI) (38) (Table 2). Interventions

with CERs less than per- capita GNI, a standard lower bound on the monetary valuation of a life year, are considered very cost-effective (35). It is important to note that this high level of cost-effectiveness of ART delivery is achieved in a public-sector ART program in rural South Africa, where ART retention and adherence are imperfect and levels of treatment failure are high (39). Our study captures the full range of patient experiences on ART.

Discussion and extensions

We describe here the full population-level impact of a public-sector ART program on adult life expectancy in a setting of high HIV prevalence in rural South Africa. Our estimates capture the net effects of ART scale-up on the survival of HIV patients receiving ART (direct effects), the mortality of people who are not on ART (spillover effects), and the unmasking of non–HIV- related mortality in HIV-infected people whose lives have been extended by ART (compositional effects). Although the reversal of the decline in adult life expectancy coincided with the scale-up of ART (Fig. 1 and fig. S1), our estimates may also capture mortality trends not linked to the scale-up of ART. First, other changes in the community may also have affected survival, such as rural electrification, improved access to safe water, expansion of non-HIV health services, or a growing burden of noncommunicable diseases. Second, HIV-specific mortality trends may be influenced by internal dynamics of the HIV epidemic; in particular, historical trends in HIV incidence.

To assess the contribution of non–HIV-related mortality to the observed gains in adult life expectancy, we estimated HIV-cause–deleted adult life expectancy (2001–2010) using verbal autopsy data collected in the population surveillance (7). Cause-deleted life expectancy provides a measure of the impact that a particular cause of death has on life expectancy. If cause-specific mortality risks are independent, then cause-deleted adult life expectancy provides an estimate of what adult life expectancy would be in the absence of HIV-related mortality (29), and a plausible upper bound on the life expectancy gains that could be attained from further investments in HIV treatment and prevention pro- grams. HIV-cause–deleted adult life expectancy remained almost constant throughout the period between 2001 and 2010 at about 70 years, even as observed adult life expectancy increased from 49.2 years in 2003 to 58.7 years in 2010 (Fig. 4). These patterns imply a decline in HIV- related mortality rates amid stable mortality rates for other causes. This analysis confirms previous research in this population that found that secular changes in adult mortality between 2004 and 2009 were attributable to reductions in HIV-related mortality, with no systematic trends in mortality due to injuries, noncommunicable diseases, and other causes (7). The absence of any trend in HIV-cause–deleted life expectancy suggests that the overall changes in survival in the population during this period were not substantially driven by ART spillover effects, compositional effects, or changes in other mortality risks in the community.

The large reduction in HIV-related mortality after 2004 is consistent with direct effects of ART on the survival of HIV patients. However, these changes could be explained in part by historical patterns in HIV incidence. For example, if HIV infection rates peaked in the late 1990s, then a decline in mortality would be expected in the late 2000s, because of the 8- to 10-year latency period from HIV infection to death. We note, however, that HIV incidence has not declined in this area (40), and prevalence has increased (12); if anything, there are more people at risk for pre- mature death due to HIV in recent years. One way to gauge the contribution of dynamics internal to the epidemic is to project trends in adult life expectancy in the absence of ART. Using the Actuarial Society of South Africa's 2008 AIDS Model, we predicted adult life expectancy for black South Africans from the beginning of the epidemic to 2011, under the assumption that ART was not available to adults (21). In contrast to the changes that we observed in individual-level surveillance data, the model projected a further

decline in adult life expectancy between 2003 and 2011, in the absence of ART (fig. S5). Although we cannot rule out internal dynamics of the epidemic playing some role in the recovery of life expectancy, the widespread provision of ART through the public sector was almost certainly the most important factor explaining these changes.

We did not use disability or quality-of-life weights in our valuation of life-years lived with HIV on ART. Accounting for possibly lower quality of life would lower the estimated gains from additional years lived with HIV on ART. However, recent evidence suggests nearly complete recovery of physical and social functioning in people on ART (41), and the latest therapeutic regimens have reduced side effects (42), allowing people with HIV on ART to lead essentially normal lives. Further, our focus on life years, rather than disability-adjusted life years, allows us to include changes in health throughout the population, given that we do not observe non–HIV-related morbidity.

We observed gains of 11.3 years in adult life expectancy between 2003 and 2011, using individually measured data from a complete population cohort. These findings have several important implications. Our estimates suggest that existing predictions of changes in adult life expectancy based on demographic models rather than directly observed data, as in our study, have substantially underestimated the effects of ART scale-up on survival in HIV-hyperendemic populations. For example, using a modified two-parameter logit prediction model, WHO estimated that adult life expectancy in South Africa did not increase, but in fact declined from 61.4 years in 2000 to 58.7 years in 2009 and from 54.6 years to 53.4 years in neighboring Swaziland (2).

Additional gains in adult life expectancy for this population may be possible. In 2011, there was still substantial excess mortality due to HIV among younger adults under 50 years, as shown in Fig. 3. Increased efforts to recruit people with HIV into care and treatment earlier, to retain patients on treatment, and to ensure access to other health services may lead to further survival gains. Of particular interest in this setting is South Africa's 2011 expansion of treatment eligibility to all patients with CD4 < 350 cells/ml, which will facilitate earlier initiation on therapy. At present, only about half of those eligible for ART under the revised eligibility definition are receiving ART in South Africa (43). Although our findings strongly suggest that additional gains in life expectancy are possible, there are several sources of uncertainty regarding future trends. For one, although ART has been scaled up rapidly, sustaining and improving on existing survival gains will depend on continued political and financial commitment to ensuring access to treatment. Future mortality trends will also be influenced by the effects of ART scale-up on HIV acquisition (26), HIV prevalence, sexual behavior, care-seeking for HIV, and other health behaviors. Another important source of uncertainty is that the long-term survival of HIV patients on ART in this context is unknown, with treatment only widely available since 2004. However, evidence from this and other settings indicates that the risk of death for people with HIV actually declines with time after ART initiation (13).

The changes in adult life expectancy associated with ART scale-up in HIV-endemic populations are important information for governments and donors debating levels of support for public- sector HIV treatment programs. Changes in adult life expectancy resulting from ART may also have implications for forward-looking decisions of individuals, households, communities, and governments. In settings with high HIV prevalence (12) and high levels of social exposure to ART (44), we would expect individuals to revise their beliefs about their own longevity because of changes in survival in the community. These beliefs may influence, among other things, family planning, investments in human capital (such as schooling and job training), savings behavior, and willingness to engage in risks with negative consequences borne in the future (such as

smoking, drug use, and criminal activity) (45–48). For households, communities, and countries, rising adult life expectancy will reduce the number of new orphans, improve the cross-generational transmission of knowledge and norms, and may lead to higher trust and social capital, as well as lower interest rates. For governments, rising adult life expectancy greatly increases the re- turns from investments in education and job training programs. Such changes will also have to be factored into projections of future pension obligations. Most important, gains in adult life expectancy provide the clearest evidence yet of the population-level impact of well-designed public-sector ART programs in settings of high HIV prevalence.

Materials and Methods

This section provides detailed information on data sources, statistical methods, and the cost-effectiveness calculations.

Data source and study population

Demographic data for this analysis were obtained from a large population surveillance system, maintained by the Africa Centre for Health and Population Studies (www.africacentre.ac.za). The Africa Centre is a research center funded by the Wellcome Trust and affiliated with the University of KwaZulu-Natal. Since 2000, the Africa Centre has collected demographic data on all households in a 434 km^2 surveillance area in Umkhanyakude district, in northern KwaZulu-Natal (22). This district is largely rural and is one of the poorest in South Africa (25). HIV prevalence among adults aged 15–49 was 29% in 2011 (12). Our analysis used surveillance data covering the period 1 January 2000 through 31 December 2011.

Data on dates of birth and death were collected through semi-annual household survey visits, with very high response rates (>99%) (22). Data were collected for all resident and non-resident members of households in the surveillance area. “Verbal autopsies” were conducted by trained nurses to determine the underlying cause of all deaths in the population under surveillance (7). In addition to demographic data, the Africa Centre collects longitudinal data on socioeconomic and health characteristics of the study population, including repeated HIV biomarker collection. These data have been described in detail elsewhere (22) and have provided insights into the demographic (6–9), economic (41, 44, 49), and health dimensions (12, 39, 50) of the HIV epidemic and treatment scale-up in this part of rural KwaZulu-Natal. A full bibliography of publications is available online at http://www.africacentre.ac.za.

We assessed changes in survival patterns among adult members of this population cohort. Individuals were included in the analysis from the date when they were first observed in the population surveillance (or from the date of their fifteenth birthday) to their date of death or the last date when they were observed in the population surveillance. We analyzed the study population as a dynamic (open) cohort, in which individuals were allowed to enter or exit at any time during the study period (28); person-time was included only for the period during which a death would have been observed, had it occurred. Most individuals (72%) were enrolled in the study in the year 2000; the remaining 28% entered the population cohort at later points through in-migration. Attrition due to permanent out-migration or loss to follow-up was low, at a rate of 3.3 per 100 person-years. In any given year, about 60,000 of the 101,286 individuals in the study were aged 15 years or older and under observation (range: 53,140, 62,984 persons).

In this analysis, we included all resident and non-resident members of households in the surveillance area. Cyclical migration is very common in rural South Africa, in part a legacy

of the legal segregation of black South Africans during the Apartheid era into "Bantustan/homeland" areas (51). Many South Africans live and work in cities and towns, but maintain close social ties with households in rural areas, sending remittances and returning on weekends or holidays. To capture the complexities of household and living arrangements, the Africa Centre collects data on both resident and non-resident members of households, with membership determined by the head of household. At any given time about one third of adults reside outside of the surveillance area but continue to be members of households in the area (22, 44). By including all household members, regardless of place of residence, our inclusion criteria for this analysis are consistent with community members' own criteria for who should be considered part of the community (52). Including non-resident household members is also appropriate given that many "come home to die" (53) or to seek HIV care and treatment (54) in this rural community.

In sensitivity analyses, we assessed the robustness of our results to several alternative definitions of the study population. First, we included individuals only while they resided in the geographic surveillance area, excluding household members who were not in residence. Second, we included people from the date when they were first observed as residents in the surveillance area, and continued to observe them after that date regardless of their place of residence, so long as they maintained household membership in the surveillance area. Third, we analyzed the population as a fixed cohort; all residents and non-residents were included, but individuals who joined the population after 2000 were excluded. Fourth, we analyzed the population as a fixed cohort of initial residents; all individuals residing in the surveillance area at some point between the 1st of January 2000 and the 31st of December 2002 were included in the analysis, and were followed up regardless of whether they continued to reside in the surveillance area, provided that they retained membership in a household under surveillance. The third and fourth sensitivity analyses exclude late entrants to the cohort who may have in-migrated selectively, e.g. to seek ART (54).

Informed consent was obtained from all respondents. Ethical approval for data collection was received from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal.

Hlabisa HIV Treatment and Care Programme

In 2004, the South African government began to scale up ART for HIV-positive adults. The local public-sector ART program, the Hlabisa HIV Treatment and Care Programme, delivers ART through seventeen primary health care clinics and Hlabisa sub-district hospital (27). The Africa Centre surveillance area is fully contained within the Hlabisa health services catchment area, and six of the clinics in the HIV treatment program are located in the surveillance area. HIV care and treatment are provided free of charge, although many patients face significant transport costs in accessing care (55). Throughout the period of study, HIV patients with a CD4 count <200 cells/μL were eligible to initiate ART (56). In April 2010, eligibility was extended to CD4 count <350 cells/μL for pregnant women and patients with active TB (42); and in August 2011 to all adults with CD4 count <350 cells/μL (57).

In 2010, the Africa Centre collected data on the population distribution of CD4 counts through the household surveillance and found that 75% of HIV-positive adults with CD4 count <200 cells/μL had initiated ART in the public-sector treatment program (58). This coverage rate is similar to national estimates for South Africa (43). Private sector utilization for ART is very rare in this community due to low rates of health insurance and the high cost of antiretroviral drugs. By mid-2011, 12.6% of adults (ages 15 and older) residing in the surveillance area had sought care in the public sector HIV treatment program; 7.0% had initiated ART (fig. S1, table S1). This represents more than a third of all HIV positive adults

in the community (26). Among HIV-positive adults aged 30–49 years, over half have sought HIV care and over a third have initiated ART (Table S1).

The Hlabisa HIV Treatment and Care Programme is administered by the Department of Health and largely publicly financed. The Africa Centre has supported the program since its inception, with funding from the US President's Emergency Plan for AIDS Relief. In particular, the Africa Centre has provided additional training to health workers, salary support for some health workers, and some health care delivery infrastructure, such as the management of an electronic database (27).

Clinical data from the Hlabisa HIV Treatment and Care Programme were linked with data from the health and demographic surveillance system by dedicated Africa Centre personnel. Individuals were matched on unique national identification number, or (when not available) full name, age and sex (44).

Life expectancy and the period survival curve

This paper assesses trends in adult life expectancy and other parameters of the period survival curve. The period survival curve, $S(t)$, is the probability that a person who is alive at baseline (15 years) would still be alive at age t if subjected to the full pattern of age-specific mortality rates observed for a particular population during a particular period of time. The period survival curve is distinct from the survivorship function of an actual cohort, which can only be fully specified after all cohort members have died; the two are identical only in the limited case in which age-specific mortality rates remain constant into the future. Life expectancy is an expectation in the statistical sense: it is the mean length of life in a population. In addition to the mean, we assessed changes in the median length of life (p50) and the full distribution of survival times. Throughout this paper, we use the terms life expectancy, survival, and length of life to describe characteristics of the period survival curve.

We report adult life expectancy and other parameters of the period survival curve as important summary indicators of the mortality experience in a population. Unlike crude or age-adjusted mortality rates, the survival measures that we report capture changes in the age distribution of deaths. The calculation of life expectancy implicitly weights deaths at each age by the potential years of life lost, based on existing survival patterns at older ages. This is an attractive feature, with two implications: first, a death at age 25 is weighted more than a death at age 70, because more potential years of life have been lost. Second, a death at age 25 receives greater weight the longer a person was expected to live had that death been averted, based on mortality rates at older ages. Accounting for the age distribution of deaths is particularly important for understanding the population-level impact of treatment for HIV, which primarily affects survival of working-age adults. Oft-cited descriptions of the impact of HIV on survival in southern Africa were based on period life expectancy estimates (3); in this paper we provide additional data to understand how life expectancy has changed following the scale-up of ART. Period survival measures are also of interest because they reflect how individuals form beliefs about their own longevity, based on the ages at which people in their households and communities are dying (59). These beliefs may have important implications for family planning, human capital investment, savings, and other forward-looking behaviors (43– 46).

Survival curves were estimated separately for each year (2000–2011) using the Kaplan-Meier estimator (30). Adult life expectancy, or mean length of life, was calculated as the area under the survival curve. For single-year estimates of adult life expectancy, data at older ages (>95 years) were sparse. To avoid bias due to variation in the age of the oldest cohort member across years, we estimated life expectancy up to an age for which the

survival curve had not yet reached zero across all years, a standard practice in medical demography (28). For each annual estimate, we estimated the expected years lived between age 15 and age 95. Ninety-five percent confidence intervals were calculated for each estimate (28). In the pooled 2000–2011 data, the difference between adult life expectancy to age 95 and adult life expectancy bounded by the age of the oldest cohort member was 0.12 years (0.04 years for men, 0.18 years for women); these constants were added to all estimates, to account for expected survival beyond age 95.

In addition to life expectancy, we assessed changes in the median survival time (p50), i.e. the number of years that it would take for half of fifteen year olds to die if subjected to the survival curve estimated for that year. We also present changes in the full distribution of survival times, calculated as $f(t) = -dS(t)/dt \approx S(t+1) - S(t)$, where $S(t)$ is the Kaplan-Meier estimator of the survival probability at time t. Pointwise 95% confidence intervals on the survival curve were estimated (29). Confidence intervals for the median survival time were defined as the range of times for which the confidence bands on the survival function included the value 0.5. We constructed percentile-bootstrap confidence intervals (1001 samples) for the difference in adult life expectancy between 2003 and 2011 and similarly for the difference in median length of life (31). Fifteen years were added to all survival estimates, to facilitate interpretation of survival times as ages at which death occurs.

Finally, to illustrate the source of life expectancy gains, we assessed changes in age-specific mortality rates from 2003 to 2011, for ten-year age intervals, 15–24, 25–34,…, 75–84. We estimated mortality rate ratios within each age band using Poisson regression, with log-exposure time as the offset. Annual estimates of cause-specific, age-specific mortality rates have been previously reported for this population (7).

Interpreting life expectancy gains

We identified large gains in adult life expectancy in this community. (Results are reported in the paper.) Although the timing of these changes coincides with the scale-up of ART in public-sector clinics, other factors may have contributed to rising life expectancy. In this section, we assess two alternative explanations. First, to what extent were changes in life expectancy attributable to changes in mortality from non-HIV-related causes? Second, how would adult life expectancy have evolved over time in the absence of ART scale-up, but accounting for possible cohort effects driven by dynamics internal to the epidemic?

Using near-complete cause-of-death data collected via verbal autopsy, we estimated HIV-cause- deleted adult life expectancy for 2001–2010 (years for which cause of verbal autopsy data were available) and compared these results with our estimates of all-cause adult life expectancy. Cause-deleted life expectancy provides a measure of the impact that a particular cause of death has on life expectancy. Under the assumption that cause-specific mortality risks are independent, cause-deleted life expectancy provides an estimate of what adult life expectancy would be in the absence of HIV-related mortality (29). This procedure allows us to assess whether changes in life expectancy were driven primarily by HIV or by other causes; it also provides a plausible upper bound on life expectancy that could be attained through further investments in HIV treatment and prevention.

HIV-related deaths were identified via verbal autopsy. About six months after a death was recorded in the population surveillance, a trained nurse visited the household and interviewed the closest caregiver of the deceased using a standardized verbal autopsy questionnaire. A caregiver was identified and consent provided for interviews following all but 3% of deaths. Interviews were transcribed and coded and underlying causes of death were assigned using the InterVA v3 program (http://www.interva.net). Tuberculosis deaths

were coded as HIV-related (7). Cause-deleted adult life expectancy was estimated using Kaplan-Meier methods described above, with HIV deaths coded as censored observations.

We used the Actuarial Society of South Africa's AIDS and Demographic Model (ASSA2008) to project how adult life expectancy would have evolved without the scale-up of ART (21). Beginning with a 1985 starting population, the ASSA2008 model simulates the evolution of HIV infection, mortality, fertility, and migration for different population groups in South Africa and is calibrated using census data, vital registration, and HIV surveillance data. The model and its documentation are publicly available (http://aids.actuarialsociety.org.za). ASSA2008 projects age-specific mortality rates by sex, and we used these to construct projections of adult life expectancy. ASSA2008 allows for the introduction of ART treatment and other HIV interventions; but these interventions can be turned "off" in the model. We projected adult life expectancy from 1985 through 2011 for black South Africans, based on ASSA2008's default assumptions, but in the absence of ART. These projections provide intuition regarding the changes in adult life expectancy that would have occurred due to internal dynamics of the HIV epidemic, but without ART.

Stata SE 11.2 (StataCorp, College Station, TX) was used for all statistical analysis. The ASSA2008 model was implemented using Microsoft Excel (Microsoft Corporation, Seattle, WA).

Cost-effectiveness analysis

As an extension of our analysis, we compare the observed changes in adult survival at the population level with the estimated costs of providing ART in this community between 2004 and 2011 to establish the cost-effectiveness of past ART delivery. Previous studies have modeled the future costs and effects of treatment for clinical (35, 60) and epidemiological cohorts (33, 34); however, there is substantial uncertainty regarding future costs and effects. We estimated costs and effects retrospectively.

Effects were assessed by comparing the total number of life years lived under the observed age-specific mortality rates between 2004 and 2011 with the number of life years that would have occurred during this period had the population been continuously exposed to mortality rates observed in 2003. Given that life expectancy probably would have continued to decline below 2003 levels in the absence of ART (Fig. 1, fig. S5), the 2003 mortality rates provide a conservative counterfactual. We assumed that observed gains in survival were due fully to ART scale-up in the community. For the purposes of the cost-effectiveness analysis, we limited the analysis to persons residing in the surveillance area at some point between the 1st of January 2000 and the 31st of December 2002. These persons were then followed up regardless of their future place of residence – so long as they remained members of households in the surveillance area. Previous research indicates that some people may have moved into the surveillance area in order to seek ART after 2004 (54). By restricting the sample to pre-2003 residents, we are able to age a cohort defined at baseline through the true evolution of age-specific mortality rates between 2004 and 2011, and through a counterfactual world in which ART had not been introduced. Trends in adult life expectancy for this population are reported in fig. S3, as sensitivity analysis number four. There were 436,135 life years lived between 2004 and 2011, based on observed mortality rates, and 427,993 life years in the counterfactual scenario without ART, a difference of 8142 life years (Table 2, table S3).

To estimate costs, we calculated the total number of person-years on ART in the community between 2004 and 2011, and multiplied this by published cost-estimates for South Africa, accounting for reductions in treatment costs over this period (36, 37). Rosen et al. (2008) estimate total facility-based treatment costs at $928 per-patient per-year for 2005 (36),

which we inflate to $1191 in 2011 US Dollars using 2006 and 2011 Dollar-to-Rand nominal exchange rates and year-on-year Rand inflation estimates from the South African Consumer Price Index (61). Condliffe et al. (2012) estimate total facility-based treatment costs in 2010 at $682 per-patient per-year, which include a 53% reduction in drug prices implemented in early 2010 (37). To account for other secular declines in treatment costs due to efficiency improvements from economies of scale, institutional learning, and other reductions in input prices, we linearly interpolated (and extrapolated) based on cost estimates of $1191 for 2005 and $886 for 2010 (the estimated cost of treatment had the 53% reduction in drug prices not occurred). We then factored in the reduced drug costs for 2010 and 2011. Per-patient per-year cost estimates used for our analysis are displayed in table S4. Person-years in pre-ART care were included at one-sixth of ART costs (patients in pre-ART care are seen semiannually, whereas ART patients are seen on a monthly basis). This is a conservative estimate for the costs of pre- ART care, since by definition such patients do not receive antiretroviral drugs.

Person-years on ART were calculated by summing up the time from date of ART initiation to death or the end of follow-up among people in the surveillance. We conservatively assumed that once initiated, a person was always on ART thereafter. Time in pre-ART care was calculated as the time from a person's first recorded CD4 count – based on a blood test taken upon enrollment in the HIV Treatment and Care Programme – to that person's date of ART initiation, death, or the end of follow-up. Systematic reporting of first CD4 counts began in 2007, so we are likely undercounting the number of person-years in pre-ART care between 2004 and 2007. However, we note that the treatment program was still very small at that point, and imputing times in pre-ART care prior to 2007 does not qualitatively change the results (estimates available from the authors upon request).

Private sector utilization is very low and the vast majority of persons residing in the surveillance area who were on ART during this period would be observed in the public-sector treatment program. People receiving ART must visit the clinic every month to pick up their medication, so anyone on ART who is residing in the surveillance area for more than a few months would be expected to enroll in the program. However, cohort members who were non-resident at the end of follow-up may have received ART outside the DSA. (Those who left the DSA but returned to the DSA would have been observed in the ART program, so these return migrants were excluded from this calculation). To estimate the person-years on ART for non-residents, we calculated the number of non-resident person-years from the date when a person was last in the DSA to the end of follow-up. We assumed that the same proportion of residents and non-residents had initiated ART or enrolled in pre-ART care (fig. S1), and multiplied these annual coverage rates by the number of non-resident person-years in each year. Finally, some persons initiating ART in the DSA may have previously initiated treatment elsewhere. To include such time on ART in our estimates, we conservatively included as "time on ART" *all* non-resident person time between an individual's last date residing in the surveillance area (or September 2004) and their date of initiation, for those who initiated ART within three months of relocating back to the DSA.

The scale-up of ART in the community is shown in fig. S1. By 2011, 7.0% of adults had initiated ART, and an additional 6.6% were in pre-ART care. During the period 2004– 2011, we observed 8,609 person-years on ART and 7,857 person-years in pre-ART care; adjusting for care-seeking of non-resident cohort members resulted in a total of 11,597 person-years on ART and 10,268 person-years in pre-ART care.

The total cost of ART in this population was estimated at $10.8 million over the study period. Table S3 presents both crude (top panel) and discounted (bottom panel) estimates of costs and effects. Discounting both costs and effects at 3% (62) and adjusting for

nonresident care-seeking, the cost-effectiveness ratio (CER) was $1593 per life year saved, less than a quarter of South Africa's 2011 per-capita gross national income (GNI) (38). Interventions with CERs less than per-capita GNI, a standard lower bound on the monetary valuation of a life year, are considered very cost-effective (35). It is important to note that this high level of cost-effectiveness of ART delivery is achieved in a public-sector ART program in rural South Africa, where ART retention and adherence are imperfect and levels of treatment failure are high (39). Our study captures the full range of real-world patient experiences on ART. To place the resource needs of the program in perspective, we calculated the amount that was spent on the ART program in 2011 on a per capita basis in this community. It cost $48 per adult member of this community to provide ART in 2011 (table S3).

These cost-effectiveness estimates are likely to be underestimated because counterfactual survival rates likely would have continued to decline below 2003 rates as shown in our simulation based on the ASSA2008 model (21) (fig. S5); and because we have included all person-time between date of ART initiation and end of follow-up, regardless of whether a person was retained on ART (39). Future benefits from reduced acquisition of HIV associated with treatment scale up (26), increased testing and care-seeking for HIV, reduced stigma, as well as current and future relief for family-based carers have not been valued here.

In the future, costs are likely to decline in South Africa due to further reductions in drug and laboratory costs, improved composition of health worker teams delivering ART (63), and economies of scale. However, cost increases are also possible as South Africa shifts to newer drugs to improve the side-effect profiles or reduce resistance levels. Cost-effectiveness is also likely to increase due to the increasing proportion of people with HIV who will have progressed to the point where their survival depends on access to ART. Although per-patient program costs are likely to decline in the future, the total (and per-capita) costs of the program are likely to increase, as HIV prevalence rises with increasing numbers of people on therapy (12).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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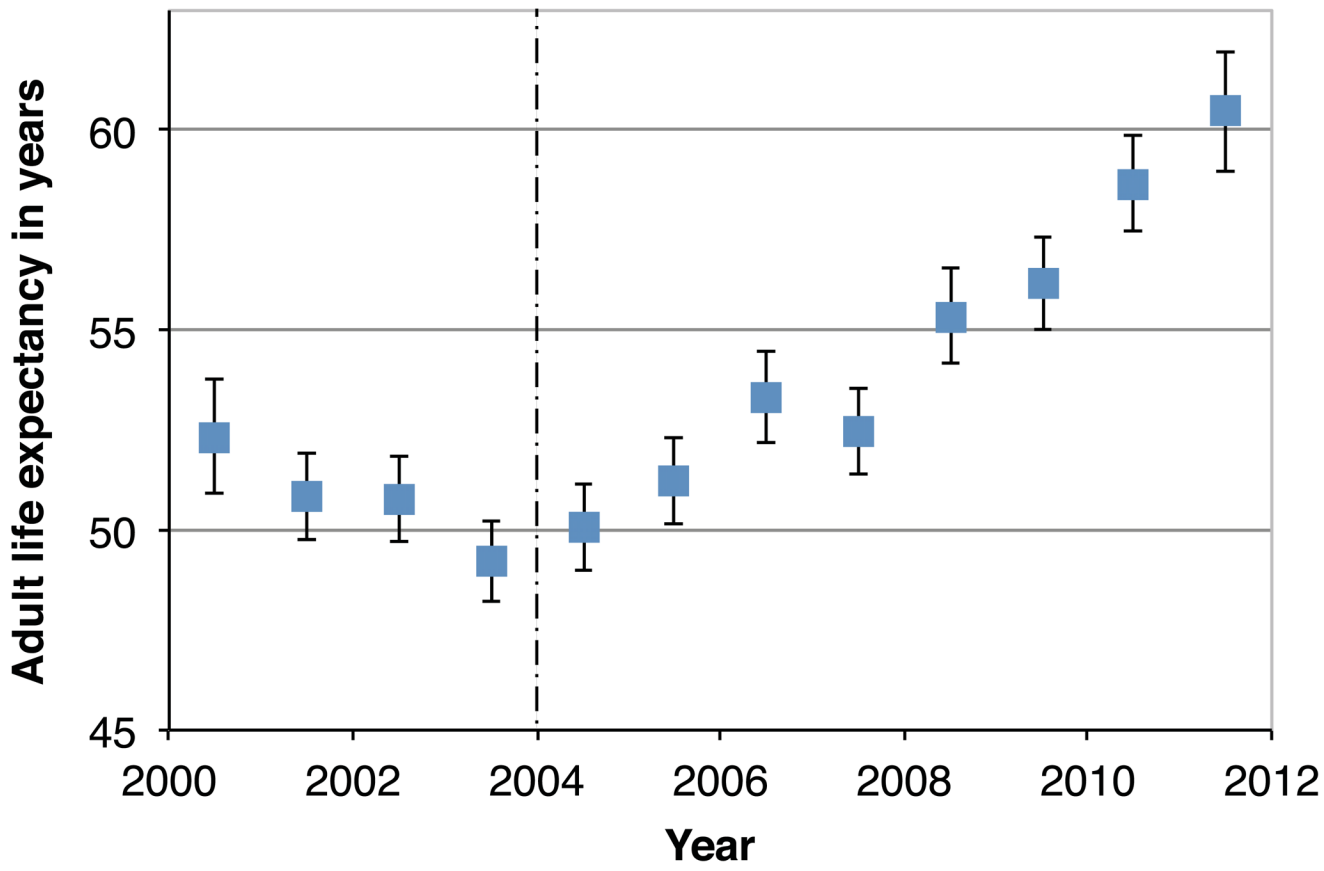

Fig. 1. Adult life expectancy and the scale-up of ART, 2000–2011

Adult life expectancy is the mean age to which a 15 year old could expect to live if subjected to the full pattern of age-specific mortality rates observed in a population for a given period of time. Annual estimates of adult life expectancy (blue squares) are plotted against year, 2000–2011, with 95% confidence intervals. Public sector provision of ART to adults in this community began in 2004, as indicated by the vertical line.

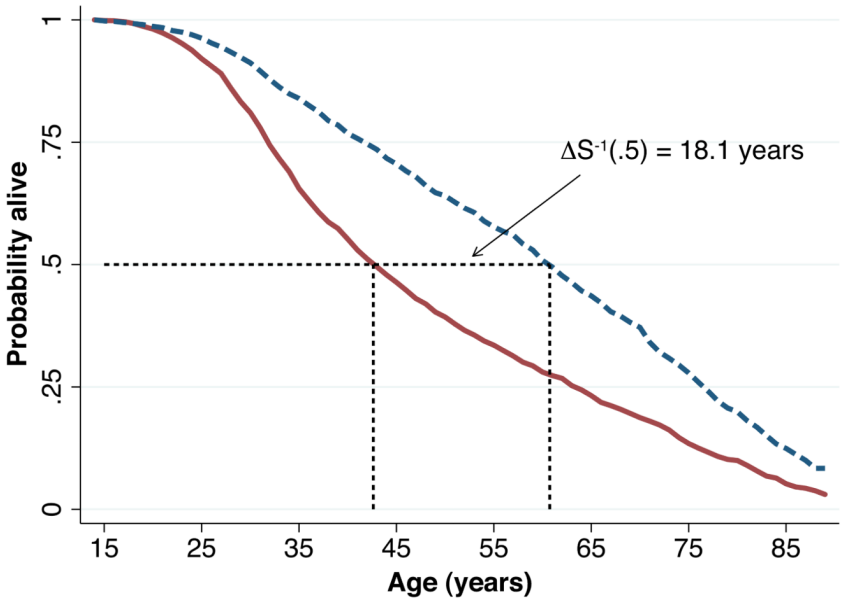

Fig. 2. Survival curves for 2003 and 2011

Kaplan-Meier survival curves for 2003 (solid red line) and 2011 (broken blue line) were estimated for the population under surveillance. Each curve displays the probability that someone would be alive at a given age if subjected to the full pattern of age-specific mortality rates observed in that year. Conditional on survival to fifteen years, the median age at death was 42.6 years (95% CI 41.2, 44.3) in 2003 and 60.7 years (95% CI 58.8, 62.7) in 2011, a difference of 18.1 years.

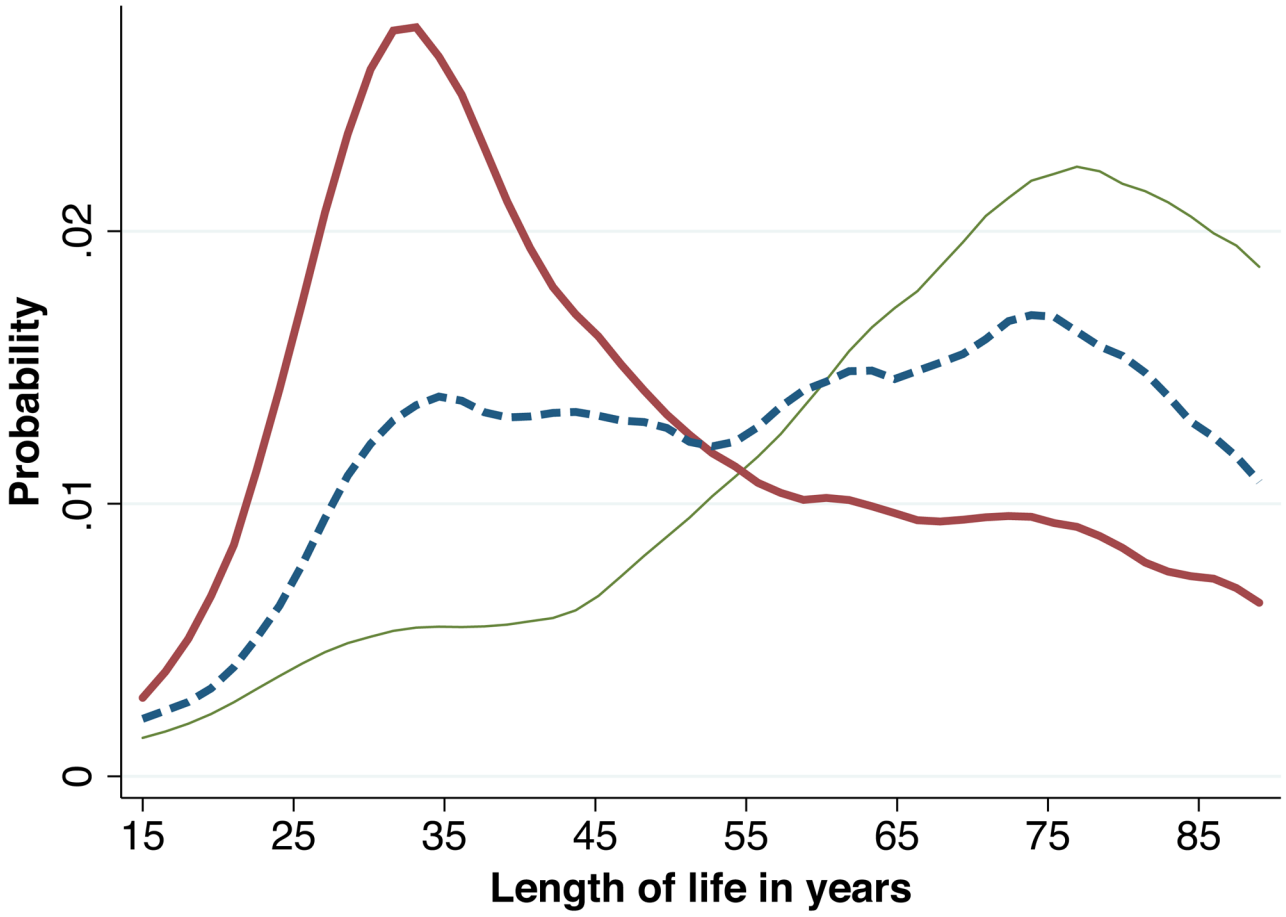

Fig. 3. Probability distributions of length of life in 2003 and 2011

Distributions of lengths of life are presented for 2003 (solid red line) and 2011 (broken blue line). The thin green line displays the distribution of HIV- cause–deleted lengths of life for 2001–2010, which are based on mortality rates that exclude HIV- related deaths. The proportion of deaths occurring in young adult- hood declined between 2003 and 2011, but there was still evidence of excess HIV-related mortality among young adults in 2011 (by comparison to the HIV-cause– deleted distribution of lengths of life).

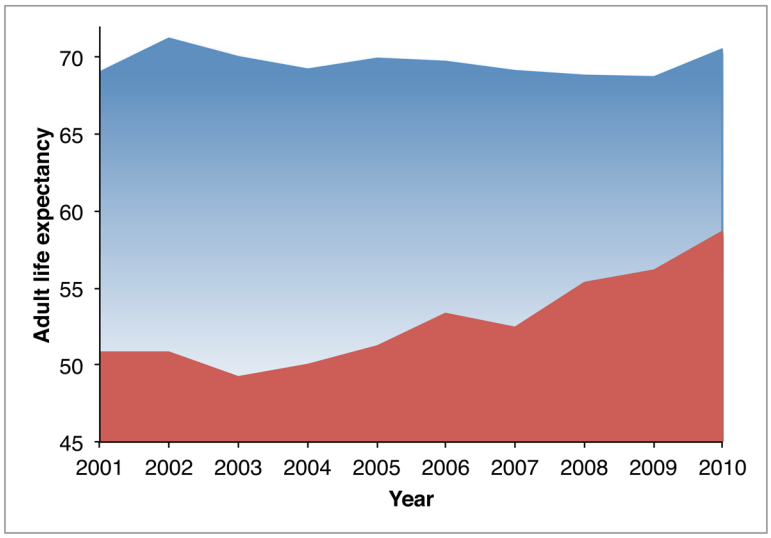

Fig. 4. HIV-cause-deleted adult life expectancy

Trends in adult life expectancy (red line) and HIV-cause-deleted adult life expectancy (blue line) for 2001–2010. HIV-cause-deleted life expectancy was estimated excluding deaths due to HIV, as identified by verbal autopsy in the Africa Centre surveillance. Whereas adult life expectancy increased after 2003, there was no systematic trend in HIV-cause-deleted adult life expectancy.

Table 1

Age-specific mortality rates for 2003 and 2011

	2003			2011			Rate Ratio2011 vs. 2003		
Age	**Deaths**	**PY[a]**	**Rate**	**Deaths**	**PY[a]**	**Rate**	**RR**	**95%**	**CI[b]**
15–24	121	204.7	0.6	67	218.5	0.3	0.52	0.39	0.70
25–34	387	131.4	2.9	201	160.2	1.3	0.43	0.36	0.51
35–44	308	84.7	3.6	143	86.5	1.7	0.45	0.37	0.55
45–54	175	53.3	3.3	117	59.6	2.0	0.60	0.47	0.75
55–64	108	31.1	3.5	90	34.2	2.6	0.76	0.57	1.00
65–74	109	21.5	5.1	84	20.1	4.2	0.83	0.62	1.10
75–84	72	8.9	8.1	89	11.5	7.7	0.95	0.70	1.30

[a] PY = hundreds of person-years;

[b] CI = Confidence interval. Age-specific mortality rates were estimated separately for 2003 and 2011. Rate ratios were estimated using a Poisson regression model, with log-exposure time as the offset. The proportion (number) of deaths due to HIV among persons ages 15–84 years was 59% (746) in 2003 and 46% (343) in 2010. Verbal autopsy data were not yet complete for 2011.

Table 2

Life-year gains and program costs, 2004–2011

Total life years gained, 2004–2011	8142
Estimated program costs, 2004–2011	$10,806,451
CER* ($/life year)	$1,593

* CER, cost effectiveness ratio, defined as program costs per life year.

Total life years gained is the difference between the number of adult life years lived between 2004 and 2011 based on observed mortality patterns and the number of adult life years that would have been lived had 2003 age-specific mortality rates persisted through 2011. Program costs were calculated by multiplying the total number of adult life years on ART or in pre-ART care by per-patient per-year cost estimates. All costs are reported as 2011 US Dollars. Total life years and program costs shown in the table are not discounted; the CER is based on cost and life year estimates that were discounted at 3%. South Africa's per-capita gross national income (GNI) was $6960 in 2011; the CER, as a percentage of per capita GNI was 23%.