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Science **339**, 961 (2013);
DOI: 10.1126/science.1230413

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005.

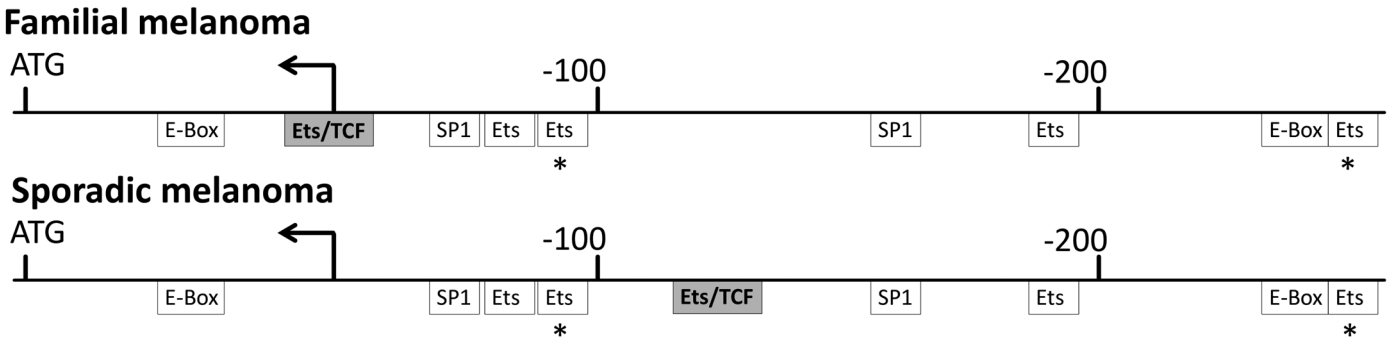

Fig. 2. The *TERT* core promoter in melanoma. Mutations creating Ets/TCF binding motifs were found in affected family members (–57 bp) immediately next to the transcription start site and in sporadic metastatic melanoma (–124 to –149 bp; sequence details in fig. S2). Binding sites for c-Myc (E-Box), SP1, and Ets transcription factors are known to exist in the wild-type *TERT* promoter. Ets2 binding was reported for Ets2 sites at –99 and –243 bp (stars) (*4*). The plus strand of DNA is shown.

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Acknowledgments: We thank Eurofins MWG Operon (Ebersberg, Germany) for sequencing service and M. Kircher and U. Stenzel for comments on sequence analysis. The study was partially supported by a grant from Deutsche Forschungsgemeinschaft (DFG). The mutation data reported in this manuscript are deposited in www.sanger.ac.uk/genetics/CGP/cosmic/.

Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1230062/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S7
Tables S1 to S7
References (*14*–*33*)

11 September 2012; accepted 11 January 2013
Published online 24 January 2013;
10.1126/science.1230062

Increases in Adult Life Expectancy in Rural South Africa: Valuing the Scale-Up of HIV Treatment

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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 the investment decisions of individuals, governments, and donors.

For most of the 20th 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 15 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; and 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 other countries receiving financial assistance for HIV programs from the U.S. government (*11*). However, the impact of ART on population-level adult life expectancy in highly affected communities has not been quantified.

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*). Because 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 15-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. Because 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

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rural KwaZulu-Natal, a setting with very high HIV prevalence (*12*). The life expectancy of HIV patients who begin 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 affect 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 nonresident 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 semiannual household survey visits, with response rates >99% (*22, 23*). This Health and Demographic Surveillance System 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*). HIV prevalence is very high; 29% of adults are HIV-positive, with about half of women aged 30 to 49 and about one-third of men aged 35 to 49 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 surveil-

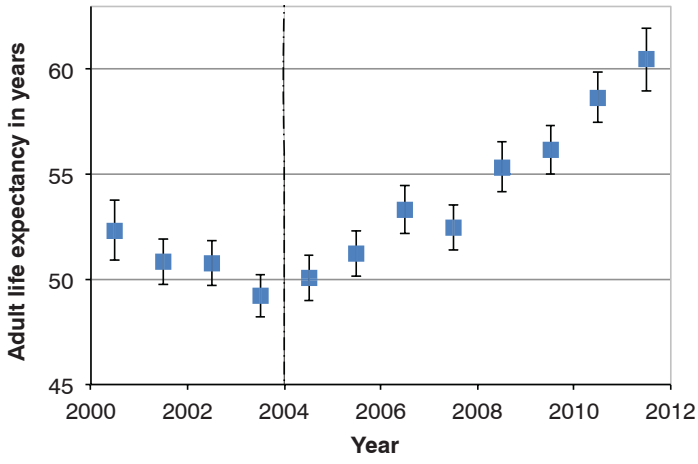

Fig. 1. Adult life expectancy, 2000–2011. Adult life expectancy is the mean age to which a 15-year-old could expect to live if subjected to the full pattern of age-specific mortality rates observed in a population for a given period of time. Annual estimates of adult life expectancy (blue squares) are shown for each year, 2000 to 2011, with 95% CIs. Public-sector provision of ART to adults in this community began in 2004, as indicated by the vertical line.

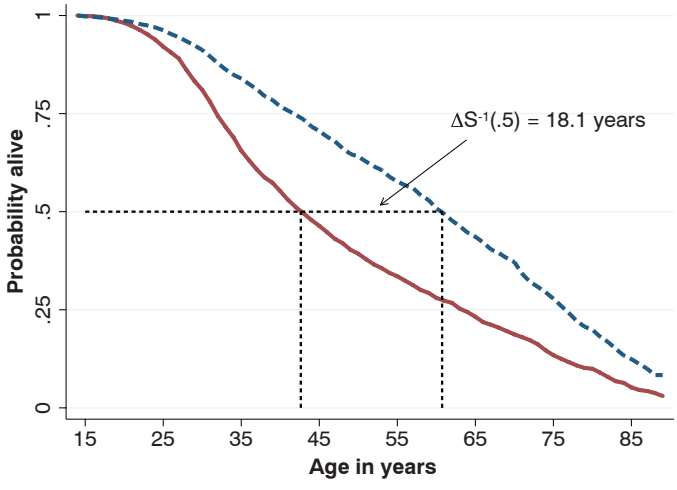

Fig. 2. Survival curves for 2003 and 2011. Kaplan-Meier survival curves for 2003 (solid red line) and 2011 (broken blue line) were estimated for the population under surveillance. Each curve displays the probability that someone would be alive at a given age if subjected to the full pattern of age-specific mortality rates observed in that year. Conditional on survival to 15 years, the median length of life was 42.6 years in 2003 and 60.7 years in 2011.

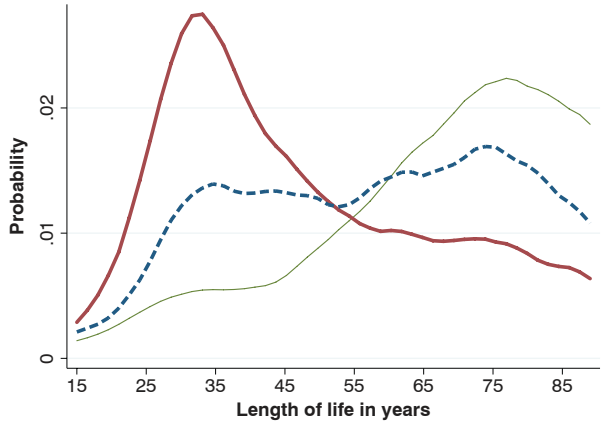

Fig. 3. Distributions of lengths of life are presented for 2003 (solid red line) and 2011 (broken blue line). The thin green line displays the distribution of HIV-cause–deleted lengths of life for 2001–2010, which are based on mortality rates that exclude HIV-related deaths. The proportion of deaths occurring in young adulthood 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).

lance 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 U.S. President's Emergency Plan for AIDS Relief (PEPFAR); in particular, the Africa Centre has provided health worker training, salary support, and technical assistance, such as the management of an electronic database.

By 1 July 2011, 12.6% of adults aged 15 and older residing in this community had sought care in the public-sector HIV treatment program; 7.0% had initiated ART, representing more than a third of all HIV-infected adults living in the community (*26*) (fig. S1 and table S1). Because of the high cost of antiretroviral drugs and low levels of health insurance coverage, private-sector ART utilization has always been very low in this community. The public-sector scale-up of ART was a clear shift in the therapeutic options available to people with HIV (*27*).

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 calendar years, we estimated life expectancy between ages 15 and 95 years. Ninety-five percent confidence intervals (CIs) 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 and 0.18 years for women); 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 50th percentile of the survival distribution) and in the full distribution of survival times. Pointwise 95% CIs on the survival curve were estimated (*29*). CIs 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 CIs (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.

Between 1 January 2000 and 31 December 2011, 13,060 deaths occurred among 101,286 individuals aged 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 World Health Organization (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 that in Swaziland (23.6%) and Lesotho (24.5%) than to that in 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 over this period: 9.0 and 13.3 years, respectively (fig. S2). Sensitivity analyses using alternative definitions of the study population (e.g., excluding nonresident members of households located in the demographic surveillance area) yielded similar results (fig. S3). Annual estimates of adult life expectancy with 95% CIs 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 before 2004, the distribution of survival times was skewed to the right, so that the median length of life was less than the mean. Changes between 2003 and 2011 in the mean and median length of life were highly statistically significant ($P < 0.001$). Comparing the full distribution of lengths of life 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*).

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

Table 1. Age-specific mortality rates for 2003 and 2011.

Age	2003			2011			Rate ratio 2011 versus 2003		
	Deaths	PY*	Rate	Deaths	PY*	Rate	RR	95% CI	
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

*PY, hundreds of person-years. Age-specific mortality rates were estimated separately for 2003 and 2011. Rate ratios (RR) were estimated using a Poisson regression model, with log-exposure time as the offset. The proportion (number) of deaths due to HIV among persons aged 15 to 84 years was 59% (750) in 2003 and 46% (344) in 2010. At time of publication, 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	$10,806,451
CER* ($ per life year)	$1593

*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 U.S. 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 GNI was $6960 in 2011; the CER, as a percentage of per-capita GNI, was 23%.

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.

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 programs. 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 premature 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*).

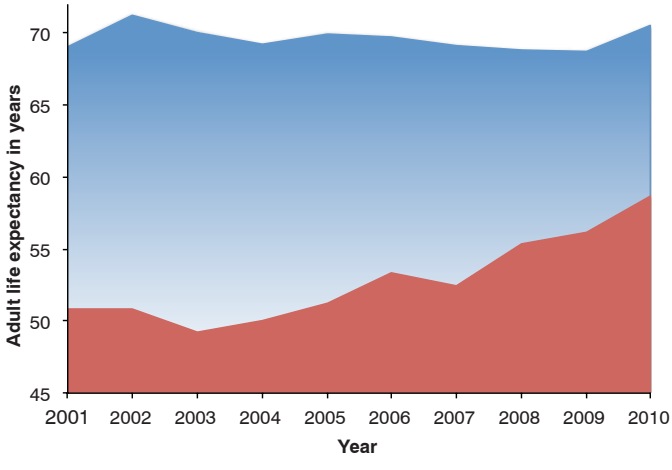

Fig. 4. HIV-cause–deleted adult life expectancy. Trends in adult life expectancy (red line) and HIV-cause–deleted adult life expectancy (blue line) for 2001–2010. HIV-cause–deleted life expectancy was estimated excluding deaths due to HIV, as identified by verbal autopsy in the Africa Centre surveillance. Whereas adult life expectancy increased after 2003, there was no systematic trend in HIV-cause–deleted adult life expectancy.

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/μl, 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 returns 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.

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Acknowledgments: We thank all the respondents who gave their time to this research and the staff of the Africa Centre for Health and Population Studies and the Hlabisa HIV Care and Treatment Programme. In particular, we thank all data collection and database management coordinators, supervisors, and managers (T. Mutevedzi, C. Newell, Z. Gqwede, H. Madida, L. Sithole, P. Dlamini, P. Gwala, T. Mngomezulu, N. Ntombela, N. Myeni, B. Ntimane), as well as all fieldworkers, verbal autopsy nurses, surveillance trackers, data capturers, document management clerks, and quality controllers. We also thank our funders: the Wellcome Trust (Africa Centre for Health and Population Studies); National Institutes of Health grants R01 HD058482-01 and 1R01MH083539-01 (T.B.); and the Harvard Global Health Institute and Harvard Center for Population and Development Studies (J.B.). Data are archived and accessible at no cost from the Africa Centre for Health and Population Studies. The authors report no conflicts of interest.

Supplementary Materials

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18 September 2012; accepted 1 February 2013
10.1126/science.1230413