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The burden of HIV mortality following the rollout of antiretroviral therapy: evidence from an observational community cohort study in KwaZulu-Natal, South Africa

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Summary

Background: Antiretroviral therapy (ART) substantially decreases morbidity and mortality among people living with HIV. In this study, we describe population-level trends in the adult life expectancy (LE), and trends in the residual burden of HIV mortality following the rollout of a public sector ART programme in one of the populations with the most severe HIV epidemics in the world.

Methods: Data come from a demographic and HIV surveillance system in northern KwaZulu-Natal (South Africa), and cover the calendar years 2001 through 2014. We use non-parametric survival analysis methods to estimate gains in the population-wide LE at age 15 since the introduction of ART, and the shortfall of the population-wide adult LE compared to that of the HIV negative population (i.e., the LE deficit). LE gains and deficits are further disaggregated by age and cause of death using demographic decomposition methods.

Findings: The dataset contains information on 93,903 adults who jointly contribute 535,428 person-years of observation to the analyses and 9,992 deaths. Since the rollout of ART in 2004, adult LE increased by 15.2 years for men (95%-CI: 12.4-17.8), and 17.2 years for women (95%-CI: 14.5-20.2). Reductions in pulmonary TB and HIV related mortality account for 79.7% of the LE gains among men, and 90.7% among women. For men, 9.5% is the result of a decline in external injuries. By 2014, the LE deficit had contracted to 1.2 years for men (95%-CI: -2.9-5.8) and to 5.3 years for women (95%-CI: 2.6-7.8). Pulmonary TB and HIV are responsible for 84.9% of the LE deficit among men in 2011-'14, and for 80.8% among women.

Interpretation: The burden of HIV on adult mortality in this population is rapidly shrinking, but remains sizable for women, despite their better engagement with HIV care services. The recent gains in adult life-years lived as well as the current LE deficit are almost exclusively due to differences in mortality attributed to HIV and pulmonary TB.

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Introduction

The rollout of antiretroviral therapy (ART) in populations with generalized epidemics has greatly improved the survival of people living with HIV (PLHIV), and that has been documented in both clinical cohorts and population-based research.¹⁻⁷ Many studies report on changes in all-cause mortality, but do not quantify how much of the overall mortality decline is due to a reduction in HIV associated mortality. In addition, most studies are not in a position to estimate the residual burden of HIV on population-level adult mortality. We seek to remedy both shortcomings with data from a demographic and HIV surveillance site in rural KwaZulu-Natal where HIV status is known for a large portion of the population.

We report on trends in the life expectancy (LE) at age 15, and the adult LE by HIV status. LE is one of the most widely used summary measures of mortality and well-suited to quantify the effects of ART because it values the prolongation of life in addition to the mere elimination of deaths from a particular cause. Other adult mortality measures, including the probability of dying in adulthood ($_{45}q_{15}$) are less sensitive to the shift in the age distribution of deaths and may therefore underestimate the mortality reductions prompted by the rollout of ART.

Our analyses focus on two quantities of great public health interest, namely the gains in adult LE since the introduction of ART, and trends in the LE deficit. The LE deficit is defined as the shortfall of the population-wide LE compared to that of the HIV negative population, and quantifies the residual burden of HIV mortality in a population. Further, we use demographic decomposition techniques to estimate the contribution of changes in HIV and other causes of death (CoD) to recent trends in the adult LE and the adult LE deficit. These analyses thus update and extend previous work on adult mortality from the same study site.^{2,8-10} All our estimates are disaggregated by sex, and add a new perspective to the literature wherein women are routinely considered to have disproportionately benefited from the expansion of treatment.^{11,12}

Methods

Study design and population

Data come from the Africa Centre Demographic Information System (ACDIS) in the uMkhanyakude District in northern KwaZulu-Natal, covering 434km² of predominantly rural area with a resident adult population of around 45,000 adults (ages 15 years and above).¹³ The population is characterized by high HIV prevalence (29% among adults aged 15-49 in 2011),¹⁴ high levels of cardiovascular risk factors, and high mortality from external injuries.²

The public sector ART programme in the study area enrolled its first patients in August 2004. By the end of 2006 over a thousand patients were receiving treatment, and by mid-2011 an estimated 37% of PLHIV in the study population were on ART.^{10,15} More detail about the expansion of the treatment programme in South Africa, and changes to the ART eligibility criteria is given elsewhere.¹⁶

Data collection

Demographic surveillance is conducted through tri-annual household visits, and population-based HIV testing of resident adults is done annually – since 2003-'04 for men and women of reproductive age, and since 2007 for all adults. HIV status information is also obtained through record linkage with health facilities providing ART in the area covered by the ACDIS.

Individuals contribute person-time to the analyses from their fifteenth birthday or from when they move into one of the villages under surveillance, and until they move out, die, or turn 100 years old.

The data extraction from the ACDIS database was done in August 2015, and observations were administratively censored at the end of 2014.

In order to allocate person-time to HIV status categories we classify the time prior to the first recorded HIV test as HIV status unknown. The time following a positive test remains positive until censoring or death. The time following the last negative test is considered negative for a duration of five years, after which it is classified as unknown. This procedure allows for the estimation of mortality rates among HIV negative individuals, but the exposure time is sufficiently short to ensure that elevated mortality among seroconvertors does not introduce bias (appendix, pp. 2-3). Time between two HIV negative tests is always counted as negative no matter how long the interval between tests.

Ethical approvals for this study were obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, and the Observational Research Ethics Committee of the London School of Hygiene and Tropical Medicine. Verbal informed consent was obtained from household representatives for the demographic surveillance, and individual written consent for the HIV surveillance. The analyses conducted for this paper consisted of secondary analysis of de-identified data. The core ACDIS dataset is publicly available through the INDEPTH Network Data Repository (INDEPTH.ZA031.CMD2014.v1).

Statistical analysis

We present non-parametric estimates of adult LE by sex, year and HIV status. Adult LE is defined as the number of additional years that a survivor to age 15 can expect to live if subject to the mortality observed in a specific period (appendix, pp. 4-5). LE estimates are computed with continuous-time survival analysis techniques as the area under the Kaplan Meier survival curve. Percentile-based confidence bounds are obtained via bootstrapping with 1,000 replications.

The discussion below focuses on two quantities: (i) *the total adult LE gain* since introduction of ART, and (ii) the remaining *adult LE deficit*. The total LE gain is the difference between the LE estimates for 2003 and 2014, which represent the calendar year before ART became available at local health facilities and the last year with available data. The adult LE deficit quantifies the extent to which the overall population LE falls short of the LE of HIV negative individuals. In other words, it is a summary measure of the mortality impact of the HIV epidemic conditional on the background health profile of its population, and is directly affected by HIV epidemic severity and efforts to mitigate its mortality impact (e.g., ART).

Adult LE gains and deficits are disaggregated by age and cause of death using a demographic decomposition method first proposed by Arriaga.¹⁷ The decomposition of the LE gains quantifies the contribution of changes in cause-specific mortality in each age group to the overall increase in adult LE from 2000-'03 (the pre-ART period) to 2011-'14. The decomposition is done for groups of calendar years because the population is too small for an analysis by single year. The same methodology is subsequently used for decomposing the LE deficit for two periods (2007-'10 and 2011-'14). Their comparison informs us of changes in the age and cause distribution of excess mortality as treatment programs come to maturation.

Information on the CoDs comes from verbal autopsy (VA) interviews with relatives of deceased individuals. VA interpretation is done with the InSilicoVA tool.¹⁸ InSilicoVA uses a Bayesian model to estimate the cause-specific mortality fractions (CSMF) at the population level, and cause-specific probabilities at the individual level. We separately generate estimates for sub-populations defined by two broad age groups (below 60 and 60 or older), gender, and HIV status at the time of death. We then aggregate the individual-level cause-specific probabilities to obtain CSMF estimates for five-year

age groups. The CoD classification scheme for reporting results distinguishes HIV/AIDS, pulmonary tuberculosis (TB), other communicable diseases, malignant neoplasms, cardiovascular disease, other non-communicable diseases, external causes, and maternal mortality. We report results for pulmonary TB and HIV separately, but we know from prior work that they are often difficult to separate on the basis of a VA interview due to the similarity of symptoms and high co-morbidity.¹⁹ The online appendix maps the CoD classification scheme onto the ICD-10 (pp. 6), and summarizes analyses wherein the CoD attribution has been done with the InterVA model (pp. 7).²⁰

Role of the funding source

The funders played no role in study design, in the collection, analysis, or interpretation of data, in the writing of this report, or in the decision to submit for publication. The corresponding author (GR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 2001 and 2014, a cumulative number of 93,903 adults ever resided in the demographic surveillance area. They jointly contribute 535,428 person-years of observation time and 9,992 deaths to the analyses (Table 1). Verbal autopsy interviews were completed for 9,605 of these deaths. Women contribute 59% of the person-years of exposure to the study, and the HIV status is known for around 36% of the total person-years lived. The online appendix (pp. 2-3) provides more detail on the HIV status information in the dataset.

Table 1 about here

The crude death rate decreased from 23.1 (95%-CI: 22.3-23.9) to 13.6 (95%-CI: 13.0-14.2) per 1,000 person-years between 2001-'04 and 2011-'14. Because HIV surveillance only commenced in 2004, mortality estimates by HIV status before the rollout of ART are not available. However, the most pronounced mortality declines took place between ages 20 and 45, which is an age range where HIV-associated mortality is common.

The mortality rate reductions translate into important gains in adult LE (Figure 1 and pp. 4-5 in the appendix). Overall adult LE reached its nadir in 2003, the year before the introduction of ART. Between 2003 and 2014, adult LE increased by 15.2 years for men (95%-CI: 12.4-17.8), and 17.2 years for women (95%-CI: 14.5-20.2). These estimates represent average increases in the adult LE of 1.38 years per annum for men and 1.58 years for women, and are much larger than the LE gains estimated for South Africa as a whole (appendix, pp. 8). In 2014, the population-wide adult LE in uMkhanyakude reached 45.9 (95% CI: 43.7-48.4) and 54.2 (95% CI: 52.2-56.2) years for men and women, respectively.

Adult LE estimates by HIV status can be computed from 2007 onwards; the year that the HIV testing eligibility criteria were expanded to all adults. The adult LE for HIV negative men and women hovered around 47 years for men and 60 years for women for the entire period (Figure 1a). Whereas the adult LE of HIV negatives did not change, the outlook for PLHIV improved dramatically. Between 2007 and 2014, the number of years that an adult HIV positive person can expect to live increased by 18.4 (95% CI: 7.5-33.8) years for men and 20.7 (95% CI: 14.5-29.2) years for women (Figure 1b). By 2014, a 15-year old HIV positive man could expect to live for another 30.5 years (95%-CI: 24.4-38.3) at the prevailing mortality rates. For women this was 44.1 years (95%-CI: 39.1-52.1). The LE of adults whose

HIV status is unknown to the study is marginally higher than that of the population as a whole, which suggests that PLHIV are under-represented among those with an unknown HIV status (Figure 1c).

Figure 1 about here

The LE estimates reported in Figure 1a are the inputs for computing the LE deficit associated with HIV (Figure 1d). In 2007, three years after the introduction of ART at local health facilities, this deficit was still 13.8 years (95%-CI: 9.7-18.6) for men and 17.7 years (95%-CI: 12.3-23.8) for women. By 2014, the LE deficit reduced to 1.2 (95%-CI: -2.9-5.8) and 5.3 (95%-CI: 2.6-7.8) years for men and women, respectively.

Figure 2 provides insight into the age groups and CoDs that have contributed to the LE gains since the introduction of ART. CoD contributions aggregated over age are reported in Table 2. The total LE gain that is decomposed in Figure 2 amounts to 10.6 years for men and 13.7 years for women, and pertains to the 10-year interval between 2001-'04 and 2011-'14. Negative values in these plots indicate that the mortality rates from a particular cause in a specific age group increased over time and thus had a negative effect on the LE trend. Their contributions are very small. The age groups with the largest contribution to the increase in adult LE over this period are 25-29 years for women, and 30-34 years for men.

The decomposition by cause indicates that almost all of the recent gains in adult LE result from reductions in mortality ascribed to HIV and pulmonary TB. Among men, these two causes alone account for a gain of 8.4 adult life-years, or, 79.7% of the total gain. The gain in adult LE ascribed to reductions in pulmonary TB and HIV mortality among women is 12.8 years, or, 90.7% of the total. The relative contribution of HIV within this group of causes is larger for women than for men. Among men, a reduction in the number of deaths from external injuries contributes one year to the increase in adult LE in the decade under consideration, which corresponds to 9.5% of the total LE gain. All the other CoD groups contribute less than one year to the change in the adult life-years lived for both men and women.

Figure 2 about here

Figure 3 shifts the focus to the age-groups and CoDs that contribute to the shortfall in the population-wide LE compared to the HIV negative population. To elicit changes over time, the age-cause decomposition of the LE deficit is done for two periods, which indicates that the age profile of the LE deficit is becoming older. This is particularly the case for women, for whom the median of the age-group contributions to the LE deficit increased from 34.9 to 36.3 years between 2007-'10 and 2011-'14.

Pulmonary TB and HIV account for most of the shortfall in the population-wide adult LE in both periods (Table 2). Among men, they account for 85.0% of the LE deficit in 2007-'10 and 84.9% in 2011-'14. Among women, their contributions are 85.5% and 80.8%, respectively. Most of the remainder is attributed to other communicable diseases. The contributions of non-communicable diseases, external injuries and maternal causes to the LE deficit are small.

Figure 3 about here

Table 2 about here

Discussion

The introduction of ART in public sector health facilities in KwaZulu-Natal marked the starting point for unprecedented population-wide increases in adult LE of 1.38 and 1.58 years per annum for men and women, respectively. The total gains in adult LE between 2003 and 2014 amount to 15.2 years for men (95%-CI: 12.4-17.8) and 17.2 years for women (95%-CI: 14.5-20.2), and extend earlier estimates for this population.⁸ In comparison, the adult LE in Japan after World War II increased at an average rate of around 0.5 years per annum for a total gain of 9.4 years between 1947-'49 and 1965-'69,²¹ and is one of the nations with the most rapid LE increases on record. The pace of the adult LE increases in this population in KwaZulu-Natal has been three times faster, and is almost exclusively driven by reductions in HIV related mortality. This conclusion is supported by concomitant increases in the adult LE of PLHIV, the lack of a decline in the mortality of HIV negatives, and an analysis of changes in the CoD structure. A decline in the deaths ascribed to pulmonary TB and HIV alone account for around 79.7 and 90.7% of the total LE gain for men and women, respectively. Among men, a decline in mortality from external injuries represents an additional 9.5% of the adult LE gain in the decade following the rollout of ART.

The LE gains directly attributable to ART are probably even larger than the observed increases in adult LE because mortality trends also depend on historical patterns of HIV incidence. The HIV epidemic in South Africa only peaked in the late 1990s, and LE would have declined for another 10 years if ART were not rolled out in 2004.²² This is an important difference with a study from rural Uganda where LE gains of a similar magnitude have been registered.⁶ In the Ugandan case, mortality declines brought about by the rollout of ART are reinforced by mortality reductions due to earlier declines in HIV incidence, and the LE gain attributable to ART is smaller than the observed increase since ART.^{6,23}

The mortality reductions in the study population are large, but they did not come about immediately. Instead, the benefits of ART gradually unfolded, possibly in accordance with lowering ART eligibility thresholds, the availability of more efficacious treatment regimens, the rollout to primary healthcare facilities, and improvements in patients' engagement with HIV services. A few studies have indeed started to document earlier treatment initiation and better patient retention,^{24,25} and suggest that the early assessments of poor engagement with HIV services in generalized epidemics no longer apply.^{26,27} The gradual progress, however, raises the question of why health systems have not been able to capitalize on the benefits of highly effective treatment faster; why it has taken over a decade to reduce the burden of HIV on adult mortality to its current level. In addition, the residual burden of HIV on adult mortality is still not negligible, particularly among women whose adult LE in 2014 is still 5.3 (95%-CI: 2.6-7.8) years lower than that of HIV negative women. Among men, the LE deficit is estimated at 1.2 years and no longer statistically different from zero (95%-CI: -2.9-5.8). The decomposition of the LE deficit by cause affirms that pulmonary TB and HIV almost exclusively account for the surplus mortality, and an earlier analysis suggests that the majority of deaths to PLHIV in this population occur among those who have yet to start treatment.⁹ Pre-treatment mortality among PLHIV is, however, declining rapidly,¹ and it will be important to continue monitoring mortality in relation to the cascade of HIV care and treatment to further improve the delivery of services.

Estimates for the LE deficit also highlight the dual nature of the gender disparities in HIV-associated mortality because the burden of HIV on adult mortality remains larger for women than for men, despite their more sizable gains in adult life-years to date. Several studies have suggested that women disproportionately benefit from the rollout of HIV care and treatment services in African populations, as indicated higher HIV testing and ART coverage rates,²⁸⁻³⁰ earlier treatment initiation, and lower attrition and mortality rates on ART.³⁰⁻³³ These conclusions are supported by our findings, but it is

important to understand that the disproportionate burden of HIV on women, as quantified by the LE deficit, has not yet been fully rectified. We also need to appreciate that gender differences in LE gains and deficits do not solely result from differences in HIV services utilisation. Because women's HIV prevalence is higher than that of men, women lost more life-years to HIV as the epidemic unfolded and, consequently, had more life-years to gain from the expansion of treatment. In addition, women are infected at younger ages,³⁴ and have lower mortality from causes unrelated to HIV. In the absence of treatment, a female HIV infection resulting in an early death will therefore incur a larger loss in life-years than a male HIV death. Conversely, preventing a female HIV death will result in a larger gain in life-years.

Another noteworthy gender difference relates to the age profile of HIV-associated mortality. As treatment programs matured, the median age of the LE deficit among women increased by 1.4 years, which indicates that the burden of HIV is not only declining, but also shifting to older ages. We do not currently observe this phenomenon among men, and that suggests that they still die in large numbers before or shortly after starting therapy.

The survival of PLHIV into older ages will inevitably complicate the attribution of CoDs among PLHIV because comorbidities are common.^{35,36} More generally, any assessment of changes in the CoD structure comes with the caveat that VAs are a relatively crude instrument for cause of death assignment and its specificity for identifying AIDS deaths remains unknown.³⁷ However, our results indicate that the misclassification of causes is limited given that VAs attribute between 80 and 86% of the LE deficit to pulmonary TB and HIV, and much of the remainder to other communicable diseases. In other words, there is a close correspondence between the VA assigned causes of death and the mortality surplus in comparison to the population with a known HIV negative status.

A final word of caution has to do with the attribution of the mortality gains to ART. Because the LE of HIV negative men and women has not changed over the period under observation, the LE gains must come from mortality reductions among PLHIV. The rollout ART is the most plausible reason for that, but we cannot exclude mortality reductions associated with improvements in TB treatment and programmes since TB and HIV are so difficult to distinguish. Similarly, PLHIV may benefit in other ways from their engagement with health services, but little is known about the existence and magnitude such spill-over effects.

Contributors

GR, BZ, and VH conceived the study. KH and ES prepared the data. GR, SB, CC, AM, JE, and ZL analysed the data. KH, JB, SC, TB, BZ and VH provided overall guidance to the conduct of the study. GR wrote the first draft. All authors reviewed the manuscript and approved it for submission.

Declaration of interests

The authors declare no competing interests

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Research in Context

Evidence before this study

We searched PubMed and Medline in June 2016 for studies on the impact of ART and the residual burden of HIV on adult mortality. We did not apply any language or date restrictions, and used combinations of the search terms “HIV”, “AIDS”, “life expectancy”, “population”, “antiretroviral therapy” and “burden”. Several studies report on the life expectancy of HIV positive individuals who started ART, and a number of institutions regularly report on mortality estimates that are the result of more complex modelling exercises. Two studies, one from Uganda and one from South Africa, provide direct nonparametric estimates of population-wide changes in (adult) life expectancy following the rollout of antiretroviral therapy in generalized HIV epidemics. The South African study is based on the same data source used here, and reported an increase of 11.3 years (both sexes) in the in the life expectancy at age 15 between 2003, the year before ART was rolled out, and 2011.

Added value of this study

We extend the analyses for KwaZulu-Natal to 2014, and document per capita adult life expectancy gains of 1.38 years per annum for men and 1.58 years for women, for a total gain since ART of 15.2 (95%-CI: 12.4-17.8) and 17.2 years (95%-CI: 14.5-20.2) for men and women, respectively. We expand on these findings in two novel ways. First, we quantify the residual burden of HIV-associated mortality as the shortfall or deficit of the population-wide life expectancy compared to the life expectancy of the HIV negative population. Among others, this demonstrates that the remaining burden of HIV has become relatively small, especially among men. Among women, the adult life expectancy deficit is still 5.3 years (95%-CI: 2.6-7.8). Second, we use verbal autopsy (VA) data and a new VA interpretation tool (*InSilicoVA*) to establish that differences in mortality from pulmonary TB and HIV explain most of the recent gains in adult life expectancy as well as the remaining life expectancy deficit.

Implications of all the available evidence

Unprecedented increases in adult life expectancy associated with a reduction in HIV-related mortality underscore the success of the ART programme in this population. The burden of HIV mortality remains, however, sizable for women, despite their better engagement with HIV care services. Women, who have to date gained more adult life-years than men, continue to bear the highest burden of HIV mortality, which is a finding that adds a new perspective to the literature wherein men are often portrayed as the “losers of the ART scale-up.”

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Table 1: Characteristics of the study population, and death rates before and after the introduction of the ART (uMkhanyakude, 2001-'14)

	Individuals ^a	Person-Years	Deaths	2001-2004 Rate (95%-CI)	2011-2014 Rate (95%-CI)
All	93,903	535,428	9,992	23.1 (22.3-23.9)	13.6 (13.0-14.2)
Men					
15-19	20,887	62,552	129	2 (1.5-2.8)	1.3 (0.9-2.0)
20-24	16,836	38,642	186	6.4 (5.0-8.1)	3.1 (2.2-4.3)
25-34	14,507	44,791	929	30.3 (27.3-33.6)	12.7 (11.0-14.6)
35-44	8,171	28,863	969	45.4 (41.1-50.2)	21.5 (18.6-24.9)
45+	7,799	46,576	2,432	59.2 (55.1-63.5)	43.2 (39.8-46.8)
All men	42,262	221,424	4,645	26 (24.8-27.3)	15.6 (14.6-16.5)
Women					
15-19	21,736	61,327	136	2.7 (2.0-3.5)	1.5 (1.0-2.2)
20-24	19,158	44,946	353	11.1 (9.4-13.1)	4.4 (3.4-5.7)
25-34	18,809	63,162	1,160	28.7 (26.3-31.3)	8.5 (7.2-9.9)
35-44	11,336	47,542	835	22.9 (20.5-25.5)	10.1 (8.5-12.0)
45+	12,812	97,029	2,863	32.8 (30.6-35.1)	24.6 (22.9-26.5)
All women	51,641	314,005	5,347	21.0 (20.1-22.0)	12.2 (11.5-13.0)
HIV status^b					
Negative	31,520	132,482	1,530	-	13.9 (12.9-14.9) ^c
Positive	15,148	59,576	2,142	-	23.4 (21.8-25.2)
Unknown	93,253	343,370	6,320	23.4 (22.7-24.2)	9.2 (8.5-9.9)

Notes:

^a Individuals can contribute to more than one category as they age or their HIV status changes during follow-up.

^b We report the HIV status information as it is known to the study and may not be the same as men and women's knowledge of their own HIV status. Unknown HIV status includes all the persons-years of exposure before the start of the HIV surveillance as well as individual time prior to the first HIV test, and exposure time more than five years after the last HIV negative test.

^c The death rate for adult HIV negatives is higher than for the population as a whole, which is due to the older age distribution of the population with a known HIV negative status (appendix, pp. 2-3).

Figure 1: Adult LE trends by sex and HIV status, and the LE deficit (uMkhanyakude, 2001-'14)

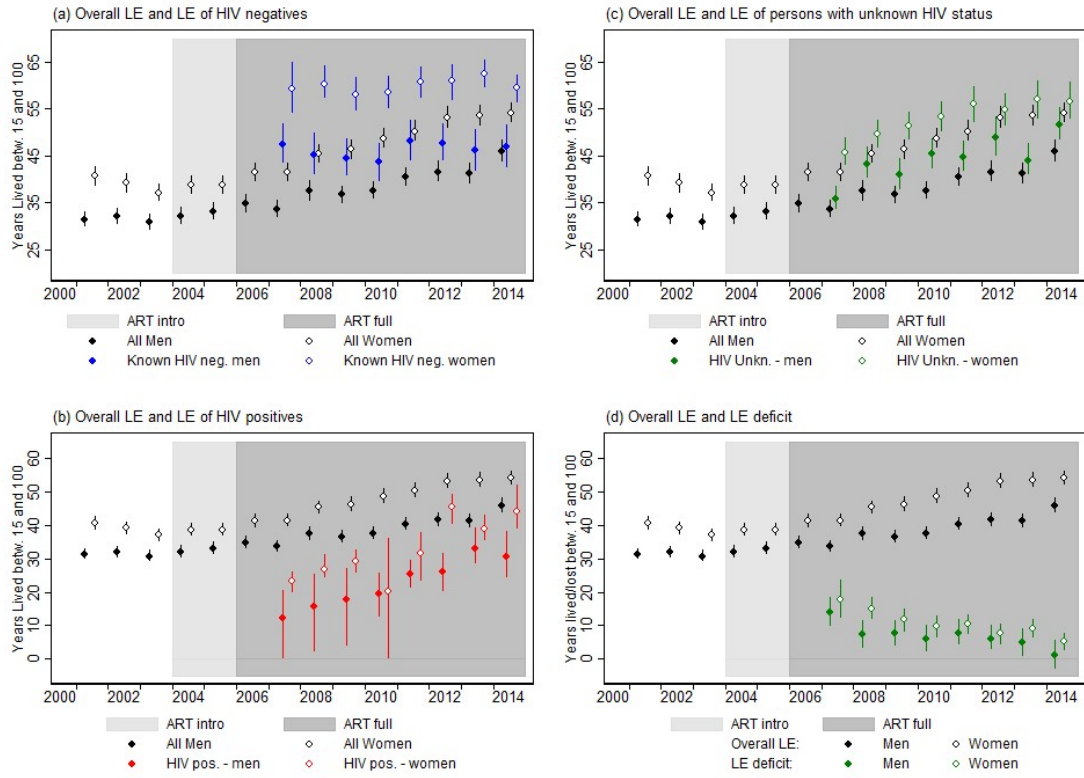


Figure 2: Age and cause-group contributions to the gross LE gains between 2001-'04 and 2011-'14, by sex (uMkhanyakude)

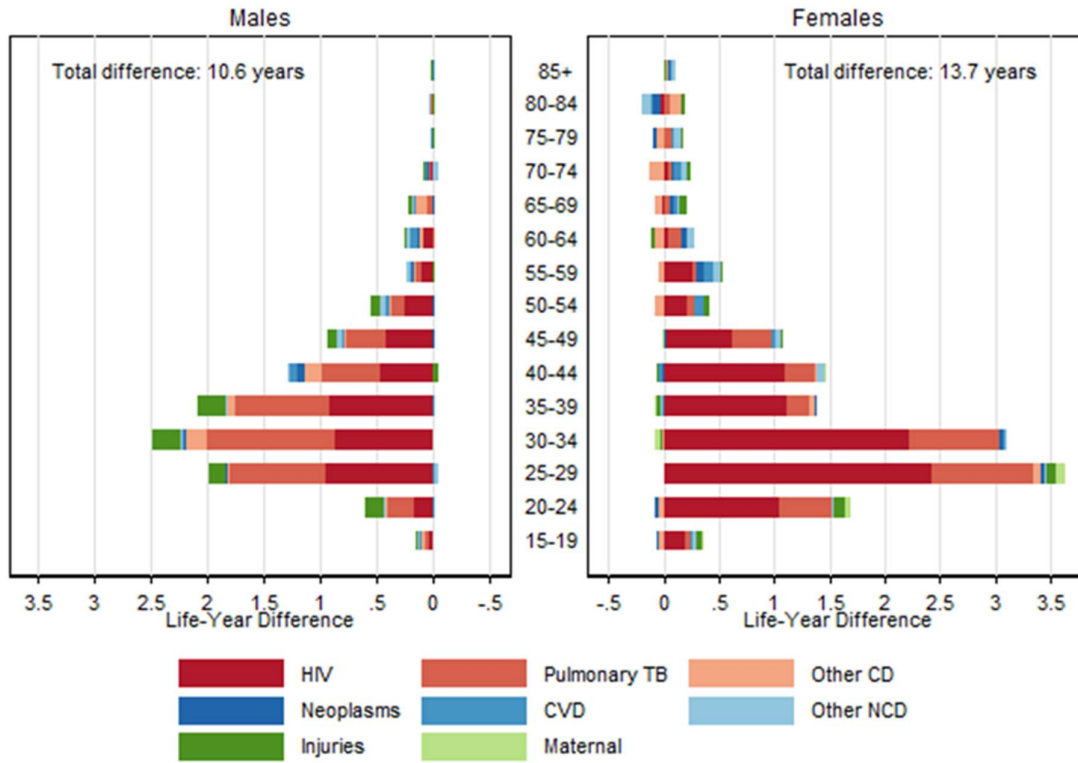
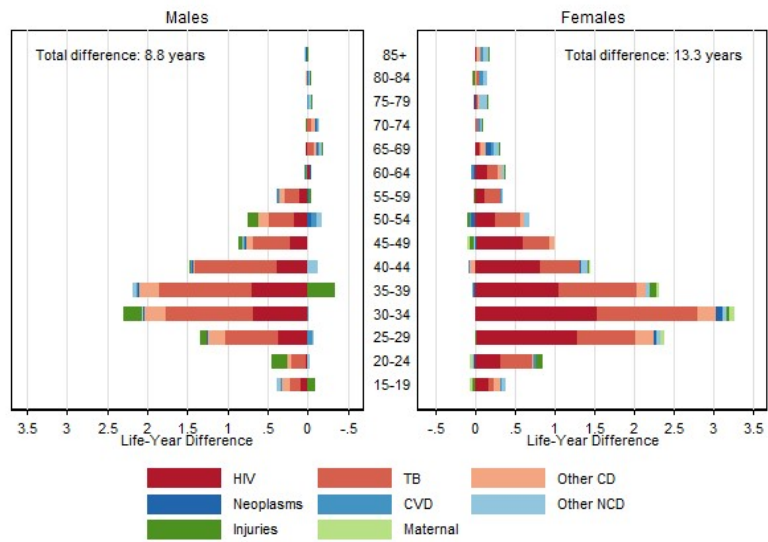


Figure 3: Age-cause decomposition of the LE deficit in 2007-'10 and 2011-'14, by sex (uMkhanyakude)

(a) 2007-'10



(b) 2011-'14

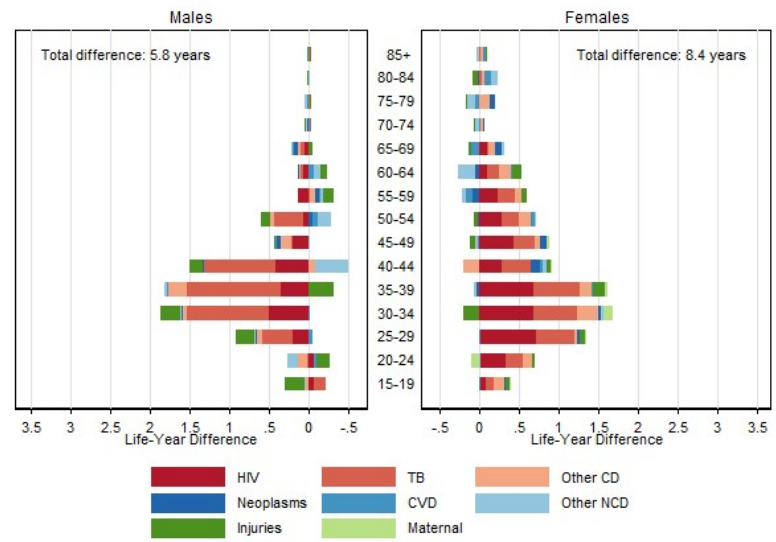


Table 2: The contribution of cause of death groups to the LE gains and deficits (uMkhanyakude, 2001-'14)

	Men		Women	
	Years	% ^a	Years	% ^a
LE gains: 2001-'04 to 2001-'14				
HIV/AIDS	4.22	39.9	9.20	65.4
Pulmonary TB	4.21	39.8	3.56	25.3
Other CD	0.67	6.4	-0.32	-
Neoplasms	0.11	1.0	0.10	0.7
CVD	0.21	2.0	0.33	2.3
Other NCD	0.15	1.4	0.41	2.9
External	1.01	9.5	0.35	2.5
Maternal	-	-	0.12	0.9
LE deficit: 2007-'10				
HIV/AIDS	2.73	29.7	6.32	47.4
Pulmonary TB	5.07	55.3	5.08	38.1
Other CD	1.16	12.6	0.86	6.4
Neoplasms	-0.06	-	0.09	0.6
CVD	-0.08	-	0.14	1.1
Other NCD	-0.18	-	0.68	5.1
External	0.21	2.3	0.10	0.8
Maternal	-	-	0.06	0.5
LE deficit: 2011-'14				
HIV/AIDS	1.79	27.4	3.92	44.5
Pulmonary TB	3.75	57.5	3.20	36.3
Other CD	0.67	10.3	1.27	14.4
Neoplasms	0.04	0.6	0.26	2.9
CVD	-0.21	-	-0.02	-
Other NCD	-0.50	-	-0.36	-
External	0.27	4.7	0.03	0.3
Maternal	-	-	0.13	1.5

Notes: ^a Percent of the sum of positive differences in adult LE. TB=tuberculosis, CD=communicable diseases, CVD=cardiovascular disease, NCD=non-communicable disease

The burden of HIV mortality following the rollout of antiretroviral therapy: evidence from an observational community cohort study in KwaZulu-Natal, South Africa – appendix

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1. HIV status information in the dataset

HIV status information comes from HIV seroprevalence surveys that are conducted annually since 2003-2004. Initially only men and women of reproductive age were invited to participate in the serosurveys; in 2007, the age-eligibility criteria were expanded to all adults. This is complemented with HIV status information retrieved via record linkage between the HDSS and HIV care and treatment facilities.¹ This exercise only identifies HIV positive men and women.

The allocation of exposure time to the various HIV status categories is done in the following manner: person-time before the first HIV test is treated as HIV status unknown, and the time following an HIV positive test is treated as HIV positive exposure time. Analyses of mortality by HIV status also require an assumption about the amount of time that individuals remain HIV negative following an HIV-negative test. In this study, we assume that persons remain HIV negative for five years after their last negative HIV test, after which their HIV status is reclassified as unknown. To test the suitability of this assumption, we calculated the probability that deaths classified as HIV negative should have been treated as HIV positive deaths because a person could seroconvert and die from an HIV related cause in the five-year window after the last HIV negative test. For each death, this calculation relied on (i) the actual duration between an individual's last HIV negative test date and date of death, (ii) the observed sex/age-specific HIV incidence rate, (iii) HIV survival as a function of age at seroconversion,² (iv) the effects of ART on HIV mortality by calendar period, and (v) the observed sex and age-specific non-HIV mortality rates.

Table A1: Duration from last negative HIV test to death and probability of death misclassification by sex, 2010-2014

Age group	Women			Men		
	Number of HIV-deaths ^a	Mean (IQR) years last neg. to death	Avg. misclassification probability (95% CI) ^b	Number of HIV-deaths ^a	Mean (IQR) years last neg. to death	Avg. misclassification probability (95% CI) ^b
15-24 years	17	1.9 (0.7-2.8)	0.034 (0.026-0.043)	27	2.1 (0.9-3.6)	0.014 (0.010-0.020)
25-34 years	14	1.9 (0.9-2.9)	0.043 (0.032-0.058)	25	2.5 (0.8-3.6)	0.036 (0.026-0.048)
35-44 years	14	2.0 (0.7-3.5)	0.028 (0.020-0.037)	20	1.6 (0.7-2.3)	0.007 (0.004-0.010)
45-54 years	32	1.5 (0.8-2.4)	0.003 (0.002-0.004)	38	1.7 (0.6-2.3)	0.004 (0.003-0.006)
55-64 years	64	1.4 (0.6-1.9)	0.001 (0.000-0.001)	78	1.8 (0.7-2.7)	0.001 (0.000-0.001)
65-74 years	134	1.7 (0.7-2.5)	<0.001	106	1.3 (0.5-2.1)	<0.001
75-84 years	179	1.6 (0.7-2.3)	<0.001	80	1.7 (0.8-2.2)	<0.001
85+ years	70	1.9 (0.8-2.9)	<0.001	50	1.4 (0.7-2.0)	<0.001
Total	524	1.6 (0.6-2.4)	0.003 (0.003-0.004)	424	1.7 (0.7-2.5)	0.004 (0.003-0.005)

Notes: ^a Number of deaths classified as being to HIV-negative adults in analyses stratified by HIV status, based on deaths that occurred within 5 years of the individuals' last negative HIV test. ^b The average probability that an individual seroconverted and died from HIV in the interval between the last HIV test and date of death. The complement (1 – probability) is the average probability that the death was truly not related to HIV.

Table A1 reports the number of deaths classified to HIV-negative adults (within 5 years of the last HIV-negative test), the mean duration from the last HIV-negative test to the observed death, and the average probability that a death was attributable to HIV. This exercise illustrates that the probability of misclassifying deaths remains under 5% for all age groups and sexes. The probability of misclassification was highest for the 15-35 year age group in which HIV incidence is highest and non-HIV mortality rates are lowest. In older age groups, the probability that HIV-negative deaths were misclassified is vanishingly small (<1%).

Table A2 illustrates that the coverage of the HIV status information in the dataset gradually increased since the start of the population-based HIV serosurveys. HIV status information remains under 60% in the most recent years, however, and that is due to the relatively low HIV survey participation rates.³

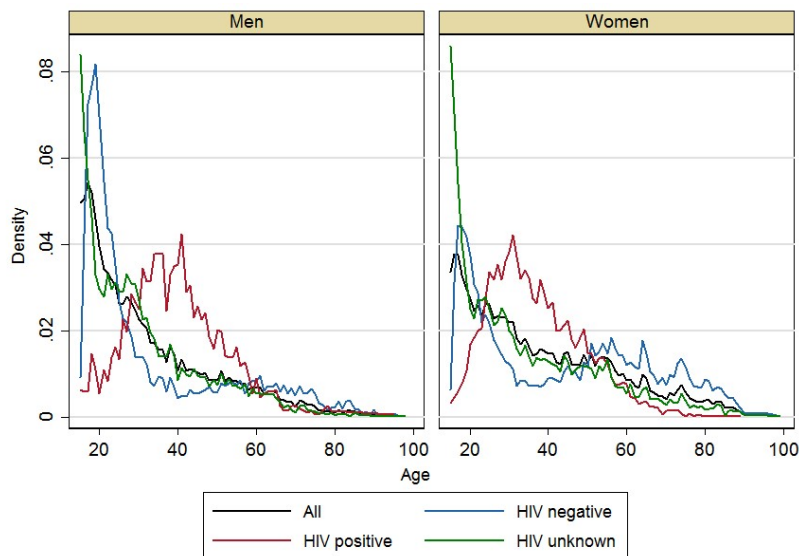
It is also worth noting that ACDIS tracks the vital status of both resident and non-resident household members, but we only include residents in our analyses because the ascertainment of HIV status and causes of death (CoD) is more complete for residents.

Table A2: Coverage of the HIV status information in the dataset by calendar year and sex (percent of person years)

Year	Men	Women	Both sexes
2000	0.0	0.0	0.0
2001	0.0	0.0	0.0
2002	0.1	0.1	0.1
2003	3.7	4.2	4.0
2004	21.2	21.9	21.6
2005	32.0	32.0	32.0
2006	36.9	36.3	36.6
2007	39.1	42.6	41.2
2008	42.5	51.1	47.6
2009	41.9	53.6	48.8
2010	40.9	55.9	49.6
2011	42.6	59.9	52.7
2012	42.6	60.4	52.9
2013	44.9	63.0	55.4
2014	45.7	64.9	56.9

The relative age distribution of the population by HIV status and sex is illustrated in Figure A1. As one would expect, most PLHIV are between 20 and 60 years old. The age profile of the HIV negative population is older than that of the population as a whole, which helps to explain the higher crude death rate (ages 15 and above) among the HIV negative population reported in Table 1 in the article.

Figure A1: One-year age densities by HIV status and sex (uMkhanyakude, July 2014)



2. Adult LE estimates and their interpretation

Table A3 contains the adult LE estimates that are the basis for Figure 1 in article. The adult LE is estimated with non-parametric survival analysis methods as the area under the Kaplan-Meier survival curve. Percentile-based confidence intervals are obtained via bootstrapping with 1,000 replications. A similar approach has been taken elsewhere.^{4,5} Because of the sparse data in old age and to avoid possible bias due to age over-reporting, we truncate the person-years lived above age 100. The precise interpretation of our LE measure is the expected number of years lived between ages 15 and 100 given the age-period mortality rates. On average, the difference with the LE at age 15 is less than 0.1 years for both men and women. Adding 15 years to our estimates gives the mean age at death conditional on survival to age 15. The latter is the measure reported by Bor and colleagues in other studies using the same data source.^{4,6}

A key attribute of adult LE as a metric for studying HIV mortality and the impact of ART is that it quantifies the postponement rather than the elimination of deaths. Measures that do not account for the shift in the age distribution of mortality (e.g., the number of AIDS deaths, death rates or the probability of dying in adulthood) are less sensitive to the nature of the mortality reductions induced by ART and will underestimate its impact. Another matter of interpretation that affects any synthetic mortality measure is that the LE may be inflated in the period that the bulk of HIV positives initiate treatment. In those years, deaths among HIV positives are averted, but their elevated mortality at older ages does not yet factor into the estimates. This phenomenon invalidates the interpretation of the synthetic or period LE as an estimate of the years lived *under current conditions*, but it remains an accurate measure of the years lived *at current rates*.⁷

Table A3: Non-parametric adult life expectancy estimates by sex, HIV status and calendar year, uMkhanyakude (2001-2014)

	Men							
	2001	2003	2005	2007	2009	2011	2013	2014
LE All	31.4 (29.9-33.1)	30.8 (29.2-32.5)	33.1 (31.2-35.0)	33.6 (31.9-35.5)	36.6 (34.8-38.5)	40.4 (38.5-42.5)	41.3 (39.1-43.3)	45.9 (43.7-48.4)
LE HIV-	-	-	-	47.4 (43.4-51.9)	44.4 (40.6-48.6)	48.1 (43.9-52.7)	46.1 (41.7-50.7)	47.0 (42.5-51.7)
LE HIV+	-	-	-	12.1 (0.0-20.6)	17.8 (3.9-27.1)	25.3 (21.1-29.4)	33.1 (28.4-39.3)	30.5 (24.4-38.3)
LE HIV unk.	-	-	-	35.8 (33.5-38.5)	40.9 (37.7-44.4)	44.7 (41.7-48.0)	44.1 (40.9-47.6)	51.6 (48.4-55.4)
LE deficit	-	-	-	13.8 (9.7-18.6)	7.8 (3.8-11.5)	7.8 (4.2-12.0)	4.8 (0.7-9.2)	1.2 (-2.9-5.8)
	Women							
	2001	2003	2005	2007	2009	2011	2013	2014
LE All	40.7 (38.6-42.8)	37.0 (35.2-38.9)	38.7 (36.8-40.7)	41.5 (39.4-43.4)	46.3 (44.3-48.5)	50.2 (48.1-52.7)	53.6 (51.3-55.8)	54.2 (52.2-56.2)
LE HIV-	-	-	-	59.2 (54.1-65.0)	58.1 (54.5-61.8)	60.7 (57.2-64.0)	62.6 (59.5-65.5)	59.4 (56.3-62.3)
LE HIV+	-	-	-	23.4 (19.7-26.2)	29.2 (25.8-32.6)	31.6 (23.3-37.9)	38.9 (35.6-42.9)	44.1 (39.1-52.1)
LE HIV unk.	-	-	-	45.8 (43.0-48.9)	51.4 (48.4-54.4)	56.1 (52.2-59.9)	57.0 (52.9-61.0)	56.4 (52.8-60.7)
LE deficit	-	-	-	17.7 (12.3-23.8)	11.8 (8.2-15.1)	10.4 (7.5-13.3)	9.0 (6.4-11.9)	5.3 (2.6-7.8)

Aside from the overall adult LE, we also report the LE by HIV status and the adult LE deficit. The LE of HIV negative adults is a measure of the background or HIV free mortality, and is an important indicator of the health profile of a population in its own right. In our case, it also serves as a benchmark of the achievable LE in the population that we use to calculate the LE deficit (see below). The LE estimates for the HIV negative population are around

47 years for men and 60 years for women. In comparison, Bor and colleagues report an HIV and TB cause-deleted adult LE of 50 years for men, and 60 years for women.⁴

The LE of HIV positive men and women quantifies the number of additional years that an HIV positive 15-year old can expect to live at current rates, and is of direct interest to any study evaluating the impact of ART. Because of the relatively small numbers, these estimates have wide uncertainty bounds. In addition, trends in the LE of PLHIV could be biased when the interval between seroconversion and the time that PLHIV become known HIV positives to the study varies.

The LE for people whose HIV status is unknown is informative about possible selection with respect to the HIV status information in the datasets. In this case, the LE of men and women with an unknown HIV status is a little higher than that of the population as a whole, which suggests that the group of residents with an unknown HIV status contains a disproportionately large share of HIV negatives. This apparently contradicts studies that have demonstrated that PLHIV are less likely to participate in HIV serological surveys,⁸⁻¹² but is explained by the fact that we are also identifying PLHIV via record linkage with medical facilities that provide HIV care and treatment services.

The adult LE deficit is the difference between the adult LE of known HIV negatives and the adult LE for the population as a whole. It is, in other words, a summary measure of the mortality burden of HIV conditional on the background health profile of its population. The LE deficit is directly affected by HIV epidemic severity and efforts to mitigate its mortality impact (e.g., ART). Not all of the LE deficit is necessarily attributable to HIV, however, as the LE deficit could be inflated due to a positive correlation between HIV infection and non-AIDS mortality risks factors including socio-economic background, smoking and substance abuse. To date, most evidence of such an association comes from high income settings and concentrated epidemics.¹³ Similarly, the expansion of treatment programs could also generate spill-over effects on non-AIDS mortality of both HIV negatives and HIV positives via changes to health services provision or health seeking behaviour, a decline in suicide rates, and so forth.^{4,14} Little is known about the magnitude of such spill-over effects. When interpreting differences in the LE deficit between population subgroups, it is also important to understand that the LE deficit is sensitive to variability in the age at infection and differences in background mortality. Finally, we also want to point at the distinction between the LE deficit as defined above, and studies that report the LE of HIV positive men and women as a percentage of the LE of HIV negatives or the population as a whole.^{15,16} The latter quantify the shortfall in the LE of PLHIV, but do not measure the population-wide burden of HIV.

3. Cause of death classification

Table A4 maps the CoD classification scheme used in the manuscript onto their respective ICD-10 codes.

Table A4: Cause of death (COD) classification

COD groups in manuscript	ICD-10 code
HIV/AIDS related	B20-B24
Pulmonary tuberculosis	A15-A16
Other communicable diseases & nutritional conditions	A00-A09; A17-A99; B00-B19; B25-B99; D50-D64; E40-E46; G00-G05; J00-J22
Maternal disorders	O00-O08; O10-O16; O20-O99
Malignant neoplasms	C00—C26; C30-C58; C60-D48
Cardiovascular diseases	D57; I00-I15; I20-I52; I60- I99
Other non-communicable diseases	D55-D89; E00-E07; E10-E35; E50-E90; F00-F99; G06—G37; G40-G41; G50-G99; H00-H95; J30-J99; K00-K31; K35-K38; K40-K93; L00-L99; M00-M99; N00-N99; R00-R94
External injuries	S00-T99; V01-V99; W00-W99; X00-X99; Y00-Y98
Indeterminate	R95-R99

4. Decomposition of LE differences based on the InterVA model for CoD attribution

Table A5 summarizes the decomposition of adult LE differences based on CSMFs estimated with the R package of the InterVA-4 model (version 1.5) with the replicate option set to false.^{17,18} InterVA-4 generates up to three probable CoDs with their corresponding likelihoods or an indeterminate CoD with 100% likelihood. If the likelihoods of the first three CoDs do not sum to 100%, the residual is treated as indeterminate. As with InSilicoVA, CoDs that were classified as missing due to incomplete VAs were excluded from the analyses.

CoD attribution was done separately by HIV status to minimize misclassification of HIV deaths. InterVA is run with malaria prevalence set to low and HIV prevalence set to high for known HIV positives and for men and women whose HIV status is unknown, and with both malaria and HIV prevalence set to low for the HIV negative population. Unlike InSilicoVA, InterVA allows for deaths to be classified as indeterminate, but their contribution to the LE differences are small. The only other noteworthy difference between the two VA interpretation tools for our analyses is that InSilicoVA tends to attribute a slightly higher fraction of the LE differences to other (unspecified) communicable diseases.

Table A5: The CoD contributions to the LE gain and deficits based on the CoD attribution with the InterVA model (uMkhanyakude, 2001-'14)

	Men		Women	
	Years	% of total ^a	Years	% of total ^a
LE gain: 2001-'04 to 2001-'14				
HIV/AIDS	3.71	35.1	7.72	55.3
TB	4.17	39.5	4.77	34.2
Other CD	0.37	3.5	0.10	0.7
Neoplasms	0.67	6.4	0.42	3.0
CVD	0.25	2.3	0.45	3.3
Other NCD	0.15	1.4	0.00	0.0
External	0.89	8.4	0.32	2.3
Maternal	-	-	0.16	1.2
Indeterminate	0.36	3.4	-0.22	-
LE deficit: 2007-'10				
HIV/AIDS	3.95	42.6	6.99	52.2
TB	4.16	44.8	4.24	31.7
Other CD	0.43	4.7	0.77	5.7
Neoplasms	0.49	5.3	0.39	2.9
CVD	-0.04	-	-0.07	-
Other NCD	-0.33	-	0.46	3.4
External	0.24	2.6	0.12	0.9
Maternal	-	-	0.07	0.5
Indeterminate	-0.06	-	0.36	2.7
LE deficit: 2011-'14				
HIV/AIDS	2.06	34.0	4.75	54.3
TB	3.68	60.7	2.57	29.5
Other CD	-0.08	-	0.49	5.6
Neoplasms	0.01	0.2	0.22	2.6
CVD	-0.17	-	-0.04	-
Other NCD	0.12	2.0	0.19	2.1
External	0.16	2.6	-0.07	-
Maternal	-	-	-0.19	-
Indeterminate	0.03	0.5	0.52	5.9

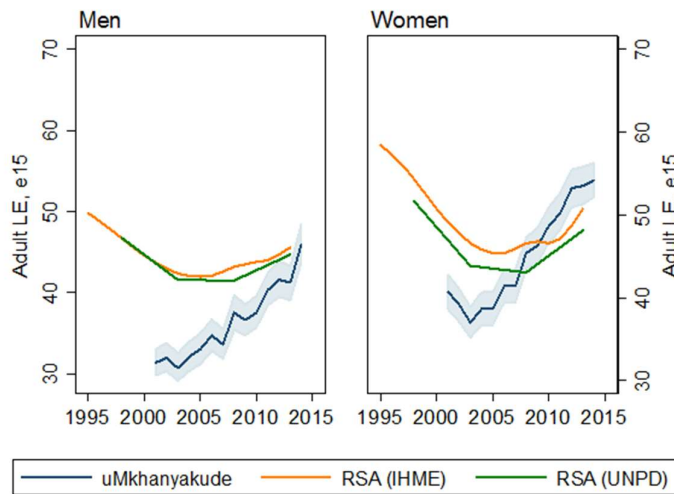
Notes: ^a Percent of the sum of positive differences in adult LE

5. Comparison of adult LE trends in uMkhanyakude and estimates for South Africa as a whole

Even though these are not directly comparable, it is useful to contrast our adult LE estimates for uMkhanyakude with two sets of estimates for South Africa as a whole: one from the United Nations Population Division's (UNPD) 2015 World Population Prospects,¹⁹ and the second set of estimates from the Institute of Health Metrics and Evaluation's (IHME) 2013 Global Burden of Disease (GBD) study.²⁰ This is done in Figure A2.

Adult LE estimates from IHME and UNPD are comparable for men, but the GBD estimates entail larger gender differences. The trend in adult LE is quite different in uMkhanyakude. Because the HIV epidemic is particularly severe in this population (29.0% among adults of reproductive age in the study population versus 18.8% for South Africa as a whole),^{21,22} one would indeed expect that adult LE bottoms out at a lower level and subsequently increases faster because mortality will fluctuate more drastically in a high prevalence population where the mortality impact of the epidemic first unfolds and is later mitigated by the rollout of ART. More surprising, however, is that the adult LE in uMkhanyakude is estimated to be as high as or even higher than the national-level estimates. It is difficult to adjudicate on the accuracy of each set of estimates on the basis of this evidence alone. Possible reasons for the discrepancy are (i) that adult mortality is underestimated in the HDSS, (ii) that the treatment programs are particularly effective in the facilities that serve the HDSS population, or, (iii) that the national-level adult LE estimates from the UNPD and IHME are too low, possibly because they underestimate the mortality reductions brought about by the rollout of ART.

Figure A2: Adult life expectancy trends in uMkhanyakude, and South Africa (RSA) as a whole, 1995-2014



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