Trends in the burden of HIV mortality after roll-out of antiretroviral therapy in KwaZulu-Natal, South Africa: an observational community cohort study

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Summary

Background: **Antiretroviral therapy (ART) substantially decreases morbidity and mortality in people living with HIV. In this study, we describe population-level trends in the adult life expectancy and trends in the residual burden of HIV mortality after the roll-out of a public sector ART programme in KwaZulu-Natal, South Africa, one of the populations with the most severe HIV epidemics in the world.**

Methods: **Data come from the Africa Centre Demographic Information System (ACDIS), an observational community cohort study in the uMkhanyakude district in northern KwaZulu-Natal, South Africa. We used non-parametric survival analysis methods to estimate gains in the population-wide life expectancy at age 15 years since the introduction of ART, and the shortfall of the population-wide adult life expectancy compared with that of the HIV-negative population (ie, the life expectancy deficit). Life expectancy gains and deficits were further disaggregated by age and cause of death with demographic decomposition methods.**

Findings: **Covering the calendar years 2001 through to 2014, we obtained information on 93 903 adults who jointly contribute 535 42 8 person-years of observation to the analyses and 9992 deaths. Since the roll-out of ART in 2004, adult life expectancy increased by 15·2 years for men (95% CI 12·4–17·8) and 17·2 years for women (14·5–20·2). Reductions in pulmonary tuberculosis and HIV-related mortality account for 79·7% of the total life expectancy gains in men (8·4 adult life-years), and 90·7% in women (12·8 adult life-years). For men, 9·5% is the result of a decline in external injuries. By 2014, the life expectancy deficit had decreased to 1·2 years for men (–2·9 to 5·8) and to 5·3 years for women (2·6–7·8). In 2011–14, pulmonary tuberculosis and HIV were responsible for 84·9% of the life expectancy deficit in men and 80·8% in women.**

Interpretation: **The burden of HIV on adult mortality in this population is rapidly shrinking, but remains large for women, despite their better engagement with HIV-care services. Gains in adult life-years lived as well as the present life expectancy deficit are almost exclusively due to differences in mortality attributed to HIV and pulmonary tuberculosis.**

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Introduction

The roll-out of antiretroviral therapy (ART) in populations with generalised epidemics has greatly improved the survival of people living with HIV and has been documented in both clinical cohorts and population-based research.[1–7] Many studies report 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 sought to remedy the above-mentioned shortcomings with data from the Africa Centre Demographic Information System (ACDIS) in rural KwaZulu-Natal, South Africa, where HIV status is known for a large portion of the population.

We report on trends in the life expectancy at age 15 years and the adult life expectancy by HIV status. Life expectancy is one of the most widely used summary measures of mortality and is 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 (45q15), are less sensitive to the shift in the age distribution of deaths and might underestimate the mortality reductions prompted by the roll-out of ART.

Our analyses focused on two measures of great public health interest: gains in adult life expectancy since ART introduction and trends in the adult life expectancy deficit. The second of these measures is defined as the shortfall of the population-wide adult life expectancy compared with that of the HIV-negative population, and quantifies the residual burden of HIV mortality in a population. Furthermore, we used demographic decomposition techniques to estimate the contribution of changes in HIV and other causes of death to recent trends in the adult life expectancy and the adult life expectancy deficit. With these analyses, we aimed to update and expand on previous work on adult mortality from the same study site.[2,8–10] All our estimates are disaggregated by

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Research in context

Evidence before this study

We searched PubMed and MEDLINE on June 15, 2016, for studies on the effect of antiretroviral therapy (ART) and the residual burden of HIV on adult mortality. We did not apply any language or date restriction, and used combinations of the search terms "HIV", "AIDS", "life expectancy", "population", "antiretroviral therapy", and "burden". Several studies reported 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, provided direct non-parametric estimates of population-wide changes in adult life expectancy after the roll-out of antiretroviral therapy in generalised HIV epidemics. The South African study is based on the same data source used here, and reported an increase of 11·3 years in the life expectancy for both sexes at age 15 years between 2003, the year before ART was rolled out, and 2011.

Added value of this study

We extended the analyses for KwaZulu-Natal from 2011 to 2014 and documented adult life expectancy gains of 1·38 years per year for men and 1·58 years for women, for a total gain since ART of 15·2 years and 17·2 years for men and women, respectively. We expanded on these findings in two novel ways. First, we quantified the residual burden of HIV-associated mortality as the shortfall or deficit of the population-wide life expectancy compared with the life expectancy of the HIV-negative population. This shows that the remaining burden of HIV has become relatively small, especially in men. In women, the adult life expectancy deficit in 2014 was still 5·3 years. Second, we used verbal autopsy data and a new verbal autopsy interpretation tool (InSilicoVA) to establish that differences in mortality from pulmonary tuberculosis and HIV explain most of the 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. However, the burden of HIV mortality remains sizable for women, despite their better engagement with HIV care services. Women, who have so far 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 published work wherein men are often portrayed as the so-called losers of the ART scale-up.

sex and add a new perspective to the scientific literature wherein women are routinely considered to have disproportionally benefited from the expansion of treatment.[11,12]

Methods

Study design and population

In this observational community cohort study, we used data from the Africa Centre Demographic Information System (ACDIS) in the uMkhanyakude district in northern KwaZulu-Natal, South Africa, covering 434 km² of predominantly rural area with a resident adult population of around 45 000 adults (aged 15 years and older).[13] The population is characterised by high HIV prevalence (29% in adults aged 15–49 years 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, more than 1000 patients were receiving treatment, and by mid-2011, an estimated 37% of people living with HIV in the study population were on ART.[10,15] Further details about the expansion of the treatment programme in South Africa and changes to the ART eligibility criteria have been described previously.[16]

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 & Tropical Medicine. Household representatives gave verbal informed consent for the demographic surveillance, and individual written consent was required for the HIV surveillance.

Data collection

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

Individuals contributed person-time to the analyses from their 15th birthday or from when they moved into one of the villages under surveillance until they moved out, died, or turned 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.

To allocate person-time to HIV status categories, we classified the time before the first recorded HIV test as HIV status unknown. The time after a positive test remained positive until censoring or death. The time after the last negative test was considered negative for a duration of 5 years, after which it was classified as unknown. This procedure allowed for the estimation of mortality rates in HIV-negative individuals, but the exposure time was sufficiently short to ensure that

increased mortality in seroconverters did not introduce bias (appendix pp 2,3). Time between two HIV-negative tests was always counted as negative no matter how long the interval between tests.

Statistical analysis

Adult life expectancy is defined as the number of additional years that a 15-year-old person can expect to live if subject to the observed mortality rates in a specific period (appendix pp 4,5). Life expectancy estimates by sex, year, and HIV status were computed with continuous-time survival analysis techniques as the area under the Kaplan Meier survival curve. Percentile-based confidence intervals were obtained via bootstrapping with 1000 replications.

We focused on two quantities: first, the total adult life expectancy gain since introduction of ART, and second, the remaining adult life expectancy deficit. The total life expectancy gain is the difference between 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 deficit quantifies the extent to which the overall population life expectancy falls short of the life expectancy of HIV-negative individuals. In other words, the life expectancy deficit is a summary measure of the mortality effect 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 effect (eg, ART).

We disaggregated adult life expectancy gains and deficits by age and cause of death with a demographic decomposition method first proposed by Arriaga.[17] The decomposition of the life expectancy gains quantifies the contribution of changes in cause-specific mortality in each age group to the overall increase in adult life expectancy from 2000–03 (the pre-ART period) to 2011–14. The decomposition was done for groups of calendar years because the population was too small for an analysis by single year. We subsequently used the same method for decomposing the life expectancy deficit for two periods (2007–10 and 2011–14), and their comparison informs us of changes in the age and cause distribution of excess mortality as treatment programmes develop.

Information about the causes of death came from verbal autopsy interviews with relatives of deceased individuals. Verbal autopsy interpretation was done with the InSilicoVA tool.[18] InSilicoVA uses a Bayesian model to estimate the cause-specific mortality fractions at the population level and cause-specific probabilities at the individual level. We separately generated estimates for subpopulations defined by two broad age groups (below age 60 years and 60 years or older), gender, and HIV status at the time of death. We then aggregated the individual-level cause-specific probabilities to obtain cause-specific mortality estimates for 5 year age groups. The causes of death classification scheme for reporting results distinguished HIV/AIDS, pulmonary tuberculosis, other communicable diseases, malignant neoplasms, cardiovascular disease, other non-communicable diseases, external injuries, and maternal mortality. We reported results for pulmonary tuberculosis and HIV separately, but know from previous studies that they are often difficult to separate on the basis of a verbal autopsy interview because of the similarity of symptoms and high co-morbidity.[19] The appendix (p 6) maps the causes of death classification scheme onto the International Classification of Diseases-10, and summarises analyses wherein the cause of death attribution was done with the InterVA model (appendix p 7).[20]

This study 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).

See Online for appendix

Role of the funding source

The funders had 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 had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Individuals*	Person-years	Deaths	Death rate (95% CI) 2001–04	Death rate (95% CI) 2011–14
Total	93 903	535 428	9992	23·1 (22·3–23·9)	13·6 (13·0–14·2)
Men's age (years)					
15–19	20 887	62 552	129	2·0 (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	8171	28 863	969	45·4 (41·1–50·2)	21·5 (18·6–24·9)
≥45	7799	46 576	2432	59·2 (55·1–63·5)	43·2 (39·8–46·8)
All men	42 262	221 424	4645	26·0 (24·8–27·3)	15·6 (14·6–16·5)
Women's age (years)					
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	1160	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	2863	32·8 (30·6–35·1)	24·6 (22·9–26·5)
All women	51 641	314 005	5347	21·0 (20·1–22·0)	12·2 (11·5–13·0)
HIV status†					
Negative	31 520	132 482	1530	..	13·9 (12·9–14·9)‡
Positive	15 148	59 576	2142	..	23·4 (21·8–25·2)
Unknown	93 253	343 370	6320	23·4 (22·7–24·2)	9·2 (8·5–9·9)

..=no data available. *Individuals can contribute to more than one category as they age or their HIV status changes during follow-up. †We report the HIV status information as it is known to the study and might 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 before the first HIV test, and exposure time more than 5 years after the last HIV negative test. ‡The death rate for adult HIV-negative individuals is higher than for the population as a whole because of the older age distribution of the population with a known HIV-negative status (appendix pp 2, 3).

***Table 1*: Study population characteristics and death rates before and after the introduction of ART (uMkhanyakude, 2001–14)**

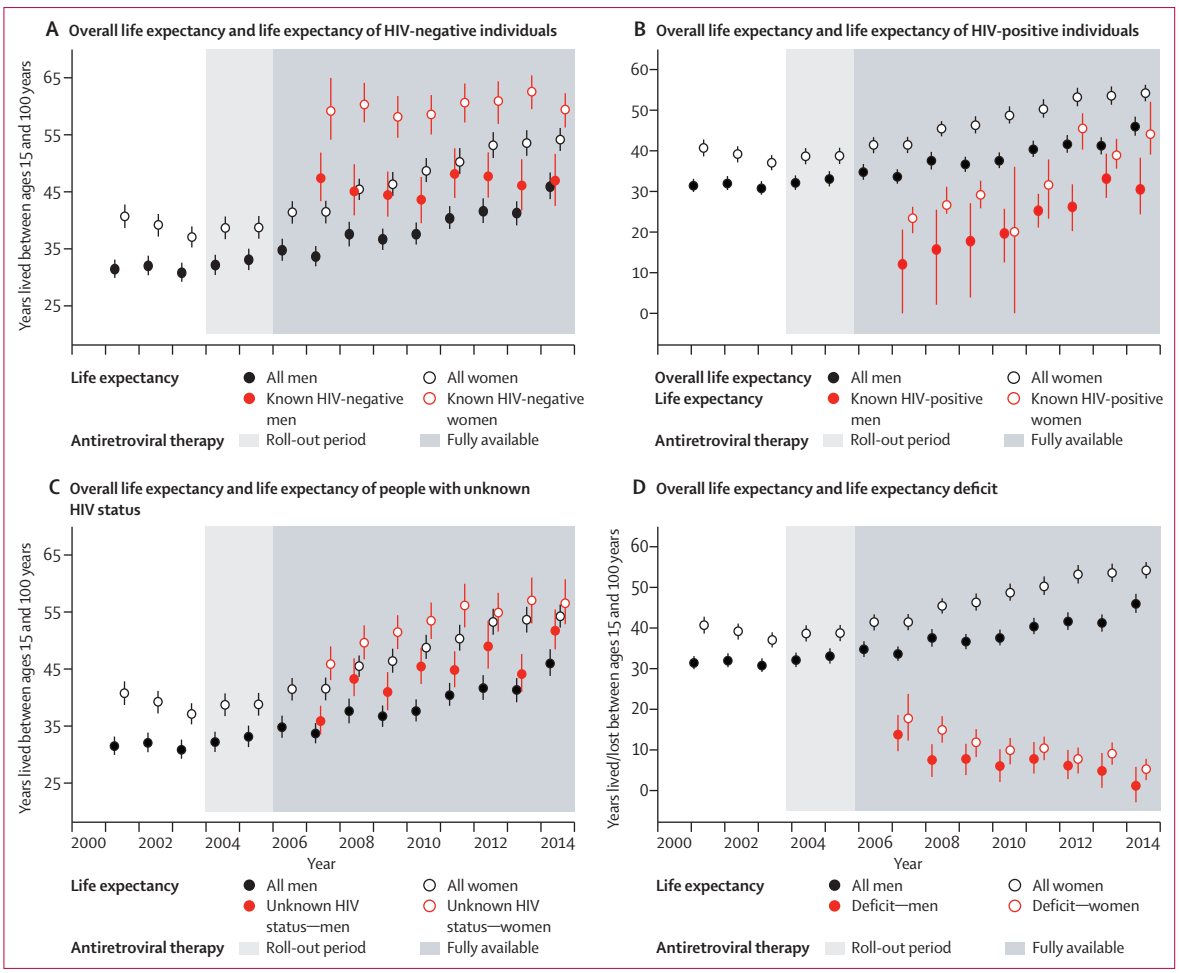

Figure 1: **Adult life expectancy trends by sex and HIV status, and life expectancy deficit (uMkhanyakude, 2001–14)**

Results

Between 2001 and 2014, a cumulative number of 93 903 adults ever resided in the demographic surveillance area of KwaZulu-Natal, South Africa. These individuals jointly contribute 535 428 person-years of observation time and 9992 deaths to the analyses (table 1). Verbal autopsy interviews were completed for 9605 of these deaths. Women contribute 314 005 (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 appendix (pp 2,3) provides more detail on the HIV status information in the dataset.

The crude death rate decreased from 23·1 deaths (95% CI 22·3–23·9) to 13·6 deaths (13·0–14·2) per 1000 person-years between 2001–04 and 2011–14. Because HIV surveillance only started in 2004, mortality estimates by HIV status before the roll-out of ART are not available. However, the most pronounced mortality declines took place between the ages of 20 years and 45 years, which is an age range where HIV-associated mortality is common.

The mortality rate reductions translate into important gains in adult life expectancy (figure 1, appendix pp 4, 5). Overall adult life expectancy reached its nadir in 2003, the year before the introduction of ART. Between 2003 and 2014, adult life expectancy increased by 15·2 years for men (95% CI 12·4–17·8) and 17·2 years for women (14·5–20·2). These estimates represent average increases in the adult life expectancy of 1·38 years per annum for men and 1·58 years for women, and are much larger than the life expectancy gains estimated for South Africa as a whole (appendix p 8). In 2014, the population-wide adult life expectancy in uMkhanyakude reached 45·9 years (43·7–48·4) for men and 54·2 years (52·2–56·2) years for women.

Adult life expectancy 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 life expectancy for HIV-negative men and women hovered around 47 years for men and 60 years for women for the entire period (figure 1A). Although the adult life expectancy of HIV-negative individuals did

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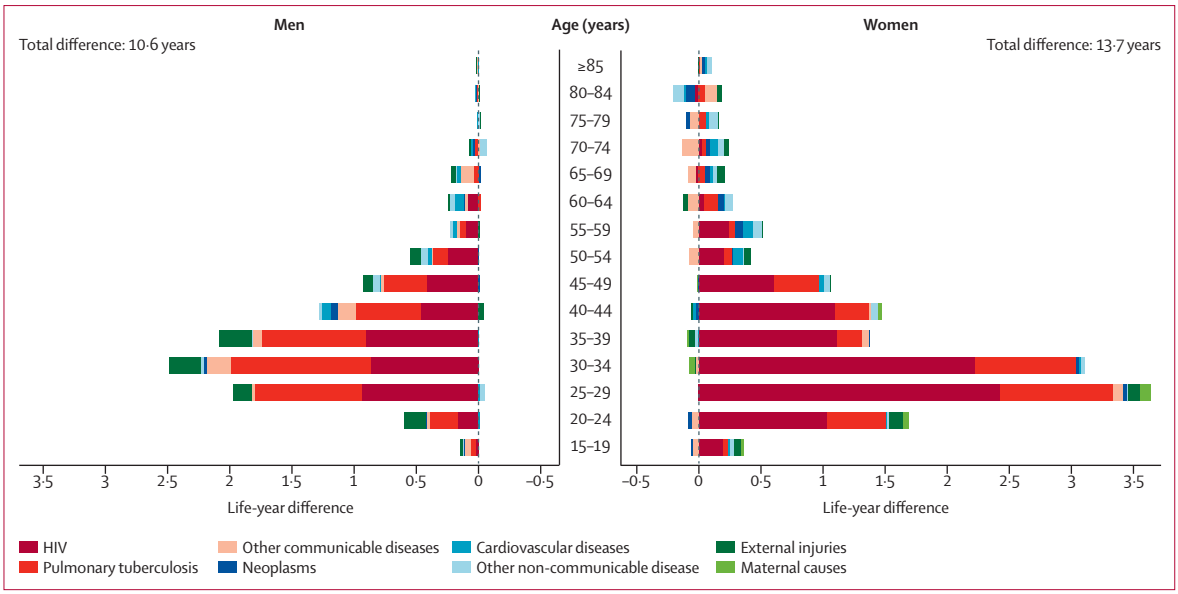

***Figure 2*: Age and cause of death-group contributions to the gross life expectancy gains between 2001–04 and 2011–14, by sex (uMkhanyakude)**

not change, the outlook for people living with HIV improved substantially. Between 2007 and 2014, the number of years that an adult HIV-positive person could expect to live increased by 18·4 years (95% CI 7·5–33·8) for men and 20·7 (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 (24·4–38·3) at the prevailing mortality rates. For women this was 44·1 years (39·1–52·1). The life expectancy of adults whose HIV status was unknown to the study was marginally higher than that of the population as a whole, which suggests that people living with HIV are under-represented among those with an unknown HIV status (figure 1C).

The life expectancy estimates reported in figure 1A are the inputs for computing the life expectancy deficit associated with HIV (figure 1D). In 2007, 3 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 (12·3–23·8) for women. By 2014, the life expectancy deficit decreased to 1·2 (–2·9 to 5·8) for men and 5·3 (2·6–7·8) years for women.

Figure 2 provides further insight into the age groups and causes of death that have contributed to the life expectancy gains since the introduction of ART. Cause of death contributions aggregated over age are reported in table 2. The total life expectancy 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 figure 2 suggest that the mortality rates from a particular cause in a specific age group increased over time and thus had a negative effect on the life expectancy trend; however, their contributions were very small. The age groups with the largest contribution to the increase in adult life expectancy over this period were 25–29 years for women and 30–34 years for men.

The decomposition by cause suggests that almost all of the gains in adult life expectancy resulted from reductions in mortality ascribed to HIV and pulmonary tuberculosis. In 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 life expectancy ascribed to reductions in pulmonary tuberculosis and HIV mortality in women is 12·8 years, or 90·7% of the total gain. The relative contribution of HIV within this group of causes is larger for women than for men. For men, a reduction in the number of deaths from external injuries contributes 1 year to the increase in adult life expectancy in the decade under consideration, which corresponds to 9·5% of the total life expectancy gain. All the other cause of death groups contribute less than 1 year to the change in the adult life-years lived for both men and women.

Figure 3 shifts the focus to the age groups and causes of deaths that contribute to the shortfall in the population-wide life expectancy compared with the HIV-negative population. To elicit changes over time, the age-cause decomposition of the life expectancy deficit is done for two periods, which suggests that the age profile of the life expectancy deficit is becoming older. This is particularly the case for women, for whom the median of the age-group contributions to the life expectancy deficit increased from 34·9 years to 36·3 years between 2007–10 and 2011–14.

Pulmonary tuberculosis and HIV account for most of the shortfall in the population-wide adult life expectancy in both periods (table 2). In men, they account for

	Men, years (%)*	Women, years (%)*
Life expectancy gains: 2001–04 to 2011–14		
HIV/AIDS	4·22 (39·9%)	9·20 (65·4%)
Pulmonary tuberculosis	4·21 (39·8%)	3·56 (25·3%)
Other communicable diseases	0·67 (6·4%)	–0·32
Neoplasms	0·11 (1·0%)	0·10 (0·7%)
Cardiovascular diseases	0·21 (2·0%)	0·33 (2·3%)
Other non-communicable diseases	0·15 (1·4%)	0·41 (2·9%)
External injuries	1·01 (9·5%)	0·35 (2·5%)
Maternal causes	NA	0·12 (0·9%)
Life expectancy deficit: 2007–10		
HIV/AIDS	2·73 (29·7%)	6·32 (47·4%)
Pulmonary tuberculosis	5·07 (55·3%)	5·08 (38·1%)
Other communicable diseases	1·16 (12·6%)	0·86 (6·4%)
Neoplasms	–0·06	0·09 (0·6%)
Cardiovascular diseases	–0·08	0·14 (1·1%)
Other non-communicable diseases	–0·18	0·68 (5·1%)
External injuries	0·21 (2·3%)	0·10 (0·8%)
Maternal causes	NA	0·06 (0·5%)
Life expectancy deficit: 2011–14		
HIV/AIDS	1·79 (27·4%)	3·92 (44·5%)
Pulmonary tuberculosis	3·75 (57·5%)	3·20 (36·3%)
Other communicable diseases	0·67 (10·3%)	1·27 (14·4%)
Neoplasms	0·04 (0·6%)	0·26 (2·9%)
Cardiovascular diseases	–0·21	–0·02
Other non-communicable diseases	–0·50	–0·36
External injuries	0·27 (4·7%)	0·03 (0·3%)
Maternal causes	NA	0·13 (1·5%)

NA=not applicable. *Percentage of the sum of positive differences in adult life expectancy.

Table 2: **The contribution of cause of death groups to life expectancy gains and deficits (uMkhanyakude, 2001–14)**

85·0% of the life expectancy deficit in 2007–10 and 84·9% in 2011–14. In 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 life expectancy deficit are small.

Discussion

The introduction of ART in public sector health facilities in KwaZulu-Natal, South Africa, marked the starting point for unprecedented population-wide increases in adult life expectancy of 1·38 per year for men and 1·58 years per year for women. The total gains in adult life expectancy between 2003 and 2014 amount to 15·2 years for men and 17·2 years for women, and expand on earlier estimates for this population.[8] In comparison, the adult life expectancy in Japan after World War 2 increased at an average rate of around 0·5 years per year 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 life expectancy increases on record. The pace of the adult life expectancy 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 life expectancy of people living with HIV, the absence of a decrease in the mortality of HIV-negative individuals, and an analysis of changes in the cause of death structure. A decrease in the deaths ascribed to pulmonary tuberculosis and HIV alone account for around 79·7% in men and 90·7% in women of the total life expectancy gain. In men, a decrease in mortality from external injuries represents an additional 9·5% of the adult life expectancy gain in the decade after the roll-out of ART.

The life expectancy gains directly attributable to ART are probably even larger than the observed increases in adult life expectancy because mortality trends also depend on historical patterns of HIV incidence. The HIV epidemic in South Africa only peaked in the late 1990s, and life expectancy would have decreased for another 10 years if ART were not rolled out in 2004.[22] This is an important difference from a study in rural Uganda where life expectancy gains of a similar magnitude have been registered.[6] In the Ugandan case, mortality decreases brought about by the roll-out of ART were reinforced by mortality reductions due to earlier decreases in HIV incidence, and the life expectancy gain attributable to ART was smaller than the observed increase since ART.[6,23]

The mortality reductions in our 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 roll-out to primary health-care facilities, and improvements in patients' engagement with HIV services. A few studies have indeed started to document earlier treatment initiation and better retention of patients,[24,25] and suggest that the early assessments of poor engagement with HIV services in generalised epidemics no longer apply.[26,27] The gradual progress, however, raises the questions of why health systems have not been able to capitalise on the benefits of highly effective treatment earlier and why it has taken over a decade to reduce the burden of HIV on adult mortality to its present level. In addition, the residual burden of HIV on adult mortality is still not negligible, particularly in women whose adult life expectancy in 2014 was still 5·3 years lower than that of HIV-negative women. In men, the life expectancy deficit is estimated at 1·2 years and no longer statistically different from zero. The decomposition of the life expectancy deficit by cause affirms that pulmonary tuberculosis and HIV almost exclusively account for the surplus mortality, and an

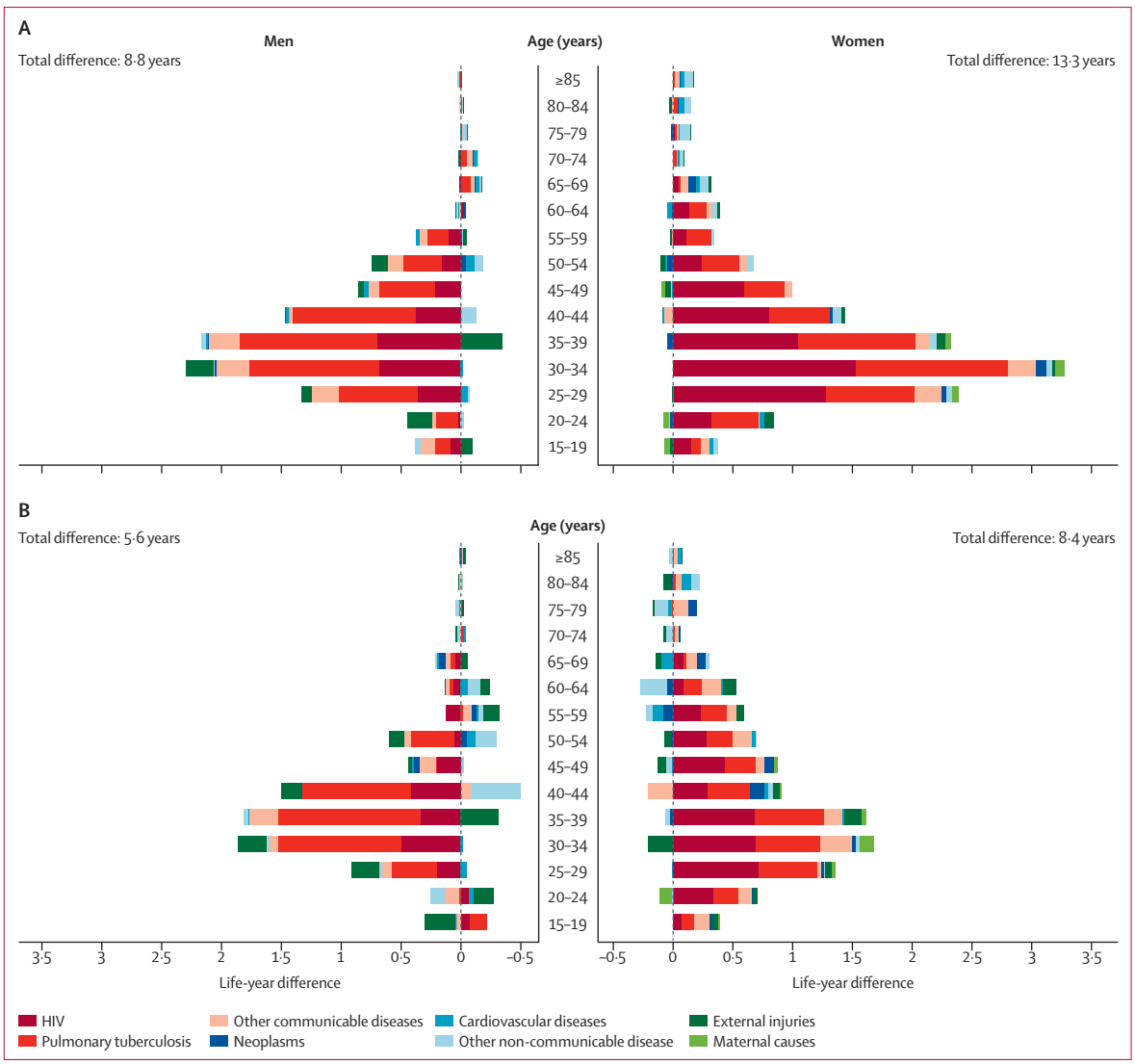

Figure 3: **Age and cause of death decomposition of the life expectancy deficit in 2007–10 (A) and 2011–14 (B), by sex (uMkhanyakude)**

earlier analysis suggests that most deaths of people living with HIV in this population occur in those who have yet to start treatment.[9] Pretreatment mortality in people living with HIV is, however, decreasing 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 life expectancy 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 larger gains in adult life-years so far. Several studies have suggested that women disproportionally benefit from the roll-out of HIV care and treatment services in African populations, as shown by increased 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 life expectancy deficit, has not yet been fully rectified. We also need to appreciate that gender differences in life expectancy gains and deficits do not solely result from differences in use of HIV services. Because HIV prevalence is higher in women than in 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 programmes developed, the median age of the life expectancy deficit in women increased by 1·4 years, which suggests that the burden of HIV is not only decreasing, but also shifting to older ages. At present we do not observe this phenomenon in men, which suggests that many still die before or shortly after starting treatment.

The survival of people living with HIV to older ages will inevitably complicate the attribution of causes of death in this group because comorbidities are common.[35,36] More generally, any assessment of changes in the cause of death structure comes with the caveat that verbal autopsies are a crude tool for cause of death assignment and their specificity for identifying AIDS deaths is still unknown.[37] However, our results suggest that the misclassification of causes is limited given that verbal autopsies attribute between 80% and 86% of the life expectancy deficit to pulmonary tuberculosis and HIV, and much of the remainder to other communicable diseases. In other words, there is a close correspondence between the verbal autopsy assigned causes of death on the one hand and the mortality surplus compared with the population with a known HIV-negative status on the other hand.

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

Contributors

GR, BZ, and VH conceived the study. AJH and ES prepared the data. GR, SB, CC, AM-O, JWE, and ZRL analysed the data. AJH, JB, SJC, 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

We declare no competing interests.

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