# Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa

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**Objective** To investigate trends in adult mortality in a population serviced by a public-sector antiretroviral therapy (ART) programme in rural South Africa using a demographic surveillance system.

**Methods** Verbal autopsies were conducted for all 7930 deaths observed between January 2000 and December 2006 in a demographic surveillance population of 74 500 in the Umkhanyakude district of northern KwaZulu-Natal province, South Africa. Age-standardized mortality rate ratios (SMRRs) were calculated for adults aged 25 to 49 years, the group most affected by HIV, for the 2 years before 2004 and the 3 subsequent years, during which ART had been available.

**Findings** Between 2002–2003 (the period before ART) and 2004–2006 (the period after ART), HIV-related age-standardized mortality declined significantly, from 22.52 to 17.58 per 1000 person-years in women 25–49 years of age ($P < 0.001$; SMRR: 0.780; 95% confidence interval, CI: 0.691–0.881), and from 26.46 to 18.68 per 1000 person-years in men 25–49 years of age ($P < 0.001$; SMRR: 0.706; 95% CI: 0.615–0.811). On sensitivity analysis the results were robust to the possible effect of misclassification of HIV-related deaths.

**Conclusion** Overall population mortality and HIV-related adult mortality declined significantly following ART roll-out in a community with a high prevalence of HIV infection. A clear public health message of the benefits of treatment, as revealed by these findings, should be part of a multi-faceted strategy to encourage people to find out their HIV serostatus and seek care.

*Une traduction en français de ce résumé figure à la fin de l'article.* *Al final del artículo se facilita una traducción al español.* **الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.**

## Introduction

Since 2003, there has been unprecedented global investment in delivering antiretroviral therapy (ART) for HIV infection to populations in resource-poor countries. The benefit of ART to an individual with advanced HIV infection is well established,[1–5] and programmes for its widespread introduction[6] can reduce the substantial increase in HIV-related adult mortality[7,8] that has occurred as the HIV pandemic has developed. The effect of ART roll-out can be measured in many ways – treatment coverage, behaviour change, the emergence of resistance, etc.[9,10] – but ultimately changes in population mortality are the most important measurable effect. In particular, national governments and international agencies faced with limited resources and competing demands need scientifically robust estimates of the potential effect at the population level of making a huge investment in ART roll-out.[11]

South Africa has over 5.5 million HIV-infected individuals and 14% of the world's HIV+ population.[8] The HIV pandemic is estimated to have reduced life expectancy in the country by about 13 years, from 64 in 1990 to 51 in 2005.[12] The northern province of KwaZulu-Natal carries the greatest burden of infection, with an estimated[12] 1.54 million HIV+ residents, which is more than the combined total of HIV+ people in Botswana and Uganda.

We composed an open cohort within an ongoing demographic surveillance system to investigate adult all-cause and HIV-related mortality trends in 2000–2006 in a population serviced by a well-functioning, public-sector ART programme initiated in 2004.[13]

## Methods

### Study area and population

The Africa Centre for Health and Population Studies hosts a demographic surveillance programme in the district of Umkhanyakude in the province of KwaZulu-Natal, South Africa.[13,14] Although it is largely rural, the demographic surveillance area (DSA), consisting of 435 square kilometres (km²), also includes a township and periurban informal settlements. Biannual surveillance visits to all homesteads within the DSA were performed by fieldwork teams to record births, deaths and any in- and out-migrations of household members. All household members reported during surveillance visits were followed up, whether or not they were residing in the homestead in subsequent visits. Thus, at each surveillance visit a key household informant is presented with a list of the household members recorded at the previous visit, and the residential and household membership status of each individual – i.e. whether or not he or she still lived in the homestead or had moved or died since the last visit – is recorded. The preferred key informant is the household head or a senior household member if the household head is absent. If by the fourth repeat visit to a homestead no suitable key informant is present, the case is referred to a tracking team that makes three more attempts,

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after hours or over weekends, to contact the key informant. The identity of the key informant is recorded and attempts are made to contact the same one for every visit. Household membership is self-defined on the basis of links to other household members. A resident is a member of a household who normally lives in the same homestead as the other members, whereas a non-resident household member normally lives elsewhere but retains links to the household. Individuals cease to be members of households when they terminate such links or die. Migrations to or from places outside the DSA (external migrations) were distinguished from those within the DSA (internal migrations). On average, 99.5% of all households participated in the biannual surveillance rounds, and the constant review of household members ensured high data quality and reduced the likelihood that any death would be missed.

Since the beginning of 2003, the HIV infection status of residents in the DSA aged 15–49 years (females) and 15–54 years (males) has been determined through separate annual serosurveillance.[15] In the study population, the prevalence of HIV infection has increased steadily since the early 1990s.[16,17] In 2004, it had reached 21.5% among residents aged 15–49 years[15] and was highest among women aged 25–29 years (51%) and men aged 30–34 years (44%).[15] But while in 2007 prevalence was essentially unchanged,[18] mortality appears to have decreased steadily. In 2000, 74% of deaths among women and 61% of deaths among men aged 15–44 years were due to HIV-related causes,[19] but an analysis of mortality trends by HIV serostatus in the population under HIV surveillance showed a progressive decline in mortality among HIV-infected individuals from 2004 to 2006.[20]

## Mortality data

All deaths notified in both residents and non-residents were followed up by a verbal autopsy interview[21] conducted an average of 6 months after the person's death by a trained nurse. The closest caregiver of the deceased was interviewed and asked to provide a narrative of the circumstances leading up to the death of the individual and to reply to a checklist of signs and symptoms and a standard structured questionnaire based on the INDEPTH standard questionnaire for verbal autopsies.[22] Two clinicians independently assigned the cause of death on the basis of the information collected during the verbal autopsy and their clinical judgement. A third clinician reviewed and codified the causes of death using the *International classification of disease, 10th revision* (ICD-10).[23] If the two clinicians disagreed, the third one organized a consensus meeting among all three clinicians. If consensus on the cause of death could not be reached in this meeting, the cause of death was recorded as "undefined". This was also done if no consent was given for the verbal autopsy interview or no suitable interviewee could be found. The ICD-10 codes were mapped into global burden of disease groups I, II and III[24] with the exception of tuberculosis and AIDS diagnoses, which were classified together into a separate group as HIV-related deaths, given the considerable overlap in mortality from HIV infection and tuberculosis.[25] Details on the verbal autopsy methods and their validation have been published previously by Hosegood.[19]

Permission for demographic and HIV serologic surveillance and for the use of data regarding clinic attendees was obtained from the University of KwaZulu-Natal Research Ethics Committee and the Research Committee of the KwaZulu-Natal Department of Health.

## Analysis

Deaths and person-years of observation were aggregated annually for the period from 1 January 2000 to 31 December 2006 for all individuals in the study population. Individuals contributed to the person-years denominator from 1 January 2000, or from any later date of birth or in-migration, until 31 December 2006, and they ceased to contribute to the denominator at death, termination of household membership, household out-migration or the last surveillance visit in which household membership was confirmed. Thus, individuals who were previous homestead residents continued to be followed when they became non-residents for as long as they remained a member of – i.e. retained links with – the household under surveillance. Over 2000–2006, approximately 90% of external out-migrants continued to be followed as non-resident household members. The previously published mortality analysis[20] was restricted to resident deaths and residential exposure only. As a result, the mortality rates given in that article are not directly comparable to those recorded in this one.

We stratified mortality rates by sex and four age groups (< 15, 15–24, 25–49 and > 49 years). The age-group boundaries were chosen to separate groups distinctly different in their rates of HIV infection prevalence,[15] risk of dying from an HIV-related cause and rates of enrolment in the local ART programme. To control for changes in the age composition over time within each stratum, we adjusted mortality rates in the different periods to the stratum-specific age distribution across all periods (using 5-year age groups). The remainder of the analysis was restricted to the 25–49-year-old group, as it had the highest AIDS-related burden of disease and also included the majority of the patients in the ART programme.

Table 1 summarizes the 25–49 year old open age cohort and the changes to this cohort during the course of each year. Cohort members were lost to follow-up if they ceased to be

Table 1. **Open cohort of adults aged 25–49 years created to investigate overall mortality trends in 2002–2006, KwaZulu-Natal, South Africa**

| Adults | 2002 | 2003 | 2004 | 2005 | 2006 |
|---|---|---|---|---|---|
| Under surveillance at start of year | 16 921 | 17 831 | 18 308 | 18 828 | 19 435 |
| Entered age group during year | 1 201 | 1 131 | 1 414 | 1 506 | 1 473 |
| In-migrated[a] during year | 2 010 | 1 310 | 1 079 | 1 071 | 1 027 |
| Died during year | 521 | 591 | 588 | 526 | 464 |
| Exited age group during year | 435 | 354 | 430 | 418 | 407 |
| Lost to follow-up during year | 1 345 | 1 019 | 955 | 1 026 | 1 184 |

[a] From outside the demographic surveillance area.

members of a household after external out-migration. In 90% of the cases, loss to follow-up occurred sometime after out-migration, rather than at the time out-migration took place. Cause-specific age-standardized mortality rates (SMRs) were calculated for: (i) communicable, maternal, perinatal, and nutritional conditions (excluding any that were HIV-related); (ii) non-communicable diseases; (iii) injuries; (iv) HIV-related conditions (AIDS and tuberculosis); and (v) undefined cause.

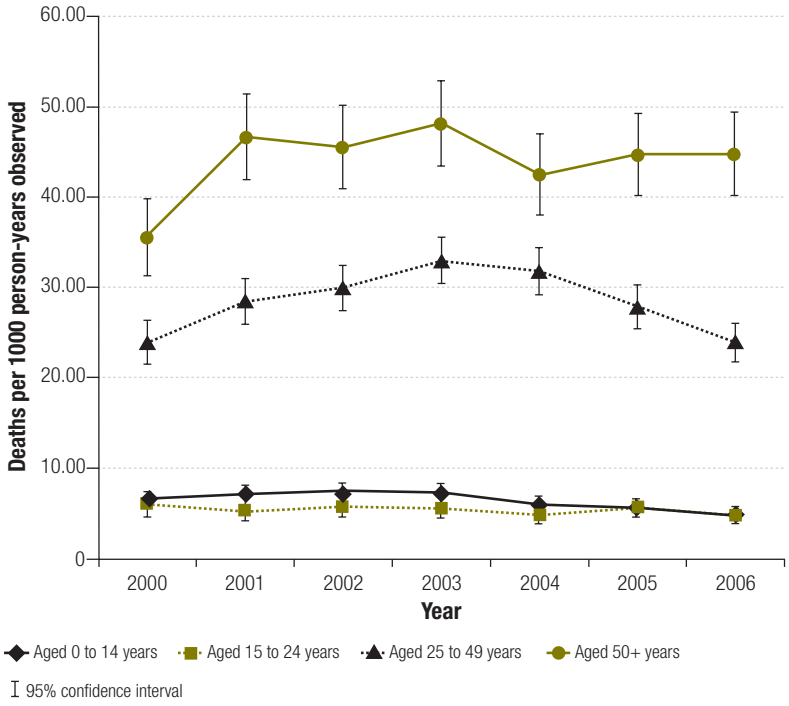
To compare mortality before and after ART became available (2002–2003 and 2004–2006, respectively), we calculated the age-standardized mortality rate ratio (SMRR). To obtain the SMRR, the crude mortality rate observed after ART introduction is divided by the rate that would have been expected had the 5-year age group-specific mortality rates remained the same as before ART was introduced.[26] SMRRs were calculated separately for males and females aged 25–49 years for all-cause mortality, HIV-related cause-specific mortality and non-HIV-related cause-specific mortality. All analyses were performed with STATA release 10.1 (StataCorp, College Station, TX, United States of America).[27]

### ART programme

As in the rest of South Africa,[28] ART first became widely available in the study area in 2004 through local private practitioners with support from employers, individual medical benefit contributions or local non-governmental organizations. The local public ART programme enrolled its first patient in August 2004. This government programme receives support through grants from the United States President's Emergency Plan for AIDS Relief (PEPFAR) administered through Elizabeth Glazer Paediatric AIDS Fund and, more recently, through Priorities in AIDS Care and Treatment. It is managed as a partnership between the local department of health and the Africa Centre for Health and Population Studies of the University of KwaZulu-Natal, in Mtubatuba, and delivers care and treatment to those who are HIV+ through a decentralized network of primary health care clinics.

Between late 2004 and end of 2006, between 40 and 100 patients a month have initiated treatment through the local ART programme, and by the end of 2006 1092 patients were being treated at clinics within the surveillance area. If one assumes that 15% of the HIV+ population requires ART,[29] the estimated crude treatment coverage in the surveillance area had reached 84% at the end of 2006. Treatment follows South African government guidelines,[30] which recommend stavudine and lamivudine combined with either nevirapine or efavirenz as a first-line regimen. Patients with a CD4+ lymphocyte (CD4) count < 200/mm³ and/or WHO clinical stage IV disease are eligible for enrolment in the programme. All patients in the programme are eligible for CD4 counts every 6 months, either before or after the initiation of antiretrovirals.

Fig. 1. **All-cause SMRs by age group, for males and females, KwaZulu-Natal, South Africa, 2000–2006**




SMR, age-standardized mortality rate.

## Results

### Mortality

A total of 7930 deaths were recorded over 517 856 person-years of observation from January 2000 to December 2006. HIV-related causes accounted for 49% of the total number of deaths in the overall population and for 71.5% of the deaths in the 25–49 year age group. Of HIV-related deaths, 65% occurred in the 25–49 year age group, and 12% in the group 50 years of age and older. Appendix A (available at: http://www.africacentre.ac.za/Portals/0/Publications/2009_AppendixAR.pdf) shows the data broken down by year (2000–2006), 5-year age groups and sex, as well as the person-years of observation and the deaths by cause.

In the 25–49 year age group, standardized all-cause mortality increased from a low of 24.0 (95% confidence interval, CI: 21.5–26.5) deaths per 1000 person-years in 2000 (Fig. 1) to a high of 33.0 (95% CI: 30.4–35.6) in 2003, and then declined to a low of 23.9 (95% CI: 21.8–26.1) in 2006. The HIV-related cause-specific mortality rate in the 25–49 year age group over the same period increased from 19.3 (95% CI: 17.1–21.5) deaths per 1000 person-years in 2000 (Fig. 2) to a high of 24.3 (95% CI: 22.0–26.6) in 2003, and then declined to 14.6 (95% CI: 12.9–16.3) by 2006.

From 2002–2003 (pre-ART period) to 2004–2006 (post-ART period), HIV-related age-standardized mortality declined significantly from 22.5 to 17.6 per 1000 person-years in women 25–49 years old ($P < 0.001$; SMRR: 0.780; 95% CI: 0.691–0.881)

(Table 2 and Table 3) and from 26.5 to 18.7 per 1000 person-years in men 25–49 years old ($P < 0.001$; SMRR: 0.706; 95% CI: 0.615–0.811). Non-HIV-related SMRs increased in 2004 for women 25–49 years old from 4.5 per 1000 person-years before ART to 7.3 per 1000 person-years after ART ($P = 0.001$; SMRR: 1.615; 95% CI: 1.275–2.045). There was no significant change in non-HIV-related SMRs for men aged 25–49 years old ($P = 0.124$; SMRR: 1.157; 95% CI: 0.957–1.400).

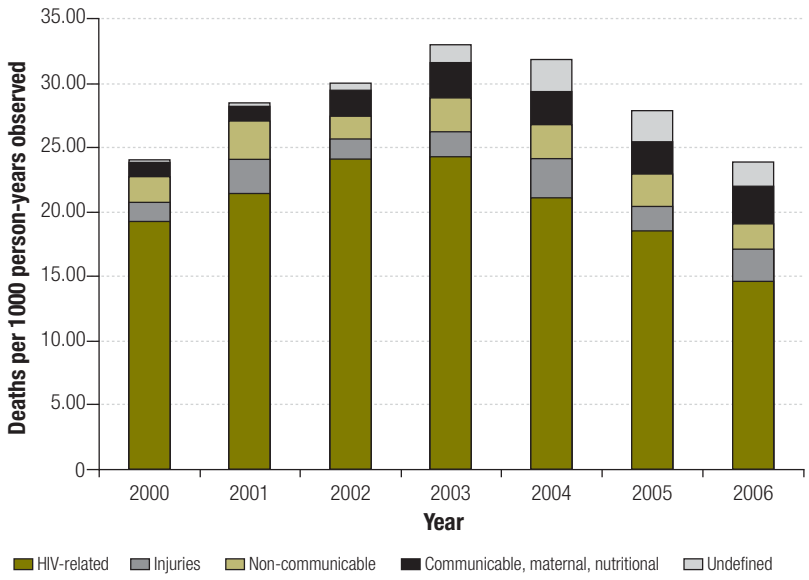
## ART programme

ART was initiated at a median age of 35 years (inter-quartile range, IQR: 29–43) and 77% of patients, mostly women, were 25–49 years of age at initiation. The median CD4 count before the initiation of ART was 115 cells/mm$^3$ (IQR 52–173). By the end of 2004, 2005 and 2006, 24, 298 and 859 patients aged 25–49 years, respectively, were enrolled at the clinics within the surveillance area. These figures do not include ART accessed through other channels, such as private practitioners. Thus, they can be considered the lower-bound estimate of true coverage, although local data suggests that the numbers of people who access care through these channels is small since ART was introduced free of cost in the public sector.

## Estimated mortality

To estimate HIV-related mortality in people 25–49 years of age in the absence of ART, we assumed that 15% of HIV-infected individuals were eligible for treatment.[29] The prevalence of HIV infection in this population for the years 2003–2006 was actually measured[15] through ongoing HIV surveillance activities; for the years 2000–2002 it was extrapolated from the measured prevalence by using the Actuarial Society of South Africa (ASSA) 2003 AIDS and Demographic model.[31] For the extrapolation, the measured prevalence in 2003 was multiplied by the ratio of the modelled prevalence for KwaZulu-Natal Blacks in 2003 to the modelled prevalence in the corresponding earlier year. An annual mortality rate of 44.5%[10] was assumed for individuals who were eligible for but did not receive ART. An annual baseline mortality rate was calculated under the assumption that ART was not available in the period 2000–2006. In Table 4, the counterfactual estimated mortality rates are compared with the actual mortality rates observed. As noted, mortality did not change significantly over time before ART was introduced in this population, but it dropped significantly beginning in 2004, and particularly in 2005 and 2006. Under the assumption that 15% of HIV-infected individuals are eligible for ART, from 2004 to 2006 the public ART programme covered 2%, 30% and 84%, respectively, of the estimated need for ART in patients 25–49 years old. We did not explore the effect of changing the assumptions underlying the ASSA model regarding prevalence estimates prior to 2003 because some of them, such as those relating to ART roll-out rates, were not

Fig. 2. **Cause-specific SMRs for adults aged 25–49 years, KwaZulu-Natal, South Africa, 2000–2006**




SMR, age-standardized mortality rate.

Table 2. **Comparison of population mortality rates in 25–49 year olds before and after the ART delivery programme was introduced in KwaZulu-Natal, South Africa, 2002–2006**

| Population mortality rates | Before programme 2002–2003 | | After programme 2004–2006 | |
|---|---|---|---|---|
| | Female | Male | Female | Male |
| Person-years of observation | 21 116 | 14 191 | 33 534 | 23 607 |
| Total deaths | 572 | 540 | 835 | 743 |
| HIV-related deaths | 476 | 377 | 589 | 435 |
| All-cause SMR[a] (CMR) | 27.07 (27.09) | 37.89 (38.05) | 24.91 (24.90) | 31.93 (31.47) |
| HIV-related cause-specific SMR (CMR) | 22.52 (22.54) | 26.46 (26.56) | 17.58 (17.57) | 18.68 (18.43) |
| Non-HIV-related cause-specific SMR (CMR) | 4.54 (4.55) | 11.43 (11.49) | 7.33 (7.34) | 13.25 (13.05) |

ART, antiretroviral therapy; CMR, crude mortality rate; SMR, age-standardized mortality rate.
[a] Per 1000 person-years of observation.

Table 3. **Ratio of pre-ART and post-ART programme SMRs in 25–49 year olds, KwaZulu-Natal, South Africa, 2002–2006**

| | Female | | | Male | | |
|---|---|---|---|---|---|---|
| | SMRR | 95% CI | *P*-value | SMRR | 95% CI | *P*-value |
| All-cause SMRR | 0.920 | 0.828–1.024 | 0.097 | 0.842 | 0.754–0.941 | < 0.001 |
| HIV-related cause-specific SMRR | 0.780 | 0.691–0.881 | < 0.001 | 0.706 | 0.615–0.811 | < 0.001 |
| Non-HIV-related cause-specific SMRR | 1.615 | 1.275–2.045 | < 0.001 | 1.157 | 0.957–1.400 | 0.124 |

ART, antiretroviral therapy; CI, confidence interval; SMR, age-standardized mortality rate; SMRR, age-standardized mortality rate ratio.

relevant in our case, as we were only interested in overall mortality in the absence of ART.

### Sensitivity analysis

To determine if the significant reductions in HIV-related mortality in the period after the ART programme was introduced could be due to misclassification[32] of HIV-related deaths in the verbal autopsies, we re-calculated the annual mortality rates in the following three scenarios. Scenaro a: All deaths in the communicable, maternal and nutritional diagnostic group were re-classified as HIV-related deaths in individuals who were known to be HIV+ (from the population-based HIV surveillance). Scenaro b: All deaths as in scenaro a, in addition to deaths in the undefined diagnostic group, were re-classified as HIV-related deaths in individuals who were known to be HIV+ (from the population-based HIV surveillance). Scenaro c: All deaths were reclassified according to scenaro b and, in addition, deaths with an underlying cause (ICD-10 codes A09 [diarrhoea and gastroenteritis of presumed infectious origin], G03 [meningitis due to other and unspecified causes], G04 [encephalitis, myelitis and encephalomyelitis], G04.9 [encephalitis, myelitis and encephalomyelitis, unspecified], J22 [unspecified acute lower respiratory infection]) that could be HIV-related but did not fulfil all the criteria to be classified as an AIDS death in the original verbal autopsy assessment were re-classified as HIV-related. The sensitivity analysis showed that ascertainment bias could not have accounted for the observed reduction in mortality. In females, the HIV-related cause-specific SMRR (post-ART/pre-ART) increased to a maximum of 0.833 (95% CI: 0.742–0.942; $P = 0.003$) in scenario c, while in males, it increased to a maximum of 0.741 (95% CI: 0.647–0.836; $P < 0.001$) in scenario b. In scenario c, a significant increase in non-HIV-related mortality was also noted in males aged 25–49 years (SMRR: 1.287; 95% CI: 1.035–1.540; $P = 0.026$).

Table 4. **Ratio of observed to estimated HIV-related SMR for adults 25–49 years old in the assumed absence of an ART programme, KwaZulu-Natal, South Africa, 2000–2006**

| Year | Observed SMR | Estimated SMR | SMRR (95% CI, *P*-value) |
|---|---|---|---|
| 2000 | 19.2 | 21.1 | 1.08 (0.91–1.24, 0.356) |
| 2001 | 21.2 | 22.6 | 1.06 (0.92–1.21, 0.398) |
| 2002 | 23.9 | 23.8 | 0.1 (0.87–1.12, 0.942) |
| 2003 | 24.2 | 25.0 | 1.03 (0.91–1.16, 0.602) |
| 2004 | 21.0 | 24.9 | 1.19 (1.04–1.34, 0.016) |
| 2005 | 18.5 | 24.4 | 1.33 (1.16–1.51, < 0.001) |
| 2006 | 14.5 | 24.2 | 1.69 (1.45–1.92, < 0.001) |

ART, antiretroviral therapy; CI, confidence interval; SMR, age-standardized mortality rate; SMRR, age-standardized mortality rate ratio.

## Discussion

There is evidence that the public-sector ART roll-out in rural South Africa is beginning to affect adult population mortality, with an approximate reduction of 22% and 29% in HIV-related mortality rates in women and men, respectively. This reduction occurred in a community with a very high prevalence of HIV infection and high mortality attributable to HIV.[19] Importantly, the longitudinal demographic surveillance system records all-cause mortality and cause-specific mortality and provides information about the coverage of the ART roll-out in the population. Because all births, deaths and migrations are recorded, the total population at any given moment is known, and this allows for a precise denominator with which to calculate mortality rates. Because the majority of out-migrants were followed as non-resident household members, the potential effect of any differential out-migration on the reported results was reduced. Further, the cause-specific mortality information obtained through verbal autopsies made it possible to distinguish changes over time in AIDS/tuberculosis-related mortality from changes in mortality unrelated to AIDS/tuberculosis. It is important to distinguish between different categories of cause of death because an ART programme would be expected to reduce HIV-related mortality primarily.

Recent work[33] from Malawi has shown a decline in population mortality shortly after the introduction of ART in the study population. Our study assessed the effect of ART in a different environment, with a larger population (74 500 versus 32 000), a higher prevalence of HIV infection in adults (21.5% versus 11.4%), higher HIV-related adult mortality (11.4 versus 6.3) before ART availability and

stricter criteria for treatment eligibility (CD4 count of < 200 cells/mm³ versus 250 cells/mm³).

## Effect of ART

First, it is highly plausible that the widespread availability of ART has led to the substantial decline in mortality observed in the study population. Not only does the decline show a temporal correspondence with the introduction of ART, but no other major health interventions were introduced in the study area during the same period. As in Malawi,[33] the effect of ART on mortality at the population level was seen soon after ART roll-out and increased with expanding coverage, perhaps because, under current South African government guidelines,[34] patients start treatment later than they should and they experience high mortality both while waiting for ART and after initiating it.[35] Thus, many patients who survived while on ART would have died within a short time had they not been treated. Data from the Western Cape province of South Africa during the pre-ART era show that without ART, 22.2% of patients with stage 4 disease (WHO classification) and a CD4 count of < 200 cells/mm³ would have died within 6 months.[35]

Second, the decline in HIV-related mortality over time is unlikely to have resulted from differential increases in the out-migration rates of HIV+ people. The out-migration rates of both HIV+ and HIV− individuals and of those with unknown HIV status remained constant over the three complete years for which data on HIV status were available (2004, 2005, and 2006).

Third, the prevalence of HIV infection measured through antenatal surveillance has not declined since the late 1990s,[36] the current population incidence rate of HIV infection is high,[37] and the prevalence of HIV infection in the study community has increased steadily.[16,17] Thus, it is unlikely that the observed decrease in overall population mortality is the late result of a sudden decline in the incidence of HIV infection. Furthermore, non-HIV-related mortality did not decline overall, so that our findings cannot be attributed to a general improvement in health and survival due to secular changes.

In the early years of our surveillance, both overall and HIV-associated mortality were still on the rise, as was expected in light of the trend in the HIV epidemic. According to estimates based on the ASSA 2003 AIDS and Demographic model,[12] mortality in KwaZulu-Natal increased sharply after the mid-1990s and levelled off only after 2006, as incidence declined. Contrary to the assumptions in the South Africa model,[12] there is as yet no evidence that incidence is declining[37] in our area, which makes the decrease in mortality even more intriguing.

Although only a small part of one of the districts in the KwaZulu-Natal province was included in this study, the findings should apply on a larger scale: the measured epidemiological distribution of HIV infection[15] and the mortality pattern[19] in this population resemble those for the province as a whole and do not differ much from those observed in other sub-Saharan populations heavily affected by the HIV pandemic.[38] The additional funds received via the PEPFAR initiative allowed for a faster, more comprehensive roll-out of the ART programme in this area, but solely within existing public health facilities and under the operational control of the provincial government's public health services.

## Non-HIV-related mortality

A significant increase in non-HIV-related mortality was observed among women after ART became available. Among males, the increase in non-HIV-related mortality during the same period was not statistically significant in the base analysis but became significant in scenario c of the sensitivity analysis. These findings require further analysis but could have several explanations: non-AIDS-related causes could have defined the mortality profile among the large group of HIV-infected people in this population who were not yet eligible for ART;[39,40] the competing risk of HIV-related mortality could have declined,[41] or the ART programme could have been expanded at the expense of health care in other areas.

## Verbal autopsies

Physician-coded verbal autopsies have known limitations,[32] and misclassification could have occurred. However, the sensitivity analysis presented here has shown that even if all deaths from undefined causes and from infectious diseases had been, in reality, misclassified HIV-related deaths, the main results of the analysis remained significant. Changes in mortality from tuberculosis among HIV− individuals are unlikely to have influenced the results, since 80% of the patients who present with active tuberculosis in the province of KwaZulu-Natal, South Africa, are co-infected with HIV[25] and this percentage is likely to be higher still among tuberculosis patients who die.

## Public health and operational aspects

The programme that delivers ART to the study population is administered through the public primary health care facilities of the South African Department of Health. Although it receives support through PEPFAR, the programme is overseen, managed and staffed largely by public sector employees, which ensures operational continuity after cessation of external support. Nevertheless, the sustainability of this large-scale ART programme faces the same challenges as in any developing country: a rapidly increasing need for health workers who can deliver ART,[42] due in part to treatment success;[43] the need to ensure long-term treatment adherence and to retain patients in the programme;[44] the unsolved question of the optimal relationship between ART programmes and the overall health care system.[45] Currently, many of these issues are being addressed in ongoing studies in our community and other sites.

In summary, we have found a substantial fall in population mortality, particularly from HIV-related causes, following the widespread availability of ART in a rural community with a high prevalence of HIV infection and high HIV-related mortality. However, this should not be a cause for complacency. Although nearly 15% of all HIV-infected individuals are receiving ART, HIV infection remains the leading cause of death in the study community. A much larger proportion of HIV-infected individuals will need to start treatment before HIV-related mortality falls to the levels seen in developed countries. These findings should be part of a clear public health message of the benefits of treatment within the context of a multi-faceted strategy to encourage people to find out their HIV serostatus and seek care. ■

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**Competing interests:** None declared.

## Résumé

### Mortalité des adultes et développement du traitement antirétroviral dans une partie rurale du KwaZulu-Natal, en Afrique du Sud

**Objectif** Étudier, à l'aide d'un système de surveillance démographique, les tendances de la mortalité adulte dans une population d'Afrique du Sud rurale desservie par un programme de traitement antirétroviral (ARV) relevant du secteur public.

**Méthodes** Des autopsies verbales ont été menées pour l'ensemble des 7930 décès relevés entre janvier 2000 et décembre 2006 dans une population sous surveillance démographique de 74500 individus habitant le district d'Umkhanyakude, au nord de la province du KwaZulu-Natal, en Afrique du Sud. Les taux de mortalité standardisés sur l'âge (TMSA) ont été calculés pour les adultes de 25 à 49 ans, tranche d'âges la plus touchée par le VIH, sur les deux années précédant 2004 et sur les 3 années ultérieures, pendant lesquelles le traitement ARV a été disponible.

**Résultats** Entre la période 2002-2003 (précédant la délivrance du traitement ARV) et la période 2004-2006 (succédant à la mise en place de ce traitement), la mortalité liée au VIH standardisée sur l'âge a baissé fortement de 22,52 à 17,58 décès pour 1000 personnes-ans chez les femmes de 25 à 49 ans ($p < 0,001$, TMSA : 0,780 ; intervalle de confiance à 95 %, IC : 0,691-0,881) et de 26,46 à 18,68 décès pour 1000 personnes-ans chez les hommes de 25 à 49 ans ($p < 0,001$ ; TMSA : 0,706 ; IC à 95 % ; 0,615-0,811). D'après l'analyse de sensibilité, les résultats étaient peu sensibles à l'effet des erreurs de classification des décès liés aux VIH.

**Conclusion** La mortalité dans la population générale et celle des adultes liée au VIH ont baissé notablement après le développement du traitement ARV dans une communauté subissant une forte prévalence des infections à VIH. Un message de santé publique clair, présentant les bénéfices du traitement tels qu'ils apparaissent d'après ces résultats, devrait faire partie de la stratégie multtifacettes pour encourager les personnes à déterminer leur statut VIH et à consulter.

## Resumen

### Mortalidad de adultos e introducción del tratamiento antirretroviral en zonas rurales de KwaZulu-Natal, Sudáfrica

**Objetivo** Investigar las tendencias de la mortalidad de adultos en una población atendida por un programa de tratamiento antirretroviral (TAR) del sector público en la Sudáfrica rural mediante un sistema de vigilancia demográfica.

**Métodos** Se realizaron autopsias verbales para la totalidad de las 7930 muertes observadas entre enero de 2000 y diciembre de 2006 en una población de vigilancia demográfica de 74 500 personas del distrito de Umkhanyakude en KwaZulu-Natal, provincia septentrional de Sudáfrica. Se calcularon las razones de tasas de mortalidad normalizadas (RTMN) por edad en los adultos de 25 a 49 años, el grupo más afectado por el VIH, para los dos años anteriores a 2004 y los 3 años subsiguientes, en los que se disponía de TAR.

**Resultados** Entre 2002–2003 (periodo anterior al TAR) y 2004–2006 (periodo con TAR), la mortalidad por VIH normalizada por edad disminuyó de forma significativa, de 22,52 a 17,58 por 1000 personas-año entre las mujeres de 25 a 49 años ($p < 0,001$; RTMN: 0,780; intervalo de confianza [IC] del 95%: 0,691–0,881), y de 26,46 a 18,68 por 1000 personas-año entre los hombres de 25 a 49 años ($p < 0,001$; RTMN: 0,706; IC95%: 0,615–0,811). En los análisis de sensibilidad realizados, los resultados demostraron ser robustos ante el posible efecto de los errores de clasificación de las defunciones relacionadas con el VIH.

**Conclusión** La mortalidad de la población general y la mortalidad de adultos relacionada con el VIH disminuyeron de forma significativa tras la introducción del TAR en una comunidad con alta prevalencia de infección por VIH. Como parte de una estrategia multiforme orientada a alentar a la gente a averiguar su serología VIH y buscar atención, debería difundirse un mensaje de salud pública que explique claramente, según demuestran nuestros resultados, los beneficios del tratamiento.

## ملخص

### وفيات البالغين والنهوض بالمعالجة بالأدوية المضادة للفيروسات القهقرية في ريف كوازولو - ناتال، جنوب أفريقيا

**الهدف:** استقصاء اتجاهات وفيات البالغين بين السكان الذين يتلقون الخدمة من برنامج المعالجة بالأدوية المضادة للفيروسات القهقرية ضمن القطاع العام في ريف جنوب أفريقيا باستخدام نظام للترصُّد الديموغرافي.

**الطريقة:** أجريت الصفات التشريحية للجثة لـ 7930 من الموتى ضمن فترة ملاحظة امتدت من كانون الثاني/يناير 2000 وحتى كانون الأول/ديسمبر 2006، في إطار الترصُّد الديموغرافي لمجموعة سكانية تعدادها 74 500 نسمة في مقاطعة أم خاني أكودي شمال ولاية كوازولو - ناتال في جنوب أفريقيا. وحسبت نسب معدلات الوفيات المصنَّفة بحسب العمر للبالغين الذين تـتراوح أعمارهم بين 25 و49 عاماً؛ وهي الفئة التي تصاب أكثر من غيرها بفيروس العوز المناعي البشري، خلال السنتين السابقتين لعام 2004 والثلاث سنوات اللاحقة لهذا العام، وهي الفترة التي أصبحت فيها الأدوية المضادة للفيروسات القهقرية متوافرة.

**الموجودات:** خلال الفترة ما بين 2002 – 2003، وهي الفترة السابقة لتوافر الأدوية المضادة للفيروسات القهقرية، وبين 2004 – 2006، وهي الفترة التي تلت توافر تلك الأدوية، انخفضت معدلات الوفيات المصنَّفة بحسب العمر والمتعلقة بفيروس العوز المناعي البشري انخفاضاً كبيراً من 22.52 إلى 17.58 لكل 1000 شخص - سنة لدى النساء اللاتي تـتراوح أعمارهن بين 25 و49 عاماً، وبقوة احتمال P أقل من 0.001، نسبة معدلات الوفيات المصنَّفة بحسب العمر 0.780 بفاصلة ثقة 95%: 0.691 – 0.881). كما انخفضت من 26.46 إلى 18.68 لكل ألف شخص - سنة لدى الرجال الذين تـتراوح أعمارهم بين 25 – 49 عاماً، وبقوة احتمال P أقل من 0.001، نسبة معدلات الوفيات المصنَّفة بحسب العمر: 0.706 بفاصلة ثقة 95%: 0.615 – 0.811). ولدى تحليل الحساسية، كانت النتائج قوية باتجاه التأثير المحتمل لسوء تصنيف الوفيات المتعلقة بفيروس العوز المناعي البشري.

**الاستنتاج:** لقد انخفضت المعدلات الإجمالية للوفيات بين البالغين من السكان، وللوفيات المتعلقة بفيروس العوز المناعي البشري بين البالغين انخفاضاً كبيراً، وذلك تلو النهوض بالمعالجة بالأدوية المضادة للفيروسات القهقرية في مجتمع يعاني من معدل مرتفع لانتشار العدوى بهذا الفيروس. ويمثل ذلك رسالة واضحة في ميدان الصحة العمومية حول منافع هذه المعالجة، كما توضحها هذه الموجودات، حيث ينبغي أن تكون هذه المعالجة جزءاً من استراتيجية متعددة الوجوه لتشجيع الناس على التعرف على وضعهم السيرولوجي بالنسبة لفيروس العوز المناعي البشري، ومن ثَمَّ التماس الرعاية.

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