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Reduction in Early Mortality on Antiretroviral Therapy for Adults in Rural South Africa Since Change in CD4⁺ Cell Count Eligibility Criteria

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Objective: To explore the impact of expanded eligibility criteria for antiretroviral therapy (ART) on median CD4⁺ cell count at ART initiation and early mortality on ART.

Methods: Analyses included all adults (≥16 years) initiated on first-line ART between August 2004 and July 2012. CD4⁺ cell count threshold 350 cells per microliter for all adults was implemented in August 2011. Early mortality was defined as any death within 91 days of ART initiation. Trends in baseline CD4⁺ cell count and early mortality were examined by year (August to July) of ART initiation. Competing risks analysis was used to examine early mortality.

Results: A total of 19,080 adults (67.6% female) initiated ART. Median CD4⁺ cell count at ART initiation was 110–120 cells per

microliter over the first 6 years, increasing marginally to 145 cells per microliter in 2010–2011 and more significantly to 199 cells per microliter in 2011–2012. Overall, there were 875 deaths within 91 days of ART initiation; early mortality rate was 19.4 per 100 person-years [95% confidence interval (CI) 18.2 to 20.7]. After adjustment for sex, age, baseline CD4⁺ cell count, and concurrent tuberculosis (TB), there was a 46% decrease in early mortality for those who initiated ART in 2011–2012 compared with the reference period 2008–2009 (subhazard ratio, 0.54; 95% CI: 0.41 to 0.71).

Conclusions: Since the expansion of eligibility criteria, there is evidence of earlier access to ART and a significant reduction in early mortality rate in this primary health care programme. These findings provide strong support for national ART policies and highlight the importance of earlier ART initiation for achieving reductions in HIV-related mortality.

Key Words: HIV-1, antiretroviral agents, CD4 lymphocyte count, mortality, access to health care

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INTRODUCTION

Rapid scale-up of public health antiretroviral therapy (ART) programmes in the past decade has led to over 8 million HIV-infected individuals receiving treatment in low- and middle-income countries.¹ One of the persistent challenges in sub-Saharan Africa has been the high rate of early mortality on ART, observed consistently in programmes from the region, and reported to be substantially higher than in high-income settings.^{2–5} There is strong evidence that mortality can be reduced with earlier initiation of ART^{6,7}; in 2010, the World Health Organization (WHO) changed the recommended CD4⁺ cell count threshold for initiation of ART from 200 to 350 cells per microliter.⁸ This recommendation has now been adopted by several countries, including South Africa, the country with the largest HIV treatment programme in the world.⁹

There is as yet limited evidence that adoption of these policies has led to changes in the timing of presentation for care and treatment or to early mortality on ART: one study from Lesotho demonstrated that earlier initiation (CD4⁺ cell count >200 cells per microliter compared with <200 cells per microliter) was feasible and associated with lower mortality in a routine programmatic setting.¹⁰ Here, our main objective was to use data from a large rural HIV treatment programme, where care is

decentralized to primary health care level, to assess trends in CD4⁺ cell count at initiation of ART, and mortality in the first three months after ART initiation. In particular, we set out to test the hypothesis that early mortality would decline after the expansion of treatment eligibility criteria in 2011. The manuscript was prepared with reference to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.^{11,12}

METHODS

The Hlabisa HIV Treatment and Care Programme

The Hlabisa HIV Treatment and Care Programme provides comprehensive HIV services at 17 primary health care clinics and 1 district hospital in the predominantly rural Hlabisa subdistrict (1430 km²) in northern KwaZulu-Natal.^{4,13} The programme is coordinated by the local Department of Health with support from the Africa Centre for Health and Population Studies (www.africacentre.ac.za). HIV treatment and care are delivered largely by nurses and counselors in adherence with national antiretroviral treatment guidelines. South Africa implemented policy recommendations regarding ART eligibility in a phased manner: between August 2004 and April 2010, eligibility for adults was based on CD4⁺ cell count <200 cells per microliter¹⁴; this was expanded initially in April 2010 to 350 cells per microliter for pregnant women and individuals with active tuberculosis (TB) disease¹⁵; in August 2011, this was extended to 350 cells per microliter for all.⁹ ART was also recommended throughout for all individuals with WHO clinical stage 4 and since April 2010 for all individuals with drug-resistant TB.

Data Collection

Clinical information is collected at time of ART initiation for all individuals and transferred from standardized paper-based clinic records to a Microsoft SQL database (Microsoft, Redmond, WA) housed at the Africa Centre. Paper-based records are used at each clinic to capture subsequent visits during follow-up on ART and to document any change in vital status [death, loss to follow-up (LTF), transfer out]. Information from these records is transferred to the database at the end of each month. As part of routine programme operations, a single tracking team attempts to contact individuals who have missed clinic visits and thus identifies deaths in those lost to follow-up. To further improve data on mortality for those lost to follow-up, mortality data from the district hospital information system (recording in-hospital deaths since January 2011) are imported to the programme database periodically. Furthermore, mortality data from the Africa Centre Demographic Surveillance System are also used periodically to update vital status for individuals lost to follow-up (approximately 40% of adults enrolled in the treatment programme are members of the surveillance system).^{13,16} With both these systems, individual records are linked between databases after a standardized protocol using the South African identity number, name, surname, age, and sex.

All CD4⁺ cell counts were performed by the National Health Laboratory Service using the Beckman Coulter EPICS XL flow cytometer (Beckman Coulter Inc., Brea, CA). Since January 2007, all CD4⁺ cell count results from the subdistrict were provided by the National Health Laboratory Service and were transferred to the programme database on a fortnightly basis; laboratory records were merged with existing clinical records after a standardized protocol using the unique South African identity number, name, and date of birth. For individuals not yet commenced on ART, the database holds only CD4⁺ cell count results but no clinical information.¹⁷

Data Analysis

All adults (≥ 16 years) initiated on first-line ART between August 2004 and July 2012 and with a baseline CD4⁺ cell count were included in the main analysis, unless they had transferred into the programme already on ART (as for this group, CD4⁺ cell count at initiation was not known). Baseline CD4⁺ cell count was defined as the last measured CD4⁺ cell count up to 180 days before the date of ART initiation. Individuals were divided into 8 groups on the basis of the date of ART initiation (12-month period from August to July). This categorization was chosen to allow clear delineation before and after the change in CD4⁺ cell count threshold to 350 cells per microliter for all (August 2011). Baseline CD4⁺ cell counts were described with summary statistics: median, interquartile range (IQR), and proportions in predefined categories (<50, 50–200, 201–350, and >350 cells per microliter). Trends in baseline CD4⁺ cell count were examined for all adults and then for separate groups (males, pregnant females, and nonpregnant females). To explore temporal changes in timing of first presentation for care since 2007, the first recorded CD4⁺ cell count was used for all adults (≥ 16 years at test date). This was defined as the earliest recorded CD4⁺ cell count in the database, providing the test date was before the ART initiation date. Again these were summarized within groups based on the test date (12-month period from August to July starting in August 2007).

Early mortality was defined for this analysis as deaths within 3 months (≤ 91 days) of ART initiation, a period previously reported to be responsible for approximately 60% of the deaths in the first year of ART in this programme.¹⁸ LTF was defined as >90 days without a recorded clinic visit; transfer out was defined as formal transfer out of the programme (this did not include transfer between 2 clinics within the programme). Analysis allowed for at least 3 months follow-up for all individuals and a further 3 months before database closure (January 13, 2013) to allow capture of deaths and LTF that occurred during the first 3 months and to minimize bias. Competing risks analysis was used to generate cumulative incidence functions for mortality.¹⁹ Follow-up time was censored at the date of last clinic visit for those who transferred out or were lost to follow-up. Analyses were also performed separately for males, nonpregnant females, and pregnant females. Competing risks regression was used to explore factors associated with early mortality.²⁰ Missing data for any categorical variable were included in the model as a separate category.

Sensitivity analyses were conducted to explore the pattern of early mortality according to CD4⁺ cell count: early mortality rates were estimated by time period, restricted to those with CD4⁺ cell count <50, ≤200, and >200 cells per microliter. Sensitivity analyses were also conducted under the assumption that either 20% or 40% of those individuals lost to follow-up in the last time period (2011–2012) had died. This was to allow for the possibility that deaths in the later cohorts were underrepresented because of the differential time for deaths to be captured both through routine programme systems and through linkage to the hospital information system and the Africa Centre Demographic Information System. We have previously shown by linking programme data to demographic surveillance data that 40% of adults lost to follow-up in the first 3 months of ART had died.²¹ All analyses were conducted using STATA 11.2 (StataCorp, College Station, TX).

Ethics Statement

Ethical approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and the Health Research Committee of the KwaZulu-Natal Department of Health for the retrospective analysis of data from the Hlabisa HIV Treatment and Care Programme (references BE066/07 and HRKM012/07).

RESULTS

Temporal Changes in CD4⁺ Cell Count at Initiation of ART

A total of 19,747 adults initiated ART during the period under analysis, among them 19,080 (96.6%) had a baseline CD4⁺ cell count recorded. Annual enrollment increased from 280 adults in 2004–2005 to 4199 in 2011–2012. Median age was 34 years (IQR: 28–42); 12,906 (67.6%) were female and, of those, 10.7% (1383/12,906) initiated ART while pregnant. Overall median baseline CD4⁺ cell count was 139 cells per microliter (IQR: 71–198) and was higher for females than males (151 vs. 111 cells per microliter, $P < 0.001$).

There was no significant change in baseline CD4⁺ cell count over the first 6 years (110–134 cells per microliter) and only a modest increase to 145 cells per microliter in 2010–2011 after the initial extension of eligibility to CD4⁺ cell count <350 cells per microliter for pregnant women and TB patients (Table 1). In the last time period (2011–2012), there was a significant increase and the median CD4⁺ cell count of 199 cells per microliter (IQR: 110–280) was more than 50 cells per microliter higher than for any other time period. This was accompanied by a substantial decline in the proportion with CD4⁺ cell count <50 cells per microliter, reaching a low of 11.5% [95% confidence interval (CI): 10.6 to 12.5] in 2011–2012. The same temporal pattern was observed when males and nonpregnant females were studied separately (Table 1; Fig. 1). The proportionate rise in median CD4⁺ cell count between 2010–2011 and 2011–2012 was similar for these 2 groups, although the differences between the 2 groups remained constant, with males having lower median CD4⁺ cell count and higher proportion with CD4⁺ cell count <50 cells per micro-

liter in all time periods. For pregnant females, a rise in median CD4⁺ cell count was observed over the last 2 time periods (2010–2011 and 2011–2012), consistent with the earlier implementation of the CD4⁺ cell count threshold of 350 cells per microliter for pregnant women in April 2010. There was a low proportion of pregnant females with CD4⁺ cell count <50 cells per microliter across all time periods.

Temporal Changes in CD4⁺ Cell Count at First Presentation for Care

A total of 41,300 adults had their first CD4⁺ cell count measurement between August 2007 and July 2012 (Table 2). Overall median CD4⁺ cell count at first presentation was 273 cells per microliter (IQR: 136–444). There was limited change in the first 4 time periods but a significant rise in 2011–2012 (median: 317 cells per microliter; IQR: 170–487). This was accompanied in the last time period by a significant decline in the proportion that presented with CD4⁺ cell count <50 cells per microliter and a rise in the proportion that presented with CD4⁺ cell count >350 cells per microliter.

Early Mortality

A total of 19,080 individuals were included in mortality analysis with 4506 person-years of follow-up (median: 86 days). There were 875 deaths (4.6%) in the first 3 months of ART giving a crude early mortality rate of 19.4 per 100 person-years (95% CI: 18.2 to 20.7). Six hundred forty-one individuals (3.4%) were lost to follow-up and 170 (0.9%) transferred out of the programme within 3 months. The deaths in the first 3 months represented 59.6% (875/1469) of all deaths observed in the first year of ART. There was no substantial change in early mortality until the last period where there was a large decline in mortality rate: from 21.3 per 100 person-years (95% CI: 18.3 to 24.8) in 2010–2011 to 9.0 per 100 person-years (95% CI: 7.3 to 11.0) in 2011–2012 (Fig. 2A). This pattern was consistent for both males and nonpregnant females (Figs. 2B,C); there were too few early deaths in the pregnant female group ($n = 9$) for temporal trends to be explored.

In competing risks regression, after adjustment for sex, age, baseline CD4⁺ cell count, and concurrent TB, the time period of ART initiation was strongly associated with mortality in the first 3 months of ART: subhazard ratio (SHR) 0.54 (95% CI: 0.41 to 0.71) for 2011–2012 compared with the reference time period of 2008–2009 (Table 3). CD4⁺ cell count <50 cells per microliter was strongly associated with early mortality (SHR: 4.25; 95% CI: 3.23 to 5.60). Compared with nonpregnant females, males had higher early mortality (SHR: 1.48; 95% CI: 1.28 to 1.70), whereas pregnant females had substantially lower early mortality (SHR: 0.23; 95% CI: 0.12 to 0.45).

When the analysis was restricted to individuals with CD4⁺ cell count <50 cells per microliter and ≤200 cells per microliter, the substantial reduction in early mortality rate was still observed for the 2011–2012 cohort (see **Table, Supplemental Digital Content 1**, <http://links.lww.com/QAI/A433>). The proportion of each annual cohort lost to follow-up within the first 3 months increased over time: 0.4% (95% CI: 0 to 1.1) for 2004–2005, 0.6% (95% CI: 0.1 to 1.0) for

TABLE 1. Trends in Baseline CD4⁺ Cell Count Overall and by Sex Categories (Males, Nonpregnant Females, and Pregnant Females)

	2004–2005	2005–2006	2006–2007	2007–2008	
Overall					
Number of individuals	280	907	1408	2754	
Median (IQR), cells/ μ L	111 (58–163)	122 (61–178)	116 (52–176)	113 (58–172)	
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	22.1 (17.7–27.4)	20.6 (18.1–23.4)	24.1 (21.9–26.4)	21.3 (19.8–22.9)	
Males					
Number of individuals	88	294	458	874	
Median (IQR), cells/ μ L	77 (40–146)	108 (49–169)	95 (37–164)	90 (42–152)	
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	30.7 (22.0–41.0)	25.5 (20.9–30.8)	31.9 (27.8–36.3)	29.1 (26.2–32.2)	
Females (nonpregnant)					
Number of individuals	190	601	934	1727	
Median (IQR), cells/ μ L	122 (68–169)	127 (65–182)	126 (62–182)	126 (65–177)	
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	18.4 (13.6–24.5)	18.5 (15.6–21.8)	20.3 (17.9–23.0)	18.5 (16.7–20.4)	
Females (pregnant)					
Number of individuals	2	12	16	153	
Median (IQR), cells/ μ L	88 (63–113)	138 (109–190)	142 (59–186)	140 (87–190)	
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	—	8.3 (0–24.7)	18.8 (0–38.5)	8.5 (4.1–13.0)	
	2008–2009	2009–2010	2010–2011	2011–2012	Overall
Overall					
Number of individuals	3079	3159	3294	4199	19,080
Median (IQR), cells/ μ L	123 (61–175)	134 (72–187)	145 (76–201)	199 (110–280)	139 (71–198)
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	20.2 (18.9–21.7)	17.4 (16.1–18.8)	16.2 (15.0–17.5)	11.5 (10.6–12.5)	17.6 (17.1–18.2)
Males					
Number of individuals	1099	1050	982	1329	6174
Median (IQR), cells/ μ L	98 (45–161)	111 (51–171)	113 (49–176)	160 (72–250)	111 (49–179)
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	27.2 (24.7–29.9)	24.9 (22.3–27.6)	25.6 (23.0–28.4)	18.6 (16.6–20.8)	25.3 (24.2–26.4)
Females (nonpregnant)					
Number of individuals	1825	1845	1859	2542	11,523
Median (IQR), cells/ μ L	133 (70–179)	143 (80–189)	149 (80–197)	212 (125–289)	147 (79–200)
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	17.5 (15.8–19.3)	14.7 (13.2–16.4)	14.5 (13.0–16.2)	9.0 (7.9–10.1)	15.1 (14.5–15.8)
Females (pregnant)					
Number of individuals	155	264	453	328	1383
Median (IQR), cells/ μ L	152 (109–191)	174 (105–246)	216 (145–280)	241 (163–294)	190 (123–265)
% CD4 ⁺ cell count <50 cells/ μ L (95% CI)	3.2 (0.4–6.0)	6.8 (3.8–9.9)	2.9 (1.3–4.4)	2.7(1.0–4.5)	4.5 (3.5–5.7)

2005–2006, 1.6% (95% CI: 1.0 to 2.3) for 2006–2007, 1.2% (95% CI: 0.8 to 1.6) for 2007–2008, 2.7% (95% CI: 2.2 to 3.3) for 2008–2009, 3.9% (95% CI: 3.2 to 4.6) for 2009–2010, 4.4% (95% CI: 3.7 to 5.1) for 2010–2011, and 5.4% (95% CI: 4.7 to 6.1) for 2011–2012. In sensitivity analyses, assuming deaths in 20% and 40% of those lost to follow-up from 2011 to 2012, estimates of corrected early mortality for that period were 13.5 per 100 person-years (95% CI: 11.4 to 16.0) and 18.0 per 100 person-years (95% CI: 15.6 to 20.9), respectively (see **Figure, Supplemental Digital Content 2**, <http://links.lww.com/QAI/A433>).

DISCUSSION

In this observational study, we found evidence not only of earlier presentation for ART but also a substantial reduction in early mortality on ART subsequent to the change in CD4⁺ cell count eligibility criteria that took effect in South Africa in August 2011. Median CD4⁺ cell count at ART

initiation remained higher and mortality remained lower for women during all time periods, consistent with the data from this region.^{22,23} However, it is encouraging that the increase in CD4⁺ cell count and reduction in early mortality for those who initiated ART in the last time period (2011–2012) were consistent for both the nonpregnant females and males. Pregnant women only represented about 7% of all adults who initiated ART and there were very few deaths in this group; so there was limited statistical power to observe any temporal trends. These data provide further encouragement at a time when substantial reductions in population-level mortality have been documented in this community and more broadly in South Africa.^{24–27}

We have previously shown that during the first phase of rapid programme scale-up, there was no significant change in CD4⁺ cell count at ART initiation.⁴ It seems that after the first policy change in 2010 to recommend ART at <350 cells per microliter for TB patients and pregnant females, there was minimal change in the overall median CD4⁺ cell count

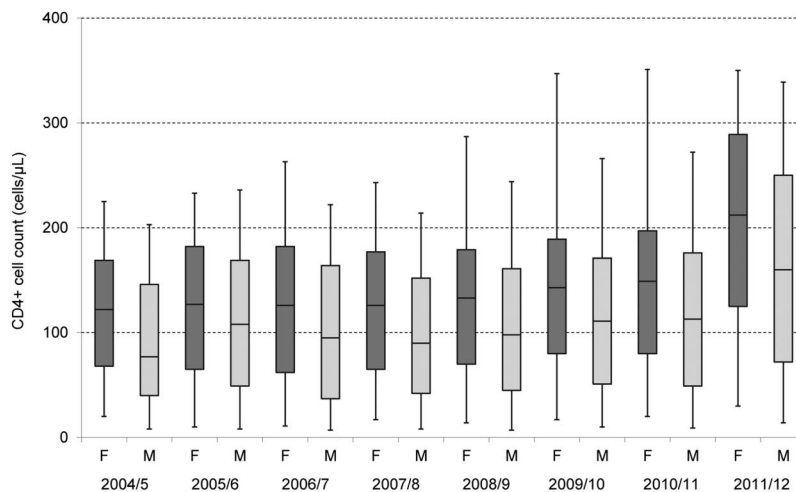


FIGURE 1. CD4⁺ cell count at initiation of ART by time period and sex (nonpregnant females and males). Upper and lower margins of the box represent the 25th and 75th percentiles, respectively, with the horizontal line representing the median; whiskers represent fifth and 95th percentiles.

at ART initiation, yet after the expansion to <350 cells per microliter for all, there has been a definite increase. This suggests that, although antenatal care and TB services remain important entry points to HIV treatment, the contribution from these groups alone was too small to see a broader impact of the expanded eligibility criteria. The increase in overall median CD4⁺ cell count between 2010–2011 and 2011–2012 was 54 cells per microliter, which corresponds approximately to 6 months earlier in terms of disease progression according to our previous data.¹⁷ The relationship between mortality risk and time period was maintained after adjustment for baseline CD4⁺ cell count, consistent with the fact that CD4⁺ cell count does not fully predict mortality,²⁸ and that other factors associated with earlier presentation, such as the absence of opportunistic infection, may have contributed to the mortality decline. It is noteworthy that in the last time period, there was a decline in the absolute number and the proportion of people who initiated ART with CD4⁺ cell count <50 cells per microliter, as this remains the factor most strongly associated with early mortality, with a 4-fold increased risk of early mortality compared with CD4⁺ cell count of 201–350 cells per microliter.

These observations provide robust evidence that the reduction in early mortality has occurred since the policy change to recommend earlier initiation of ART, although a direct causal association cannot be inferred from these observational data. In common with data from other large

programmes in South Africa, early mortality did not change in the first few years of programme scale-up.^{29–31} Only in the last time period (2011–2012), there was a real decline in early mortality. There have been no specific interventions or programmatic changes that could easily explain the decline in early mortality. There is no formal package of care for individuals before eligibility for ART and retention in this group is suboptimal.³² We have previously shown that TB is the most common cause of early mortality on ART and that prevalent TB at time of ART initiation is associated with almost double the risk of mortality on ART, in line with other studies in the region.^{32–34} In this analysis, there was no independent association between TB and early mortality, although the statistical power to observe an association might have been affected by the lower risk of TB disease at higher CD4⁺ cell counts.³⁵ The implementation of isoniazid preventive therapy was scaled up from early 2010, yet provision remains patchy in this programme. It could be that improved integration of ART with TB treatment has contributed to the reduction in mortality, in line with findings from clinical trials.^{36,37} Alternatively, although there was no specific programmatic change, it could be related to clinic systems becoming more efficient over time, increased use of nurse-initiated ART, or by the shorter time needed for pre-ART work-up for people with higher CD4⁺ cell counts. Finally, given the change in the first-line antiretroviral regimen in 2010 from a stavudine-

TABLE 2. Temporal Changes in CD4⁺ Cell Count at First Presentation for Care

	2007–2008	2008–2009	2009–2010	2010–2011	2011–2012	Overall
Number of first CD4 ⁺ cell count tests	9662	8655	7584	6860	8539	41,300
CD4 ⁺ cell count, median (IQR), cells/μL	253 (128–420)	263 (129–438)	267 (127–446)	263 (132–431)	317 (170–487)	273 (136–444)
CD4 ⁺ cell count, cells/μL, % (95% CI)						
<50	10.4 (9.8–11.0)	10.9 (10.2–11.6)	10.4 (9.7–11.1)	10.7 (10.0–11.5)	7.8 (7.3–8.4)	10.0 (9.8–10.3)
50–200	29.5 (28.6–30.5)	27.8 (26.8–28.7)	27.7 (26.7–28.7)	27.7 (26.7–28.8)	21.8 (21.0–22.7)	26.9 (26.5–27.4)
201–350	25.8 (25.0–26.7)	24.8 (23.9–25.7)	25.0 (24.0–26.0)	25.8 (24.8–26.9)	26.4 (25.4–27.3)	25.6 (25.2–26.0)
>350	34.2 (33.2–35.1)	36.6 (35.6–37.6)	36.9 (35.8–37.9)	35.7 (34.6–36.8)	44.0 (42.9–45.0)	37.5 (37.0–37.9)

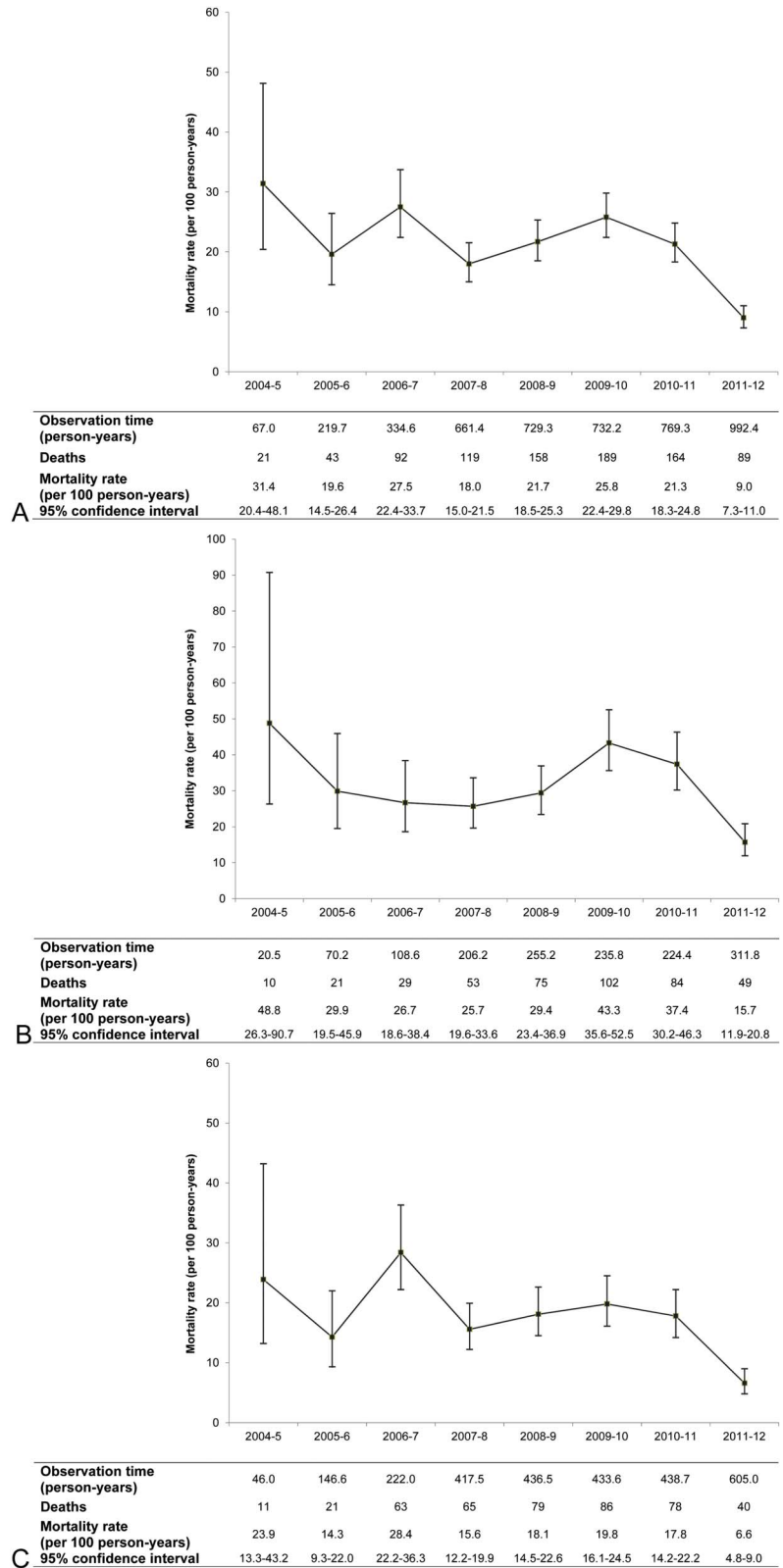


FIGURE 2. Mortality in the first 3 months of ART in all adults (N = 19,080) (A), males (N = 6174) (B), nonpregnant females (N = 11,523) (C).

TABLE 3. Competing Risks Regression Model (N = 19,080) for Factors Associated With Mortality in the First 3 Months of ART

Variable	n	SHR (95% CI)	P
Sex			
Nonpregnant female	11,523	1	
Pregnant female	1383	0.23 (0.12–0.45)	<0.001
Male	6174	1.48 (1.28–1.70)	<0.001
Age (yrs)			
16–24	2289	0.70 (0.53–0.93)	0.014
25–34	7598	1	
35–44	5536	0.91 (0.77–1.06)	0.225
45–54	2669	1.09 (0.89–1.32)	0.412
≥55	988	1.11 (0.83–1.49)	0.467
Baseline CD4⁺ cell count, cells/μL			
<50	3365	4.25 (3.23–5.60)	<0.001
50–200	11,175	1.46 (1.11–1.91)	0.006
201–350	3969	1	
>350	571	0.74 (0.38–1.45)	0.384
Concurrent TB disease*			
No	13,943	1	
Yes	3331	1.08 (0.92–1.28)	0.357
Missing	1806	1.19 (0.96–1.48)	0.121
Time period of ART initiation			
2004–2005	280	1.37 (0.87–2.15)	0.121
2005–2006	907	0.88 (0.63–1.24)	0.470
2006–2007	1408	1.18 (0.91–1.54)	0.204
2007–2008	2754	0.84 (0.66–1.06)	0.139
2008–2009	3079	1	
2009–2010	3159	1.27 (1.03–1.58)	0.027
2010–2011	3294	1.16 (0.93–1.44)	0.191
2011–2012	4199	0.54 (0.41–0.71)	<0.001

*Concurrent TB disease was TB disease treated at the time of ART initiation.

based to tenofovir-based regimen, we cannot discount that this may have accounted for some of the mortality change, although against this would be the fact that the majority of fatal adverse events related to stavudine (eg, lactic acidosis) occur after the first 3 months.³⁸

Earlier presentation for treatment may be not only indirectly related to the policy changes but also to improved HIV testing coverage in the community, facilitated by the nationwide HIV counseling and testing (HCT) campaign and local initiatives to scale up home- and community-based HIV counseling and testing.³⁹ This is supported by the fact that the CD4⁺ cell count at enrollment in the programme also shifted substantially in the period since August 2011, to the extent that almost half of the adults who enrolled into care between August 2011 and July 2012 had a CD4⁺ cell count >350 cells per microliter. Policy changes alone have no impact unless the health system is able to provide the services and individuals are able and willing to access those services. Our data are, therefore, important to show not only that people are accessing treatment earlier but that, so far, the health system has been able to cope with the increasing patient load. Not all countries are following WHO recommendations with regard to ART eligibility criteria, and these data should contribute to the evidence base around the impact of earlier access to ART.⁴⁰

As early LTF increased over time, mortality may have been underestimated, especially in the last time period because of the shorter time for deaths to be captured. The correction of mortality for LTF is complicated in our programme as, before analysis, some correction occurs routinely through linkage to the hospital information system and demographic surveillance system. Under a worst-case but unrealistic scenario, where the proportion of LTF in the last time period attributable to mortality was 40%, the estimated mortality decline was much less marked, but under a more realistic assumption of 20%, the decline remained significant.

The strengths of this analysis relate to the simplicity and quality of the data from a well-characterized treatment programme. Only 6% of adults who initiated ART had a missing baseline CD4⁺ cell count (considerably lower than the 25% reported from a multicohort collaboration in South Africa⁴¹), thus minimizing potential bias. Nevertheless, interpretation of the findings should be subject to some caution. We were unable within this analysis to explore outcomes for those people who, while eligible, did not initiate ART. We cannot, therefore, exclude the possibility that unmeasured variations over time in mortality for those who did not access ART could offset the mortality decline observed for those who access ART, although the consistent decline in population-level mortality would argue against this.²⁷ Data regarding in-hospital deaths from the Hospital Information System were only available from January 2011 and in-hospital deaths during earlier time periods might have been missed if they had not been reported through the routine systems of the HIV treatment and care programme. However, this would be expected to bias the findings away from the null hypothesis and therefore would strengthen our findings. Although the findings should be broadly generalizable to public-sector programmes in South Africa, it is possible that not only extra financial support to the programme but also the research and community engagement activities in the area might influence access to and uptake of treatment and replication of this analysis should be performed with other programmes.

In conclusion, we have demonstrated that in this rural area, since the policy shift to recommend ART for all adults with CD4⁺ cell count <350 cells per microliter, there has been a significant increase in the median baseline CD4⁺ cell count and a significant reduction in mortality within the first 3 months of ART. These findings provide support for national and international ART policies and highlight the importance of earlier ART initiation for achieving reductions in HIV-related mortality.

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