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Population-level associations between antiretroviral therapy scale-up and all-cause mortality in South Africa

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Summary

Our aim was to describe the association between increasing access to antiretroviral therapy and all-cause mortality in South Africa from 2005 to 2009. We undertook a longitudinal, population-level study, using antiretroviral monitoring data reported by PEPFAR implementing partners and province-level and national all-cause mortality records from Statistics South Africa (provider of official South African government statistics) to analyse the association between antiretroviral treatment and mortality. Using mixed effects models with a random intercept for province, we estimated the contemporaneous and lagging association between antiretroviral treatment and all-cause mortality in South Africa. We also conducted subgroup analyses and estimated the number of deaths averted. For each 100 HIV-infected individuals on antiretroviral therapy reported by PEPFAR implementing partners in South African treatment programs, there was an associated 2.9 fewer deaths that year (95% CI: 1.5, 4.2) and 6.3 fewer deaths the following year (95% CI: 4.6, 8.0). The associated decrease in mortality the year after treatment reporting was seen in both adults and children, and men and women. Treatment provided from 2005 to 2008 was associated with 28,305 deaths averted from 2006 to 2009. The scale-up of antiretroviral treatment in South Africa was associated with a significant reduction in national all-cause mortality.

Keywords

Antiretroviral therapy, mortality decline, Africa, PEPFAR

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Introduction

South Africa has the highest burden of HIV infection in the world, with over 5.2 million people living with HIV infection and over a 1000 new infections a day.[1] Antiretroviral therapy decreases individual mortality[2] and reduces HIV transmission to sex partners[3–5] and from HIV-infected mothers to infants.[6]

However, access to antiretroviral treatment in South Africa has had a challenging past.[7] The government did not begin to provide antiretroviral therapy until 2003.[8] The National Strategic Plan for 2007–2011 focused on increasing access to antiretroviral therapy for those with severely advanced HIV infection.[9] Currently, the National Department of Health provides antiretroviral therapy to all individuals with a CD4 T-cell count below 350 cells/mm^3, consistent with current WHO recommendations.[10,11]

Through the recent South African government-led efforts, a dramatic increase in the number of persons receiving antiretroviral treatment has been achieved.[12] That scale-up has been assisted by multiple donors including the US government, through the President's Emergency Plan for AIDS Relief

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(PEPFAR), which has provided support since 2004 to increase access to antiretroviral treatment and other HIV-related services.

Shortly after the global scale-up of antiretroviral therapy in resource-limited settings began, reports showed a leveling off of population-level mortality, and predicted that population-level mortality may continue to decline as the scale-up continues.[13–15] However, some have argued that the focus on HIV/AIDS has displaced funding and resources from other priority health issues, which could have a detrimental affect on overall mortality[16,17] This study examined the effect of scaling-up access to antiretroviral treatment on population-level mortality in South Africa, the country with the largest absolute burden of HIV/AIDS.

Methods

We assessed the population-level effects of antiretroviral therapy on all-cause mortality. Data used for these analyses were based on the total number of persons reported as currently on antiretroviral therapy from October through December (the last quarter) of the given calendar year. These data were obtained from routinely collected PEPFAR monitoring data from 2005 to 2009. Data were reported quarterly through a web-based system (MySQL, MySQL AB, Sweden) by PEPFAR-supported implementing treatment partners (primarily local and international non-governmental organizations). We could only access data from South African treatment programs that received at least some assistance from PEPFAR implementing partners. The proportion of patients receiving antiretroviral therapy via PEPFAR-assisted South African treatment programs increased from approximately 43% in 2005 to 80% in 2009.[18] Reported treatment data were cleaned for double counting, and because pediatric treatment data for 2009 were not collected by sex, a 50:50 male: female ratio was assumed for that year based on data from previous years.

The most recent all-cause mortality data, 2005–2009, were obtained from Statistics South Africa. In South Africa, death registration occurs through death notification to the Department of Home Affairs. Notification data are managed and analysed by Statistics South Africa.[19]

We used multiple models to assess the association between antiretroviral treatment (independent variable) and all-cause mortality (dependent variable) in order to account for potential limitations of any single model and assess robustness of the conclusions. Both treatment and mortality data were stratified by sex, province and age group (0–14 years versus 15 years and older).

National model

The first model used ordinary least squares linear regression to assess the national-level association between number of persons on antiretroviral treatment and number of all-cause deaths, controlling for sex, age group, and year. This regression model included data points for each year by sex and age group, not disaggregated by province. In the national model, we were able to include data even if the province was not reported.

Provincial model

The second model was a longitudinal provincial-level model for all nine South African provinces from 2005 to 2009. We used mixed effects models with maximum likelihood estimation to assess the association between the number of persons on treatment and the number of deaths. This model included a random intercept to account for the variance among clusters. Variance among clusters could be due to a number of factors, including, but not limited to differences in governance, ethnicity, population economic status and population density. The random intercept was a group identification code for each group of province, sex and age group.

Each provincial model initially controlled for sex, age group, year, province and HIV prevalence and population using the HIV prevalence from 2008 and the mid-year population estimates for each year, by sex, age group and province.[20–25] To create our final model, we used backward selection to remove all covariates with $p > 0.10$ that did not change the point estimate by more than 10%.

To account for a potential lag between treatment and the effect on mortality, for both the national and provincial model, we conducted the analyses comparing treatment and mortality data from the same year and again comparing treatment data to the mortality data from the following year. In the provincial-level analysis, province, provincial HIV prevalence, age group and year remained as covariates in both the models where treatment and mortality were assessed in the same year, and in the model where one year lag was allowed between treatment and mortality. Provincial population also remained in the model that assessed treatment and mortality for the same year.

We calculated the number of deaths averted each year by multiplying the overall provincial level point estimate for the number of fewer deaths per person on treatment by the number of persons on treatment the previous year. Finally, we did subgroup analysis by age group (0–14 years versus 15 years and older), sex and province. All analyses were conducted using Stata/SE 12.1, StataCorp LP, College Station, Texas.

Alternative data source and analysis

In order to assess the consistency of the trends observed using the PEPFAR antiretroviral data, we conducted the above analyses again using data from public sector, Comprehensive Care Management and Treatment (CCMT), sites. These data are publicly available at the provincial level, segregated by adults and children.[18]

Results

Compared to 2005, in 2009 there were 10.9 times as many people receiving antiretroviral therapy at PEPFAR-assisted medical facilities in South Africa (67,479 persons in 2005 versus 738,429 persons in 2009) (Appendix). There was an increase in reported antiretroviral treatment in both men and women, children and adults, and in all provinces. In all provinces except Northern Cape, PEPFAR-implementing partners assisted treatment programmes in all years of analysis. In Northern Cape, PEPFAR assistance for treatment programmes started in 2007.

National mortality decreased from 597,634 reported deaths in 2005 to 571,039 reported deaths in 2009. There was not a consistent decrease in mortality in all subgroups analysed. Of the nine provinces, Eastern Cape and KwaZulu Natal were the only provinces in which mortality declined each year from 2005 to 2009. In no province did mortality increase every year from 2005 to 2009.

In the national model for each 100 additional persons on treatment, there were 2.5 fewer deaths that year (95% CI: 0.1, 4.9) and 4.2 fewer deaths the following year (95% CI: 2.3, 6.2). In the provincial model, for each 100 additional persons on treatment, there were 2.9 fewer deaths that year (95% CI: 1.5, 4.2) and 6.3 fewer deaths the following year (95% CI: 4.6, 8.0). Analyses in sub-populations demonstrated similar trends (Table 1, Figure 1).

Of the variables included in the provincial models, the only covariates that were significantly associated with mortality ($p < 0.05$) were age group and province.

Antiretroviral therapy from 2005 to 2008 was associated with approximately 28,305 total deaths averted

Table 1. Fewer deaths per 100 persons on treatment by model and population subgroup, South Africa 2005–2009.

	PEPFAR[a]	PEPFAR[a]	CCMT[b] public sector	CCMT[b] public sector
	No lag for mortality[c]	One year lag for mortality[c]	No lag for mortality[c]	One year lag for mortality[c]
Population				
All (National level)	2.5 (0.1, 4.9)	4.2 (2.3, 6.2)	1.1 (−3.3, 5.5)	2.7 (−1.0, 6.5)
All (Provincial level)	2.9 (1.5, 4.2)	6.3 (4.6, 8.0)	3.6 (2.0, 5.1)	3.8 (2.1, 5.6)
Provincial-level subgroups				
By sex				
Men	4.8 (–1.6, 8.0)	7.5 (3.2, 11.8)	Data not available	Data not available
Women	3.1 (1.5, 4.6)	6.2 (4.3, 8.1)	Data not available	Data not available
By age group				
Children (0–14)	21.2 (17.1, 25.1)	25.3 (19.4, 31.3)	17.7 (13.8, 21.6)	18.4 (10.7, 26.1)
Adults (15+)	3.8 (1.7, 5.9)	7.4 (4.7, 10.0)	4.3 (2.6, 5.9)	
By province				
Eastern Cape	13.2 (10.2, 16.3)	12.5 (8.5, 16.5)	13.6 (11.3, 15.8)	16.8 (14.0, 19.7)
Free State	6.1 (1.3, 10.9)	7.3 (4.1, 10.5)	0.6 (−6.8, 8.1)	7.1 (3.8, 10.4)
Gauteng	−0.7 (−2.8, 13.5)	0.3 (−1.7, 2.3)	−2.6 (−6.1, .9)	0.2 (−1.8, 1.5)
KwaZulu-Natal	3.6 (1.4, 5.8)	6.2 (4.6, 7.8)	2.4 (1.5, 3.4)	3.9 (3.3, 4.4)
Limpopo	−0.4 (−4.1, 3.3)	−2.7 (−6.3, 0.9)	−1.2 (−8.1, 5.5)	−3.7 (−6.0, −1.5)
Mpumalanga	−3.9 (−7.6, −0.1)	−14.7 (−21.9, −7.5)	−7.4 (−11.1, −3.6)	−9.2 (−13.0, −5.3)
Northern Cape	−3.4 (−9.0, 2.2)	−3.8 (−8.5, 0.9)	−9.2 (−14.8, −3.6)	−6.2 (−8.7, −3.7)
North West	2.2 (0.1, 4.3)	1.1 (−2.2, 4.4)	0.3 (−1.4, 2.0)	−2.6 (−6.4, 1.2)
Western Cape	3.2 (−0.2, 6.6)	40.1 (−10.9, 91.0)	−2.7 (−6.9, 1.5)	−2.8 (−10.2, 4.5)

[a]Model used data from sites receiving some assistance from PEPFAR (President's emergency plan for AIDS relief).
[b]Model used data from public sector CCMT (comprehensive care, management, and treatment) sites.
[c]Number of fewer deaths for each 100 additional persons on treatment (95% CI).

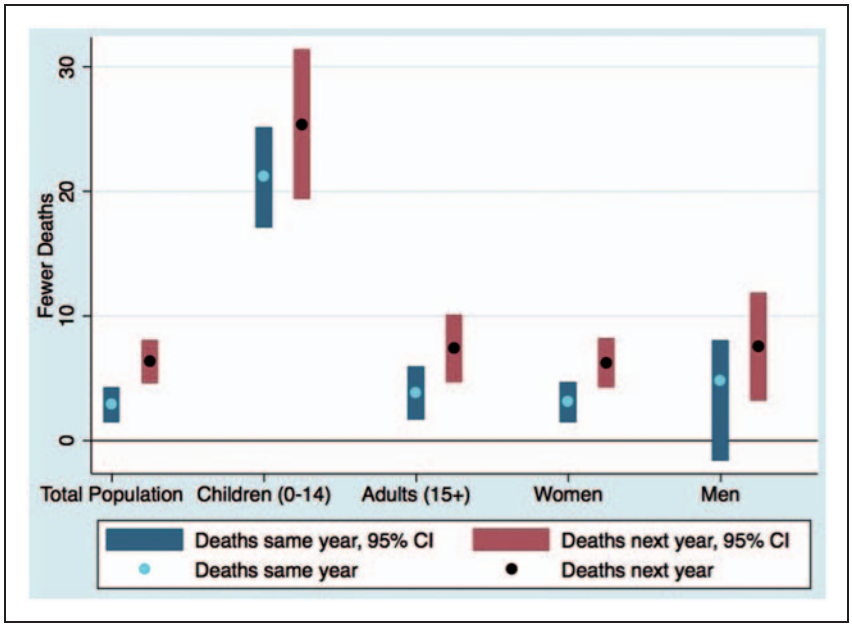

Figure 1. Number of fewer deaths by model and population subgroup, PEPFAR treatment data, South Africa, 2005–2009.

from 2006 to 2009: 2276 deaths averted in 2006, 3741 deaths averted in 2007, 6990 deaths averted in 2008 and 15,297 deaths averted in 2009.

Discussions

We used routinely collected monitoring data of donor-assisted antiretroviral treatment scale-up and national mortality records to evaluate the association of treatment and overall mortality in South Africa. We found that the scale-up of antiretroviral therapy in South Africa was associated with a significant and important reduction in national all-cause mortality. As access to antiretroviral therapy is scaled up in countries with high burdens of HIV/AIDS, the positive effects could be seen at the population level.

A significant association was seen between increased antiretroviral therapy and decreased mortality the subsequent year in all subgroups analysed and in four provinces. This finding is consistent with the known survival benefits of antiretroviral therapy, where some mortality reductions are realized immediately, but the survival benefits for those on treatment extends over many years. As the antiretroviral therapy scale-up continues and more years of observation are added, variability in the underlying data would likely decrease and the robustness of the findings would increase, particularly in the provincial sub-analysis, which had fewer observations.

While some regions in the world saw a decline in adult mortality between 1970 and 2010, there were significant increases in adult mortality in sub-Saharan Africa during that same period, particularly in the 1990s, followed by a very recent stabilization and decline.[26] Those trends mirror the increase in HIV prevalence and AIDS deaths in those countries and then the subsequent reversals due to the increase in access to antiretroviral therapy. Other studies of HIV/AIDS-specific mortality in South Africa have also found an inverse relationship between treatment and mortality similar to the trends found in our report.[14,27] In KwaZulu-Natal (the province with the largest number of people living with HIV/AIDS in South Africa), Herbst et al. found a decline in both all-cause and disease-specific mortality corresponding to the increased availability of antiretroviral therapy for HIV/AIDS.[28] In addition to a reduction in mortality, the most recent mid-year population estimates released by Statistics South Africa show an increase in life-expectancy,[15] and a recent paper using rigorous modeling demonstrated a very significant increase in life expectancy in KwaZulu-Natal.[29] Our results add to and further validate those findings.

Bendavid previously demonstrated an association between declines in HIV-related and all-cause deaths in countries in which PEPFAR programmes have supported the country-level response to HIV/AIDS[30,31] and Cohen looked at the impact of PEPFAR programs on different health systems-level indicators.[32] Those analyses looked at the trends in mortality before and after PEPFAR involvement in order to evaluate the effectiveness of donor programs. Alternatively, our analysis looked at trends over just the period of the antiretroviral therapy scale-up and was thus not an evaluation of PEPFAR, but rather the impact of increasing access to antiretroviral therapy itself.

The overall findings demonstrated that increasing coverage of antiretroviral therapy was associated with the reduction of deaths in South Africa. The population-level data used in this study allowed us to look at an impact beyond the individual, and to examine concerns that population-level benefits of increasing resources for treating HIV/AIDS might be negated by worse health outcomes in other program areas. Because of the overall benefit of HIV/AIDS treatment on all-cause mortality, those concerns were not supported by our analysis. However, this study did not have a direct comparison group, which limited our ability to attribute the decrease in overall mortality to antiretroviral therapy. It is possible that the decline in mortality seen during that time could be attributable to other causes. However, the association between increased antiretroviral therapy and reduced mortality was seen in multiple subgroups and in several geographic areas. Those results, combined with the observation that the one province that saw a delay in antiretroviral therapy implementation (Northern Cape) until 2007 was the only province that had increased mortality every year, increase the likelihood that the association between antiretroviral therapy scale-up and mortality reductions is valid. Only one province, Mpumalanga, saw increased mortality with increased treatment. This may have been due to instability in service delivery, low and delayed treatment coverage or poor data capture.

As with any study that uses routine monitoring data, there were limitations. Quality assurance measures were applied to varying degrees by PEPFAR implementing partners, and therefore there were missing data and potential misclassification of reported data. Using data from only PEPFAR-assisted sites does not include all South Africans who have been placed on antiretroviral therapy by the South African government, whose scale-up has reached the goal of 80% coverage as advocated by WHO. However, data from PEPFAR-assisted sites include both public and private facilities, and therefore have the advantage of representing a subset of the general population who are accessing antiretroviral therapy. Finally, there was population migration between provinces, and the geographic borders of provinces have changed slightly over the years. Because we used monitoring data reported only by PEPFAR-implementing partners, the treatment data we used in our analysis will also underestimate the total number of persons receiving antiretroviral therapy in South Africa. However, the analysis conducted with public sector data from the CCMT demonstrated similar trends. These data are not completely comparable as they represent the number of patients cumulatively enrolled, not accounting for patients who were lost to follow-up, deregistered or died.[18] They also suffer from quality control issues similar to the PEPFAR data; however, the overall trends agree with those found using the PEPFAR monitoring data.

The mortality data also might have missing information, and death notification is estimated above 90% for 2004–2009.[19] The reporting system used the same death notification form over the period of our study. There were changes to the provincial borders in 2005 and 2009. Those changes may have biased the results slightly, causing misclassification; although those changes only affected a small population of residents, the effect, if any, was likely minimal. Although HIV/AIDS-related deaths are registered, the numbers of these cases appear to be underestimates when compared to other estimates, and as such, HIV-specific mortality data were not used.[1,19,33,34]

This analysis included ecologic-level data and therefore did not assess the direct impact of antiretroviral treatment on the treated individual. The goal was to more broadly assess the impact of treatment of the population as a whole. The national and provincial models have complementing strengths. The national model allowed for the inclusion of data where province was missing and was not affected by individuals who may have died in provinces different from those in which they would have accessed treatment, whereas the provincial-level model allowed for more group data points each year and accounted for potential provincial-level confounders such as changes in population, HIV prevalence and varying degrees of health system capacity between provinces. The consistent findings across the two models further support the notion that increased access to antiretroviral therapy leads to reduced all-cause mortality.

We may have observed a stronger association between increased access to ART and decreased mortality in children than adults because ART provided to adults indirectly benefits their children. This is because they live longer and are able to provide for them, and pregnant women are less-likely to transmit HIV to their infants. It is also possible that the association seen here is confounded by improvements in the health system, which could allow for both the scale-up of ART and decrease in all-cause mortality. Because there is no counterfactual or comparison group, the associations seen in these models may be due to factors not directly related to an individual's receipt of ART. The causal pathway between improved health systems, increased access to ART and all-cause mortality cannot be demonstrated in this analysis.

Our study draws strength from its national focus, which allowed us to look at the potential wider impact of the antiretroviral therapy scale-up in South Africa. By using all-cause mortality versus HIV/AIDS specific mortality, we were able to reduce opportunities

for misclassification in causes of mortality, a common limitation in similar analyses when HIV/AIDS-specific mortality is used as the outcome.[33,34] Additionally, this study included children, an understudied population affected in many important ways by the HIV/AIDS epidemic and the corresponding treatment scale-up.

Recent evidence has demonstrated that the benefits of antiretroviral therapy can go beyond individuals receiving the treatment and protect their uninfected sex partners from becoming infected.[3–5] Even beyond the benefits for an HIV-infected individual and his or her HIV-uninfected partner, this study demonstrated that increasing access to antiretroviral therapy was associated with a population-level benefit: decreased all-cause mortality. This study contributes to the growing body of knowledge that shows that universal access to antiretroviral therapy is associated with saving lives, and underlies that continued support and technical assistance to further the expansion of antiretroviral therapy to those in need are crucial.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix Treatment and mortality data for national models.

	Sex	Age[a]	# On treatment	# of deaths in the current year	# of deaths next year
2005	Male	Children	3336	37,740	39,193
2005	Male	Adults	20,996	260,904	268,422
2005	Female	Children	2945	33,878	34,026
2005	Female	Adults	38,622	260,342	265,124
2006	Male	Children	6989	39,193	37,656
2006	Male	Adults	38,665	268,422	268,162
2006	Female	Children	6090	34,026	32,971
2006	Female	Adults	69,643	265,124	265,124
2007	Male	Children	14,066	37,656	37,100
2007	Male	Adults	78,028	268,162	265,660
2007	Female	Children	13,234	32,971	32,651
2007	Female	Adults	150,541	265,124	256,305
2008	Male	Children	26,251	37,100	31,435
2008	Male	Adults	146,407	265,660	260,952
2008	Female	Children	24,717	32,651	27,135
2008	Female	Adults	302,171	256,305	249,313
2009	Male	Children	34,155	31,435	–
2009	Male	Adults	216,654	260,952	–
2009	Female	Children	34,155	27,135	–
2009	Female	Adults	440,244	249,313	–

[a]Children are persons under 15 years old; adults are persons 15 years old and older.