THE POPULATION HEALTH IMPACT OF THE DISTRIBUTION OF FREE ANTIRETROVIRAL MEDICATION IN SOUTH AFRICA

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ABSTRACT

This paper examines the population health impact the roll out of free ARVs in South Africa between 2006 and 2014. We use four-waves of the nationally representative NIDS panel data linked to the facility-level District Health Information System on ARV provision to estimate the mortality reduction from ARVs based on reported information. We find that amongst the high prevalence subgroup of Black Africans between 25 and 49, access to ARVs led to a large and significant reduction in two-year non-injury mortality of 1.6 percentage points and decreased the likelihood of reporting poor health by 3 percentage points.

Keywords: HIV, antiretrovirals, mortality, South Africa

1. INTRODUCTION

HIV is one of the most destructive epidemics in history, alongside diseases such as smallpox, Black Death, malaria and the Spanish Flu. It has placed an unprecedented toll on developing countries through human suffering and loss of life. Fortunately the successful roll out and implementation of antiretroviral therapy has curbed the devastation caused by this disease.

HIV has been particularly destructive on the African continent. The greatest burden was borne by South Africa, home to nearly one in five of the world's HIV positive individuals (Simelala et al., 2015). In South Africa, the introduction of ARV therapy was unnecessarily delayed due to a period of AIDS denialism[1], which was estimated to have caused 330 000 deaths (Chigwedere et al, 2008).

Since 1 April 2004 the South African government, with substantial support from PEPFAR and The Global Fund, distributed free ARV treatment at public health care facilities throughout the country. However, accreditation requirements imposed a significant administrative burden, and consequently provision was almost entirely hospital-based until the accreditation was abandoned in 2010. Subsequently, all public facilities were allowed to distribute ARVs. In 2010 ARV provision was expanded by lowering the CD4 count eligibility from below 200 cells/μL to below 350 cells/μL (Simelala et al., 2015). 1.85 million people received ARV treatment in 2011, compared to an estimated 47 500 in 2004 (Johnson, 2012).

While community-based trials have demonstrated that antiretroviral treatment has been effective (Coetzee et al, 2004) and can lead to substantial gains in survival (Bor et al, 2013), no prior studies have estimated the impact of ARTs on survival based on nationally representative statistics of reported deaths. Existing estimates are either reliant on epidemiological and statistical modelling (April et al, 2013) - which is sensitive to assumptions about crucial unknown parameters such as implementation efficacy and patient adherence - or based on demographic surveillance sites or community-based ART programmes that are not representative of South Africa's population (Bor et al, 2013; Coetzee et al, 2004; Herbst et al, 2011, Herbst et al, 2009). In fact, Bor et al (2013: 962) warns that extrapolating their demographic surveillance site estimates to population-level estimates would "not be straightforward, owing to the difficulties of measuring treatment coverage, adherence and retention, and survival for patients presenting at later stages of HIV disease."

These estimates are crucial because they help us to accurately document the legacy of ARVs, but also, in looking forward, such estimates can help to inform decisions about the funding of ARVs in a resource-constrained setting, amidst competing demands on the public health budget. Despite ARV coverage of 50% (Johnson, 2012) and a decline in HIV related mortality across all provinces over the past decade, HIV remains the leading cause of death, accounting for almost one third of all deaths (Van Wyk-Pillay et al, 2016). Since September 2015 the WHO supports and endorses the expansion of treatment to all HIV positive individuals, irrespective of CD4 count (WHO, 2015). This recommendation is motivated in part by new evidence that show that earlier enrolment on HIV care can help reduce the spread of the disease, with the ultimate goal of ending HIV (Cohen, et al, 20). There are serious concerns about the long-term affordability of universal access to HIV treatment due to the duration of patient treatment and the accumulating numbers of treated patients. Due to the high prevalence of HIV with an estimated 6.4 million

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[1] The apex of AIDS denialism occurred in 2002. There were sufficient scientific evidence on the safety and effectiveness of ARVs to motivate South Africa's neighbours to launch large scale ARV programmes, but the South African government chose to postpone the launch of a Prevention of Mother-to-Child Transmission (PMTCT) programme to first carefully assess the operational challenges (Simelala et al., 2015). Civil society challenged President Thabo Mbeki's decision to stall the implementation of PMTCT in the High Court and the court ruled that the operational challenges were not sufficient to delay a phased roll out of PMTCT. This court case turned the tide against AIDS denialism, and in November 2003 the ARV programme was presented to cabinet and approved (Simelala et al., 2015).

HIV positive individuals in South Africa (Simelela, 2015), treatment is expensive and estimated to cost $400 million US dollars per year (Mayosi & Benatar, 2014).

We estimate the nationwide impact of antiretroviral treatment on mortality in South African in the period 2006 to 2014. We match household member deaths reported in a large representative panel survey to community-level ARV treatment enrolment indicators to provide an estimate of lives saved via access to ARVs. We include total population estimates, but focus our analysis on high HIV prevalence subgroups such as the 25 to 49 age group and Africans. According to Shisana et al (2014) HIV prevalence was 25.2% amongst the 25 to 49 age group, but only 2.4% and 7.1% amongst the 0 to 14 and 15 to 24 age group. HIV prevalence was 7.6% amongst those 50 and older. Shisana et al (2014) reports that HIV prevalence was 15% amongst Black Africans, but 0.3%, 3.1% and 0.8% amongst White, Coloured and Asian South Africans. We do not report estimates for other races because the White, Coloured and Indian groups are relatively small cf. Black African sample and we can therefore not estimate such effects reliably.[2]

We do not expect delay in the health response to ARVs. According to Barth et al (2010) meta-analysis shows that ART works fast with efficacy benchmarked as 78% viral suppression at 24 weeks.

We find that the ARV programme rollout has reduced mortality of Black African adults in the high HIV prevalence age range of 25 to 49 by one percentage point. The likelihood of reporting poor health is examined and the analysis shows a significant reduction of 3 percentage points, suggesting that ARV treatment does not only prolong life, but also restores physical health.

2. DATA AND METHODS

2.1 DATA

For this analysis we link data on mortality and other socioeconomic characteristics of a panel survey from the National Income Dynamics Study (NIDS) with data on the availability of ARVs in clinics from the District Health Information System (DHIS). The NIDS is a bi-annual panel survey that was conducted 4 times between 2008 and 2014 (SALDRU, 2016a – d). The sample is nationally representative and stratified by district council. Each of the 4 waves includes information on approximately 8000 households and just below 30 000 individuals.

We extract information from it on the recent death of household members (also their race and age), current health of household members and the socio-economic circumstances of the household. We do not observe cause of death, other than deaths from violence or accident. Excluding injury mortality, we measure total non-injury mortality obtained from questions regarding deaths in the households over the past two years. Please note that for conceptual simplicity we will use mortality as shorthand for two-year non-injury mortality from this point forward.

The DHIS data is an administrative data set reflecting facility level records. We use the ARV cohort module[3] that contains information on the number of new and existing enrolments at each public health facility for each month since January 2004. These data were collected prospectively from 2011 and retrospectively for the years prior to 2011 (by asking current ARV patients when they initially started treatment). A maximum

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[2] According to the 2011 Census 76% of South Africans were Black African, 9.1% were White, 8.9% were Coloured, 2.5% were Asian at 2.5% and 5% were Other or Unspecified.

[3] The ARV enrolment data is captured at facilities via the TIER.net program and then loaded into DHIS.

likelihood algorithm is applied to monthly facility-level ARV enrolment data to estimate the launch date for ARVs at each facility.

Census 2011 took place in October 2011 and a 10% sample of household records were made publicly available. The 10% sample was stratified according to province and district council. Within each District Council, the records were further stratified by local authority and enumeration area type. The Census contains information on household characteristics and community demographics.

2.2 DATA LINKAGES

For each household in NIDS the distance to the closest dispensing facility was estimated by calculating the shortest distance between the household's GIS coordinates and any of the GIS coordinates for the set of facilities providing ARVs at that point in time. DHIS and Census data were merged by matching community (enumerator area or PSU) GIS information to facility GIS information.

2.3 STUDY DESIGN

The causal effect of ARV access on non-injury mortality is estimated using two model specifications and two definitions of ARV access. In the first specification, ARV access is regressed on mortality in a pooled regression model, including controls for individual and cluster characteristics and a time trend. In this specification access is defined as living within 10kms of a facility providing ARVs.

We neither observe HIV positive status, not ARV treatment. We can therefore only estimate the intention to treat effect of ARV availability on the likelihood of dying in the following two years, controlling for individual and cluster characteristics, geographical factors (by include cluster effects) and a time trend. The identifying assumption is that the trends in mortality in treated and control areas are parallel in the absence of treatment.

When considering the impact of ARVs on mortality, there are immediate concerns about the exogeneity of the roll out of the ARVs. Anecdotal evidence from government and funders as well as empirical analysis indicate that there was no systematic pattern favouring specific types of facilities, but it is still a concern that there are systematic patterns in the distribution of facilities. We match the Census data to our DHIS ARV rollout data and find that factors correlated with access to facilities such as population density, wealth and race do have significant correlation to the sequencing of ARV roll outs. Fortunately, these observables can be included in our regression analysis. The appendix documents these results in more detail. These findings are in line with the results from McLaren (2015) considering the same question for the earlier period of 2002 to 2009.

A cluster-level fixed effects specification is estimated to account for time-invariable unobservable factors that could distort the estimates. ARV access is measured as the share of the 24 months where the community cluster lived within 10 kilometres of a facility providing ARV treatment. This analysis included clusters that contained Black African individuals within the 25 to 49 age range. Clusters were weighted according to the number of individuals that were African and within the 25 to 49 age range in the first year of the panel survey. Although there were 400 sampled clusters, 36 of these clusters did not include any Black Africans.

A cluster-level fixed effects specification is also estimated for self-assessed health[4]. An indicator variable was created to capture the self-reported health at the bottom end of the scale, by flagging all cases where the individual described their health as poor (the lowest category) with a 1 and allocating a 0 to all other cases. ARV access is again defined as the share of the two-year period that the community lived within 10 kilometres of a facility providing ARV treatment.

2.4 EMPIRICAL MODEL

We are interested in estimating the casual effect of ARV access on mortality in South Africa[5].

The following outcome equation is modelled

$$Y_{ijt} = \tau ARV_{ijt} + \gamma_{ijt}X_{ijt} + \gamma_j X_j + \lambda_t + v_{jt} + u_{ijt}$$

where Y_{ijt} is a binary variable that takes the value of 1 if individual i died within the following two years and 0 if they did not. ARV_{ijt} denotes the availability of antiretroviral drugs. The model has a full set of time effects, λ_t, a set of individual-specific covariates, X_{ijt}, a set of geographical covariates, X_{jt}, unobserved geographic-specific error, v_{ijt}, and individual-specific error, u_{ijt}.

We are interested in the coefficient, τ, which estimates the average effect of ARV access on mortality. Observable correlates and time dummies are added to control for the endogeneity in treatment that could bias our results. Since it has been shown that the roll out of ARVs are correlated to wealth and population density we explicitly control for both these correlates in our individual level pooled regression.

In the second portion of the empirical part of the paper we also introduce a cluster-level fixed effects regression which allows us to control for time invariant region specific fixed effects.

3. RESULTS

3.1 DESCRIPTIVE RESULTS

Figure 1 provides a visual illustration of the expansion of ARV access. The figure was created using the DHIS information of ARV availability and the GIS coordinates of each facility that had individuals on ARV at a specific period. The red blocks represent hospitals providing ARVs and blue blocks represent primary care facilities providing ARVs. From 2006 to 2012 the map of South Africa changed drastically: in 2006 ARVs were only provided by a few hospitals, by 2010 there were far more hospitals providing ARVs, but still only very few clinics providing ARVs. By 2014 there were far more facilities providing ARVs and primary care facilities have overtaken hospitals as providers.

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[4] In the National Income Dynamics Survey, respondents of ages 15 and above were asked "How would you describe your health at present? Would you say it is excellent, very good, good, fair or poor?".

[5] Since we do not have any information on HIV status we are unable to isolate our analysis to only HIV positive individuals. We will therefore be measuring the average treatment effect for the population as a whole
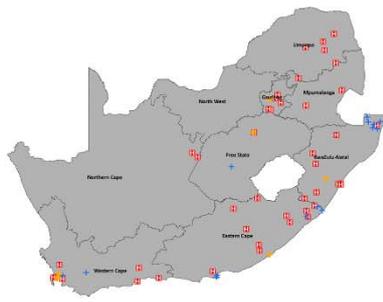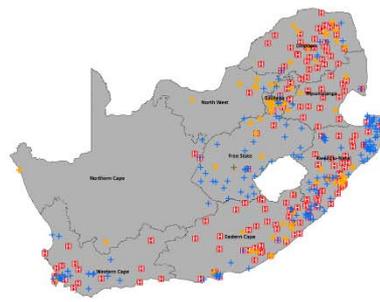
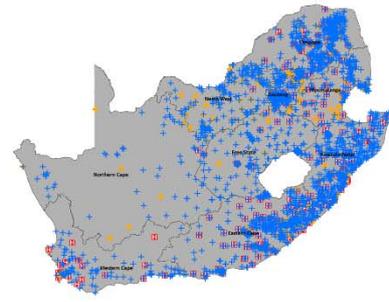| Figure 1a: ARV access in 2006 | Figure 1b: ARV access in 2010 | Figure 1c: ARV access in 2014 |

Initially ARVs where only available in richer more urban regions where hospitals resided. Over time, however ARVs were rolled out to clinics, which are located in poorer and less densely populated regions than hospitals. Over time we see a drop in the overall density and the average wealth of those regions that are treated (see figure C2 and C3 in the appendix). Many of these poorest and most isolated areas however remain untreated. These findings are in line with the results from McLaren (2015) considering the same question for the earlier period of 2002 to 2009.

ARV coverage shows a sharp upward trend over time. In Figure C1 in the appendix ARV coverage was defined as the proportion of the individuals in the Census that have a facility providing ARVs within 10 kilometres of them. According to our estimates the share of the population within 10 kilometres of a facility that provides ARV treatment increased from 0% in 2004 to 82% of the South African population by 2014.

Importantly the NIDS mortality information we plan to use for most of our analysis only spans from 2006 to 2014. Luckily, however, this happens to be the period when most of the facilities started over ARVs. In Figure 2 we consider trends in ARV access across three definitions of the concept (within 5, 10 and 15kms). Across all three definitions of the concept there is a gradual upward trend. If we define coverage as being within a 10 kilometres of an ARV facility, then ARV coverage sharply increases from 18% to 90% between 2008 and 2014.

There has been a decline in reported non-injury mortality over the past two years in NIDS between 2008 and 2014. Reported deaths over the past two years fell from 2.6% in 2008 to 1.6% in 2014. Figure 3 shows a decline in all reported non-injury related deaths between 2006 and 2014, but with large differences between age groups. The group that was 50 and older had the highest mortality rates, but see only a less steep decline in mortality from 7% to 6.3% over this period. The 15 to 24 age group has the lowest mortality rates, but also has a much less steep downward trend over this period from 0.8% to 0.4%. By contrast, the 25 to 49 group's mortality fell from 5.1% to 1.9% over this period.

The mortality rates for all three groups were compared to the mortality derived from the 2011 Census[6]. The rates were very comparable. The probability of mortality among the three groups was 7.3%, 2.8% and 0.6% using NIDS and 6.8%, 2.4% and 0.5% using Census. All three groups were undercounted in Census relative to NIDS.

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[6] Unlike in NIDS, in the Census survey household members were asked if anyone died in the last year. In NIDS household members were asked if anyone died in the last two years. The one year mortality rates were transformed to two year mortality rates in the following manner $r_2 = r_1 + (1 - r_1)r_1$ for each of the age-cohorts.
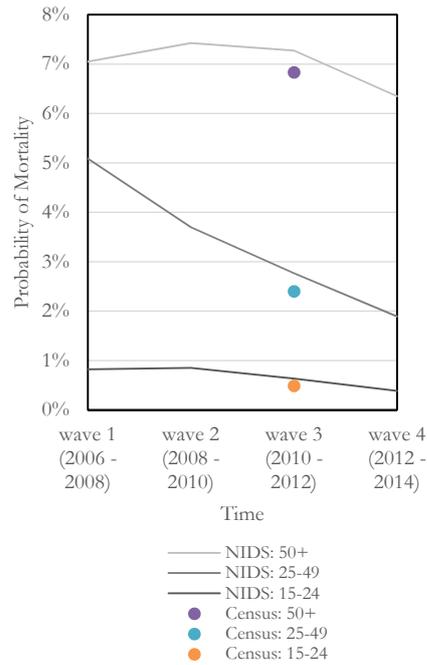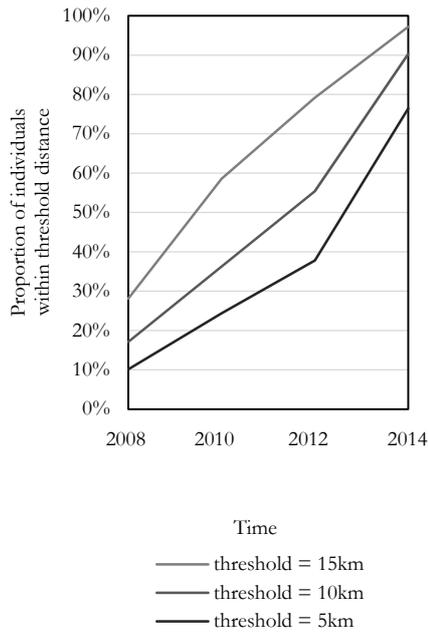
Figure 2: ARV coverage from 2006 to 2014, by distance from facility   **Figure 3: Mortality over time by age group, 2006 – 2014**

## 3.2 ESTIMATING THE IMPACT OF ARV ACCESS ON MORTALITY

To estimate the effect of ARV availability on mortality among Africans, non-injury mortality over the past two years is regressed on ARV availability with an individual-level pooled linear probability model. Income information, geographical characteristics and time trend are added to the model specification to control for the influence of factors correlated with access to facilities.

The analysis considers three age groups: 15 to 24, 25 to 49 and 50 and older.

Table 1: Linear Probability Model: Two-year mortality for three age-groups of black Africans, 2006 - 2014

VARIABLES	(1) 15-24	(2) 25-49	(3) 50+	(4) 15-24	(5) 25-49	(6) 50+
ARV access	-0.00444***	-0.0195***	-0.00479	-0.00300**	-0.00678***	0.00499
Quintile = 2				0.00228	-0.00105	-0.00570*
Quintile = 3				0.00150	-0.00309*	-0.00977***
Quintile = 4				-0.00108	-0.00293*	-0.0130***
Quintile = 5				-0.0126	-0.00367	-0.0235***
Period = 2				0.000834	-0.0137***	0.00429
Period = 3				-0.000876	-0.0203***	0.000385
Period = 4				-0.00201	-0.0262***	-0.0119*
Constant	0.00904***	0.0428***	0.0730***	0.0144***	0.0548***	0.0414**
Demographic variables	No	No	No	Yes	Yes	Yes
Observations	21,821	28,034	15,290	21,816	28,029	15,283
R-squared	0.001	0.003	0.000	0.003	0.008	0.029

The mortality impact was the most pronounced for the two younger groups and insignificant for the group aged 50 and above. Since the first three regressions do not control on any covariates, they merely report the average mortality rates of the treated and control groups within each age cohort. The figure below shows how these averages compare graphically.
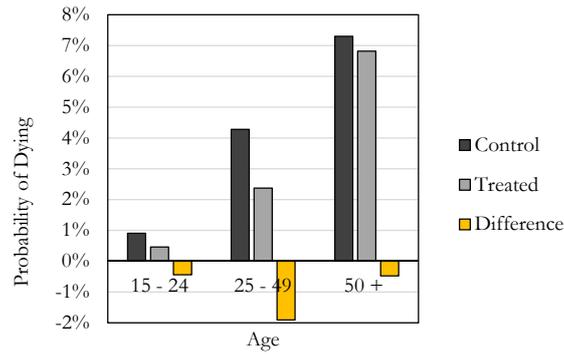
Figure 4: Mortality by age and treatment

15 to 24 year old Black Africans with ARV access had a 0.5% likelihood of dying over the next two years while those without ARV access had a 0.9% likelihood of dying in the next two years. Access to ARVs thus represented a 50% reduction in mortality. The mortality impact remains significant but drops from a 0.4 to a 0.3 percentage point when time trends and individual and geographical attributes are added to the regression.

Black Africans aged 25 to 49 without ARV access had a 4.3% likelihood of dying over the next two year, while those who lived within 10km of an active ARV facility had a 2.3% likelihood of dying in the next two years, representing a 50% reduction in mortality. The effect remains significant but drops to from a 1.95 percentage points to 0.68 percentage points when we control for individual and geographical attributes.

The difference in mortality was negligible among those aged 50 and up. On average, those who stayed close to active ARV facilities had a 6.8% likelihood of dying, while those who stayed further away from ARV facilities had a 7.3% likelihood of dying.

When considering the impact of ARVs on mortality, there are concerns about whether there were systematic bias in the roll out of the ARVs. For instance, the coefficient estimates on the mortality variable could be biased if the most severe HIV prevalence would receive care first. However, there are systematic patterns that correlate with access to facilities such as population density and wealth, which were included in our regression analysis. These findings are in line with the results from McLaren (2015) considering the same question for the earlier period of 2002 to 2009.

3.3 PANEL DATA ANALYSIS OF REGIONAL MORTALITY

The cluster-level fixed effects regression accounts for these unobservable differences between regions since it compares the variation in mortality within regions rather than between regions. In table 2 below we used a cluster-level fixed effect regression to compare the mortality rates for the three groups.

As before (see Table 1) ARV access had a significant effect for the two younger cohorts, but no significant effect for the older cohort, where HIV prevalence is higher.

Table 2: Fixed Effects Panel Regression: Two-year mortality for three age-groups of black Africans, 2006 - 2014

VARIABLES	(1) 15-24	(2) 25-49	(3) 50+	(4) 15-24	(5) 25-49	(6) 50+
ARV access	-0.00699***	-0.0355***	0.00142	-0.00704***	-0.0164***	0.00951
Period = 2				0.00121	-0.0150***	0.00523
Period = 3				0.000828	-0.0182***	-0.000648
Period = 4				0.000160	-0.0237***	-0.00869
Constant	0.0110***	0.0552***	0.0688***	0.0105***	0.0576***	0.0651***
Observations	1,324	1,390	1,308	1,324	1,390	1,308
R-squared	0.020	0.097	0.000	0.020	0.122	0.004
Number of Clusters	349	357	344	349	357	344

As before (see table 1), ARV access had a significant effect for the two younger cohorts, but no significant effect for the older cohort. This is consistent with the prior that ARVs help those age groups with higher HIV prevalence rates most.

For the subgroup of black Africans that are aged between 15 and 24, receiving ARVs decreased the likelihood of non-injury mortality over the next two years from 1.1% to 0.4%. That is a 64% reduction. For this demographic subgroup the estimated impact of ARV access is unaffected by the inclusion of time dummies.

The mortality rates was far higher for the subgroup aged 25 to 49. Receiving ARV's decreased the likelihood of non-injury mortality over the next two years by 60%, from 5.5% to 2.0%. When time dummies are added the effect drops from 3.55 percentage points to 1.64 percentage points.

3.4 IMPACT OF ARV ACCESS ON LIKELIHOOD TO SELF-REPORT POOR HEALTH

The analysis shows that for two of the three groups there was a significant negative relationship between ARV availability and the likelihood to report poor health. For individuals aged 15 to 24, the availability of ARV access decreased the probability of being in poor health by 0.7 percentage points. For individuals aged 25 to 49, the availability of ARV decreased the likelihood of reporting poor health by 3 percentage points. Interestingly, for this latter group sharp drop is observed between the first wave and the second wave.

Table 3: Fixed Effects Panel Regression: Self-assessed health for three age-groups of black Africans, 2006 – 2014

VARIABLES	(1) 15-24	(2) 25-49	(3) 50+
ARV access	-0.00650*	-0.0294***	-0.0159
Period = 2	-0.0101***	-0.0448***	-0.0972***
Period = 3	-0.00687**	-0.0406***	-0.0949***
Period = 4	-0.00687**	-0.0408***	-0.101***
Constant	0.0223***	0.0949***	0.209***
Observations	1,324	1,390	1,308
R-squared	0.039	0.199	0.163
Number of Clusters	349	357	344

4. CONCLUSION

These findings follow shortly after ex-President Mbeki's recent letter to the press where he reiterated his AIDS denialism and scepticism, citing StatsSA statistics. In his letter Mbeki writes that "these increases in [the HIV burden] are puzzling given the fact that it is precisely during the period since 2008 that, avowedly, the South African Government engaged in a large scale distribution of anti-retroviral drugs." (Mbeki, 2016). While this is a minority view, we feel that evidence presented here is important because it can help to dispel any remaining doubts about the legacy of ARVs.

This research represents a significant contribution to the literature describing the population health impact of ARVs. We provide national estimates that are based on reported information and not reliant on modelling assumptions or based on surveys covering specific geographic areas. Additionally, the estimates can account for all unobserved time-invariant community-level factors.

Household level survey information on mortality was linked to facility level data on ARV access to examine the population health impact of ARV roll out. ARV access has significantly decreased the likelihood of mortality by 1.6 percentage points for Black Africans aged 25 to 49 and has decreased the likelihood of poor health by 3 percentage points for the same high HIV risk demographic group. As expected, we find a noticeably more pronounced effect of ARV rollout on mortality and poor health amongst the 25 to 49 age group that has the highest HIV prevalence. The impact is much lower amongst the younger and older age groups with lower HIV prevalence.

The reported results are aligned with previous research (Bor et al, 2013; Herbst et al, 2011, Herbst et al, 2009)) that find that ARV access has decreased mortality, expanded life expectancy and has improved lives. Although it covers an earlier time period and is based on data from a surveillance site in Umkhanyakude in KwaZulu-Natal, the estimates of Herbst et al (2009) are viewed as broadly comparable to the results shown here. They report an annual mortality decline of 0.9 percentage amongst adults 25 to 49 cf. our two-year estimates of 1.6 percentage points for Black African adults aged 25 to 49. Black Africans represent the overwhelming share of the district's residents (99% according to the last Census) and therefore these surveillance site estimates would be for a similar demographic group.

One of the limitations of this study is that our empirical work mainly captures the first round and direct effects of ARVs because we use indicators such as mortality and poor health that are associated with the last and most advanced stages of HIV and AIDS that would typically occur 10 to 15 years after infection[7] if left untreated. During our 8-year window we are therefore unlikely to observe ARV treatment's second round and indirect effects via preventing future infections.

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[7] Accoding to the WHO the time between acquiring HIV and an AIDS diagnosis is usually between 10–15 years, but sometimes longer. See http://www.who.int/features/qa/71/en/

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Appendix A: Method used for Deriving ARV Roll out

The aggregate quarterly data on new ARV treatments initiators within the DHIS data was used to best estimate the quarter for which ARV's became available at each facility.

For each facility we attempt to fit the amount of ARV initiators ($Initiators_{it}$), but allowing for allowing for one structural break at a specific period. A maximum likelihood method was adopted to find the set of values for each facility that would minimised the following equation.

$$\min_{\alpha_0, \alpha_1} \sum_{t=2004q1}^{2015q2} [Initiators_{it} - \alpha_0(t > \alpha_1)]^2$$

where α_0 denotes the quarter in which ARV's became readily available and α_1 denotes the average amount of new ARV patients who start treatment every quarter since ARV's have become readily available.

Appendix B: Method used for Matching Data

Matching DHIS to Census

We have GIS coordinates for the facilities within the DHIS data and midpoint coordinates for each enumerator area in Census. The midpoints are used to find the earliest date for which ARVs could have been obtained for individuals who resided within enumerator area.

Matching DHIS to NIDS

The individuals in NIDS were matched to facilities using the GIS coordinates for their place of residence. In our modelling we acquire when ARV's were first available for each individual. The GIS coordinates allowed us to see how far each household was to a health facility that was dispensing ARVs at that period. We played around with three different radius.

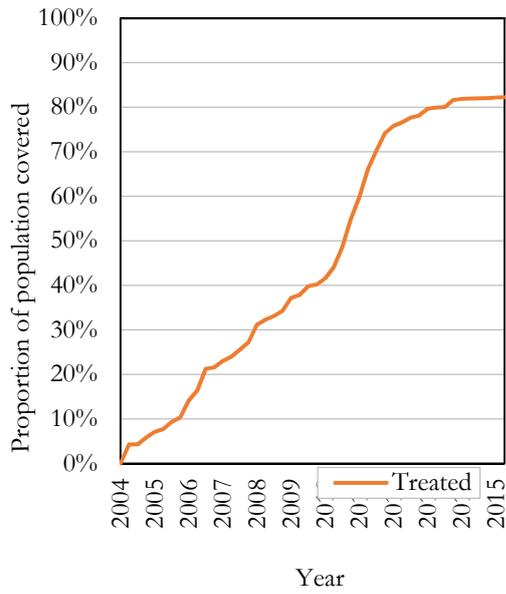## Appendix C: Assessing evidence of ARV roll out
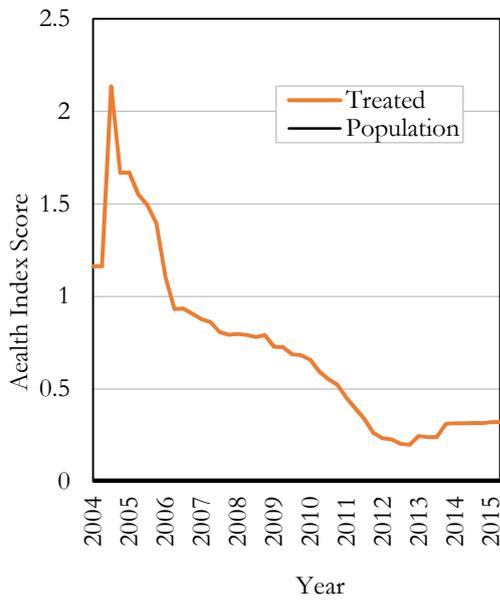

Figure C1: Expansion of ARV coverage from 2004 to 2015
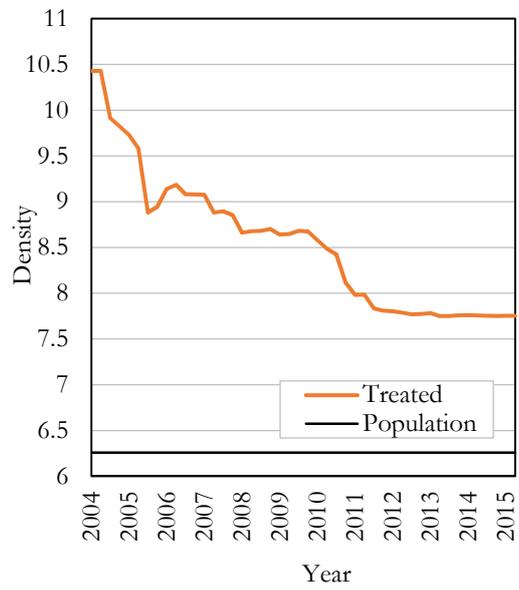

Figure C2: Overall density by Year

Figure C3: Relative Wealth by Year