The Impact of AIDS Treatment on Tuberculosis Detection at the National Level in South Africa

Zoë M. MCLAREN, Alana SHARP, Elizabeth BROUWER, Ananta NANOO

Zoë M. McLaren, PhD [corresponding author]
Affiliation: Department of Health Management and Policy, School of Public Health, University of Michigan, 1415 Washington Heights, M3166, Ann Arbor, MI 48109, USA
Contact information: zmclaren@umich.edu, 734-615-3633

Alana Sharp
Affiliation: Department of Health Management and Policy, School of Public Health, University of Michigan, 1415 Washington Heights, M3166, Ann Arbor, MI 48109, USA

Elizabeth Brouwer, MPH
Affiliation: Department of Global Health, University of Washington, 1510 San Juan Road #310e, Seattle, WA 98195

Ananta Nanoo, MSc
Affiliation: Centre for Tuberculosis, National Institute for Communicable Diseases, 1 Modderfontein Road Sandringham, Johannesburg, South Africa

Abstract

Objective
HIV/TB co-infection is particularly prevalent in South Africa, where TB has been the leading cause of death for over a decade. The 2004-2008 national rollout of ART provides a unique opportunity to examine the population-level impact of ART on the TB epidemic.

Design and Methods
We performed a longitudinal regression analysis that follows the evolution of TB outcomes before and after the introduction of ART using a large data set from the National Health Laboratory Service. This is the first study to produce estimates of the impact of the ART rollout net of confounders by exploiting staggered timing and geographic variation in the rollout.

Results
After ART became available in a health facility, 3·7% (p<0·0001) more patients were tested for TB and 3·2% (p<0·0001) more received follow-up tests, however there was a steep rise in testing just prior to the introduction of ART. Though the number of TB-positive patients increased by 4·3% (p=0·0002) in the first year post-ART, the TB rate among tested patients fell by 2 percentage points (8%, p=0·001) after two years. Sputum smear testing declined relative to more technologically advanced diagnostics post-ART.

Conclusions
ART availability increased attention to TB screening and drew new patients into the health care system. Small increases in the numbers of repeat patients are indicative of retention in care. The decline in TB rates post-ART suggest that the reduction in TB risk due to improved immune functioning and more contact with health care likely outweighed any increased TB risk due to the longer lifespan of ART initiators.
Introduction
The HIV/AIDS epidemic has largely fueled the resurgence of tuberculosis (TB) in Sub-Saharan Africa. The relative risk of TB doubles in the first year after HIV infection and continues to rise as CD4 counts drop [1], reaching rates 20- to 37-fold higher than in those without HIV [2]. Co-infection is particularly prevalent in South Africa, where co-infected patients make up 62% of TB cases compared to the 13% global average [3]. TB has been the leading cause of death in South Africa for over a decade [4], and is the leading cause of death among AIDS patients [2]. In 2010, TB accounted for 11.6% of deaths in South Africa compared to 3.4% for HIV alone and HIV/TB co-infection (9th largest cause of death) [4]. Today, South Africa has the third highest TB incidence rate in the world after Swaziland and Lesotho, with a rate of 860 per 100,000 population compared to the global average of 126 [3].

Because HIV/AIDS drives the TB epidemic, investments in care for HIV/AIDS patients, such as anti-retroviral therapy (ART), are likely to have significant positive spillovers to TB outcomes. The national rollout of ART in South Africa between 2004-2008 provides a unique opportunity to examine the population-level impact of ART on the TB epidemic. During this period over US$1 billion was spent on the rollout, ART was introduced at approximately 400 health facilities, and more than 500,000 patients were enrolled on ART. This program, which dwarfed previous investments in TB care such as TB-DOTS, increased adult life expectancy by 11.3 years [5].

This study estimates the impact of ART on TB, and is only the second study to capture the benefits of ART investment on TB outcomes at the national level[6]. We perform a longitudinal analysis that follows the evolution of TB outcomes for patients in health facilities before and after the introduction of ART in that facility using a large data set from the National Health Laboratory Service, which includes TB test results from almost all public health facilities in South Africa. We examine the impact of ART on TB testing patterns, the TB incidence rate among those tested, and the composition of patients tested.

This is the first study to produce an unbiased estimate the impact of ART on the population by simultaneously applying three methods to account for all the likely measured and unmeasured confounding factors. It is also the second study to capture national-level spillover effects of ART on TB incidence for those who were not accessing ART, including both HIV positive and HIV negative individuals. We (1) exploit the staggered timing and geographic variation in the ART rollout around the country, (2) use facility-level longitudinal data to account for trends prior to the availability of ART, and (3) apply facility-level controls (multi-level analysis) to further purge the estimates of time-invariant facility-level confounders. The staggered timing and geographic variation in ART comes from the National Department of Health (DOH) accreditation process, which required on-site evaluations and was therefore the main bottleneck in determining the pace of the ART roll-out. The accreditation process focused on ensuring the equitable geographic distribution of ART facilities which results in a rollout pattern that was statistically uncorrelated with potential confounding factors in this analysis [7]. For example, aside from a focus on accrediting large hospitals early in the rollout, there was no clear pattern of the rollout systematically favoring or disfavoring areas with wealthier populations, higher HIV prevalence rates, or greater political power [7]. Our methodology should assuage concerns about confounders since potential confounding factors would therefore need to change at the same time as ART becomes available at each facility around the country over a 4 year period in order to bias our estimates.

Understanding the impact of ART on TB is essential to inform the optimal design of new HIV/AIDS and TB policies and determine the necessary level of HIV/TB coordination that will maximize potential spillovers and reduce mortality from both diseases.
Systematic Review and Hypotheses

ART is hypothesized to have multiple effects on TB outcomes – we identify and address five. The local availability of ART will increase the numbers of HIV-infected individuals seeking medical care, especially those at later stages of AIDS, thereby increasing opportunities for diagnosis and treatment of TB (Hypothesis 1) [8-11]. Furthermore, ART implies lifelong clinical involvement, which allows for ongoing TB testing opportunities and improved follow-up care (Hypothesis 2) [12].

Initially, ART access would lead to an increase in the detection of TB cases since during this period nearly 20% of ART initiators in South Africa had undiagnosed TB [13]. Over time, however, ART will reduce incidence of TB in the population by significantly reducing the infection risk among HIV-infected individuals and decreasing transmission (Hypothesis 3) [12,14-18]. The effect of ART on the TB epidemic typically lags the introduction of ART by between 2 and 5 years [6,19].

Reduced TB mortality in co-infected patients and the increase in TB infectiousness that accompanies the immune system recovery of co-infected ART patients may limit, but not likely outweigh, the forces that reduce TB in the population [20,21].

The ART rollout was made possible by approximately USD $1.2 billion in additional funding [22]. These increased health care resources likely led to a greater use of more effective diagnostic tests for TB (i.e. more expensive, resource intensive tests), which improve the accuracy of TB diagnosis and reduce loss to follow-up before treatment initiation (Hypothesis 4) [23].

Finally, the demographic composition of the population tested for TB likely shifted to reflect the composition of ART seekers. Specifically, we expect that the population tested for TB will include more women, since the ART-seeking population in South Africa was approximately 79% female (Hypothesis 5) [24]. The average age of the TB-tested population is expected to fall since the average age of ART seekers is 34 for women and 37 for men [24].

Methods

Sources of data
We extracted data from the NHLS database on every tuberculosis test performed on patients aged 16-64 in public health facilities for the period January 2003- December 2011 that fell within 2.5 years before or after the date of ART availability in each facility. The data include unique patient identifiers created by the NHLS as well as information on the date, type of test performed, test result, testing facility location, and basic patient demographics. The sample for our analysis includes laboratory database records of TB diagnostic tests taken from a total of 10,544,350 unique patients at 4,697 facilities around the country, 429 of which were accredited to provide ART during the study period. We split the data into 3-month periods (quarters of the year) to examine trends over time, and aggregated patient records by facility for each quarter, resulting in 10,039 data points used in the analysis.

TB-positive cases are based on the presence of at least one positive result from smear microscopy, TB culture, PCR test or Xpert MTB/RIF. For smear microscopy, we consider scanty positives of 3 or more acid fast bacilli (AFB) per 100 immersion fields as TB-positive based on the cutoff value used in practice. We exclude 270,573 records (1.02% of the sample) that were missing gender from the gender analysis. Repeat visits were defined as occurring at least one-quarter (91 days) after the initial date a patient was tested for TB. The National Department of
Health provided dates when ART became available at each facility. Ethics approval was obtained from the University of Michigan Institutional Review Board and the University of Cape Town Faculty Ethics in Research Committee in South Africa.

Statistical analysis

We performed the following linear regression to capture the evolution of outcomes for ten quarters (2.5 years) before and after the date when ART became available at the facility:

\[
Y_{it} = \beta_0 + \sum_{t=1}^{10} \delta_{at} + \sum_{t=1}^{10} \gamma_{it} + \alpha_i + \varepsilon_{it},
\]

where \(Y_{it}\) is the TB-related outcome for facility \(i\) in quarter \(t\), \(\beta_0\) is the constant which captures the sample average, \(\sum_{t=1}^{10} \delta_{at}\) is the set of indicator variables that capture the time pattern of outcomes for the ten quarters prior to ART availability and \(\sum_{t=1}^{10} \gamma_{it}\) is the set of indicator variables for the ten quarters after ART. The set of \(\alpha_i\) facility-level fixed effects (facility indicator variables) control for potentially confounding unobserved (unmeasured) time-invariant facility characteristics such as location, size or socioeconomic status of the patient catchment area. Non-ART facilities are included to calculate nationally representative sample averages. Standard errors are clustered by facility.

All analysis was performed in Stata 13.

Results

Hypothesis 1: Widespread availability of ART created the opportunity to bring more HIV-infected individuals into medical care, thereby increasing TB diagnosis and treatment

Statistically significantly more patients were tested for TB 9 months after ART became available in a health facility relative to the date when ART became availability in the facility (x axis Time=0) (Figure 1). Nine months (3 quarters) after ART became available in a facility there was a 3.7% (35 patients, CI 21-50, p<0.0001) increase in the quarterly number of patients tested for TB relative to the rate of 953 patients per quarter at the introduction of ART, and this rate remained steady through the end of the study period. The steep increase in patients tested in the year prior to ART availability is driven mainly by increased TB testing in district hospitals after the rollout began, but before they were accredited to provide ART.

Hypothesis 2: ART implies a longer lifespan and lifelong clinical involvement, which allowed for ongoing TB testing opportunities.

We find a small but statistically significant increase in the number of follow up TB tests, defined as those occurring more than 90 days from the initial testing visit, which is consistent with the ART rollout resulting in somewhat better TB patient retention (Figure 1). TB tests among follow up patients rise by 3.2% (14 patients, CI 8-19, p<0.0001) from the rate of 42 patients per quarter in the first year post-ART.

Hypothesis 3: ART availability lowered incidence of TB by reducing susceptibility in HIV+ population, which led to reduced incidence and transmission in the general population.

As the number of TB patients increased with the availability of ART, there was a concomitant 4.3% increase in the number of TB-positive patients tested per quarter in the first year post-ART.
off the rate of 215 patients per quarter (CI 4-14, p=0.0002) on average, though it declines somewhat in the following year (Figure 2). Figure 3 shows that the TB rate among tested patients is fairly stable within 0.5 percentage points of the facility average of 24% from one year before until 1.5 years after ART becomes available. Subsequently, the TB rate among tested patients declines steadily in the post-ART period, falling to 22% after 2 years (CI 21-23, p=0.001). These patterns are most evident in the sample of new patients, so the effect is not driven by repeat patients.

For TB testing of repeat patients, the steep pre-ART decline in the rate of TB positive tests per patient levels off slightly just after ART is introduced (Figure 3). The estimated TB rate among repeat patients falls by 1 percentage point in the first quarter after ART introduction in an apparent continuation of the pre-period trend, but then stays approximately level until 1.5 years post-ART when it begins to decline again.

_Hypothesis 4: Health care resources associated with the ART rollout led to increased use of higher technology diagnostic tests for TB._

Prior to ART availability, the proportion of patients with at least one sputum smear test rose while the proportion having had at least one culture test fell (Figure 4). However, when ART was introduced, this pattern reversed and the proportion of patients with culture tests rose over time. One year post-ART, 76% of tests were sputum smear (CI 74.5-77.9, p=0.0013), 20.8% were culture (CI 21.4-24.2, p=0.0027). More expensive tests (Xpert MTB/RIF, PCR, and line probe) that may be faster and/or more accurate than smear or culture tests make up the remaining 3.2% of the sample, and also increased in the post-ART period.

_Hypothesis 5: The demographics of the TB tested population more closely resembled the HIV+ population as more patients sought ART enrollment._

The proportion of patients tested for TB that are female exhibited a slight upward trend prior to the availability of ART and leveled off at 52%, however there are no significant differences around the time of ART introduction (Figure 5). The fraction of new patients between the ages of 30-40 increased slightly post-ART, while the fraction between the ages of 20-30 decreased (results not shown). However, the overall average age of new patients remained constant at 38 years.

**Discussion**

Our results are consistent with ART availability increasing attention to TB screening and drawing new patients into the health care system. TB screening remained approximately level for two years after a facility was accredited to provide ART because HIV+ patients continue to have an elevated risk for TB even after ART initiation. The unique methodology exploiting the staggered rollout of ART, accounting for pre-period trends and including facility-level controls ensures that the observed results are driven by the ART rollout rather than potential confounders.

With access to ART, individuals with HIV have a longer lifespan (but still an elevated risk of TB) and are required to visit facilities on a regular basis for follow-up HIV/AIDS care. Small observed increases in the numbers of repeat patients are indicative of this retention in care and likely reflect an increase both in screening for TB and monitoring of TB cases.
The fairly constant TB rate leading up to ART availability suggests that ART-eligible patients were unlikely to have sought care prior to ART availability. Instead, the rise in TB testing may have been due to greater concern about the disease over time. The slow but steady decline in TB rates post-ART demonstrates that the reduction in TB risk due to improved immune functioning and more contact with health care likely outweighed the composite effect of the sicker ART-eligible population accessing health care and any increased TB risk due to the longer lifespan of ART initiators. The declining TB rate among repeat patients (Fig.3) slows after ART becomes available, likely reflecting the reduced TB mortality among those initiating ART. Our finding of declining TB rates among tested patients is consistent with recently published data from South Africa that shows declines in population level incidence of TB associated with ART expansion but occurring with a time lag [6].

Our results contribute to the debate on the impact that policies targeting HIV/AIDS have on the TB epidemic in South Africa [11,17,25,26]. Although other studies have shown that the introduction of ART reduces the TB incidence rate among ART initiators, it also increases their lifetime likelihood of contracting TB and the length of TB infection if contracted [11]. One model estimated that the risk of TB transmission in patients on ART is likely to remain high enough that ART alone is insufficient to control TB [14].

The proportion of patients receiving sputum smear testing reaches its peak at the time ART is introduced to the facility and declines thereafter. More effective and more expensive TB diagnostic technology is indicated for HIV+ patients because of the low sensitivity of sputum smear testing, as well as for repeat patients due to their need for drug resistance and confirmatory testing. The staggered rollout of ART exploited by the methodology ensures that these results are not driven by secular technology improvements or changes in national TB policy or TB clinic guidelines, but by the ART rollout itself.

The fraction of tested patients that is female showed a small but steady increase prior to ART introduction and then leveled off. While South African women are more likely to seek routine health care in general, the modest shift in gender proportions may be due to a relative increase in men eligible for ART [27]. The slight increase in the fraction of TB tested patients between age 31-40 is consistent with the average age of patients who were eligible for ART during the first four years of the ART rollout [28]. This also reflects reduced mortality among ART initiators.

Addressing potential threats to validity

The staggered timing and geographic variation in the ART rollout supports our assumption that, in the absence of ART, trends in TB-related outcomes would have followed the trends observed in the pre-ART period. The staggered rollout of ART also minimizes confounding factors due to one-time changes in other programs targeting TB such as DOTS. To threaten the validity of our results, another program would have to have been introduced in health facilities in a similar staggered pattern as the ART rollout for a substantial portion of approximately 400 health facilities that were accredited to provide ART during this period.

Limitations

The NHLS does not have information on the HIV status or ART enrollment status of all patients tested for TB, so we cannot separate the direct effect of the ART rollout on ART enrollees from the indirect effect on the rest of the population. The rate of under-detection of TB in HIV-positive patients is likely to have fallen in the post-ART period, due to the shift away from sputum smear testing and toward more sensitive TB tests such as culture, especially for ART-eligible patients.
Because our data do not have full coverage of KwaZulu-Natal, which has the highest HIV/AIDS burden, our estimates underestimate the magnitude of the national effect of the ART rollout. The unique methodology we employ is only valid during the early years of the rollout when the ART accreditation process was required. We cannot therefore produce similar unconfounded estimates of the impact of ART on TB outcomes beyond 2011.

Conclusion

Our results demonstrate that the national rollout of ART in South Africa was accompanied by an increase in the demand for TB testing, both from new and repeat (follow-up) patients. We show evidence that, over time, ART reduced TB rates among those tested, despite the fact that post-ART a greater proportion of the tested population would have been late-stage AIDS patients who were at greater risk for TB.

Neither the magnitude of positive spillovers from the 2004-2008 ART rollout to TB rates we show here nor the continued decline in TB incidence relative to increases in ART coverage between 2008-2012 modeled by Nanoo and colleagues appear to be large enough to control TB alone [6]. However, guidelines that recommend early initiation of ART for patients regardless of CD4 counts are likely to improve TB control, especially if there are preventative effects of early ART on TB, which would produce a larger impact on TB rates than during the period of study.

Both HIV/AIDS and TB face similar challenges of ensuring prompt diagnosis, enrolling patients on appropriate treatment, and monitoring for side effects and drug resistance over the long-term. Closer HIV/TB integration is needed to increase demand for TB testing by HIV/AIDS patients and vice versa (such as making follow-up testing for both diseases at once more convenient) and retain patients in care for both diseases. Better integration is also required to design complementary HIV/AIDS and TB policies so as to improve the effectiveness of controlling both diseases with limited resources. HIV/TB integration saves lives. When integrated HIV/TB management and policy design capitalizes on spillovers within the system, it maximizes program impact to prevent TB and reduce mortality from both diseases.
**Acknowledgements:** We thank Sue Candy, Michelle Potgeiter and Andrew Whitelaw for assistance with the data and helpful comments. We thank Jacob Bor, Sean Wasserman, Josh Wilde and two anonymous reviewers for helpful comments. We thank Yubraj Acharya, David Ederer, Kathryn Fischer, Gaurav Khanna, Yi Mao, Alex Russov, Ryoko Sato, Reinhard Schiel, Kristefer Stojanovski, Will Story, Ben Thompson, Samuel Tzou, Jifang Zhou, and Sasha Zhou for research assistance. Financial support was provided by the University of Michigan School of Public Health Global Public Health Program, the Center for Global Health, Rackham School of Graduate Studies, and the University of Michigan Health Management and Policy Department McNerney Award.

**Authors' contributions:** ZM conceived and designed the study which was implemented by AS. ZM, AS, EB and AN interpreted the data and provided important intellectual input. ZM, AS and EB wrote the first draft.

**Declaration of interests:** All authors declare no competing interests.

**Ethics committee approval:** Ethics approval was obtained from the University of Michigan Institutional Review Board and the University of Cape Town Faculty Ethics in Research Committee in South Africa.
References


26 Dodd PJ, Knight GM, Lawn SD, Corbett EL, White RG. Predicting the long-term impact of antiretroviral therapy scale-up on population incidence of tuberculosis. *PLoS One* 2013; **8**:e75466.


**Figure 1**: Number of patients tested for TB during quarters before (δ coefficients from equation 1) and after (γ coefficients from equation 1) ART introduction relative to time=0. Time (quarter) is calculated as quarter of observation minus quarter of ART introduction. Dotted lines indicate facility-clustered, heteroskedasticity-robust 95% confidence intervals. (All TB tests N=10,039, time0=953; Follow up TB tests N=5,098, time0=42; TB tests in hospitals N=5,268, time0=193; TB tests in clinics N=5,220, time0=106).
Figure 2: Number of TB-positive patients tested for TB during quarters before ($\delta$ coefficients from equation 1) and after ($\gamma$ coefficients from equation 1) ART introduction relative to time=0. Time (quarter) is calculated as quarter of observation minus quarter of ART introduction. Dotted lines indicate facility-clustered, heteroskedasticity-robust 95% confidence intervals. (All TB tests N=10,039, time0=215; Follow up TB tests N= 5,098, time0=15).
Figure 3: Proportion of TB-positive patients among patients tested for TB during quarters before ($\delta$ coefficients from equation 1) and after ($\gamma$ coefficients from equation 1) ART introduction relative to time=0. Time (quarter) is calculated as quarter of observation minus quarter of ART introduction. Dotted lines indicate facility-clustered, heteroskedasticity-robust 95% confidence intervals. (All TB tests N=10,039, time0=24%; Follow up TB tests N= 5,098, time0=30%).
Figure 4: Proportion of TB tests performed by sputum smear, culture and PCR among patients tested for TB during quarters before (δ coefficients from equation 1) and after (γ coefficients from equation 1) ART introduction relative to time=0. Time (quarter) is calculated as quarter of observation minus quarter of ART introduction. Dotted lines indicate facility-clustered, heteroskedasticity-robust 95% confidence intervals.
N=10,039. (Sputum smear time0=79%, culture time0=19%, PCR time0=1%)
Figure 5: Proportion of patients tested for TB who were female estimated during quarters before ($\delta$ coefficients from equation 1) and after ($\gamma$ coefficients from equation 1) ART introduction relative to time=0. Time (quarter) is calculated as quarter of observation minus quarter of ART introduction. Dotted lines indicate facility-clustered, heteroskedasticity-robust 95% confidence intervals. (All TB tests $N=10,039$, time0=53%; Follow up TB tests $N=5,098$, time0=50%).