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Antiretroviral Scale-up and Tuberculosis Mortality in High-Burden Countries

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ABSTRACT

Background
Antiretroviral therapy (ART) is thought to reduce mortality from active TB. We investigate the extent to which increasing population coverage with ART in countries with high dual HIV-TB burden predicts reductions in TB mortality.

Methods
We analyzed annual TB mortality rates in 41 countries that the World Health Organization (WHO) defines as high HIV-TB burden, between 1996 and 2011. Mortality outcomes analyzed included, in turn, (1) program-reported TB death notifications – which we adjusted for varying TB case detection rates, and (2) World Health Organization estimates. National coverage with ART, as % of HIV-infected people in need, was obtained from UNAIDS. Panel linear regressions with country fixed effects tested the relationship of TB mortality to ART coverage scale-up, controlling for time-varying HIV prevalence (5-year lagged), coverage of TB interventions, gross domestic product per capita, health spending from domestic sources, and urbanization.

Results
Across multiple model specifications, we consistently observed that increasing ART coverage was followed by reduced TB mortality. Using death notifications and a 2-year lag from ART scale-up to mortality impact, we find that a 1% increase in ART coverage predicted a 0.9% faster decline in TB death rates (p=0.006). Using WHO death estimates as outcome, a 1% increase in ART predicted a 1.1% reduced TB death rate (p<0.001). TB mortality was higher at higher HIV prevalence (p<0.001), but not related to coverage of isoniazid preventive therapy (IPT), cotrimoxazole preventive therapy (CPT), or other covariates.

Conclusion
This econometric analysis finds empirical evidence supporting an impact of ART scale-up on population-level TB mortality.

BACKGROUND

1. HIV is a major risk factor for TB disease and mortality. In high-burden countries, TB may be responsible for more than a fourth of all deaths among HIV-infected individuals.
2. Providing ART has been linked to lower TB mortality among individual patients, and this relationship is assumed in models of TB burden over time.
3. However, the impact of ART on TB mortality at a population level has not been empirically demonstrated.

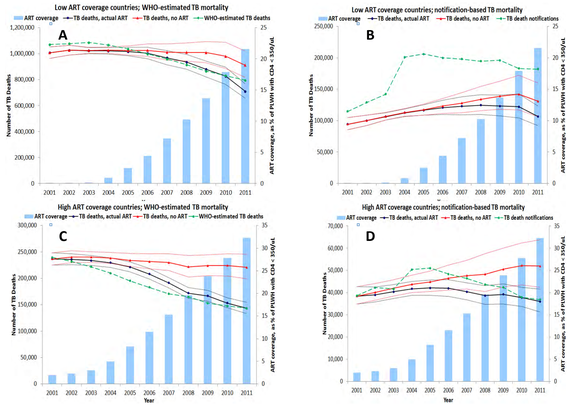
METHODS

1. Overview: We analyze the longitudinal relationship between ART scale-up and deaths from TB between 1996 and 2011 in 37 countries identified as high HIV-TB burden by the World Health Organization.
2. We used two alternative measures of TB deaths: the official (modeled) WHO Stop TB estimates of TB deaths; and our own estimate based on death notifications from each country's National TB Program, which we adjusted for under-reporting using the case-detection rate.
3. We control for improvements in TB control programs using coverage of isoniazid preventive therapy. We also control for HIV prevalence and general measures of health and development such as domestic health spending, GDP per capita, and urbanization.
4. Statistical analysis using fixed-effects panel regressions with variable lag structure to allow for the delay between intervention implementation and any mortality effect.

Relationship of changing ART coverage and other covariates to TB mortality with 2-3 year lag between covariate and TB mortality years of observation. Effect size (and p-value) represents % change in TB mortality with each unit change in the covariate. Results show consistent effect size for ART when using WHO or death notification data.

TB mortality data source	Death notifications		WHO death estimates	
Lag years from ART to TB mortality	2 years	3 years	2 years	3 years
ART coverage (%)	**-0.91 (0.006)**	**-0.88 (0.011)**	**-0.97 (0.000)**	**-0.97 (0.001)**
IPT coverage (%)	-1.79 (0.43)	-1.05 (0.71)	**-3.37 (0.04)**	-1.46 (0.57)
CPT coverage (%)	-0.05 (0.45)	-0.07 (0.34)	-0.05 (0.26)	-0.06 (0.29)
HIV prevalence (%)	4.58 (0.19)	4.35 (0.20)	**5.89 (0.001)**	**5.56 (0.002)**
Urban population (%)	4.17 (0.12)	3.35 (0.20)	-1.98 (0.25)	-3.08 (0.11)
GDP per capita (in 2005 USD, PPP-adjusted, natural log)	-2.90 (0.41)	-3.50 (0.33)	-1.58 (0.95)	-7.76 (0.77)
Health expenditure per capita (in 2005 USD, natural log)	-12.06 (0.28)	-12.69 (0.29)	-11.21 (0.14)	-11.70 (0.20)
Number of countries	37	37	37	37
R-square (within)	23%	21%	67%	64%

Predicted and Counterfactual Estimates of TB Mortality. Each panel shows ART coverage (blue bars), measured TB deaths (green line), predicted TB deaths under the actual ART scale-up (black line), and counterfactual TB deaths with no ART scale-up (zero coverage; red line). Top panels show estimates for 18 countries with low ART coverage; bottom panels for 19 countries with high ART coverage. Left panels use WHO modeled mortality; right panels show mortality estimates using death notifications.



MAIN FINDINGS

1. Regardless of TB death estimation method, we observe a rise in TB deaths from 1996 to 2003 or 2004, and a decline from 2003/4 through the end of the observation period in 2011.
2. Similarly, the decline in mortality from TB that was nearly 1% faster with each 1% increase in ART coverage regardless of TB death estimation method.
3. We estimate a 27% reduction in the number of deaths from TB in 2011 using notifications-based data (143,000 observed vs 197,000 predicted without ART), and a 31% reduction using WHO-based death data (855,000 vs 1.23 million estimated with and without ART, respectively).
4. TB mortality declines were faster and larger in those countries with greater ART scale-up compared with countries with lesser, slower or later ART scale-up. However, TB mortality rises slowed and reversed in all countries with a meaningful ART scale-up.
5. 3. This effect remained stable in multiple sensitivity analyses, for example when expanding the dataset beyond high HIV/TB countries to 92 total low- and middle-income countries, and when limiting the notification-based mortality outcome to smear-positive TB cases only (for which reporting was most reliable).

Limitations

1. WHO estimates of TB mortality partly presuppose the effect of ART on TB mortality.
2. On the other hand, notifications-based death measures may substantially under-estimate true deaths from TB.
3. We could not fully capture the effect of improving TB control programs. The concurrent emphasis on improving TB treatment programs may have contributed to population-level declines in TB deaths. Controlling for IPT coverage as a proxy for TB control program performance did not modify the effect of ART.

CONCLUSIONS

1. We find that increasing ART coverage has contributed to reducing TB mortality within a few years of the onset of ART roll-out.
2. The concordance between WHO-based death estimates and notification-based estimates suggests that the benefits of ART assumed in WHO models may be close to the real benefits that we estimated from national program data.
3. The impact of ART on TB mortality may be instrumental in the observed adult mortality reductions attributed to global HIV/AIDS donors who drove the scale-up or ART, including PEPFAR and the Global Fund.
4. Variations among countries in quality and completeness of TB death notifications and estimates, justify rigorous evaluations of TB mortality trends and its drivers, including the effects of large-scale ART programs, and of strategies to further improve ART effectiveness.
5. Despite these benefits of ART, TB mortality remains high in dual-burden countries, and in these contexts ART could be used as an important intervention for TB control.

ACKNOWLEDGMENTS

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