Title: Antiretroviral therapy is the principal cause of tuberculosis decline in southern and eastern Africa

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Abstract: The incidence of tuberculosis (TB) in southern and eastern Africa was driven sharply upwards during 1980s and 1990s by coinfection with *Mycobacterium tuberculosis* and the human immunodeficiency virus (HIV). Although drug treatments for TB infection (isoniazid preventive therapy) and disease (combinations of TB drugs) can reduce TB incidence if implemented effectively, we find that antiretroviral therapy (ART) for HIV infection was the principal cause of TB decline in 12 of the worst affected African countries between 2003 and 2016. ART prevented up to 1.92 million HIV-positive TB cases, or 17.3 percent of the total number expected. In these 12 countries, over the period 2003-16, ART made the most significant contribution towards achieving international targets for the reduction of TB incidence.

One Sentence Summary: The reduction in TB case incidence in southern and eastern Africa since year 2000 is due mainly to the expanded provision of antiretroviral therapy to people living with HIV, rather than to improvements in the treatment of TB infection and disease.

Main Text: Among people infected with *Mycobacterium tuberculosis*, co-infection with the human immunodeficiency virus (HIV) carries a 10- to 15-fold risk of developing tuberculosis disease (TB) (*1*-*3*). As HIV infection spread through the populations of southern and eastern Africa from the 1980s onwards, the worst affected countries, including Botswana, Lesotho and Swaziland, have reported national adult (15-49 years) HIV prevalence rates over 20% and exceptionally high TB incidence rates above 0.5%/year (Table 1, Figure 1). Across the whole of Africa in 2016, there were an estimated 764,000 new cases of TB among people living with HIV (PLHIV) leading to 320,000 deaths (*4*).

To reduce the incidence of TB in populations with high rates of *M. tuberculosis* and HIV coinfection, the World Health Organization (WHO) and the Joint United Nations Programme on

HIV/AIDS (UNAIDS) recommend primarily drug treatments to prevent TB disease (isoniazid preventive therapy, IPT, acting on *M. tuberculosis* infection, and antiretroviral therapy, ART, acting on HIV infection) and to prevent the further transmission of infection from HIV-positive and HIV-negative patients with TB disease (combinations of TB drugs) (*4, 5*). The efficacy of these treatments has been demonstrated in experimental and observational studies (*6-11*) and they have the potential markedly to reduce incidence nationally if high rates of coverage can be achieved in target populations (*1, 2, 12-14*). In view of these empirical studies and forecasts, the purpose of the present retrospective analysis is to investigate, drawing on data collected annually since 1990, which of these recommended methods have in practice had the greatest impact on TB incidence in twelve African countries that carry high burdens of TB linked to HIV infection (map in supplementary materials).

Figure 1 illustrates for two countries, Botswana and South Africa, the general time course of TB and HIV epidemics and their control measures between 1990 and 2016 (all 12 countries are shown in the supplementary materials). The numbers of TB cases reported each year increased following the rise of HIV incidence and prevalence. The subsequent downturn in TB case incidence in both countries appeared to be associated with improvements in the proportion of TB cases successfully treated (i.e. proportion of cases detected × proportion successfully treated), but more obviously with the expanded coverage of ART. The scale-up of ART coverage from 2003 onwards was more rapid in Botswana than in South Africa (Figure 1), and the decline in TB incidence occurred earlier and more quickly. The provision of IPT, compared with ART for PLHIV and the treatment of TB patients, was very low in both countries (Figure 1).

To examine the effect of control measures systematically across all 12 countries, we begin with the effect of ART on TB incidence. The annual incidence rate of TB among PLHIV in year t can be estimated from $T_t = \alpha H_{t-\tau}(1 - \beta A_{t-\tau})$. In this model α is the per capita rate at which TB cases arise in the untreated population of PLHIV (H) after a delay of τ years (i.e. the incidence of TB disease), which depends on the prevalence and incubation period of *M. tuberculosis* in HIV-positive individuals and on the average age of HIV infection in PLHIV. In the absence of drug treatment of either *M. tuberculosis* or HIV infection, α would change little over the period 2003-16, so we take α to be constant in this analysis. A is the fraction of PLHIV receiving ART, which takes effect after τ years, and coefficient β scales the effect of ART under the hypothesis that ART prevents TB. If ART coverage is measured precisely, and if ART is the sole determinant of TB decline, then β measures the efficacy of ART in preventing TB (a value between 0 and 1). But if ART coverage is underestimated, or if other interventions add to the effect of ART, then β will overestimate ART efficacy (and may exceed 1). This model, and this analysis, do not explore the separate effect of ART on HIV, which is to interrupt viral transmission and to increase population prevalence by greatly improving survival and life expectancy (*15-17*). For each of the 12 countries, T is obtained from routine surveillance data (annual TB case notifications), and from estimates of the proportions of cases detected and infected with HIV (*4*),

and H and A from national estimates derived from national and subnational survey data (*18*) (supplementary materials). Rewriting the model as $T_t/H_{t-\tau} = \alpha - \alpha\beta A_{t-\tau}$, parameters α and β can be estimated from a linear regression of $T_t/H_{t-\tau}$ on A, with intercept α and gradient -$\alpha\beta$. The time delay, τ, is set at 2 years, based on the fit of the regression model to data, and on the recovery rate of CD4 cell count after patients are started on ART (*19*) (supplementary materials). The number of HIV-positive TB cases prevented is obtained by comparing the numbers expected (modelled) under the hypothesis that ART prevents ($\beta > 0$, estimated) or does not prevent ($\beta = 0$, counterfactual) TB.

Between 2003 and 2016, ART coverage was highest on average, and the greatest fractions of HIV-positive TB cases were prevented, in Botswana, Namibia and Rwanda (Table 1; Figure 2, column 4). South Africa prevented the greatest number of TB cases (570,000) between 2003 and 2016, being the country with the largest number of PLHIV (7.1 million in 2016). But South Africa prevented the smallest fraction of cases (12%) because ART coverage was relatively low on average (22%, Table 1).

These measures of ART as the putative cause of TB decline within each country could be confounded by other unmeasured factors that also change with time. However, the causal role of ART becomes clear when the results are compiled for all 12 countries: Figure 3a shows that the estimated fraction of HIV-positive TB cases prevented by ART was strongly associated with the provision of ART ($r^2 = 0.64$, $p < 0.001$). Based on the fit of the model to data for each of the 12 countries (Figure 2, column 4), a total of 1.76 million HIV-positive TB cases were prevented by ART over the period 2003 to 2016, or 15.9 percent of the total number expected. Alternatively, the number of TB cases prevented can be calculated from the systematic, region-wide association with ART coverage (Figure 3a): summing the predictions for each country gives a total of 1.92 million HIV-positive TB cases prevented between 2003 and 2016, or 17.3% of the total expected.

The estimated effect of ART in reducing TB incidence among PLHIV (β) differed among countries, varying from 0.62 (s.d. 0.08) in Uganda to 1.32 (s.d. 0.14) in Lesotho, with an unweighted average among countries of 0.96 (s.d. 0.07) (Table 1). This variation among countries is not surprising given the diversity of surveillance, survey and estimation methods upon which these calculations are based. The average value of β is somewhat higher than estimates of ART efficacy reported from a previous meta-analysis of experimental trials and cohort studies, which calculated efficacy overall as 0.65 (95%CL 0.56-0.72), rising to 0.84 (95%CL 0.64-0.93) for patients with CD4 cell counts less than 200 cells/ml (*8*). The present estimates of β may be higher (and >1 for some countries) because our model assumes that ART coverage is measured precisely (i.e. not underestimated), and that ART is the sole reason for TB decline even though other factors could have contributed, including the treatment of TB infection

and disease. For this reason, our estimates of the number of HIV-positive TB cases prevented should be considered upper bounds; that is, up to 1.92 million HIV-positive TB cases prevented.

Considering the possible role of other interventions, there is little evidence that the treatment of TB directly, either prophylactic drug treatment of *M. tuberculosis* infection (IPT) or the treatment of TB disease with combinations of drugs, contributed substantially to the rapid decline in TB incidence as ART was rolled out in these 12 countries between 2003 and 2016.

First, IPT used continuously with ART generally gives coinfected adults additional protection from TB, augmenting that provided by ART alone (*9-11, 20*). In the 12 countries investigated here, the coverage of IPT among PLHIV over the period 2003-16 was generally low (Table 1). South Africa started the largest number of people on IPT in 2016, 385,932 or 51% of those newly enrolled in HIV/AIDS care in that year. But only 4.2% of PLHIV, on average, received IPT between 2003 and 2016, compared with 22% who started ART. Behind South Africa, 3.1% of PLHIV received IPT in Malawi and 2.9% in Zimbabwe. These three countries together reported 91% of all PLHIV who started IPT in the 12 countries (Table 1). Thus IPT may have protected thousands of coinfected people from developing TB in Malawi, South Africa and Zimbabwe, but the effect on TB incidence at population level would have been relatively small in these three countries, and negligible in the other nine.

Second, the detection of infectious, pulmonary TB cases early in the course of illness, followed by successful drug treatment, should interrupt the transmission of *M. tuberculosis*, thereby reducing TB incidence in the rest of the population, including drug-resistant TB and TB among PLHIV (*3, 12, 14*). Fewer infections would be transmitted from both HIV-positive and HIV-negative TB patients, but especially the latter who are generally responsible for more transmitted infections per capita (*3*). The proportion of patients detected and successfully treated (overall and for HIV-positive TB patients) did improve in the majority of countries between 2003 and 2016 as TB incidence declined, though not in Malawi, Uganda and Zambia (Table 1; Figure 2, column 1). However, in contrast to the effect of ART, there was no association between the change in proportion of TB cases successfully treated and the estimated proportion of TB cases prevented across the 12 countries, either for all TB (Figure 3b, $r^2 = 0.02$, $p > 0.05$) or for HIV-negative TB (supplementary materials). We therefore reject the hypothesis that TB treatment was responsible for the systematic decline of TB across the 12 countries.

Taken together, these results suggest that ART should continue to be a high priority for TB control, as well as for HIV/AIDS prevention and treatment, in southern and eastern Africa. One reason why ART has been relatively effective in preventing TB disease among PLHIV, compared with the TB case detection and treatment, is that the risk to coinfected people of developing TB increases over a period of years (*1-3*). Such a long latent period offers the opportunity to discover coinfected people, coupling HIV testing with ART treatment, before they

progress to infectious disease. On the contrary, to stop transmission from patients with active TB requires rapid diagnosis because pulmonary disease, once established, is immediately infectious.

Our results do not imply that drug treatment of *M. tuberculosis* infection or TB disease could not accelerate TB decline in populations with high rates of *M. tuberculosis* and HIV coinfection, if these interventions can be implemented promptly, widely and continuously. Nor do they imply that the improved treatment of infection and disease had no effect in any country over the period 2003-16. In an analysis of any single country, the effects of TB and HIV drug treatments on TB incidence are potentially confounded, hence our emphasis on cross-country, region-wide effects (Figure 3).

With regard to TB preventive therapy, while millions of PLHIV now receive ART continuously in southern and eastern Africa, a relatively small number also receive IPT (*4, 20*). In this context, South Africa's success in starting more than 350,000 patients on IPT in 2016, over half of those enrolled in HIV/AIDS care in that year, will add wisdom on how to identify candidates for IPT (recognizing that efficacy is greater for those who are tuberculin skin test positive, and that patients with TB disease must be excluded), on how to maintain adherence to prolonged prophylaxis (typically, daily treatment for 6 months), and on how to manage the liver toxicity that affects a small fraction of patients on isoniazid (*21*).

Concerning the detection and treatment of TB patients, the mainstay of TB control worldwide, the most important recent trend in Africa has been a sharp growth in the number of TB patients tested for HIV infection. Across Africa in 2016, 82% of reported TB patients had a documented HIV test result, up from just 2% in 2004 (*4*). Having been tested for HIV, TB patients become eligible for ART, increasing the chance of successful treatment and reducing the risk of death.

But far less progress has been made in finding and treating TB among PLHIV, and among HIV-negative people living in settings with high rates of coinfection. And yet both are imperative for TB control, and ultimately for TB elimination (*3*). To find infectious TB cases earlier among people with and without HIV infection requires a greater awareness of TB and HIV among people at risk, and a more active approach to TB diagnosis at home, in the community and in health facilities (*22-25*).

This analysis has revealed large variations among countries in the estimated fraction of TB cases prevented by ART, linked to differences in ART coverage. The reasons for these differences in coverage need to be understood because they are likely to influence the future success of HIV and TB control programmes. Botswana prevented the largest fraction of TB cases between 2003 and 2016 by achieving the highest coverage of ART. Since independence in 1966, Botswana has invested in public services to tackle ill health and poverty (*26*) and, in that broader context, was the first African country to provide universal free ART (*27*). South Africa prevented the smallest

fraction of TB cases among the 12 countries investigated here. Following controversy over the link between HIV and AIDS, South Africa was slower to expand treatment for PLHIV, but now has the largest number of people on ART and IPT worldwide. More recently, South Africa was the first country in the region to approve pre-exposure prophylaxis (PrEP), in which ART protects HIV-negative people from acquiring infection. Consistent with these recent developments, the rate of TB decline among PLHIV has accelerated to 4.6%/year between 2010 and 2016 (cf 0.5%/year in Table 1).

From a global perspective, TB incidence is falling far too slowly (2%/year) to reach international targets, and TB is still the largest cause of death from a single infectious agent worldwide (*4*). The WHO End TB Strategy aims to cut the TB incidence rate worldwide by 80% between 2015 and 2030 (i.e. 10%/year). Given the slow pace of technological development in TB control ─ including diagnostics, drugs and vaccines (*4*) ─ there is a strong argument for maximizing the effectiveness of all the tools that are currently available. The best strategy for doing so will vary from one setting to another but, for populations suffering high rates of TB-HIV coinfection, ART is evidently a leading intervention.

Acknowledgments:

Funding: none. Author contributions: CD conceived the study, carried out preliminary analysis and drafted the paper. Both authors compiled the data, carried out the full analysis and interpretation, and finalised the text. Competing interests: the authors declare no competing interests.

Supplementary Materials:

Materials and Methods
Figs. S1 to S7
Table S1

Table 1. TB and HIV epidemics, and interventions to reduce TB incidence, in 12 countries of southern and eastern Africa, 2003-16.

Location		TB and HIV burden and trends							Interventions					
Country	Code	HIV prevalence (15-49 yr, max *H*)	HIV prevalence in TB (%, max)	TB incidence (per 100,000 population, max)	HIV+ TB incidence (per 100,000 population, max)	Change HIV+ TB incidence 2003-16 (%/year)	Change HIV-TB incidence 2003-16 (%/year)	Change total TB incidence 2003-16 (%/year)	ART coverage 2003-16 (%PLHIV, *A*)	IPT coverage 2003-16 (%PLHIV)	Increase TB detected and successfully treated 2003-16 (%)	Coefficient β (ART on TB incidence)	HIV+ TB cases prevented by ART (000s)	HIV+ TB cases prevented by ART (%)
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Botswana	BWA	0.24	71	816	579	-8.1	-4.0	-6.9	45	0.51	12.5	0.89	45	31
Kenya	KEN	0.08	51	397	331	-7.6	-1.2	-3.8	28	0.56	6.3	1.07	332	20
Lesotho	LSO	0.24	77	1280	979	-4.1	-2.1	-3.7	23	0.11	10.4	1.32	69	23
Malawi	MWI	0.13	71	397	283	-7.5	-3.1	-5.9	29	3.09	-9.0	0.96	103	19
Namibia	NAM	0.14	59	935	552	-9.0	-2.5	-5.7	35	0.44	30.5	1.14	52	31
Rwanda	RWA	0.04	45	102	46	-5.2	-3.1	-4.7	42	0.01	14.8	0.94	17	29
South Africa	ZAF	0.17	65	977	607	-0.5	-0.1	-0.4	22	4.21	28.2	0.77	570	12
Swaziland	SWZ	0.27	84	1280	973	-6.8	-2.2	-5.8	32	0.17	91.9	1.19	48	28
Tanzania	TZA	0.07	47	510	243	-7.1	-2.7	-4.4	23	0.18	16.9	0.90	165	13
Uganda	UGA	0.08	59	248	146	-4.3	1.0	-1.7	27	0.001	-0.4	0.62	73	12
Zambia	ZMB	0.14	70	662	445	-5.3	-2.7	-4.3	33	0.02	-7.5	0.75	144	19
Zimbabwe	ZWE	0.19	78	617	471	-8.7	-6.0	-7.8	29	2.93	21.1	1.00	141	19

Footnotes (by column number)

1. "United Republic of Tanzania" has been abbreviated.
2. ISO 3166-1 alpha-3 country codes used to label Figure 3.
3. Maximum value of *H*, the prevalence of HIV infection in persons aged 15-49 years, over the period 2003-16 (*18*).
4. Maximum prevalence of HIV infection in new TB cases (%), 2003-16 (*4*).
5. Maximum estimated TB incidence per 100,000 population per year, 2003-16 (*4*).
6. Maximum estimated HIV-positive TB incidence per 100,000 population per year, 2003-16 (*4*).
7. Average annual rate of change in HIV-positive TB incidence rate per 100,000 population (%/year), 2003-16. Negative values represent declining incidence.
8. Average annual rate of change in HIV-negative TB incidence rate per 100,000 population (%/year), 2003-16. Negative values represent declining incidence.
9. Average annual rate of change in all TB incidence rate per 100,000 population (%/year), 2003-16. Negative values represent declining incidence.
10. Average of *A*, ART coverage among PLHIV (%), 2003-16.
11. Average coverage of IPT among PLHIV (total number of PLHIV who start treatment/total number of PLHIV 15-49 years, %), 2003-16.
12. Increase in the number of TB cases detected and successfully treated over the years 2003-16, as a percentage of the number that would have been detected and treated had there been no change since 2002.
13. Estimates of coefficient β under the hypothesis that ART treatment of PLHIV reduces TB incidence.
14. Estimated number ('000s) of HIV-positive TB cases prevented by ART, 2003-16.
15. Estimated percentage of HIV-positive TB cases prevented by ART, 2003-16.

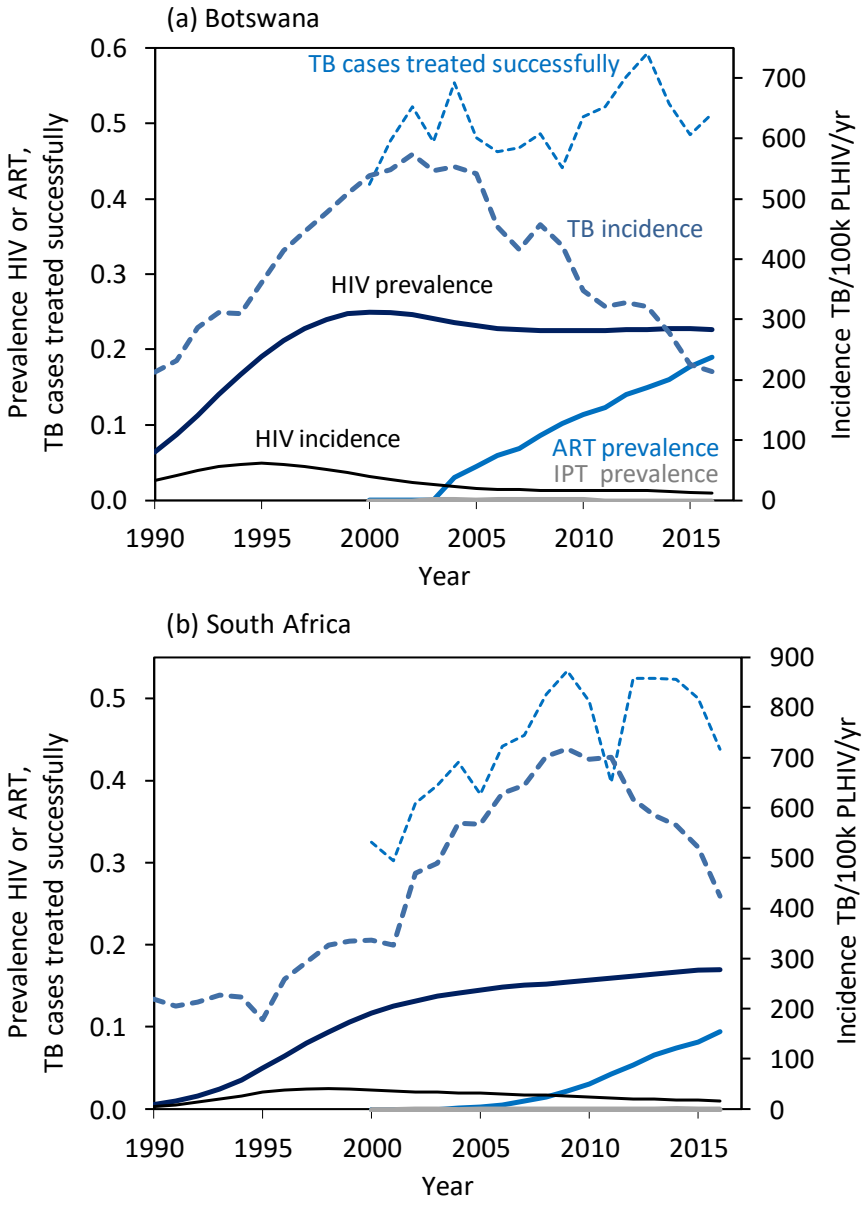
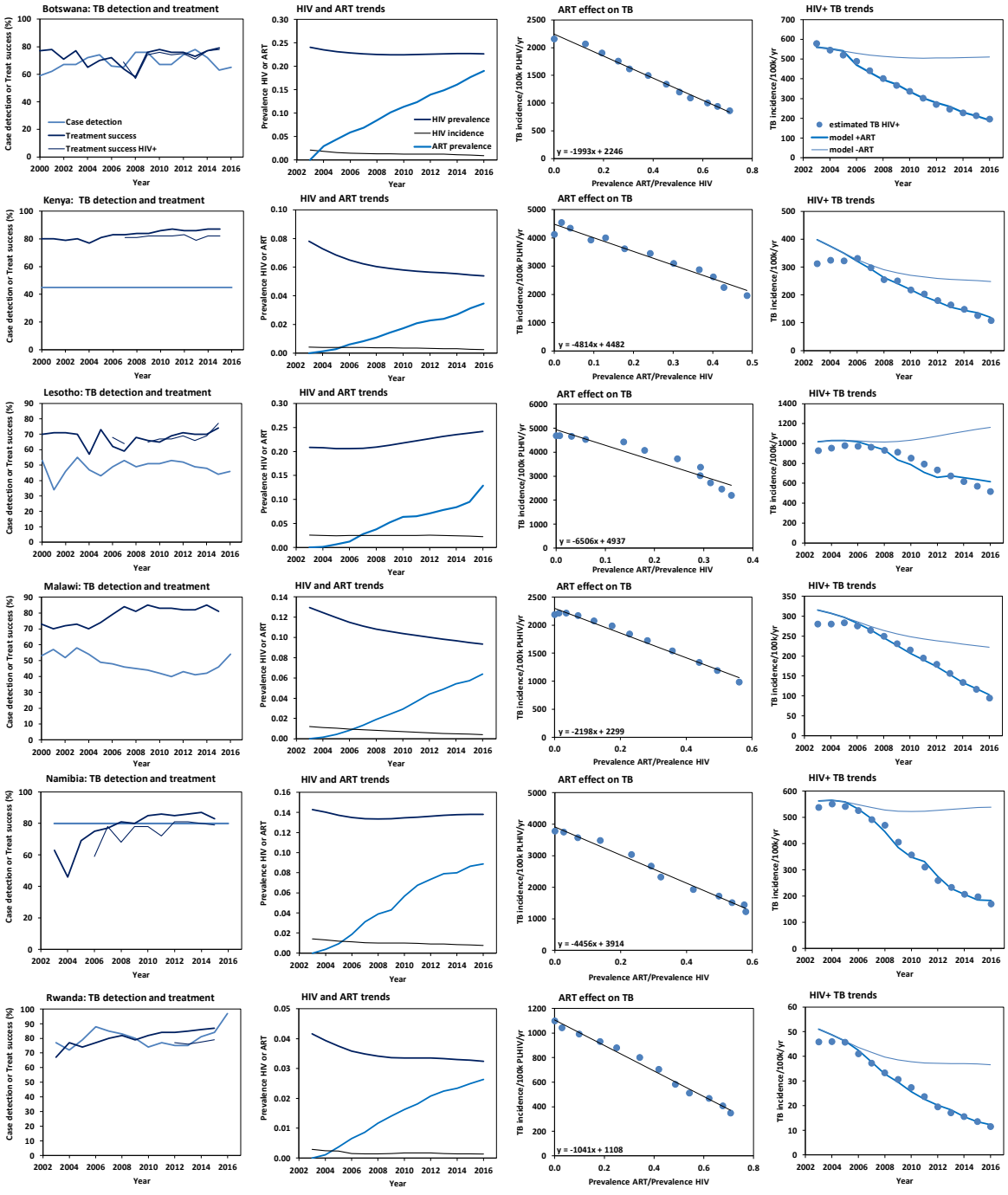


Fig. 1. Time course of TB and HIV epidemics in southern and eastern Africa, 1990-2016, illustrated by (a) Botswana and (b) South Africa. Continuous lines (y-axis left) show trends in estimated HIV incidence and prevalence in adults (15-49 years), and ART and IPT prevalence (coverage in the whole population). Broken lines show the reported TB incidence (y-axis right) and the proportion of cases detected and successfully treated, i.e. the product of proportions of cases detected and successfully treated (y-axis left). Data are from WHO and UNAIDS (*4, 18*).



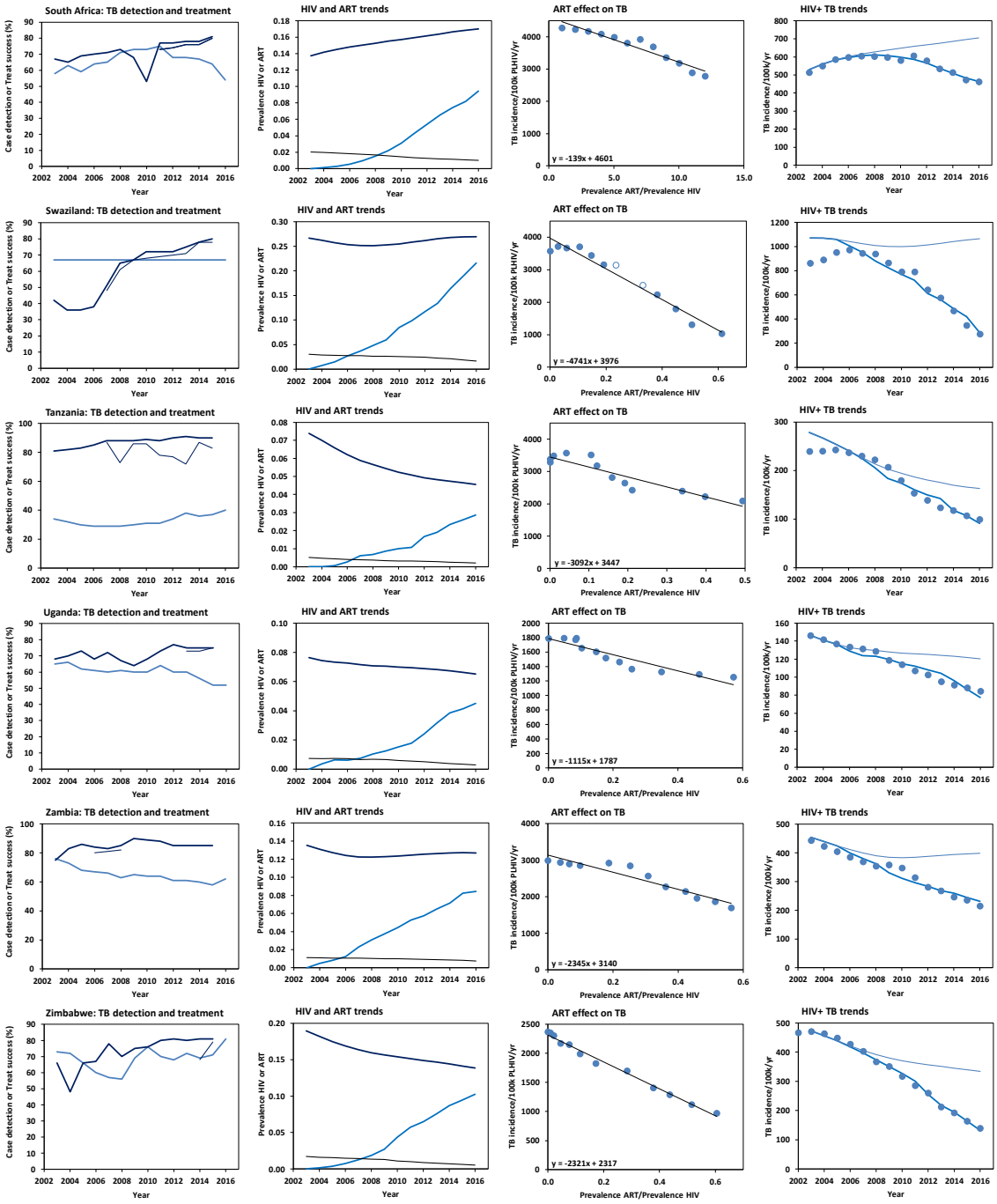


Fig. 2. Time trends in TB case detection and treatment success (column 1), HIV incidence, prevalence and ART coverage (column 2), ART impact on HIV-positive TB incidence (column 3) and trends in HIV-positive TB (column 4) for 12 countries in southern and eastern Africa, 2003-16. Column 1: estimated percentage of cases detected and the measured proportion of cases successfully treated for all forms of TB, and treatment success for HIV-positive TB cases where data are available. Column 2: estimates of HIV incidence and prevalence, and ART prevalence, in the whole population. The ratio of ART/HIV prevalence is the coverage of ART in PLHIV. Column 3: the fit of linear regressions that generate the parameter estimates in Table 1. Column 4: points are the reported incidence of HIV-positive TB cases/100,000 population/year; solid lines represent the fit of the model under the hypothesis that ART prevents ($\beta > 0$, lower lines) or does not prevent TB (counterfactual $\beta = 0$, upper lines).

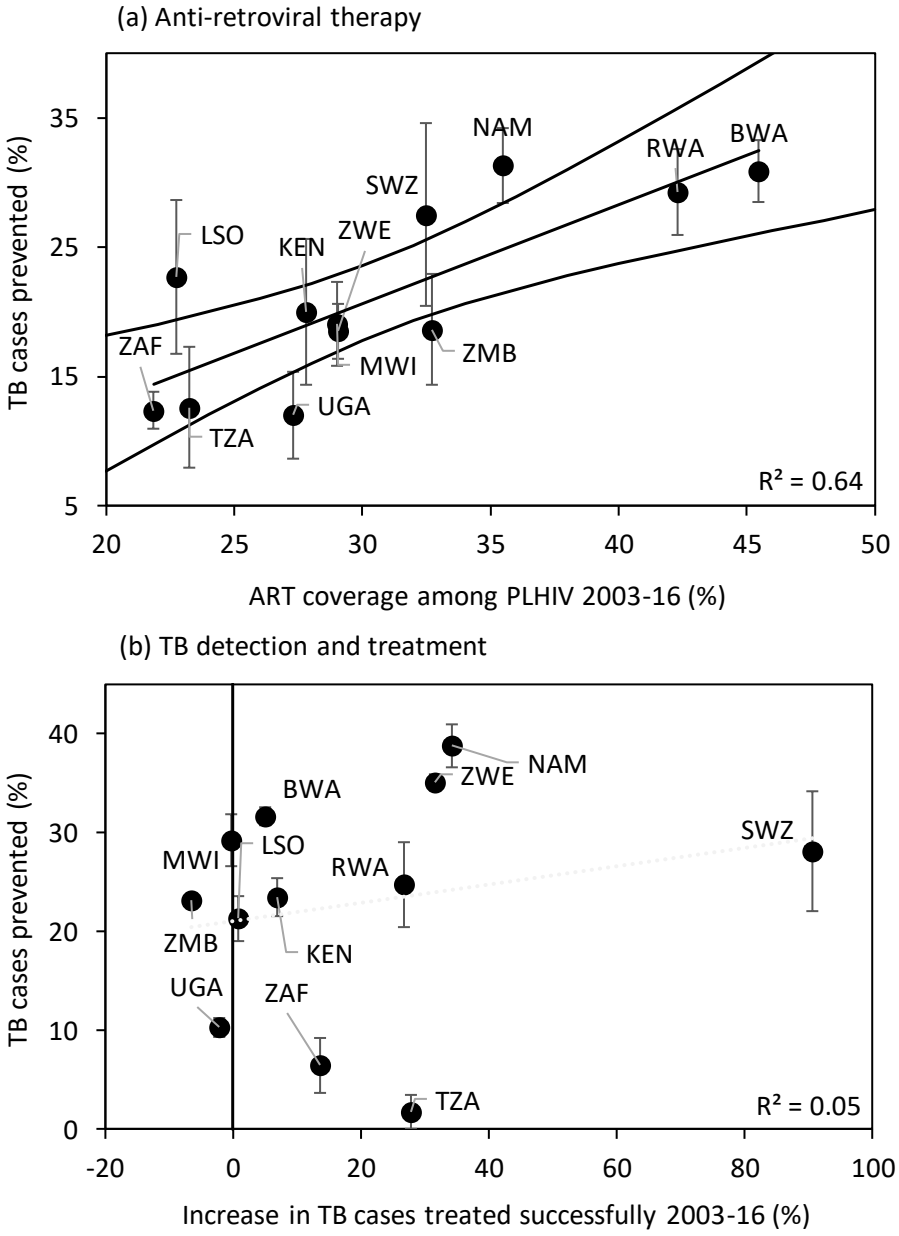


Fig. 3. Effect of interventions to prevent TB in 12 countries of southern and eastern Africa, 2003-16. The graphs show the percentage of TB cases prevented under the hypotheses that (a) ART coverage or (b) TB case detection and successful treatment are causal factors in TB decline. In (a), ART coverage explains 64% of the variation in HIV-positive TB cases prevented ($r^2 = 0.64$, $p < 0.001$). In (b), net changes in case detection and treatment success were negative in Malawi (MWI), Uganda (UGA) and Zambia (ZMB), and the percentage of all TB cases prevented across all 12 countries was not systematically associated with changes in case detection and treatment success ($r^2 = 0.05$, $p > 0.05$). Standard deviations are attached to each point estimate for each country in each panel, and to the regression line in (a). Full country names are listed in Table 1.

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