Antiretroviral Program Associated with Reduction in Untreated Prevalent Tuberculosis in a South African Township

Keren Middelkoop[1,2], Linda-Gail Bekker[1,2], Landon Myer[3,4], Andrew Whitelaw[5,6], Alison Grant[7], Gilla Kaplan[8], James McIntyre[9], and Robin Wood[1,2]

[1]Desmond Tutu HIV Centre, Institute of Infectious Diseases & Molecular Medicine, University of Cape Town, Cape Town, South Africa; [2]Department of Medicine, University of Cape Town, Cape Town, South Africa; [3]Centre for Infectious Diseases Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa; [4]International Centre for AIDS Care and Treatment Programs, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York; [5]National Health Laboratory Service, Cape Town, South Africa; [6]Division of Medical Microbiology, Department of Clinical Laboratory Sciences, University of Cape Town, Cape Town, South Africa; [7]London School of Hygiene and Tropical Medicine, London, United Kingdom; [8]Laboratory of Mycobacterial Immunity and Pathogenesis, the Public Health Research Institute, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; and [9]Anova Health Institute, Johannesburg, South Africa

***Rationale*: In 2005, we reported high prevalence of untreated pulmonary tuberculosis (TB) in a South African community. Prevalent untreated TB is the main source of transmission. In settings with large burdens of human immunodeficiency virus (HIV) and TB, highly active antiretroviral therapy (HAART) may contribute to TB control.**

***Objectives*: To assess the community-level impact of HAART on TB prevalence, we repeated a community-based TB prevalence cross-sectional survey in 2008 following HAART roll-out.**

***Methods*: A random 10% adult population sample was identified from the community. Participants provided two sputum specimens for acid-fast bacilli microscopy and TB culture. Oral transudate specimen was collected for anonymous HIV testing, linked to TB diagnosis. An interviewer-administered, structured questionnaire identified TB and HIV history and risk factors.**

***Measurements and Main Results*: In the 2008 survey, 1,250 adults participated (90% response rate); 306 (25%) tested HIV positive, of which 60 (20%) were receiving HAART. A total of 20 TB cases were identified (12 receiving TB treatment), representing a significant decline in prevalence from 3.2 to 1.6% ($P = 0.02$) between the surveys. TB prevalence in participants not infected with HIV was unchanged ($P = 0.90$). The decline occurred among participants not infected with HIV, decreasing from 9.2 to 3.6% in 2005 to 2008, respectively ($P = 0.003$). In participants infected with HIV, prevalence of treated TB declined from 4 to 2.3% ($P = 0.06$), and untreated TB prevalence from 5.2 to 1.3% ($P = 0.02$). The proportion of untreated TB in patients receiving HAART decreased significantly, from 22 to 0% ($P < 0.001$).**

***Conclusions*: Prevalence of undiagnosed TB declined significantly over a period of increasing HAART availability. The decline was predominantly in individuals infected with HIV receiving HAART.**

Keywords: tuberculosis; prevalence; human immunodeficiency virus; antiretroviral therapy

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Prevalent untreated tuberculosis (TB) is the main source of *Mycobacterium tuberculosis*. However, little data are available on the impact of highly active antiretroviral therapy (HAART) on TB prevalence at a community level.

What This Study Adds to the Field

Our evidence suggests that the significant decline in undiagnosed TB prevalence is associated with the introduction of a rapid and large-scale HAART program, particularly in adults infected with human immunodeficiency virus. This decline is due to the increased case finding in the HAART program, and may also be a result of the impact of HAART-associated immune recovery on the risk of TB.

Tuberculosis (TB) prevalence is the proportion of a population with active TB disease, both treated (diagnosed) and untreated (undiagnosed), at a given point in time. Patients with TB receiving TB chemotherapy are considered to be less infectious (1), and it is this group of patients that is reflected in notification data. Untreated or inadequately treated TB disease, in contrast, is often unrecognized, and is the primary driver of transmission in a population (1–4). Therefore, prevalence of untreated TB is often considered a useful measure of this transmission factor.

One of the Stop TB Partnership targets is to reduce TB prevalence by 50% from 1990 to 2015 (5). The World Health Organization (WHO) has called for national surveys in high burden countries, such as South Africa, to monitor progress toward this target (5). However, evaluating population TB prevalence is logistically challenging, and cross-sectional surveys are costly due to the large sample sizes required, particularly in low-prevalence settings (6). Moreover, surveys require well trained staff and reliable laboratory services (6, 7), and, therefore, few population surveys have been performed in resource-poor settings (8–11). Reported surveys have often been limited to high-risk groups, such as prisoners (12–14), miners (15), or patients infected with human immunodeficiency virus (HIV) (16, 17). Thus, due to the paucity of national data, TB prevalence reported by the WHO for most countries is not measured directly, but is an indirect estimate based on related parameters (18). In the particular example of South Africa, prevalence data has been estimated from TB incidence and trends in TB mortality (5).

(*Received in original form April 16, 2010; accepted in final form June 16, 2010*)

Supported by National Institutes of Health (NIH) CIPRA (Comprehensive Integrated Program of Research on AIDS) grant 1 U19AI053217 (K.M., L.G.B., and R.W), NIH CIPRA grant 1 U19AI05321 and NIH RO1 grant AI058736–02 (R.W. and J.M.) and NIH R01 grant AI54361 (G.K.).

The content of this publication does not necessarily reflect the views or policies of the National Institute of Allergy and Infectious Diseases, nor does mention of trade names, commercial projects, or organizations imply endorsement by the U.S. Government.

Correspondence and requests for reprints should be addressed to Keren Middelkoop, MBChB, P.O. Box 13801 Mowbray 7705, Cape Town, RSA. E-mail: keren.middelkoop@hiv-research.org.za

Am J Respir Crit Care Med Vol 182. pp 1080–1085, 2010
Originally Published in Press as DOI: 10.1164/rccm.201004-0598OC on June 25, 2010
Internet address: www.atsjournals.org

In South Africa, 73% of TB incidence is HIV related (5). Highly active antiretroviral therapy (HAART) has been shown to reduce TB incidence in treatment cohorts (19, 20), and, therefore, wide-scale availability of HAART may play a role in TB control. However, little data are available on the impact of ART on TB prevalence—in particular, undiagnosed TB prevalence, at a community level.

In 2005, before the extensive roll-out of an ART program, we performed a community-based TB prevalence cross-sectional survey in a well defined, peri-urban township in South Africa. The survey reported a 3% overall TB prevalence in this community, and, in particular, a high rate of untreated, laboratory-confirmed pulmonary TB (PTB) among individuals infected with HIV (21). The residents of this community were of predominantly poor socioeconomic status, with high unemployment rates and overcrowded living conditions. The community had a high TB and HIV burden (21, 22), and was serviced by a single primary health care clinic. The clinic managed all patients with TB in accordance with the National TB Control Guidelines (23), which have not changed substantially since 2005. However, since 2005, there has been a significant scale-up of the ART program in this community, with ART coverage among individuals infected with HIV increasing from 5% in 2004 to 13% and 21% of the HIV-infected population in 2005 and 2008, respectively (24).

To assess the impact of a wide-scale HAART program on TB prevalence in this community, we repeated the cross-sectional survey in 2008, measuring both TB disease and HIV infection. Some of the results of these studies have been previously reported in the form of a conference abstract (25).

METHODS

This study was performed from June to December 2008, and the same methodology as the 2005 survey was used (21). A house-to-house enumeration of the community provided a database of 14,592 residents, of whom 1,500 residents 15 years of age or older were randomly selected for study participation (10% of the community).

All participants completed a structured questionnaire investigating participant demographic characteristics, TB history, TB symptoms (cough, night sweats, loss of appetite, and loss of weight), risk factors for TB (including housing, alcohol use, smoking, recreational drug use, prior incarceration, and employment history), and risk factors for HIV (including number of sexual partners and condom use). Questionnaires were interviewer administered in the participants' home language. Two sputum specimens were collected from each participant: an early-morning sputum produced at home, and a second, induced sputum collected at the site with saline nebulization. Both sputum specimens were tested at the same laboratory for acid-fast bacilli (AFB) by microscopy and for *Mycobacterium tuberculosis* (*Mtb*) growth by culture. An oral transudate specimen was collected for anonymous HIV testing, with HIV results linked to TB diagnosis. The study was approved by the Research Ethics Committee of the University of Cape Town, and all participants provided written informed consent.

Laboratory Procedures

Sputum specimen smears were examined for AFBs with an auramine-O stain. Sputum sediments were cultured in the mycobacterial growth indicator tubes automated system (Sparks, MD) and incubated for 6–8 weeks before being reported as negative. Positive cultures were examined for the presence of AFB by Ziehl Neelsen staining, and were identified as *Mtb complex* with a polymerase chain reaction assay. The oral mucosal transudate specimen for HIV testing was collected with the Orasure oral fluid collection device (Orasure Technologies, Bethlehem, PA). The Vironostika Uni-Form II HIV-1 and HIV-2 plus 0 ELISA test (bioMérieux SA, Marcy l'Etoile, France) was used to test for HIV-1 and HIV-2 antibodies.

Case Definitions

Following on the 2005 methodology, participants who reported on the questionnaire that they were currently receiving TB treatment were classified as "treated TB cases." "Untreated TB cases" were defined as participants' without a prior known TB diagnosis, but with laboratory-confirmed infection, as defined by two positive AFB smear results or two positive *Mtb* culture results, or a positive AFB smear result confirmed by a positive *Mtb* culture on separate specimens. All untreated TB cases were referred to the local TB clinic for chemotherapy.

Statistical Analysis

Data were analyzed with STATA 10.0 (StataCorp, College Station, TX).

Bivariate analyses employed Student's *t*, Wilcoxon's rank sum, and Chi-square tests, as appropriate. Multiple logistic regression models were developed to examine changes in overall TB prevalence, as well as treated and untreated TB prevalence between the two surveys, after adjusting for variation in individual participant characteristics. These models were weighted for the proportion of the population sampled in each survey. Median CD4 counts were calculated for the total HAART cohorts in 2005 and 2008, based on each HAART patients' averaged CD4 count recorded in the survey year. Annual median CD4 counts were compared across the two years with Wilcoxon's rank sum test. Case-finding proportion was calculated as the proportion of prevalent cases, overall and by HIV strata, that were reported as treated TB cases. The 95% confidence intervals (CIs) were based on the Poisson distribution, and all statistical tests were two-sided (at $\alpha = 0.05$).

RESULTS

Of the 1,500 residents selected for participation in the 2008 survey, home visits confirmed that 1,383 of these individuals were still resident in the community, and eligible for the study. Of these, 1,250 (90%) consented to enroll in the study, 121 (9%) refused participation and 12 (1%) were not contacted after five home visits. In the initial survey (2005), 762 (78%) of 971 randomly selected, eligible residents were enrolled in the study, with a refusal rate of 15% (21). Demographic characteristics of the two samples are shown in Table 1.

TABLE 1. CHARACTERISTICS OF TWO SURVEY SAMPLES

Characteristics	2005 Survey	2008 Survey
Community size (≥15 yr old), *n*	9,935	11,958
Study sample, *n*	762 (15% refusal)	1,250 (9% refusal)
Demographics		
Median age (IQR), yr	27 (22–35)	27 (22–33)
Male sex, *n* (%)	340 (45)	648 (52)
Median school grade completed (IQR)	10 (8–11)	10 (8–11)
Presently employed, *n* (%)	398 (52)	662 (53)
Median residence, yr (IQR)	5 (3–7)	5 (2–10)
Median residents in household (IQR)	3 (2–5)	3 (2–4)
Median persons sleeping in same Room (IQR)	2 (2–3)	2 (1–3)
Risk factors, *n* (%)		
Ever had TB in past	58 (8)	101 (8)
Alcohol intake in past 6 mo	324 (43)	408 (33)
Visited shebeen (bar) in past 6 mo	180 (24)	261 (21)
Smoked in past 6 mo	205 (27)	289 (23)
Recreational drugs in past 6 mo	29 (4)	54 (4)
Employment History, *n* (%)		
Past mining	43 (6)	44 (4)
Health Care Worker	21 (3)	21 (2)
Prison in the past 6 mo	11 (1)	15 (1)
HIV positive (95% CI)*	174 (23; 20–26%)	306 (25; 22–27%)
HIV positive on HAART (% of HIV infected; 95% CI)	9 (5; 2–10%)	60 (20; 15–25%)

Definition of abbreviations: CI = confidence interval; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; IQR = Interquartile range; TB = tuberculosis.

* In 2005, four participants declined HIV testing, and in 2008, 43 participants declined HIV testing.

TABLE 2. TUBERCULOSIS PREVALENCE SURVEY RESULTS, OVERALL AND BY HUMAN IMMUNODEFICIENCY VIRUS AND ANTIRETROVIRAL THERAPY STATUS, 2005 AND 2008

Tuberculosis Survey	No. at Risk	Total Prevalence % (*n*)	Treated Prevalence % (*n*)	Untreated Prevalence % (*n*)	Case-Finding Proportion (%)
2005					
Total TB cases	762	3.0 (23)	1.5 (11)	1.6 (12)	48
HIV-negative cases	584	1.2 (7)	0.7 (4)	0.5 (3)	57
HIV-positive cases	174	9.2 (16)	4.0 (7)	5.2 (9)	44
HIV-positive no ART	165	7.3 (12)	3.0 (5)	4.2 (7)	42
HIV-positive ART	9	44.4 (4)	22.2 (2)	22.2 (2)	50
2008					
Total TB cases	1250	1.6 (20)	1.0 (12)	0.6 (8)	60
HIV-negative cases	901	1.0 (9)	0.6 (5)	0.4 (4)	56
HIV-positive cases	306	3.6 (11)	2.3 (7)	1.3 (4)	64
HIV-positive no ART	246	2.8 (7)	1.2 (3)	1.6 (4)	43
HIV-positive ART	60	6.7 (4)	6.7 (4)	0.0 (0)	100

Definition of abbreviations: ART = antiretroviral therapy; HIV = human immunodeficiency virus; TB = tuberculosis.

In 2005, overall, 23% (95% CI, 20–26%) of the participants were HIV infected, and four participants (1%) declined HIV testing (21). Of the 174 participants infected with HIV, 5% (95% CI, 2–10%) were receiving HAART. In 2008, 43 participants (3%) declined HIV testing; among those that were tested, 25% (95% CI, 22–27%) were HIV infected ($P = 0.23$), and, of these, 20% (95% CI, 14–23%) were receiving HAART.

Total Study Population TB prevalence

In 2008, 12 participants (1%) reported receiving TB treatment at the time of study participation, and a further eight (0.6%) untreated cases were identified. The prevalence results of the 2005 and 2008 surveys, overall and by HIV strata, are reported in Table 2 and shown in Figure 1. The overall TB prevalence (treated and untreated cases) declined significantly, from 3% in 2005 (21) to 1.6% in 2008 ($P = 0.04$). When adjusted for age, sex, HIV status, as well as demographic and risk profile characteristics that differed between the two surveys, this reduction in prevalence remained significant ($P = 0.05$), as shown in Table 3. The reduction in prevalent treated TB (from 1.5 to 1.0%) was not significant (adjusted $P = 0.34$); however, the reduction in prevalent untreated TB from 1.6 to 0.6% was significant, and remained significant after adjustment as described previously here (crude and adjusted $P = 0.05$) (Table 3).

In 2005, 50% ($n = 6$) of the untreated TB cases had smear-positive PTB (21), whereas, in 2008, 13% ($n = 1$) of the untreated cases had smear-positive PTB ($P = 0.09$).

In 2008, untreated TB was not associated with reported cough ($P = 0.90$), night sweats ($P = 0.35$), loss of appetite ($P = 0.32$), or loss of weight ($P = 0.22$). This was in keeping with the 2005 survey findings (21).

Participants Not Infected with HIV

The total TB prevalence in participants not infected with HIV remained unchanged between surveys (adjusted $P = 0.90$), as did the prevalence of both treated TB (adjusted $P = 0.90$) and untreated TB (adjusted $P = 0.69$) in this group.

Participants Infected with HIV

The total TB prevalence dropped significantly in participants infected with HIV, from 9.2 to 3.6% (adjusted $P = 0.013$). Although the decrease in treated TB prevalence was not significant in this group (4.0% in 2005 versus 2.3% in 2008; $P = 0.22$ after adjustment for age, sex, HAART status, and demographic and risk profile characteristics, as described previously here), the prevalence of untreated TB cases declined significantly, from 5.2% in 2005 to 1.3% in 2008 (adjusted $P = 0.02$). The multivariate logistic models for total TB prevalence and untreated TB prevalence in participants infected with HIV are reported in Table 4.

HAART

The distribution of treated and untreated TB cases by HAART status in patients infected with HIV is shown in Table 2 (2005

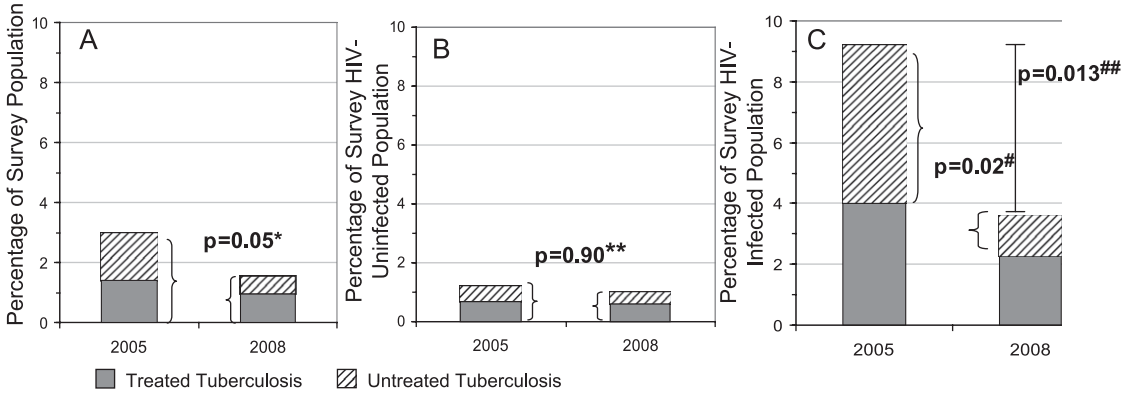

Figure 1. Prevalence of treated and untreated tuberculosis (TB) in the (*A*) total study sample, and in (*B*) human immunodeficiency virus (HIV)–uninfected and (*C*) participants infected with HIV. *Adjusted for age, sex, HIV status, education level, mean residents in household, reported alcohol use, smoking, and history of working in a mine; **adjusted for age, sex, education level, mean residents in household, reported alcohol use, smoking, and history of working in a mine; †comparison of untreated TB in HIV-infected population, adjusted for age, sex, education level, mean residents in household, reported alcohol use, smoking, and history of working in a mine; ††comparison of overall TB in HIV-infected population, adjusted for age, sex, education level, mean residents in household, reported alcohol use, smoking, and history of working in a mine.

TABLE 3. MULTIVARIATE LOGISTIC MODEL FOR OVERALL, TREATED, AND UNTREATED TUBERCULOSIS PREVALENCE IN THE TOTAL STUDY POPULATION

	Total TB Prevalence		Treated TB Prevalence		Untreated TB Prevalence	
	OR (*95% CI*)	*P* Value	OR (*95% CI*)	*P* Value	OR (*95% CI*)	*P* Value
Survey year						
2005	1		1		1	
2008	0.53 (0.28–0.97)	0.05	0.66 (0.28–1.56)	0.34	0.39 (0.15–0.96)	0.05
Age, yr	1.01 (0.97–1.05)	0.61	1.03 (0.97–1.07)	0.19	0.98 (0.91–1.04)	0.48
Sex						
Male	1		1		1	
Female	0.88 (0.40–1.96)	0.75	0.71 (0.25–2.09)	0.52	1.08 (0.31–3.84)	0.90
Education, yr in school	0.99 (0.89–1.11)	0.92	0.90 (0.79–1.02)	0.11	1.26 (0.99–1.60)	0.06
No. of residents in household	1.08 (0.94–1.25)	0.29	1.17 (0.98–1.40)	0.09	1.00 (0.78–1.27)	0.98
Alcohol intake in past 6 mo	0.96 (0.46–1.97)	0.90	0.84 (0.31–2.31)	0.74	1.12 (0.40–3.12)	0.83
Smoked in past 6 mo	2.14 (0.94–4.90)	0.07	2.27 (0.74–6.90)	0.15	1.77 (0.49–6.40)	0.38
Past employment in mines	1.97 (0.62–6.30)	0.25	0.34 (0.04–3.03)	0.34	12.19 (2.48–59.92)	0.002
HIV status						
HIV negative	1		1		1	
HIV positive	6.42 (3.34–12.32)	<0.001	6.14 (2.55–14.80)	<0.001	6.48 (2.43–17.25)	<0.001

Definition of abbreviations: CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; TB = tuberculosis.

and 2008). The proportion of overall and untreated TB cases on HAART decreased significantly from 2005 to 2008 ($P = 0.01$ and $P < 0.001$, respectively). The median CD4 count for the total HAART cohort in this community was 269 (interquartile range, 177–350) in 2005, and 350 (interquartile range, 240–504) in 2008 ($P < 0.001$).

Case-Finding Proportions

As shown in Table 2, the case-finding proportion by the TB clinic in this community increased from 48% in 2005 to 60% in 2008. Case-finding proportions did not change significantly in participants not infected with HIV (57 versus 56%). However, in the HIV-infected population, case finding increased substantially, from 44 to 64%. Case finding increased for patients on HAART, from 50% in 2005 to 100% in 2008.

DISCUSSION

To our knowledge, this is the first repeated cross-sectional prevalence survey following the large-scale availability of HAART in a sub-Saharan Africa community. The study was performed among randomly selected individuals in a well defined community, with HIV and HAART data linked to TB results. The main finding was that the prevalence of PTB in adults declined significantly between 2005 and 2008, and this decline was due to a nearly threefold decrease in TB prevalence in the HIV-infected population(from 9.2 to 3.6%). In the HIV-infected group, the decrease was predominantly due to a fourfold decline in untreated TB. In patients infected with HIV on HAART, TB prevalence dropped from 44 to 6.7%, and the largest decline was also seen in untreated TB cases.

To explain these findings, we postulate that a widespread HAART program can decrease prevalent TB in a community through two mechanisms: increased TB active case finding, and immune recovery associated with HAART.

Increased Case Finding in the HAART program

When patients entered the HAART program, they underwent active screening for TB, based on the National and WHO policy (26, 27). Screening for TB is based on symptom review. In patients with symptoms suggestive of TB, sputum staining for AFB and/or culture for *Mtb* growth is performed. The implementation of this policy is demonstrated by the increased proportion of case finding in the HIV-infected population, from 2005 to 2008, whereas the case-finding proportion in the HIV-uninfected population remained unchanged. This has resulted in a significant decrease in the previously large burden of undiagnosed, untreated TB in patients infected with HIV reported in the first survey. Furthermore, the decrease in untreated, smear-positive TB cases was greater than the decrease in the

TABLE 4. MULTIVARIATE LOGISTIC MODEL FOR OVERALL AND UNTREATED TUBERCULOSIS PREVALENCE IN THE HUMAN IMMUNODEFICIENCY VIRUS–INFECTED STUDY POPULATION

	Total TB prevalence OR (*95% CI*)	*P* Value	Untreated TB prevalence OR (*95% CI*)	*P* Value
Survey year				
2005	1		1	
2008	0.35 (0.15–0.80)	0.01	0.20 (0.07–0.74)	0.02
Age (in years)	1.03 (0.98–1.09)	0.22	1.04 (0.96–1.14)	0.29
Sex				
Male	1		1	
Female	0.93 (0.31–2.83)	0.90	1.40 (0.23–8.45)	0.72
Education, yr in school	1.00 (0.87–1.16)	0.95	1.24 (0.92–1.67)	0.15
No. of residents in household	0.98 (0.79–1.23)	0.86	0.80 (0.55–1.17)	0.25
Alcohol intake in past 6 mo	1.01 (0.41–2.50)	0.99	1.80 (0.50–6.43)	0.37
Smoked in past 6 mo	1.26 (0.40–3.98)	0.70	1.57 (0.28–8.97)	0.61
Past employment in mines	2.81 (0.67–11.76)	0.16	7.44 (1.12–49.58)	0.04

Definition of abbreviations: CI = confidence interval; OR = odds ratio; TB = tuberculosis.

overall untreated TB prevalence, and this finding may suggest that active case finding is removing the more infectious cases (28, 29) from the community. It is therefore possible that part of the decrease in TB prevalence may be due to a reduction in TB transmission. Patients infected with HIV have a more rapid rate of progression to TB disease after recent infection compared with individuals not infected with HIV (30). As a result, any benefit to the HIV-uninfected population accruing from decreased transmission may not be evident in the short interval between these surveys. The impact of active-case finding on TB prevalence is in keeping with results of mathematical models, which have assessed the impact of intervention strategies on population TB rates (31, 32).

Risk of Disease: Immune Recovery on HAART

Active case finding would transfer untreated TB cases into the treated, notified group. However, rates of treated TB did not increase in this population; in contrast, treated TB in participants infected with HIV had declined between the two surveys. This finding may reflect changes in the immune status of the HIV-infected population related to high HAART coverage. It is well documented that HAART, and the subsequent CD4 count recovery, is associated with a substantial reduction in TB risk in patients infected with HIV (19, 33–35). The rapid scale-up of the ARV program in this community (with 20% of the HIV-infected population receiving HAART in 2008) would have resulted in a large treatment cohort, with an increasing mean CD4 count (as found in treatment cohorts in similar settings [36]), and, therefore, a decrease in risk of TB disease in patients infected with HIV. Although the ART cohort had a higher mean CD4 count in 2008 compared with 2005, the median CD4 count in 2008 was still relatively low. Therefore, it is possible that the impact on reduction of TB prevalence will continue to increase with ongoing ART initiation and accumulative immune recovery.

Alternative Explanations for Study Findings

The decrease in TB prevalence in this community is unlikely to be due to changes in the TB control program other than the active case finding in HAART patients, nor to increased population awareness of TB due to the surveys. This is supported by the stable rates of treated and untreated TB in participants who are HIV negative in this study, and furthermore, that overall TB notification rates of participants who are HIV negative have remained constant over the last decade (37). Similarly, TB-associated mortality rates have declined in this community (data not shown), particularly in patients infected with HIV, and, as such, an increase in mortality is not likely to be responsible for the decrease in TB prevalence. Emigration could result in a decreased prevalence of disease, but biennial censuses, performed from 2002 to 2008, show that net immigration is greater than emigration in this growing community, with a 12% increase in population size between the two surveys. Furthermore, the same TB control program laboratory services, with consistent protocols, were used for the microscopy, culture, and differentiation of sputum specimens in both surveys.

It should be noted that the 2008 survey participants had a lower TB risk profile compared with the participants in the 2005 survey. However, after adjusting for these factors, the decrease in both overall TB prevalence as well as untreated TB prevalence in participants infected with HIV between the two surveys remained statistically significant. HIV testing was accepted by 98% of the participants (averaged across both surveys); however, HIV status was available for all TB cases, both treated and untreated. This relatively small community is typical of many recently urbanized populations in South Africa, but there is a need for further investigation to confirm our findings in other high HIV and TB prevalence settings.

Undiagnosed TB prevalence is an important driver of TB transmission (1–4). We have shown a significant decline in adult TB prevalence—in particular, undiagnosed TB prevalence in patients infected with HIV—associated with the introduction of a rapid and large-scale HAART program in this community. This decline appears to be due to the increased case finding in the HAART program, and may also be a result of the impact of HAART-associated immune recovery on TB risk. These findings suggest that large-scale HAART programs may contribute to TB control in high HIV prevalence settings.

Author Disclosure: K.M. received more than $100,001 from the National Institutes of Health (NIH) in sponsored grants for the Comprehensive Integrated Program of Research on AIDS, South Africa (CIPRA-SA); L.-G.B. received more than $100,001 from the NIH in sponsored grants for the CIPRA-SA; L.M. received $10,001–$50,000 from the NIH for various grants (R01, etc.); A.W. received up to $1,000 from Merck, Sharpe, & Dohme in lecture fees for nonpromotional continuing medical education; A.G. received up to $1,000 from the NIH in sponsored grants; G.K. received $10,001–$50,000 from the Celegene Corporation as a board member, and holds more than $100,001 in options accumulated over a number of years from the Celgene Corporation; J.M. received $1,001–$5,000 from Abbott in speakers fees, more than $100,001 from the NIH in sponsored grants for the CIPRA-SA and International Maternal Pediatric Adolescent AIDS Clinical Trials, $10,001–$50,000 from UNITAID as chair of proposal review committee, and up to $1,000 from the World Health Organization as a Prevention of Mother To Child Transmission guideline committee chair; J.M.'s institution received more than $100,001 from the NIH in research grants; R.W. received more than $100,001 from the NIH in sponsored grants (including CIPRA-SA).

Acknowledgment: A.G. was supported by a Public Health Career Scientist Award from the UK Department of Health.

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