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# A prospective study of TB and AIDS stigma as barriers to TB treatment adherence using validated stigma scales

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## SUMMARY

**Background—**Adherence to TB treatment is important for TB control. The effect of stigma on adherence has not been well quantified.

**Objective—**Identify the effects of TB and AIDS stigma on missed doses during TB treatment.

**Design—**Prospective cohort of 459 TB patients. Validated TB and AIDS stigma scales assessing perceived and experienced/felt stigma were administered at TB treatment initiation and after two months. Repeated measures, multivariable models estimated the effects of stigma on the rate of missed doses.

**Results—**Fifty-six percent of patients missed no doses, and associations between stigma and missed doses were minimal. Heterogeneity of effects were observed, however, with higher *experienced and felt TB stigma* increasing missed doses among women (adjusted RR 1.22; 95% CI: 1.10, 1.34) and HIV co-infected patients (aRR 1.39; 95% CI: 1.13, 1.72). *Experienced and felt AIDS stigma* also increased missed doses among HIV co-infected patients (aRR 1.43; 95% CI: 1.31, 1.56).

**Conclusion—**Stigma has a minimal effect in this population with good adherence. Among women and HIV co-infected patients, however, experienced and felt stigma, not perceived stigma, increased the rate of missed doses. Further research is needed to determine if stigma or coping interventions among these sub-groups would improve adherence.

### Keywords

Tuberculosis; Adherence; Stigma

## INTRODUCTION

Adherence to a full course of tuberculosis (TB) treatment is essential for achieving cure and reducing the development of drug resistance[1]. Both default (treatment interruption ≥2 months[2]) and missing any doses of treatment can lead to persistent infectiousness, treatment failure, disease relapse, drug resistance, or death[3, 4]. In a review of qualitative studies, Munro et al.[5] identified general factors affecting adherence to TB treatment: organization of treatment and care; interpretation of illness and wellness; financial burden; knowledge, attitudes, and beliefs about treatment; law and immigration; personal characteristics; drug side effects; and family, community, and household influence. A number of quantitative

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studies confirm these factors to be associated with default specifically[6–9] missing one or more doses total[10], missing >20% of prescribed doses[4], or the proportion of doses ingested[11]. The effect of stigma on missed doses during TB treatment has not been well quantified.

Stigma involves "exclusion, rejection, blame, or devaluation resulting from experience or reasonable anticipation of an adverse social judgment" because of a particular condition[12]. Tuberculosis has historically been stigmatized because of contagiousness, incorrect knowledge of its cause, transmission, or treatment, or its association with marginalized groups[13–18]. AIDS is stigmatized for similar reasons, along with the fear of death and moral judgment of behaviors related to HIV infection[19–21]. More recently TB has been stigmatized due to its association with HIV/AIDS[14, 16, 22], in part because of its increased occurrence among those infected with HIV[23]. Qualitative studies suggest that TB stigma is a risk factor for missed doses because taking medication or going to the clinic to pick up prescriptions may inadvertently disclose a patients' TB disease or cause others to suspect an AIDS[14, 24–26]. AIDS stigma may also lead to missed doses because TB is strongly linked to having AIDS and because HIV co-infected patients may fear disclosure of their HIV status[16, 22, 25].

Only two published studies have quantitatively investigated the association between TB stigma and treatment adherence. Comolet et al. found that defaulters were more likely to believe that TB was a shameful disease[27], while Woith and Larson reported that higher levels of shame were associated with taking a higher proportion of prescribed doses[11]. No published studies have quantitatively assessed the impact of AIDS stigma on missed doses during TB treatment. The purpose of this study was to estimate the effect of TB and AIDS stigma on missed doses during TB treatment among a cohort of patients with TB in southern Thailand using formally developed and validated stigma scales.

## STUDY POPULATION AND METHODS

### Study participants, data collection, and definitions

Data for this analysis come from a larger study to measure TB and AIDS stigma in an area of Thailand with two distinct religious groups (Buddhist majority and Muslim minority), which were hypothesized to differ in levels of stigma[16, 28]. Adults 18 years and older in southern Thailand with TB were consecutively enrolled from a regional TB center and seven TB clinics between August 2005 and July 2006 and followed prospectively through treatment. To avoid confounding of stigma's effects on adherence due to prior TB treatment, patients were only eligible if they had been receiving TB treatment for less than one month and did not have a prior history of TB treatment. Upon enrollment, participants were interviewed to obtain information on demographics, socioeconomic status, TB knowledge, and TB symptoms (See Table 1). Participants were referred for counseling and testing if their HIV status was unknown or if they had tested negative for HIV more than six months prior to enrollment. An HIV test was not required for participation. Cotrimoxazole and antiretroviral treatment were provided to HIV co-infected patients according to Thailand TB/HIV guidelines[29]. Participants received standard TB treatment: two months of daily isoniazid, rifampicin, pyrazinamide, and ethambutol (intensive phase) followed by four months of daily isoniazid and rifampicin (continuation phase). Directly observed therapy (DOT) at the clinic or by a family or community member was recommended in accordance with the National TB treatment guidelines[30]. The DOT decision was made jointly by clinic staff and the patient, and depended on the patient's access to the clinic and availability of family or community members to perform observation.

Stigma was measured at enrollment and after two months of treatment using four scales previously developed in southern Thailand[28]: *Experienced and felt TB stigma* (12 items) assessing the experiences, thoughts and feelings of TB patients (e.g. “Some people who have TB lose friends when they share with them they have TB”; “Some people who have TB feel alone”); *perceived TB stigma* (11 items) assessing the TB patients’ perception of how the community feels about or acts toward people with TB (e.g. “Some people try not to touch others with TB”; “Some people are afraid of those with TB”); and corresponding e*xperienced and felt AIDS stigma* (11 items) and *perceived AIDS stigma* (10 items). Items were scored as strongly disagree (0), disagree (1), agree (2), and strongly agree (3). Internal reliability (Cronbach’s alpha) was high for all four scales, ranging from 0.82 to 0.93. Responses were summed for each scale to create stigma scores, with higher responses indicating higher stigma. All stigma scores were normally distributed.

Pill counts were conducted every time a patient was seen by clinic staff and included the number of pills remaining, number of days a dose was missed, reason for missing doses, and number of doses newly prescribed. Missed doses were the outcome of interest, calculated as the number of days with a missed dose per person-days on treatment, excluding doses missed due to adverse side effects. Among patients who defaulted, missed doses were assigned for each day beginning with their last clinic visit up until the time treatment would have been completed. For all patients, the rate of missed doses was zero if all prescriptions were collected on time and pills were taken each day.

### Longitudinal analysis of missed doses

Missed doses were analyzed as a repeated observation when stigma was re-measured. All patients, regardless of treatment outcome, were included in the analysis. Multivariable, negative binomial regression (SAS 9.2, PROC GENMOD with log link and negative binomial distribution) was used to assess the effect of stigma on missed doses while controlling for measured confounders. A negative binomial model was used to properly account for the large number of participants with zero missed doses. Generalized estimating equations with an exchangeable correlation matrix were specified to account for within subject correlations due to the repeated observations. Separate regression models with time-varying stigma, HIV, and knowledge of TB cause were built for each of the four stigma measures.

Confounders were included in the model based on the literature and substantive knowledge about covariates causally associated with both stigma (TB and AIDS) and treatment adherence (see footnote of Table 2 for covariates in each model). Assignment of DOT may in part have been a result of the patient’s stigma and would not meet the criteria for a confounder because it lies on the causal pathway between stigma and adherence[31]. Modification of the effects of stigma by gender, HIV status, and presenting symptoms were assessed *a priori* based on literature suggesting that stigma may disproportionately affect adherence among women[17] and the hypothesis that stigma may have more of an effect among HIV co-infected patients or those presenting with TB symptoms that may appear similar to AIDS in the absence of cough, such as weight loss, fever, or non-cough symptoms. A homogeneity test p-value $<0.20$ was interpreted as evidence of effect measure modification and stratum-specific effects were reported. P-values $\geq 0.20$ suggest no effect measure modification and therefore stratum-specific results were not necessary. Rather, a single summary estimate was appropriate.

A secondary analysis was performed where defaulters were censored at their last visit to assess the impact of assigning missed doses to defaulters.

### Ethics approval

This study was approved by the Institutional Review Boards of the University of North Carolina, the Prince of Songkla University, and the Thai Ministry of Public Health. Written informed consent was obtained from all participants.

## RESULTS

### Patient characteristics

During the study period, 896 patients with TB were eligible of whom 30% refused participation and 16% could not communicate clearly with interviewers. Of the remaining 480 who were enrolled, 21 (4.4%) were excluded from this analysis because they were determined to not have TB (5), had missing adherence data (3), or were asymptomatic (13), resulting in a final study size of 459. Nearly half (219; 47.7%) were cured, 143 (31.2%) completed treatment, 41 (8.9%) defaulted, 27 (5.9%) died, 12 (2.6%) transferred out, 10 (2.2%) failed treatment, and seven (1.5%) were still on treatment at study completion. Of the defaulters, 35 (85.4%) occurred during the first two months of treatment and 26 (63.4%) missed no doses up to the time of default. Fifty-six percent (n=258) of all patients did not miss any doses during the complete course of treatment or until death or transferring out. The remaining 44% defaulted or missed at least one dose. Among these, the median number of missed doses was two, corresponding to a median rate of 2.2 missed doses per 100 days prescribed. HIV co-infection was reported by 72 (15.7%) patients at baseline with an additional 21 (4.6%) identified after voluntary counseling and testing. Patients who missed doses were younger and reported higher TB stigma, a larger proportion received no DOT, knew TB is caused by infection, and were HIV co-infected (Table 1).

### Longitudinal analysis of stigma and missed doses

In the multivariable analysis among all patients together (no sub-group stratification), there was little evidence that stigma had an effect on missed doses (Table 2, left results column). There was considerable heterogeneity of the rate ratio, however, with higher *experienced and felt TB stigma* associated with increased rates of missed doses among women (aRR 1.22; 95% CI: 1.10, 1.34), HIV co-infected patients (aRR 1.39; 95% CI: 1.13, 1.72), patients who did not know their HIV status (aRR 1.10; 95% CI: 1.02, 1.20), and patients who presented with non-cough symptoms (aRR 1.12; 95% CI: 1.00, 1.26). *Experienced and felt AIDS stigma* was associated with missed doses among HIV co-infected patients (aRR 1.43; 95% CI: 1.31, 1.56).

Compared with the above results where missed doses were assigned to defaulters for the remaining portion of their treatment regimen, the analysis that censored defaulters at the time of default attenuated nearly all the results (Table 2, right results column). The only result that remained consistent between both analyses was the interaction between *perceived TB stigma* and gender (analysis 1: p=0.18; analysis 2: p=0.09), where higher perceived TB stigma among women resulted in higher rates of missed doses.

## DISCUSSION

Overall, the effect of TB and AIDS stigma on missed doses was minimal among patients with TB in southern Thailand. Only among women, HIV co-infected patients, and patients presenting with non-cough symptoms was *experienced and felt TB stigma* associated with higher rates of missed doses. That these associations were observed when controlling for AIDS stigma suggests that TB stigma, particularly actual experiences of TB stigma, may be a barrier among certain groups for reasons other than its link with HIV/AIDS. *Experienced and felt AIDS stigma* also increased the rate of missed doses among patients with HIV co-

infection, possibly due to concerns that taking TB treatment or visiting TB clinics may inadvertently disclose the patients' HIV status. AIDS stigma has been described as a barrier to antiretroviral adherence due to fears of involuntary disclosure[32–34].

These findings that experienced and felt stigma, rather than perceived stigma, were barriers to taking medication suggest that interventions to help patients cope with stigmatizing experiences and feelings of shame or guilt may prove the best intervention to improve adherence. This was studied by Macq et al. using an intervention to reduce internalized (felt) TB stigma[35]. While TB stigma was reduced in the intervention group, overall adherence was very good and no difference in treatment completion or default was found between groups. Such a coping intervention may be most important among HIV co-infected patients, among whom we found that experienced and felt stigma for both TB and AIDS greatly increased the rate of missed doses.

One result that warrants further comment before conclusions can be made is the finding that higher *experienced and felt TB stigma* was associated with missed doses among patients with unknown HIV status. In this study, a patient's HIV status remained unknown if he or she refused HIV testing. It is possible that patients feeling high TB stigma *refused* to be tested for HIV because of stigma. If so, inferences about the effect of TB stigma among this sub-group may be biased because refusing an HIV test may lay on the causal pathway from stigma to missed doses, rather than being effect modifier.

It should be noted that nearly all effects of stigma were attenuated when defaulters were censored. In the absence of an analysis of stigma and default, for which we had insufficient numbers, this could suggest stigma primarily has an effect on default, rather than on missed doses.

Few other studies have prospectively quantified the association between stigma and adherence to TB treatment. In addition to Macq et al.[35], A Russian study found higher feelings of shame were associated with improved adherence, but this study only considered adherence during the continuation phase of treatment and did not report on the HIV status of participants[11].

While our study was prospective and used validated stigma scales, several limitations remained. First, a large proportion of eligible patients refused to participate. This could bias the results if patients refused to participate because of high levels of stigma. Second, adherence measurement is prone to errors due to its reliance on patient recall and bringing remaining pills to the clinic. Third, there were an insufficient number of defaulters to perform a specific analysis of stigma and default. Nevertheless, we felt it was important to include defaulters in this analysis, rather than exclude them, by accounting for the fact that defaulting patients are missing the remainder of their doses. A limitation of this approach, however, is that defaulters who restart shortly after their treatment interruption are misclassified as having missed a large number of doses. Finally, the overall rate of missed doses in the study population was low, which lowered the power to detect small effects of stigma. The subgroup analyses further limited the power to detect small effects.

## CONCLUSIONS

Stigma appears to have a minimal effect on missed doses in this Thai population with both TB and AIDS stigma and good adherence rates. Stigma interventions in this population may not be cost effective for improving adherence. Our findings do, however, add to the growing literature on stigma as a barrier to adherence, particularly among women and HIV co-infected patients where actual experiences and feelings of stigma, rather than perceived stigma, increased the rate of missed doses independent of any effect from AIDS stigma.

Further research is needed in areas with different stigma levels and poorer adherence to determine if stigma or coping interventions among these sub-groups would improve adherence.

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## Table 1

Baseline patient characteristics, by adherence status.

| | | No missed doses (N=258) | Missed doses (N=201) | |
|---|---|---|---|---|
| **Stigma scales** | **Possible range** | **Mean (Std dev)** | **Mean (Std dev)** | **p-value*** |
| Perceived TB stigma | 0 to 33 | 17.99 (4.72) | 18.81 (5.25) | 0.09 |
| Experience/Felt TB stigma | 0 to 36 | 19.40 (4.36) | 20.47 (4.47) | 0.01 |
| Perceived AIDS stigma | 0 to 33 | 18.28 (5.18) | 18.97 (5.25) | 0.16 |
| Experienced/Felt AIDS stigma | 0 to 30 | 19.58 (3.37) | 19.92 (3.82) | 0.31 |
| **Continuous characteristics** | | **Median (Range)** | **Median (Range)** | |
| Age | | | | |
| Age in years | | 38 (18–79) | 34 (18–78) | 0.008 |
| Income | | | | |
| Thousand Baht per month | | 10 (0–90) | 10 (1–60) | 0.76 |
| **Categorical characteristics** | | **N (%)** | **N (%)** | |
| Gender | | | | |
| Male | | 167 (64.7) | 134 (66.7) | 0.66 |
| Female | | 91 (35.3) | 67 (33.3) | |
| Religion | | | | |
| Buddhist | | 173 (67.1) | 129 (64.2) | 0.62 |
| Muslim | | 85 (32.9) | 70 (34.8) | |
| Education | | | | |
| Less than primary school | | 87 (33.7) | 65 (32.3) | 0.59 |
| Completed primary | | 100 (38.8) | 87 (43.3) | |
| Completed secondary | | 71 (27.5) | 49 (24.4) | |
| Directly Observed Therapy | | | | |
| None | | 116 (45.0) | 136 (67.7) | <0.0001 |
| Health care worker | | 65 (25.2) | 19 (9.5) | |
| Family member | | 77 (29.8) | 46 (22.9) | |
| TB Knowledge: Cure | | | | |
| No | | 9 (3.5) | 7 (3.5) | 1.0 |
| Yes | | 249 (96.5) | 194 (96.5) | |
| TB Knowledge: Cause | | | | |
| Infection | | 34 (13.2) | 48 (23.9) | 0.003 |
| Non-infectious cause | | 224 (86.8) | 153 (76.1) | |
| TB Knowledge†: | | | | |
| TB increases chance of AIDS | | 123 (47.7) | 110 (54.7) | 0.13 |
| TB/AIDS | | | | |
| AIDS increases chance of TB | | 188 (72.9) | 145 (72.1) | 0.86 |

| Stigma scales | Possible range | No missed doses (N=258) Mean (Std dev) | Missed doses (N=201) Mean (Std dev) | p-value* |
|---|---|---|---|---|
| TB, AIDS symptoms appear similar | | 178 (69.0) | 146 (72.6) | 0.40 |
| HIV Status‡ | | | | |
| Negative | | 64 (24.8) | 40 (19.9) | 0.07 |
| Positive | | 32 (12.4) | 40 (19.9) | |
| Unknown | | 162 (62.8) | 121 (60.2) | |
| Symptoms§ | | | | |
| Cough | | 134 (51.9) | 101 (50.2) | 0.55 |
| Hemoptysis | | 65 (25.2) | 49 (24.4) | |
| Non-cough | | 59 (22.9) | 51 (25.3) | |

*P-values for t-test, Wilcoxon rank-sum test, and chi-square test, as appropriate

†Responses are not mutually exclusive

‡Self-reported

§Cough and hemoptysis may include other symptoms; non-cough primarily includes weight loss, fever, chest ache/pain, swollen neck, and/or fatigue

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**Table 2**

Adjusted rate ratios for the effect of continuous stigma scores on missed doses during TB treatment using two different techniques for calculating missed doses among treatment defaulters (n=459 with 41 defaulters)[*].

| | | Missed doses assigned to defaulters[†] | | Defaulters censored at last visit[‡] | |
|---|---|---|---|---|---|
| **Stigma scale** | | **aRR[§] (95% CI)** | **Homog. P-value** | **aRR[§] (95% CI)** | **Homog. P-value** |
| Perceived TB stigma | | 1.02 (0.92, 1.12) | | 0.99 (0.90, 1.09) | |
| Experienced/Felt TB stigma | | 1.07 (0.98, 1.17) | | 1.03 (0.93, 1.13) | |
| Perceived AIDS stigma | | 1.01 (0.97, 1.05) | | 1.00 (0.97, 1.04) | |
| Experienced/Felt AIDS stigma | | 1.01 (0.95, 1.08) | | 1.00 (0.95, 1.05) | |
| **Stratified by gender** | | | | | |
| Perceived TB stigma | Male | 0.99 (0.88, 1.11) | 0.18 | 0.96 (0.87, 1.06) | 0.09 |
| | Female | 1.09 (0.99, 1.20) | | 1.06 (0.95, 1.17) | |
| Experienced/Felt TB stigma | Male | 1.03 (0.92, 1.15) | 0.02 | 1.02 (0.91, 1.15) | 0.69 |
| | Female | 1.22 (1.10, 1.34) | | 1.05 (0.94, 1.17) | |
| Perceived AIDS stigma | Male | 1.04 (0.98, 1.10) | 0.03 | 1.01 (0.97, 1.06) | 0.49 |
| | Female | 0.95 (0.90, 1.00)[**] | | 0.99 (0.94, 1.04) | |
| **Stratified by HIV status** | | | | | |
| Experienced/Felt TB stigma | Negative | 0.95 (0.80, 1.12) | 0.01 | 1.08 (0.96, 1.21) | 0.40 |
| | Positive | 1.39 (1.13, 1.72) | | 0.90 (0.70, 1.16) | |
| | Unknown | 1.10 (1.02, 1.20) | | 1.03 (0.93, 1.14) | |
| Experienced/Felt AIDS stigma | Negative | 1.01 (0.93, 1.09) | <0.001 | 1.02 (0.93, 1.11) | 0.81 |
| | Positive | 1.43 (1.31, 1.56) | | 0.99 (0.91, 1.07) | |
| | Unknown | 0.97 (0.86, 1.08) | | 0.98 (0.91, 1.05) | |
| **Stratified by TB symptoms**[††] | | | | | |
| Experienced/Felt TB stigma | Cough | 1.10 (0.96, 1.27) | 0.17 | 1.01 (0.89, 1.14) | 0.31 |
| | Hemoptysis | 0.95 (0.82, 1.09) | | 1.00 (0.88, 1.13) | |
| | Non-cough | 1.12 (1.00, 1.26)[‡‡] | | 1.11 (0.98, 1.24) | |
| Perceived AIDS stigma | Cough | 1.03 (0.96, 1.10) | 0.41 | 0.98 (0.93, 1.02) | <0.01 |
| | Hemoptysis | 0.98 (0.93, 1.05) | | 1.02 (0.95, 1.08) | |
| | Non-cough | 0.97 (0.91, 1.04) | | 1.10 (1.04, 1.17) | |

[*] All models included age, gender, religion, education, income, presenting symptoms, knowledge of the link between TB and AIDS, and HIV status as covariates; TB stigma models also included knowledge of the cause of TB and AIDS stigma.

[†] Analysis included missed doses assigned to defaulters from date of last visit until the time treatment should have been completed

[‡] Analysis included only data collected on missed doses for all patients with defaulters censored at the last recorded visit.

[§] aRR, adjusted rate ratio; CI, confidence interval; Homog. p-value, p-value for homogeneity test of stratum-specific effects ($p<0.20$ considered evidence of effect measure modification). P-values ≥0.20 suggest there is no effect modification and therefore it is unnecessary to report stratum-specific effects

[**] Unrounded upper confidence interval is 0.9977

[††] Cough and hemoptysis may include other symptoms; non-cough primarily includes weight loss, fever, chest ache/pain, swollen neck, and/or fatigue

[‡‡] Unrounded lower confidence interval is 1.0038