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Patterns of Suboptimal Adherence among Adolescents Treated for Drug-Susceptible Tuberculosis in Lima, Peru

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Dear Editor:

During treatment for tuberculosis (TB) disease, adolescents—defined as 10–19 year-olds by the World Health Organization (WHO)—are at high risk of missed doses and loss to follow-up; yet, few studies have characterized TB treatment adherence in this age group.^{1–6} Because most adolescent pulmonary TB is transmissible,^{6–8} poor adherence leads to continued transmission of *Mycobacterium tuberculosis*, in addition to worse patient outcomes. In this retrospective cohort study, we identified patterns and risk factors of suboptimal adherence among adolescents treated for drug-susceptible TB disease in Lima, Peru.

Peru has an estimated TB incidence of 123 per 100,000 population.⁹ Lima, the capital, accounts for 54% of all TB cases.^{9,10} Patients with TB disease present to the government-run health center nearest their home six days a week for directly observed therapy. Each patient has a treatment card, on which basic demographic and clinical data—including all completed and missed doses—are recorded. First-line TB therapy consists of daily isoniazid, rifampin, ethambutol, and pyrazinamide for a two-month intensive phase (50 doses), followed by thrice weekly isoniazid and rifampin for a four-month continuation phase (54 doses).¹¹ Physicians may add doses to either treatment phase for severe disease, slow therapeutic response, and/or poor adherence.

We enrolled patients who (1) had microbiologically confirmed or clinically diagnosed drug-susceptible TB of any anatomical site; (2) initiated a first-line TB regimen between January 1, 2018–December 31, 2018 at a public health center in one of seven high-TB burden districts in Lima; and (3) were 10–19 years-old at treatment initiation. Patients were

excluded if a *M. tuberculosis* isolate obtained prior to or within the first month of therapy was confirmed to be isoniazid- and/or rifampin-resistant.

Between July 2018-August 2019, we identified eligible patients from registries at participating centers. From the treatment cards, we abstracted age; gender; human immunodeficiency virus (HIV) status; previous TB treatments; results of smear microscopy, culture, and drug susceptibility tests; duration of therapy; numbers of missed doses in the intensive and continuation phases; and treatment outcome, defined per WHO guidelines.¹² Missed doses and treatment outcomes were updated between June-August 2019 for all participants still in treatment at initial data abstraction. The institutional review boards of Peru's National Institute of Health and Rhode Island Hospital approved this study and waived informed consent.

We defined suboptimal adherence as missing 10% of doses and/or loss to follow-up. The 10% cutoff is based on an individual patient data meta-analysis that found a six-fold increased hazard of unfavorable outcomes among subjects who missed 10% of doses of first-line TB therapy, compared to subjects with better adherence.¹³ We classified participants as having optimal or suboptimal adherence for the intensive phase, the continuation phase, and overall. We calculated the percentage of missed doses by dividing the number of missed doses by the number of prescribed doses. Because doses may be added to compensate for suboptimal adherence, we conducted sensitivity analyses using alternative percentages, calculated by dividing missed doses over the standard numbers of doses in each phase (50 in the intensive phase and 54 in the continuation phase).¹¹ Adolescents still in treatment at the end of data collection had either missed enough doses that they required extra time to complete the standard 104 doses, or had perfect adherence but were prescribed extra doses due to severe illness. For this small group, we considered the number of missed doses to date.

Using McNemar's test, we compared the percent of adolescents with suboptimal adherence in the intensive phase vs. the continuation phase. Patients lost to follow-up in the intensive phase were considered to have poor adherence in the continuation phase. We used logistic regression to examine the following predictors of suboptimal overall adherence: age, gender, anatomic site of TB, and presence vs. absence of microbiological confirmation. Small numbers precluded consideration of HIV status or previous TB treatment. We included all explanatory variables in the adjusted model. We conducted analyses using R version 3.5.1.

Data were unavailable at two of the 65 health centers in our study area. At the remaining centers, we identified 264 adolescents who initiated first-line TB treatment in 2018. We excluded one adolescent in whom isoniazid resistance was confirmed in the first month of therapy; seven who transferred out of the study area; and seven whose treatment cards could not be located. One adolescent initiated two first-line TB regimens during the study period; we considered only the first.

Of 249 included participants, 157 (63.1%) were male; the median age was 17 (interquartile range: 15–18) years. Three (1.2%) adolescents were HIV co-infected. Six (2.4%) participants received a prior regimen for TB disease before 2018: one was cured in 2012,

four were lost to follow-up or completed therapy with suboptimal adherence between 2016–2018, and no additional information was available for the last. Table 1 further describes the cohort.

Twenty-four (9.6%) participants were prescribed additional doses in the intensive phase; five (2.0%), in the continuation phase; and three (1.2%), in both phases. Of all 249 adolescents, 225 (90.0%) were cured or completed treatment, 14 (5.6%) were lost to follow-up, one (0.4%) died (after eight months of suboptimal adherence), one (0.4%) experienced treatment failure (after four months of perfect adherence), and nine (3.6%) were in treatment at the end of data collection. Forty-nine (19.7%) adolescents missed 10% of prescribed doses. Of these 49 participants, 30 (61.2%) were cured or completed treatment, 12 (24.5%) were lost to follow-up, one (2.0%) died, and six (12.2%) remained in treatment. One HIV-coinfected adolescent died; the other two were successfully treated.

Suboptimal adherence was less frequent in the intensive phase than in the continuation phase (9.1% vs. 22.9%, $p < 0.001$). Altogether, 51 (20.4%) participants—including all three HIV-coinfected participants and three of the six adolescents who received a prior TB regimen—had suboptimal adherence. In logistic regression, only male gender predicted suboptimal adherence (adjusted odds ratio 2.26; 95% confidence interval: 1.13–4.80) (Table 1). In sensitivity analyses, only one participant's adherence status changed; this change did not impact interpretation of the findings.

In this study, we observed that 20% of adolescents on treatment for drug-susceptible TB missed 10% of prescribed doses or were lost to follow-up, rendering them vulnerable to unfavorable outcomes. This high proportion illuminates an urgent need to improve adherence in this age group. Similar to studies in adults and one study in adolescents with TB,^{4,14} we observed worse adherence in the continuation phase and among males. These findings highlight targets for intervention. Psychosocial factors—including parental supervision and adolescent substance abuse—also likely impact adolescent adherence to TB therapy.¹⁵ Further work, including qualitative research, is needed to achieve a more nuanced understanding of this problem in order to optimize solutions.

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Table 1:

Predictors of Suboptimal Adherence among Adolescents Treated with First-Line Therapy for Drug-Susceptible Tuberculosis (N=249)

	Total number	Number (%) with poor adherence	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age				
10–14 years	44	10 (22.7)	Ref	
15–19 years	206	41 (19.9)	0.84 (0.40, 1.93)	0.83 (0.37, 2.02)
Gender				
Female	93	12 (12.9)	Ref	
Male	157	39 (24.8)	2.23 (1.13, 4.69)	2.26 (1.13, 4.80)
Disease site				
Pulmonary	217	43 (19.8)	Ref	
Extrapulmonary or both #	33 #	8 (24.2)	1.29 (0.52, 2.96)	1.83 (0.61, 5.37)
Microbiological confirmation *				
No	81	15 (18.5)	Ref	
Yes	167	35 (21.0)	1.17 (0.60, 2.34)	1.63 (0.73, 4.01)

One participant had both pulmonary and extrapulmonary TB.

* N=247. Two participants did not have either smear or culture results documented; 57 had negative smear results but no documented culture results.