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Adolescent, caregiver and provider perspectives on tuberculosis treatment adherence: a qualitative study from Lima, Peru

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ABSTRACT

Objectives To understand the perspectives of adolescents (10–19 years old), their caregivers and healthcare providers regarding factors that impact adherence to tuberculosis (TB) treatment among adolescents.

Design We conducted in-depth interviews using semistructured interview guides based on the World Health Organization (WHO)'s Five Dimensions of Adherence framework, which conceptualises adherence as being related to the health system, socioeconomic factors, patient, treatment and condition. We applied framework thematic analysis.

Setting Between August 2018 and May 2019, at 32 public health centres operated by the Ministry of Health in Lima, Peru.

Participants We interviewed 34 adolescents who completed or were lost to follow-up from treatment for drug-susceptible pulmonary TB disease in the preceding 12 months; their primary caregiver during treatment; and 15 nurses or nurse technicians who had ≥6 months' experience supervising TB treatment.

Results Participants reported numerous treatment barriers, the most common of which were the inconvenience of health facility-based directly observed therapy (DOT), long treatment duration, adverse treatment events and symptom resolution. The support of adult caregivers was critical for helping adolescents overcome these barriers and carry out the behavioural skills (eg, coping with the large pill burden, managing adverse treatment events and incorporating treatment into daily routines) needed to adhere to treatment.

Conclusion Our findings support a three-pronged approach to improve TB treatment adherence among adolescents: (1) reduce barriers to adherence (eg, home-based or community-based DOT in lieu of facility-based DOT, reducing pill burden and treatment duration when appropriate), (2) teach adolescents the behavioural skills required for treatment adherence and (3) strengthen caregivers' ability to support adolescents.

INTRODUCTION

An estimated 800 000 adolescents, defined by the World Health Organization (WHO) as persons between the ages of 10 and 19

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This qualitative study had a robust sample size (N=83).
⇒ The study includes different perspectives, including adolescent patients with tuberculosis (TB), their caregivers and their healthcare providers; moreover, adolescents with varying degrees of treatment adherence were interviewed.
⇒ A Community Advisory Committee provided input on the interview guides, which were piloted and further modified based on feedback from adolescents who had undergone TB treatment.
⇒ We were unable to contact nearly one-third of eligible adolescents who were lost to follow-up from TB care, and we did not include adolescents whose caregivers did not agree to participate; these adolescents may have experienced greater treatment obstacles, and thus, we may not have captured the most challenging circumstances.

years, become ill with tuberculosis (TB) each year.[1] Adolescents are at risk of suboptimal TB treatment adherence, comprising both missed doses and loss to follow-up.[2–4] An individual patient-data meta-analysis of clinical trials found that missing >10% of prescribed doses of first-line TB therapy—which consists of isoniazid, rifampicin, pyrazinamide and ethambutol—is associated with a nearly sixfold increased risk of unfavourable outcomes, including regimen failure, relapse and death.[5] Regimen failure and relapse also have public health implications, as they increase community transmission of *Mycobacterium tuberculosis*, which is particularly concerning in the context of adolescents' extensive social networks.[6–10]

Various studies have analysed programmatic data to identify predictors of loss to follow-up to drug-susceptible TB therapy among adolescents.[4 11–14] Several risk factors,

including HIV coinfection and prior TB treatment, were observed in multiple settings. Qualitative studies are critical for better understanding of suboptimal adherence and identifying risk factors beyond routinely collected surveillance data. However, few qualitative studies have been published on adolescent TB, and no studies have conducted an in-depth evaluation of adolescent adherence to TB treatment.[15–19] With the goal of informing interventions to improve treatment outcomes in this age group, we conducted a qualitative study to identify facilitators and barriers to adherence among adolescents on first-line TB therapy in Lima, Peru.

METHODS
Study setting
This study took place in Lima, the capital of Peru, and was conducted in partnership with Socios En Salud (SES; the Peruvian branch of Partners In Health). Peru is an upper middle-income country of 33.7 million with an estimated TB incidence of 116 per 100 000 population.[20 21] In Peru, 74% of people with TB disease receive treatment at primary health centres run by the Ministry of Health (MOH).[22] Per MOH guidelines, people on TB treatment receive daily, in-person, directly observed therapy (DOT) under direct supervision by nurses or nurse technicians, the equivalent of licensed vocational nurses, for the entire duration of treatment.[23] Patients must receive DOT at the health centre nearest their home. Transferring care to another health centre is possible, but the patient must obtain a transfer request from the new health centre and submit it to the current facility. The first-line regimen for drug-susceptible TB consists of daily isoniazid, rifampin, ethambutol and pyrazinamide for a 2-month intensive phase, followed by three times a week isoniazid and rifampin for a 4-month continuation phase.[24] Physicians may extend treatment for severe disease, slow therapeutic response and/or suboptimal adherence. All completed and missed doses are recorded on treatment cards. Patients at MOH-run health centres receive free evaluation and treatment of TB[23 25]; however, radiograph machines at MOH facilities often malfunction and providers send patients to private diagnostic imaging centres to obtain chest radiographs, which incur out-of-pocket costs.[26]

Inclusion criteria
Between August 2018 and May 2019, we conducted individual, in-depth interviews with three groups of participants: (1) adolescents 10–19 years old who completed or were lost to follow-up from treatment for drug-susceptible pulmonary TB in the 12 months before study enrolment; (2) the adult identified by each adolescent as their primary caregiver during TB treatment and (3) healthcare providers. We included only adolescents whose caregiver agreed to participate in a separate interview. The pairing of adolescent–caregiver interviews increased the validity of our findings and enriched our understanding

of each case by adding the perspective of the caregiver, who plays a key role in the treatment of adolescents.[19] We divided adolescents into three groups based on treatment adherence: (1) optimal adherence, defined as having completed treatment with ≤20% missed doses, (2) suboptimal adherence, defined as having completed treatment with >20% missed doses, and (3) lost to follow-up, defined as missing ≥2 consecutive months of treatment. The 20% cut-off comes from TB trials that defined >20% missed doses as inadequate adherence.[27 28] We excluded adolescents who received any second-line TB drugs; had extrapulmonary TB; did not have a caregiver who agreed to participate in a separate interview; or for those <18 years old, did not have a parent or legal guardian who could sign informed consent on their behalf. We included healthcare providers who were nurses or nurse technicians and had supervised TB treatment at a MOH facility for ≥6 months.

Sampling and recruitment
We used purposive sampling to maximise variability with respect to adolescent adherence status, age group and health centre where treatment was received. Within each adherence group, we aimed to enrol 10–15 participants to achieve thematic saturation and to include at least three adolescents from three age strata: 10–13 years, 14–16 years and 17–19 years. We also aimed to achieve gender balance among adolescents, but we expected caregivers and providers to consist primarily of women.[16 26]

Study personnel visited 67 health centres to identify eligible adolescents from treatment rosters, beginning with those who most recently received treatment. Healthcare providers, who were not study team members, contacted all consecutive eligible adolescents—or their parent/guardian if they were minors—to obtain permission for study staff to contact them. Study personnel then telephoned or visited potential participants to explain the study and invite them and their caregivers to participate. We directly approached nurses and nurse technicians at their workplace to invite them to participate in an interview. To avoid potential coercion, study personnel explained to healthcare providers that the study was not sponsored by the MOH, their employer, and that the decision to participate would not impact their job.

Data collection
We recorded the age and sex of each participant; adolescents' treatment adherence (optimal, suboptimal or loss to follow-up) and number of doses missed; the relationship of the caregiver to the adolescent; and the health centre where the participant received treatment or worked.

As the theoretical framework for the semistructured interview guides (online supplemental material 1), we used the WHO's Five Dimensions of Adherence, which conceptualises adherence as a multidimensional phenomenon determined by five sets of factors: socioeconomic, therapy related, patient related, condition related

and health system related.[29] The semistructured format allowed interviewers to ask questions out of order or add follow-up questions to elicit clarifying details.

Individual, in-depth interviews were conducted in Spanish by several coauthors with experience in clinical TB research and extensive training in qualitative methods, including interviewing techniques. Interviews with adolescents and caregivers were conducted in participants' homes or SES's offices. Interviews with healthcare providers were conducted at their workplace. Whenever possible, a second interviewer was present to take notes and ask additional clarifying questions, which allowed the primary interviewer to focus on dialoguing with the participant instead of being solely responsible for listening, questioning, observing and taking notes.[30 31] Additionally, the second interviewer, who was present in 41 of 83 (49.4%) interviews, helped probe details that the primary interviewer might have overlooked. Only the interviewer(s) and the participant were present during the interviews, which were 40–60 min long, audio-recorded and transcribed verbatim. Participants received grocery gift cards valued at 45 Peruvian soles, approximately equal to US$13.40, in appreciation for their time.

Patient and public involvement

SES's Community Advisory Committee (CAC), comprised of nine volunteers, ensures that research conducted by the institution aligns with community needs and priorities. The CAC approved this study and provided input on the interview guides. The interview guides were also piloted and refined in response to feedback from the first several participants in each adherence group. The results of our study will be shared with the CAC and the Peruvian MOH.

Data analysis

Using framework thematic analysis, we identified treatment barriers within the Five Dimensions of Adherence and additional themes that emerged from participant narratives. In the first step of the analysis, three coauthors listened to and read 10 interviews to immerse themselves in the content. Next, they created and applied two initial codebooks, one for adolescents/caregivers and one for healthcare providers (online supplemental material 2), to a sample of interviews; compared codes; resolved discrepancies through a consensus and refined the codes. They repeated this process until the codebooks adequately captured the interview content. Then, five coauthors independently applied the final codebooks to all interviews with NVivo V.12 (QSR International, Cambridge, USA). Eight (9.6%) of the interviews were double-coded by two coauthors; we observed ≥90% inter-rater agreement.

Using the coded transcripts, we compared codes within and across adherence groups and checked that circumstances and events were reported consistently within adolescent–caregiver pairs.[32] Through a consensus, we decided on the final themes, developed an explanatory model for adherence, and selected and translated

participant quotes to illustrate the emergent themes. We reported this research according to Consolidated criteria for Reporting Qualitative research guidelines (online supplemental material 3).[33] To protect the anonymity of our participants, adolescents' ages are reported as standardised ranges. We included a reflexivity statement in online supplemental material 4.

RESULTS

Participant characteristics

Figure 1 shows the number of eligible adolescents and caregivers invited to participate and enrolled. Of 16 healthcare providers invited to participate, 1 declined, citing time constraints. We achieved thematic saturation in the optimal and suboptimal adherence groups but not the lost to follow-up group. Despite extensive efforts, we could not enrol additional adolescents and caregivers in the lost to follow-up group. We also achieved thematic saturation in the healthcare provider group.

We analysed 83 interviews with adolescents (n=34), their caregivers (n=34) and healthcare providers (n=15) across 32 different health centres. Fourteen of 34 (41.2%) adolescent participants had optimal adherence, 11 (32.4%) had suboptimal adherence and 9 (26.4%) had been lost to follow-up (table 1). Three of the nine adolescents in the lost to follow-up group had restarted TB treatment by their interview. In these cases, the interview focused on the adolescents' experiences during the prior treatment episode, from which they had been lost to follow-up. We interviewed 10 nurses and 5 nurse technicians; their median age was 41 (IQR: 32–49) years, and 13 (86.7%) were female.

Overview of findings

Adolescents and their caregivers identified similar treatment barriers, whereas healthcare providers had a slightly different perspective (table 2). In the text below, we elaborate on the principal barriers identified by study participants and highlight differences between the adherence groups. In online supplemental material 5, we present the treatment barriers reported by each adolescent–caregiver pair.

Health system-related barriers

The most important health system-related barrier was the requirement of daily, facility-based DOT. Regular DOT hours were limited to mornings and conflicted with school and work. Some adolescents in the optimal adherence group obtained permission to arrive late to school or work to go to DOT in the mornings, but none of the adolescents in the other groups mentioned this arrangement. To accommodate adolescents, healthcare providers occasionally allowed a caregiver to pick up the pills and supervise the adolescent taking treatment at home, even though this practice is not permitted per Peru's current TB guidelines.[24] More commonly, providers allowed adolescents to take their pills after school or work: 'The
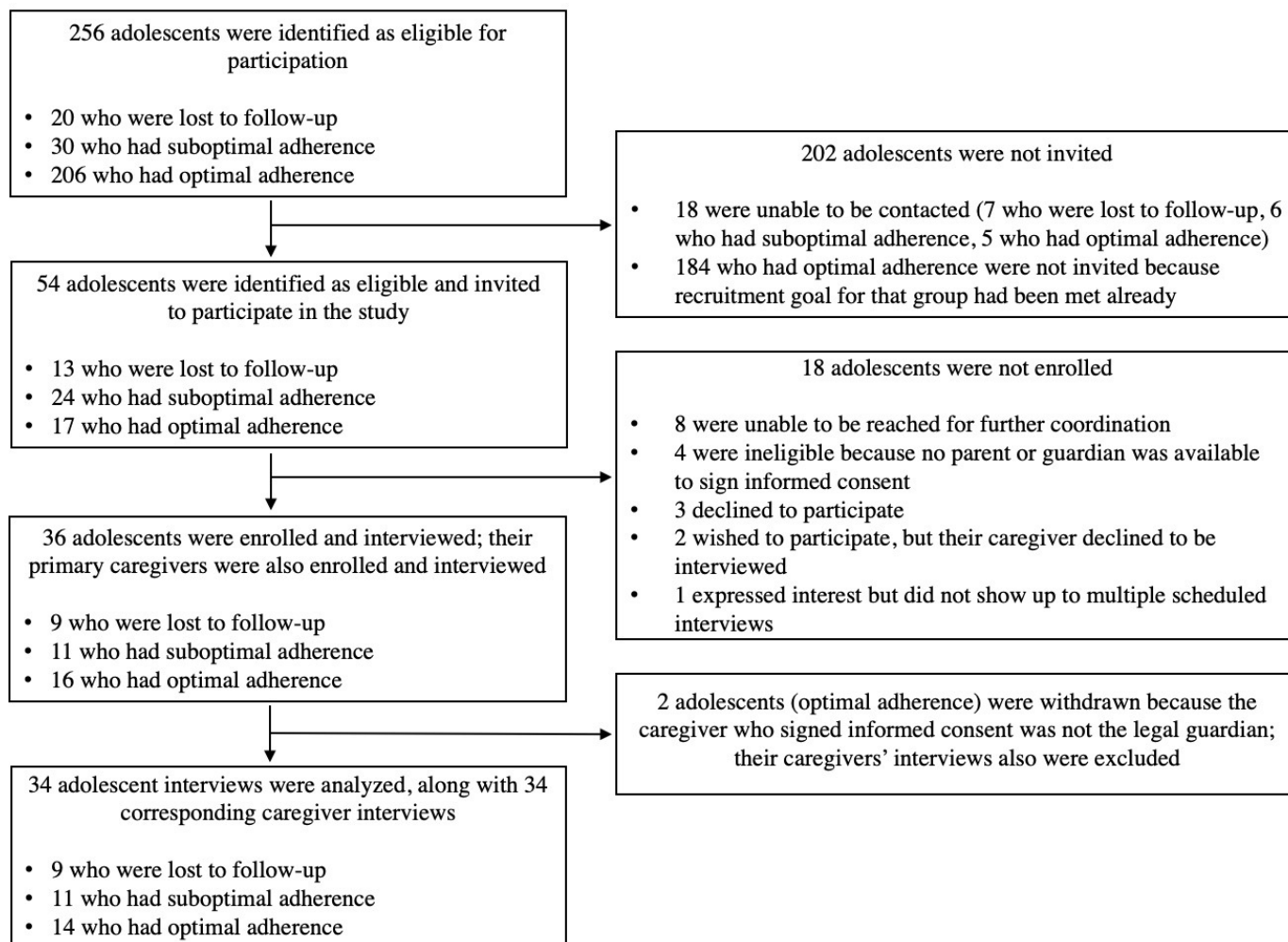
Figure 1 Participant screening, recruitment and enrolment.

main schedule is the morning from 8 to 1, but when there are patients, adolescents in this case, where many of them are still school-aged or studying, we offer them another schedule in the afternoon' (#9, female, nurse). However, two adolescents reported missing multiple doses because when they arrived at the health centre in the afternoon as instructed, no one was available to administer treatment, as providers had other responsibilities at that time (table 2). Additionally, some adolescents were denied medications when they arrived late to DOT without prior notice.

> One time I arrived late. No one was around […]; the assistant had just left for lunch. [I asked], "Doctor, I've arrived a little late. I don't know if I still can [take my pills.]" [She said], "No, I'm not going to give them to you because I'm going to lunch." (#66, 14–16 years, male, suboptimal adherence)

Sometimes, adolescents needed exceptions to facility-based DOT for other reasons, including trips out of town. Healthcare providers accommodated most, but not all, of these requests.

> [W]e went on a trip. It was an emergency […] and we missed like two weeks […] It was a family problem, and I […] asked permission from the [nurse] at the health center […] They gave me pills for only one day because it was not possible to give more, they told me. (mother of #71, 10–13 years, male, suboptimal adherence)

Unless they requested an official transfer to another facility, patients had to receive DOT at the health centre nearest their home. Therefore, travel, relocation, or, in the case of adolescents with divorced/separated parents, staying at the other parent's house were all obstacles to adherence. Four adolescents cited travel or relocation as contributing to loss to follow-up. However, in three of these cases, travel was not the chief reason, and these adolescents did not make any attempts to continue treatment. As one adolescent explained, "I no longer wanted to take my treatment, and, and I stopped it to go to other places" (#32, 17–19 years, male, loss to follow-up). In contrast, the fourth adolescent wanted to support his family financially, so he went to work at a mine in southern Peru. He was told he could transfer his care to another health

Table 1 Characteristics of adolescents and caregivers, stratified by adherence status

	Optimal adherence (n=14)	Suboptimal adherence (n=11)	Loss to follow-up (n=9)*
Characteristics of adolescents			
Age in years, median (IQR)	15.5 (11.2–18.0)	16.0 (14.0–17.5)	17.0 (15.0–19.0)
Male, n (%)	6 (42.9)	7 (63.6)	8 (88.9)
Living with HIV, n (%)	0 (0.0)	2 (18.2)	0 (0.0)
Recurrent TB, n (%)	1 (9.1)	0 (0.0)	0 (0.0)
Missed doses, median (IQR)†	0.5 (0.0–1.8)	33.0 (27.0–44.0)	17.0 (1.0–63.3)
Characteristics of caregivers			
Primary caregiver relationship to adolescent, n (%)			
▶ Mother	13 (92.9)	9 (81.8)	5 (55.6)
▶ Aunt	1 (7.1)	0 (0.0)	2 (22.2)
▶ Older sister	0 (0.0)	2 (18.2)	1 (11.1)
▶ Father	0 (0.0)	0 (0.0)	1 (11.1)
Age of caregiver in years, median (IQR)	41.0 (37.2–44.8)	45.0 (35.5–52.0)	44.0 (38.0–48.0)

*One participant was lost to follow-up twice, and another was lost to follow-up three times. Three of the nine participants had restarted treatment by the time of their interview.
†For those participants who had been lost to follow-up more than once, the number of missed doses refers to the most recent treatment episode from which they were lost to follow-up.
n, sample size; TB, tuberculosis.

centre, but transportation from the mine to the nearest health centre was prohibitively expensive, so he stopped treatment (#42, 14–16 years, male, loss to follow-up). Two adolescents with divorced/separated parents missed doses when they went to stay with their fathers and lacked bus fare back to the health centre near their mothers' homes, which were their primary residences. The mother of one of these adolescents asked to take the pills to her son at his father's home, but 'the [nurse] said no, that wasn't allowed […] They cannot give [pills] to patients to take at home' (mother of #83, 14–16 years, male, loss to follow-up).

Socioeconomic-related barriers
Although most adolescent/caregiver pairs reported household financial challenges, only four said that economic limitations contributed to missed doses or loss to follow-up. Three of these cases are described in table 2: the adolescent who took a job at a mine outside of Lima to help support his family (#42, 14–16 years, male, loss to follow-up) and the two adolescents who went to stay with their fathers and lacked money for bus fare to the health centre near their primary residence (#83, 14–16 years, male, loss to follow-up; #87 17–19 years, male, suboptimal adherence). A fourth adolescent had no money for the chest radiograph required to transition from the intensive phase to the continuation phase of treatment, and this was one of the reasons for loss to follow-up (#54, 17–19 years, female, loss to follow-up). Notably, other adolescents and caregivers in all three groups reported that the health centre helped them with treatment-related expenses.

Patient-related barriers
Facility-based DOT exacerbated patient-related barriers to adherence. First, adolescents in all three adherence groups felt ashamed to be seen at DOT visits. Two adolescents and one-third of healthcare providers cited anticipated TB-related stigma (ie, perception, expectation and/or fear of stigma) as a common barrier to adolescent treatment adherence: 'Sometimes I didn't go to take my pills because I was ashamed, because [people in the neighborhood] know me, that they'll see me, and I didn't go down to take my pills' (#40, 10–13 years, female, suboptimal adherence).

Second, healthcare providers overwhelmingly agreed that emotional support from family members and caregiver supervision of treatment were key to adolescent treatment adherence. 'The adolescent patients with good adherence, well, they are the ones that have the support of their families, of their parents. They bring them to take their pills' (#9, female, nurse). However, facility-based DOT made it more difficult for caregivers to be involved in treatment, as they had to take time off from work or other activities to accompany the adolescent to DOT. Occasionally, providers required caregivers to be present at DOT: 'They wouldn't let him take [the medicine] because I had to be present' (mother of #83, 14–16 years, male, loss to follow-up). Sometimes, caregivers sent adolescents by themselves, but not all adolescents would go on their own. If no other responsible adult was available to accompany the adolescent, caregivers had to choose between working and taking the adolescent to DOT: 'The first day

Table 2 Treatment barriers reported by each participant group

	Adolescents and caregivers	Healthcare providers
Health system related	▶ The most substantial barrier was the requirement of daily, in-person DOT, which was administered during limited hours. This barrier was mitigated by allowing adolescents to access treatment after-hours. However, after-hours DOT was not always reliable. ▶ Adolescents could receive DOT only at the health centre nearest their home. Therefore, adolescents had difficulty accessing treatment when they travelled, relocated, and for those with divorced/separated parents, stayed at the other parent's house. ▶ A few adolescents and caregivers reported disrespectful treatment by health providers. ▶ Very few adolescents complained about long wait times at the health centre.	▶ DOT hours conflicted with school or work; however, healthcare providers allowed adolescents to access treatment after-hours. Unlike adolescents and caregivers, healthcare providers did not report any problems with after-hours DOT.
Socioeconomic related	▶ One adolescent needed to work to support his family, and the best job opportunity for him was located in a rural part of Peru where TB treatment was difficult to access. ▶ Two adolescents with divorced/separated parents missed doses when they went to stay with their fathers and lacked bus fare back to the health centre, which was near their mothers' homes. ▶ TB diagnosis and treatment were free, but sometimes CXR machines at health centres did not work, and families had to pay for CXRs at private facilities. One adolescent did not have enough money for the CXR that is required to transition to the continuation phase of treatment.	▶ Occasionally, adolescents did not have enough money for transportation to the health centre. ▶ Like adolescents and caregivers, providers also reported that TB diagnosis and treatment were free of charge, but sometimes CXR machines at health centres did not work, and adolescents had to pay for CXRs at private facilities.
Patient related	▶ Adolescents often felt ashamed to be seen in the TB treatment area of their neighbourhood health centre. ▶ Some adolescents felt invulnerable to TB and believed that they would be fine regardless of TB treatment adherence. ▶ Adolescents occasionally forgot to go to the health centre for DOT, but forgetfulness was not a major treatment barrier. ▶ Three adolescents missed doses due to fears about TB treatment. One adolescent missed a dose because she skipped breakfast one morning and thought the pills would harm her if she did not eat first. Another adolescent was nearly lost to follow-up because she was pregnant, and family members told her that TB treatment would harm her fetus. The third adolescent missed doses because he feared TB medications were addicting.	▶ Adolescents who were not supervised and supported by their parents or other family members during treatment tended to have worse adherence. ▶ Providers also observed that many adolescents felt ashamed to be seen in the TB treatment area of their neighbourhood health centre. ▶ Some adolescents were described as too 'lazy' or 'unmotivated' to adhere to treatment. A few healthcare providers complained that some adolescents could not manage to show up at the health centre during the designated hours. ▶ Most adolescents and their families were able to be educated about the importance of treatment, though occasionally, adolescents' family members believed that alternative therapies (such as herbs or moving to the mountains) were sufficient to cure TB.
Therapy related	▶ Adolescents had difficulty staying motivated throughout the long treatment. ▶ Adolescents did not like to take so many pills at once. ▶ Adolescents experienced frequent adverse treatment events. For some adolescents, these adverse treatment events were barriers to adherence. ▶ Two of the youngest adolescents were unable to swallow the pills, which had to be crushed by their caregivers.	▶ Providers agreed that adolescents had difficulty staying motivated throughout the long treatment and did not like to take so many pills at once. ▶ According to healthcare providers, adverse treatment events occurred infrequently in adolescents, especially in comparison with older patients.
Condition related, including comorbidities	▶ Once adolescents began feeling better, they became less motivated to adhere strictly to TB treatment. ▶ Comorbidities, specifically depression and substance use disorders, were treatment obstacles for several adolescents.	▶ Multiple factors that occur at the transition from intensive to continuation phase—symptom resolution, treatment fatigue, three times a week (instead of daily) dosing and resumption of normal activities—impeded treatment adherence. ▶ Substance use disorders were mentioned much more frequently by healthcare providers than by adolescents or caregivers.

CXR, chest X-ray; DOT, directly observed therapy; TB, tuberculosis.

that I started missing [work] was because [my son] didn't take his pills' (mother of #24, 14–16 years, male, loss to follow-up). In some instances, caregivers only discovered the adolescent was not going to DOT when healthcare providers contacted them:

> We also have encountered parents who are completely indifferent. They send […] the adolescent, and sometimes the adolescent comes, but sometimes they start to miss [treatment], and the parent doesn't even find out. So, when we go to the home because [the adolescent] is non-adherent, and we go to the house to visit them because the patient isn't coming, and that's when the mom, the dad finds out. (#10, female, nurse)

According to providers, compared with adolescents with suboptimal adherence or those lost to follow-up, adolescents with optimal adherence were more often accompanied to DOT. Among the adolescent participants, all but three with optimal adherence were routinely accompanied by a family member for at least the first several weeks, with half routinely accompanied throughout treatment. Half of the adolescents in the suboptimal adherence group and one-third of those lost to follow-up were regularly accompanied throughout treatment, and the remaining adolescents in these two groups were accompanied for a week or less. Providers explained that caregivers of optimally adherent adolescents were involved in other ways even if they did not accompany adolescents to DOT: 'The parents are always involved […] they come [to DOT], or they call us [to make sure their children come]. That also really influences the patient or the adolescent to take their illness seriously and take treatment' (#10, female, nurse).

Multiple providers cited adverse childhood experiences (ACEs), which are potentially traumatic events that occur in childhood (eg, abuse, neglect and household dysfunction[34]), as barriers to family support and involvement in treatment (#11, female, nurse; #19, female, nurse technician; #26, female, nurse technician; #58, male, nurse technician; #75, female, nurse). ACEs were mentioned most frequently as part of participant narratives about their family background and illness experience by the lost to follow-up group and least frequently by the optimal adherence group. All but two adolescents who were lost to follow-up and half of the adolescents with suboptimal adherence group experienced one or more of the following: parental separation, parental abandonment, incarceration of the adolescent themselves or their father, substance use disorder in a household member, and exposure to or being the victim of domestic violence. In contrast, few adolescents with optimal adherence reported parental separation, one witnessed domestic violence and another's father hit her once for drinking alcohol at a party.

Some adolescents missed doses or stopped treatment altogether—despite understanding the consequences of suboptimal adherence (ie, resistant TB, more severe symptoms, relapse and/or death)—because they believed they were invulnerable to negative disease outcomes and, thus, did not take treatment seriously.

I would stay asleep until 12 [pm], and the health center closes at 2 [pm]. Sometimes I would [get up] early, work on the car, do other things […] I made excuses. One makes one's own excuses to not go […] I took [treatment] lightly. I thought that I was going to recover. (#44, 17–19 years, male, loss to follow-up)

Providers again emphasised the importance of caregiver supervision to ensure adherence since some adolescents have a difficult time believing that they are ill.

Adolescents […] they don't really believe that they are sick. They don't place importance on treatment, most of all between the ages of 16 and 17. They think it's a joke. Sometimes, um, we have problems with the parents who work, who work all day […] and there is no one responsible [for the adolescent]. So, this is where grandparents come in, where we can get some help. (#58, male, nurse technician)

Therapy-related barriers

Adolescents across all three adherence groups and their caregivers cited long treatment duration, large pill burden, and adverse treatment events as reasons for missing doses and not continuing treatment. Adolescents, including those with optimal adherence, reported difficulty staying motivated to go to the health centre for such a long time. When asked why he missed a few doses, one adolescent responded, "Sometimes, you don't feel like [going to the health center]" (#47, 17–19 years, male, optimal adherence).

Many adolescents reported that the pills were big and bitter, which made them uncomfortable to take: 'I didn't like those [pills] because of the taste and the size, because they were big, and I wasn't sure I could swallow them' (#77, 14–16 years, female, optimal adherence). Participants often conflated pill burden and adverse events.

They gave me like 11 pills, and it was horrible, and I felt kind of, kind of strange. My stomach hurt; my skin itched […] The pills were gross. It's just that I took a lot, and I didn't want to take so many anymore, and I didn't like it because the pills made me, like, vomit, and I didn't want so many pills anymore. (#32, 17–19 years, male, loss to follow-up)

Most adolescents in all three adherence groups experienced adverse treatment events, most commonly gastrointestinal upset, fatigue, dizziness and rashes. Almost all adolescents and/or their caregivers reported adverse treatment events to healthcare providers, who usually reassured them that these side effects were common, transient and benign. In some cases, providers offered additional medications for symptomatic relief, and about half of the adolescents reported that the side effects were mild and/or resolved within the first few weeks of treatment. These mitigating factors did not appear to differ between adherence groups, yet most adolescents lost to follow-up cited adverse treatment events as a motivating factor (online supplemental material 5). Of note, no participants reported any severe reactions, such as yellowing of the skin or eyes.

Adolescents who completed treatment despite therapy-related barriers cited consistent family support—encouragement, reminders and accompaniment to the health centre—in helping them overcome treatment fatigue and side effects. Caregivers often reminded adolescents that discontinuing treatment could lead to drug-resistant TB, requiring daily injectable agents. When her daughter told

her that she wanted to stop treatment because the pills made her nauseous and sleepy, one mother responded, "Do you want them to inject that painful needle into you? It's very painful. That's what happens when you don't [comply]. No, you need to do your part" (mother of #1, 17–19 years, female, optimal adherence).

Other adolescents decided to continue treatment because they understood there was no other option if they wanted to be cured of TB.

> The only thing that I didn't like [about treatment] was taking the pills […] taking them every day and so many is tiring, like I didn't want to take them, but I had to if I wanted to be cured […] I just had to swallow [the pills] quickly, so I wouldn't feel them much, and drink a lot of water. (#21, 14–16 years, female, optimal adherence)

Frequently, the combination of family support and the adolescent's own motivation facilitated treatment completion.

> I wanted to be cured as soon as possible […] At the beginning, I was very motivated to take [treatment] and all that, but it's like, after two months, it's like you get bored, but it's your decision. Also, I needed my family to tell me, 'You have to go [get your pills], you have to go' […] I wanted to get healthy […] I didn't want to give up because [my TB] made my mom cry. One of my motives was that, my mom, and my dad, too. He was also there supporting me. And the other of my motives was because I wanted to [return to] study. I didn't want to lose my scholarship. (#3, 17–19 years, male, optimal adherence)

Condition-related barriers

The primary condition-related barrier reported by adolescents in all three adherence groups, as well as most healthcare providers, was symptom resolution.

> I didn't finish taking my medications at that time because it was six months that they were giving me, and I took like four months, and well, I don't know, now I feel better […] Since I was feeling better, I didn't, as I told you, I didn't go back anymore. (#38, 17–19 years, male, loss to follow-up)

One adolescent stopped treatment because a follow-up chest X-ray showed improvement:

> I felt practically that I was normal because there had been a hole in my x-ray, and when I got another x-ray, [the hole] was more or less invisible […] They told me that I had improved […] that the hole had closed up. [I thought,] 'Great, I'm better, so I'm going to join the army.' (#84, 17–19 years, male, loss to follow-up)

Once he joined the army, he stopped his treatment because he feared dismissal if they knew he had TB. However, shortly thereafter, his symptoms returned, and the army found out about his incompletely treated TB and dismissed him.

According to providers, multiple factors that occur at the transition from intensive to continuation phase—symptom resolution, treatment fatigue, three times a week (instead of daily) dosing and resumption of normal activities—impeded treatment adherence: 'They return to their studies, their friends […] They say, 'I'm no longer contagious, I'm fine, I feel better.' So, they say, 'Today I'm not going [to DOT].' They get bored going every day, three times a week. The patient gets bored, and they no longer want to come' (#16, female, nurse technician). Moreover, 'when they begin to come three times a week, many think that treatment is no longer so important because they are no longer taking [it] daily' (#10, female, nurse).

In contrast, adolescents with optimal adherence were able to comprehend the importance of continuing treatment despite symptom resolution, and/or they had caregivers who motivated and supported them to continue treatment.

> Yes, I thought about [quitting treatment]. The fact that I was better, that I wasn't feeling the symptoms like before, so I said, 'Now that I feel better, why should I continue [treatment]? […] I don't think I'll get sick again.' But the more I heard about the disease, that they said, if I quit [treatment], it may come back worse, so with this fear I did not quit. (#77, 14–16 years, female, optimal adherence)

> [T]he adolescent is a person who is still learning, so we can't make them responsible […] At first, they get scared because they are sick, they have symptoms, so they take their medicines. But they feel better, they think they are fine, so they don't take it as seriously as they did in the beginning. That's where the parents come in. It's necessary that the parents supervise their children to comply. (#75, female, nurse)

Condition-related barriers to adherence also included comorbidities.[29] Substance use and depression were the most commonly reported comorbidities by our study participants. Two adolescents lost to follow-up and most providers identified substance use as a treatment obstacle. As one nurse explained, "In the case of those who have some type of addiction, the family member simply gets tired of bringing them [to DOT … the family member] cannot control them" (#13, female, nurse). Depression, which was more commonly reported among adolescents with suboptimal adherence or loss to follow-up, was perceived as a treatment barrier for three adolescents, one in each adherence group. When these adolescents became depressed, they lost the motivation to continue treatment. As one mother explained, when her son 'no longer wanted to go to the [health] post to take the pills. He lost all desire […] to continue getting better' (mother of #65, 10–13 years, male, optimal adherence).
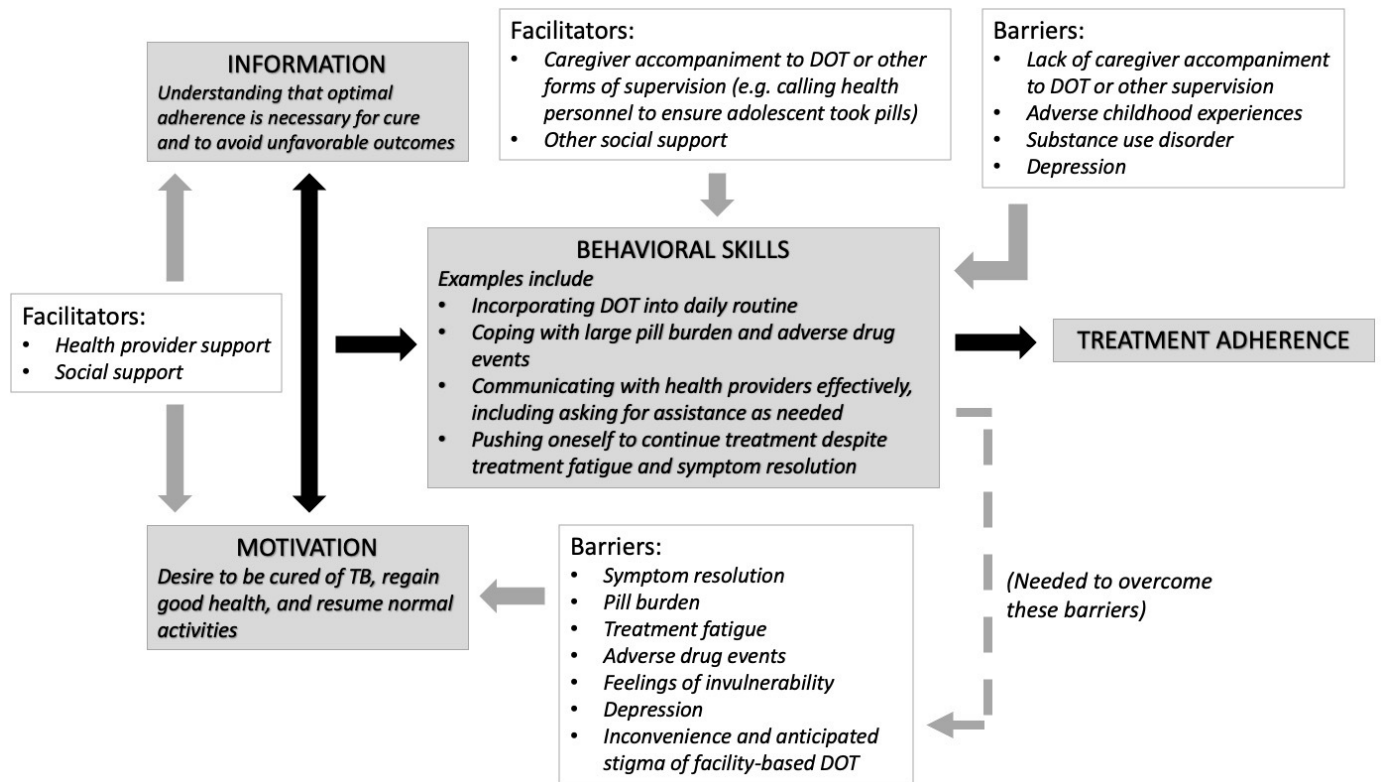
Figure 2 Explanatory model of treatment adherence among adolescents with drug-susceptible tuberculosis in Lima, Peru. DOT, directly observed therapy; TB, tuberculosis.

DISCUSSION

In this study, we observed a complex interplay of factors impacting adherence. Key barriers were the requirement for in-person DOT, long treatment duration and symptom resolution; the most critical treatment facilitator was caregiver support. Our findings concur with other studies on TB treatment adherence among adolescents.[12 13] Consistent with the observation that treatment fatigue impedes treatment adherence, we previously reported that adolescents in Lima had worse adherence to TB treatment during the continuation phase (23%) than the intensive phase (9%).[13] Healthcare providers in our study blamed substance use for loss to follow-up; similarly, an association between substance use and loss to follow-up among adolescents with TB was also reported in Rio de Janeiro, Brazil.[12] Like the participants in our study, healthcare providers from Gaborone, Botswana cited family support, stigma, school and work conflicts, and migration as barriers to TB adherence among adolescents.[18]

We synthesised our findings using the information–motivation–behavioural skills model (figure 2), which has been applied to understanding and promoting adherence and other health behaviours.[35] This model posits that information, motivation and behavioural skills—both an individual's objective and perceived abilities—are essential for adherence. Accurate information relevant to TB treatment effectiveness and safety is necessary for optimal adherence. This information is delivered by healthcare providers and reinforced by caregivers. In our study, adolescents and caregivers generally understood that

missed doses lead to unfavourable outcomes. Another determinant of adherence is the patient's motivation to take treatment as prescribed. All adolescent participants wanted to be cured of TB, regain good health and resume their normal activities. However, motivation was diminished by multiple barriers (figure 2). Support from healthcare providers, family and friends was important for reducing these barriers.

Behavioural skills, including the ones listed in figure 2, are needed to carry out the actions needed for treatment adherence, as well as to overcome barriers to motivation. Without effective behavioural skills, even informed and motivated individuals struggle to adhere to treatment. Due to their developmental stage, adolescents, despite their growing autonomy, often have a limited ability to acquire, comprehend, and effectively use health information and services.[36] Therefore, caregiver accompaniment to DOT or other forms of supervision, such as calling healthcare providers to verify an unaccompanied adolescent's adherence, often are needed to ensure proper treatment completion. We observed that, compared with adolescents who were optimally adherent, those who were suboptimally adherent or lost to follow-up were more likely to have experienced ACEs. Children and adolescents who have experienced ACEs have challenging family situations,[34] so it is plausible that in these families, caregivers are less able to be involved in the adolescent's treatment.

Our explanatory model supports a three-pronged approach to improve treatment adherence among

adolescents with drug-susceptible TB: (1) reduce barriers to motivation, (2) reinforce effective behavioural skills and (3) strengthen caregivers' ability to support adolescents. A key barrier to motivation is facility-based DOT, which disrupts normal routines, has limited flexibility to accommodate patient needs and adds to TB-related stigma. These characteristics not only impede adherence but also contradict the principles of patient-centred care, the first pillar of the WHO's End TB Strategy.[37] Treatment should be administered at the patient's home or another convenient location instead of the health centre. (Although study participants reported that adolescents occasionally were allowed to take part of their treatment at home, this practice is not permitted per Peru's current TB treatment guidelines.[24]) The WHO's recent guidelines on TB care and support acknowledge the need to shift away from facility-based DOT for all patients. First, the WHO has replaced the term 'DOT', which implies a paternalistic approach of supervising patients taking medicines, with 'treatment support', which aligns more closely with the concept of supporting patients according to their needs and preferences in order to optimise adherence.[38] The guidelines recommend home-based or community-based treatment support over facility-based treatment support, as the former is associated with higher rates of adherence, cure and treatment completion.[38] The WHO also suggests video-supported treatment (VST) as an alternative to in-person treatment support.[39] In studies conducted in adults in high-income countries, VST has been associated with higher rates of adherence compared with in-person treatment support.[39 40] Further research is needed to develop and evaluate VST platforms for adolescents in resource-limited settings.

Other important barriers to motivation include pill burden and treatment fatigue. Fixed-dose combination pills—which combine multiple first-line TB drugs and reduce pill burden—should be used more widely for drug-susceptible TB.[23 41 42] Adherence may also improve by implementing two newly recommended shorter, 4-month regimens for drug-susceptible pulmonary TB: one for patients <16 years old with non-severe disease and the other for patients ≥12 years old with any disease severity.[43–46]

To optimise adolescents' ability to apply effective behavioural skills to achieve optimal adherence to TB treatment, providers should screen adolescents for substance use disorder and depression and refer them for further evaluation and therapy as appropriate. No published studies have evaluated peer treatment support for adolescents with TB, but this type of intervention has benefited adolescents living with HIV.[47 48] In Zimbabwe, a cluster-randomised trial showed that coaching adolescents and their caregivers to strengthen coping strategies, improve treatment literacy and navigate health services led to lower risks of high viral load and death for adolescents living with HIV.[47] A qualitative evaluation of this intervention revealed that role modelling by peer treatment supporters, supportive relationships, and enhanced treatment literacy of both adolescents and caregivers improved adolescent adherence to antiretroviral therapy.[47] Importantly, the work in Zimbabwe recognises the importance of caregivers to adolescents' treatment success and involves caregivers in the intervention. Multiple other studies have found caregiver support to positively influence adolescent adherence to treatments for HIV and other chronic diseases.[49–53] These common findings underscore the value of family-centred interventions that promote developmentally appropriate skills for adolescents and strengthen caregivers' ability to provide positive guidance and emotional support.

Our study had limitations. First, we were unable to contact nearly one-third of eligible adolescents who were to follow-up from TB care (figure 1), and we did not reach thematic saturation in this group. Moreover, we excluded adolescents whose caregiver was unable or unwilling to participate and, in the case of minors, those without a parent or legal guardian to sign informed consent. The adolescents we were unable to include may have experienced more difficult treatment obstacles. Thus, there may have been a selection bias, as we may not have captured the most challenging circumstances. However, this limitation was partially ameliorated by the inclusion of healthcare providers. Second, most adolescent participants were male and older. Although this distribution reflects the higher incidence of TB in this subgroup, our dataset may not fully represent the experiences of younger and/or female adolescents. Finally, like all qualitative studies that use non-probabilistic sampling, our findings may have limited generalisability to other settings. Nonetheless, as already discussed, some of the themes that emerged align with reports from Brazil and Botswana.[12 18]

CONCLUSION
Multiple factors impact adolescent adherence to TB treatment in Lima. Home-based or community-based DOT in lieu of facility-based DOT, reductions in pill burden and treatment duration when medically appropriate, detection and treatment of depression and substance use disorder, and support from peers and caregivers may improve adolescent treatment adherence.

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Ethics approval This study involves human participants. The institutional review boards of Peru's National Institute of Health (protocol number OEE-001-18) and Rhode Island Hospital (protocol number 1122843) approved this study. We obtained written informed consent from all study participants ≥18 years old. For adolescents <18 years old, we obtained written informed consent from their parent or legal guardian, as well as participant assent.

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