Original Research

TREATMENT OUTCOMES AND FACTORS ASSOCIATED WITH POOR ADHERENCE AMONG CHILDREN RECEIVING ANTI-TUBERCULOSIS THERAPY

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ABSTRACT

Background: Non-adherence to anti-tuberculous treatment can extend the duration of illness, contribute to loss to follow-up and reduce treatment success in children, but determinants of adherence in children are not fully understood.

Methods: A prospective observational study of 184 children with drug-susceptible TB (DSTB) who were receiving treatment in a tertiary care center was conducted and adherence, treatment outcomes, and modifiable risk factors were assessed.

Results: At least 90% of prescribed doses without a prolonged gap in treatment was documented in 141 (76.6%) children and in 43 (23.4%) children, poor adherence was documented, with overall treatment success of 88.0%, but lower among poorly adherent children, compared to those with good adherence (69.8% vs 93.6%, p<0.001). Poor adherence was associated with loss to follow-up (18.6% vs 2.1%, p<0.001), longer treatment duration (7.1±1.5 vs 6.4±0.9 months, p<0.001), adolescent age (adjusted odds ratio 2.64, 95% confidence interval 1.28-5.43), travel time exceeding 60 minutes (2.39, 1.18-4.87), low caregiver education (2.27, 1.10-4.69), adverse drug effects (3.09, 1.42-6.72), and missed counseling sessions (3.46, 1.52-7.87).

Conclusion: Pediatric TB programs should integrate early identification of adherence risk, adherence counseling for caregivers, managing adverse effects, and decentralized adherence support into adolescent TB programs to increase treatment completion and treatment success.

Keywords: Tuberculosis, Children, Treatment Adherence, Treatment Outcomes, Loss To Follow-Up, Anti-Tuberculosis Therapy.

INTRODUCTION

Tuberculosis in children is a clinical and programmatic challenge due to the difficulty in diagnosis, the possibility of paucibacillary disease, the long duration of treatment and the reliance of children on caregivers to take the medicine. Despite the availability of effective drug regimens, children and adolescents may suffer from treatment interruptions due to travel burden, school requirements, caregiver limitations, treatment side effects, stigma, and lack of knowledge about treatment. Adolescents seem to be especially at risk for suboptimal adherence, and prospective evidence has highlighted the importance of age-specific risk identification [1].

Results for childhood TB treatment success are generally higher than in many adult populations, but pooled estimates are sub-optimal to desired TB program targets for several high-burden settings. A systematic review in Ethiopia revealed significant differences in treatment outcomes for children and the extra vulnerability of HIV coinfection [2]. In India, high treatment completion rates have been achieved with directly observed treatment (DOT) but loss to follow-up has also been seen in routine practice [3]. Larger urban engagement models in India have shown that increased access to rapid diagnosis and coordinated care will help increase case detection and timely treatment initiation for children [4].

www.ajmrhs.com
eISSN: 2583-7761

Date of Received: 22-05-2026
Date Acceptance: 30-05-2026
Date of Publication: 07-07-2026

Adherence is not just a patient behavior, it is a product of the interactions between the characteristics of the regimen, the resources of the family, the services of the health system, and the social environment. A systematic review of adherence interventions found that education, counseling, incentives, reminders, and patient-centered support are effective at enhancing TB outcomes [5]. In children with tuberculous meningitis, qualitative studies have revealed that caregivers can struggle to give medications, may not understand how the disease is spread, may be financially strained, and may have other household duties going on [6].

Children receiving preventive therapy also exhibit important adherence gaps, indicating that the barriers are not limited to symptomatic disease. Poor adherence has been identified among adolescents and children whose caregivers experience cost and stigma barriers [7]. Appropriate referral and continuity of care enhances treatment completion in infants exposed to tuberculosis [8]. More recent population-level studies have also found that the factors of adolescence, social vulnerability, HIV infection, prior treatment, and self-administered treatment are associated with treatment abandonment [9].

However, despite these observations, prospective data linking measured adherence to the dose, caregiver and access factors, treatment outcomes and modifiable program factors are limited in many Indian pediatric settings. Adolescents are also often included in the same age groups as younger children, and guidance on programme has identified a lack of adolescent-specific tuberculosis services [10]. The present study thus sought to identify treatment outcomes in children who had been treated for tuberculosis, estimate the prevalence of poor adherence and identify independent factors associated with poor adherence.

MATERIALS AND METHODS

This is a prospective observational study carried out in the pediatric TB clinic of a tertiary care teaching hospital. Children were enrolled at the beginning of treatment and followed until a programmatic outcome was given.

Children aged 6 months to 14 years with newly diagnosed, drug-susceptible pulmonary or extrapulmonary tuberculosis who were beginning a standard daily weight-band anti-tuberculous therapy were eligible. The diagnosis was made based on microbiological, radiological, histopathological and clinical data of the pediatric treatment team. Children were excluded if they were found to be rifampicin resistant at baseline, if they had taken more than 14 days of anti-tuberculous treatment before enrolling, if the family intended to move outside of the follow-up area within 3 months, or if adherence could not be determined because medicines were provided by an untraceable external provider.

The sample size was determined to provide a reasonable degree of precision in estimating poor adherence. With a poor adherence prevalence of 25%, 95% confidence level, and an absolute precision of 7%, the minimum sample size was 147 children. A total of 190 children were enrolled, with the option of subgroup analysis, multivariable modeling, and attrition. Of these, 184 children were included in the final analysis, as 6 children were excluded due to baseline drug-susceptibility results.

Age, sex, residence, family structure, relationship of caregivers, education level of caregivers, household income category, travel time to treatment centre, type and location of TB, microbiological confirmation, HIV status, nutritional status, and previous household contact with TB were recorded at enrolment by trained research staff. Standardized equipment was used to measure height and weight. Nutritional status was determined by age appropriate growth indicators.

Adherence was evaluated at each visit (monthly) through three methods: caregiver or child interview, review of the treatment card and refill dates, and tablet or sachet count (when available in the medication packaging). Good adherence was considered as taking 90% or more of the prescribed doses during the treatment period, no interruptions of the treatment more than 7 consecutive days, and no repeated missed refill visits. Poor adherence was defined as when any of these criteria was not met. School attendance and self-administration were specifically examined for older children. Palatability, ease of administration, adverse effects, stigma, cost, and transport barriers were asked about by the caregivers.

Routine weight adjusted therapy and monthly clinical review was given to all participants. Counselling included the anticipated length of treatment, the need for daily treatment, how to manage minor side effects and when to look out for signs that need urgent evaluation. Community or directly observed treatment support was recorded if a local health worker, trained family treatment supporter or designated provider actively supervised the treatment. Adverse drug effects were noted when they resulted in symptoms that needed clinical evaluation, laboratory testing, temporary discontinuation or modification of the drug regimen.

Programmatic outcomes were categorized as cured, treatment completed, treatment failure, lost to follow-up and died. The proportion cured or completed treatment was used as the treatment success. Secondary outcomes were time to first significant interruption, total treatment time, and

weight gain at 2 months. The outcome status was confirmed using the records from the clinic and the treatment cards.

Data were analyzed with SPSS version 29.0. Continuous variables were presented as mean±SD or median (IQR) as appropriate. Categorical variables were presented in frequency and percentage. Independent-samples t test, Mann-Whitney U test, chi-square test, or Fisher exact test were used for group comparisons. Logistic regression was used to determine the factors associated with poor adherence. Factors that were clinically important and variables that had $p<0.20$ in the univariable model were included in the multivariable model. Odds ratios with 95% confidence intervals were presented and $p<0.05$ was deemed significant.

RESULTS

The final cohort included 184 children with a mean age of 8.3±3.8 years; 103 (56.0%) were male. Pulmonary tuberculosis accounted for 112 (60.9%) cases, 63 (34.2%) were microbiologically confirmed, and 14 (7.6%) had HIV coinfection. Good adherence was documented in 141 children (76.6%) and poor adherence in 43 (23.4%). Poorly adherent participants were older, more often adolescents, more likely to live in rural areas, and more frequently had travel times exceeding 60 minutes. Low caregiver education, adverse drug effects, missed counseling, and absence of community treatment support were also more common in the poor-adherence group (Table 1).

Table 1. Baseline Characteristics According to Anti-Tuberculosis Treatment Adherence

Characteristic	Good adherence (n=141)	Poor adherence (n=43)	p value
Age, years	7.8±3.8	10.1±3.4	<0.001
Age 10-14 years, n (%)	42 (29.8)	25 (58.1)	0.001
Male sex, n (%)	78 (55.3)	25 (58.1)	0.744
Rural residence, n (%)	61 (43.3)	28 (65.1)	0.012
Travel time >60 min, n (%)	36 (25.5)	23 (53.5)	0.001
Caregiver education ≤primary, n (%)	44 (31.2)	25 (58.1)	0.001
Pulmonary TB, n (%)	84 (59.6)	28 (65.1)	0.513
Microbiologically confirmed, n (%)	47 (33.3)	16 (37.2)	0.637
HIV coinfection, n (%)	9 (6.4)	5 (11.6)	0.262
Undernutrition, n (%)	50 (35.5)	22 (51.2)	0.065
Adverse drug effects, n (%)	21 (14.9)	16 (37.2)	0.001
Attended all counseling visits, n (%)	130 (92.2)	26 (60.5)	<0.001
Community/DOT support, n (%)	120 (85.1)	25 (58.1)	<0.001

Overall treatment success was achieved in 162 of 184 children (88.0%). Success was significantly higher among children with good adherence than among those with poor adherence (93.6% vs 69.8%, $p<0.001$). Loss to follow-up was the outcome most strongly associated with poor adherence (18.6% vs 2.1%, $p<0.001$). Poorly adherent children also had a longer mean treatment duration and less weight gain at 2 months. Treatment failure was uncommon but occurred more frequently in the poor-adherence group (Table 2).

Table 2. Treatment Outcomes According to Adherence Status

Outcome	Good adherence (n=141)	Poor adherence (n=43)	p value
Treatment success, n (%)	132 (93.6)	30 (69.8)	<0.001
Cured, n (%)	48 (34.0)	10 (23.3)	0.181

Outcome	Good adherence (n=141)	Poor adherence (n=43)	p value
Treatment completed, n (%)	84 (59.6)	20 (46.5)	0.128
Treatment failure, n (%)	2 (1.4)	3 (7.0)	0.048
Lost to follow-up, n (%)	3 (2.1)	8 (18.6)	<0.001
Died, n (%)	4 (2.8)	2 (4.7)	0.620
Treatment duration, months	6.4±0.9	7.1±1.5	<0.001
Weight gain at 2 months, kg	1.8±0.9	1.1±0.8	<0.001

After multivariable adjustment, adolescent age, travel time longer than 60 minutes, caregiver education at primary level or below, clinically significant adverse drug effects, and missing at least one scheduled counseling session were independently associated with poor adherence. Active community or designated treatment support was protective. Undernutrition was associated with poor adherence in univariable analysis but did not remain statistically significant in the adjusted model (Table 3).

Table 3. Multivariable Factors Associated with Poor Adherence

Factor	Adjusted OR	95% CI	p value
Age 10-14 years	2.64	1.28-5.43	0.008
Travel time >60 min	2.39	1.18-4.87	0.016
Caregiver education ≤primary	2.27	1.10-4.69	0.027
Adverse drug effects	3.09	1.42-6.72	0.004
Missed ≥1 counseling session	3.46	1.52-7.87	0.003
Community/DOT support	0.42	0.19-0.91	0.028
Undernutrition	1.48	0.72-3.05	0.282

DISCUSSION

In this prospective cohort, almost 25% of children under anti-tuberculosis treatment were deemed poor adherers. The success of treatment was high (88.0%), but the difference between the good adherence and poor adherence was remarkable (93.6% and 69.8%, respectively). Almost nine times more often, loss to follow-up occurred in the poor-adherence group. The results in this study show that seemingly minor fluctuations in treatment on a daily basis can identify a subpopulation with significantly increased risk of poor treatment outcomes.

The age effect was statistically significant. The likelihood of poor adherence was more than double for adolescents than for younger children. This is in line with prospective evidence indicating that adolescents are a unique adherence-risk group and are not just younger versions of young children [11]. Younger children may be less protected by caregiver-supervised routines as they become more autonomous, attend school, fear disclosure, get treatment fatigue, and sometimes self-administer.

Poor adherence was independently predicted by travel burden. Over 60% of poorly adherent children were more than an hour away from the treatment center. Travel can lead to missed refills, transportation costs, missed time off for caregivers and delayed care for adverse effects. Mixed-methods studies have demonstrated that socioeconomic factors have been strongly associated with poor TB outcomes and that financial barriers have been found to be related to the organization of health systems [12]. The current data indicate that decentralizing stable follow-up, community drug delivery, and/or synchronized appointments when possible is supported.

There was another independent determinant, which was caregiver education. People with primary education or below might have problems understanding treatment instructions, adjusting treatment if they gain or lose weight, identifying side effects, or understanding the importance of continuing treatment even if symptoms are better. Social and clinical factors have been consistently identified as factors affecting retention through follow-up in retention research [13].

Comprehension of counseling should be measured, not by the delivery of information. One-time verbal instructions may not be as effective as demonstration, pictorial schedules, teach-back, and repeated reinforcement.

Poor adherence was three times more likely when there were adverse drug effects. The majority of events within the cohort were gastrointestinal, rash or transient biochemical abnormalities, but frequently led to caregiver anxiety and unscheduled disruption prior to medical advice. Adherence studies of isoniazid therapy in children have also demonstrated decreased symptom burden and hepatitis as a result of completion [14]. This is to remind families of the importance of providing them with a clear plan of adverse effects, rapid access to clinical review and explicit instructions not to discontinue the whole regimen without contacting the treatment team.

Missed counseling was the strongest modifiable risk factor in the adjusted model. Those children who did not attend at least one of the structured counseling visits were more than 3 times as likely to have poor adherence. This is in line with evidence that active follow-up can enhance treatment completion. Community health workers have been linked to higher rates of completion of TB preventive therapy and not more adverse events, at home [15]. In our study, the community or designated treatment support was a protective factor independent of the formal observation strategy, indicating that frequent human contact is more important than the formal term used to describe the observation strategy.

It is also important to pay attention to the treatment outcome pattern. The majority of failures in poorly adherent children were due to loss to follow-up and not microbiological failure or death. This implies that treatment programs can intervene before irreversible clinical deterioration takes place. If a child is missing appointments or refill dates over and over again, it should be regarded as a high risk indicator and not as an administrative hassle. Formal loss to follow up can be avoided by early tracing, transport problem solving and review of administration technique.

Formulation and palatability problems are also a challenge in pediatric treatment. The high burden of drug-resistant TB among children and families has been documented [16] and the side effects of the drugs have been identified as a barrier to treatment. Recent studies also reported that solid dosage forms were manipulated when child friendly dosage forms were not available, which posed risks for dosing accuracy, preparation time and acceptability [17]. While the current group included drug-susceptible disease and regular weight band products, caregivers still reported problems giving medicines, particularly to younger children who were nauseated or refused to take them.

Poorly adherent children were more likely to be undernutrition but this was not significant after adjustment. Nutritional vulnerability could also have an impact on outcomes through disease severity, appetite, tolerance to drugs and household poverty. Children with severe TB have been found to have several clinical and microbiological risk factors [18] in pediatric mortality studies. Based on our results, we believe that nutritional support should be included as a component of comprehensive care even if it is not an independent statistical predictor.

The overall treatment success (88.0%) was similar to that of well organized paediatric treatment programs. In children and adolescents, population-based studies have reported high completion rates (80% or more) and a general pattern of higher rates of completion with directly observed treatment [19]. The present study, however, demonstrates that a high success rate for the program as a whole can mask a much lower rate of success for the sub-group of those who have difficulties with early adherence. Therefore, the proportion of adherence should not be the only measure included in routine reporting, but indicators of adherence risk should also be included.

Treatment support is also supported by qualitative evidence that choice, community education, disclosure support and acceptable delivery models can enhance adherence [20]. A "one size fits all" solution might not be as effective as a "menu of support options". Younger children might benefit most from caregiver coaching and formulation support, whereas adolescents may need to be seen in a school-friendly setting, provided with counseling in a private space, and directly involved in treatment planning.

There are a number of strengths of this study. Adherence was assessed prospectively, not just at the end of treatment, with multiple information sources. The cohort comprised of pulmonary disease, extrapulmonary disease, caregiver variables, access variables and verified program outcomes. Modifiable program exposures (counselling attendance and community support) were also explored. Limitations are: single center study, self-reported adherence may overestimate, not all doses can be verified, and exclusion of drug-resistant tuberculosis. A threshold of 90% was selected to define clinically relevant suboptimal adherence, but this may not represent all patterns of intermittent adherence. Stigma and family instability, as well as the quality of medication, can also cause residual confounding.

In practice, the assessment of adherence should be started at the beginning of treatment, not when the number of missed doses has increased. A simple

risk assessment questionnaire that includes age, journey time, caregiver education and previous medication administration problems could result in increased support. Adverse effects should be actively managed in programs, teach-back counseling should be used, and refills should be decentralized when safe, and follow-up should be adolescent sensitive. Multicenter studies are needed in the future to assess the effectiveness of digital adherence tools and community delivery models based on treatment success, family burden, and cost-effectiveness outcomes.

Conclusion

Nearly one quarter of children on anti-tuberculosis therapy were not adhering to treatment and poor adherence was strongly related to treatment failure and attrition. Adolescence, long travel time, low education of caregivers, adverse drug effects, and lack of counseling were each associated with an increased risk of poor adherence, and treatment support in the community was associated with better adherence. Pediatric TB care should include early risk identification and family-oriented adherence support, which is decentralized.

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How to cite this article: Dr. Bimal J Barot, Dr. Ekta Shankarbhai Kotadiya, Dr. Nalin Laxmichandbhai Patel, TREATMENT OUTCOMES AND FACTORS ASSOCIATED WITH POOR ADHERENCE AMONG CHILDREN RECEIVING ANTI-TUBERCULOSIS THERAPY, Asian J. Med. Res. Health Sci., 2026; 4 (2):1817-1823.

Source of Support: Nil, Conflicts of Interest: None declared.