

# Successful Implementation of Isoniazid Preventive Therapy at a Pediatric HIV Clinic in Tanzania

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## Research

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# Abstract

**Background:** In accordance with international guidance for tuberculosis (TB) prevention, the Tanzanian Ministry of Health recommends isoniazid preventive therapy (IPT) for children aged 12 months and older who are living with HIV. Concerns about tolerability, adherence, and potential mistreatment of undiagnosed TB with monotherapy have limited uptake of IPT globally, especially among children, in whom diagnostic confirmation is challenging. We assessed pediatric IPT implementation and adherence at a pediatric HIV clinic in Tanzania.

**Methods:** Eligible HIV-infected children aged 1-15 years receiving care at the DarDar Pediatric Program in Dar es Salaam who screened negative for TB disease signs and symptoms were offered a 6-month regimen of daily isoniazid. Patients could choose to receive their IPT via facility- or community-based care. Isoniazid was dispensed with the child's antiretroviral therapy every 1-3 months. IPT adherence and treatment completion was determined by pill counts, appointment attendance, and self-report. Patients underwent TB symptom screening at every visit.

**Results:** We enrolled 66 children between July and December 2017. No patients/caregivers declined IPT. Most participants were female (n=43, 65.1%) and the median age was 11 years (interquartile range [IQR] 8, 13). 63 (95.5%) participants chose the facility-based model; due to the small number of participants who chose the community-based model, valid comparisons between the two groups could not be made. Forty-nine participants (74.2%) completed IPT within 10 months. Among the remaining 17, most (n=11, 64.7%) had IPT discontinued by their provider due to adverse drug reactions; 5 patients (29.4%) lacked documentation of completion. Of those who completed IPT, the average monthly adherence was 98.0%. None of the participants were diagnosed with TB while taking IPT or during a median of 4 months of follow-up.

**Conclusions:** High adherence and treatment completion rates can be achieved when IPT is integrated into routine, self-selected facility-based pediatric HIV care. Improved record-keeping may yield even higher completion rates. IPT was well tolerated and no cases of TB were detected. IPT for children living with HIV is feasible and should be implemented throughout Tanzania and in similar high TB/HIV-burden settings.

## Background

Tuberculosis (TB) represents an enormous global disease burden, especially for people living with human immunodeficiency virus (HIV)<sup>1,2</sup>. Rates of TB disease are particularly high in children living with HIV<sup>3,4</sup>. Deaths from HIV/TB co-disease can be reduced by preventing or by treating LTBI<sup>5,6</sup>. Standard HIV antiretroviral therapy (ART) alone is insufficient in preventing pediatric TB in high TB-burden countries<sup>7</sup>.

Consequently, the World Health Organization (WHO) has recommended expanded delivery of isoniazid preventive therapy (IPT) to reach those at greatest risk for progressing to TB disease<sup>3</sup>, including children

living with HIV. In this population, IPT has been shown to reduce mortality by 50% and incidence by more than 70% in high TB-burden countries<sup>10</sup>. Due to the low likelihood of drug-drug interactions, evidence of effectiveness, and low cost, the WHO recommends that people living with HIV, including children older than 12 months receive at least six months of IPT as part of comprehensive HIV care<sup>11</sup>.

Despite international endorsement<sup>12</sup>, IPT enrolment and completion has remained low, especially in low-income countries with a high TB-burden<sup>13</sup>. In South Africa and Uganda, for example, IPT uptake was found to be as low as 15% even when available<sup>14</sup>. Barriers to uptake include fear of drug resistance, difficulty of screening for TB due to lack of access to TB diagnostic tests, negative or unfriendly interactions between healthcare workers and parents, stigma, and fears of side effects<sup>15-19</sup>. To support IPT rollout, the WHO has created a simplified screening algorithm based on clinical symptoms that increases cost-effectiveness of TB screening<sup>20,21</sup>. Furthermore, provision of choice of IPT delivery models, such as community-outreach versus facility-based care, combining IPT and ART refills into single visits, and providing flexible appointment schedules have been associated with rates of completion and adherence of over 80%<sup>22-24</sup>.

Tanzania, one of the 22 high TB-burden countries, has a TB prevalence of 6.5% amongst those living with HIV<sup>25</sup>. While the Ministry of Health in Tanzania has officially recommended IPT for children living with HIV since 2009<sup>26</sup>, implementation is still not the standard of care at many healthcare facilities<sup>25</sup>. This study sought to determine which patient-selected IPT delivery method would yield high adherence and treatment completion in children living with HIV in Dar es Salaam, Tanzania.

## Results

We enrolled 66 eligible children between July and December of 2017, and the last child finished IPT in July 2018. Although not formally documented, the clinic nurses reported that out of the 66 children approached, all accepted IPT. Most participants were female (n=43, 65.1%) and all were on ART. The median age was 11 years (interquartile range [IQR] 8-13). Most children did not have a history of TB (n=54, 81.8%) and 33 (50.0%) were at WHO clinical stage III for HIV at initiation. Detailed participant characteristics are shown in Table 1.

INSERT TABLE 1 HERE

The facility-based model was selected by 63 (95.5%) participants at IPT initiation. (Table 2). Most cited confidentiality concerns (n=30, 45.5%) as their main reason for choosing the facility-based model, specifically because they feared that the community-based model would inadvertently disclose their HIV status to their neighbors. Other reasons for choosing the facility-based model included ease (n=9, 13.6%) as visits to the facility for HIV-related care were already integrated into their routine, and a preference to maintain their routine (n=18, 27.2%). Most participants (n=61, 92.4%) retained their initially chosen model throughout the study. Of the 5 participants who switched models, 3 (60%) switched once after the first IPT visit, and 2 (40%) switched multiple times throughout the study. Of the 5 participants who switched their models (either once or many times), 3 (60.0%) initiated the study by selecting the facility-based model and 2 (40.0%) initiated with the community-outreach model.

**Table 2.** Patient Selection of Facility-based versus Community-based IPT Delivery Model

Characteristic	Total
	(n=66)
	n (%)
<b>Model at Initiation</b>	
Facility-based	63 (95.5)
Community-based	3 (4.5)
<b>Model Consistency</b>	
Maintained chosen model	61 (92.4)
Switched model once	3 (4.5)
Switched models multiple times	2 (3.0)
<b>Reason for Model Choice</b>	
General preference (unspecified)	18 (27.2)
Protect confidentiality	30 (45.5)
Easier for patient	9 (13.6)
Better treatment support	2 (3.0)
Other	4 (6.1)
Missing or not reported	3 (4.5)

### *Adherence and treatment outcomes*

49 (74.2%) participants were confirmed to have completed IPT. Of those that completed IPT, pill count data showed a 98% average monthly adherence. Only one child had an adherence of less than 70%, and 33 (50%) had adherence rates between 93%-100%. The recorded monthly adherence of 98% is well above the 80% standard threshold for adherence. The estimated mean time to complete IPT was 27.6 weeks (6.4 months) among the 35 participants for whom a precise completion date could be determined. Incomplete record keeping meant that not all participants had an exact date of IPT completion. All

participants who completed their IPT did so within 10 months of initiation, and no participants missed more than 90 days of IPT doses. Data on IPT adherence and treatment completion are shown in Table 3.

**Table 3.** Adherence rates for 49 patients who completed treatment with adherence data confirmed by pill count

Characteristic	Total (n=49)  n (%)	Summary Statistic
Average monthly adherence		
median (Q1, Q3) <sup>1</sup>		98.0% (93.0%, 100%)
<50%	0 (0.0)	
50-79%	1 (2.0)	
80-100%	45 (91.8)	
Missing or incalculable	3 (6.1)	
Days of IPT missed, median (Q1, Q3)		11 (1, 33)
Approximate duration of IPT (weeks), mean (range) <sup>2</sup>		27.6 (20-38)

<sup>1</sup> (First Quartile, Third Quartile)

<sup>2</sup> This value could only be estimated in 35 participants.

Among the 17 (25.8%) children who were not included in the adherence analysis, 5 (29.4%) were lacking IPT completion documentation in their medical records, 11 (64.7%) discontinued treatment, and 1 (5.9%)

had an unknown outcome due to missing paperwork. Inconsistent documentation practices and patients forgetting to bring their pill bottles for adherence review (pill counts) resulted in incomplete IPT documentation that prevented adherence determinations in some cases. Among the 11 participants who discontinued IPT, 7 (63.6%) did so at the recommendation of the physician due to one or more adverse reactions including joint pain (n=2), vomiting (n=2), numbness (n=3), oral ulcers (n=1) and rashes (n=1). No cases of TB were suspected or confirmed among participants while on IPT or during a median of four additional months of follow up.

## Discussion

Our study findings demonstrate that high rates of IPT adherence and treatment completion are achievable in a pediatric HIV clinic population through IPT delivery coordinated with ART refills. While too few patients selected the community-based model of delivery to compare the effectiveness of the two models, the overall model of self-selected IPT delivery led to high adherence across the entire study cohort. Integrated care, achieved by pairing IPT with ART refills, meant that no additional medical visits were necessary and subsequently no additional burden was incurred for the child and their family. Maintaining routine care patterns likely contributed to the high adherence outcomes, as many patients cited this as a reason for choosing their delivery model. Of the six children who were not included in adherence analysis, 5 (83.3%) are believed by the clinic staff who administer their HIV care to have completed IPT but simply lacked official documentation. Among these 5, the mean estimated IPT completion date was 6.5 months after initiation. Thus it is likely that these five children completed their IPT within the 10-month limit, even if their files did not specify an end date. Using these estimated completion dates, a total of 81.8% (54/66) completed their IPT within the specified timeframe.

Where data were available, adherence was very high (98% monthly average). The fact that this study examined an “ART-established” cohort of participants (with all but one participant having initiated ART > 1 year before IPT initiation) likely contributed to the excellent adherence as participants were habituated to taking daily medication. Our study parallels other similar findings in IPT adherence and tolerability. Previous studies have found high adherence to IPT amongst pediatric populations living with HIV, suggesting that IPT is a feasible intervention for wider implementation<sup>23,27</sup>. This study is the first to examine IPT adherence and tolerability amongst an HIV-infected pediatric population in Tanzania. Furthermore, it is the first to examine IPT delivery models within Tanzania. Shared decision making and a patient-centered approach to care has been shown to improve child/patient satisfaction with their healthcare and increase medication adherence<sup>28</sup>.

Concerns regarding breakthrough TB disease and a lack of tolerability of INH in the pediatric population were not borne out in this study. There were no cases of breakthrough TB and no presentations that

warranted further evaluation with bacteriological investigation. INH was well tolerated by the study population. Only 16.7% (n = 11) of children stopped IPT, primarily due to minor adverse reaction.

Our study had two main limitations. First, data on adherence were limited due to incomplete data capture of pill counts by nurses and inconsistent presentation of pill bottles by participants at every appointment (to enable accurate adherence calculations). Similar difficulties in record keeping for IPT delivery have been documented in other similar studies in the region<sup>29</sup>. Nonetheless, while pill count data were incomplete for individual patients, the aggregate data indicate that IPT adherence was consistently high in this pediatric population. Furthermore, a recently published study by Martelli et al. (2019)<sup>30</sup> on pediatric ART adherence in Tanzania found that there was a large lack of agreement between pill count/observed adherence data and adherence data derived from the patient's viral load (39.9%), suggesting that pill counts may not be an accurate indicator of adherence. Further study to identify the most reliable measures of any medication adherence is needed. Second, due to the fact that medication could be dispensed to the patient or the parent/caregiver, sometimes the child was not present at follow-up visits. This potentially limited the study team's ability to capture all of the participants' adverse events.

Our study demonstrates that high adherence and treatment completion rates can be achieved when IPT is integrated into pediatric HIV care and when patients and their parent/caregiver are involved in choosing delivery methods that best fit their needs. Improved record-keeping and patient pill bottle presentation at appointments may yield even higher completion rates. IPT was well tolerated, with few adverse events and no detected cases of TB. For children living with HIV, IPT can be implemented effectively and should be recommended throughout Tanzania.

## Conclusions

Our study is the first to demonstrate IPT feasibility and high completion rates among children living with HIV in Tanzania. When flexible delivery models and shared decision making are included in standard care, high adherence and treatment completion rates of IPT can be achieved. Coordinating IPT and ART is an effective way to minimize patient visit burden and streamline care delivery. IPT was well tolerated and no cases of TB were detected during or after the study. Improved record-keeping, which may yield even higher completion rates. IPT should be implemented into routine pediatric HIV care within Tanzania and in similar high TB/HIV-burden settings.

## Methods

We conducted a prospective cohort study of patient-selected IPT delivery models at the DarDar Pediatric Program clinic (DPP) in Dar es Salaam. The clinic provides routine outpatient HIV care for children aged 15 and below together with their HIV-infected parents/caretakers. DPP is located in the Dar es Salaam city center and serves a mixed urban and rural population, with a total patient enrollment of approximately 285 pediatric patients and 162 parents/caretakers.

### *Enrollment procedures*

The DPP clinical staff identified a convenience sample of HIV-infected children who were eligible for IPT according to national guidelines during the study enrollment period. Specifically, eligible patients were 1) HIV-infected, 2) between the ages of 1 and 15 years, 3) enrolled in care at DPP, 4) ruled out for TB disease by using the National Tuberculosis and Leprosy Program (NTLP) symptom screen tool, 5) without contraindications to IPT as per national guidelines (e.g. severe liver disease or known adverse reaction to INH), and 6) not planning to move outside of Tanzania in the next 6-months. The study nurses obtained verbal informed consent from the child and their parent/caregiver in Kiswahili using a standardized form, which included counseling on the risks and benefits of IPT. The child in conjunction with their parent/caregiver then selected their IPT delivery model and were dispensed INH (dosed at 10-15mg/kg up to a maximum of 300mg/day). Most children received a 1 or 2 months' supply of INH, based on the timing of their next scheduled appointment for ART.

### *IPT delivery models*

Children (and their parent/caregiver) were offered a choice of either facility- or community-based IPT delivery models. In the facility-based model, TB screening, adherence assessment, and INH refills were coordinated with the child's routine ART refill appointments at the clinic, typically in monthly or bimonthly intervals. In the community-based model, staff performed the same functions in the child's home and dispensed both their INH and ART refills. Patients were allowed to switch models at any time during the study, and were reminded of this at each follow-up appointment.

### *Follow-up visits and monitoring*

IPT refill intervals followed the child's pre-existing ART refill schedule. The study nurses contacted all study participants who missed their appointments via telephone call. Adherence was assessed at each visit and IPT completion was documented after the final IPT refill. Average monthly adherence was determined via pill counts. At each visit, participants were screened for TB disease using the NTLP-recommended symptom screen. If any TB signs or symptoms were present, a chest x-ray and sputum for AFB smear, culture, and Xpert MTB/RIF testing was performed. Participants with confirmed TB disease were referred to a separate TB clinic for treatment; if TB was excluded, the child resumed IPT.

### *Outcomes*

The primary outcome was IPT completion, defined as completing a 6-month course of INH within 10 months. When exact treatment completion dates were not documented, the completion date was estimated by adding the days of IPT remaining (as indicated by the number of pills that the patient had remaining) at the time of their last IPT appointment. The secondary outcome was adherence, defined as the percentage of prescribed INH taken. Adherence was measured and treatment completion was determined using a combination of pill counts at follow-up appointments, appointment adherence, and patient self-reporting.

### *Training and monitoring*

One clinic physician and two nurses were trained in IPT administration. The study team conducted staff training through didactic lectures, discussion, and role-play. Training sessions focused on 1) review of the national IPT policy, 2) review of the benefits of IPT, 3) results from the IPT program evaluation, 4) patient motivational interviewing techniques and shared decision-making, 5) overview of the project using the approved standard operating procedures, and 6) transfer of data collection tools.

### *Data analysis*

Study data were collected using standard paper registers. We recorded basic demographics, method of IPT delivery, reasons for choosing that delivery method, pill counts, dates of IPT initiation and refills, adverse reaction, deviations from prescribed treatment, and patient-initiated switches from the initially-selected delivery model. These data were transferred to a password-protected Microsoft Excel 2010 spreadsheet on password-protected study laptops. Data were exported to JMP v13 for final analysis. All data were validated by comparison between paper and electronic entries. Descriptive analyses using means/medians and proportions were conducted for continuous and categorical data respectively. Adherence was calculated at the first follow-up and for all subsequent visits with available data.

The study protocol was approved by the National Institute for Medical Research in Dar es Salaam, Tanzania; Muhimbili University of Health and Allied Sciences (MUHAS) Institutional Review Board in Dar es Salaam, Tanzania; and the Dartmouth Committee for the Protection of Human Subjects in Hanover, NH, USA.

## **Abbreviations**

ART  
Antiretroviral Therapy  
INH  
Isoniazid  
IPT

Isoniazid Preventive Therapy  
HIV  
Human Immunodeficiency Virus  
LTBI  
Latent Tuberculosis Infection  
TB  
Active Tuberculosis disease  
WHO  
World Health Organization

## Declarations

**Ethics approval and consent to participate:** The study protocol was approved by the National Institute for Medical Research in Dar es Salaam, Tanzania; Muhimbili University of Health and Allied Sciences (MUHAS) Institutional Review Board in Dar es Salaam, Tanzania; and the Dartmouth Committee for the Protection of Human Subjects in Hanover, NH, USA.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors' contributions:** OH analyzed and interpreted the study data and was a major contributor in writing the manuscript. FK co-designed the study protocol and oversaw study implementation. ND and AA collected and cleaned patient enrollment data and performed preliminary analyses. PM and FvR contributed to the study design and manuscript. LVA co-designed the study, contributed greatly in writing the manuscript, and provided study oversight.

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## Table

**Table 1.** Characteristics of 66 Pediatric Participants Receiving Isoniazid Preventative Therapy

Characteristic	Total (n=66) n (%)	Summary Statistic
<b>Sex</b>		
Female	43 (65.1)	
<b>Age at Initiation, median (Q1, Q3)<sup>1</sup></b>		
0-5 years	6 (9.1)	11 (8, 13)
6-10 years	21 (31.8)	
11-15 years	39 (59.1)	
<b>WHO Clinical Staging for HIV at Initiation</b>		
I	3 (4.5)	
II	26 (39.4)	
III	33 (50.0)	
IV	3 (4.5)	
Missing or not reported	1 (1.5)	
<b>History of Tuberculosis</b>		
Yes	12 (18.2)	
No	54 (81.8)	
<b>ART Status</b>		
On ART	66 (100.0)	
Duration of ART at initiation in years, median (Q1, Q3)		5 (2.25, 8)
<b>History of Liver Disease</b>		
Yes	0 (0.0)	
No	57 (86.4)	
Missing or not reported	9 (13.6)	

<sup>1</sup> (First Quartile, Third Quartile)

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