Implementation of the WHO 2011 Recommendations for Isoniazid Preventive Therapy (IPT) in Children Living With HIV/AIDS: A Ugandan Experience

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Background: Intensified tuberculosis (TB) case finding and isoniazid preventive therapy (IPT) are strongly recommended for children who are HIV infected. Data are needed to assess the feasibility of the WHO 2011 intensified tuberculosis case finding/IPT clinical algorithm.

Methods: Children who are HIV infected and attending Nsambya Home Care at Nsambya Hospital, Uganda, were screened for TB following WHO recommendations. IPT was given for 6 months after excluding TB. Factors associated with time to IPT initiation were investigated by multivariate Cox proportional hazard regression. Health care workers were interviewed on reasons for delay in IPT initiation.

Results: Among the 899 (49% male) children with HIV, 529 (58.8%) were screened for TB from January 2011 to February 2013. Children with active TB were 36/529 (6.8%), 24 (4.5%) were lost to follow-ups and 280 (52.9%) started IPT, 86/280 (30.7%) within 3 months of TB screening and 194/280 (69.3%) thereafter. Among the 529 children screened for TB, longer time to IPT initiation was independently associated with cough at TB screening (hazard ratio 0.62, $P = 0.02$, 95% confidence interval: 0.41 to 0.94). Four children (1% of those starting treatments) interrupted IPT because of a 5-fold increase in liver function measurements. In the survey, Health care workers reported poor adherence to antiretroviral therapy, poor attendance to periodic HIV follow-ups, and pill burden as the 3 main reasons to delay IPT.

Conclusion: In resource-constrained settings, considerable delays in IPT initiation may occur, particularly in children with HIV who are presenting with cough at TB screening. The good safety profile of isoniazid in antiretroviral–therapy-experienced children provides further support to IPT implementation in this population.

Key Words: IPT, isoniazid, tuberculosis, HIV, children

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INTRODUCTION

Early combined antiretroviral therapy (cART) initiation and cotrimoxazole prophylaxis are critical interventions to reduce mortality among infants and children who are HIV infected.[1] Tuberculosis (TB) is a major cause of morbidity and mortality in individuals with HIV, accounting for 360,000 HIV-associated adult deaths in 2013.[2] Although an estimation of TB-related mortality is unavailable for children living with HIV,[2] several studies showed that this population is highly vulnerable to TB,[3,4] with an increased mortality, particularly if not receiving cART.[5–7] Challenges with TB diagnosis and care in children living with HIV still persist in Sub-Saharan Africa, where weak health systems, poor access to health facilities, and lack of adequate diagnostic tools add to the well-known drug–drug interactions. Also, increasing pill burden and side effects can compromise adherence. TB prevention is therefore a critical component in the integrated approach to tackle these two diseases and reduce child mortality in Sub-Saharan Africa.

A recent systematic review showed a 59% reduced risk of active TB in older children who are given isoniazid preventive therapy (IPT).[8] However, conflicting results from randomized controlled trials conducted in South Africa were

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reported for children who are HIV infected. Although Zar et al observed a 50% reduction of mortality and a 70% reduction of new TB cases among children infected with HIV on IPT compared to placebos,[9,10] these findings were not confirmed in the P1041 trial undertaken in children who are HIV-exposed and HIV infected.[11] Differences in the enrolled population potentially contributed to the difference in results because 31% of infants enrolled in the Mahdi trial were receiving cART, whereas only 9% of children enrolled in the Zar trial were on cART, translating to an increased risk of underdiagnosed TB. Although differences in baseline patient characteristics were the most compelling reason for discordance in the study findings, the clinical value of IPT among children infected with HIV is still debated. Existing challenges in ruling out TB, concerns that IPT may promote isoniazid (INH) resistance, and economic and health system constraints, have contributed to slow the implementation of IPT among children who are HIV infected. In addition, limited data still exist on IPT acceptability. Therefore even in countries with high TB incidence, IPT is often not provided in the absence of exposure to a TB case,[12] despite this being a potentially effective, low-cost measure to prevent TB morbidity and mortality.

Since the increasing availability of cART in Sub-Saharan Africa, IPT provision has necessarily become a part of a larger debate on the urgent need to ensure long-term comprehensive care for people living with HIV. The integration and linkage of cART-related services to TB prevention and treatment and maternal and child health routine services were endorsed by WHO 2013 recommendations and is supported by recent findings.[1,13] However, in Sub-Saharan Africa, HIV treatment and care are still often disconnected from other services because of inadequate financial and human resources, working in weak health services primarily organized to provide episodic acute care.[14] Therefore, IPT implementation still has several challenges.

Since 2011, the World Health Organization (WHO) has strongly recommended intensified case finding (ICF) and IPT for people living with HIV in resource-constrained settings and high prevalence of TB.[15] A new simplified clinical algorithm that includes fever, current cough, and failure to thrive, was officially endorsed to screen for TB in children infected with HIV, and IPT was strongly recommended for children older than 12 months without these symptoms and signs, regardless of a TB contact history. However, the low quality of evidence still supports the new WHO 2011 clinical algorithm,[16,17] suggesting the urgent need for documenting its feasibility, particularly in resource-constrained settings.

To date limited data are available on ICF/IPT implementation in pediatric HIV care outside clinical trial settings,[18] and to the best of our knowledge, no studies that are available in the public domain have explored the feasibility of ICF/IPT using the clinical algorithm promoted by the WHO in 2011.[15] In addition, although limited data on the safety of IPT in children who are on cART are reassuring, with severe hepatotoxicity rates ranging from 0.4% to 1.7%,[11,19] more evidence is needed for informed program planning and further encouraging the IPT scale-up.

We describe the results of an implementation project to introduce the WHO 2011 ICF/IPT clinical algorithm in the package of care provided to a cohort of children who are HIV infected in Kampala, Uganda. Tolerability, toxicity and, feasibility of providing IPT were explored using routine data collection and qualitative methodologies.

METHODS

Setting and Study Design

A prospective cohort study was conducted among children with HIV attending the pediatric HIV/AIDS clinic at the Nsambya Home Care (NHC) department of St. Raphael of St. Francis Nsambya Hospital in Kampala, Uganda, in the "Abaana Bee Ggaba" project partnering with the Italian nongovernmental organization, *Associazione Casa Accoglienza alla Vita Padre Angelo*. The program provides HIV counseling and testing, infant diagnosis, cotrimoxazole prophylaxis, cART, laboratory monitoring, and management of opportunistic infections. In the absence of contraindications, cART is prescribed after counseling and written consent of the caregiver, in keeping with national guidelines. Since 2011, ICF for TB and IPT are integrated into routine HIV treatment and care.[15] All children enrolled in ICF/IPT implementation from January 2011 to February 2013 are included in this study.

Data Collection

Data were recorded in paper-based patient files and registries and entered in an electronic interface by trained staff. Children were seen on a monthly basis, during and after the completion of the implementation**.** Full blood counts, liver function tests (LFTs), and glucose and creatinine assays were performed before cART initiation and every 6 months, with CD4 counts performed every 6–12 months. At each follow-up visit, active TB screening was performed as part of ICF, based on the WHO 2011 clinical algorithm[15] and regardless of the TB contact history. In particular, since the first systematic TB screening, all children infected with HIV enrolled in the study have been evaluated monthly, for current cough, fever, and failure to thrive. Adolescents have also been examined for current cough, fever, weight loss and night sweat**.** If active, TB was suspected. Further examinations were conducted as the treating physician saw fit, including chest radiography and acid-fast bacilli testing on sputum and/or other specimens. Trained nurses collected data on past TB and on a positive TB contact history**.** All children with confirmed or probable active TB started TB treatment, following recommendations of the National TB and Leprosy Control Programme.[20] A 6-month course of IPT was started in children who were unlikely to have active TB, after ruling out contraindications to INH. In particular, before starting IPT, peripheral neuropathy was excluded clinically, and active hepatitis was excluded by assessing alanine and aspartate aminotransferase (ALT/AST) LFTs within the previous 3 months of IPT initiation. INH was provided by the Ugandan Ministry of Health through the National TB and Leprosy Control

Programme and was administered according to child weight (300 mg INH tablets were crushed by health care workers (HCWs) to provide 10–15 mg/kg daily) with vitamin B6, 25 mg daily. To facilitate ICF/IPT activities and data collection, several standard operating procedures were defined and included in the "IPT card," which is a paper-based tool developed in accordance with the WHO 2011 clinical algorithm. All personnel implementing ICF/IPT were trained on effective use of this tool before project implementation. IPT was distributed at the TB unit, an open air structure close to the HIV clinic. Children eligible for IPT initiation were referred to the TB unit soon after the clinical follow-up, to receive INH, vitamin B6, and all IPT-related advices.

The monthly IPT follow-up focused on INH toxicity, tolerability, and self-reported adherence, and on the occurrence of signs or symptoms of active TB. LFTs were performed 1–2 months after IPT initiation and at the end of the INH course, or more frequently if clinically required. Adverse events were graded according to US National Institutes of Health Division of Acquired Immune-Deficiency Syndrome (DAIDS) toxicity criteria.[21] For children with grade 3 or 4 events, IPT was immediately interrupted, and the liver toxicity was monitored until complete normalization of laboratory parameters. Adherence to IPT was self reported on a specific "INH card," a paper-based time table that the children and/or their caregiver had to mark every single day of INH assumption. At each clinical follow-up, HCWs assessing adherence monitored the patient's "INH card" and counted the remaining INH pills.

End-Point Definitions and Study Population

Children aged 1–18 years with confirmed HIV infection enrolled in the Abaana Bee Ggaba project and in active care during the study were included. Those with contraindications for INH and those with documented treatment for active TB over the 2 years preceding screening were excluded.

Active TB was classified as probable with a positive smear microscopy for acid-fast bacilli testing from sputum or a chest radiograph suggestive of TB, in children with positive TB contact history and/or unexplained weight loss or failure to gain weight and/or fever and/or cough.

The time of TB screening refers to the date of first TB screening, systematically performed, following WHO 2011 recommendations. Early IPT initiation was defined as starting IPT within 3 months of first TB screening, and late IPT initiation was defined as a start date more than 3 months after first TB screening. Caregivers completed diaries for IPT adherence. They were requested to mark a cross for each day INH was administered and were requested to return all empty medicine containers and remaining medication at each visit, along with the completed diaries.

Statistical Analysis

Frequency distributions and medians with interquartile ranges were used to describe patient characteristics at TB screening. These included the gender, age, WHO stage, cART status, and time from enrollment in HIV care to TB screening. Contact with a TB source case, current cough, fever, and failure to thrive were documented. Laboratory parameters included CD4 count/percent, hemoglobin, and LFTs. Receipt of IPT and time from TB screening to IPT initiation were noted. Descriptive analyses were stratified by participation in TB screening, initiation of IPT, and time to initiation of IPT, with between-group differences determined using Pearson χ^2 or Wilcoxon rank-sum tests as appropriate.

Factors associated with time from TB screening to IPT initiation were investigated using a Cox proportional hazard regression model including gender, past TB contact history, and time from enrollment to TB screening, and age, cough, fever, failure to thrive, receipt of cART, and CD4 Z-scores at the time of TB screening. Missing values of independent variables in the model were imputed using multiple imputation by chained equations with 20 iterations.

Operational challenges were qualitatively assessed through anonymous paper-based multiple-choices questionnaires documenting HCWs' views on the reasons for IPT delay in May 2013. All HCWs involved in IPT implementation consented to the proposed questionnaire and anonymity was guarantee. Options provided included poor adherence to cART at TB screening, stigma, failure to recognize IPT importance, failure to rescreen children if IPT was not immediately initiated, distance to the clinic, poor compliance/lost to follow-up, symptoms (current cough, fever, or failure to thrive) at TB screening, increased pill burden, severe immune depression or WHO stage III-IV event at TB screening, and fear of side effects. All quantitative analyses were conducted in Stata version 12.0 (Stata Corporation, College Station, TX).

RESULTS

Among the 899 children positive for HIV, who were enrolled between January 2011 and February 2013, in the Abaana Bee Ggaba project, 529 (250 male, 47%) were systematically screened for TB and included in the study. Of these, 36 (7%) had active TB, 24 (5%) were lost to follow-ups, and 24 (5%) had missing clinical data. Among the remaining children, 280 (52.9% of all screened) initiated IPT for 6 months in the study period. The study population is described in Figure 1.

Characteristics of all patients eligible, screened for TB, and initiating IPT are presented in Table 1. Patients screened for TB were significantly more likely to be on cART than those not screened. Among the 529 patients screened for TB in this cohort, 16 (3.0%) had a record of previous TB and 108 (20.4%) screened positive by the WHO algorithm for possible TB. Children starting IPT were significantly more likely to have lower WHO clinical stages, higher CD4 count Z-scores at TB screening, and lower age at cART initiation compared to patients not initiating IPT.

Of the 280 children who initiated IPT, 86 started within 3 months of TB screening and 194 after more than 3 months. Patient characteristics stratified by the time of initiation of IPT are presented in Table 1. Early IPT initiators had significantly higher CD4% and hemoglobin (Hb) rates at TB screening compared to children starting IPT later.

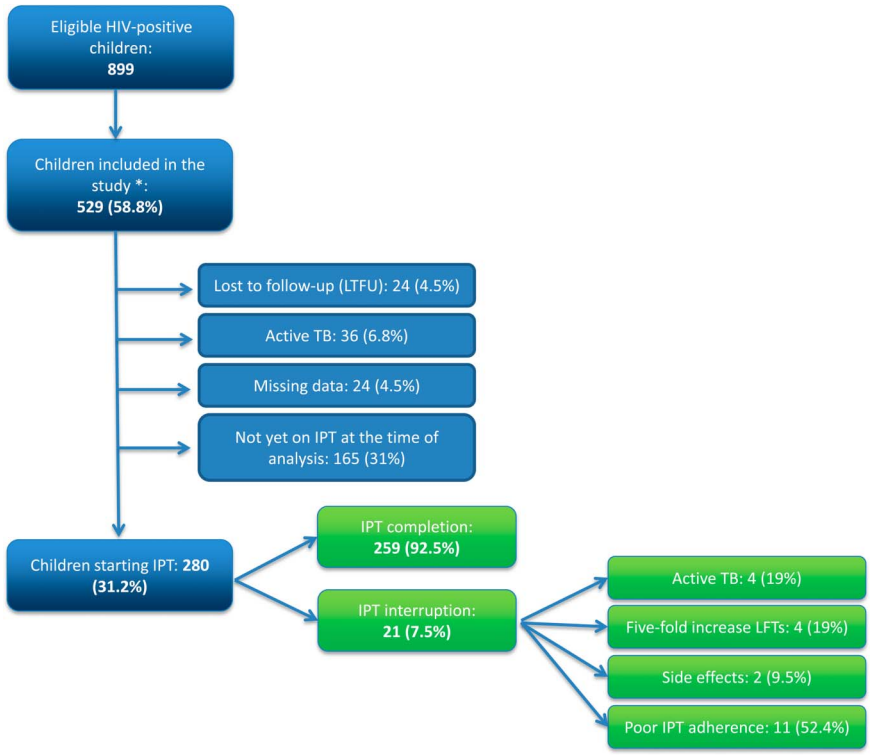

FIGURE 1. Study population: children infetcted with HIV eligible for TB screening, screened for TB and starting IPT. *Children starting active TB screening according to WHO 2011 clinical algorithm.

Overall, 259 (92.5%) children completed a 6-month IPT course, whereas 21 interrupted IPT. Of those, 4/280 (1.43%) children interrupted because of a 5-fold increase of AST/ALT levels 1 month after initiation, however, in 3 cases baseline data were missing (Table 2). The one remaining case was a female child defined as probable liver toxicity related to INH who was not receiving cART and was aged 4.5 years at IPT initiation, with AST/ALT levels of 39/26 U/L 1–3 months before IPT initiation and of 195/251 U/L afterward, although other causes of liver impairment were not excluded (Table 2, child C). Four children (1.43%) interrupted IPT because of active TB diagnosis during therapy, 2 (0.71%) for INH-related side effects (one for nausea/vomiting and one for an allergic reaction), and 11 (3.93%) for poor IPT adherence. Among 259 children who completed IPT, in 1 (0.39%) case active TB was diagnosed 205 days after IPT initiation.

Details of missing data among the 280 children infected with HIV receiving IPT are in the Supplemental Digital Content (http://links.lww.com/QAI/A734). No more than 1.4% of data were missing for any covariate among children stratified by time to IPT initiation.

The results from the adjusted Cox proportional hazards model of time to IPT initiation are provided in Table 3. Among children starting IPT, children presenting with cough at the time of TB screening were 38% less likely to start IPT over 3 months of the follow-up period (hazard ratio 0.62, $P = 0.02$, 95% confidence interval: 0.41 to 0.94). No evidence of association was found for the remaining characteristics explored.

Although our study was initially designed to target children who are HIV positive, we noted that adolescents who routinely followed up in our HIV clinic were also screened for TB, following the adolescent/adult WHO 2011 clinical algorithm, based on the evaluation of current cough, fever, weight loss, and night sweat. Adolescents were not excluded from IPT initiation after ruling out active TB, however, the presence of the sign "night sweat" was not reported systematically. Restricting the analysis to 402 (M 197, F 205) children aged 0–15 year old, the results from adjusted analysis lose significance due to decreased statistical power, but are in keeping with the overall results from the whole cohort: patients with cough at the time of TB screening were 37% less likely to start IPT over 3 months of the follow-up period (hazard ratio 0.63, 95% confidence interval: 0.39 to 1.01, $P = 0.06$). Unadjusted and adjusted analyses of 402 children are included in Tables S2 and S3 present in the Supplemental Digital Content (http://links.lww.com/QAI/A734).

Qualitative Survey

In February 2013, questionnaires from 20 HCWs in charge of ICF/IPT implementation, including 3 doctors, 5 counselors, 8 nurses, 2 social workers, and 2 additional staff members, were collected. All HCWs agreed on the importance of IPT, however, 2 of 3 doctors believed that the clinical algorithm promoted by WHO in 2011 was neither so helpful nor too complicated for ruling out active TB. Moreover, only 30% of HCWs (6/20) believed that starting IPT is not difficult in children who were screened for TB**.** The 3 most frequent reasons for IPT delay were poor adherence to cART at TB screening (reported by 24% of HCWs), poor attendance to the periodic HIV follow-up (17%), and pill burden (17%). Other reasons included TB-related stigma (10%), clinical signs

TABLE 1. Characteristics of Children Infected With HIV Enrolled in the Abaana Bee Ggaba Project Eligible for TB Screening (n = 899), Screened for TB (n = 529), and Starting IPT (n = 280), Early (n = 86) or Late (n = 194), Between January 2011 and February 2013

n (%) or Median (IQR)	Eligible (n = 899)	Screened for TB (n = 529)	Univariate *P*, Eligible/Screened	Starting IPT (n = 280)
Screened	529 (58.8%)	—	—	—
Receiving IPT	280 (31.1%)	280 (52.9%)	—	—
Female	458 (50.9%)	279 (52.7%)	0.198	140 (50.0%)
Time in HIV care before TB screening, yrs	—	3.9 (1.1 to 6.0)	—	4.1 (1.2 to 5.7)
Time from TB screening to IPT initiation, d	—	—	—	141 (84 to 289.5)
Age at cART initiation, yrs	8.1 (4.3 to 12.1)	8.1 (4.5 to 11.8)	0.976	7.4 (4.4 to 11.0)
Age, yrs*	—	10.74 (6.5 to 14.6)	—	10.36 (6.4 to 13.8)
Past TB contact*	—	122 (23.1%)	—	58 (20.7%)
Cough*	—	57 (10.8%)	—	31 (11.1%)
Fever*	—	26 (4.9%)	—	13 (4.6%)
Failure to thrive*	—	65 (12.3%)	—	42 (15%)
WHO stage*	—	—	—	—
I	—	180 (34.1%)	—	94 (33.6%)
II	—	190 (35.9%)	—	122 (43.6%)
III	—	20 (3.8%)	—	6 (2.2%)
IV	—	1 (0.2%)	—	1 (0.4%)
Receiving cART*	572 (63.6%)	442 (83.5%)	<0.01	232 (82.8%)
Hemoglobin, g/dL†	—	11.2 (10.1 to 12.2)	—	11.1 (10 to 12.2)
AST, U/L†	—	39 (30 to 51)	—	38 (29 to 49)
ALT, U/L†	—	26 (19 to 36)	—	25 (18 to 37)
CD4, %‡	—	23 (11 to 34)	—	24 (12 to 35)
CD4 count Z-score‡	—	−0.13 (−0.6 to 0.5)	—	−0.07 (−0.5 to 0.5)

n (%) or Median (IQR)	Univariate *P*, Screened/no IPT	Early IPT Initiation (n = 86)	Late IPT Initiation (n = 194)	Univariate *P*, Early IPT/Late IPT
Screened	—	—	—	—
Receiving IPT	—	—	—	—
Female	0.181	50 (58.1%)	90 (46.4%)	0.070
Time in HIV care before TB screening, yrs	0.850	3.5 (1.2 to 5.7)	4.24 (1.2 to 5.8)	0.585
Time from TB screening to IPT initiation, d	—	57.5 (35 to 78)	228.5 (140 to 329)	<0.01
Age at cART initiation, yrs	0.009	6.9 (4.6 to 11.4)	7.6 (4.1 to 10.9)	0.854
Age, yrs*	0.053	10.0 (6.7 to 13.6)	10.52 (6.2 to 14.1)	0.865
Past TB contact*	0.074	24 (27.9%)	34 (17.53%)	0.089
Cough*	0.458	10 (11.6%)	21 (10.8%)	0.953
Fever*	0.458	5 (5.8%)	8 (4.12%)	0.803
Failure to thrive*	0.057	14 (16.3%)	28 (14.4%)	0.899
WHO stage*	<0.01	—	—	0.423
I	—	23 (26.7%)	71 (36.6%)	—
II	—	41 (47.7%)	81 (41.8%)	—
III	—	3 (3.5%)	3 (1.6%)	—
IV	—	0 (0.0%)	1 (0.5%)	—
Receiving cART*	0.647	67 (77.9%)	165 (85.1%)	0.143
Hemoglobin, g/dL†	0.257	11.5 (10 to 12.5)	10.9 (10 to 12)	0.0243
AST, U/L†	0.095	35.5 (28 to 51)	39 (31 to 49)	0.2615
ALT, U/L†	0.816	27 (18 to 37)	25 (18 to 37)	0.7283
CD4, %‡	0.368	25 (18 to 35)	23 (9 to 34.3)	0.2903
CD4 count Z-score‡	0.015	−0.04 (−0.52, −0.44)	−0.11 (−0.49 to −0.57)	0.5997

*At the time of TB screening.
†Within 3–4 months of TB screening. LFTs thresholds for male children: AST 0–37 U/L and ALT 7.2–43.3 U/L; thresholds for female children: AST 0–37 U/L and ALT 5.3–39.9 U/L.
‡Within 6 months before TB screening.

TABLE 2. Characteristics of 4 Children With HIV Who Had a 5-Fold Transaminase Increase Soon After IPT Initiation

	Child A	Child B	Child C*	Child D
Gender	Male	Female	Male	Female
Age at IPT initiation, yrs	7	8.5	4.5	8.4
cART at IPT initiation	AZT-3TC-NVP	AZT-3TC-NVP	Not on cART	Not on cART
AST, ALT 1–3 mo before IPT initiation, U/L†	No data	No data	39, 26	No data
AST, ALT 1 mo after IPT initiation, U/L†	108, 285	494, 601	195, 251	178, 235
Time on IPT at LFT elevation, d	28	35	29	28
AST, ALT 2–4 mo after previous LFT, U/L†	47, 39	42, 41	39, 17	—‡

*Child C was the only case defined as probable liver toxicity related to INH.
†LFT thresholds for male children: AST 0–37 U/L, ALT 7.2–43.3 U/L; thresholds for female children: AST 0–37 U/L, ALT 5.3–39.9 U/L.
‡Missing data: child D was transferred to another clinic soon after IPT interruption.

(10%) and lack of recent LFTs at TB screening (10%), fear of INH-related side effects (7%), distance from the clinic (3%), and severe immunosuppression at TB screening (2%). Findings from the survey are reported in Figure 2.

DISCUSSION

To the best of our knowledge, this study represents the first example of ICF and IPT implementation following WHO 2011 recommendations in a pediatric HIV care program. Within 24 months of systematic TB screening using the WHO 2011 clinical algorithm, IPT was started in 52.9% (280/529) children, and more than 90% completed a 6-month course of INH, confirming that ICF/IPT implementation is feasible in a resource-constrained setting. However, only less than 60% (529/899) of children positive for HIV were systematically screened for active TB, suggesting that systematic active TB-screening coverage may be essential to successful ICF/IPT implementation. Indeed, we believe that this analysis provides important observational findings to inform future implementation in similar settings.

The INH prophylaxis was safe and well tolerated in children with HIV, of whom more than 80% were on cART. Only 1.4% (4/280) of children interrupted IPT because of a 5-fold increase in LFTs, and among them only 1 was identified as a case of probable INH-induced liver toxicity. However, excluding the other causes of liver impairment was limited by testing costs and availability of assays. Only 0.7% of children stopped IPT because of other INH-related side effects, confirming that INH is well tolerated among children who were HIV positive even with cART. These findings provide additional evidence on safety and tolerability of IPT in older children receiving cART similar to what has been reported elsewhere.[19,22,23] Nevertheless, studies of IPT in children receiving cART are still limited, suggesting the need, where possible, for pharmacovigilance assessment conducted alongside implementation.

High adherence to IPT was reported by previous trials conducted among children infected with HIV, irrespective of the dosing schedule.[11,23–25] In our cohort, eleven patients (3.9%) stopped IPT because of poor adherence to INH, suggesting that satisfactory adherence can be obtained in program settings outside clinical trials. Limitations related to self-reported adherence exist, and the low percentage of poor adherence found in our cohort may reflect a selection bias, as clinicians may be more inclined to start IPT in patients with good adherence to a clinical HIV follow-up.

In our cohort, considerable delays in starting IPT were observed with a median time of 141 days from TB screening to IPT initiation. This finding seems to be in line with unpublished observational data presented by Houston et al,[18] in which IPT initiation occurred after a median time of 9 months.

Delays in systematic TB screening and IPT initiation may limit the feasibility of IPT, potentially leading to reduction in the effectiveness of the intervention. Reasons of delay in IPT initiation were explored and after adjusting for other factors, current cough at TB screening was independently associated with starting of IPT later. This finding is not surprising because upper and lower respiratory infections, mostly related to viral and bacterial infections, are very common even in high resource settings and are expected to increase in the context of poor health conditions, poor hygiene, overcrowding, and pollution in resource-constrained settings. The triad of "current cough, fever, and failure to thrive" recommended by the WHO 2011 algorithm[15] has high sensitivity and is likely to identify a potential active TB case, however, limited evidence supports this clinical algorithm, and its specificity appears limited to around 62–65%.[16,17] As a result, a number of children presenting

TABLE 3. Adjusted Hazard Ratios for the Relationship Between Patient Characteristics and Time From TB Screening to IPT Initiation Among 529 Children Positive for HIV Screened for TB Between January 2011 and February 2013

	Hazard Ratio (95% confidence interval)	*P*
Gender (female)	0.92 (0.72 to 1.17)	0.49
Age at TB screening, yrs	0.97 (0.94 to 1.01)	0.15
Time in HIV care before TB screening	1.00 (1.00 to 1.00)	0.32
Past TB contact history	1.11 (0.83 to 1.49)	0.48
Cough at TB screening	0.62 (0.41 to 0.94)	0.02
Fever at TB screening	0.85 (0.46 to 1.55)	0.59
Failure to thrive at TB screening	1.30 (0.91 to 1.85)	0.15
CD4 Z-score within 6 mo before TB screening	1.01 (0.87 to 1.16)	0.94
On cART at TB screening (yes/no)	0.89 (0.63 to 1.24)	0.48

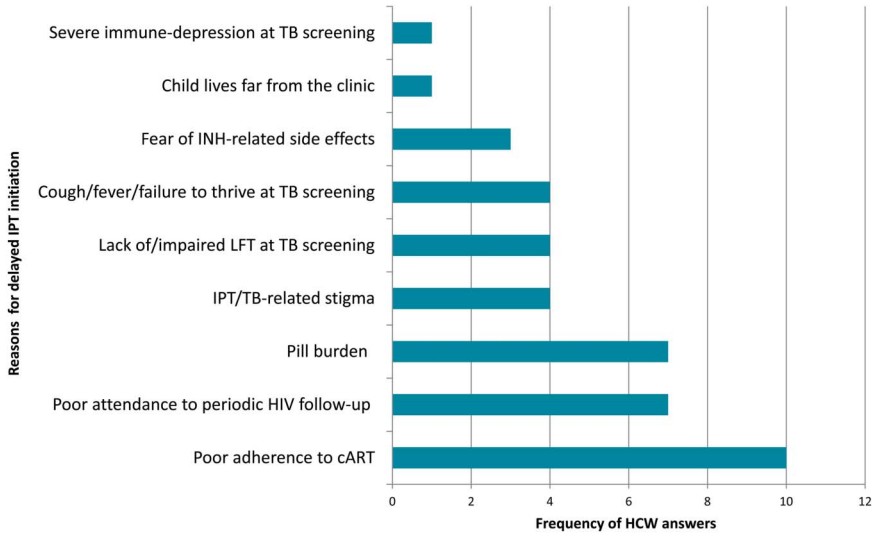

FIGURE 2. Most frequent reasons of delayed IPT initiation reported by HCWs participating (n = 20) in a qualitative survey.

with current cough, likely due to minor respiratory infections, underwent additional investigations to rule out active TB, delaying IPT initiation. Hence, our findings reflect some operational challenges attached to the limited specificity of the WHO 2011 clinical algorithm and highlight the additional resources required to exclude active TB in children presenting with cough.

HCWs reported that poor adherence was often a barrier to IPT initiation. Clinicians seemed to be more comfortable in initiating IPT if a child with good adherence to cART were also less likely to present with cough (independently associated with delayed IPT initiation). Unfortunately, this attitude may have delayed IPT initiation in children with poorer immunity, despite these children being, in principle, most likely to benefit from IPT and being at a greater risk of developing active TB.

Assessing the view of HCWs involved in the program was a critical step to explore the reasons of delays in implementing IPT. Several HCWs noted that IPT implementation was difficult, particularly in the postscreening phase. The 3 elements identified as reasons for delay in IPT initiation were: increased pill burden, poor adherence to cART at TB screening, and poor attendance to periodical HIV follow-ups. These findings confirmed the hypotheses that clinicians may have been more comfortable in initiating IPT if a child had good adherence to cART.

TB-related stigma, reported by other studies conducted in adults,[26,27] was another factor highlighted by HCWs, probably due to IPT being provided in the TB unit. It is possible that the need to be referred to the TB unit and the fear of queuing near those on TB treatment contributed to the delay in IPT initiation. For this reason, future IPT implementation programs should be fully integrated within routine HIV delivery systems, rather than be a part of TB-related activities. In addition, child and family awareness of the importance and benefits of IPT should be improved, focusing on more effective education, as suggested by other studies conducted among adults who are HIV infected.[27] Finally, clinical signs and/or the lack of recent LFTs at TB screening, fear of INH-related side effects, and distance from the clinic were reported as additional reasons for delayed IPT initiation.

These observational findings do not rule out either measured or unmeasured confounders. Difficulties in ruling out active TB because of either the poor specificity of the WHO 2011 clinical algorithm or the lack of adequate diagnostic tools, could have led to the selection bias. High turnover of HCWs and poor motivation could also have had considerable implications in delaying IPT initiation. Data were collected through several steps, from paper-based files and registers to an electronic interface; inappropriate data collection and reporting could have led to the reporting bias. Another major limitation of our study is the lack of a definite estimation of INH toxicity rates, because of either the missing baseline LFTs or lack of further examinations to investigate other causes of liver toxicity.

We were unable to investigate the efficacy of IPT in reducing TB incidence and mortality. As most children were receiving cART, the generalizability of our findings to untreated children who are HIV positive or those with poor cART compliance or clinical follow-ups, was reduced.

Our experience shows that ICF/IPT is safe for children with HIV receiving cART and can be integrated within routine HIV programs, however, further implementation projects are urgently needed to explore operational challenges affecting the feasibility of IPT implementation and for better identifying the optimal strategies of IPT delivering in a resource-constrained setting. Major efforts should be made to allocate adequate human, technical and, financial resources to IPT implementation. Additional operational research can be instrumental to evaluate the currently recommended screening algorithm to maximize case finding without delaying critical TB-preventive interventions such as IPT. Preventing TB in children living with HIV means saving lives.

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