Original Article

Tuberculosis in Pediatric Antiretroviral Therapy Programs in Low- and Middle-Income Countries: Diagnosis and Screening Practices

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Background. The global burden of childhood tuberculosis (TB) is estimated to be 0.5 million new cases per year. Human immunodeficiency virus (HIV)–infected children are at high risk for TB. Diagnosis of TB in HIV-infected children remains a major challenge.

Methods. We describe TB diagnosis and screening practices of pediatric antiretroviral treatment (ART) programs in Africa, Asia, the Caribbean, and Central and South America. We used web-based questionnaires to collect data on ART programs and patients seen from March to July 2012. Forty-three ART programs treating children in 23 countries participated in the study.

Results. Sputum microscopy and chest Radiograph were available at all programs, mycobacterial culture in 40 (93%) sites, gastric aspiration in 27 (63%), induced sputum in 23 (54%), and Xpert MTB/RIF in 16 (37%) sites. Screening practices to exclude active TB before starting ART included contact history in 41 sites (84%), symptom screening in 38 (88%), and chest Radiograph in 34 sites (79%). The use of diagnostic tools was examined among 146 children diagnosed with TB during the study period. Chest Radiograph was used in 125 (86%) children, sputum microscopy in 76 (52%), induced sputum microscopy in 38 (26%), gastric aspirate microscopy in 35 (24%), culture in 25 (17%), and Xpert MTB/RIF in 11 (8%) children.

Conclusions. Induced sputum and Xpert MTB/RIF were infrequently available to diagnose childhood TB, and screening was largely based on symptom identification. There is an urgent need to improve the capacity of ART programs in low- and middle-income countries to exclude and diagnose TB in HIV-infected children.

Key words. HIV; low-income countries; pediatric; survey; tuberculosis.

INTRODUCTION

The global burden of tuberculosis (TB) was estimated to be 8.7 million new cases in 2011, and approximately 0.5 million were children [1]. Children are at high risk of progression to active TB and severe forms of TB. Young children with immature immune systems and human immunodeficiency virus (HIV)–infected children with severe immune deficiency have the highest risk of developing TB [2, 3]. Early mortality is a

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major issue among children starting antiretroviral treatment (ART) with advanced immunodeficiency in sub-Saharan Africa [4]. TB mortality and incidence in HIV-infected children can be substantially reduced by provision of isoniazid preventive therapy (IPT) following TB exposure and by ART [5–7]. However, TB-HIV co-infection poses significant therapeutic challenges due to overlapping drug toxicities, medication load, and drug interactions [8, 9].

The diagnosis of childhood TB is complicated by the paucibacillary nature of the disease in children, which may be even more pronounced in HIV-coinfected patients [10]. Traditionally, the diagnosis of pediatric TB relies on exposure history, chest radiography, tuberculin skin testing (TST), and sputum smear microscopy [11, 12]. Molecular tests have recently been introduced to improve TB diagnosis and detect drug resistance [13–15]. However, it is unknown to what extent these approaches have been implemented in pediatric ART programs, especially in low- and middle-income countries.

We conducted a comprehensive survey among pediatric ART programs from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) network, a large collaboration of ART programs in low- and middle-income countries, with the aim of assessing the availability and use of TB diagnostic tools, screening practices, and treatment.

METHODS

Study Setting

The IeDEA collaboration (www.iedea.org) includes ART programs from sub-Saharan Africa, the Caribbean, Central and South America, Asia-Pacific, and North America [16]. For the present study, we surveyed ART programs treating children in low- and middle-income countries from the African IeDEA regions, the Caribbean, Central and South American region, and Asia-Pacific between March 1 and July 1, 2012. Participating sites as well as members of the TB and pediatric IeDEA working groups are listed in the Acknowledgments.

Data Collection and Definitions

Data on ART programs and patients seen during the study period were collected using REDCap (http://project-redcap.org/), a web-based platform to create online questionnaires [17]. The overall survey project and the participating sites are described in detail elsewhere [18]. The first part of the survey collected data on program-level characteristics related to the management of childhood TB (availability of diagnostic tools, screening, and treatment practices). The second part of the survey collected individual data on active pediatric TB cases seen consecutively during the study period (March 1–July 1, 2012) and whose clinical data were available. Eighteen sites did not contribute individual-level patient data because the data collection was not covered by the local Institutional Review Board (IRB) approval, because of logistical reasons, or because no pediatric HIV-infected TB cases were seen during the study period. TB cases were defined based on the local case definition; all received anti-TB treatment.

Children were defined as aged below 15 years at start of ART. Sputum smear microscopy, mycobacterial culture, Xpert MTB/RIF, chest radiograph, and TST were considered to be available for the diagnosis of childhood TB if these tools were available on site or within 50 km of a given ART program. Induced sputum or gastric aspiration for the collection of TB samples were defined as available whenever these tools were reported to be part of the TB screening practices of an ART program.

Statistical Analyses

Descriptive statistics were used to describe the characteristics of participating ART programs, the characteristics of pediatric TB patients seen during the study period, the availability of diagnostic tools for pediatric TB, and the screening and treatment practices. We used χ^2 tests to assess differences in the availability of pediatric TB diagnostic tools by site characteristics.

If not otherwise stated, missing data were individually recovered from the sites. All analyses were performed in Stata version 12.1 (Stata Corporation, College Station, TX).

Ethics Statement

Data were collected through IeDEA cohorts. Ethics committees and/or IRBs in all host countries approved the collection and transfer of anonymized data. Where requested per local regulations, informed consent was provided. In addition, the Vanderbilt University Health Science Committee (Nashville, TN), the Ethics Committee of the University of Bern (Switzerland), and the University of Cape Town (South Africa) approved the analyses of these observational data for this specific project.

RESULTS

Characteristics of Participating Pediatric ART Programs

Seventy-one sites treating adults or children were invited and 58 (81.7%) participated in the survey. Fifteen sites were treating adults only. Here, we analyzed the data from the 43 ART programs treating children across 23 countries. Of these, 11 (25.6%) sites were only treating children and 32 (74.4%) were treating both adults and children. Thirteen (30.2%) sites were primary health care centers or clinics, 6 (14.0%) were secondary, district, or provincial hospitals, and 23 (55.8%) were tertiary teaching

or referral hospitals. Thirty-four sites (79.1%) were urban, 7 (16.3%) periurban, and 2 (4.6%) were rural (Table 1).

The geographical distribution of the 43 participating pediatric ART programs is shown in Figure 1.

Availability of TB Diagnostics and Associated Factors

Sputum microscopy and chest radiograph were available for the diagnosis of TB in all sites (43, 100%), mycobacterial culture in 40 (93.0%), gastric aspiration in 27 (62.8%), TST in 26 (60.5%), induced sputum in 23 (53.5%), and Xpert MTB/RIF in 16 (37.2%) sites (Table 1). Eleven (25.6%) sites had no access to either gastric aspiration or induced sputum for specimen collection. When restricting to childhood TB diagnostic tools available on site only (and not distantly), we found that 34 programs (79.1%) had direct access to radiographs, 31 (72.1%) to sputum microscopy, 19 (44.2%) to TST, 9 (20.9%) to mycobacterial culture, and 9 programs (20.9%) had direct access to Xpert MTB/RIF.

The availability of sputum collection and diagnostic tools for pediatric TB by the characteristics of participating ART programs is described in Table 2. The availability of gastric aspiration was lower in East Africa and Southern Africa than in the other regions ($P < .001$). In contrast, the availability of induced sputum and Xpert MTB/RIF did not significantly vary across geographical regions. Gastric aspiration ($P = .04$) and TST ($P = .008$) were available more often in urban sites than in periurban or rural settings. Xpert MTB/RIF tended to be more frequently available in larger ART programs that in smaller ones ($P = .07$), and in periurban or rural sites than in urban ones, although not significantly (55.6% versus 32.4%, respectively, $P = .2$).

TB Screening Practices

Screening practices to rule out active TB before starting ART are shown in Table 3. They included contact history (41 sites, 95.4%), weight loss (41 sites, 95.4%), fever screening (38, 88.4%), cough screening (36, 83.7%), chest radiograph (34, 79.1%), sputum microscopy (25, 58.1%), gastric aspiration (15, 34.9%), TST (15, 34.9%), mycobacterial culture (12, 27.9%), and induced sputum microscopy (6, 14.0%). Some screening practices varied across regions (Table 3). Gastric aspiration microscopy as part of screening practices was the least common in Southern Africa (7.7% of sites included it in their screening practices) and most common in the Caribbean, and Central and South America (100% of sites). Mycobacterial culture as part of screening practices was the least common in West Africa (0% of sites included it in their screening practices) and most common in the Caribbean, Central and South America (100% of sites). The use of Xpert MTB/RIF for the screening of childhood TB varied between 0% of sites in Asia-Pacific, Central and West Africa, and 33.3% of sites in the Caribbean, Central, and South America.

TB Treatment Practices

The pediatric treatment regimens for both drug susceptible and multidrug resistant (MDR) TB are presented in Table 3 and Supplementary Table 1 (see online supplementary material for Supplementary Table 1), respectively. The most common first-line regimen was composed of 2 months on isoniazid, rifampicin, and pyrazinamide, followed by 4 months on isoniazid and rifampicin (14 sites, 32.6%). MDR-TB regimens varied across sites (Supplementary Table 1); 18 sites (41.9%) reported not to have a specific MDR-TB regimen. IPT for children was given for 6 months by 17 (39.5%) sites, for 9 months by 3 (7.0%) sites, and lifelong by 1 (2.3%) site (Table 3). Thirteen (30.2%) sites reported never providing IPT to HIV-infected children after ruling out active TB.

Use of TB Diagnostics

The use of TB diagnostics was examined in 146 children with active TB seen and treated during the study period in 25 of the participating ART programs from 16 countries. Forty-nine (33.6%) children were seen in Asia-Pacific, 43 (29.4%) in Southern Africa, 19 (13.0%) in West Africa, 15 (10.3%) in Central Africa, 15 (10.3%) in East Africa, and 5 (3.4%) in the Caribbean, and Central and South America. Eighteen sites out of 43 did not contribute individual-level patient data (3 in Asia-Pacific, 2 in the Caribbean, Central and South America, 3 in Central Africa, 4 in Southern Africa, and 6 in West Africa) because the data collection was not covered by the local IRB approval, or because of logistical reasons (eg, lack of staff resources).

Median age was 4.7 years (interquartile range [IQR] 1.6–8.3), 78 (53.4%) were female, 113 (77.4%) had pulmonary TB, and the median CD4 cell count was 280 cells/μL (interquartile range: 53–773, Table 4). Overall, chest radiography was performed in 125 (85.6%) children, sputum microscopy in 76 (52.0%), induced sputum microscopy in 38 (26.0%), gastric aspiration in 35 (24.0%), culture in 25 (17.1%), and Xpert MTB/RIF in 11 (7.5%).

DISCUSSION

We surveyed 43 pediatric sites participating in a network of ART programs in low- and middle-income countries to assess the availability and the use of diagnostic tools and treatment for childhood TB, as well as screening practices. We found that sputum microscopy and chest radiography were the most commonly available TB diagnostic tools in pediatric ART programs, followed by mycobacterial

Table 1. Program Characteristics and Availability of Tuberculosis Diagnostic Tools in 43 ART Programs Treating Children in Low- and Middle-Income Countries Within the IeDEA Collaboration, Overall and by IeDEA Regions in 2012

Characteristic *n* (%)	All (*n* = 43)	Asia-Pacific (*n* = 6)	Caribbean, Central and South America (*n* = 3)	Central Africa (*n* = 5)	East Africa (n = 6)	Southern Africa (n = 13)	West Africa (*n* = 10)
Number of countries, *n*	23	4	3	4	3	5	4
Setting							
Urban	34 (79.1)	6 (100)	3 (100)	5 (100)	2 (33.3)	9 (69.2)	9 (90)
Periurban	7 (16.3)	0	0	0	2 (33.3)	4 (30.8)	1 (10)
Rural	2 (4.6)	0	0	0	2 (33.3)	0	0
Level of care							
Primary	13 (30.2)	0	0	0	2 (33.3)	9 (69.2)	2 (20)
Secondary	6 (14.0)	0	1 (33.3)	2 (40.0)	1 (16.7)	1 (7.7)	1 (10)
Tertiary	24 (55.8)	6 (100)	2 (66.7)	3 (60.0)	3 (50.0)	3 (23.1)	7 (70)
Patients treated at ART program							
Children only	11 (25.6)	5 (83.3)	0	0	0	1 (7.7)	5 (50)
Adults and children	32 (74.4)	1 (16.7)	3 (100)	5 (100)	6 (100)	12 (92.3)	5 (50)
Number of children followed in HIV care at time of survey[a]	33,432	2,066 (6.2)	422 (1.3)	1358 (4.1)	17,788 (53.2)	6861 (20.5)	4937 (14.7)
New pediatric TB cases per year,[b] *n*	1,606	79	42	78	247	879	83
Sputum smear microscopy available	43 (100)	6 (100)	3 (100)	5 (100)	6 (100)	13 (100)	10 (100)
Induced sputum microscopy available[c]	23 (53.5)	5 (83.3)	1 (33.3)	3 (60.0)	2 (33.3)	7 (53.9)	5 (50.0)
Gastric aspirate microscopy available[c]	27 (62.8)	6 (100)	3 (100)	4 (80)	1 (16.7)	4 (30.8)	9 (90)
Mycobacterial culture available	40 (93.0)	6 (100)	3 (100)	4 (80.0)	5 (83.3)	12 (92.3)	10 (100)
Xpert MTB/RIF available	16 (37.2)	1 (16.7)	1 (33.3)	1 (20.0)	3 (50.0)	7 (53.9)	3 (30.0)
Chest radiograph available	43 (100)	6 (100)	3 (100)	5 (100)	6 (100)	13 (100)	10 (100)
Tuberculin skin test available	26 (60.5)	5 (83.3)	2 (66.7)	5 (100)	1 (16.7)	4 (30.8)	9 (90.0)

Abbreviations: ART, antiretroviral treatment; HIV, human immunodeficiency virus; IeDEA, International Epidemiologic Databases to Evaluate AIDS; TB, tuberculosis.

[a]Actively followed up at the time of the survey.

[b]Most recent year.

[c]Induced sputum and gastric aspiration microscopy were defined as available when these tools were reported as part of the TB screening recommendations in place at a given ART program.

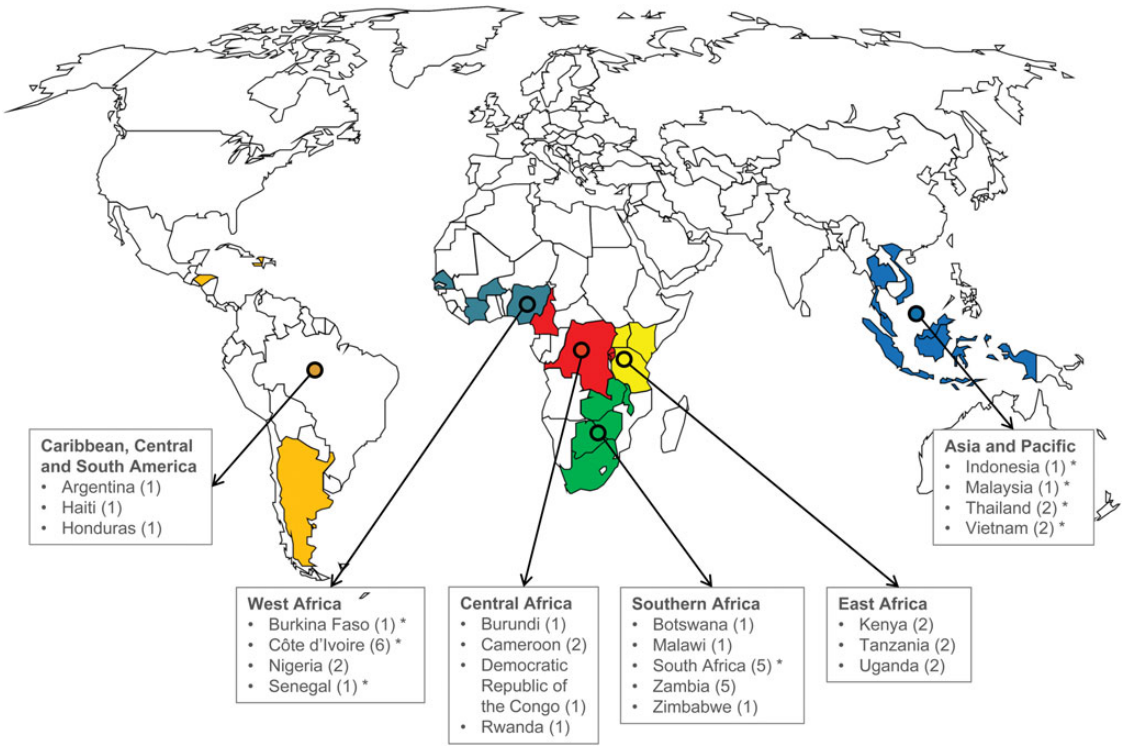

Figure 1. Geographical distribution of the 43 pediatric human immunodeficiency virus treatment programs from the International Epidemiologic Databases to Evaluate AIDS (IeDEA) network participating in the project. Numbers in parentheses indicate the number of participating sites in each country. Asterisk indicates a country with at least one site treating pediatric patients only.

culture. Screening practices mainly relied on TB symptoms and less frequently on the use of tools such as induced sputum microscopy, gastric aspiration, or Xpert MTB/RIF. Nearly a third of the participating ART programs reported never providing IPT to HIV-infected children even after active TB was ruled out. At the patient-level, Xpert MTB/RIF and pediatric-specific sputum collection tools such as induced sputum or gastric aspirate were used in only a few children.

One quarter of the sites did not have access to either gastric aspiration or induced sputum microscopy, and almost two thirds did not have access to Xpert MTB/RIF, even though these techniques have been shown to be safe and useful for the diagnosis of childhood TB [15, 19, 20]. A previous study surveyed pediatric ART programs of the IeDEA collaboration in Asia-Pacific and Africa and reported a lower availability of TB diagnostic tools in 2010 compared to our observations [21]. This may be partly explained by the fact that the latter study restricted its analyses to the availability of TB diagnostics on site directly, whereas our study considered availability on or off site. When restricting the definition to diagnostic tools for pediatric TB accessible directly on site, the availability was indeed drastically reduced. For instance, the availability of mycobacterial culture dropped from 93% to 21% when restricting to sites with direct access only. A recent survey by the International Center for AIDS Care and Treatment Programs (ICAP) program showed a lower availability of pediatric-specific TB diagnostic tools in HIV care centers from sub-Saharan Africa than in the current study [22]. However, the ICAP program includes a larger proportion of smaller sites in remote areas, and also fewer tertiary care sites; hence, sophisticated diagnostic tools may be scarcer in these settings.

Our study has several limitations. The description of program characteristics reflects the situation observed at the time of the survey. Therefore, we cannot exclude exceptional irregularities in the availability and use of TB diagnostic tools or treatments. Furthermore, the ART programs participating in the IeDEA collaboration may not necessarily represent all ART programs in a country or region. Indeed, heterogeneity in TB diagnostic practices has been shown within and between countries [23]. This survey covered a majority of urban sites and tertiary care sites, where access to pediatric-specific TB diagnostic tools was likely to be better than rural and lower level of care sites. Although pediatric HIV/TB co-infected cases are rarer than adult cases, we cannot exclude the possibility that some children seen during the study period did not participate in the survey or were not screened for TB, which could explain the

Table 2. Program-Level Characteristics and Availability of Induced Sputum Microscopy, Gastric Aspirate Microscopy, Xpert MTB/RIF, Mycobacterial Culture, and Tuberculin Skin Testing (TST) in 43 ART Programs Treating Children in Low- and Middle-Income Countries

Program Characteristic	Total	Induced Sputum[a]		Gastric Aspiration[a]		Xpert MTB/RIF		Mycobacterial Culture		TST	
		n (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value	*n* (%)	*P*-value
Total		23 (53.5)		27 (62.8)		16 (37.2)		40 (93.0)		26 (60.5)	
IeDEA region			0.59		0.001		0.561		0.607		0.003
Asia-Pacific	6	5 (83.3)		6 (100)		1 (16.7)		6 (100)		5 (83.3)	
Caribbean, Central and South America	3	1 (33.3)		3 (100)		1 (33.3)		3 (100)		2 (66.7)	
Central Africa	5	3 (60.0)		4 (80.0)		1 (20.0)		4 (80.0)		5 (100)	
East Africa	6	2 (33.3)		1 (16.7)		3 (50.0)		5 (83.3)		1 (16.7)	
Southern Africa	13	7 (53.9)		4 (30.8)		7 (53.9)		12 (92.3)		4 (30.8)	
West Africa	10	5 (50.0)		9 (90.0)		3 (30.0)		10 (100)		9 (90.0)	
Setting			0.17		0.040		0.200		0.584		0.008
Urban	34	20 (58.8)		24 (70.6)		11 (32.4)		32 (94.1)		24 (70.6)	
Periurban and rural	9	3 (33.3)		3 (33.3)		5 (55.6)		6 (85.7)		1 (14.3)	
Level of care			0.36		0.005		0.727		0.557		0.149
Primary	13	6 (46.2)		4 (30.8)		6 (46.2)		12 (92.3)		5 (38.5)	
Secondary	6	2 (33.3)		3 (50.0)		2 (33.3)		5 (83.8)		4 (66.7)	
Tertiary	23	15 (62.5)		20 (83.3)		8 (33.3)		23 (95.8)		17 (70.8)	
Patients treated at ART program			0.14		0.003		0.025		0.292		0.093
Children only	11	8 (72.7)		11 (100)		1 (9.1)		11 (100)		9 (81.8)	
Children and adults	32	15 (46.9)		16 (50.0)		15 (46.9)		29 (90.6)		17 (53.1)	
Number of children followed in HIV care at time of survey[b]			0.33		0.228		0.011		0.976		0.329
<500	29	17 (58.6)		20 (69.0)		7 (24.1)		27 (93.1)		19 (65.5)	
500 and above	14	6 (42.8)		7 (50.0)		9 (64.3)		13 (92.9)		7 (50.0)	
New TB cases per year[c]			0.054[d]		0.086[d]		0.071[d]		0.949[d]		0.339[d]
<10	18	13 (72.2)		14 (77.8)		4 (22.2)		17 (94.4)		13 (72.2)	
10–29	10	3 (30.0)		6 (60.0)		3 (30.0)		9 (90.0)		6 (60.0)	
≥30	13	5 (38.5)		5 (38.5)		8 (61.5)		12 (92.3)		6 (46.1)	
Missing information	2	2 (100)		2 (100)		1 (50.0)		2 (100)		1 (50.0)	

Results for sputum microscopy and chest X-ray are not shown because these diagnostic tools were available at all sites.

P values from χ^2 tests.

Abbreviations: ART, antiretroviral treatment; TB, tuberculosis; TST, tuberculin skin testing.

[a]Induced sputum and gastric aspiration microscopy were defined as available when these tools were reported as part of the TB screening recommendations in place at a given ART program.

[b]Actively followed up at the time of the survey.

[c]Most recent year.

[d]*P* values calculated excluding sites with missing information.

Table 3. Practices Related to Tuberculosis Screening, Isoniazid Preventive Therapy, and Tuberculosis Treatment at 43 ART Programs Treating Children in Low- and Middle-Income Countries Within the IeDEA Collaboration, Overall and by IeDEA Regions in 2012

ART Program Data n (%)	All	Asia- Pacific	Caribbean, Central and South America	Central Africa	East Africa	Southern Africa	West Africa
Total number of ART programs	43	6	3	5	6	13	10
TB screening practices before starting ART[a]							
Cough	36 (83.7)	5 (83.3)	3 (100)	5 (100)	5 (83.3)	12 (92.3)	6 (60.0)
Fever	38 (88.4)	5 (83.3)	3 (100)	5 (100)	6 (100)	11 (84.6)	8 (80.0)
Night sweats	38 (88.4)	5 (83.3)	3 (100)	5 (100)	5 (83.3)	12 (92.3)	8 (80.0)
Weight loss	41 (95.4)	6 (100)	3 (100)	4 (80.0)	6 (100)	12 (92.3)	10 (100)
Contact history	41 (95.4)	6 (100)	3 (100)	5 (100)	5 (83.3)	12 (92.3)	10 (100)
Sputum smear microscopy	25 (58.1)	4 (66.7)	2 (66.7)	3 (60.0)	3 (50.0)	6 (46.2)	7 (70.0)
Induced sputum microscopy	6 (14.0)	0	1 (33.3)	0	1 (16.7)	3 (23.1)	1 (10.0)
Gastric aspirate microscopy	15 (34.9)	5 (83.3)	3 (100)	3 (60.0)	0	1 (7.7)	3 (30.0)
Chest radiograph	34 (79.1)	6 (100)	3 (100)	4 (80.0)	4 (66.7)	9 (69.2)	8 (80.0)
Culture	12 (27.9)	3 (50.0)	3 (100)	1 (20.0)	1 (16.7)	4 (30.8)	0
Xpert MTB/RIF	3 (7.0)	0	1 (33.3)	0	1 (16.7)	1 (7.7)	0
TST	15 (34.9)	3 (50.0)	2 (66.7)	1 (20.0)	0	3 (23.1)	6 (60.0)
Administration of IPT							
Never	13 (30.2)	1 (16.7)	0	1 (20.0)	4 (66.6)	3 (23.1)	4 (40.0)
Not applicable	6 (14.0)	0	0	1 (20.0)	0	2 (15.4)	3 (30.0)
Always (any age)	4 (9.3)	1 (16.7)	1 (33.3)	0	1 (16.7)	1 (7.7)	0
Only children >12 months	3 (7.0)	1 (16.7)	0	1 (20.0)	1 (16.7)	0	0
Only if TST-positive	2 (4.6)	0	2 (66.7)	0	0	0	0
Other	15 (34.9)	3 (49.9)	0	2 (40.0)	0	7 (53.8)	3 (30.0)
Duration of IPT							
6 months	17 (39.5)	4 (66.7)	0	3 (60.0)	1 (16.7)	7 (53.9)	2 (20.0)
9 months	3 (7.0)	1 (16.7)	1 (33.3)	0	1 (16.7)	0	0
Lifetime	1 (2.3)	0	1 (33.3)	0	0	0	0
Others	22 (51.2)	1 (16.7)	1 (33.3)	2 (40.0)	4 (66.7)	6 (46.1)	8 (80.0)
TB treatment regimen (first-line)							
2HRZ, 4HR	14 (32.6)	1 (16.7)	0	3 (60.0)	3 (50.0)	3 (23.1)	4 (40.0)
2HRZE, 4HR	10 (23.7)	2 (33.3)	1 (33.3)	1 (20.0)	1 (16.7)	4 (30.7)	1 (10.0)
Other	13 (30.2)	3 (50.0)	0	1 (20.0)	1 (16.7)	3 (23.1)	5 (50.0)
None	6 (13.9)	0	2 (66.6)	0	1 (16.7)	3 (23.1)	0
MDR-TB treatment regimen							
Specific regimen reported[b]	8 (18.6)	1 (16.7)	0	2 (40.0)	0	1 (7.7)	5 (50.0)
No specific regimen reported	18 (41.9)	0	2 (66.7)	2 (40.0)	3 (50.0)	9 (69.2)	2 (20.0)
Individualized[c]	9 (20.9)	5 (83.3)	0	0	2 (33.3)	2 (15.4)	0
Referral	8 (18.6)	0	1 (33.3)	1 (20.0)	0	1 (7.7)	5 (50.0)

Abbreviations: ART, antiretroviral treatment; IPT, isoniazid preventive therapy; leDEA, International Epidemiologic Databases to Evaluate AIDS; MDR, multidrug-resistant; TB, tuberculosis; TB treatment regimens: E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide; TST, tuberculin skin testing.

[a]Multiple answers were possible.

[b]See Supplementary Table 1.

[c]Individualized MDR-TB treatment regimens based on drug susceptibility testing and/or availability of drugs.

Table 4. Characteristics of 146 HIV-Infected Children Diagnosed with Tuberculosis During the Study Period in 25 Participating ART Programs from 16 Low- and Middle-Income Countries

Characteristic	*n* (%)
IeDEA region	
Asia-Pacific	49 (33.6)
Caribbean, Central and South America	5 (3.4)
Central Africa	15 (10.3)
East Africa	15 (10.3)
Southern Africa	43 (29.4)
West Africa	19 (13.0)
Age, median (IQR) years	4.7 (1.6–8.3)
Female sex, *n* (%)	78 (53.4)
Site of disease, *n* (%)	
Pulmonary	113 (77.4)
Extrapulmonary	33 (22.6)
Patient category, *n* (%)	
New case	132 (90.4)
Relapse	2 (1.4)
Other	12 (8.2)
CD4 cell count (cells/μL),[a] median (IQR)	280 (53–773)
CD4 percentage (%),[a] median (IQR)	12 (3–20)
WHO clinical stage,[a] *n* (%)	
I/II	6 (4.1)
III/IV	134 (91.8)
Unknown	6 (4.1)
Median delay between TB treatment and ART, days, (IQR)	34 (0–103)
On TB treatment before starting ART, *n* (%)	77 (52.7)
Previous history of TB, *n* (%)	12 (8.2)
Diagnostic test done, *n* (%)	
Chest radiograph	125 (85.6)
Sputum microscopy	76 (52.0)
Induced sputum microscopy	38 (26.0)
Gastric aspirate microscopy	35 (24.0)
Culture	25 (17.1)
Xpert MTB/RIF	11 (7.5)
Fever, *n* (%)	108 (74.0)
Coughing >3 weeks, *n* (%)	98 (67.1)
Weight loss, *n* (%)	98 (67.1)
Night sweats, *n* (%)	60 (41.1)

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; leDEA, International Epidemiologic Databases to Evaluate AIDS; TB, tuberculosis; WHO, World Health Organization.
[a]At the start of ART.

low number of patients included in the patient data collection. This might potentially reduce the generalizability of the results from the individual-level patient data analyses. The strength of our study was the inclusion of sites in various regions, which is likely to provide a global representation of TB care practices in ART programs. In addition, the structure of the survey allowed comparing the availability of pediatric TB diagnostic tools with their use at the patient level. This provides information on the important gap between access to tools and their actual use for diagnosis.

In conclusion, we found that childhood TB diagnostic tools are still infrequently available and used in pediatric ART programs of low- and middle-income countries. The use of TB diagnostic tools, particularly rapid molecular diagnostics such as Xpert MTB/RIF, remain a challenge in pediatric ART programs worldwide, despite an increasing number of studies demonstrating that these tests are valid and useful in children and in adults [15, 24, 25]. The successful rollout of Xpert MTB/RIF certainly requires that the machines be made available close to points of care and used within an algorithm process to increase the TB diagnosis accuracy according to the prevalence context. Beyond the machine provision, the success of Xpert MTB/RIF will need to be accompanied by adequate training and equipment maintenance, regular reagent supply, and affordable cost to the patient in order to increase use. The paucibacillary nature of TB in children is associated with low yield of microscopy and cultures. Therefore, the scale-up of highly sensitive molecular diagnostics such as Xpert MTB/RIF, alone or in combination with additional diagnostics, may become a key element in ART programs caring for HIV-infected children in high TB prevalence settings.

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