Published in final edited form as:

Int J Tuberc Lung Dis. 2014 November ; 18(11): 1327–1336. doi:10.5588/ijtld.14.0106.

Detection and management of drug-resistant tuberculosis in HIV-infected patients from lower income countries

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Abstract

Setting—Drug resistance threatens tuberculosis (TB) control, particularly among HIV-infected persons.

Objective—We surveyed antiretroviral therapy (ART) programs from lower-income countries on prevention and management of drug-resistant TB.

Design—We used online questionnaires to collect program-level data in 47 ART programs in Southern Africa (14), East Africa (8), West Africa (7), Central Africa (5), Latin America (7) and Asia-Pacific (6 programs) in 2012. Patient-level data were collected on 1,002 adult TB patients seen at 40 of the participating ART programs.

Results—Phenotypic drug susceptibility testing was available at 36 (77%) ART programs, but only used for 22% of all TB patients. Molecular drug resistance testing was available at 33 (70%)

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Authors' contributions

Conceived and designed the study: CG TRS ME LF. Analyzed the data: MB CG. Contributed patient data: VN RW JCD EJC CPC CCM LD LR DH SK QTD. Wrote the manuscript: MB VN RW JCD EJC CPC CCM LD CG LR DH SK QTD TRS ME LF. All authors approved the final version of the manuscript, and met the criteria of the ICMJE.

Competing interests

TRS reports grant support to Vanderbilt University from Pfizer, Bristol Myers Squibb and Virco. TRS has acted as a consultant to Sanofi-Aventis and as a member of a Data Safety Monitoring Board for Otsuka. All other authors declare that they have no competing interests.

programs and used for 23% of all TB patients. Twenty ART programs (43%) provided directly observed therapy (DOT) during the whole treatment, 16 (34%) during intensive phase only and 11 (23%) did not follow DOT. Fourteen (30%) ART programs reported no access to second-line TB regimens; 18 (38%) reported TB drug shortages.

Conclusions—Capacity to diagnose and treat drug-resistant TB was limited across ART programs in lower income countries. DOT was not always implemented and drug supply was regularly interrupted, which may contribute to the global emergence of drug resistance.

Keywords

MDR-TB; ART programs; Africa; Asia; Latin America

INTRODUCTION

Tuberculosis (TB) is one of the most common opportunistic co-infections among HIV-infected individuals, particularly in resource-limited settings (1). HIV infection is associated with higher risk of TB and increases the lifetime risk of progression from *Mycobacterium tuberculosis* infection to active disease (2–4). The increasing number of multidrug-resistant (MDR) TB cases presents another challenge to TB control (5–7). Resistance to first-line drugs is emerging globally, included in HIV-coinfected individuals. It is estimated that about 3–4% of all new TB cases have MDR-TB, and only few of them are diagnosed and appropriately treated (8).

Strategies to prevent the spread of drug-resistant TB include rapid diagnosis, early initiation of adequate treatment, patient follow-up and surveillance (9–11). The diagnosis of drug-resistant TB using molecular tools targeting resistance-conferring mutations offers advantages over mycobacterial cultures, which can be difficult to implement in resource-limited settings (12–14). When drug resistance is suspected and in case of HIV/TB co-infection, the World Health Organization (WHO) recommends the use of culture-independent molecular tools, such as Xpert MTB/RIF (Cepheid, USA), to rapidly identify MDR-TB (10, 15). Apart from prompt identification of drug resistance, adequate treatments are crucial for the prevention and management of drug-resistant TB (10, 16). The DOTS strategy contributes to maintaining patient adherence to treatment. Directly observed therapy (DOT) and uninterrupted drug supply are central elements in preventing of drug resistance (10, 17).

We surveyed ART programs from low- and middle-income countries in sub-Saharan Africa, Asia-Pacific, the Caribbean, Central and South America. We describe practices related to prevention, diagnosis and treatment of drug-resistant TB in HIV-infected adults.

METHODS

Participating ART programs

The International epidemiologic Databases to Evaluate AIDS (IeDEA) is a global network of ART programs (11, 16, 18). Participating programs routinely collect data on HIV-infected persons. We surveyed IeDEA ART programs in Sub-Saharan Africa, Asia-Pacific, and the

Caribbean, Central and South America. Seventy-one programs were invited, 58 (81.7%) participated. Forty-seven ART programs were treating adults, 11 were pediatric clinics. Here, we focused on the 47 programs treating adult HIV-infected patients (>15 years) (19), and excluded pediatric-specific sites (20).

Survey and definitions

The survey project is described in details elsewhere (18). In brief, we surveyed ART programs treating HIV-infected adults in sub-Saharan Africa, Asia and Latin America between March 1 and July 1, 2012. Forty-seven sites from 26 countries participated. We used the Research Electronic Data Capture (REDCap) tool to collect data (www.project-redcap.org) (21). The first section of the survey collected data on prevention and management of TB in HIV-infected persons at participating ART programs, including program characteristics, proximity of phenotypic drug susceptibility testing (DST) and molecular tests to detect drug-resistant TB, DOT practices, drug supply, and treatment regimens. The second section collected individual-level data, including age, sex, CD4 cell counts, TB disease characteristics, and use of DST or molecular drug resistance tests at the time of TB diagnosis for all adult HIV-infected persons with active TB seen at the participating ART programs during the study period, irrespective of drug resistance status.

When not otherwise specified, we defined the proximity of drug resistance detection tools as availability on site or within 50km. We defined the proximity of molecular tests for drug resistance identification as availability of GenoType MTBDR*plus* (Hain Lifescience, Germany) and/or Xpert MTB/RIF on site or within 50km. MDR-TB was defined when resistance to isoniazid and rifampicin was confirmed by any method (or rifampicin resistance only if Xpert MTB/RIF was used). Country incomes were categorized into “low income”, “lower-middle income” or “upper-middle income” according to the World Bank classification (<http://data.worldbank.org/about/country-classifications/country-and-lending-groups>).

Statistical analyses

We used descriptive statistics to explore characteristics of participating ART programs, availability of drug resistance detection methods, treatment practices and patient characteristics. We used χ^2 tests to investigate associations between ART program characteristics and availability of drug resistance detection methods, their use, and history of drug shortages. We also used χ^2 tests to investigate associations between patient characteristics and use of drug resistance detection methods. Analyses were performed in Stata version 12.1 (Stata Corporation, USA).

Ethics approval

Data were collected through IeDEA cohorts. Ethics committees and/or institutional review boards in all countries approved the collection and transfer of anonymized data. Written informed consent was obtained in places where it was requested per local regulations. Vanderbilt University School of Medicine (Nashville, USA), the Ethics Committee of the University of Bern (Switzerland) and University of Cape Town (South Africa) approved the analyses.

RESULTS

ART program and patient characteristics

Forty-seven adult ART programs from 26 countries participated: 14 (29.8%) in Southern Africa, eight (17.0%) in East Africa, seven (14.9%) in West Africa, seven (14.9%) in the Caribbean, Central and South America, six (12.8%) in Asia-Pacific, and five (10.6%) in Central Africa. The majority of ART programs were urban (38, 80.9%), tertiary health care centers (24, 51.1%), and had a specialized TB clinic on site with dedicated staff (28, 59.6%). Fifteen programs (31.9%) were in low-income countries, 18 in lower-middle-income countries (38.3%), and 14 in upper-middle-income countries (29.8%).

We analyzed data from 1,002 HIV-infected adult TB patients seen during the study period in 40 of the participating ART programs from 22 countries: 488 in Southern Africa (48.7%), 257 in East Africa (25.6%), 99 in West Africa (9.9%), 73 in the Caribbean, Central and South America (7.3%), 50 in Central Africa (5.0%) and 35 in Asia-Pacific (3.5%). Median age was 34.8 years (interquartile range: 29.4–41.2), 449 (44.8%) were female, 875 (87.3%) were new cases, 81 (8.1%) relapse cases, and 15 (1.5%) retreatment cases (Supplementary Table 1).

Seven ART programs from four regions (Asia-Pacific, the Caribbean, Central and South America, Central Africa, and Southern Africa) did not contribute patient-level data because this part was not covered by local IRB approvals (four programs), or for logistical reasons (three programs).

Drug resistance detection methods

Table 1 shows the proximity of drug resistance detection tools. Phenotypic DST was available at 36 ART programs (76.6%). Of these, 9 (19.1%) had phenotypic DST directly on site. Eleven programs (23.4%) did not have access to phenotypic DST at all. Thirty-three ART programs (70.2%) had access to molecular tests for drug-resistant TB on or off site: GenoType MTBDR*plus* was available at 24 (51.0%) and Xpert MTB/RIF was available at 23 programs (48.9%). When available, 18 ART programs (75.0%) reported using GenoType MTBDR*plus* if drug resistance was suspected or after treatment failure. In contrast, only six ART programs (26.1%) reported using Xpert MTB/RIF if drug resistance was suspected or after treatment failure. Other reasons for using Xpert MTB/RIF included patient screening or smear-negative TB. Nineteen (40.4%) ART programs had access to at least one drug resistance detection method (phenotypic DST, molecular tool) directly on site. Four ART programs (8.5%) did not have access to any of the drug resistance detection methods on or off site.

The Caribbean, Central and South America, and Central Africa had the best access to phenotypic DST (100% of ART programs, on or off site). The poorest access was in East Africa (three ART programs with access to phenotypic DST [37.5%]; *P*-value 0.026). Urban ART programs had better access to phenotypic DST than peri-urban or rural ones (81.6%, 71.4% and 0%; *P* value 0.028). Eight ART programs (53.3%) had access to phenotypic DST on or off site in low-income countries, 14 (77.8%) in lower-middle-income countries and all 14 programs from upper-middle-income countries (*P* value 0.012, Table 2).

The availability of molecular tests on or off site to detect drug-resistant TB did not significantly differ across ART programs (Table 2).

Use of drug resistance detection methods

The use of drug resistance detection methods was assessed using patient-level data. Of 719 TB patients from ART programs with access to phenotypic DST, 158 (22.0%) were tested for drug resistance at the time of TB diagnosis by this method. Molecular tests were used to detect drug resistance at the time of TB diagnosis on 175/761 (23.0%) patients at ART programs where available (on or off site) (Table 3).

ART programs in upper-middle-income countries and in urban settings were more likely to have access to phenotypic DST (Table 2) and used phenotypic DST significantly more frequently than other ART programs (Table 3). Cost was associated with phenotypic DST use: 2.2% of patients were tested with phenotypic DST in ART programs where full costs were paid by patients, versus 31.6% where tests were free of charge (P value <0.0001). When available (on or off site), molecular tests to detect drug-resistant TB were most frequently used in Southern Africa (42.4% of patients tested). In contrast, none of the TB patients in Central Africa were tested with molecular tests where available (P value <0.0001). Molecular tests were used primarily in peri-urban ART programs (P value 0.018), and as for phenotypic DST, usage increased if tests were free for patients (P value <0.0001).

TB treatment and drug supply

Forty ART programs (85.1%) adopted the National TB Control Program recommendations for first-line treatment; seven (14.9%) used modified guidelines (Table 4). Twenty ART programs (42.6%) followed DOT over the whole treatment course, 16 (34.0%) only during the intensive phase, and 11 (23.4%) did not follow DOT at all. DOT was reported to be hospital-based at 12 (25.5%) and community-based at 4 (8.6%) ART programs. Specific MDR-TB treatment regimens were available at 26 ART programs (55.3%). Nineteen programs provided the detailed regimen (Supplementary Table 2). Fourteen programs (29.8%) reported not having specific MDR-TB regimens, seven (14.9%) referred their MDR-TB patients to other clinics. TB drugs were most commonly obtained from National TB Control Programs (44 ART programs, 93.6%).

Eighteen ART programs (38.3%) reported at least one TB drug shortage at present or in the previous two years (Table 5). Shortages were rare in Asia-Pacific (0%) and in the Caribbean, Central and South America (1 ART program, 14.3%), but most frequent in Africa: 62.5% of ART programs in East Africa experienced drug shortages, 60.0% in Central Africa, 50.0% in Southern Africa, and 28.6% in West Africa (P value 0.09). ART programs reported that shortages affected both first- and second-line drugs, between one week and 6 months. Common reasons for shortages were related to supply chain, poor communication at provincial or national level, low stocks or expired drugs. Drug shortages were not significantly associated with ART program characteristics (Table 5).

DISCUSSION

Our survey showed that the prevention and management of drug-resistant TB were poor in ART programs from low- and middle-income countries. Access to drug resistance detection was limited in some regions. And even when available, phenotypic or molecular tests were infrequently used. We observed a limited availability of specific MDR-TB regimens, inconsistent DOT implementation and common TB drug shortages, which may be obstacles to the completion of adequate TB treatments.

We observed that the availability and use of drug resistance detection tools varied across ART programs, although drug resistance testing is crucial to identify MDR-TB cases promptly and start adequate treatment regimens (5). A previous study also showed disparity in access to TB diagnostics across ART programs in low- and middle-income countries (22).

Even when available (on or off site), molecular tests to detect drug-resistant TB were not always used despite WHO recommendations of using Xpert MTB/RIF in all HIV-infected persons (15). This could reflect local guidelines, for example if molecular tests should only be used for retreatment or presumptive MDR-TB cases. It could also highlight, that operational aspects need to be considered when introducing new diagnostic tools (23). The successful implementation of Xpert MTB/RIF depends on the introduction of appropriate diagnostic algorithms, staff training, management of reagent supplies, and political commitment (6, 23, 24). Our results also indicate that available drug resistance tests may not be used unless they are free or affordable for patients.

Our study shows that 57% of ART programs did not use DOT throughout TB treatment course, and 38% reported shortages of first-line TB drugs. DOT can improve adherence to treatment, while the absence of DOT can lead to treatment discontinuation and emergence of drug resistance. Therefore, prevention and control of TB drug resistance essentially includes adherence to TB treatment, prompt drug resistance testing and availability of second-line drugs (17, 25, 26). We observed that almost one third of participating ART programs did not have specific regimens for MDR-TB and 15% would refer MDR-TB patients elsewhere. This could partly be explained by the need for extensive clinical experience on MDR-TB case management, principally due to the toxicity and duration of second-line regimens. It may also reflect national guidelines encouraging treatment of MDR-TB cases at centralized centers. The combination of low availability of DST and second-line drugs could result in unsuccessful treatment outcomes for patients with drug-resistant TB. It may also lead to prolonged infectious time and an increased risk of drug-resistant TB spread in the community.

This study is limited by the fact that our observations may only represent situations at the time of the survey. The individual-level data may in turn reflect general clinical practices at participating ART programs. It is also possible that ART programs from the IeDEA collaboration are not representative of TB general management. However, our survey covered rural and urban ART programs with different levels of care, in different continents. Therefore, our study is likely to accurately reflect the prevention and management of drug-resistant TB across a wide range of health care settings, including outside ART programs.

Our survey may not always reflect the situation at National TB Control Programs, and did not cover other aspects of the prevention and management of drug-resistant TB, such as delays before second-line treatment initiation, patient support during treatment and treatment outcomes.

CONCLUSIONS

In conclusion, we found that the diagnosis and treatment of drug-resistant TB need to be strengthened in ART programs from low- and middle-income countries. Molecular tests for the detection of drug-resistant TB were still rarely available and used, although they can potentially reduce delays between diagnosis and adequate treatment, and thus limit the spread of drug resistance. They can be particularly useful in remote settings where phenotypic DST is rarely feasible. Furthermore, enhancing DOT and maintaining uninterrupted drug supply could avoid unnecessary treatment interruptions, which may contribute to the emergence of drug resistance (27). Further studies are needed to better understand the magnitude of the MDR-TB burden in ART programs from low- and middle-income countries, as well as to understand why essential elements for the control of drug-resistant TB are not well implemented in the context of HIV care and how this could be improved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank all ART programs that participated in this survey and the patients whose data were used in this study. We are indebted to the advisory panel that helped to develop the survey project and the IeDEA Tuberculosis Working Group for following up on the project's progress. We thank Peter Cegielski for advice on the survey content. We also would like to thank all regional data centers that contributed to the coordination of the study, as well as the recording and entry of data. We are grateful to Marcel Zwahlen for his advice on the statistical analyses. We thank Kali Tal for her editorial contributions.

Sources of support: Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number Southern Africa: U01AI069924, Asia: U01AI069907, Central Africa: U01A096299, East Africa: U01AI069911, Caribbean, Central and South America: U01AI069923 and West Africa: U01AI069919. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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APPENDIX

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We acknowledge the contributions of the East African IeDEA ART programs to this analysis and would like to thank Dr. Constantin Yiannoutsos at Indiana University, Dr. Ayaya at the The Academic Model Providing Access To Healthcare (AMPATH) Program, Eldoret Kenya ; Dr. Elizabeth A. Bukusi and Ms. Jayne Lewis-Kulzer at Family AIDS Care and Education Services (FACES), Kisumu Kenya ; National AIDS Control Programme in Tanzania (PI, Dr. Geoffrey Soti) Morogoro Regional Hospital (PI, Dr. Rita Lyamuya), Tumbi Regional Hospital (PI, Dr. Kapella Ngonyani), Masaka Regional Referral Hospital (Dr. John Ssali and Mr. Haruna Ssemuwemba), Mbarara University of Science and Technology (MUST) ISS Clinic (Dr. Bosco Bwana Mwebesa), Infectious Diseases Institute, Mulago (Dr. Andrew Kambugu and Dr. Serbine Hermans) and Rakai Health Sciences Program (Dr. Fred Nalugoda and Dr. Kasule Jjingo).

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Table 1

Proximity of tuberculosis (TB) drug resistance detection methods in 47 antiretroviral therapy programs from low- and middle-income countries, overall and stratified by region.

Drug resistance detection method n (%)	All ART programs	Asia – Pacific	Caribbean	Central and South America	Central Africa	East Africa	Southern Africa	West Africa
Total	47	6 (12.8)	7 (14.9)	5 (10.6)	8 (17.0)	14 (29.8)	7 (14.9)	
Phenotypic DST								
Not available	11 (23.4)	1 (16.7)	0	0	5 (62.5)	2 (14.3)	3 (42.9)	
Available on site	9 (19.1)	3 (50.0)	5 (71.4)	0	1 (12.5)	0	0	
Available within 5 km	8 (17.0)	2 (33.3)	1 (14.3)	2 (40.0)	1 (12.5)	2 (14.3)	0	
Available >5 km away	19 (40.4)	0	1 (14.3)	3 (60.0)	1 (12.5)	10 (71.4)	4 (57.1)	
GenoType MTBDR_{plus}								
Not available	23 (49.0)	3 (50.0)	4 (57.1)	3 (60.0)	5 (62.5)	7 (50.0)	1 (14.3)	
Available on site	5 (10.6)	1 (16.7)	2 (28.6)	0	1 (12.5)	1 (7.2)	0	
Available within 5 km	7 (14.9)	2 (33.3)	1 (14.3)	1 (20.0)	1 (12.5)	0	2 (28.6)	
Available >5 km away	12 (25.5)	0	0	1 (20.0)	1 (12.5)	6 (42.8)	4 (57.1)	
Xpert MTB/RIF								
Not available	24 (51.0)	2 (33.3)	5 (71.4)	4 (80.0)	4 (50.0)	5 (35.7)	4 (57.1)	
Available on site	13 (27.7)	2 (33.3)	2 (28.6)	0	3 (37.5)	5 (35.7)	1 (14.3)	
Available within 5 km	2 (4.3)	1 (16.7)	0	1 (20.0)	0	0	0	
Available >5 km away	8 (17.0)	1 (16.7)	0	0	1 (12.5)	4 (28.6)	2 (28.6)	
Any drug resistance detection method¹								
Not available	4 (8.5)	0	0	0	3 (37.5)	1 (7.1)	0	
Available on site	19 (40.4)	4 (66.7)	5 (71.4)	0	3 (37.5)	6 (42.9)	1 (14.3)	
Available within 5 km	9 (19.2)	2 (33.3)	1 (14.3)	2 (40.0)	0	2 (14.3)	2 (28.6)	
Available >5 km away	15 (31.9)	0	1 (14.3)	3 (60.0)	2 (25.0)	5 (35.7)	4 (57.1)	

Abbreviations: DST: Drug susceptibility testing

¹ Availability of at least one drug resistance detection method (phenotypic DST, GenoType MTBDR_{plus}, and/or XpertMTB/RIF)

Characteristics of 47 antiretroviral therapy programs where phenotypic drug susceptibility testing (DST) or molecular tests (GenoType MTBDRplus and/or Xpert MTB/RIF) were available to detect drug resistance, compared to ART programs without access to these tools

Characteristic n (%)	All	Phenotypic DST			Molecular test for drug resistance identification		
		Available <i>I</i>	Not available	<i>P</i> value	Available <i>I</i>	Not available	<i>P</i> value
Total	47	36 (76.6)	11 (23.4)		33 (70.2)	14 (29.8)	
Region				0.026			0.26
Asia – Pacific	6	5 (83.3)	1 (16.7)		5 (83.3)	1 (16.7)	
Caribbean, Central and South America	7	7 (100)	0		4 (57.1)	3 (42.9)	
Central Africa	5	5 (100)	0		2 (40.0)	3 (60.0)	
East Africa	8	3 (37.5)	5 (62.5)		5 (62.5)	3 (37.5)	
Southern Africa	14	12 (85.7)	2 (14.3)		10 (71.4)	4 (28.6)	
West Africa	7	4 (57.1)	3 (42.9)		7 (100)	0	
Setting				0.028			0.55
Urban	38	31 (81.6)	7 (18.4)		28 (73.7)	10 (26.3)	
Peri-urban	7	5 (71.4)	2 (28.6)		4 (57.1)	3 (42.9)	
Rural	2	0	2 (100)		1 (50.0)	1 (50.0)	
Level of care				0.145			0.86
Primary clinic	15	12 (80.0)	3 (20.0)		11 (73.3)	4 (26.7)	
Secondary (provincial hospital)	8	4 (50.0)	4 (50.0)		5 (62.5)	3 (37.5)	
Tertiary (referral hospital)	24	20 (83.3)	4 (16.7)		17 (70.8)	7 (29.2)	
Number of HIV-infected persons in care²				0.364			0.28
1000	5	5 (100)	0		5 (100)	0	
1001–3000	20	14 (70.0)	6 (30.0)		14 (70.0)	6 (30.0)	
>3000	22	17 (77.3)	5 (22.7)		14 (63.6)	8 (36.4)	
Newly detected adult TB cases³				0.448			0.95
50	17	14 (82.4)	3 (17.6)		12 (70.6)	5 (29.4)	
51–300	18	12 (66.7)	6 (33.3)		13 (72.2)	5 (27.8)	
>300	12	10 (83.3)	2 (16.7)		8 (66.7)	4 (33.3)	
Cost model for diagnostics				0.179			0.31
Full payment by the patient	2	2 (100)	0		2 (100)	0	

Characteristic n (%)	All	Phenotypic DST		Molecular test for drug resistance identification	
		Available <i>I</i>	Not available	Available <i>I</i>	Not available
Partial payment by the patient	22	19 (86.4)	3 (13.6)	17 (77.3)	5 (22.7)
Available at no cost for the patient	23	15 (65.2)	8 (34.8)	14 (60.9)	9 (39.1)
World Bank income groups					
Low income country	15	8 (53.3)	7 (46.7)	10 (66.7)	5 (33.3)
Lower middle income country	18	14 (77.8)	4 (22.2)	6 (33.3)	
Upper middle income country	14	14 (100)	0	3 (21.4)	

P values are obtained from χ^2 tests

Abbreviations: TB: tuberculosis

¹ On site or off site

² Number of adult cases followed at the time of the study

³ All cases per year at the treatment program

Table 3

Associations between the use at the patient level of phenotypic drug susceptibility testing (DST) or molecular tests (GenoType MTBDR_{plus} and/or Xpert/MTB/RIF) to detect drug-resistant tuberculosis and program and patient characteristics. This analysis is restricted to patients from ART programs with access to phenotypic DST (n=719) or molecular diagnostic tests (n=761), respectively.

Characteristic n (%)	Phenotypic DST		Molecular test for drug resistance identification	
	Done	Not done	Done	Not done
Total	158 (22.0)	561 (78.0)	175 (23.0)	586 (77.0)
Program characteristics				
Region				
Asia – Pacific	2 (9.5)	19 (90.5)	9 (25.7)	26 (74.3)
Caribbean, Central and South America	43 (58.9)	30 (41.1)	15 (25.0)	45 (75.0)
Central Africa	3 (6.0)	47 (94.0)	0	33 (100)
East Africa	2 (1.6)	126 (98.4)	7 (3.6)	190 (96.4)
Southern Africa	107 (27.9)	276 (72.1)	143 (42.4)	194 (57.6)
West Africa	1 (1.6)	63 (98.4)	1 (1.0)	98 (99.0)
Setting				
Urban	132 (24.0)	417 (76)	141 (23.2)	467 (76.8)
Peri-urban	26 (15.3)	144 (84.7)	33 (27.1)	89 (72.9)
Rural	0	0	1 (3.2)	30 (96.8)
Level of care				
Primary clinic	57 (15.9)	301 (84.1)	81 (24.9)	245 (75.1)
Secondary (provincial hospital)	46 (42.6)	62 (57.4)	43 (32.8)	88 (67.2)
Tertiary (referral hospital)	55 (21.7)	198 (78.3)	51 (16.8)	253 (83.2)
Cost model for diagnostics				
Full payment by the patient	1 (2.2)	44 (97.9)	0	45 (100)
Partial payment by the patient	61 (16.5)	309 (83.5)	68 (18.2)	305 (81.8)
Available at no cost for the patient	96 (31.6)	208 (68.4)	107 (31.2)	236 (68.8)
World Bank income groups				
Low income country	26 (11.7)	196 (88.3)	30 (9.4)	288 (90.6)
Lower middle income country	1 (0.4)	220 (99.6)	13 (7.2)	167 (92.8)
Upper middle income country	131 (47.5)	145 (52.5)	132 (50.2)	131 (49.8)

Characteristic n (%)	Phenotypic DST		Molecular test for drug resistance identification	
	Done	Not done	Done	Not done
Patient characteristics				
Age at ART start, median (IQR) years	34.8 (28.7–41.7)	34.6 (29.5–41.2)	34.0 (28.2–39.8)	35.0 (30.0–42.0)
Sex				
Female	73 (22.1)	258 (77.9)	82 (23.5)	267 (76.5)
Male	85 (21.9)	303 (78.1)	93 (22.6)	319 (77.4)
Site of disease				
Pulmonary	110 (22.7)	375 (77.3)	116 (22.5)	399 (77.5)
Extrapulmonary	46 (20.4)	179 (79.6)	57 (24.1)	180 (75.9)
Unknown	2 (22.2)	7 (77.8)	2 (22.2)	7 (77.8)
Patient category				
New case	122 (20.0)	488 (80.0)	140 (21.4)	513 (78.6)
Relapse	19 (29.2)	46 (70.8)	20 (30.3)	46 (69.7)
Retreatment after default or failure	6 (40.0)	9 (60.0)	3 (25.0)	9 (75.0)
Other	11 (37.9)	18 (62.1)	12 (40.0)	18 (60.0)
CD4 cell count, median (IQR) cells/μl	120 (44–253)	137 (48–253.5)	107 (39.5–220.5)	136.5 (41.5–254)
<i>Missing observations</i>	11 (7.0)	45 (8.0)	7 (4.0)	74 (12.6)
WHO clinical stage at ART start				
Stage I/II	11 (40.7)	16 (59.3)	13 (27.7)	34 (72.3)
Stage III/IV	143 (21.9)	510 (78.1)	159 (23.2)	525 (76.8)
Unknown	4 (10.3)	35 (89.7)	3 (10.0)	27 (90.0)
On TB treatment before starting ART				
Yes	75 (24.4)	233 (75.6)	76 (27.6)	199 (72.4)
No	83 (20.2)	328 (79.8)	99 (20.4)	387 (79.6)
Previous history of TB				
Yes	37 (33.3)	74 (66.7)	36 (31.0)	80 (69.0)
No	111 (20.1)	441 (79.9)	124 (20.8)	473 (79.2)
Unknown	10 (17.9)	46 (82.1)	15 (31.2)	33 (68.8)

P values are obtained from χ^2 tests

Abbreviations: TB: tuberculosis; ART: antiretroviral therapy; IQR: interquartile range; DST: drug susceptibility testing; WHO: World Health Organization

I At the start of ART

Table 4

Tuberculosis treatment practices in 47 antiretroviral therapy programs from low- and middle-income countries, overall and stratified by region.

Characteristics n (%)	All	Asia – Pacific	Caribbean	Central and South America	Central Africa	East Africa	Southern Africa	West Africa
Total	47	6 (12.8)	7 (14.9)	5 (10.6)	8 (17.0)	14 (29.8)	7 (14.9)	
Treatments in line with NTP recommendations								
Strictly	40 (85.1)	4 (66.7)	5 (71.4)	5 (100)	8 (100)	11 (78.6)	7 (100)	
Somewhat modified	7 (14.9)	2 (33.3)	2 (28.6)	0	0	3 (21.4)	0	
DOT¹								
Never	11 (23.4)	2 (33.3)	2 (28.6)	0	2 (25.0)	5 (35.7)	0	
During intensive phase only	16 (34)	2 (33.3)	1 (14.3)	3 (60.0)	2 (25.0)	5 (35.7)	3 (42.8)	
During the whole treatment duration	20 (42.6)	2 (33.3)	4 (57.1)	2 (40.0)	4 (50.0)	4 (28.6)	4 (57.2)	
Type of DOT								
Community-based	4 (8.6)	0	2 (28.6)	0	0	1 (7.1)	1 (14.3)	
Hospital-based	12 (25.5)	1 (16.7)	1 (14.3)	2 (40.0)	3 (37.5)	2 (14.3)	3 (42.8)	
Home-based	2 (4.2)	0	0	0	0	0	2 (28.6)	
Self-administered	2 (4.2)	1 (16.7)	0	0	1 (12.5)	0	0	
Mixed	15 (32.0)	2 (33.3)	1 (14.3)	3 (60.0)	2 (25.0)	6 (42.9)	1 (14.3)	
Unknown	12 (25.5)	2 (33.3)	3 (42.8)	0	2 (25.0)	5 (35.7)	0	
TB drug supplier²								
National TB program	44 (93.6)	5 (83.3)	7 (100)	5 (100)	8 (100)	13 (92.9)	6 (85.7)	
Private pharmacy	4 (8.5)	2 (33.3)	0	0	1 (12.5)	1 (7.1)	0	
Global Fund	3 (6.4)	0	0	2 (40.0)	0	0	1 (14.3)	
MDR-TB treatment³								
Available	26 (55.3)	5 (83.3)	4 (57.1)	4 (80.0)	4 (50.0)	5 (35.7)	4 (57.1)	
Patient referred elsewhere	7 (14.9)	0	1 (14.3)	1 (20.0)	0	3 (21.4)	2 (28.6)	
Not available	14 (29.8)	1 (16.7)	2 (28.6)	0	4 (50.0)	6 (42.9)	1 (14.3)	

Abbreviations: NTP: National TB Control Program; DOT: Directly Observed Therapy; TB: tuberculosis; MDR: multidrug-resistant; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin

¹ DOT reflects its general use at the participating ART programs, irrespective of drug resistance.

² Not mutually exclusive

³ The list of MDR-TB regimens is given in Supplementary Table 2

Table 5

Characteristics of antiretroviral therapy programs having experienced at least one drug shortage (first and/or second line drugs) in the two years preceding the survey (2010–2012), compared to ART programs having never experienced drug shortages.

Characteristic n (%)	Experienced at least one drug shortage	Never experienced drug shortages	P value
Total	18 (38.3)	29 (61.7)	
Region			0.091
Asia – Pacific	0	6 (100)	
Caribbean, Central and South America	1 (14.3)	6 (85.7)	
Central Africa	3 (60.0)	2 (40.0)	
East Africa	5 (62.5)	3 (37.5)	
Southern Africa	7 (50.0)	7 (50)	
West Africa	2 (28.6)	5 (71.4)	
Setting			0.17
Urban	13 (34.2)	25 (65.8)	
Peri-urban	3 (42.9)	4 (57.1)	
Rural	2 (100)	0	
World Bank income groups			0.65
Low income country	6 (40.0)	9 (60.0)	
Lower middle income country	8 (44.4)	10 (55.6)	
Upper middle income country	4 (28.6)	10 (71.4)	
Level of care			0.99
Primary clinic	6 (40.0)	9 (60.0)	
Secondary (provincial hospital)	3 (37.5)	5 (62.5)	
Tertiary (referral hospital)	9 (37.5)	15 (62.5)	
Number of HIV-infected persons in care ¹			0.097
1000	1 (20.0)	4 (80.0)	
1001–3000	5 (25.0)	15 (75.0)	
>3000	12 (54.6)	10 (45.4)	
Newly detected adult TB cases ²			0.067
<50	3 (17.7)	14 (82.3)	
51–300	8 (44.4)	10 (55.6)	
>300	7 (58.3)	5 (41.7)	
Treatment in line with NTCP recommendations			0.57
Strictly	16 (40.0)	24 (60.0)	
Somewhat modified	2 (28.6)	5 (71.4)	
Directly Observed Therapy			0.19
Never	3 (27.3)	8 (72.7)	
During intensive phase	9 (56.3)	7 (43.7)	
During the whole treatment duration	6 (30.0)	14 (70.0)	

P values are obtained from χ^2 tests

Abbreviations: TB: tuberculosis; NTCP: National TB Control Program

¹ Number of adult cases followed at the time of the study

² All cases per year at the treatment program