

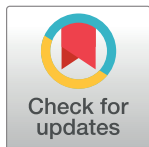
RESEARCH ARTICLE

Integrating services for HIV and multidrug-resistant tuberculosis: A global cross-sectional survey among ART clinics in low- and middle-income countries

Kathrin Zürcher^{1*}, Samyra R. Cox², Marie Ballif¹, Leslie A. Enane³, Olivier Marcy⁴, Marcel Yotebieng⁵, Gary Reubenson⁶, Worarat Imsanguan⁷, Larissa Otero^{8,9}, Nishi Suryavanshi^{2,10}, Stephany N. Duda¹¹, Matthias Egger^{1,12,13}, Jeffrey A. Tornheim², Lukas Fenner¹, International Epidemiology Databases to Evaluate AIDS (IeDEA)¹¹

1 Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, **2** Division of Infectious Diseases, Center for Clinical Global Health Education, Johns Hopkins University School of Medicine, Baltimore, MD, United States of America, **3** The Ryan White Center for Pediatric Infectious Disease and Global Health, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, United States of America, **4** U1219 Bordeaux Population Health Research Center, University of Bordeaux, Inserm, IRD, Bordeaux, France, **5** Division of General Internal Medicine, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, United States of America, **6** Faculty of Health Sciences, Department of Paediatrics and Child Health, University of the Witwatersrand, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa, **7** Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand, **8** Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru, **9** Facultad de Medicina, Universidad Peruana Cayetano Heredia, Lima, Peru, **10** Johns Hopkins India, Pune, India, **11** Department of Biomedical Informatics, Vanderbilt University School of Medicine, Nashville, TN, United States of America, **12** Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, Rondebosch, Western Cape, South Africa, **13** Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom

¶ Participating programs and members of IeDEA can be found in [S7 Table](#)
* kathrin.zuercher@ispm.unibe.ch



OPEN ACCESS

Citation: Zürcher K, Cox SR, Ballif M, Enane LA, Marcy O, Yotebieng M, et al. (2022) Integrating services for HIV and multidrug-resistant tuberculosis: A global cross-sectional survey among ART clinics in low- and middle-income countries. *PLoS Glob Public Health* 2(3): e0000180. <https://doi.org/10.1371/journal.pgph.0000180>

Editor: Christian Wejse, Aarhus University: Aarhus Universitet, DENMARK

Received: September 30, 2021

Accepted: January 19, 2022

Published: March 1, 2022

Copyright: © 2022 Zürcher et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Complete data for this study cannot be posted in a [supplemental file](#) or a public repository because of legal and ethical restrictions. The Principles of Collaboration of this multi-national consortium and the regulatory requirements of the different countries' IRBs require the submission and approval of individual project concept sheets that describe the planned analyses. Specifically, while the data held by the IeDEA consortium may be available to other

Abstract

Tuberculosis (TB) is the leading cause of death among PLHIV and multidrug-resistant-TB (MDR-TB) is associated with high mortality. We examined the management for adult PLHIV coinfecting with MDR-TB at ART clinics in lower income countries. Between 2019 and 2020, we conducted a cross-sectional survey at 29 ART clinics in high TB burden countries within the global IeDEA network. We used structured questionnaires to collect clinic-level data on the TB and HIV services and the availability of diagnostic tools and treatment for MDR-TB. Of 29 ART clinics, 25 (86%) were in urban areas and 19 (66%) were tertiary care clinics. Integrated HIV-TB services were reported at 25 (86%) ART clinics for pan-susceptible TB, and 14 (48%) clinics reported full MDR-TB services on-site, i.e. drug susceptibility testing [DST] and MDR-TB treatment. Some form of DST was available on-site at 22 (76%) clinics, while the remainder referred testing off-site. On-site DST for second-line drugs was available at 9 (31%) clinics. MDR-TB treatment was delivered on-site at 15 (52%) clinics, with 10 individualizing treatment based on DST results and five using standardized regimens alone. Bedaquiline was routinely available at 5 (17%) clinics and delamanid at 3 (10%) clinics. Although most ART clinics reported having integrated HIV and TB services, few had fully

investigators, proposed use must be based on a concept note that is approved by the Response to editorial office 2 regional Steering Groups and the IeDEA Executive Committee (Chairperson; Annette Sohn, MD; email: annette.sohn@treatasia.org).

Funding: The International Epidemiology Databases to Evaluate AIDS (IeDEA) is supported by the US National Institutes of Health, National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, the National Institute on Drug Abuse, the National Heart, Lung, and Blood Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Diabetes and Digestive and Kidney Diseases, the Fogarty International Center, and the National Library of Medicine: Asia-Pacific, U01AI069907; CCASAnet, U01AI069923; Central Africa, U01AI096299; East Africa, U01AI069911; NA-ACCORD, U01AI069918; Southern Africa, U01AI069924; West Africa, U01AI069919. Informatics resources are supported by the Harmonist project, R24AI124872. ME was supported by special project funding (grant 189498) from the Swiss National Science Foundation. JAT was supported by NIH/NIAID (K23AI135102). LO was supported by an NIH/Fogarty International Center (K43TW011137). The contents of this publication are solely the responsibility of the authors and do not represent the official views of any of the institutions mentioned above. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

integrated MDR-TB services. There is a continued need for increased access to diagnostic and treatment options for MDR-TB patients and better integration of MDR-TB services into the HIV care continuum.

Introduction

Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV) [1]. In 2019, PLHIV accounted for about 8% of incident TB patients and 15% of TB mortality globally [1]. Compared to HIV-negative individuals, PLHIV have an increased risk of developing active TB disease, even when on antiretroviral therapy (ART) [2,3]. There is also evidence of an association between HIV and drug-resistant TB; outbreaks involving PLHIV have been well-documented in high HIV burden countries [4,5].

Multidrug-resistant tuberculosis (MDR-TB) challenges global TB control and is associated with high mortality [4]. Strategies for controlling MDR-TB include drug susceptibility testing (DST) to guide treatment and the completion of an adequate treatment regimen. However, managing MDR-TB is difficult, particularly in low- and middle-income countries (LMICs), where there is limited access to both DST to diagnose MDR-TB as well as effective MDR-TB drugs to optimally treat MDR-TB [6,7].

For PLHIV coinfecting with MDR-TB, effective coordination among services is particularly important given the complexity of second-line anti-TB treatment and the need for a careful monitoring of side effects. The integration of HIV and TB services has been identified as a global priority, [8,9] especially in regions where both diseases are widespread, which include sub-Saharan Africa, Asia and Latin America. In a multi-regional study conducted in 2012 among 47 ART clinics, we showed that only 26% offered integrated HIV-TB services, with large regional disparities [10]. A study from Uganda showed that integrated HIV and TB services was associated with reduced mortality compared to clinics with no HIV and TB integration [11]. However, it is unclear to what extent integrated services included the management of drug-resistant TB, especially MDR-TB, among PLHIV. Therefore, we conducted a multi-regional survey assessing the capacity and routine practices of ART clinics related to the diagnosis and treatment of MDR-TB among PLHIV.

Methods

Study design

This cross-sectional survey was conducted within the International Epidemiology Databases to Evaluate AIDS (IeDEA, www.iedea.org) network, a large consortium of ART clinics predominantly located in LMICs [12,13]. ART clinics within IeDEA are mostly public facilities but are often supported by non-governmental organizations or academic institutions. ART clinics from the Asia-Pacific, Africa, and South America IeDEA regions located in countries defined by the World Health Organization (WHO) as high MDR-TB, high TB, or high TB/HIV burden and countries with TB incidence rates of $\geq 20/100,000$ population were eligible to participate [14]. In this analysis, we focused on the management of adults living with HIV coinfecting with MDR-TB.

Ethics statement

The Cantonal Ethics Committee Bern (Switzerland), Vanderbilt University Medical Center IRB (Tennessee, USA), and Johns Hopkins University School of Medicine IRB (Maryland,

USA) approved this project. All participating sites obtained approvals from their local institutional review boards or ethics committees to participate in IeDEA research. All participants provided written informed consent before participating.

Data collection

IeDEA representatives from each region and an advisory group of TB experts were involved in developing the survey tool. The survey was available in English and French and pilot-tested in both languages by the advisory group of TB experts and selected clinics. Survey data were electronically collected and managed using REDCap (Research Electronic Data Capture) [15,16]. The English version of the online questionnaire is shown in the Supporting Information (S1 Table). All survey respondents were health care workers (HCWs) involved in managing TB patients as clinicians (medical doctors, clinical officers or nurses). The survey consisted of three components: (A) basic information on the ART clinic, including level of care, size, adult/paediatric services, cost of services, and infection control measures; (B) information about the management of adult TB, including case definitions, and availability of diagnostic tools; (C) hypothetical clinical scenarios presenting cases of adult patients co-infected with TB/HIV to assess the clinical practices of treating HCWs. Components A and B were completed by one respondent per clinic. Component C was completed by two to three different respondents per clinic who were asked to respond based on routine practices. The respondent was required to be a HCW at the ART facility who provided care to TB patients (e.g. medical doctor, clinical officer, nurse, etc.) and could consult with others to answer questions. Data collection took place between September 2019 and March 2020.

Definitions

We defined MDR-TB as resistance to both isoniazid and rifampicin, and extensively drug-resistant TB (XDR-TB) as MDR plus resistance to any fluoroquinolone and at least one second-line injectable drug [17]. We defined an ART clinic with integrated HIV-TB basic services as a clinic where: 1) HIV-positive people are actively screened for TB at enrollment using symptom screening; 2) TB and HIV clinical services are located in the same facility, under the same roof, or available with same-day appointments; and 3) facilities have a specialized clinic/ward on-site with dedicated staff for patients with TB [10]. We categorized the degrees of service integration for MDR-TB as follows: i) *full integration* if both DST and MDR-TB treatment were available on-site, ii) *partial integration*, if either DST or MDR-TB treatment was available on-site, and iii) *off-site services* if both DST and MDR-TB treatment were available off-site. Clinical officers were defined as trained non-physician clinicians and medical doctors as physicians with a university degree.

Any of the following were considered initial TB diagnostic tools: smear microscopy; chest x-ray; any GeneXpert including Xpert MTB/RIF, Ultra, Omni, or XDR (Cepheid, USA); any line probe assay (LPA) including Genotype MTBDRplus or Genotype MTBDRsl (Hain Life-science GmbH, Germany); mycobacterial liquid or solid culture; or urine lipoarabinomannan (LAM). DST was categorised as either molecular (any GeneXpert or any LPA) or phenotypic (mycobacterial culture). The injectable-containing short regimen (also known as the "Bangladesh regimen") is a standardized short course MDR-TB treatment regimen of 9 to 12 months with or without minor modifications. It consists of an initial 4–6 months of kanamycin, moxifloxacin, ethionamide/prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol [18,19].

Analyses

We described ART clinics by the degree of service integration, by region and explored the availability of on-site versus off-site diagnostic tools and treatment for MDR-TB. We analyzed differences among ART clinics using chi-square or Fisher's exact. Using descriptive statistics, we assessed routine practices related to MDR-TB management captured by hypothetical clinical scenarios. All analyses were done in Stata version 15.1 (Stata Corporation, College Station, TX, USA).

Results

Description of the ART clinics

We collected data from 29 adult ART clinics across 19 high TB burden countries (Fig 1). Of 29 ART clinics, 20 (69.0%) were in Africa, 6 (20.7%) were in Asia-Pacific, and 3 (10.3%) were in South America. Clinic-level survey components were completed by medical doctors (23/29, 79.3%), clinical officers (4/29, 13.8%), and nurses (2/29, 6.9%). The majority of respondents (24, 88.9%) had worked at the participating ART clinic for more than five years at the time of survey completion. Overall, 25/29 (86.2%) participating clinics were in urban and 4/29 (13.8%) were in rural settings. Most participating sites (19, 65.5%) were tertiary care clinics (Table 1).

Almost all ART clinics (27, 93.1%) reported following their national TB guidelines to screen, diagnose and treat TB patients. In 2018, the number of people newly diagnosed with MDR-TB at the ART clinics ranged from a few patients to more than 100 patients. For infection control, environmental measures, such as regular natural ventilation, were reported to be in place at 26 (89.8%) of the ART clinics, 19 clinics (65.5%) reported that staff regularly wore masks when in close contact with TB patients or people with presumptive TB (S1 Table), and

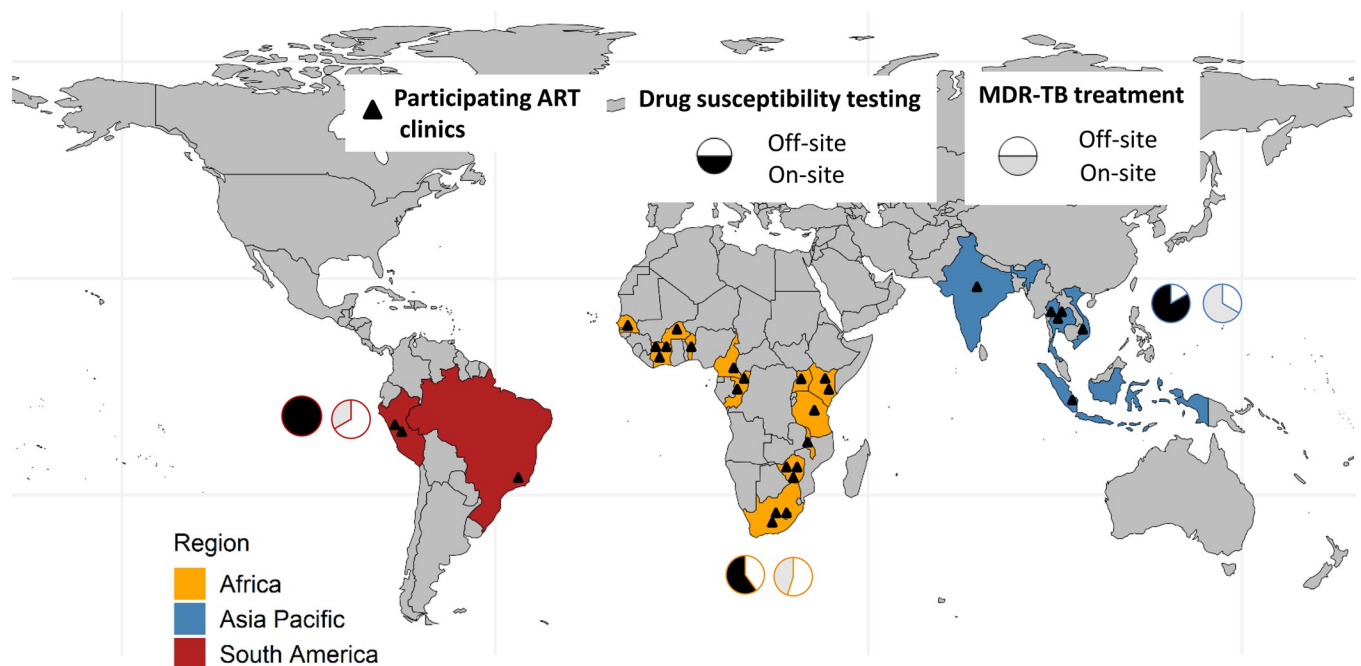


Fig 1. Map showing the participating ART clinics by regions. Pie charts indicate the proportion of clinics with drug-susceptibility testing (DST) (black) and MDR-TB treatment (grey) available on-site by region. Types of DST available included Xpert MTB/RIF, line probe assay, and culture. Abbreviations: MDR, multidrug resistance; TB, Tuberculosis.

<https://doi.org/10.1371/journal.pgph.0000180.g001>

18 (62.1%) conducted TB screening among clinic staff who were in contact with TB patients or people with presumptive TB.

Integration of HIV and MDR-TB services

The majority of participating clinics (25, 86.2%) reported offering integrated HIV-TB basic services, with 25 clinics (86.2%) offering initial TB diagnosis and 20 clinics (69.0%) first-line TB treatment on-site (Table 1). Fourteen clinics (48.3%) reported full integration of HIV and MDR-TB services and nine (31.0%) reported partial integration, of which eight offered on-site DST only and one offered on-site MDR-TB treatment only. Six clinics (20.7%) had access to off-site MDR-TB services only for both diagnosis and treatment (Fig 2, S3 Table).

We describe care pathway for patients coinfecting with TB/HIV at participating clinics in Fig 3, from the identification of presumptive TB to drug resistance testing and treatment. Initial TB diagnosis was conducted off-site in four clinics (13.8%), of which half referred patients while the other half sent samples for off-site testing. Three out of four of these clinics received initial TB diagnostic result from the off-site clinic. For any type of DST, seven clinics (24.1%) relied on off-site services, of which three referred patients and four sent samples for off-site testing. Five out of seven of these clinics (71.4%) received DST results from the referral clinic. Treatment of pan-susceptible TB was prescribed off-site in nine clinics (31.0%), of which five (55.6%) received treatment outcome reports from the off-site clinic. For MDR-TB treatment, fourteen clinics (48.3%) referred patients off-site, of which nine (64.3%) received treatment outcome reports for from the referral clinic (Fig 3).

Drug susceptibility testing

DST, in some form, was available on-site at 22/29 (75.9%) ART clinics. Ten ART clinics reported having molecular and phenotypic DST available on-site, whereas the remaining 12 ART clinics reported having molecular DST only (S4 Table). Molecular DST was most frequently available on-site in South America (3/3, 100%) followed by Asia-Pacific (5/6, 83.3%) and Africa (14/20, 70.0%). In contrast, phenotypic DST was most frequently available on-site in Asia-Pacific (5/6, 83.3%), followed by South America (2/3, 66.7%) and Africa (3/20, 15.0%) (Table 1). Two ART clinics (6.9%) reported access to sequencing technologies.

Mycobacterial culture was available on-site at 10/29 (34.5%) clinics for identifying resistance to first-line drugs. All clinics with some form of DST on-site had a rapid molecular DST for first-line drugs available (22/29, 72.4%). Specifically, Xpert MTB/RIF was available on-site at 21/29 (72.4%), Xpert Ultra at 7/29 (24.1%), and first-line LPA (MTBDRplus) at 3/29 (10.3%, S4 Table). Five (17.2%) ART clinics reported any GeneXpert cartridge stock-outs in the preceding 12 months. In the hypothetical clinical scenario of a patient whose TB treatment is failing, 57/72 (79.2%) HCWs would request a rapid molecular DST to identify resistance to first-line drugs (S5 Table, Scenario 1). The proportion of HCWs who selected this response was higher among ART clinics with full integration of MDR-TB services (31/35, 88.6%) and lower among ART clinics with partial integration and only off-site MDR-TB services (17/24, 70.8%, and 9/13, 69.2%, respectively).

In contrast to first-line DST, DST for second-line drugs was available on-site at 9/29 (31.0%) clinics. Mycobacterial culture for second-line drugs was available at 8/29 (27.6%) clinics; rapid molecular DST for second-line drugs was rarely available. Specifically, Xpert MTB/XDR was available on-site at 2/29 (6.9%) clinics and second-line LPA (MTBDRsl) at 3/29 (10.3%) clinics (S3 and S4 Tables).

Table 1. General clinic-level information, availability of TB services and cost model of care in the 29 ART clinics participating in the study, by region.

	Total (n = 29) n (%)	Asia-Pacific (n = 6) n (%)	South America (n = 3) n (%)	Africa (n = 20) n (%)
Clinic-level information				
Setting				
Urban	25 (86.2)	6 (100)	3 (100)	16 (80.0)
Rural	4 (13.8)	0	0	4 (20.0)
Highest level of care				
Primary	8 (27.6)	0	0	8 (40.0)
Secondary	2 (6.9)	0	0	2 (10.0)
Tertiary	19 (65.5)	6 (100)	3 (100)	10 (50.0)
Adults and/or children care				
Adults and children	17 (58.6)	1 (33.3)	2 (66.6)	14 (70.0)
Adults only	12 (41.4)	5 (66.7)	1 (33.3)	6 (30.0)
Integrated HIV-TB basic services				
Yes	25 (86.2)	6 (100)	3 (100)	16 (80.0)
No	4 (13.8)	0	0	4 (20.0)
Availability of TB services				
Initial TB diagnosis				
On-site	25 (86.2)	6 (100)	3 (100)	16 (80.0)
Off-site	4 (13.8)	0	0	4 (20.0)
Molecular DST				
On-site	22 (75.9)	5 (83.3)	3 (100)	14 (70.0)
Off-site	7 (21.1)	1 (16.7)	0	6 (30.0)
Phenotypic DST				
On-site	10 (34.5)	5 (83.3)	2 (66.7)	3 (15.0)
Off-site	19 (65.5)	1 (16.7)	1 (33.3)	17 (85.0)
Treatment pan-susceptible TB				
On-site	20 (69.0)	5 (83.3)	1 (33.3)	14 (70.0)
Off-site	9 (31.0)	1 (16.7)	2 (66.7)	6 (30.0)
Treatment MDR-TB				
On-site	15 (51.7)	5 (83.3)	1 (33.3)	9 (45.0)
Off-site	14 (48.3)	1 (16.7)	2 (66.7)	11 (55.0)
Drug-resistant TB Integration Models				
Full integration	14 (48.3)	5 (83.3)	1 (33.3)	8 (40.0)
Partial integration	9 (31.0)	0	2 (66.7)	7 (35.0)
Off-site only)	6 (20.7)	1 (16.7)	0	5 (25.0)
Cost Model				
Initial TB diagnosis				
Full payment by the patient	1 (3.4)	1 (16.7)	0	0
Cost sharing (partial payment by the patient)	6 (20.7)	2 (33.3)	0	4 (20.0)
Available at no cost for the patient	22 (75.9)	3 (50.0)	3 (100)	16 (80.0)
Pan-susceptible TB treatment				
Full payment by the patient	1 (3.4)	1 (16.7)	0	0
Cost sharing (partial payment by the patient)	1 (3.4)	1 (16.7)	0	0
Available at no cost for the patient	27 (93.1)	4 (66.7)	3 (100)	20 (100.0)
MDR-TB treatment				
Cost sharing (partial payment by the patient)	1 (3.4)	1 (16.7)	0	0
Available at no cost for the patient	28 (96.6)	5 (83.3)	3 (100)	20 (100)

Abbreviations: ART, antiretroviral therapy; DST, drug susceptibility testing; MDR, multidrug resistance; TB, Tuberculosis; XDR, extensive drug resistance.

<https://doi.org/10.1371/journal.pgph.0000180.t001>

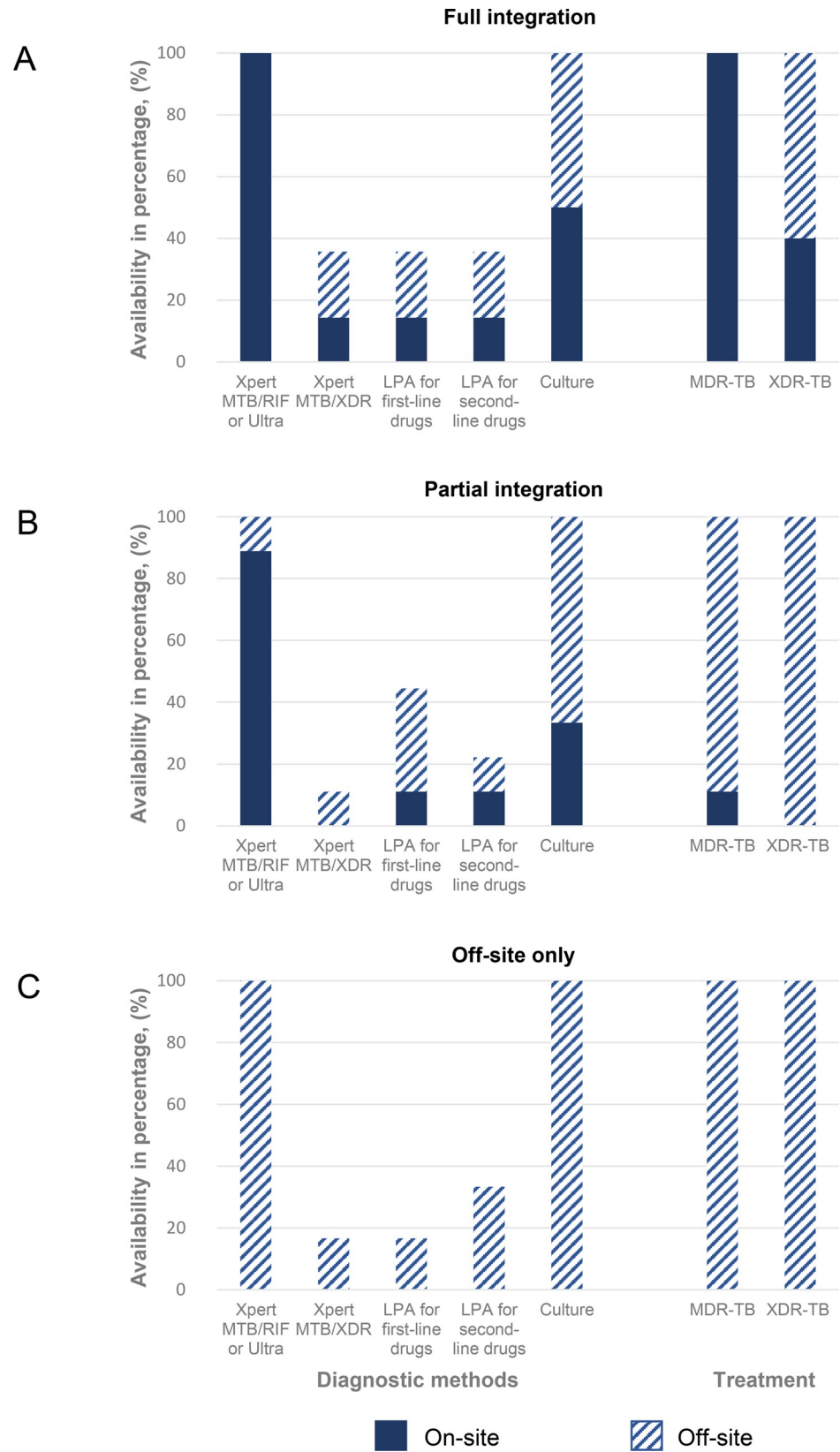


Fig 2. Models of integration of HIV and MDR-TB care. Models of integration of HIV and MDR-TB care. **Panel A:** Fourteen clinics with full integration of DST and MDR-TB treatment on-site; **Panel B:** Partial integration of eight clinics with DST on-site and MDR-TB treatment off-site and one clinic with the opposite; and **Panel C:** Both DST and MDR-TB treatment available off-site only at six clinics. The solid bars represent the percentage of the different molecular or phenotypic DST or MDR/XDR-TB treatment available on-site. The dashed bars represent the percentage of DST or MDR/XDR-TB treatment available off-site. Abbreviations: DST, drug susceptibility testing; MDR, multidrug resistance; TB, Tuberculosis; XDR, extensive drug resistance.

<https://doi.org/10.1371/journal.pgph.0000180.g002>

Treatment of MDR-TB

MDR-TB treatment was reported to be offered on-site at 15/29 (51.7%) ART clinics—83.3% of clinics in Asia-Pacific, 45.0% of clinics in Africa, and 33.3% of clinics in South America (Tables 1 and 2). When treated on-site, MDR-TB treatment was most frequently prescribed by medical doctors (10/15, 66.7%), followed by clinical officers (3/15, 20.0%), and nurses (2/15, 13.3%).

The remaining 14 ART clinics (48.3%) referred their MDR-TB patients off-site for MDR-TB treatment. When treated off-site, MDR-TB patients were referred to specific TB clinics (9/14, 64.3%), 6/14 (42.9%) to tertiary care facilities or 3/14 (21.4%) to secondary care facilities. Most referral clinics were located more than 20 km away from the ART clinic (12/14,

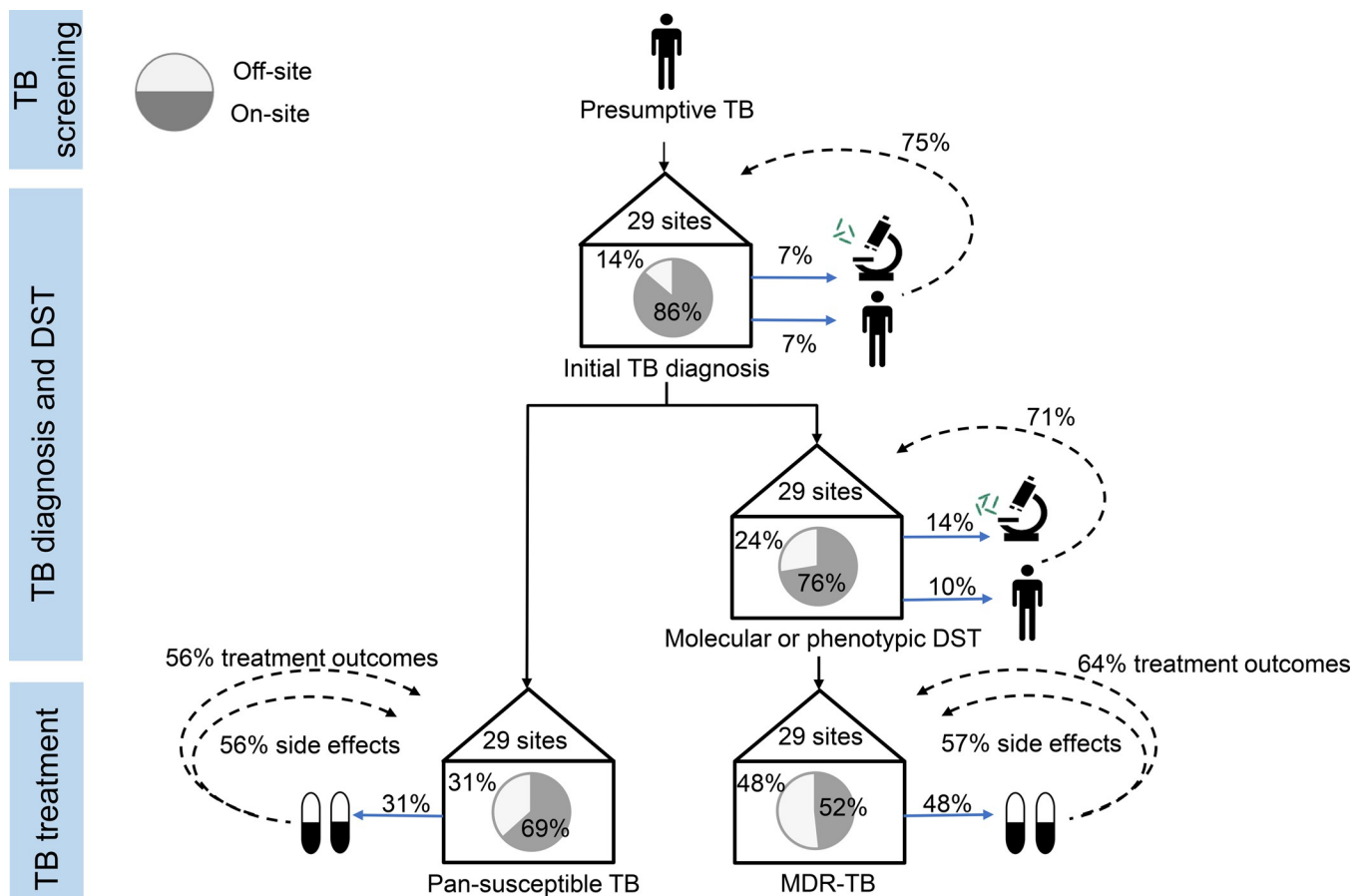


Fig 3. Care pathway for patients with HIV-TB coinfection at 29 ART clinics. Solid blue lines indicate patients or samples sent off-site for TB diagnosis, drug susceptibility testing (DST), or treatment. Dotted lines indicate feedback loops when diagnostic results, DST results, side effect or treatments outcomes are directly communicated back to the ART clinic by phone, written correspondence, or shared database entry. Abbreviations: DST, drug susceptibility testing; MDR, multidrug resistance; TB, Tuberculosis; XDR, extensive drug resistance.

<https://doi.org/10.1371/journal.pgph.0000180.g003>

Table 2. Management and treatment of MDR-TB at 29 ART clinics.

	Total (n = 29, %)	On-site (n = 15, %)	Off-site (n = 14, %)	p-value
Treatment in line with National TB Program				0.37
Strictly in line with National TB Program	27 (93.1)	13 (86.7)	14 (100)	
Somewhat modified	1 (3.4)	1 (6.7)	0	
Individualised MDR-TB treatment	1 (3.4)	1 (6.7)	0	
Directly observed treatment				
During initiation phase only	5 (17.2)	0	5 (35.7)	0.017
During the whole duration of treatment	24 (82.8)	15 (100)	9 (64.3)	
Clinical visits intensive phase				0.75
Daily	8 (27.6)	5 (33.3)	3 (21.4)	
Weekly	9 (31.0)	4 (26.7)	5 (35.7)	
Monthly	12 (41.4)	6 (40.0)	6 (42.9)	
Clinical visits continuation phase				0.81
Daily	2 (6.9)	1 (6.7)	1 (7.1)	
Weekly	2 (6.9)	2 (13.3)	0	
Monthly	22 (75.9)	11 (73.3)	11 (78.6)	
Every third month	3 (10.3)	1 (6.7)	2 (14.3)	
Type of directly observed treatment				0.79
Self-administered	5 (17.2)	4 (26.7)	1 (7.1)	
Health facility based	11 (37.9)	5 (33.3)	6 (42.9)	
Health and self-administered	11 (37.9)	6 (40.0)	5 (35.7)	
Unknown	2 (6.9)	0	2 (14.3)	
MDR-TB regimens				
Individualised according to the resistance profile	13 (44.8)	10 (66.7)	3 (21.4)	0.062
Standardised	11 (37.9)	3 (30.0)	8 (57.1)	
Standardised or according to the resistance profile	5 (17.2)	2 (13.3)	3 (21.4)	
Use of injectable-containing short regimen "Bangladesh"				1.0
Yes	18 (62.1)	9 (60.0)	9 (64.3)	
No	9 (31.0)	5 (33.3)	4 (28.6)	
Unknown	2 (6.9)	1 (6.7)	1 (7.1)	
Availability of new drugs				
Bedaquiline				0.02
Yes, always	5 (17.2)	4 (26.7)	1 (7.1)	
Upon request	7 (24.1)	6 (40.0)	1 (7.1)	
No	17 (58.6)	5 (33.3)	12 (85.7)	
Delamanid				0.08
Yes, always	3 (10.3)	3 (20.0)	0	
Upon request	7 (24.1)	5 (33.3)	2 (14.3)	
No	19 (65.5)	7 (46.7)	12 (85.7)	

Abbreviations: MDR, multidrug resistance; TB, Tuberculosis.

<https://doi.org/10.1371/journal.pgph.0000180.t002>

85.7%). However, more than half of ART clinics received reports from the referral clinic about their patients' treatment outcomes (9/14, 64.3%) and side effects (8/14, 57.1, Fig 3).

Overall, 44.8% (13/29) of clinics reported that MDR-TB treatment was individualized, whereas 37.9% (11/29) reported only following standardized and pre-determined MDR-TB treatment protocols, and the remaining reported both individualized and standardized MDR-TB treatment (Table 2). In ART clinics with full integration of MDR-TB services,

MDR-TB treatment was most frequently individualized (10/14, 71.4%), whereas in ART clinics with off-site services only, MDR-TB treatment was generally standardized (5/6, 83.3%, [S3 Table](#)). Similarly, overall on-site MDR-TB treatment was more frequently individualized than standardized ([Table 2](#)). However, all national TB guidelines for participating clinics mentioned a standardized short MDR-TB regimen and most of them a standardized long MDR-TB regimen. Specifically, the standardized injectable-containing short regimen was mentioned in 13/19 (68.4%) national TB guidelines and reported to be in use at 18/29 (62.1%) ART clinics. Additionally, in the hypothetical clinical scenario of a newly diagnosed patient with HIV and rifampicin-resistant TB, 58/72 (80.6%) HCWs would start the patient on a standardised MDR-TB regimen as soon as possible ([S5 Table](#), Scenario 2). All HCWs from ART clinics with full integration selected this response (35/35, 100%), while 17/24 (70.8%) HCWs from partially integrated and 6/13 (46.2%) HCWs from ART clinics with only off-site MDR-TB services selected this option.

DOT was recommended during the entire MDR-TB treatment course at 24/29 (82.8%) ART clinics, whereas 5/29 (17.2%) clinics recommended it only during the intensive phase. [Table 2](#) presents the different types of DOT strategies. XDR-TB treatment was available on-site at 7/29 (24.1%) ART clinics. Among the seven ART clinics that reported treating XDR-TB patients, six used individualized regimens (85.7%). Bedaquiline was routinely available at 5/29 (17.2%) clinics and upon request at another seven (24.1%); delamanid was routinely available at 3/29 (10.3%) clinics and upon request at another seven clinics (24.1%, [Table 2](#)).

Discussions

The integration of TB services into HIV care is key to TB control, especially in regions where the burden of both diseases is high. Yet, little is known about the management of MDR-TB at ART clinics in LMICs. We surveyed 29 ART clinics across three continents about referral practices and the integration of HIV and MDR-TB services. About half of them offered full MDR-TB services on-site, and about three-quarters had at least access to rapid molecular testing for MDR-TB. A fifth of the clinics entirely relied on off-site services to which presumptive MDR-TB patients were referred. We observed substantial regional differences in the management of MDR-TB at ART clinics.

To improve quality of care, ART clinics must strengthen the integration of HIV-TB services [9]. There is evidence that full HIV-TB integration improves HIV and TB care [20]. Studies found a higher proportion of TB treatment success and lower mortality during TB treatment among integrated clinics than non-integrated clinics [11,21]. Inadequate referral mechanisms and poor communication can hamper integrated HIV-TB services in LMICs in settings with partial integration, whereas limited human resources, training, and infrastructure affect settings with full integration [22]. Our findings highlight the challenge of coordinating care when MDR-TB services are partially or entirely performed off-site: less than two-thirds of ART clinics received reports of treatment outcomes when their patients with MDR-TB were treated off-site.

In 2013, WHO recommended that Xpert MTB/RIF should be used as an initial diagnostic test in individuals with presumptive MDR-TB or HIV-associated TB [23]. Our study showed that Xpert MTB/RIF was available in about three-quarters of participating clinics. In 2012, we reported that Xpert MTB/RIF was only available on-site at 28% of ART clinics surveyed in the IeDEA consortium [24]. The increase that we observed reflects efforts to roll out Xpert MTB/RIF over the last decade, including in LMICs. Although 76% were able to diagnose MDR-TB using any Xpert MTB, fewer sites (15/29) were able to treat patients with MDR-TB. In contrast to molecular based drug resistance testing, we found that culture-based phenotypic DST was

only available on-site among 35% of clinics, a marginal increase from the 26% reported in 2012 [24]. Culture is currently considered the gold standard DST method. Still, the technical challenges inherent to this method, including biosafety concerns, costly infrastructures, and slow turnover, limit its routine use at smaller ART clinics. We found that culture-based phenotypic DST was generally available at larger facilities outside of ART clinics, to which presumptive MDR-TB cases were referred to or samples were sent.

Fifty-nine per cent of clinics could test for resistance to the first-line drugs rifampicin and isoniazid and 52% to resistance of fluoroquinolones—irrespective of whether DST was performed on-site or off-site. Although DST and treatment of drug-resistant TB remains challenging in many LMICs countries, particularly at smaller clinics, it will be important to strengthen diagnostic and treatment capacities in the future. Importantly, the introduction of short-course fluoroquinolone-based treatment regimens for pan-susceptible TB, which may result in patients on failing treatment, will require DST beyond the common first-line drugs. The lack of rapid drug resistance testing to second-line drug resistance can lead to inadequate treatment and increased mortality during TB treatment [6,7]. Moreover, in a prior study, we showed that the agreement between DST performed in LMICs compared to WGS performed at a central reference laboratory was 86% for rifampicin and 65% for isoniazid, but substantially lower for second-line drugs [7]. Recent developments in genome sequencing technologies are promising, allowing point-of-care identification of resistance to first- and second-line drugs simultaneously and directly on unprocessed sputum samples [25]. Hopefully, this will allow for rapid diagnosis and effective, individualized treatment. However, next-generation sequencing methods were only available at two participating clinics. Targeted genome sequencing approaches using portable sequencers may provide promising new opportunities for rapid and reliable prediction of TB drug resistance [26].

There have been major changes in MDR-TB treatment guidelines in the last five years, including WHO's endorsement of the injectable-containing short regimen in 2016 [18,19]. Several studies have shown high treatment success with the injectable-containing short regimen with minor modifications (80.2% to 95.5% success rates) [19,27–29]. However, one review found that patients with fluoroquinolone-resistant MDR-TB were much more likely to have an unfavorable outcome ($\geq 50\%$) than those with a susceptible strain ($< 20\%$) using the injectable-containing short regimen with or without minor modifications [30]. We found that 18/29 (62%) participating clinics used the injectable-containing short regimen, and the vast majority of HCWs surveyed would use a standardized MDR-TB regimen in routine care. This was particularly evident among sites with fully integrated MDR-TB services, suggesting that access to diagnostic tools may improve guideline adherence. Overall, the clinical scenarios demonstrated reliance on a DST-guided treatment strategies. However, only a few sites had access to rapid second-line DST. Without this important test information, sites in high MDR-TB burden settings may be unable to prescribe adequate and individualized treatment regimens and struggle to achieve widespread treatment success using a standardized MDR-TB regimen [31].

A recent meta-analysis of individual patient data in MDR-TB treatment demonstrated that new or reassigned oral drugs (bedaquiline, linezolid, clofazimine, later generation fluoroquinolones and the carbapenems) were associated with increased treatment success and reduced mortality [32]. This led to new WHO guidelines, recommending the treatment of MDR-TB with only oral drugs [33]. However, we observed that access to bedaquiline and delamanid remains limited among ART clinics in LMICs. In addition improving access to new TB drugs, implementation of new MDR-TB regimens will require adherence support for MDR-TB patients to these TB drugs to ensure adequate treatment and avoid further development of drug resistance. Adherence to MDR-TB regimens remains challenging due to adverse drug

reactions and drug-drug interactions, especially among PLHIV on ART [30,34]. The DOT strategy has been implemented for decades and has been considered crucial for the adherence to TB treatment [35]. However, several studies, including a systematic review, showed that more supportive interventions, such as counseling, DOT provided by trained community workers, short messaging service combined with education, monthly TB vouchers, and drug box reminders are effective for the adherence of MDR-TB patients, especially among PLHIV [35–38]. In our study, DOT was recommended during the entire MDR-TB treatment course in over 80% (24/29) of clinics.

Our study is limited in that it relies on clinicians' reports of available services and drugs at each site rather than patient level data. Furthermore, most participating ART clinics were in urban settings and offered tertiary level care, which could have led to an overestimation of HIV-TB service integration overall. However, a notable strength of our study is the global coverage of ART clinics in LMICs with high TB burden and the detailed information collected on the on-site and off-site service availability. We have previously shown that the availability of diagnostic methods or second-line drugs do not necessarily imply that they were regularly used in routine practice [24]. We explored this gap by assessing clinical practice with the presentation of clinical scenarios.

Although most surveyed ART clinics in LMICs reported integrated HIV-TB services, less than half reported full integration of MDR-TB services and access to DST for second-line anti-TB drugs was rare. There is a continued need for increased availability of diagnostic and treatment options for MDR-TB patients and better integration of advanced MDR-TB services into the HIV care continuum in TB high-burden settings. Furthermore, there is a need for novel rapid and reliable technologies for genome-based DST such as on-site targeted genome sequencing and increased availability of newer and more effective MDR-TB drugs [26]. Repeating site-level surveys is a practical method that allows for ongoing evaluation of progressive access to such testing and treatment.

Supporting information

S1 Table. Questionnaire.

(DOCX)

S2 Table. Infection control measures in place at the 29 ART clinics offering TB services on- and off-site. Abbreviations: ART, antiretroviral therapy; MDR, multidrug resistance; TB, Tuberculosis.

(DOCX)

S3 Table. Availability of TB services by the degree of integration of HIV and MDR-TB services at 29 ART clinics. Abbreviations: DST, drug susceptibility testing; DR, drug-resistant; MDR, multidrug resistance; TB, Tuberculosis; XDR, extensive drug resistance.

(DOCX)

S4 Table. On- and off-site availability of diagnostic tests for initial TB diagnosis and diagnosis of drug-resistant TB. Abbreviations: DST, drug susceptibility testing; LAM, urine lipoarabinomannan. * Unknown availability.

(DOCX)

S5 Table. Hypothetical clinical scenarios assessing clinical practice related to the testing and treatment of MDR-TB at ART-clinics (n = 72). Abbreviations: ART, antiretroviral therapy; DST, drug susceptibility testing; MDR, multidrug resistance; TB, Tuberculosis; H,

isoniazid; R, rifampicin, Z, pyrazinamide; E, ethambutol.
(DOCX)

S6 Table. Strobe checklist.
(DOCX)

S7 Table. Participating programs and members of IeDEA.
(DOCX)

Acknowledgments

We would like to thank all the participating clinics and all those who completed the questionnaire. Further, we would like to thank the advisory panel and the TB & Lung Health IeDEA working group for their inputs and feedbacks. A complete table of participating programs and members can be found in [S7 Table](#).

Author Contributions

Conceptualization: Kathrin Zürcher, Samyra R. Cox, Marie Ballif, Jeffrey A. Tornheim, Lukas Fenner.

Data curation: Kathrin Zürcher.

Formal analysis: Kathrin Zürcher.

Methodology: Kathrin Zürcher, Samyra R. Cox, Marie Ballif, Jeffrey A. Tornheim, Lukas Fenner.

Project administration: Kathrin Zürcher.

Writing – original draft: Kathrin Zürcher, Samyra R. Cox, Marie Ballif, Jeffrey A. Tornheim, Lukas Fenner.

Writing – review & editing: Kathrin Zürcher, Samyra R. Cox, Marie Ballif, Leslie A. Enane, Olivier Marcy, Marcel Yotebieng, Gary Reubenson, Worarat Imsanguan, Larissa Otero, Nishi Suryavanshi, Stephany N. Duda, Matthias Egger, Jeffrey A. Tornheim, Lukas Fenner.

References

1. World Health Organization. Global tuberculosis report 2020. World Health Organization. 2020.
2. Lawn SD, Myer L, Edwards D, Bekker LG, Wood R. Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS (London, England)*. 2009; 23(13):1717–25. Epub 2009/05/23. <https://doi.org/10.1097/QAD.0b013e32832d3b6d> PubMed Central PMCID: PMC3801095. PMID: 19461502
3. Tchakounte Youngui B, Coffie P, Messou E, Poda A, Fortes Deguenonvo L, Hawerlander D, et al. Incidence of Tuberculosis During the First Year of Antiretroviral Treatment in West African HIV-Infected Adults. *Open Forum Infectious Diseases*. 2020; 7(6). <https://doi.org/10.1093/ofid/ofaa203> PMID: 32607387
4. Gandhi NR, Shah NS, Andrews JR, Vella V, Moll AP, Scott M, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *American journal of respiratory and critical care medicine*. 2010; 181(1):80–6. Epub 2009/10/17. <https://doi.org/10.1164/rccm.200907-0989OC> PMID: 19833824
5. Post FA, Grint D, Werlinrud AM, Panteleev A, Riekstina V, Malashenkov EA, et al. Multi-drug-resistant tuberculosis in HIV positive patients in Eastern Europe. *J Infect*. 2014; 68(3):259–63. Epub 2013/11/20. <https://doi.org/10.1016/j.jinf.2013.09.034> PMID: 24247067
6. Zurcher K, Ballif M, Fenner L, Borrell S, Keller PM, Gnokoro J, et al. Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: a multicentre cohort study. *The Lancet Infectious diseases*. 2019; 19(3):298–307. Epub 2019/02/13. [https://doi.org/10.1016/S1473-3099\(18\)30673-X](https://doi.org/10.1016/S1473-3099(18)30673-X) PMID: 30744962

7. Zürcher K, Reichmuth ML, Ballif M, Loiseau C, Borrell S, Reinhard M, et al. Mortality from drug-resistant tuberculosis in high-burden countries comparing routine drug susceptibility testing with whole-genome sequencing: a multicentre cohort study. *The Lancet Microbe*. 2021. [https://doi.org/10.1016/S2666-5247\(21\)00044-6](https://doi.org/10.1016/S2666-5247(21)00044-6)
8. World Health Organization. The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015a. World Health Organisation Document. 2014.
9. World Health Organization. WHO policy on collaborative TB/HIV activities. Guidelines for national programmes and other stakeholders. World Health Organization Document. 2012;WHO/HTM/TB/2012.1:1–34. PMID: 23586124
10. Charles MK, Lindegren ML, Wester CW, Blevins M, Sterling TR, Dung NT, et al. Implementation of Tuberculosis Intensive Case Finding, Isoniazid Preventive Therapy, and Infection Control ("Three I's") and HIV-Tuberculosis Service Integration in Lower Income Countries. *PLoS one*. 2016; 11(4):e0153243. Epub 2016/04/14. <https://doi.org/10.1371/journal.pone.0153243> PMID: 27073928
11. Burnett SM, Zawedde-Muyanja S, Hermans SM, Weaver MR, Colebunders R, Manabe YC. Effect of TB/HIV Integration on TB and HIV Indicators in Rural Ugandan Health Facilities. *J Acquir Immune Defic Syndr*. 2018; 79(5):605–11. Epub 2018/11/02. <https://doi.org/10.1097/QAI.0000000000001862> PubMed Central PMCID: PMC6422342. PMID: 30383587
12. McGowan CC, Cahn P, Gotuzzo E, Padgett D, Pape JW, Wolff M, et al. Cohort Profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme. *Int J Epidemiol*. 2007; 36(5):969–76. dym073 [pii]; <https://doi.org/10.1093/ije/dym073> PMID: 17846055
13. Chammartin F, Dao Ostinelli CH, Anastos K, Jaquet A, Brazier E, Brown S, et al. International epidemiology databases to evaluate AIDS (IeDEA) in sub-Saharan Africa, 2012–2019. *BMJ Open*. 2020; 10(5):e035246. <https://doi.org/10.1136/bmjopen-2019-035246> PMID: 32414825
14. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. World Health Organisation Document. 2015:1–22.
15. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009; 42(2):377–81. S1532-0464(08)00122-6 [pii]; <https://doi.org/10.1016/j.jbi.2008.08.010> PMID: 18929686
16. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019; 95:103208. Epub 2019/05/13. <https://doi.org/10.1016/j.jbi.2019.103208> PubMed Central PMCID: PMC7254481. PMID: 31078660
17. World Health Organization. Definitions and reporting framework for tuberculosis— 2013 revision (updated December 2014 and January 2020). World Health Organization Document. 2014:1–47.
18. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *American journal of respiratory and critical care medicine*. 2010; 182(5):684–92. <https://doi.org/10.1164/rccm.201001-0077OC> PMID: 20442432
19. Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2014; 18(10):1180–7. Epub 2014/09/14. <https://doi.org/10.5588/ijtld.14.0100> PMID: 25216831
20. Owiti P, Zachariah R, Bissell K, Kumar AM, Diero L, Carter EJ, et al. Integrating tuberculosis and HIV services in rural Kenya: uptake and outcomes. *Public health action*. 2015; 5(1):36–44. Epub 2015/09/25. <https://doi.org/10.5588/pha.14.0092> PubMed Central PMCID: PMC4525370. PMID: 26400600
21. Hermans SM, Castelnovo B, Katabira C, Mbidde P, Lange JM, Hoepelman AI, et al. Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr*. 2012; 60(2):e29–e35. <https://doi.org/10.1097/QAI.0b013e318251aeb4> PMID: 22395671
22. Legido-Quigley H, Montgomery CM, Khan P, Atun R, Fakoya A, Getahun H, et al. Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review. *Tropical medicine & international health: TM & IH*. 2013; 18(2):199–211. Epub 2012/12/12. <https://doi.org/10.1111/tmi.12029> PMID: 23217030
23. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. World Health Organization Document. 2013;WHO/HTM/TB/2013.16:1–97. PMID: 25473701

24. Fenner L, Ballif M, Graber C, Nhandu V, Dusingize JC, Cortes CP, et al. Tuberculosis in antiretroviral treatment programs in lower income countries: availability and use of diagnostics and screening. *PLoS one*. 2013; 8(10):e77697. <https://doi.org/10.1371/journal.pone.0077697> PubMed Central PMCID: PMC3798412. PMID: 24147059
25. World Health Organization. The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in *Mycobacterium tuberculosis* complex: technical guide. World Health Organization. 2018.
26. Cabibbe AM, Spitaleri A, Battaglia S, Colman RE, Suresh A, Uplekar S, et al. Application of Targeted Next-Generation Sequencing Assay on a Portable Sequencing Platform for Culture-Free Detection of Drug-Resistant Tuberculosis from Clinical Samples. *Journal of clinical microbiology*. 2020; 58(10). Epub 2020/07/31. <https://doi.org/10.1128/JCM.00632-20> PubMed Central PMCID: PMC7512157. PMID: 32727827
27. Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trébuq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2015; 19(5):517–24. Epub 2015/04/14. <https://doi.org/10.5588/ijtld.14.0535> PMID: 25868018
28. Trébuq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease*. 2018; 22(1):17–25. Epub 2017/11/19. <https://doi.org/10.5588/ijtld.17.0498> PMID: 29149917
29. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. *The New England journal of medicine*. 2019; 380(13):1201–13. Epub 2019/03/14. <https://doi.org/10.1056/NEJMoa1811867> PMID: 30865791
30. Trébuq A, Decroo T, Van Deun A, Piubello A, Chiang CY, Koura KG, et al. Short-Course Regimen for Multidrug-Resistant Tuberculosis: A Decade of Evidence. *J Clin Med*. 2019;9(1). Epub 2019/12/29. <https://doi.org/10.3390/jcm9010055> PubMed Central PMCID: PMC7019808. PMID: 31881691
31. Udwardia ZF, Tornheim JA, Ganatra S, DeLuca A, Rodrigues CS, Gupta A. Few eligible for the newly recommended short course MDR-TB regimen at a large Mumbai private clinic. *BMC Infect Dis*. 2019; 19(1):94. Epub 2019/01/30. <https://doi.org/10.1186/s12879-019-3726-8> PubMed Central PMCID: PMC6350313. PMID: 30691407
32. Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018; 392(10150):821–34. Epub 2018/09/15. [https://doi.org/10.1016/S0140-6736\(18\)31644-1](https://doi.org/10.1016/S0140-6736(18)31644-1) PubMed Central PMCID: PMC6463280. PMID: 30215381
33. World Health Organization. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment—Drug-Resistant Tuberculosis Treatment. World Health Organization. 2020.
34. Stephens F, Gandhi NR, Brust JCM, Mlisana K, Moodley P, Allana S, et al. Treatment Adherence Among Persons Receiving Concurrent Multidrug-Resistant Tuberculosis and HIV Treatment in Kwa-Zulu-Natal, South Africa. *J Acquir Immune Defic Syndr*. 2019; 82(2):124–30. <https://doi.org/10.1097/QAI.0000000000002120> PMID: 31513073
35. Metcalfe JZ, O'Donnell MR, Bangsberg DR. Moving Beyond Directly Observed Therapy for Tuberculosis. *PLoS Med*. 2015; 12(9):e1001877–e. <https://doi.org/10.1371/journal.pmed.1001877> PMID: 26372602
36. Pradipta IS, Houtsma D, van Boven JFM, Alffenaar J-WC, Hak E. Interventions to improve medication adherence in tuberculosis patients: a systematic review of randomized controlled studies. *npj Primary Care Respiratory Medicine*. 2020; 30(1):21. <https://doi.org/10.1038/s41533-020-0179-x> PMID: 32393736
37. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. *The Cochrane database of systematic reviews*. 2007;(4):Cd003343. Epub 2007/10/19. <https://doi.org/10.1002/14651858.CD003343.pub3> PMID: 17943789
38. Liu X, Lewis JJ, Zhang H, Lu W, Zhang S, Zheng G, et al. Effectiveness of Electronic Reminders to Improve Medication Adherence in Tuberculosis Patients: A Cluster-Randomised Trial. *PLoS Med*. 2015; 12(9):e1001876. <https://doi.org/10.1371/journal.pmed.1001876> PMID: 26372470