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A five-year audit of gaps in HIV testing and associations with TB treatment outcomes in Armenia, 2015-2019

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Abstract

Introduction: Poor human immunodeficiency virus (HIV) testing practices and underreporting of HIV-related data in TB information systems remain barriers to effective care for TB-HIV co-infected patients. HIV testing and recording practices in national TB program have not been formally evaluated in Armenia. This study aimed to assess the recording completeness of HIV testing and HIV status in the national TB program electronic database, and to determine trend in HIV testing and the association between HIV testing and treatment outcomes for all TB patients registered in Armenia (2015-2019).

Methodology: A cohort study of TB patients using routine programmatic data from the national TB program of Armenia.

Results: From 2015 to 2019, the electronic database was completed for HIV testing and HIV status by 48.1% and 97.5%, respectively. Of all registered TB patients 93.6% were tested for HIV. Of a total 4,674 patients, 1,085 (23.2%) had unsuccessful outcomes. Patients with HIV status "not tested" and "not recorded" compared to HIV "negatives" had 1.76 (95%CI 1.42-2.11) and 1.6 (95%CI 1.20-2.06) times higher risk of unsuccessful outcomes, respectively. Lost to follow-up was the most frequent unsuccessful outcome in HIV status "not tested" group.

Conclusions: An analysis of nationwide data revealed incompleteness of the national TB electronic database for HIV data. Patients with HIV status "not tested" and "not recorded" had higher risk of unsuccessful TB treatment outcomes. Upgrade of the electronic database with information on key indicators of TB-HIV services will facilitate improved monitoring and reporting.

Key words: SORT-IT; operational research; presumptive TB; not tested for HIV; database completeness; HIV; status unknown.

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Introduction

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) [1]. The burden of TB is exacerbated by immunosuppression caused by human immunodeficiency virus infection (HIV). One in five TB deaths globally were associated with HIV in 2018 [2]. In Armenia, while the rates of TB are decreasing (incidence dropped from 41 to 31 per 100,000 population during 2015-2018), the rates of TB/HIV co-infection are not declining as much (from 3.7 to 3.2 per 100,000 population between 2015 and 2018) [2, 3]. In 2018, HIV status was known for 95% of TB patients and, out of those that were tested, 10% were HIV-positive [2]. Lower rates of successful TB treatment outcomes and overall higher mortality have been found among TB-HIV co-infected patients [4–7]. Early detection and treatment of HIV infection in TB patients is key to improved TB treatment outcomes and reduced mortality in this group [8]. HIV detection rate among TB patients can be affected by testing practices, such as lack of universal HIV testing and test result reporting for TB patients [9,10]. In addition, TB patients may refuse HIV testing [9, 10], which is associated with higher risk of unfavorable treatment outcomes [11,12]. The model of disease control programs for TB and HIV is another factor influencing the uptake of HIV testing. Studies show that vertical, siloed programs for TB and HIV result in low uptake of diagnostic services [13,14]. Since 2004, the World Health Organization (WHO) has recommended and included in its End TB Strategy [15] a package of interventions to reduce the burden of TB and HIV through integrated services [16]. The key interventions of the "collaborative TB-HIV activities" include HIV testing and counseling for presumptive and confirmed TB patients, co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) for TB patients living with HIV [16]. Several countries which have adopted TB-HIV integrated care have shown improvements in TB treatment outcomes and reduced TB mortality [17–19]. Overall, implementation of

collaborative TB-HIV activities contributed to an estimated 1.3 million lives saved from 2005 to 2011 [20]. Underreporting of HIV-related patient outcomes and treatment information in TB information systems remains a barrier to effective care in some settings, but there remains little evidence on this topic [21]. Information from both National TB (NTP) and HIV programs is essential to support effective surveillance [20]. Clinicians require information on ART start dates and regimens in order to monitor drug interactions as new TB drugs may be introduced [21]. Therefore, information on patient and program management must be shared between integrated programs. In the context of "global commitments to end TB and multisectoral accountability", WHO emphasizes the importance of disaggregated analysis and reporting of data on the national and global levels. In addition, WHO has standardized indicators for monitoring of joint TB/HIV programs and recommends that countries have a system for linkage between HIV and TB reporting databases [20]. In Armenia, all TB patients are to be tested for HIV on enrollment, and all TB patients with HIV are to receive CPT and ART [22,23]. Routine TB data is collected for all TB cases through the NTP electronic information system (eTB Manager) throughout the country. To date, no formal evaluation has been undertaken on how well these procedures are implemented in practice. An understanding of the status of collaborative TB-HIV services in National TB and HIV programs and related reporting mechanisms is lacking. Similarly, little is known about the effects of key HIV interventions on treatment outcomes of TB patients in Armenia. Such information is essential to understand the current operational model between the two programs, which may inform establishment and strengthening of TB-HIV integrated care systems in Armenia. The current study aimed to assess the recording completeness of HIV testing and HIV status in the electronic database, and to determine trend in HIV testing, and the association between HIV testing and treatment outcomes for all TB patients registered in NTP from January 2015 to December 2019 in Armenia.

Methodology

Study design

This was a cohort study using routine programmatic data from the NTP of Armenia.

Study setting

Armenia is an upper-middle-income country in the South Caucasus with roughly three million people [24]. TB and HIV services are provided at no cost, and predominantly funded by the state budget and The Global Fund to Fight AIDS, Tuberculosis, and Malaria. The management, financing, monitoring and evaluation, coordination of international programs, and other activities related to TB and HIV care are under the responsibility of the Ministry of Health of Armenia through the National TB Control Center (NTCC) and National Center for AIDS Prevention (NCAP) [23,25].

Specialized TB services (including management and treatment of TB cases) are provided in TB dispensaries, in-patient TB departments, and TB cabinets (outpatient facilities) located in primary health care (PHC) units. Directly Observed Treatment (DOT) is used for the treatment of TB cases. In general, treatment is initiated at in-patient facilities and then patients are transferred to PHC units for the continuation of the treatment. According to the National Clinical Guideline for Tuberculosis Treatment in Armenia, all TB patients are to receive HIV testing, and those testing positive, receive CPT and ART [23]. However, details on the service delivery mechanism or program responsible are not specified for HIV services for TB patients. Blood samples are collected at TB treatment facilities and are sent to NCAP for testing. Anecdotally, patients who receive TB inpatient services receive ART administered by the specialist from NCAP at the TB inpatient facilities; whereas those receiving TB services in outpatient facilities are referred to NCAP service centers for accessing ART services. Routine TB data has been collected for all TB cases through the electronic information system (eTB Manager) throughout the country as part of the NTP since 2011. Data on CPT and ART administration are not available in the electronic database, but are documented in the NTP program enrollment form of the patient's medical card and collected in the national paper-based TB registry.

Study population and period

The study population included all TB cases registered in the e-TB Manager with a confirmed TB diagnosis between January 2015 and December 2019. No exclusion criteria were applied.

Data variables

The data on TB case demographics and clinical characteristics were extracted from the NTP electronic database (eTB Manager). Lab confirmation of TB, history of previous TB treatment and TB treatment outcome were defined according to WHO definitions: "A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear

microscopy, culture or WHO-recommended rapid diagnostic (such as Xpert MTB/RIF).” (Tables 1 and 2). HIV status “not tested” was defined as HIV status of TB cases with HIV test “No”. HIV status and HIV test “not recorded” were defined for missing data points in the electronic database.

Analysis and statistics

Data were extracted into an Excel spreadsheet (Microsoft Inc., USA). Analysis was conducted using R software version 3.6.1 (R Foundation for Statistical Computing, Austria, 2019). Descriptive statistics were used to characterize the study population, using frequencies, proportions, and measures of central tendency (mean) and variation (standard deviation, SD). Recording completeness was defined as all required data points for the variable were non-missing in eTB Manager for the case. HIV testing was calculated based on percentage of cases with known HIV status. Trends were presented per annum. To explore the relationship between HIV status and treatment outcomes, we ran a multivariable logistic regression. Crude relative risks (cRR) and respective confidence intervals (CI) were calculated for the variables of interest. Variables that showed significance level < 0.05 were considered for inclusion in the final model. We applied forward selection method to build the final model. Variables with low relative contribution to the model and which showed multicollinearity were dropped from the final model.

Ethics approval

The study protocol was approved by the Ethics Review Committee of the Health Research and Development Initiative of Armenia and the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease, Paris, France.

Results

A total of 4,674 cases were included in the study. Mean age was 43.2 years and male to female ratio was 3.4:1.0. The majority of cases had pulmonary TB (77.6%, 3,629/4,674) and underwent laboratory confirmation (94.8%, 4,429/4,674). Of all cases, 76.6% were new and 12.5% relapse cases. About one fifth of the cases had drug resistance (17.4%). Detailed sociodemographic and clinical characteristics are presented in Table 3.

During the five-year period, HIV testing was recorded in the electronic database for 2,247 cases, representing 48.1% recording completeness for the study period. Out of 2,247 cases with no recorded HIV

Table 1. Patient types in tuberculosis (TB): World Health Organization classification based on history of previous TB treatment.

Type	Definition
New	Patients have never been treated for TB or have taken anti-TB drugs for < 1 month
Relapse	Patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)
Treatment after failure	Patients who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment
Treatment after loss to follow-up	Patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment
Other previously treated	Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented
Unknown previous TB treatment history	Patients who do not fit into any of the categories listed above

Table 2. Tuberculosis (TB) treatment outcomes: World Health Organization classification.

Outcome	Definition	Outcome
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion	Successful
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable	
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment	Unsuccessful
Died	A TB patient who dies for any reason before starting or during the course of treatment	
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for ≥ 2 consecutive months	

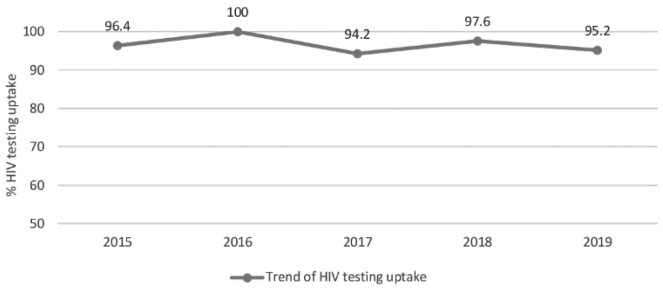
Table 3. Sociodemographic and clinical characteristics of all tuberculosis patients registered in Armenia, between January 2015 and December 2019.

Characteristics	Total N = 4,674 n (%)
Sociodemographic	
Age (years, M ± SD)	43.2 ± 17.4
Gender	
Male	3,612 (77.3)
Female	1,062 (22.7)
Clinical	
History of previous TB treatment	
New case	3,582 (76.6)
Relapse	585 (12.5)
Treatment after failure	107 (2.3)
Treatment after LTFU	118 (2.5)
Other previously treatment	282 (6.0)
Anatomical site of TB	
Pulmonary	3,629 (77.6)
Extrapulmonary	1,045 (22.4)
Lab confirmation	
Positive	2,064 (44.2)
Negative	2,365 (50.6)
No data*	245 (5.2)
TB drug resistance	
Monoresistance	54 (1.2)
Polyresistance	264 (5.6)
MDR/RR	430 (9.2)
Extensive drug resistance	63 (1.3)
Drug sensitive	3863 (82.7)
TB treatment Outcomes	
Successful	3,302 (70.6)
Unsuccessful	1,085 (23.2)
HIV Status	
Positive	378 (8.1)
Negative	3,998 (85.5)
Not tested	183 (3.9)
Not recorded	115 (2.5)

*Patients with missing data both smear and culture results. HIV: human immunodeficiency virus; M: mean; LTFU: lost to follow-up; MDR/RR: Multidrug- and rifampicin-resistant; SD: standard deviation; TB: tuberculosis.

test, 2,312 cases had recorded HIV status. The completeness of HIV status recording was 97.5% for the study period. Annual recording completeness of national electronic database in respect to HIV testing and HIV status is represented in Table 4.

Figure 1. Trend of HIV testing in tuberculosis patients registered in the National Tuberculosis Program from January 2015 to December 2019 in Armenia.



Of 4,674 TB cases, 4,376 were tested for HIV (93.6%), of which 8.1% were HIV positive. Figure 1 demonstrates the trend of HIV testing for the study period.

Overall, the treatment outcome was successful for 70.6% of cases. During the treatment, 13% of cases were lost to follow-up, 6.5% died, and treatment failed was recorded for 3.1%. In the unadjusted multivariable logistic regression model, the risk of unsuccessful treatment outcome was 1.88 (95% CI 1.64-2.15) times higher in HIV-positive cases (149/1,085, 13.7%), compared with those who were HIV-negative (842/1,085, 77.6%). In addition, cases with HIV status "not tested" (60/1,085, 5.5%) and HIV status "not recorded" (34/1,085, 3.1%) had a higher risk of unsuccessful outcome compared with HIV-negatives (cRR = 1.52, 95%CI 1.23-1.88 and cRR=1.38, 95%CI 1.03-1.83, respectively). After adjusting for age, gender and drug resistance, cases with HIV status "not tested" and "not recorded" had 1.76 (95%CI 1.42-2.11) and 1.6 (95%CI 1.20-2.06) times higher risk of having unsuccessful outcomes, respectively, compared to HIV-negatives (Table 5). The final model was statistically significant. Among those with HIV status "not tested" having unsuccessful treatment outcome (n=60), the majority were lost to follow-up cases (80.0%).

Table 4. Completeness of national electronic database with respect to HIV testing and HIV status for tuberculosis patients registered between January 2015 and December 2019 in Armenia.

Year	Number of patients in database (n)	Variable completeness			
		HIV test*		HIV status**	
		n	(%)	n	(%)
Total	4,674	2,247	(48.1)	4,559	(97.5)
2015	1,147	1,140	(96.4)	1,140	(96.4)
2016	1,072	1,072	(100.0)	1,072	(100.0)
2017	956	25	(2.6)	897	(94.2)
2018	818	4	(0.5)	799	(97.6)
2019	682	6	(0.9)	651	(95.2)

*HIV testing variable complete if "Yes" or "No". **HIV status complete if "positive," "negative," or "unknown".

Discussion

Our study demonstrated that the majority of TB cases were screened for HIV (93.6%), which is, however, below the WHO recommended target of 100% [26]. HIV testing did not vary much from 2015 to 2019, but reached the WHO target only in the year 2016. However, the screening rate was much higher than recent global and WHO European Region statistics. The proportion of notified TB cases with a documented HIV test result in WHO European region was 55% in 2015 and 61% in 2018 [27].

Different factors influence HIV testing practices among TB cases, including socioeconomic and psychological determinants and models of service delivery [28,29]. Absence of HIV testing services at sites providing TB care services and poor referral practices among providers are other reasons for poor uptake of HIV testing among cases with TB [19]. In India, the coverage of HIV testing among TB cases increased after the decentralization of HIV testing facilities to all peripheral health institutions [14]. Similarly, in Vietnam, on-site HIV testing at TB registration and treatment sites resulted in an increase of HIV testing uptake among TB cases from 58.5% in 2011 to 82.9% in 2017 [30]. In Armenia, HIV diagnostic services for TB cases are centralized within NCAP laboratories and on-site testing is not available, which may explain any gaps in testing uptake.

Our findings suggest that the practices of HIV testing reporting and recording are highly variable in Armenia. For the five-year study period (2015-2019), HIV testing was completed by 48.0% of TB cases, while HIV status was recorded in 97.5%. Of note, the gap was predominantly observed for period from 2017 to 2019. The observed lack of concordance between these two interrelated variables in the electronic database can be explained by the current mechanisms of service delivery and notification systems in Armenia. Usually, TB cases receive provider-initiated testing where blood samples are collected at the TB treatment facilities and sent to NCAP laboratories. The waiting time of the results usually varies between 5 and 30 days [26]. It is possible that HIV test results may have been known by the responsible physician and were captured in the paper-based registry, but not fully entered in the electronic database. Nevertheless, understanding the situation requires thorough review of the service delivery and notification systems.

We identified only few studies from South African and European countries that reported on related database completeness, however, those assessed electronic database completeness comparing with paper-based registries, and these results may not be comparable to those of this study [31,32].

In this study, overall treatment success rate of registered TB cases with or without HIV was 70%, which is much less than the WHO recommended target of 85%. HIV co-infection rate among all TB cases registered in the study period was 8.1%, which is consistent with TB-HIV co-infection rate in WHO European Region (ranging from 6.1% to 13.6%) [29]. In our study, 3.9% (183/4,674) had HIV status "not tested", and for 2.5% (115/4,674) information was missing in the electronic database. The risk of unsuccessful treatment outcome in these two groups of cases was higher compared with those who tested negative (HIV status "not tested", adjRR = 1.76, 95%CI 1.42-2.11, and HIV status "not recorded"; adjRR = 1.6,

Table 5. Results of the crude and adjusted multivariable logistic regression analysis for predictors of the tuberculosis (TB) treatment outcomes, National TB Program, Armenia 2015-2019.

Characteristics	Total n	Treatment Outcomes				Crude RR [95% CI]	*p*-value	Adjusted RR [95% CI]	p-value
		Successful		Unsuccessful					
		n	(%)	n	(%)				
Total	4,387	3,302	(75.3)	1,085	(24.7)	-	-	-	-
HIV status									
Negative	3,748	2,906	(77.5)	842	(22.5)	1	-	1	-
Positive	353	204	(57.8)	149	(42.2)	1.88 [1.64,2.15]	< 0.001	1.84 [1.60,2.10]	< 0.001
Not tested*	176	116	(65.9)	60	(34.1)	1.52 [1.23,1.88]	< 0.001	1.76 [1.42,2.11]	< 0.001
Not recorded**	110	76	(69.1)	34	(30.9)	1.38 [1.03,1.83]	0.044	1.62 [1.20,2.06]	0.002
Age									
Mean±SD	43±17	42±18		46±17		1.01 [1.006,1.012]	< 0.001	1.01 [1.007,1.014]	< 0.001
Gender									
Female	999	802	(80.3)	197	(19.7)	1	-	1	-
Male	3,388	2,500	(73.8)	888	(26.2)	1.30 [1.16,1.52]	< 0.001	1.23 [1.08,1.41]	0.003
TB drug resistance									
No	3,687	2,915	(79.1)	772	(20.9)	1	-	1	-
Yes	700	387	(55.3)	313	(44.7)	2.14 [1.93,2.37]	< 0.001	2.19 [1.99,2.40]	< 0.001

*HIV status "Not tested" defined as HIV status of TB patients with HIV test "No". **HIV status "Not recorded" defined for missing data points in the electronic database. SD: Standard Deviation; CI: Confidence Interval; RR: Relative Risk.

95%CI 1.20-2.06). Walter *et al.* (2012) reported that odds of developing unsuccessful treatment outcomes was higher among TB patients who were not tested for HIV compared with those whom test results were negative [11]. The same study reported adjusted estimates for each unfavorable treatment outcome. The results showed that not being tested for HIV was associated with treatment failure (adjOR = 2.37), death (adjOR = 2.48) and transferred out (adjOR = 2.79) [11]. Gebremariam *et al.* (2016) reported four times higher odds of treatment failure and 2.7 times higher odds of lost to follow-up (LTFU) among patients without known HIV status [12]. Patients who were not tested for HIV and those tested positive might share similar characteristics, and, as suggested by the Walter et al. (2012), those not tested may further comprise a consistent number of HIV-positive patients [11]. This means that, despite the high uptake of HIV testing in TB patients in Armenia, there is a probability of missed opportunities to link HIV co-infected cases to the appropriate care. In our study, about 80% of cases with "not tested" status of HIV and unsuccessful treatment outcome were LTFU, which is consistent with the existing literature [12,33]. One explanation would be that the patient's refusal for HIV test may influence the provider's interaction with the patient, which may cause the patient to feel pressure and interrupt the treatment or leave the program and non-consent for HIV test might be an indicator of overall poor adherence to TB treatment [11]. On the other hand, patients with "not tested" status of HIV could represent severely ill people, who died before starting their treatment, and due to lack of follow-up information were registered as LTFU.

This study had strengths, including following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies. To our knowledge, this was the first study that explored reporting completeness of HIV data in the electronic database of NTP in Armenia. The use of nationwide data allows these results to be generalized to the entire country. This study also has several limitations. We did not have data on TB patients' nationality and residency, which are a known factors influencing the TB treatment outcome [33,34]. Previous studies in Armenia indicated about 95% of the registered TB patients in Armenia are natives, holding Armenian citizenship [32], which means that effect of this variable in our adjusted estimates would be minimal. However, the information on resident status of non-Armenian citizens is not included in the routine surveillance, which makes further investigation of those cases difficult. There are many migrant workers in Armenia and increased risk for drug-resistant TB has been recently reported for this group [33]. However, data on immigration status of patients, which would enhance an explicit understanding of our findings, was not available in the electronic database. Initially, we aimed to analyze overall uptake of HIV interventions in NTP, including data on CRT and ART from patient's medical records, considering that treatment outcomes of TB-HIV co-infected patients are influenced by appropriate CPT and ART treatments as well. However, due to the restrictions imposed by the 2020 COVID-19 pandemic, including a prolonged country lockdown and healthcare workforce mobilization, we were not able to access the medical records in NTCC. The study has several policy and practice implications. Improvement of health information systems in the TB program is essential. The national electronic database (eTB manager) should be upgraded in order to achieve an acceptable data agreement with paper-based registries. This will provide an opportunity for having sound surveillance and higher quality disaggregated reporting and monitoring, which are essential for the improvement of overall quality of care. Finally, improvement of the current operational system between National TB and HIV programs can be achieved by transition from vertical to integrated systems, as recommended by WHO [16]. As a first step to establishment of integrated care, a formative evaluation should be undertaken in order to have a deep understanding of performance in both programs. This can be done by using WHO's guidelines for monitoring and evaluation of collaborative TB-HIV services [20]. Considering the possibility of missed opportunities for testing for HIV, it is important to have a comprehensive understanding of underlying socioeconomic, psychological and service-quality related factors in this group of patients. Further qualitative and quantitative research in this subgroup of patients could help to understand these factors.

Conclusions

An analysis of nationwide data in Armenia revealed incompleteness of the national TB electronic database for HIV data. In addition, we found that patients with HIV status "not tested" and "not recorded" had higher risk of poor TB treatment outcomes. Improvement of the current health information systems and operational system between National TB and HIV programs is recommended.

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Authors' Contributions

Arpine Abrahamyan (AA), Katrina Hann (KH), Kristina Akopyan (KA), Ruzanna Grigoryan (RG), Ofelya Petrosyan (OP), Hayk Davtyan (HD). AA is the study principal investigator, together with KH and RG conceptualized study aims and methodologies. AA and OP were involved in the data collection. KH, KA, and AA carried out the data analysis. KH, RG, KA, and AA drafted the manuscript. HD provided comments and suggestions throughout the development of methods, data collection and summarizing the results. KH, KA, and AA finalized the manuscript.

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