

## SORT IT TB Key Population

### Gaps in tuberculosis control in Armenia: How to improve the care system?

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#### Abstract

**Introduction:** Tuberculosis (TB) continues to be a global public health problem. People with weakened immune systems are more vulnerable to TB. It is one of the top 10 causes of death worldwide and is a leading cause of death for people living with HIV (PLWH). The aim of the current study was to perform programmatic data analysis of TB cases treated with the first-line drugs, registered in Armenia for the period of January 2017 – August 2018, and to identify gaps in TB care system in Armenia.

**Methodology:** A retrospective cohort study using programmatic data from National TB Program.

**Results:** Overall treatment success rate for the period of study was 79%. HIV had impact only on “died” outcome with odds ratio (OR) of 20.9. More than a third (34%) of all HIV-positive patients died during TB treatment and 45% of patients who had non-Armenian citizenship were lost to follow-up during the treatment (OR = 3.3). Treatment duration for the 8% of all cases (mainly with brain or bone localization) was > 9 months and lasted up to 500 days.

**Conclusions:** Better collaboration and partial integration of TB and HIV services in Armenia is required. The access to care for non-Armenian citizens needs to be improved. The national TB treatment guideline needs to be updated based on scientific evidence. This study demonstrates that continuous analysis of the available data and tailoring of the system is required to address the needs of key populations and achieve universal care coverage.

**Key words:** Tuberculosis; people living with HIV; PLWH; migrants; TB treatment outcomes; Armenia.

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#### Introduction

Tuberculosis (TB) continues to be a global public health problem. Around 30% of the world’s population is infected with *Mycobacterium tuberculosis* and small portion of these people are falling ill [1,2]. People with a weakened immune systems are more vulnerable [1,2]. The risk of developing active TB is about 20 to 30 times higher in people living with HIV (PLWH) [1–5]. In 2017, 10 million people were diagnosed with this opportunistic infection. It is one of the top 10 causes of death worldwide and is a leading cause of death for PLWH. In 2017, one of three HIV deaths were due to TB [1,2].

According to the Stop TB Partnership, apart from PLWH other TB key populations (those with higher risk of having the disease) include mobile populations (including migrants), miners, prisoners and detainees, as well as people who use drugs [4]. The Global Fund Advocates Network includes children, healthcare

workers, indigenous populations and urban poor people into key populations as well [3]. However, each country’s contexts and situations are different and key populations might also differ [4].

The “End TB Strategy” adapted by the World Health Assembly in 2014, calls for a 90% reduction in TB deaths, and an 80% reduction in the TB incidence rate by 2030 compared to 2015. Successful TB treatment target rate is set at 90%. Many countries are far from reaching these targets. Identifying gaps and addressing needs of key populations should contribute to achieving these goals [1].

In recent years, several reforms in TB care took place in Armenia [6–12]. As a result, efficiency of the services was increased and unnecessary use of services was reduced [6,10]. The TB incidence rate is decreasing starting from 60 (95% CI: 46 – 76) in 2013 to 36 (95% CI: 27 – 45) among 100,000 population in 2017[1]. On the contrary, the percentage of HIV/TB coinfections

among all TB cases is increasing. It reached 7.9% (95% CI: 6.1 – 9.9) in 2017 while in 2013 it was only 4.7% (95% CI: 3.6 – 5.9) [1].

Migration and tourism are other key factors making TB management more complex. There are known increased risks of acquiring TB and multidrug resistant (MDR) TB among migrant workers [13–15]. This makes migrants one of the key population groups in Armenia. Migration trends and number of refugees across the world are highly affected by wars. There was an increased number of registered immigrants from Iraq, Lebanon and Syria due to conflicts in recent years [16]. The TB care system needs to be adapted to provide proper level of TB care to an increased number of migrants. On the other hand, the increased number of tourists in Armenia pose a threat to appropriate TB management during short stays in the country [17,18].

The aim of the current study is to perform routine programmatic data analysis of TB cases treated with first-line drugs, registered in Armenia for the period of January 2017 – August 2018, to identify gaps, key or underserved populations and provide recommendations accordingly for improving quality of TB care in Armenia. Specific objectives are: a) to determine factors associated with treatment outcomes of TB patients and b) to perform survival analysis to identify time related patterns for the identified factors.

## Methodology

### *Study design*

This is a retrospective cohort study using routine programmatic data from National TB Program.

### *Study setting*

Armenia is a small, upper-middle income country located in South Caucasus with population of around 3 million and GDP of 12.4 Billion USD (2018) [19]. The percentage of the population living below the national poverty lines was 25.7% in 2017 according to World Bank data [19]. Treatment of TB and HIV is free of charge and is funded by State budget, as well as by international organizations [1,20].

### *TB and HIV care in Armenia*

The management, financing, monitoring and evaluation, coordination of international programs, projects and other activities related to TB and HIV care is carried out by the Ministry of Health of the Republic of Armenia through the National TB Control Office (NTCO) and Center for AIDS Prevention (NCAP).

Specialized TB services (including management and treatment of TB cases) are provided in TB

dispensaries, in-patient TB departments, and TB cabinets (out-patient facilities) located in primary health care (PHC) units throughout the country. Directly Observed Treatment (DOT) is used for the treatment of TB cases. Usually treatment is initiated in the in-patient facilities (intensive phase of treatment) and then patients are transferred to PHC units for continuation of the treatment. All registered TB cases in Armenia are passing HIV screening and counselling as per national guidelines [20]. According to WHO data, all TB cases have known status of HIV [1]. Blood samples are collected at TB treatment facilities and are sent to NCAP for testing. Once HIV is detected, patients are referred to the same institution for consultation and treatment. Then NCAP, which coordinates and provides HIV care, is reaching out to patients for their education and treatment.

Management and treatment of PLWH is organized and conducted at the NCAP. According to the current national guidelines, PLWH need to be screened for TB every year. After the review of the National TB Program, WHO recommended to open a TB diagnostic center in NCAP in order to improve TB diagnostics in PLWH. Center was established with the support of the Global Fund to Fight AIDS, Tuberculosis, and Malaria. However, according to WHO, the Center is not fully operational, and in 2013 only 233 out of 1,041 (22.3%) PLWH were tested for TB. Isoniazid preventive therapy (IPT) is included in a national TB care guideline, but practically is not being implemented. According to WHO, none of HIV-positive patients received IPT during the period of 2011-2014 [21]. For HIV/TB co-infected patients, care is not fully provided within the same facility. HIV is managed by treating doctor at NCAP and TB is managed by local TB cabinet doctor. National treatment guidelines for TB and HIV care are developed by respective institutions based on international evidence based guidelines including WHO one.

### *Study population and period*

The study used data of all TB cases registered in the national electronic database (e-TB Manager) with confirmed TB diagnosis over the period of January 2017 – August 2018. Routine data is being collected for all TB cases throughout the country as part of the national TB program. The following variables were used during the study: age, gender, weight before and after treatment, TB registration and diagnosis dates, treatment start and end dates, HIV status, microscopy and culture examinations, citizenship (resident status unknown), extra-pulmonary type, patient type and

treatment outcome. The last two variables are collected according to WHO definitions which are presented in Table 1 and Table 2 [22].

### Analysis and statistics

Findings are presented using descriptive statistics: frequencies, proportions, measures of central tendency (mean), and variation (standard deviation). Differences between the groups were assessed with the use of Pearson's  $\chi^2$  test for categorical variables and Student's t-test for continuous variables. The level of significance was set at  $p < 0.05$ . Along with the parameter estimates 95% confidence intervals (CI) are presented as well. Odds ratios (OR) and mean differences are presented in respective tables. Cox regression was used to compare the probabilities of surviving from unsuccessful outcomes.

### Ethics approval

The NTCO provided access to the data, and ethics approval was obtained from the Center for Medical Genetics and Primary Healthcare institutional review board, Yerevan, Armenia.

## Results

A total of 1,168 patients were included in the study, of which 77% were males. Among them 80% were new,

and 15% were relapse cases. The remaining 5% were cases who have failed previous treatment (1.5%), those who were lost to follow-up during the last treatment (2.5%), and other retreatment cases (1%). Overall treatment success rate for the period was 79%. During the treatment, 13% of cases were lost to follow-up, 6.5% died (not necessarily due to TB), and treatment failed for 1.5%.

Patients in the categories “Treatment after loss to follow-up” or “Other previously treated” had 2.4 (95% CI: 1.1 – 5.3) and 5.3 (95% CI: 1.4 – 21.2) times higher odds of having an unsuccessful outcome, respectively, compared to the new patients. As expected, HIV was also increasing chances of having unsuccessful outcome (OR = 4.0, 95% CI: 2.6 – 6.2). Having non-Armenian citizenship was negatively impacting the TB treatment outcome as well (OR = 3.3, 95% CI: 1.3 – 8.0). Age and weight after treatment were also associated with the treatment outcome. Successfully treated patients were younger and had higher weight on average compared to those having unsuccessful treatment outcomes. All associations and characteristics are presented in Table 3.

Further analysis revealed that HIV had statistically significant impact only on “Died” outcome (OR = 20.9, 95% CI: 6.8 – 86.8): 34% of all HIV-positive patients were dying during the treatment course.

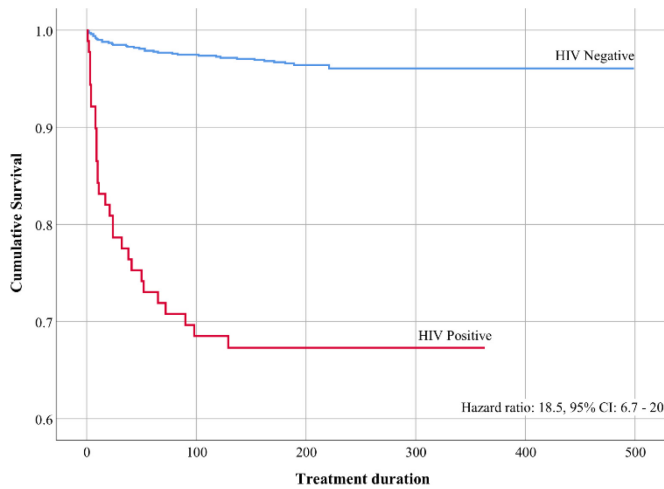
**Table 1.** Patient types in tuberculosis (TB): World Health Organization classification based on history of previous TB treatment.

| 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   |

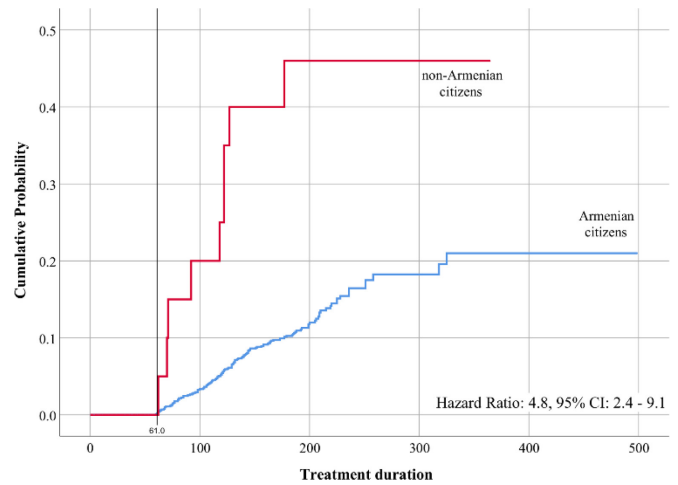
**Table 2.** Tuberculosis (TB) treatment outcomes: World Health Organization classification.

| 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 $\geq 2$ consecutive months  |              |

**Figure 1.** Survival of HIV-positive vs HIV-negative patients during treatment course for susceptible TB cases registered from January 2016 – August 2017.



**Figure 2.** Probability of having “Lost to Follow-up” outcome for non-Armenian versus Armenian citizens registered as TB cases from January 2016 – August 2017.



**Table 3.** Characteristics of TB cases with successful and unsuccessful treatment outcomes for patients registered from January 2017 to August 2018.

| Characteristics |                  | Total<br>N = 1168,<br>n (%) / M ± SD | Outcomes, n (%) / M ± SD |                       | OR / MD ± SD | 95%CI      | p value |
|-----------------|------------------|--------------------------------------|--------------------------|-----------------------|--------------|------------|---------|
|                 |                  |                                      | Unsuccessful<br>N = 249  | Successful<br>N = 919 |              |            |         |
| Gender          | Female           | 273 (23.4%)                          | 54 (21.7%)               | 219 (23.8%)           | 0.9          | 0.6, 1.2   | 0.478   |
|                 | Male             | 895 (76.6%)                          | 195 (78.3%)              | 700 (76.2%)           | 1            | -          | -       |
|                 | Missing          | 77 (6.6%)                            | 26 (10.4%)               | 51 (5.5%)             | -            | -          | -       |
| Citizenship     | Non-Armenian     | 20 (1.7%)                            | 9 (3.6%)                 | 11 (1.2%)             | 3.3          | 1.3, 8.0   | 0.006*  |
|                 | Armenian         | 1071 (91.7%)                         | 214 (85.9%)              | 857 (93.3%)           | 1            | -          | -       |
| Extra-pulmonary | Extra-pulmonary  | 274 (23.5%)                          | 52 (20.9%)               | 222 (24.2%)           | 0.8          | 0.6, 1.2   | 0.289   |
|                 | Both             | 39 (3.3%)                            | 9 (3.6%)                 | 30 (3.3%)             | 1.1          | 0.5, 2.3   | 0.873   |
|                 | Pulmonary        | 855 (73.2%)                          | 188 (75.5%)              | 667 (72.6%)           | 1            | -          | -       |
| Patient type    | After failure    | 17 (1.5%)                            | 3 (1.2%)                 | 14 (1.5%)             | 0.8          | 0.2, 2.9   | 1       |
|                 | ALFU             | 28 (2.4%)                            | 11 (4.4%)                | 17 (1.8%)             | 2.4          | 1.1, 5.3   | 0.020*  |
|                 | Other            | 12 (1%)                              | 7 (2.8%)                 | 5 (0.5%)              | 5.3          | 1.4, 21.2  | 0.006*  |
|                 | Relapse          | 178 (15.2%)                          | 32 (12.9%)               | 146 (15.9%)           | 0.8          | 0.5, 1.3   | 0.359   |
| HIV             | New              | 933 (79.9%)                          | 196 (78.7%)              | 737 (80.2%)           | 1            | -          | -       |
|                 | Missing          | 80 (6.8%)                            | 24 (9.6%)                | 56 (6.1%)             | -            | -          | -       |
|                 | Positive         | 91 (7.8%)                            | 43 (17.3%)               | 48 (5.2%)             | 4.0          | 2.6, 6.2   | <0.001* |
| Lab confirmed   | Negative         | 997 (85.4%)                          | 182 (73.1%)              | 815 (88.7%)           | 1            | -          | -       |
|                 | Positive         | 230 (19.7%)                          | 42 (16.9%)               | 188 (20.5%)           | 0.8          | 0.6, 1.1   | 0.206   |
| Age, years      | Negative         | 938 (80.3%)                          | 207 (83.1%)              | 731 (79.5%)           | 1            | -          | -       |
|                 | -                | 42 ± 18                              | 45 ± 19                  | 42 ± 18               | 3 ± 1        | 0.3, 5.6   | 0.026   |
| Weight, Kg      | Before treatment | 61 ± 18                              | 59 ± 20                  | 61 ± 15               | -2 ± 1       | -4.7, 0.7  | 0.143   |
|                 | After treatment  | 63 ± 18                              | 59 ± 21                  | 64 ± 16               | -5 ± 1       | -7.4, -1.7 | 0.002*  |

ALFU: After Lost to Follow-up; CI: Confidence Interval; M: Mean; MD: Mean Difference; OR: Odds Ratio; SD: Standard Deviation; \* Statistically significant result.

A Survival analysis revealed that almost all deaths were occurring during the first 100 days of treatment (Figure 1).

Non-Armenian citizenship had statistically significant impact on having “lost to follow-up” outcome (OR = 3.3, 95% CI: 1.3 – 8.0): 45% of patients having non-Armenian citizenship were lost to follow-up during the treatment and the rest had successful treatment outcome. All of the cases were lost to follow-up after day 61 (end of intensive phase of treatment) as presented in Figure 2.

Additional analysis revealed that treatment duration for the 8% of cases was longer than 9 months (WHO recommended duration) and lasted up to 500 days. Majority of these cases had extra-pulmonary TB localized either in brain or bones.

## Discussion

This is one of the first studies in Armenia, which focuses on analysis of routine data to identify factors that have negative impact on treatment outcomes and reveals time-related patterns for having certain outcomes by grouping and comparing people with or without these factors.

The study shows that one third HIV patient dies during the TB treatment course, which is alarming, since the proportion of HIV-infected patients among all TB patients increases over time [1]. The death occurs in the first 100 days of treatment. Lack of information in the routine data regarding the anti-retroviral treatment and co-trimoxazole preventive therapy, as well as AIDS status, makes further evaluation of these patients impossible. Miscommunication or lack of collaboration between treatment facilities may explain these results, however thorough review of the system is required to understand root cause of the observations. This finding shows that PLWH are underserved, and adaptation of the care system is required to meet needs of key population. This is proven by comparing mentioned findings with other studies reporting death rate among HIV/TB co-infected patients in other countries. Engelbrecht *et al.* (2017) reported 17% deaths in susceptible HIV/TB co-infected cases' treatment outcomes in South Africa for the period of 2009–2012 [23]. Similarly, Carlucci *et al.* (2017) stated that in children with co-infection this rate amounts only to 8% (data from International Epidemiology Databases to Evaluate AIDS) [24]. Viktorova *et al.* (2018) have reported a 41% death rate in treatment outcomes of MDR TB/HIV cases in one region of Russia [25]. For susceptible HIV/TB patients Podlekareva *et al.* (2017) reported a 16% cumulative probability of dying during

one year after TB diagnosis in Eastern and Western Europe and Latin America. It is remarkable that in Western Europe death rate for HIV/TB co-infected cases was only 4% [26].

Another identified factor that increases the chance of having a “lost to follow-up” outcome is having a non-Armenian citizenship. Unfortunately, the information on resident status of non-Armenian citizens is not routinely collected making further investigation of these cases difficult. Time pattern analysis revealed that patients are ceasing the treatment after the intensive phase of treatment. This indicates that there might be constraints related to access to the care in PHC facilities as the continuation phase of the treatment is conducted there. Having citizenship as a determinant of treatment outcome demonstrates that the system is not adapted to serve visitors from foreign countries.

The longer than WHO recommended treatment duration of patients with cerebral or bone TB is another observation that is problematic and requires attention. A review of the current national treatment guideline revealed that it is required to have 12 months of TB treatment for cases with meningitis and spine TB (i.e. TB localized in brain or bones). It is justified that penetration for some anti-TB medications through blood–brain barrier is unknown and evaluation of outcome for the spine TB is hard [20]. However, in these cases, since there is no scientific evidence justifying long-term use, patients might be getting unnecessary long-term treatment, which increases the likelihood of side effects from drugs. Moreover, the same drugs could be used more efficiently being allocated for treatment of other TB patients, which will reduce overall case management costs.

This study followed STROBE statement for reporting of observational studies [27]. Nationwide data was used and observations are generalizable to the whole country. However, main limitation of the study was the fact that it fully relied on available data from the national database and the probable bias that might be present in the original data cannot be eliminated. Another limitation was the fact that 6.8% and 6.6% of the cases did not have recorded HIV and citizenship status, respectively. This could have resulted into skewed observations. Strain data and immigration status of patients which would help to understand problems related to immigration and tourism more clearly was not available as well.

This study has some policy and practice implications. A closer collaboration of the NTCO and NCAP is required in order to achieve seamless management of HIV/TB co-infected cases. Better data



exchange between the two institutions could be achieved by implementing the WHO recommendation mentioned earlier, which would make the TB diagnostic center more accessible for PLWH. In order to provide them with a proper level of care, integration of TB and HIV services could be explored, e.g. by having fully operational TB treatment center within NCAP. This may result in an efficient case management of co-infected patients and improved access to timely care.

The adaptation of the TB care system to make access easier for non-Armenian citizens, especially during the treatment at PHC level, is necessary to improve their treatment outcomes. This is important from a global health perspective, as untreated foreign nationals will transfer TB to other countries. More data regarding residence status and duration of stay in Armenia needs to be collected as a routine data. Further exploration of this data is necessary to understand who exactly is having problems with access to care. Moreover in depth review of current processes for care coverage is required to understand how treatment is being provided to non-Armenian citizens. Current TB treatment guidelines are not specific to citizenship (it is not mentioned that the system is serving only to Armenian citizens), but registration and provision of free of charge care to patients in PHC units requires proof of Armenian residency.

Finally, revision of the current national TB treatment guideline is required. It needs to be based on scientific evidence as currently no references are provided for the included information. This can result in shortening of treatment duration for meningitis and spine TB cases. One of the sources that could be used for that purpose is the WHO treatment guidelines.

## Conclusion

Analysis of routinely collected TB data revealed several gaps in the TB care system. Better collaboration and partial integration of TB and HIV services in Armenia is the key to having improved care for PLWH. Access to care for non-Armenian citizens is another important step in system improvement. The national TB treatment guideline needs to be based on scientific evidence in order to avoid unnecessary use of drugs and longer than required treatments. This study demonstrates that continuous analysis of the available data and tailoring of the care system is required in order to achieve universal care coverage and satisfactory treatment results.

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