



Invited lecture/Scientific contribution

# Observation on Tuberculosis Preventive Treatment in Georgia

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## Abstract:

The uptake of latent tuberculosis infection treatment (LTBI) is an important measure to prevent active tuberculosis (TB), but has not been well studied in low and middle-income countries (LMICs). The lifetime risk of developing active TB for people with LTBI is 10-15%. Within the national guidelines of National Tuberculosis control Program (NTP) 2020 in Georgia, 6 months isoniazid preventive treatment (IPT) was replaced with 3 months rifampentine treatment. Here we present the results of the care cascade of LTBI treatment of subjects to whom the Tuberculosis Preventive Treatment (TPT) in Georgia was recommended. We performed a cohort-study during 2020-2021 in which we applied a mixed method recommended for TPT. We assessed active pulmonary TB cases to whom IPT was recommended and in cases not completing a tuberculosis preventive treatment, the respective reasons. Among 678-contacted subjects, 54% were female and 46% were male. There was no age limit. Overall 164 participants initiated TPT, among them 107 completed the treatment. 72% from all participants were in close contact with TB-patients/ index cases and were living in the same household. 49% of index cases were positive to culture test (culture test involves studying bacteria by growing the bacteria on different substances) and 45% were Drug Sensitive Tuberculosis (DST) positive. 23 cases of index cases were MultiDrug-Resistant (MDR) TB patients. 95 (14%) participants were treated at the National Center for Tuberculosis and Lung Diseases, other participants were treated at other regions of Georgia (Kakheti, Kutaisi, Rustavi, Gori). From 22 children under 5 years of age who were recommended for the Tuberculosis Skin Test (TST), 2 were positive. Our findings highlight very low rates of LTBI treatment recommendation, initiation and completion in Georgia and hence the need for improved monitoring and treatment programs.

**Keywords:** Communicable disease, Infectious disease, Tuberculosis, Latent tuberculosis, Prevention, Epidemiology.

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**Abbreviations:**

TB-Tuberculosis

LTBI-Latent Tuberculosis Treatment

MDR-TB- Multy drug resitance tuberculosis

DS-TB-Drug Ssensitive Tuberculosis

IPT-Isonizid Preventive Treatment

TPT-Tuberculosis Preventive Treatment

Lfx-Levofloxacin

TST-Tuberculine Skin Test

NCTLD-National Center for Tuberculosis and Lung Disease

**1. Introduction**

A key component of the END TB Strategy is to prevent new TB cases through TB preventive treatment (TPT). Implementing this intervention is critical given that the World Health Organization (WHO) estimates that a quarter of the global population has LTBI thus serving as a large reservoir for incident TB cases. Historically, due to limited resources and inadequate tools, highly burdened countries have focused on diagnosing and treating active TB cases with a lower priority placed on LTBI. The momentum to combat LTBI has increased in recent years partly driven by commitments provided at the 2018 UN High Level Meeting on TB to provide TPT to 30 million people by 2022. However, WHO data indicated that only ~500,000 household contacts of active TB were treated in 2019 and highlighted that the track to meet targets are way off. ("Global Tuberculosis Report 2020" n.d.)

Since 2015, the country of Georgia no longer belongs to the highly burdened countries, however the number of drug-resistant TB cases remains a major problem. According to the WHO, the number of TB cases in Georgia detected in 2021 was 2400, among them 410 were MultiDrug-Resistant TB (MDR) cases and only 13% from all TB cases that were in contact with infected subjects initiated TB preventive treatment (TPT). ("WHO Operational Handbook on Tuberculosis: Module 1: Prevention: Tuberculosis Preventive Treatment" n.d.; "Global Tuberculosis Report 2022" n.d.)

Georgia follows WHO's recommendations and updates national TB strategy based on the newest recommendation. Till 2020, TPT was recommended only for two prioritized groups of people, HIV positive patients and children aged 0-5, who were close contacts of bacteriologically confirmed drug sensitive TB cases (DS-TB). TPT regimen was 6-month isoniazid treatment (6INH). Results of a previous study showed a very low rate of TPT initiation and completion. In addition, 4 children among 135 who were recommended for TPT developed an active TB in one year of period. All children were from the group which did not initiate the preventive treatment ("LTBI Preventive Treatment in Children in Country of Georgia," n.d.).

After March 2020 the strategy of TPT was updated based on WHO's guidance, which means that all persons who were in close contact with active TB cases in any age are recommended to start TPT: not only the persons that were in close contact with DS-TB patients, but also MDR-TB cases. In addition, the treatment regimen 6INH was replaced with 3PH (3-month rifapentine) for DS contacts and 6lfx (6-month levofloxacin) - for MDR contacts. Beside this, targets of recommendations were widened. Risk groups such as - (1) HIV positive people, who are initiating anti-TNF treatment; (2) receiving dialysis, (3) preparing for an organ or (4) hematological transplant, (5) who have silicosis should be systematically tested and treated for LTBI (Gabunia 2019). After the changes of the recommendations, we have evaluated the LTBI care cascade among people who were recommended for TPT at the National Center for Tuberculosis and Lung Disease in four regions of Georgia such as: Kakheti, Kvemo Kartli, Shida Kartli and Imereti.

**2. Methods**

We conducted a prospective and retrospective cohort study looking at the implementation of preventive TB treatment in Georgia. The target group was in close contact with active



TB patients of any age and with other risk groups (HIV patients, Dialysis patients, Organ Transplant patients and cancer patients treated with TNF-alpha) during the year 2020-2022 as defined by the National treatment guidelines at National Center for Tuberculosis and Lung Disease (NCTLD) and three regions of Georgia, Kakheti, Imereti and Kvemo Kartli.

### 2.1 Settings and procedures

TB hot-spot contact investigation was performed by the National Center for Disease Control and Public Health (NCDC) epidemiologists. During contact investigation epidemiologists referred all close family contact to the specialized TB service clinics for further investigation and for ruling out active TB. In parallel, pulmonary TB patients were asked to bring their family and close contacts for investigation at specialized TB facilities. This was the countrywide practice including the National Center for Tuberculosis and Lung Disease.

After excluding active tuberculosis, TB contacts were consulted to receive preventive treatment. Preventive treatment regimen depended on the age group of contact person and drug sensitivity or resistance of index case. Children under 2 years, who were contacts of drug sensitive pulmonary TB cases are receiving 6 month INH therapy while, other contact persons were given Rifapentin for 3 months (12 doses). Contact persons with MDR index cases were recommended to start 6-month Levofloxacin (Lfx) treatment.

Baseline visit included tuberculosis skin test (TST) or Interferon-Gamma Release Assays (IGRA) assay, chest X-Ray and examination by a physician including a collection of anamnesis. Patients under treatment visited their personal physicians every month for further analysis and examination that included blood and urine tests and X-ray imaging if needed ("Detection and Treatment Latent Tuberculosis Infection in Georgia," n.d.).

### 2.2 Data collection

Special data collection tools (eCRFs) were developed for the primary data collection. The baseline form included socio-demographic information, details on co-morbidities and other risk factors for developing active TB diseases, TST status and information on chemoprophylaxis. A questionnaire was collected including "yes/no" or multiple choice questions. Data from 2020 were collected retrospectively to have complete data on new treatment regimens. Patients' medical charts were collected for informations relevant for research and are currently stored in TB units' archives. The subjects were followed for 1 year. The data were collected by the Research Electronic Data Capture - REDCap. The analysis was performed by the SPSS software. The univariable and bivariable analysis were performed to look at the potential risk factors for incidence of TB disease and barriers for Isoniazid Preventive Treatment (IPT) start/completion. The Mantel-Haenszel odds ratios (ORMH) and corresponding 95% confidence intervals were obtained as the measures of association. A multivariable logistic regression analysis was conducted and the relevant adjusted Odds Ratio OR will be obtained. Kaplan Meier survival analysis was performed for evaluating the time to TB disease incidence comparing between IPT and non-IPT groups.

### 2.3 Ethics

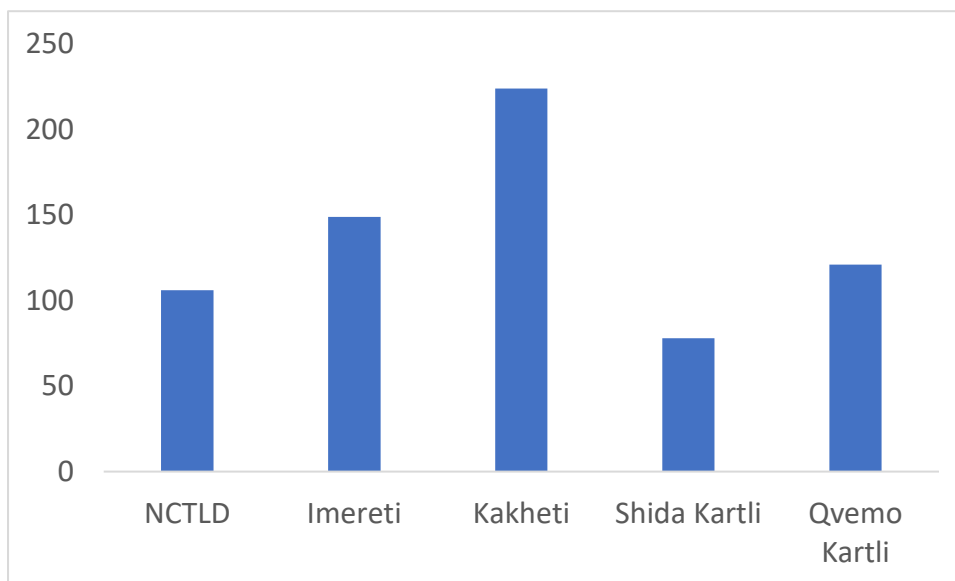
Permission for the study was obtained at the Local Ethics Committee of the National Center for Tuberculosis and Lung Diseases. Patients' informed consents were asked from all patients who underwent the ICF procedure. Only those who provided signed informed consent were considered in the study further based on eligibility criteria. All obtained informations were anonymized and unique identifiers were used for the records in the study database without possibility to identify the person. The electronic databases were kept on a password protected computer of the principal investigator. There were no direct benefits or any cash incentives to those individuals included in the study.

## 3. Results

At the first stage, we conducted a descriptive analysis, which took into account the number of recommended participants. The participants' sample included the information on how many of them started TPT, how many stopped and how many completed the preventive

treatment. An ongoing research aims to follow-up all participants every 3 months during 2023 to detect active TB cases from the national TB electronic database. After one year of follow-up period, the results were considered for further analysis looking for the effectiveness of the preventive treatment and treatment of active TB.

Among all 678-contacts of DS and DR TB cases and people from other risk groups, 54% were female and 46% male. 95 (14%) participants were from NCTLD, all other cases from other regions of Georgia (Kakheti, Kutaisi, Rustavi, Gori) (**Figure 1**). 22 Children under 5 years of age were recommended to have the TST test, among them 2 were TST positive. 72% from all participants had close contacts with index cases and were living in the same household. According to WHO, index case is defined as a person who has an active TB. A close contact is defined as living in the same household or in frequent contact with a source case with sputum smear-positive TB patient. 49% of index cases were culture positive and 45% were DST positive, 23 cases of index cases were MDR TB patients. Overall 164 (24%) persons from total 678 initiated TPT, among them 107 (65%) completed the treatment.



**Figure 1.** Distribution of test subjects over the regions.

#### 4. Discussion

We found that 24% of subjects initiated the treatment of TB prophylaxis and from these, 65% completed the treatment. Due to the fact that we do not have comparable data from previous years, since the work of this program started for the first time in 2020, we cannot interpret the results as neither positive nor negative. We can compare only the results on children aged 0-5 years that were in close contact with TB patients with the results of a previous study, where the number of treatment initiation was 64% and among them 16% completed TPT. However, these data are also not relevant for comparison, as the children in the previous study were only prescribed 6 months of INH.

According to the systematic review of Sandgren et al. (2016) our completion rates were higher for the short LTBI treatment than for long LTBI treatment regimens. In the general population the reported initiation rate varied between 26–99 % and the completion rate between 39–96 %, In persons that were in close contact with TB patients initiation rate was 40–95 % and completion rate was 48–82 % (Sandgren et al., 2016). A study by Gullón Blanco et al. (2022) showed high rate of treatment initiation (86.6%, where only 12 persons refused to take part) while 262 (88.5%) completed 3 month TP. If we compare treatment completion rate (65%) with these results we are far from a high rate, but considering the novelty of a program we can estimate an increased number in the future.



## 5. Conclusion.

As our results show a low number of treatment initiation with unknown reasons for not entering into the program. Further research is needed to identify the issues of the programme. A qualitative research is planned to conduct in-depth analysis through the interviews with those participants who did not initiate or stopped the treatment.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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