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Programmatic Management of Tuberculosis during COVID-19 Pandemic in Georgia

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Abstract

The article reveals the real problems caused by the pandemic associated with the new coronavirus. The problems affected the implementation of the National Tuberculosis Program. It is important for National TB Programs to put all efforts in active case detection, treatment adherence and preventive treatment implementation in response to COVID-19 impact on TB epidemics.

KEY WORDS: diagnosis of tuberculosis, treatment of tuberculosis, prevention of tuberculosis

Introduction

Georgia has decreased the Tuberculosis (TB) burden by more than 50% over the last 10 years compared to 2009, however TB disease burden still remains high with 2,590 and 2,448 reported cases of TB in 2018 and 2019 respectively, resulting in the notification rates of 69.4 and 65.7 per 100 000. On average, TB incidence in Georgia has been decreasing by approximately 10% per year. In 2019, the proportion of TB cases with rifampicin-resistant or multi-drug resistant TB (RR/MDR-TB) was 12.1% of new cases and 32.1% of previously treated cases. In absolute numbers, among all TB cases (pulmonary or extrapulmonary) notified in 2018 and 2019, the total numbers of laboratory-confirmed

RR/MDR-TB cases were 311 and 319 respectively, with 35% and 27% exhibiting fluoroquinolone drug resistance. Georgia detects 100% of the WHO estimates of RR/MDR-TB, but remains among the high Multi-drug resistant Tuberculosis (MDR-TB) priority countries within the WHO European region [1,2].

Diagnosis, treatment and prevention of tuberculosis is free of charge in Georgia is covered by the state and the Global Fund grant funding. According to the Law of Georgia on State Budget, the amount of funding for the TB State Program is determined annually for the diagnostic and treatment services provided to high risk groups and people confirmed with TB. The state budget covers for the inpatient and outpatient treatment services, active drug safety monitoring (aDSM) activities, and post-treatment follow-up (once every 6 months for 24 months most treatment) funded through the per capita voucher system for the outpatient level and based on the DRG for the inpatient level. 100% of First line anti-TB drugs (FLDs) and 80% of Second Line anti-TB Drugs (SLDs) are also covered by the state budget, with remaining 20% covered by the Global Fund. TB is not part of the health insurance schemes and the free of charge services are supported through the state TB program funding to the private health care facilities, as the latter represent 99% of the healthcare facilities in Georgia. RR/MDR-TB patients receive monthly incentives for good adherence, partly covered by the state and partly by the Global Fund. Patients also receive DOT related transportation reimbursement and android cell phones for accomplishing the VTS both covered by the Global Fund grant.

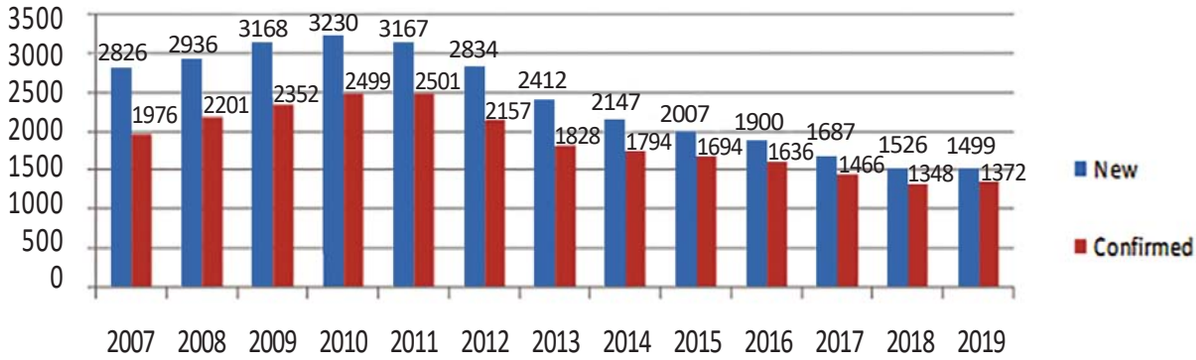
The National Center for Tuberculosis and Lung Diseases (NCTLD), in Tbilisi serves as a TB reference clinic and as a methodological center within National Tuberculosis Program (NTP) of Georgia. The National Reference Mycobacteriology Laboratory (NRL) is a structural part of the NCTLD. The NRL has a capacity to perform the below listed tests with the following turnaround time from sample collection to results submission (Table 1).

The national TB diagnostic algorithm ensures that every person investigated for TB in Georgia is tested using a WHO-recommended rapid molecular test such as GeneXpert and or HAIN LPA. Culture and DST is performed for every person diagnosed with TB. Every RR-TB patient is tested using HAIN MTBDRsl test and phenotypic DST to SLDs listed in the table above. Georgia has increased the proportion of bacteriological confirmation of TB cases over the last 10 years and in 2019 is 92% (picture 1) [3,4].

Table 1. The National Reference Mycobacteriology Laboratory capacity

Test Name	Test turnaround time
Ziehl-Neelsen (ZN) staining	24 hours
LED fluorescent microscopy	24 hours
Culture on solid Löwenstein-Jensen (LJ) media	21- 56 days
Culture on liquid media in MGIT (Mycobacteria Growth Indicator Tube) on Bactec 960 system	5-14 (positive) 42 (negative) days
Genotype MTBDRplus Assay, HAIN Lifescience	2-3 days
Genotype MTBDRsl Assay, Hain Lifescience	2-3 days
DST on 1st line drugs (SIRE) on Bactec 960 system	7-14 days
DST to 2nd line drugs: Ofloxacin, Moxifloxacin (2 concentrations), Kanamycin, Capreomycin, Bedaquiline, Levofloxacin, Linezolid, Clofazimine, Amicacin; Delamanid (validation in process) on Bactec 960 system	7-14 days
Xpert MTB/Rif and Xpert MTB/Rif Ultra	Same day

Picture 1. Bacteriological confirmation among pulmonary TB cases in Georgia 2007-2019



Monthly smear microscopy and culture is used to monitor the treatment effectiveness, along with the rapid molecular and phenotypic DST to monitor for drug resistance amplification.

A majority (80%) of RR/MDR-TB patients in Georgia start treatment at the NCTLD hospital. However, s the average length of stay is 29 days, after which patients are discharged to the community where patients receive treatment and monthly monitoring based on the nationally approved protocols. Decision on the treatment initiation, or regimen modification and the model of care is made by the Central DR-TB Clinical Committee (DRC) based on the available national policy.

Georgia is widely using the innovative modes of treatment observation and follow-up such as Video Supported Treatment (VTS) with almost 80% of MDR-TB patients and 30% of drug-susceptible TB (DS-TB) patients receiving the fully oral treatments through this mode at the outpatient level of care. Other option of DOT, such as facility based, home based by a nurse and home based by a family member for pediatric patients also exist and are implemented whenever needed.

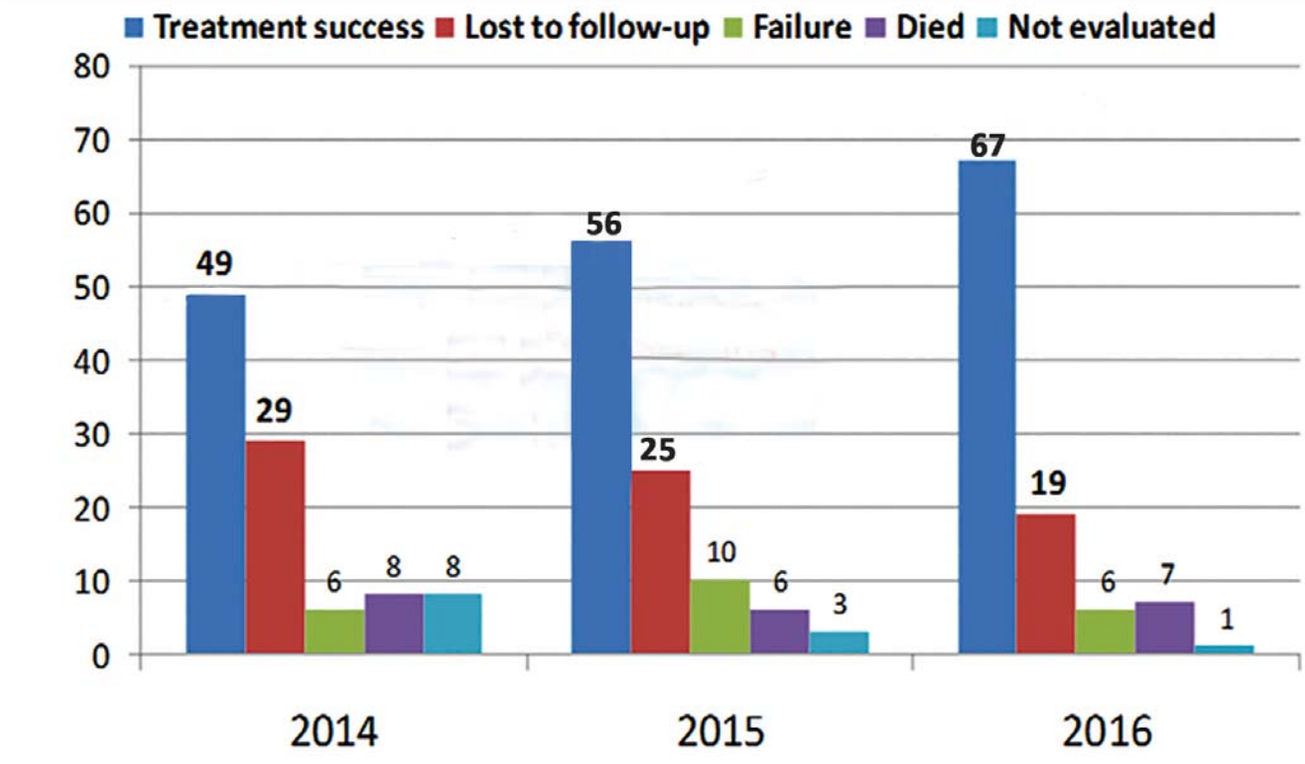
Treatment policy documents are regularly updated by the NCTLD in line with the WHO guidelines and recommendations. Current national TB treatment and management guideline includes chapters and separate protocols on Drug Sensitive (DS) and Drug-resistant (DR) TB diagnosis, treatment, treatment monitoring and follow-up, models of TB care, criteria for hospitalization and discharge, TB and HIV management, TB and HCV management, TB and other co-morbidities management, active drug safety monitoring and management, management of adverse events and drug toxicities, extra-pulmonary TB (EPTB), TB and pregnancy, TB and Surgical management, LTBI diagnosis and TB prevention strategies. The guideline and protocols were endorsed by the Ministry of health in June 2019 and includes WHO recommended fully oral longer regimens and also a mechanism to implement modified shorter treatment regimens with focus on data collection for the OR purposes. The guideline implementation started since June 2019. The major revisions in the guideline that target adults and children include: a) themodified fully oral shorter regimen of 9 months BDQ/Lzd/Lfx/Cfz/Cswith DLM the first drug to substitute in case of toxicity and used in case of children under 6 years of age in RR-TB patients with the same inclusion and exclusion criteria as listed for the WHO mSTR OR, and b) longer 18-20 month regimens for all other patients, e.g. quinolone resistance, extensive TB disease with a backbone of BDQ/Lzd/Lfx/Cfz, with additional drugs based on treatment history and drug resistance patterns.

To ensure adequate guideline implementation the relevant training of the TB program doctors and programmatic staff has been conducted in May-June 2019. In addition to training NCTLD holds a central supervision team, which conducts regular supportive supervision to treatment facilities countrywide and NCTLD in- and out-patient units.

Georgia started programmatic implementation of new and re-purposed TB drugs since early 2015. Since 2016 Georgia implemented the active Drug Safety and Monitoring and Management (aDSM) framework to ensure safe administration of new treatment regimens. All baseline and monthly laboratory and instrumental investigations are covered by the State TB Program funding for all RR/MDR/XDR-TB patients in Georgia. Information on SAEs and AEIs are routinely collected by the NCTLD pharmacovigilance system. The

treatment outcomes of RR-TB patients have improved with the implementation of new drugs and are shown in the picture below (Picture 2).The key driver for the improved treatment outcomes seems to be the better tolerance of new treatment regimens, hence better adherence and less loss to follow-up (LFTU), which was and still is the major challenge for treatment in Georgia. However, the country has progress in decreasing the number of the LTFU patients and hopefully with the implementation of the fully oral longer and mSTR regimens the impact on LFTU will be significant [5].

Picture 2. RR/MDR-TB Treatment Outcomes 2014-2016



Interventions

The anti-COVID-19 interventions started since mid January 2020 in Georgia. By the time when the first case of COVID-19 was detected on February 26th 2020, Georgia was in the phase of active disease surveillance and risk mitigation with: airport and other border screening, closed flight communications with China and Iran, established capacity to transport countrywide samples and conduct PCR testing at the Lugar Center of the National Center for Disease Control and Public Health (NCDC), elaborated recommendations and trained key personnel and operational overarching “COVID-19 Coordination Council”.

In parallel, the National Tuberculosis Program started training of health care workers and other staff by epidemiologists on key infection control and self protection measures, revised the distribution and the utilization rules of existing in stock N95 respirators and initiated the process of developing a TB and COVID-19 co-infection screening and clinical management guide. It is worth mentioning that as fully oral injecting agent free DR-TB treatment regimens have been programmatically implemented since June 2019 in Georgia, the country was already widely using the innovative modes of treatment observation and follow-up such as Video Supported Treatment (VST) with almost 80% of MDR-TB patients and 30% of Drug Sensitive TB (DS-TB) patients receiving the fully oral treatments through this mode. With the glooming COVID-19 pandemic, measures were taken to protect already diagnosed and on treatment TB patients from contracting the COVID-19. Specifically, since March 16, 2020, all patients at the outpatient level are given one month stocks of drugs on hand; the remaining MDR-TB patients were moved to VST, with very few exceptions of six patients to whom a TB nurse was delivering drugs weekly. The drug sensitive patients not on VTS are receiving drugs at home without observation. Every newly diagnosed TB patient is receiving free of charge COVID-19 PCR or antigen based testing.

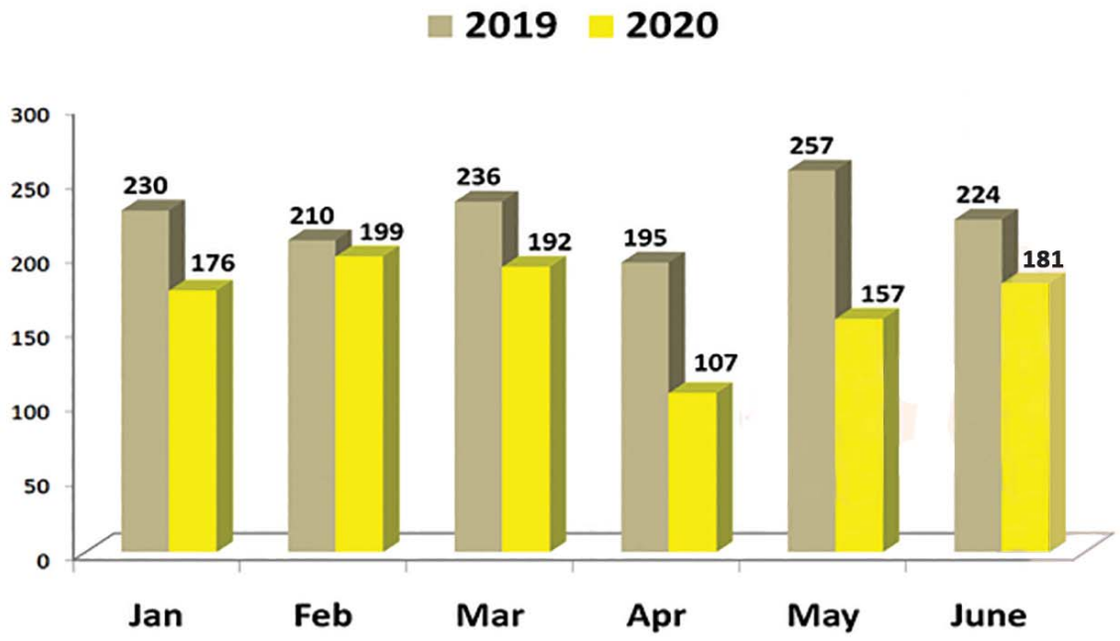
In April 2020 NCTLD in collaboration with the Infectious Diseases, AIDS and Immunology Research Center (IDACIRC) has developed a protocol on management of Tuberculosis and COVID-19 co-infected cases. The protocol has been approved by the Ministry of Health in May 2020 and was the first such protocol in the EU region.

The National Center for TB and Lung Diseases (NCTLD) and its staff has been involved in the different aspects of COVID-19 control since the emergence of the epidemics. Since mid-March to mid-April, the pediatric TB department of the NCTLD which is a separate isolated building within the NCTLD campus was closed and transformed to a quarantine facility. A team of TB doctors and nurses were within NCTLD were transferred from TB activities and assigned to work for the COVID-19 quarantine space. Since mid-April through the end of May the same pediatric TB department was assigned to function as a so called “Fever Center”, where patients with fever were evaluated for COVID-19 as COVID-19 suspect cases. Inpatient DS and DR-TB doctors (8 doctors) were removed from daily TB practice, including the night shifts and allocated to the fever center for the full time work. With decreased referrals to TB clinics, the inpatient wards where the doctors worked were not as busy as usual, thus this temporary shift in functions did not impact much the TB care within the NCTLD. Since September 1st 2020, with increased number of COVID-19 cases in Georgia, the pediatric department was re-profiled to the COVID clinic and is performing this function since then. The 20 bed department is always full of patients, with beds being occupied immediately after a patient is discharged.

Impact of COVID -19 on tuberculosis in Georgia

Talking about the preliminary trends at the country level in terms of the impact of COVID-19 pandemic on the TB health indicators, it is important to understand the restrictive measures implemented by Georgia. Based on the national TB Data Base, number of TB cases detected during the first six months of 2020 have been decreased by overall 25% in comparison to 2019 (Graph 1). This decrease is unexpected and lies outside the statistically significance range of 10%.

Graph 1. TB cases enrolled in the TB program in January-June 2019-2020.



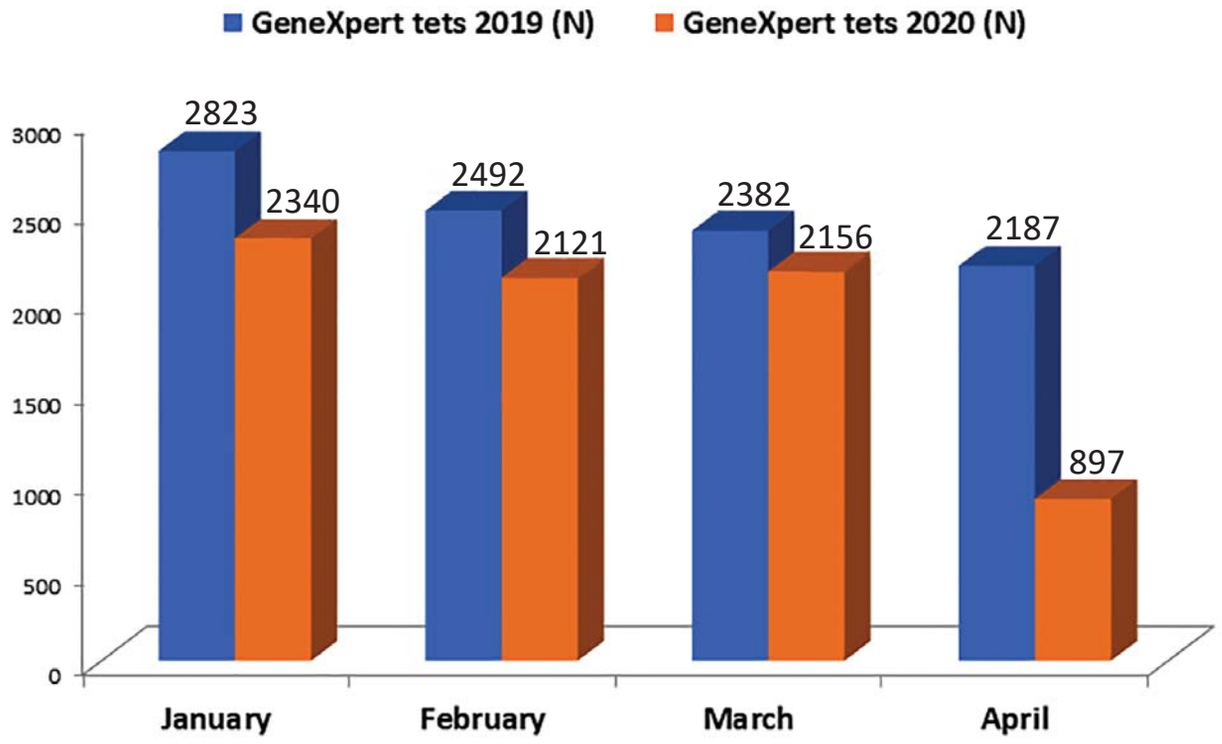
So, the preliminary trend of TB detection indicates that COVID-19 might have impacted greatly and that might have translated into further disease transmission and spread. It is early to explore the impact of the epidemics on the treatment retention and hence the TB treatment outcomes. However, with all the measures the TB program undertook, it should be estimated that the impact on the treatment outcomes will be less dramatic than the impact on the case detection.

The sole TB laboratory capacity and function has not been impacted by the COVID-19 epidemics. Also was not impacted the sample transportation capacity, because the latter is accomplished by the Georgian Postal Service since 2014 and the postal service vehicles transportation was not restricted during the lock down and curfew periods mentioned above. Also, the laboratory personnel were working in shifts covering the need as usual. Georgian government has made a direct communication with Cepheid to ensure the rapid supply of SARS-Cov-2 express cartridges that were planned to be used on the 3 of the

existing GeneXpert machines, one outside TB program in Lugar Center and 2 within TB Program. However, the selection of machines was made in a way that it could not impact the TB program diagnostic needs.

The TB diagnostic algorithm in Georgia implies conducting the GeneXpert MTB/Rif testing for every TB suspect. On average the NTP performs 25,000 Xpert test per year with a plan to increase the number of tests in line with the roll out of extra GeneXpert machines. The analysis of the Xpert testing trends in 2019 and 2020 is shown in graph 2 below:

Graph 2. GeneXpert testing in Jan-April 2019-2020 in Georgia



As the graph shows there is on average 14% drop in Xpert tests in Jan-March and extreme 59% drop in April. Not surprising, as the source of the test samples are from the TB suspects visiting the health facilities, but with complete lock down in April persons with mild symptoms would be postponing their visits to health care facilities as the only way to get to the clinic would be either by walking or ambulance. With the ease of the lock down measures it is expected to see increased number of TB suspects tested using GeneXpert for next 6 months until another wave of the restrictions goes in force.

Conclusion

COVID-19 has proven to be a real challenge for every sector and program, including the National Tuberculosis Program as well. It has also impacted the functionality of the non-governmental and community organizations. However the representatives of the community organizations in Georgia did manage to transform their modus operandi in a way that had allowed them to still deliver their services to at least certain categories of patients. In line with measures taken within NTP in response to COVID-19, many of the TB patients were left without daily in-person interaction with health care workers and peers that could have impacted the treatment adherence and overall psychological well being of the patients.

The decreased case detection of TB due to COVID-19 will have long term negative impact on TB epidemics globally and nationally. WHO estimates, that COVID-19 will decrease the case detection by 50% and that this major disruption will result in additional 400,000 lives lost globally. It is important for National TB Programs to put all efforts in active case detection, treatment adherence and preventive treatment implementation in response to COVID-19 impact on TB epidemics.

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