JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

EECA Region SORT IT

Short and long-term outcomes of video observed treatment in tuberculosis patients, the Republic of Moldova

Svetlana Doltu[1], Ana Ciobanu[2,3], Yuliia Sereda[4], Ruth Persian[5], Luke Ravenscroft[5], Liana Kasyan[6], Nune Truzyan[6], Andrei Dadu[2], Anthony Reid[7]

[1] *NGO 'AFI', Chisinau, Republic of Moldova*
[2] *WHO Regional Office for Europe, Copenhagen, Denmark*
[3] *University of Medicine and Pharmacy 'N. Testemitanu', Health Primary Care Center, Chisinau, Republic of Moldova*
[4] *Independent Consultant, Kyiv, Ukraine*
[5] *The Behavioural Insight Teams, London, United Kingdom*
[6] *American University of Armenia, Erevan, Republic of Armenia*
[7] *Médecins Sans Frontières, Brussels, Belgium*

Abstract

Introduction: The Republic of Moldova is among the 18 high priority countries for tuberculosis (TB) in Europe. This study compared adherence and short and long-term TB treatment outcomes for TB patients who experienced asynchronous Video Observed Treatment (aVOT) during three months of outpatient treatment versus Directly Observed Treatment (DOT) in operational conditions in 2016-2017 in Chisinau.

Methodology: We used secondary data from the 2016-2017 Randomized Clinical Trial (RCT) that piloted the aVOT Strategy in Chisinau and data from the national TB register. Relative risk was selected as a measure of association in analysis of treatment strategies (aVOT and DOT under operational conditions) and short and long-term treatment outcomes.

Results: From 647 TB patients included in the study, 169 followed the treatment strategy in the RCT (83 in aVOT and 86 in DOT) and 478 were on DOT in operational conditions. Those in aVOT were more likely to have favourable short-term outcome than patients with DOT in operational conditions (RR 0.07; $p < 0.001$). TB recurrence as an indicator for the long-term outcome, was observed in group with DOT in operational conditions (40 cases, $p = 0.006$).

Conclusions: This study demonstrated that the aVOT treatment strategy was associated with better adherence and both short and long-term TB treatment favourable outcomes. aVOT as a new patient-centred approach supporting TB patients on improving treatment adherence and outcomes might be recommended as an alternative to DOT strategy in the Republic of Moldova.

Key words: SORT IT; video observed treatment; tuberculosis; outcomes.

J Infect Dev Ctries 2021; 15(9.1):17S-24S. doi:10.3855/jidc.14601

(Received 30 December 2020 – Accepted 08 May 2021)

Introduction

Despite major advances in tuberculosis (TB) control, TB is still one of the largest public health challenges globally predominantly affecting low and middle-income countries [1]. According to the World Health Organisation (WHO), the burden of TB places the Republic of Moldova among the 18 high priority countries in the WHO European Region and among 30 countries with a high rifampicin-resistant or multi-drug-resistance tuberculosis (RR/MDR) TB burden in the world [2]. The country is placed sixth among the 10 countries of the world with a high burden of RR/MDR-TB [1]. Considerable investments were made in the Republic of Moldova to improve TB surveillance, diagnosis, adherence, and treatment as well as to reform TB control and health care systems in line with WHO recommendations over recent years [3]. These efforts improved the key impact indicators such as TB mortality and TB notification rate which decreased respectively by 66% (from 18 to 6 per 100,000) and 38% (from 113 to 72 per 100,000) from 2010 to 2019 [3]. The latest treatment success rates were 85% (2018) in newly and relapses cases TB patients and 56% (started treatment in 2017) in all RR/MDR-TB patients [4]. Prevention and response to the spread of TB are public health priorities in the Republic of Moldova and are reflected in the National Tuberculosis Program (NTP) for 2016–2020; included is implementation of

innovative TB treatment programs for improving adherence and treatment outcomes. In recent years, video-observed therapy (VOT) has gained attention [5] as an alternative to Directly Observed Treatment (DOT) - the most commonly used adherence intervention in the last decades [6]. As part of End TB Strategy [7], WHO's Global TB Programme, has developed a conceptual framework to demonstrate the potential roles of digital health in TB prevention, care and control efforts that include the introduction of VOT [8] to support patient-centred care [9].

VOT is a technological alternative to in-person DOT whereby patients are observed swallowing their medications remotely using live (synchronous) or recorded (asynchronous) video technology via smartphones, tablets or computers [10,11]. Asynchronous video observed therapy (aVOT), allows patients to video-record their medication ingestion for providers to watch at another time [12]. The VOT Treatment Strategy Randomized Clinical Trial (RCT) was carried out in Chisinau from 2016 to 2017, and recently published in 2020 [13]. It showed that aVOT resulted in better adherence at a lower cost than DOT, and provided evidence that these benefits were achievable in a low-income country. All patients who took part in the RCT were followed by NTP according to the usual follow up guidelines to determine treatment outcomes. Taking this into account we proposed to do a complementary analysis of the parent study adding TB patients who received DOT in usual operational conditions who had the same eligibility criteria but not were included in the RCT. The specific objectives of our study were: 1) to describe the socio-demographic and clinical characteristics of TB patients from the RCT and in those who received DOT in operational conditions; 2) to provide additional adherence analysis in the RCT groups; and 3) to compare the short and long-term outcomes in aVOT and DOT under operational conditions groups.

Methodology

Study design

This was a cohort study that combined data from the RCT on Treatment Strategy [13] and DOT data under operational conditions in Chisinau in 2016-2017.

General setting

The Republic of Moldova is situated in the South Eastern Europe, bordering Romania and Ukraine. The population of the country is about 3.5 million, with 42% living in urban areas. The capital city is Chisinau with a population of 636,000 inhabitants. According the World Economic Outlook Report of the International Monetary Fund (April 2014) the Republic of Moldova is a lower middle-income economy, with a GDP per capita of 3,900 US Dollars.

National TB control

The Ministry of Health, Labour and Social Protection has primary responsibility for TB control in the country and carries out its tasks through the National Tuberculosis Program (NTP), in collaboration with other government entities, development partners and civil society organizations. The diagnosis and management of TB, case definitions, recording and reporting all comply with WHO guidelines [14]. There is a national TB case-based database in the country – the System of Information for Monitoring and Evaluation of TB patients (SIME TB) for the reporting and follow-up of TB patients [4]. Only a third of TB patients have health insurance before being diagnosed with TB. The absence of health insurance can create barriers to access TB diagnostic services, and may limit access to medications for side effects, consequently affecting treatment adherence. However, TB investigations and all treatments are free of charge to all TB patients. TB treatment in the Republic of Moldova is carried out in inpatient and outpatient settings. All adherent to TB treatment patients receives vouchers for food and hygienic products (2 USD per day). In Chisinau, outpatient TB treatment is provided in 15 TB sites distributed throughout five city districts.

Study population

The study participants comprised patients who had previously been enrolled in the RCT and those who were registered in the TB national registry. Inclusion criteria were: diagnosed with TB; being adult (≥18 years); receiving outpatient treatment for at least three months in Chisinau from January 2016 to December 2017; and having a treatment outcome recorded by the end of December 2019. Exclusion criteria: diagnosis of drug-resistant (DR) TB at the time of diagnosis or later, being homeless, drug and alcohol users, former prisoners or refusing to participate in the RCT (only for RCT groups).

Data variables

Data variables were combined from two data sources: the RCT conducted in 2016-2017 [13] and the national TB register (SIME-TB). Data included socio-demographic and clinical characteristics (age, gender, status of employment, level of education, living conditions, health insurance status before TB, history of

TB treatment, site of TB disease, smear and culture results at time of diagnosis, HIV status and comorbidity with diabetes. Data were extracted from the parental study for the RCT groups and from SIME-TB for those who received DOT under operational conditions and who, in our study, were considered as a control group (control-DOT). Data on the number of taken doses-days, number of missed doses-days, number of interruptions, self-reported side effects and the average time spent on visiting a TB facility to receive TB medications over the three patient treatment months were extracted from the RCT database. Data on TB treatment outcomes were extracted from SIME-TB for all RCT and control-DOT participants. In contrast to the RCT, our study, based on a literature review [15], we considered optimal adherence as when the number of taken doses-days of anti-TB medications during the three months were equal to or exceeded the threshold of 80% of doses prescribed by the physician. TB treatment outcomes were defined in line with the WHO guidelines. Treatment results "cured" or "treatment completed" were considered as favourable while "treatment failure", "death" or "lost to follow-up" were unfavourable for short-term treatment outcomes. Presence of TB recurrence was considered an unfavourable result for long-term treatment outcome. Details on treatment strategies (aVOT and DOT) and definitions for other variables are provided in Table 1.

Data collection procedures and data analysis

Data were extracted from the Excel RCT dataset and from the SIME TB into Epi Data (version 2.2.2.183, EpiData Association, Odense, Denmark). The data were assessed for accuracy and completeness. Analysis was performed using software IBM® SPSS® Statistics (version 20.0). All data were summarized

Table 1. Definitions used in the study.

Characteristics	Definitions
Short-term TB treatment outcomes [14]	**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. **Treatment completed**. A TB patient who completed treatment without evidence of failure BUT with no record showing 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. **Failed**. A TB patient whose sputum smear or culture was positive at month five or later during treatment. **Died**. A patient who died for any reason during the treatment **Lost to follow up**. A patient whose treatment was interrupted for two consecutive months or more. **Favourable**: cured or treatment completed. **Unfavourable**: failed, died or lost to follow up.
Long-term outcome	Was considered a recurrence episode of TB after short term treatment outcome
History of treatment [14]	**New** – a patient who had never been treated for TB or had taken anti-TB drugs for less than one month **Previously treated patients** – a patient who have received one month or more of anti-TB drugs in the past. There were included patients with relapse, started treatment after failure, and started treatment after lost to follow up.
Recurrent TB [14]	TB patients who 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 due to reactivation of the disease or a new episode of TB caused by reinfection).
Adherence	Proportion of number of taken doses-days of anti-TB medications during three months and number of doses prescribed by the physician.
Interruption	Period of days not covered by anti-TB medications during three months trial.
Time to visit TB site	Time required, on average, for a trip to/from the TB treatment site from where the patient usually started DOT/VOT.
Treatment Strategy	**TB patients in DOT** were those who took their medicines directly observed by TB nurses five times per week in the clinic setting. For holidays and weekends patients administered their medications by themselves without being supervised by the medical staff. For these days, DOT participants received their pills from the TB clinic in advance. **TB patients on VOT** were those who were observed swallowing their medications using recorded (asynchronous) video technology via smartphones, tablets or computers. VOT participants received their pills from the TB clinic for 14 days.
Living conditions	Not standardized. It was subjectively assessed by physicians based on the circumstances affecting the way in which people live, especially with regard to their well-being.

using descriptive statistics in absolute numbers and proportions, means (and standard deviations) or medians (and interquartile range). Patients' profiles were stratified by the treatment strategy (aVOT, or DOT received in the RCT and DOT received in operational conditions). Adherence was measured in the RCT groups (aVOT and DOT) taking into account history of treatment, living conditions, health insurance status before TB, and mode of intensive phase. Differences were measured using Chi-square tests for categorical variables and T-tests for continuous variables. If expected cell frequency was less than five, Fisher test was used instead of Chi-square. Relative risk was selected as a measure of association in treatment strategy (aVOT-RCT) applied in clinical trial and DOT applied in operational conditions and short- and long-term treatment outcomes.

Ethics approval

Permission for this research was obtained from the National Committee for Ethical Expertise of Clinical Trial of the Republic of Moldova [16] and the Ethics Advisory Committee of the International Union against TB and Lung Disease, Paris, France [17].

Table 2. Comparison of socio-demographic and clinical characteristics of TB patients who were under Asynchronous Video Observed Treatment and Directly Observed Treatment Strategies in the Randomised Clinical Trial (RCT-groups) and those who received Directly Observed Treatment in operational conditions (control-DOT group) in Chisinau, Republic of Moldova (January, 2016 – December, 2017).

Characteristics	Total	RCT-groups	control-DOT	p-value
	N = 647	N = 169	N = 478	
Age				
Mean (± SD)	44.6 (± 15.6)	38.5 (± 13.9)	46.8 (± 15.6)	< 0.001
	N (%)	N (%)	N (%)	
Gender				0.005
Male	417 (64.5)	94 (55.6)	323 (67.6)	
Female	230 (35.5)	75 (44.4)	155 (32.4)	
Education level				0.05
No education/primary	121 (18.7)	25 (14.8)	96 (20.1)	
Secondary	244 (37.7)	56 (33.1)	188 (39.3)	
Vocational	209 (32.3)	61 (36.1)	148 (31%)	
High	73 (11.3)	27 (16.0)	46 (9.6%)	
Employment status				0.074
Employed	191 (29.5)	59 (34.9)	132 (27.6)	
Not employed	456 (70.5)	110 (65.1)	346 (72.4)	
Living conditions**				0.744
Satisfactory	436 (79.0)	127 (79.9)	309 (78.6)	
Unsatisfactory	116 (21.0)	32 (20.1)	84 (21.4)	
Health insurance before TB				0.488
Yes	372 (57.5)	101 (59.8)	271 (56.7)	
No	275 (42.5)	68 (40.2)	207 (43.3)	
Site of disease				0.198
Pulmonary	598 (92.4)	160 (94.7)	438 (91.6)	
Extrapulmonary	49 (7.6)	9 (5.3)	40 (8.4)	
Smear results**				0.681
Positive	132 (20.6)	33 (19.5)	99 (21.0)	
Negative	508 (79.4)	136 (80.5)	372 (79.0)	
Culture results**				0.711
Positive	210 (34.9)	61 (36.1)	149 (34.5)	
Negative	391 (65.1)	108 (63.9)	283 (65.5)	
Previous treatment history				0.002
New case	468 (72.3)	138 (81.7)	330 (69.0)	
Retreatment	179 (27.7)	31 (18.3)	148 (31.0)	
HIV*				0.875
Positive	36 (5.6)	9 (5.3%)	27 (5.6)	
Negative	611 (94.4)	160 (94.7)	451 (94.4)	
Diabetes				0.294
Yes	16 (5.6)	6 (3.6)	10 (2.1)	
No	631 (94.4)	163 (96.4)	468 (97.9)	

TB: tuberculosis; RCT: randomised clinical trial; HIV: Human Immunodeficiency Virus; DOT: Directly Observed Treatment; aVOT: Asynchronous Video Observed Treatment; SD: Standard Deviation; Min: minimum; Max: maximum; *Chi-square (or Fisher) tests for categorical variables and T-test for age; **Missing data was excluded during hypothesis testing: living conditions (95); smear results (7) culture results (46).

Results

Patient characteristics

A total of 647 participants were included in our analysis; 169 were from the RCT and 478 from the national TB registry. Of 169 patients from the RCT, 83 patients received treatment by aVOT and 86 patients by DOT. The other 478 patients, not included in the RCT, received DOT treatment under operational conditions (control-DOT).

Table 2 shows the baseline socio-demographic and clinical characteristics in the two groups, RCT and control-DOT. Overall, the mean age of the study population was 45 years, 65% were male and 71% were unemployed. Baseline characteristics differed between the RCT and control-DOT patients: RCT patients were younger, more likely to be women, and somewhat better educated. As for the RCT groups, there were no differences in baseline characteristics of age, gender, level of education, status of employment, smear and cultures results at the diagnosis, history of treatment, site of disease, HIV-coinfection and comorbidity with diabetes; this was similar to the RCT findings [13]. An additional two variables (health insurance status before TB and living conditions) were assessed for the RCT groups. Similarly, there were no differences in the presence of health insurance before TB diagnosis (50/83, 60% in aVOT and 51/86, 59% in DOT; p = 0.901) and satisfactory living conditions (67/80, 83% in aVOT and 60/79, 76% in DOT; p = 0.22; missing data were excluded = 10) in the RCT groups.

Adherence

Adherence was assessed in the RCT groups (aVOT and DOT). There were significant differences in the adherence (≥80%) to treatment between the aVOT-RCT group: 90% (75/83) compared to the DOT-RCT group, 19% (16/86), p<0.001 (Table 3). Participants in the aVOT-RCT group who had an adherence ≥ 80% were more likely to have satisfactory living conditions, health insurance before TB, and being newly treated for TB in either in or outpatient settings (Table 3). At the same time, the median treatment interruptions among patients with ≥ 80% adherence was 1 doses-day [IQR: 0-2] in the aVOT-RCT group and 6 [IQR: 4-8] in DOT-RCT group (p < 0.001). Median maximum number of consecutive days of interruption was 1 doses-day [IQR: 1-2] in aVOT-RCT and 3 doses-days [IQR: 2-3] in the DOT-RCT group (p < 0.001). There was a higher proportion of optimal adherence in newly diagnosed TB patients (64/67, 96%) in comparison with retreatments (11/16, 69%) in the aVOT group (p = 0.006) that is not observed in the DOT-RCT group (12/71, 17% for newly and 4/15, 27% for retreatment, p = 0.465, Table 3).

Short and long-term outcomes

There were no differences in short-term outcomes for the aVOT-RCT and DOT-RCT groups, even when considering living conditions, health insurance status before TB and mode of intensive phase of TB treatment. However, TB patients who were in the aVOT arm of the RCT were more likely to have a favourable short-term outcome than those under control-DOT in operational

Table 3. Comparison of adherence (≥ 80%) in patients who used Asynchronous Video Observed Treatment versus Directly Observed Treatment strategies in the Randomized Clinical Trial, in Chisinau, Republic of Moldova (January, 2016 – December, 2017).

Name	Treatment strategy		p-value*
	aVOT-RCT N = 83 N (%)	DOT-RCT N = 86 N (%)	
Total	**75 (90.4)**	**16 (18.6)**	**< 0.001**
Living conditions**			
Satisfactory	61 (91.0)	9 (15.0)	< 0.001
Unsatisfactory	13 (100.0)	5 (26.3)	< 0.001
Health insurance before TB			
Yes	45 (90.0)	10 (19.6)	< 0.001
No	30 (90.9)	6 (17.1)	< 0.001
Previous treatment history			
New	64 (95.5)	3 (4.5)	< 0.001
Retreatment	11 (68.8)	4 (26.7)	< 0.001
Mode of intensive phase			
Outpatient	20 (95.2)	3 (11.1)	< 0.001
Inpatient	55 (88.7)	13 (22.0)	< 0.001

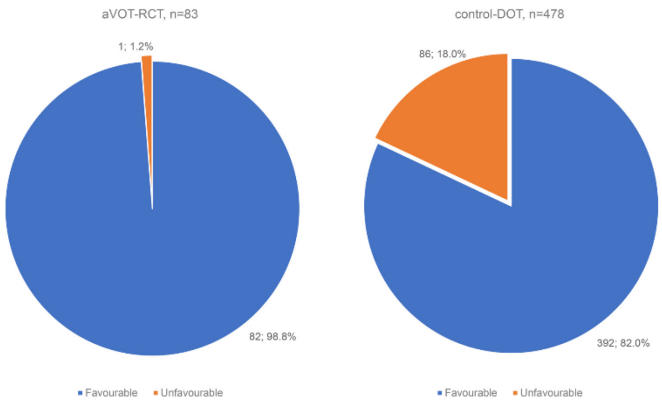
TB: tuberculosis; RCT: randomised clinical trial; DOT: Directly Observed Treatment; aVOT: Asynchronous Video Observed Treatment; Descriptive statistics were summarized as n (%); *Chi-square (or Fisher) tests for categorical variables was used; **Missing data was excluded during hypothesis testing: Life conditions (n=10).

conditions (Risk Ratio [RR] = 0.07; 95% confidence interval [CI]: 0.0-0.5; $p < 0.001$) (Figure 1). Regarding long-term outcomes, there were no registered TB recurrences in the aVOT-RCT group compared to 40 cases in control-DOT group ($p = 0.006$).

Discussion

Our study complimented and extended the findings of the RCT where the aVOT treatment strategy was applied as a pilot in Chisinau, Republic of Moldova. We described the adherence between RCT participants considering optimal adherence - the proportion of taken doses-days at the cut-off value ≥ 80% of prescribed doses by physicians. We compared short and long-term TB treatment outcomes of the aVOT group with a larger group of patients who received DOT in operational conditions (control-DOT). As in the RCT, we found better adherence in the aVOT participants in comparison with those in RCT-DOT [13]. In our supplementary analysis we found that optimal adherence was associated with not only the aVOT treatment strategy but satisfactory living conditions, having health insurance before TB, being newly treated for TB and mode of intensive phase for optimal adherence. Studies conducted in United States [5,12,18–21], United Kingdom [22], Australia and in low-middle income countries such as Belarus [23], Vietnam [24], and Kenia [25] show that VOT supported daily medication adherence in TB treatment. A systematic review of RCTs confirms that VOT has the potential to support professional treatment observation that makes it more convenient and cheaper than in-person DOT [26]. Excellent adherence to TB treatment is critical to cure TB and avoid the emergence of resistance [24]. The RCT did not find a significant difference in short-term treatment outcomes between aVOT and DOT-RCT [13]. However, a higher proportion of favourable outcomes was observed in the aVOT patients versus those in control-DOR. This supports the conclusion of a systematic review that showed that TB treatment outcomes were improved with the use of digital health technologies [27]. Regarding long-term outcomes, our study showed that the risk of recurrent TB was higher in the control-DOT than in the aVOT group. Recurrent tuberculosis continues to be a significant problem and is an important indicator of the effectiveness of TB control [28]. High disease recurrence after successful treatment suggests that end-of-treatment outcomes may not reflect the longer-term status of patients [29]. At the same time, we could not measure the adherence among participants in control-DOT, but it is well known that poor adherence to anti-TB treatment is a risk factor for recurrence of disease [29, 30]. The strengths of this study are: good quality of RCT data, accurate follow-up data from the national TB register, and good numbers in the control-DOT group.

Figure 1. Comparison of short-term treatment results of TB patients who were under Asynchronous Video Observed Treatment in Randomized Clinical Trial (aVOT-RCT) and those who received Directly Observed Treatment in operational conditions (control-DOT).



RCT- randomized clinical trial; DOT-Directly Observed Treatment; aVOT-Asynchronous Video Observed Treatment; p-value < 0.001 (Fisher test); RR (risk ratio) = 0.07; CI (confidence interval) [0.0-0.5].

There are some limitations to this study, starting with the RCT study [13]. The RCT recruited a limited number of people and its inclusion criteria may have influenced the treatment results, since vulnerable patients were excluded. Fear regarding data confidentiality and the inability of some patients to use digital technology were limitations in recruiting for the RCT. A smaller number of elder TB patients were included in the RCT. Additionally, exclusion of vulnerable populations may have influenced the treatment outcomes because this group, quite numerous in Chisinau, included homeless people, drug and alcohol users, and former prisoners, and would likely have had worst treatment outcomes. Another limitation was the exclusion of patients with MDR-TB from the RCT; their treatment regimens were more complicated and not suited for VOT. A third limitation was that the study was only conducted in the capital city of the Republic of Moldova and therefore represents the situation there and cannot be applied to the rest of the country. Future research with a larger sample size, inclusion of vulnerable populations, those living in rural areas, and patients with drug-resistance TB assessing the VOT treatment strategy is recommended.

Conclusions

Confirming the results of the RCT, this study showed that aVOT increased adherence to TB treatment while being more convenient for patients. Our additional results show that aVOT was superior to DOT in operational conditions in terms of short and long-term treatment outcomes. It suggests expanding VOT to rural areas in the country, and possibly to MDR-TB patients and more vulnerable groups. This study confirms that aVOT is a viable, innovative option for TB control in the Republic of Moldova.

Acknowledgements

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership coordinated by TDR (the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases). The specific SORT IT programme that led to these publications included a partnership between TDR and the European Tuberculosis Research Initiative (ERI-TB) at the WHO Regional Office for Europe, and was implemented by: the Tuberculosis Research and Prevention Centre, Armenia; The Alliance for Public Health, Ukraine; The Centre for Operational Research, The Union, France; the Operational Research Unit (LuxOR), Médecins Sans Frontières, Brussels Operational Centre, Luxembourg; Sustainable Health Systems Sierra Leone; and TDR. It is also worth mentioning Sevak Alaverdyan (TB Research and Prevention Centre, Yerevan, Armenia) for his contribution to the data analysis stage.

Funding

TDR and partners can conduct their work thanks to the commitment and support from a variety of funders. These include our long-term core contributors from national governments and international institutions, as well as designated funding for specific projects within our current priorities. A full list of TDR donors is available on our website at: https://www.who.int/tdr/about/funding/en/. This SORT IT programme was funded by USAID and supported by implementing partners. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This analysis did not include some additional costs. Open access publication costs will be covered by the SORT IT programme (WHO/TDR).

Authors' contributions

SD, NT and AR contributed to the conception of the study and protocol development. Data collection and data entry were done by SD. Data analysis was done by AC and YS. Data interpretations were done by SD, AC, YS, RP, LR, LK, NT, AD and AR. The first draft of the paper was prepared by SD, AC and AR. All the authors reviewed the paper critically and gave final approval of the paper.

References

1. Global Tuberculosis Report 2019 (2019) https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-report-2019. Accessed 2 May 2021
2. World Health Organization, Regional Office for Europe (2015) Use of high burden country lists for TB by WHO in the post-2015 era. Geneva: World Health Organization.
3. World Health Organization, Regional Office for Europe (2017) Analysis of the epidemiological impact of tuberculosis in the Republic of Moldova. Copenhagen: World Health Organization.
4. Ministry of Health of the Republic of Moldova (2020) "SIME TB -Moldova national database for notification and follow-up on tuberculosis cases. https://simetb.ifp.md/SimeTB.ViewDB/. Accessed 2 May 2021.
5. Mirsaeidi M, Farshidpour M, Banks-Tripp D, Hashmi S, Kujoth C, Schraufnagel D (2015) Video directly observed therapy for treatment of tuberculosis is patient-oriented and cost-effective. Eur Respir J 46:871–874.
6. Bayer R, Wilkinson D (1995) Directly observed therapy for tuberculosis: history of an idea. Lancet 345:1545–1548.
7. World Health Organization, Regional Office for Europe (2014) The End TB Strategy: Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization.
8. Falzon D, Raviglione M, Bel EH, Gratziou C, Bettcher D, Migliori GB (2015) The role of eHealth and mHealth in tuberculosis and tobacco control: a WHO/ERS consultation. Eur Respir J 46: 307–311.
9. World Health Organization, Regional Office for Europe (2017) A people-centred model of TB care. Available: https://www.euro.who.int/en/health-topics/communicable-diseases/tuberculosis/publications/2017/a-people-centred-model-of-tb-care-2017. Accessed 2 May 2021.
10. World Health Organization (2015) Digital health for the End TB Strategy - an agenda for action. Available: http://www.who.int/tb/publications/digitalhealth-TB-agenda/en/. Accessed 2 May 2021.
11. World Health Organization (2018) Handbook for the use of digital technologies to support tuberculosis medication adherence. Available: http://www.who.int/tb/publications/2018/TB_medication_adherence_handbook_2018/en/. Accessed 2 May 2021.
12. Garfein RS, Doshi RP (2019) Synchronous and asynchronous video observed therapy (VOT) for tuberculosis treatment adherence monitoring and support. J Clin Tuberc Other Mycobact Dis 17: 100098.
13. Ravenscroft L, Kettle S, Persian R, Ruda S, Severin L, Doltu S, Schenck B, Loewenstein G (2020) Video observed therapy (VOT) and medication adherence for TB patients: RCT in Moldova. Eur Respir J 56: 200093.
14. World Health Organization (2020) Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). Available: https://apps.who.int/iris/handle/10665/79199. Accessed 2 May 2021.
15. Van den Boogaard J, Lyimo RA, Boeree MJ, Kibiki GS, Aarnoutse RE (2013) Electronic monitoring of treatment adherence and validation of alternative adherence measures in tuberculosis patients: a pilot study. Available:

https://www.who.int/bulletin/volumes/89/9/11-086462/en/. Accessed 2 May 2021.
16. National Committee for Ethical Expertise of Clinical Trial of the Republic of Moldova (2020), https://gov.md/ro/content/cu-privire-la-comitetul-national-de-expertiza-etica-studiului-clinic. Accessed 2 May 2021
17. Ethics Advisory Group (2020) The Union. https://theunion.org/our-work/research/ethics-advisory-group. Accessed 2 May 2021.
18. Browne SH, Umlauf A, Tucker AJ, Low J, Moser K, Gonzalez Garcia J, Peloquin CA, Blaschke T, Vaida F, Benson CA (2019) Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. PLoS Med 16: e1002891.
19. Chuck C, Robinson E, Macaraig M, Alexander M, Burzynski J (2016) Enhancing management of tuberculosis treatment with video directly observed therapy in New York City. Int J Tuberc Lung Dis 20: 588–593.
20. Garfein RS, Liu L, Cuevas-Mota J, Collins K, Muñoz F, Catanzaro DG, Moser K, Higashi J, Al-Samarrai T, Kriner P, Vaishampayan J, Cepeda J, Bulterys MA, Martin NK, Rios P, Raab F (2018) Tuberculosis Treatment Monitoring by Video Directly Observed Therapy in 5 Health Districts, California, USA. Emerg Infect Dis 24: 1806–1815.
21. Holzman SB, Zenilman A, Shah M (2018) Advancing Patient-Centered Care in Tuberculosis Management: A Mixed-Methods Appraisal of Video Directly Observed Therapy. Open Forum Infect Dis 5: ofy046.
22. University of Edinburgh (2017) Virtual Observed Therapy for Patients With Tuberculosis. Available: https://clinicaltrials.gov/ct2/show/NCT02680470. Accessed 2 May 2021.
23. Sinkou H, Hurevich H, Rusovich V, Zhylevich L, Falzon D, de Colombani P, Dadu A, Dara M, Story A, Skrahina A (2017) Video-observed treatment for tuberculosis patients in Belarus: findings from the first programmatic experience. Eur Respir J 49: 1602049.
24. Nguyen TA, Pham MT, Nguyen TL, Nguyen VN, Pham DC, Nguyen BH, Fox GJ (2017) Video Directly Observed Therapy to support adherence with treatment for tuberculosis in Vietnam: A prospective cohort study. Int J Infect Dis 65:85–89.
25. Hoffman JA, Cunningham JR, Suleh AJ, Sundsmo A, Dekker D, Vago F, Munly K, Igonya EK, Hunt-Glassman J (2010) Mobile direct observation treatment for tuberculosis patients: a technical feasibility pilot using mobile phones in Nairobi, Kenya. Am J Prev Med 39: 78–80.
26. Osório C, Müller A, Silva D, Sbruzzi G, Dalcin P de T (2018) Interventions to improve adherence to tuberculosis treatment: Systematic review and meta-analysis. Int J Tuberc Lung Dis 22: 731–740.
27. Alipanah N, Jarlsberg L, Miller C, Linh NN, Falzon D, Jaramillo E, Nahid P (2018) Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. PLoS Med 15: e1002595.
28. Mirsaeidi M, Sadikot R (2018) Patients at high risk of tuberculosis recurrence. Int J Mycobacteriol 7: 1-6.
29. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, Stone C, Niemann S, Rüsch-Gerdes S, Blok L, Doshetov D (2006) Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance. PLoS Med 3: e384.
30. Panjabi R, Comstock GW, Golub JE (2007) Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. Int J Tuberc Lung Dis 11: 828–837.

Corresponding author

Svetlana Doltu, MPH
Executive Director, NGO AFI
Varsovia street, 7 off. 2
MD-2003
Chisinau city, Republic of Moldova
Tel: +373022600490
E-mail: svetlana.doltu@gmail.com; sdoltu@afi.md.

Conflict of interests: No conflict of interests is declared.