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THE ADVANTAGES AND CHALLENGES IN THE IMPLEMENTATION OF THE VIDEO-OBSERVED ANTI-TUBERCULOSIS TREATMENT

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Summary

Objectives. The national policy allows tuberculosis patients to benefit from 3 types of treatment options: 1. community directly observed treated when the treatment is delivered close to the patient's home, which is most extended. 2. directly observed treatment administrated in hospitals. 3. video-observed treatment. The purpose of the study was to assess the peculiarities of patients treated with video-observed compared with directly observed and the treatment effectiveness.

Material and methods. A prospective, case-control study, conducted in the 2020 year, which included 276 patients, from which 78 were treated remotely and included in the video-observed group and 198 cases were monitored by a trained health care worker when the patient swallow every dose, and included in the directly observed group.

Results. The remote treatment can be provided if the patient has an electronic device, wideband internet, have no contraindications, as deep social vulnerability, and mental impairment as a consequence of psychic diseases, alcohol abuse, and drug use. The complexity of the patient's risk factors endangers the treatment outcome, which did not differ significantly compared with patients treated with directly-observed treatment.

Conclusions. Video-observed treatment can be implemented at the national level in the actual epidemiological conditions of the Republic of Moldova if supporting measures for patients will be performed.

Keywords: tuberculosis, risk factors, video-assisted treatment, outcome

Introduction

Tuberculosis is an infectious and contagious disease caused by the *Mycobacterium tuberculosis* complex. It is one of the priorities of the health system of any state, and prevention and infection control are national strategic objectives [1]. According to the report of the World Health Organization (WHO), the Republic of Moldova (Moldova) is one of the countries in the WHO European region where tuberculosis control is a priority and one of the 30 countries in the world with the highest-burden of multidrug-resistant tuberculosis (MDR-TB) [1]. The global incidence, which included the new cases and relapses of tuberculosis in 2020 was 43.9/100.000 population (1.762 cases), in 2019 was 71.6/100.000 population (2.877 cases); in 2018 - 75.1/100.000 population (3.016 cases); in 2017 - 83.3/100.000 population (3.352 cases); in 2016 – 88.5/100.000 population (3.569 cases) [2, 3]. In 2000 the Republic of Moldova approved the first National Program for Control and Prophylaxis of Tuberculosis, which led to the national implementation of the Directly Observed Treatment Short Course Chemotherapy (DOTS) also known as directly observed treatment (DOT) [4-6]. The activities corresponding to the Strategy's objectives were: 1. to ensure universal access to early diagnosis of all forms of tuberculosis, at least 85% of the estimated cases with rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis by the end of 2020; 2. to ensure universal access of the patients to treatment through a patient-centered approach, achieving at least 85% success rate confirmed in new cases with bacteriologically confirmed tuberculosis and at least 75% success rate

confirmed in new cases with confirmed rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis; 3. to perform complementary activities with other national health programs for reducing the burden of the co-infection TB and HIV co-infection to 5%; 4. to ensure prevention and maintaining the BCG vaccination rate of at least 95% in all newborns; 5. to strengthen the capacities of the health system to ensure effective control of tuberculosis. 6. to develop and implement new methods and innovative interventions in tuberculosis control; 7. to strengthen the involvement of the community and civil society organizations in tuberculosis control through the patient-centered approach, which is based on the principle to ensure the continuation of the treatment in the most affordable manner [6]. According to the national policy, the patients may benefit from the following treatment options: 1. community or home-based DOT when the treatment is delivered in the community close to the patient's home or work. 2. DOT is administered by specialized healthcare providers in hospitals or specialized services. 3. video-observed treatment (VOT), based on the principle that the staff involved in its performing can observe the administration of the anti-tuberculosis drugs using electronic devices (personal computer, notebook, smartphone with Android system) through a web camera [7]. The technology required for VOT is a broadband Internet and the availability of an electronic device connected to a specialized VOT platform. The option for VOT are real-time communication or recorded video. VOT can replace the DOT when video communication technology is available and the

healthcare providers and the patients are well trained. VOT allows evaluation the adherence to treatment from distance, avoiding the direct contact of the patient with the healthcare worker. VOT is more flexible for patients, achieves a higher level of interaction between patients and medical staff, and probably has a lower cost than DOT [7].

In the Republic of Moldova, the methodology of the VOT was established by the law no. 153-XVI from 4.07.2008 related to the control and prevention of tuberculosis, recommendations of the National Tuberculosis Control Program for 2016-2020, approved by decision no. 1160 from 20.10.2016, the objective of the Strategic Program for the Technological Upgrade of the Government (E-Transformare) approved by decision no. 710 from 10.09.2011 and the National Clinical Protocol "Tuberculosis in adults" 123 approved by the decision no.1081 from 29.12.2017 [7-10]. The regulation established that the responsibility for the initiation of the VOT lies on the pulmonologist specializing in tuberculosis and the primary healthcare worker responsible for the case management in the outpatient settings. In the Republic of Moldova (RM), the VOT facilitates the interaction between the healthcare worker and the patient, however, it does not replace the DOT. The enrolling criteria in video-observed treatment (VOT) in the RM are: 1) the patient has an available electronic device (personal computer, notebook, smartphone with android system) and a web camera through which the medical staff involved in its performing can observe the administration of the anti-tuberculosis drugs; 2) the patients are residing in the RM. 3) the patient can administrate independently the anti-tuberculosis treatment [7]. The technology required for VOT and the patient should have are broadband Internet and the availability of an electronic device connected to a specialized electronic platform. The platform should record the video which will be sent for validation. The steps to be performed by the trained healthcare worker are: a) before the initiation of the VOT the patient must be informed about the possibility to accomplish the treatment using the video assistance; b) to create an account on the site www.vot.tuberculosis.md on E-Sanatate platform on the page "Medici"; c) to identify if the patient is eligible according to the including criteria established in the "Eligibility Checklist for Including in VOT"; d) if the patient accomplishes 14 days of 100% treatment compliance the healthcare worker will appreciate him eligible according to the evaluation form "Eligibility Checklist for Including in VOT"; e) to decide to include or exclude the patient from VOT; f) to monitor and follow-up the patient according to the recommendations of the National Clinical Protocol 123 "Tuberculosis in adults" [7]. The trained patient will receive the anti-tuberculosis drugs for 14-30 days confirmed by his signature on the TB01 register. Before the video recording, the patient must prepare the drugs on white paper, visible on the webcam, and transparent glass with water in an illuminated place. After the onset of the video recording, the patient has to present himself and enumerate the drugs prepared and the number of the pills. The patient should be placed in front of the webcam and swallow the drugs one by one with the water prepared in the transparent glass.

The patient has to open the mouth and show the tongue after swallowing the pills. At the end of the administration, the patient will stop the video recording and will send it to validation. The healthcare worker must assess and validate the video recording from 1 to 3 points. The value 1 means the treatment was administrated and the dose was validated. The value 2 means that there is no certainty that the pills were swallowed. The value 3 means that the treatment was not administrated or the dose of a drug was not swallowed. The patient is responsible for storing the anti-tuberculosis drugs in special conditions such as dry and dark places, far from children. The regulation establishes excluding from VOT criteria or criteria which does not allow the patient to be enrolled in VOT. The patient should be treated using the DOT instead of VOT if: a) refuses to sign the informed consent for VOT; b) the therapeutic regimen includes injectable drugs; c) has no available electronic device (personal computer, notebook, smartphone); d) the electronic device has no Internet connection or the connection has a low speed; d) is unable to take independently the anti-tuberculosis drugs, e) is diagnosed with mental disorders. There are several criteria that ensure the transfer of the patient from VOT to DOT: a) the patient's requirement; b) the patient fails to transmit for validation the recorded video for at least 2 days; c) the patient does not answer at the telephone; d) the hospitalization in the emergency department; e) imprisonment; f) the patient left the Republic of Moldova for more than 1 month; g) the patient has a low tolerance of the anti-tuberculosis drugs or experiences adverse drug effects; h) the referral pulmonologist decides to stop the VOT. Before the initiation of the VOT, the healthcare worker must register the patient on the site www.vot.tuberculoza.md and complete the electronic file of the health state ("Dosarul electronic de sănătate") with the patient's data about diagnosis and treatment. Special duties are attributed to the nurse specialized in the patient's case management, such as: a) supporting the patient in creating the account on www.vot.tuberculoza.md, b) explaining what means VOT and its principles; c) establishing the number of the doses, the frequency of the administration, the modality of the video recording and sending for validation, the steps to be followed in different issues (technical problems, lack of electricity, low Internet speed); d) receive and validate the video files and confirm the administration of the antituberculosis drugs according to the recommended regimens; e) fill the treatment register TB01 after the VOT the validation of the video files; f) explain and ensure that the patient could recognize the clinical signs of the adverse drug reactions and declare them.

In the literature, there are no published studies about the peculiarities of patients enrolled in the VOT for tuberculosis and their treatment effectiveness which constituted the overall aim of the study.

The objectives of the study were: 1. assessment of the general peculiarities, social and epidemiological risk factors of patients with tuberculosis who undergone the VOT compared with DOT; 2. evaluation of the microbiological characteristics of tuberculosis patients who undergone the VOT compared with DOT; 3 assessment the final treatment

outcome in patients undergone the VOT compared with DOT establishing the main advantages and challenges in the implementation of the VOT.

Material and methods

There was realized a prospective, case-control research, conducted between 01.01.2020-31.12.2020 in Chisinau, the Republic of Moldova, in which were included 276 patients, from which 78 cases with pulmonary tuberculosis were treated remotely and included in the VOT group and 198 cases monitored by a trained health care worker when the patient swallow every dose, included in the DOT group. The research reported ethics committee approval (no. 14 from 21/11/2017) and the patient's consent was obtained. Including criteria in the research were: age more than 18 years old; diagnosis of pulmonary tuberculosis and informed consent. The main enrolment criteria in the VOT group was the treatment accomplished partially or totally as VOT and in the DOT group was the entire treatment was physically monitored. The study investigation schedule included information about sex, age, radiological aspects, microbiological patient status, treatment regimen, and the results of the treatment outcome. All patients with tuberculosis were investigated and treated according to the national clinical protocol. Statistical analysis was carried out using quantitative and qualitative research tests of the SPSS Statistics 23.0 software in which the paired sample t-test was performed. The differences were considered statistical significant with the probability of more than 95% and p < 0.05.

Table 1Distribution of patients by sex, age and demographic data

Indices	Indicators	DOT group n=198 n (P%)	VOT group n=78 n (P%)	р
Women	50 (25,2)	32 (40,1)	<0,001	
Age groups	18-24 years	15 (7,6)	17 (21,8)	<0,01
	25-34 years	49 (24,7)	21 (26,9)	>0,05
	35-44 years	49 (24,7)	22 (28,2)	>0,05
	45-54 years	44 (22,2)	12 (15,4)	>0,05
	55-64 years	33 (16,7)	6 (7,7)	>0,05
	65 and more	8 (4,1)	0	>0,05
Residence	urban	112 (56,6)	72 (92,3)	<0,001
	rural	86 (44,5)	6 (7,7)	<0,001

When distributing patients from the VOT group, according to their economic status, it was established that the employed persons, which were contributing to the health budget by paying taxes, were one half of the group – 40 (51,3%) cases, followed by the unemployed – 24 (30,8%) patients. Every seventh patient was a student – 11 (14,1%) and a very low proportion – 3 (3,8%) cases were retired. In

Results

According to the obtained data, the distribution according to sex, the male/female rate was 1.4/1, or 46 (58,9%) men and 32 (40,1%) women in the VOT group, and 148 (74,8%) men and 50 (25,2%) women in the DOT group. Statistical analysis proved that women were more frequently eligible for VOT and can be easily enrolled. The rate of men is statistically higher in the DOT groups, showing the complexity of the risk factors which exclude more frequently men from the VOT.

Repartition of patients in age groups, according to the WHO recommendation identified that the largest subgroups treated remotely were aged between 35 and 44 years old – 22 (28,2%) and between 25 and 34 years old – 21 (26,9%) patients. It was followed by patients from the youngest group, between 18 and 24 years old – 17 (21,8%). A lower rate was aged between 45 and 54 years old – 12 (15,4%) cases, and between 55 and 64 years old – 6 (7,7%) patients. Patients older than 65 years were not included in the VOT group.

In the DOT group, there were similar proportions of patients who that were included in the age groups 25 and 34 years old – 49 (24,7%), 35-44 years – 69 (24,7%) and 45-54 years – 44 (22,2%) were identified. In a lower proportion were patients aged between 18 and 24 years – 15 (7,6%), between 55 and 64 years – 33 (16,7%) and older 65 years – 8 (4,1%) cases. Statistical analysis demonstrated that young patients, which were more familiar with the information technologies (IT) tools were more frequently enrolled in VOT and should be the target of the new programs related to the implementation of the video technologies in the antituberculosis therapeutic continuity (Table 1).

the DOT, the majority of the patients were unemployed – 117 (59,1%), followed by the employed – 52 (26,2%), retired – 16 (8,1%), and students – 12 (6,1%) cases. The statistical analysis established that the low economical level significantly predominated in the DOT group and constituted a challenge that should be addressed before enrolment in remote treatment follow-up.

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When distributing patients included in the VOT group, according to the civil state, was established that two-thirds of the group, 57 (73,1%) cases, were married and 21 (26,9%) were single state persons. In the DOT group, every second patient was married – 102 (51,5%), followed by the single-state patients – 96 (48,5%). The statistical evaluation concluded that single state patients were in an insignificantly higher proportion in the DOT group.

Assessing the educational level in the VOT group, it was established that most of the patients had completed the secondary educational level – 42 (53,8%) cases. Incomplete secondary level or primary level had 19 (24,4%) cases and professional or superior studies were identified in 17 (21,8%) patients. In the DOT group, incomplete secondary level or primary level had 118 (59,6%). Graduated the general secondary education in 51 (25,8%) cases and graduated professional-level – 29 (14,6%) cases. Statistical analysis identified the predominance of the low level of education, comprising the incomplete general and primary studies in the DOT group, and constitutes a challenge that should be taken into account before enrolling the patients in VOT.

Poor living conditions are related to the lack of centralized heating, water supply, and poor waste management. It is usually associated with a lack of knowledge, IT devices, the internet, as well as poor sanitation. Poor living conditions statistically predominated in the DOT group compared with the VOT group and must be taken into account before proposing remote treatment.

Following criteria as homelessness and lack of stable residence excluded the patients from the remote treatment and thus were not found in the VOT group. In the DOT group, almost every fourth patient had no stable living place or was homeless, which constituted a contraindication for the enrolment in remote therapeutic follow-up. It should be compulsory addressed if the extension of VOT is envisaged.

Migration constitutes a challenge for the completion of the anti-tuberculosis treatment and a contraindication for remote treatment. The patients with a recent history of migration, who returned from abroad in the last 12 months were 21 (10,7%) cases. The patients who were in the past or are actually labor migrants were every fourth, 16 (20,5%) cases, in the VOT group. So, one of the main advantages of remote treatment is to give the possibility to the patient to continue his economic activity and reduce the financial burden of the disease on his income.

Other mixed factors, which comprise social, economic, and epidemiological compounds evaluated were history of detention, harmful habits, and TB contact. The patients with a history of detention and detained during the course of the study were not enrolled in the remote treatment. A low number of patients with a history of detention was established in the DOT group. Mental disorders or neurological organic pathologies were established in 2 (1%) patients. So, those peculiarities should remain the indications for DOT, requiring hospitalization. The TB contact or the fact to be a member of a TB cluster predominated in the VOT group compared with the DOT group. This feature allowed the patient to acquire knowledge about the continuation and

duration of the treatment, and the follow-up and made them conscious of the advantages given by the VOT.

Comorbid patients were in a similar proportion in both groups and constituted almost one-third of selected cases. In the VOT group among the associated diseases were diagnosed 6 (10%) patients with gastrointestinal diseases, cardiovascular diseases – 9 (14%), nonspecific respiratory diseases – 5 (8%) cases, 2 (3%) patients with chronic renal disease, mental disorders in 2 (3%), diabetes in 2 (3%) and 5 (8%) patients were diagnosed with another nosological group of diseases. The HIV infection was a contraindication for the remote treatment and no patients were identified in the VOT group.

In the DOT group, 61 (30,8%) patients were diagnosed with associated diseases, among which the HIV infection constituted every seventh patient – 10 (16%) cases. Gastrointestinal diseases were diagnosed in 9 (15%) patients and chronic non-specific respiratory diseases in 7 (11%) patients. Cardio-vascular diseases were diagnosed in 8 (13%) cases, diabetes in 4 (6%) cases, mental diseases in 15 (24%), and other diseases in 5 (7%) patients (Table 2).

Mental impairment as the consequence of organic disorders, and addictions (alcohol abuse, drug use) were criteria that did not allow remote treatment, and no such patients were identified in the VOT group. In the DOT group, 12 (6,1%) patients were abusing alcohol and 1 (0,5%) drug user.

Tobacco smoking was established in a higher proportion in the DOT group. Patients living in TB clusters or who were in contact with TB patients were more frequently identified in the VOT group. Patients with comorbidities were identified in a similar proportion in both groups. There were not eligible to treat remotely the patients with HIV coinfection and no such patients were established in the VOT group (table 2).

The microbiological investigations revealed that onethird of the VOT group was microscopic positive for acidfast-bacilli, 30 (38,5%) patients, specifying the low degree of positivity was confirmed in all patients. A low proportion of patients were identified to have positive bacteriological results at cultivation on solid Lowenstein-Jensen or liquid MGIT BACTEC media - 38 (48,7%) cases. The molecular genetic assay was performed in all cases, but positive results were obtained in 51 (65%) cases and all were rifampicin sensitive. No rifampicin-resistant patient was enrolled in the VOT treatment in the selected group as an excluding criteria from the remote follow-up. Patients with Rifampicin resistant or MDR-TB (RR/MDR-TB) were advised to undergo treatment in the specialized sanatorium for this type of tuberculosis. In the DOT group, 73 (36,8%) patients were microscopic positive and 81 (40,9%) positive on culture. A positive molecular genetic assay was established in 102 (51,1%) cases, in which 23 (11,7%) cases were resistant to rifampicin. All patients from the DOT were treated during the intensive phase in the specialized medical institutions.

All the patients from the VOT group were treated standardized with the first line of anti-tuberculosis drugs for confirmed or presumptive drug-susceptible TB. Successfully

Table 2Distribution of patients by risk factors

Indices	Indicators	DOT group n=198	VOT group n=78	р
		n (P%)	n (P%)	
Social-economic risk factors	Low economic state	117 (59,1)	24 (30,8)	<0,001
	Lack of insurance	116 (58,5)	24 (30,8)	<0,001
	Low educational level	118 (59,6)	19 (24,4)	<0,001
	Single matrimonial state	97 (48,5)	67 (33,8)	>0,05
	Poor living conditions	58 (29,3)	20 (11,3)	<0,01
	Homelessness	26 (13,3)	0	<0,05
	Lack of stable residence	25 (12,6)	0	<0,05
	Migration (internal/external)	21 (10,7)	16 (20,5)	>0,05
Other risk factors	History of detention	7 (3,5)	0	>0,05
	Alcohol abuse	12 (6,1)	0	>0,05
	Active tobacco smoking	141 (71,2)	38 (49,1)	<0,001
	Illicit drug use	1 (0,5)	0	>0,05
	From TB cluster	19 (9,6)	31 (39,7)	<0,001
	Associated diseases	61 (30,8)	31 (36,5)	

treated were 68 (87,2%) cases, including 38 (48,7%) cured and 30 (58,5%) cases who completed the treatment. The therapeutic failure was established in 2 (2,6%) patients and was confirmed the loss to follow-up in 5 (6,4%). Died 3 (3,8%) patients, but no one from the progression of tuberculosis. In the DOT group successfully ended the treatment 151 (76,3%), from which 81 (40,9%) were cured and 70 (35,3%) cases completed the treatment. The therapeutic failure was confirmed in 8 (4,1%) patients and were lost to follow-up 16 (8,1%) patients. Died 23 (11,6%), from which 18 (9%) due to progression of tuberculosis. The statistical analysis did not find significant differences in treatment outcomes between groups, regardless of the delivery method.

Discussions

Our research was focused on the assessment of the peculiarities of the patients treated remotely in comparison with the patients treated under the supervision of a trained health care provider. An important research outcome was the identification of the main challenges in the implementation of the VOT and the evaluation of the groups of patients suitable for this kind of treatment. The general characteristics of the patients enrolled in VOT were dominated by men and patients aged between 18 and 44 years. However, with the predominance of women and the age group between 18 and 24 years old in the VOT group was demonstrated that the remote treatment should primarily target women and young people. No such evidence was provided by the specialized literature. The patients residing in urban sectors of Chişinău predominated in the VOT group, proving evidence that technical skills, electricity, and high-speed internet are more affordable for the urban population. So, the patients residing in an urban area should be invited to follow the remote treatment. The affordable accessibility of remote treatment

in populations from urban localities was provided by several studies [11]. The low level of the economic state is frequently associated with a low educational state and poor living conditions in the majority of the patients diagnosed with tuberculosis as a social disease. Enumerated characteristics statistically predominated in the group treated under the direct supervision of the trained healthcare professional. If the enlargement of the implementation of VOT is required with the aim to reduce the burden of hospitalization on the national health care system, the improvement of the economical state, knowledge, and quality of life of the tuberculosis patients should be raised. Such conclusions were obtained by other studies [11-14]. The deepest social vulnerability associated with the homeless state or lack of stable residence, which were contraindicating the remote treatment. If such patients will be eligible for VOT, the special hosting spaces should be provided at least during the anti-tuberculosis treatment.

The rate of co-morbid patients was similar in both groups treated remotely or under direct supervision, however, the HIV-infected patients were excluded from the VOT group. For the national implementation, HIV-infected people should be admitted for remote treatment if the patient's general state allows the treatment in ambulatory conditions. The TB contact was more frequently identified in the group of the patients treated remotely and demonstrated that they are eligible and can follow up. Generally, the treatment outcome was close to achieving the recommended 85% therapeutic success. The final results were diminished by a low proportion of patients, showing therapeutic noncompliance. The relation between tuberculosis indices and treatment delivery was widely studied [11-14]. Globally, the epidemics of tuberculosis are much higher in socially vulnerable subpopulations [1]. It can be explained by the complexity of risk factors, which reflects

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the barriers to accessing healthcare services and achieving treatment completion [15, 16]. In the RM, the specialized institutions offer a standard approach, which corresponds to the international recommendations and national regulations [4-10]. The actual international recommendation imposes the ambulatory treatment of tuberculosis patients and the wide implementation of the VOT [7]. Our research established an increased rate of socially vulnerable, with a low level of professional education patients treated remotely and directly supervised, as well. Those risk factors were identified to reduce the treatment effectiveness and should be addressed regardless of the method of delivery of the treatment. Our study has limitations because a limited number of the criteria did not allow to include a higher rate of patients. There is a need to expand the research on a higher number of patients treated remotely.

Conclusions

• VOT represents a modality for the anti-tuberculosis

treatment delivery when certain conditions such as electronic devices and wideband internet are put at the disposition of the patient.

- The advantage of the VOT is that it facilitates the treatment follow-up, but does not replace DOT when patients have contraindications: deep social vulnerability, and mental impairment as a consequence of psychic diseases, alcohol abuse, and drug use.
- Among the associated diseases, TB/HIV is one of the contraindications for VOT that could be ignored if the patient's general state allows it.
- The challenging impact of the complex risk factors on the treatment outcome did no differences significantly in patients treated remotely compared with the patients treated under direct supervision.
- VOT can be implemented at the national level in the actual epidemiological conditions of the Republic of Moldova if supporting measures for patients will be performed.

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