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Video observed therapy (VOT) and medication adherence for TB patients: RCT in Moldova

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Summary:

We conducted a randomised controlled trial with 197 Tuberculosis patients in Chisinau, the capital city of Moldova, in Eastern Europe. Patients were assigned to either in-person observed treatment (as normal) or asynchronous video-observation. We find improved observed medication adherence, satisfaction and reduced loss in patient time and costs during treatment.

Data analyses conducted by Stewart Kettle, PhD, and Persian.

ABSTRACT

Introduction

The effectiveness of Video Observed Therapy (VOT) for treating Tuberculosis (TB) has not been measured in low and middle-income countries (LMICs), where more than 95% of TB cases and deaths occur. In this study, we analyse the effectiveness, and patient cost-difference, of VOT compared to clinic-based Directly Observed Therapy (DOT) in improving medication adherence in Moldova, a LMIC in Eastern Europe.

Methods

The study was a 2-arm individually randomised trial with 197 TB patients (n = 99 in DOT control group; 98 in VOT treatment group, MDR-TB cases were excluded). The primary outcome was observed medication adherence, measured by the number of days that a patient failed to be observed adhering to medication for every two-week period during the course of their treatment

Results

VOT significantly decreased non-adherence by 4 days (95% CI, 3.35 to 4.67 days; p<0.01) per two-week period: 5.24 days missed per two-week period for DOT and 1.29 days for VOT. VOT patients spent 504 Moldovan Leu (MDL) (approximately €25; 95% CI, 277 to 730 MDL; P < .01) and 58 hours (95% CI, 48 to 68 hours; P < .01) less on their treatment. VOT also increased self-reported satisfaction with treatment. We found no significant results pertaining to treatment success, patient well-being or patient employment status and some evidence of an increase in side effects.

Discussion

In this trial, Video Observed Therapy (VOT) increased observed medication adherence for tuberculosis patients in Moldova, a LMIC, when compared to clinic-based Directly Observed Therapy (DOT). VOT also significantly reduced the time and money patients spent on their treatment.

[Pre-registered at ClinicalTrials.gov Identifier: NCT02331732]

INTRODUCTION

Among medical conditions requiring adherence to treatment regimens, adherence to tuberculosis (TB) medication is particularly important due to risks of transmission. Patients who fail to follow the recommended treatment closely are also more likely to develop drug-resistant forms of TB, which further complicates the treatment process [1]. TB poses special challenges when it comes to adherence for several reasons, including the absence of immediately observable benefits, time-lags between administration and impact, and the long duration of anti-TB regimens [2]. TB patients also tend to be from lower education and income groups, characteristics that are generally associated with lower levels of adherence [3]. In combination, all of these factors help to explain why TB treatment in many countries is legally mandated and monitored via in-person visits to clinics, as is the practice in Moldova.

In 1993, the World Health Organization recommended "effective case management via direct observation of treatment (DOT) by an independent and trained third party" as a response to decades of reports documenting the failure of patients to complete treatment [4]. Since the WHO DOT recommendations were provided, two Cochrane reviews - Volmink and Garner (2007), and Karumbi and Garner (2015) - found no evidence that DOT was more effective than self-administered treatment [5,6]. With the advent and proliferation of mobile devices equipped with internet and video capabilities, however, a new approach to treatment has been developed: Video Observed Therapy (VOT), whereby observation is conducted remotely. In a VOT procedure, patients use mobile devices and a secure application for recording and sending videos to case workers, who view and document each event [7]. VOT can be synchronous (S-VOT), where patients and providers engage in a live videoconference, or asynchronous (A-VOT), where patients upload the videos to a secure content management system that can be accessed by the provider [8].

In 2015, the World Health Organization Global TB Programme established the Global Task Force on digital health in partnership with the European Respiratory Society to support the development of digital health innovations [9]. The agenda, which supports the WHO's End TB Strategy, advocates that TB programmes use digital health solutions, such as VOT, in their implementations, and that they invest in research to measure the effectiveness of digital health interventions [10,11,12]. VOT was one of nine products identified by the Task Force for a Target Product Profile (TPP), a strategic document that specifies the features of an information & communication technology product [13].

The most comprehensive study to date which evaluates VOT versus DOT in an experimental setting was a randomised controlled superiority trial in London, England [14]. Similar to our study, the participants were randomised into VOT and DOT, and researchers found a substantial increase in observed adherence. With the vast majority of TB cases occurring in developing nations, the authors made a call for "more research in this area, including comparative studies between different digital adherence interventions in high-burden settings..." A 2018 review on the impact of digital health technologies on tuberculosis treatment by Ngwatu et al made a similar call for more studies of better quality: "...further evaluation of digital health interventions is urgently needed - ideally in adequately powered RCTs...." [15] Finally, a review by Nsengiyumva et al on the costs and impact of different digital health technologies for TB treatment found support for VOT reducing patient costs in a high burden country, Brazil, by using decision analysis model simulations [16]. Our aim in this study is to start to fill this research gap by rigorously evaluating the effectiveness and cost differences of VOT for non-MDR-TB patients in a LMIC with a high disease burden.

In 2015, at 152 per 100,000 population, Moldova had the highest incidence of TB in Europe [17]. Moldova follows a clinic-based strategy of DOT. Interviews with patients and discussions with the Ministry of Health suggested the current implementation of DOT was challenging for some patients, providing a use case for testing out a potentially more convenient approach to monitoring adherence. Under DOT, TB patients in Moldova are required by law to come to a clinic daily to take their medication under the supervision of a TB nurse. To date, there has not been a robust evaluation of the efficacy of VOT compared to DOT in a LMIC, despite more than 95% of all deaths caused by TB occurring in these countries [18].

METHODS

Study design

We conducted the RCT in Chisinau, the capital of Moldova, because of its high rate of internet penetration compared to the rest of the country at the time we designed the trial. The RCT ran for 22 months, from January 2016 to November of 2017, when the 4-month monitoring period for the last patient recruited into the trial was completed.

The study was a 2-arm individually randomised clinical trial with a parallel design. Patients were approached just before the beginning of their treatment continuation phase. In order to be eligible to participate, patients needed to consent to taking part in the trial and meet the following criteria: 1) Live in Chisinau with no plans to move away from Chisinau during the four months of the trial, 2) Be at least 18 years of age, 3) Have at least four months of treatment remaining, 4) Do not have MDR-TB, 5) Are not homeless, 6) Do not suffer from alcoholism or drug misuse, 7) Are not in prison 8) Are either category I (intensive phase and/or continuation phase) or category II (continuation phase or phase after finishing

intensive intramuscular injection of streptomycin) phase of treatment. Patients did not need to be proficient with mobile phones, tablets or mobile applications to be included in the study.

Recruitment occurred on a rolling basis from the list of patients declared by the Municipal Coordinator. These cases were verified by doctors, then visited in the hospital or in their first visits to an outpatient unit. Patients completed the Baseline Questionnaire (Appendix 1), and those that met the above eligibility requirements were provided with verbal and written information on the trial and the two treatment types. Immediately following this, patients were given the option to participate in the trial. If they agreed and provided written consent to participate, they were immediately randomised to DOT or VOT using a custom made online randomisation tool. Patients then started DOT or VOT at the very beginning of their continuation phase of treatment. Given the rolling nature of recruitment, simple randomisation (i.e. no blocking) was used, and given the tangible difference between the treatments, it was not feasible to blind patients to their assignment. VOT patients that continued their treatment beyond 4 months, continued VOT to the end of their treatment. In the event a patient in VOT was hospitalised, they would continue VOT once they left hospital.

Our power analysis indicated that 188 patients would allow us to see a 1.5 day shift in observed adherence between groups. Therefore, our aim was to recruit a sample of about 200 patients. For treatment success, this sample size would allow for the detection of a difference 9.9 percentage points in treatment success at a 12-month cut-off. Of the 197 patients who entered the trial, 99 were assigned to the control group and received the standard provision of DOT from their local clinic (one of the 15 clinics in Chisinau) and 98 were assigned to VOT.

All patients were also incentivised to adhere to their treatment using food vouchers worth 980 MDL (approximately €50) a month, as was standard practice for DOT TB treatment at the time. Both DOT and VOT patients received their food voucher on a weekly or monthly basis if they adhered at least 90% of the time.

We received approval from the Moldovan Ministry of Health to conduct the trial. The Ministry of Health, Labour and Social Protection in Moldova (MoHLSP) relaxed current TB treatment guidelines to enable implementation of the trial. We also received ethical clearance from the Moldovan ethics board and the University College London (UCL) ethics board.

Procedure - DOT

The patients assigned to DOT underwent the same procedure that has been used in Moldova for over ten years: they were required to go to their local TB clinic daily (Monday to Friday) and be observed taking their medicine. During this visit, patients would also be asked to report any side effects. Under the official guidelines, patients in the DOT arm can only take their medication between Monday and Friday at their local clinic. However, in practice, patients are sometimes given additional medications to take at home if they know they are going to miss a subsequent DOT visit, in which case the patient would be automatically marked as adhering for the subsequent visits they will miss. Given this occasional informal arrangement, to ensure the accuracy of the adherence outcome, we implemented a new monitoring procedure for DOT patients. In addition to marking attendance on paper as normal, patients were required to sign a tablet which recorded date and time, removing the possibility described above that patients could be marked as adhering for multiple days in one visit. This provided an accurate measure of observed adherence in the control group.

All DOT patients were assigned to one of 15 clinics, all in the capital Chisinau, based on proximity to their home address. For DOT patients, the nurse would mark their attendance on a paper "TB-01" form and the patient would sign. The patient would also be asked to electronically sign-in on a tablet. Then the nurse would give the patient their medication, and observe them taking it. If the patient did not turn up for more than two days consecutively the clinic would try and call the patient to encourage them to come back to the clinic.

Procedure - VOT

The patients assigned to VOT underwent training to understand all steps involved involved in performing asynchronous VOT. First, they visited an observation centre and were given a VOT Medication Sheet (Appendix 2), VOT Video Recording Procedure (Appendix 3), and detailed instructions of how to show that they swallowed the medications. Each time patients sent a video they were also asked to report side effects. Finally, an mHealth app, designed for the trial, was installed on any internet-enabled devices that they owned. If they didn't own one, they were loaned a tablet with the mHealth app already installed for the remainder of the trial.

VOT patients were assigned to a clinic where they received a 14-day supply of medicine. The patient was instructed to send a video daily of him/herself swallowing the medication to the VOT observer, who determined if they could clearly see the patient taking the medicine. After each video, the observer would respond with a video confirming receipt of the clip and encouraging patients to keep taking their medicine as a way to provide personalised patient-provider interaction, one of the main advantages of synchronous VOT and DOT [8]. If a VOT patient missed sending a video, the observer would phone the patient to find out if there were any problems and encourage the patient to submit a video on the following day. These

reminders and video feedback aimed to provide the practical and emotional social support that has been found to be associated with higher medication adherence [19].

The VOT observers were certified medical assistants, with basic knowledge about TB. Additionally, we conducted training with the observers on: database data entry, communication with patients (video feedback and reminders in case of missing doses), distribution of drugs and side effects management.

Sample

Of 197 eligible participants, 99 were randomised to the DOT control group and 98 to the VOT treatment group. After randomisation, 13 participants (5 in DOT, 8 in VOT) were excluded for medical reasons, such as developing MDR-TB; 6 (1 in DOT, 5 in VOT) refused to participate at either the beginning of the trial or later. In addition, 1 patient (DOT) died, and 2 (DOT) were lost to follow-up. The only differences that were statistically significant were a higher rate of lost to follow-up in the DOT condition (significant at the 5% level) and a greater initial refusal of participation in the VOT treatment condition (significant at the 10% level), but the numbers of both were small and are unlikely to have had much of an impact on results. Adherence analysis was conducted on the remaining 178 patients in the sample, with 93 in DOT and 85 in VOT (Figure 1).

There were no statistically significant differences between age, sex, employment status, having drug or alcohol abuse problems, being homeless, or imprisoned in the last 5 years, suggesting that our control and treatment groups were balanced across these demographic characteristics (Table 1 and Table 2). We also observe balance on most clinical characteristics (measured at baseline), apart from history of non-adherence, having experienced fatigue (both differences significant at 10% level) and satisfaction with treatment at baseline (which we control for in our analysis as detailed below).

Table 1: Summary of Baseline Characteristics (demographic)[1]

Demographic characteristics	DOT		VOT		p-values[2]
	Mean	Std Dev	Mean	Std Dev	
Age (in years)	38.28	14.11	38.73	13.95	0.831
Employed at baseline (binary)	0.33	0.47	0.44	0.50	0.164
Drug abuse problem (binary)	0.00	0.00	0.02	0.15	0.138
Alcohol abuse problem (binary)	0.01	0.10	0.04	0.19	0.272
Homeless at baseline (binary)	0.00	0.00	0.01	0.11	0.297
Imprisoned in last 5 years (binary)	0.00	0.00	0.01	0.11	0.297
Female (binary)	0.45	0.50	0.45	0.50	0.952
N	93		85		

Table 2: Summary of Baseline Characteristics (clinical)[3]

Clinical characteristics	DOT		VOT		p-values[4]
	Mean	Std Dev	Mean	Std Dev	
Height (in cm)	169.55	8.36	170.82	8.42	0.312
Weight (in kg)	64.13	12.89	66.60	10.77	0.169
Smear positive (binary)	0.19	0.40	0.21	0.41	0.764
Culture positive (binary)	0.33	0.47	0.35	0.48	0.785
History of non-adherence (binary)	0.04	0.20	0.00	0.00	0.054*
Location of TB					
Pulmonary (binary)	0.95	0.23	0.92	0.28	0.450
Miliara (binary)	0.01	0.10	0.00	0.00	0.340
Spinal (binary)	0.00	0.00	0.02	0.15	0.138
Osteoarticular (binary)	0.01	0.10	0.01	0.11	0.949
Sensitivity					
Totally sensitive (binary)	0.88	0.33	0.84	0.37	0.682
Isoniazid resistant (binary)	0.01	0.10	0.02	0.15	0.511
Rifampicin resistant (binary)	0.01	0.10	0.00	0.00	0.340
Ethambutol resistant (binary)	0.00	0.00	0.00	0.00	.
Pyrazinamide resistant (binary)	0.00	0.00	0.00	0.00	.
Side effects					
Nausea, vomiting (binary)	0.09	0.28	0.05	0.21	0.303

[1] Measured at beginning of continuation period, i.e. before randomisation
[2] P-values are from t-tests of the differences of the means
[3] Measured at beginning of continuation period, i.e. before randomisation
[4] P-values are from t-tests of the differences of the means

Stomach pain (binary)	0.09	0.28	0.05	0.21	0.303
Fatigue (binary)	0.10	0.30	0.20	0.40	0.052*
Fever (binary)	0.01	0.10	0.00	0.00	0.340
Rash, severe itching (binary)	0.02	0.15	0.04	0.19	0.581
Paraesthesiae (binary)	0.01	0.10	0.01	0.11	0.949
Vertigo (binary)	0.00	0.00	0.00	0.00	.
Jaundice (binary)	0.00	0.00	0.01	0.11	0.297
Arthralgia (binary)	0.02	0.15	0.02	0.15	0.928
Loss of appetite (binary)	0.03	0.18	0.06	0.24	0.396
Any side effects (binary)	0.20	0.41	0.31	0.46	0.121
Satisfied with treatment (binary)	0.82	0.39	0.97	0.19	0.002***
Self-rated health (scale 0 - 100)	89.09	10.76	89.80	8.72	0.629

Outcomes and analysis

Our primary outcome, adherence to medication, is the number of days over each two-week period (10 working days, excluding weekends and public holidays) that a patient was not observed adhering to their medication. For DOT patients, this was based on whether they electronically signed the tablet at their clinic to indicate their attendance. For VOT patients, this was based on whether they sent a video showing them taking their medication. Across the monitoring period, each patient contributed around 8 two-week periods.

We also recorded several secondary outcome measures. On a daily basis, patients were asked to record any side effects (at the clinic for DOT and on the video for VOT). After four months, patients received an Endline Questionnaire (Appendix 4). These self-reported questions provide the secondary outcomes for the time and money spent on their treatment, satisfaction with treatment, employment status, and well-being (measured using a short-form of the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)) [20]. We also measured treatment success by sputum smear and X-Ray, according to the national TB protocol and WHO Guidelines at 4, 10 and 12 months after the start of the continuation phase [21].

All continuous outcome measures were evaluated with ordinary least squares multiple regression using data from up to a four-month period following randomisation into the trial (Table 3). All binary outcome measures were evaluated with a logistic regression (also shown in Table 3). Statistical analysis was conducted by Stewart Kettle, PhD, and Ruth Persian. Neither were blinded to the trial arm while conducting the analysis.

RESULTS

Primary Outcome: Adherence

In the DOT control group, patients failed to adhere 5.24 days per two-week period. The VOT treatment significantly decreased non-adherence to 1.29 days per two-week period – i.e., by nearly 4 days (95% CI, 3.35 to 4.67 days; $p<0.01$; standard errors are clustered by patient to account for multiple observations per individual). The only other statistically significant characteristic was drug abuse problems at baseline. However, there were only two VOT patients reporting drug abuse problems and none in DOT, so this result should be interpreted with caution.[5]

[5] As a robustness check, we also run the main regression (column 1, Table 3) but including history of non-adherence and satisfaction with treatment at baseline (significantly different at 10% and 5% level at baseline as shown in Table 2). The results do not meaningfully change: the coefficient of VOT is 3.764** (0.354) instead of 4.009** (0.335).

Table 3: Regression of Primary and Secondary Outcome Measures

	(1) Non-adherence (Count per 10 days) (Linear)	(2) 12 months treatment success (Logistic, Odds Ratio)	(3) 80% adherence (Logistic, (OR)	(4) Wellbeing (WEMWBS5) (Linear)	(5) Patient Satisfaction (Logistic, (OR)	(6) Time spent (in hours) (Linear)	(7) Money spent (in MDL) (Linear)	(8) Employed (Logistic, (OR)	(9) Any side effects (Logistic, (OR)
VOT	**-4.009**** (0.335)	1.548 (0.901)	**12.795**** (2.738)	-0.520 (0.419)	**11.879*** (14.262)	**-58.058**** (5.122)	**-503.376**** (115.415)	1.479 (0.502)	1.882^{+} (0.711)
Female	-0.087 (0.347)	1.658 (0.977)	0.948 (0.201)	-0.147 (0.420)	0.688 (0.644)	-1.042 (5.434)	-117.491 (127.890)	0.583 (0.204)	1.668 (0.616)
Age (in years)	-0.007 (0.012)	1.015 (0.023)	0.991 (0.007)	-0.012 (0.016)	1.021 (0.031)	-0.103 (0.173)	-8.062^{+} (4.244)	0.979^{+} (0.013)	**1.026*** (0.012)
Employed at baseline	-0.171 (0.346)	1.516 (0.925)	1.190 (0.254)	-0.232 (0.421)	3.643 (3.234)	8.617 (5.263)	12.020 (122.227)	**3.296**** (1.144)	0.546 (0.215)
Drug misuse problem at baseline	**3.632**** (0.310)		**0.293**** (0.065)	**-6.242**** (0.448)		-6.558 (4.643)	-142.430^{+} (74.172)		
Alcohol misuse problem at baseline	0.377 (1.148)		1.153 (0.716)	-2.254 (2.921)		-8.632 (6.818)	**-250.613*** (123.216)	0.848 (1.148)	
Homeless at baseline	-1.097 (1.258)		0.396 (0.279)	**11.299**** (2.999)		2.175 (9.487)	214.223 (195.636)		
=1 if satisfied at baseline (Binary)					**239.180**** (229.852)				
Control group mean	5.240	0.903	.019	22.697	0.820	80.865	696.800	0.333	0.211
Observations	1571	173	1571	172	167	163	155	169	170

Standard errors in parentheses
Model: Column 1: Linear regression with standard errors clustered at the patient level; Columns 4, 6 and 7: Linear regression with heteroskedasticity robust standard errors.
Columns 2, 3, 5, 8 and 9: Logistic regression with heteroskedasticity robust standard errors, coefficients show odds ratios.
Coefficients are omitted when they predict success perfectly/are collinear.
$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Secondary Outcomes (Figure 2)

We observed an encouraging and statistically significant impact on whether a patient achieved 80% adherence in any given two-week period, a canonical threshold used to measure "good" adherence [22]. DOT patients achieved 80% medication adherence 19.5% of the time. The VOT treatment significantly increased patients' likelihood to meet this threshold to 75.1%, or by 55.6 percentage points (95% CI, 48 to 63 percentage points; $p<0.01$).

Patients in the VOT condition saved an average of 58 hours (95% CI, 48 to 68 hours; $P < .01$) over the course of the 4-month period. This was calculated from self-reported spending on treatment. Patients in the VOT condition also saved an average of 504 MDL (95% CI, 277 to 730 MDL; $P < .01$), or around 25 EUR over the course of the 4-month period, again based on self-reports.

Patients in the VOT condition also reported greater satisfaction with their treatment. Controlling for satisfaction at baseline, the cumulative log-odds increment in satisfaction of being in the treatment group is 3.29 (95% CI, 1.66 to 4.92; $P < .01$). A regression of binary and 5-point treatment satisfaction outcomes controlling for satisfaction at baseline is included in Table S4.

Measuring treatment success by sputum smear and X-Ray, as according to the national TB protocol and WHO Guidelines [21], we did not find a significant impact of treatment allocation on treatment success at 4 months after starting the continuations phase (DOT=15.0%, VOT=11.1%), 10 months (DOT=86.0%, VOT=92.1%), or 12 months (DOT=90.3%, VOT=93.5%). Our sample size allowed for the detection of a difference 9.9 percentage points for the 12-month cut-off; to detect a five-percentage point increase with 5% statistical significance and 80% power would have required a sample of 976 individuals.

We also observed no statistically significant difference in patient well-being or patient employment status between DOT and VOT patients. Finally, patients in the VOT condition are 11 percentage points (95% CI, -1.9 to 24.31 points; $P < .10$) more likely to report side effects in the Endline Questionnaire than in the DOT condition.

DISCUSSION

In this trial, Video Observed Therapy (VOT) increased observed medication adherence for tuberculosis patients compared to clinic-based Directly Observed Therapy (DOT), a difference of 4 days of adherence per 2-week period. In addition, VOT saved patients time and money and increased their satisfaction, which can all be seen as explanations for higher adherence and as benefits of VOT over DOT. The study demonstrates both the feasibility of using VOT on challenging medication adherence problems in LMICs, and the substantial time and monetary savings that result from doing so. The monetary savings are likely an underestimate, as the Endline Questionnaire (Appendix 4) only asked for self-reported expenditures on transportation, not foregone wages and the increase of child/dependent care resulting from in-person treatment.

The 11 percentage point increase in reported side effects is important and worth discussing. The increase in reported side effects should not be seen as a drawback of the study. It could simply be that more side effects were reported by VOT patients because more medicine was taken. It could also be that the new approach to and training on reporting side effects - asking VOT patients had to report any side effects every day when submitting the video - encouraged more regular reporting of side effects compared with the approach adopted by the TB nurse at the clinic. This would also be a positive result as it is important to identify side effects as medical attention or a change in treatment may be required. While our study

doesn't capture these measures, this potential improvement in quality of care is one of the advantages of digital adherence technologies.

The implications of the study are important but there are also some important limitations. The first is that our primary outcome measure - observed adherence - only measures whether we observe the patient adhering, not whether the patient actually adheres. The difference in observed adherence could overestimate the true difference in adherence if patients in the DOT condition took their medication when they did not go to the clinic, and could be an underestimate if patients in the VOT condition took their medication without sending the video. However, a key finding is that measured adherence in the VOT condition was very high: 75% of VOT patients took at least 80% of their medicine. This could underestimate the true adherence but is very unlikely to be an overestimate, given that each episode of adherence was confirmed by video by a trained observer.

The second main limitation is the sample size. When evaluating the impact on treatment success, although there was directional improvement in treatment success at 10- and 12-month cut-offs, the findings are non-significant. We would have needed 976 patients in our study to detect a five-percentage point increase in treatment success after a year which was beyond the scope and resources of the study. However, it is still important to consider, given the large improvement in observed adherence, why we didn't see a larger change in treatment success. It could be, as described above, that our measure of observed adherence overestimates the improvement in actual adherence due to VOT. However, it could also be, given the minimum rate at which TB medication has to be taken to be effective is unknown, that while DOT patients showed poorer adherence than VOT, it was sufficient to reach the threshold for treatment success.

A third limitation of the study is the generalisability of the findings to regions where internet is less accessible because the VOT arm required patients to have internet access to upload the videos. However, as internet and smartphone penetration increase in LMICs, VOT should become an increasingly viable option for TB treatment.

Despite these limitations, the implications of this study are important. This is the first study that measures the difference between DOT and VOT treatment strategies in a LMIC. As connectivity to remote areas and voice/video quality improves, VOT will more closely emulate the patient-provider interaction, one of the benefits of DOT. Our findings not only confirm that VOT is more effective and lower-cost than DOT, but also provide evidence that these benefits are achievable in LMICs where more than 95% of TB cases and deaths are observed.

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Figure 1: Consort Flow Diagram

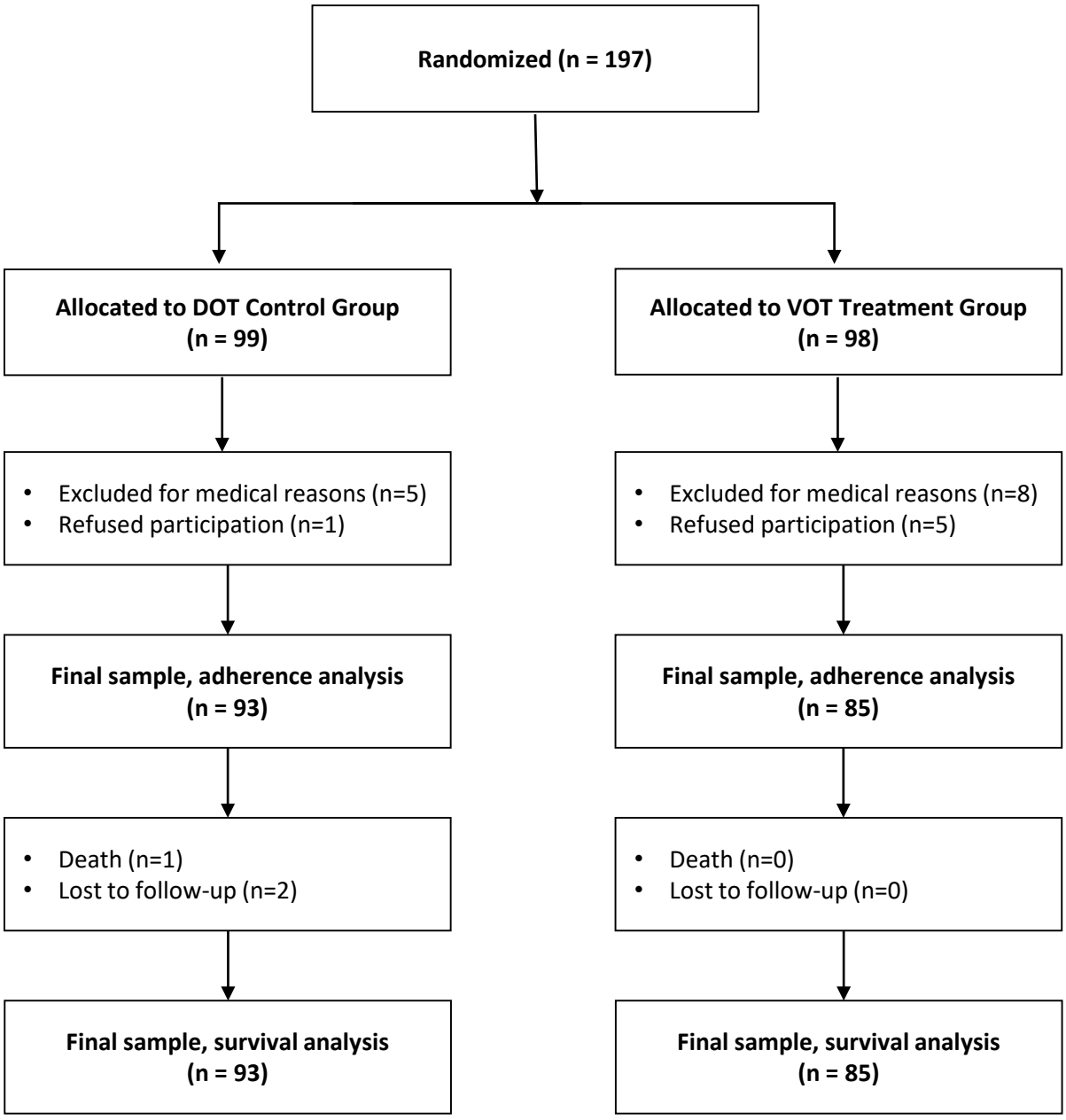
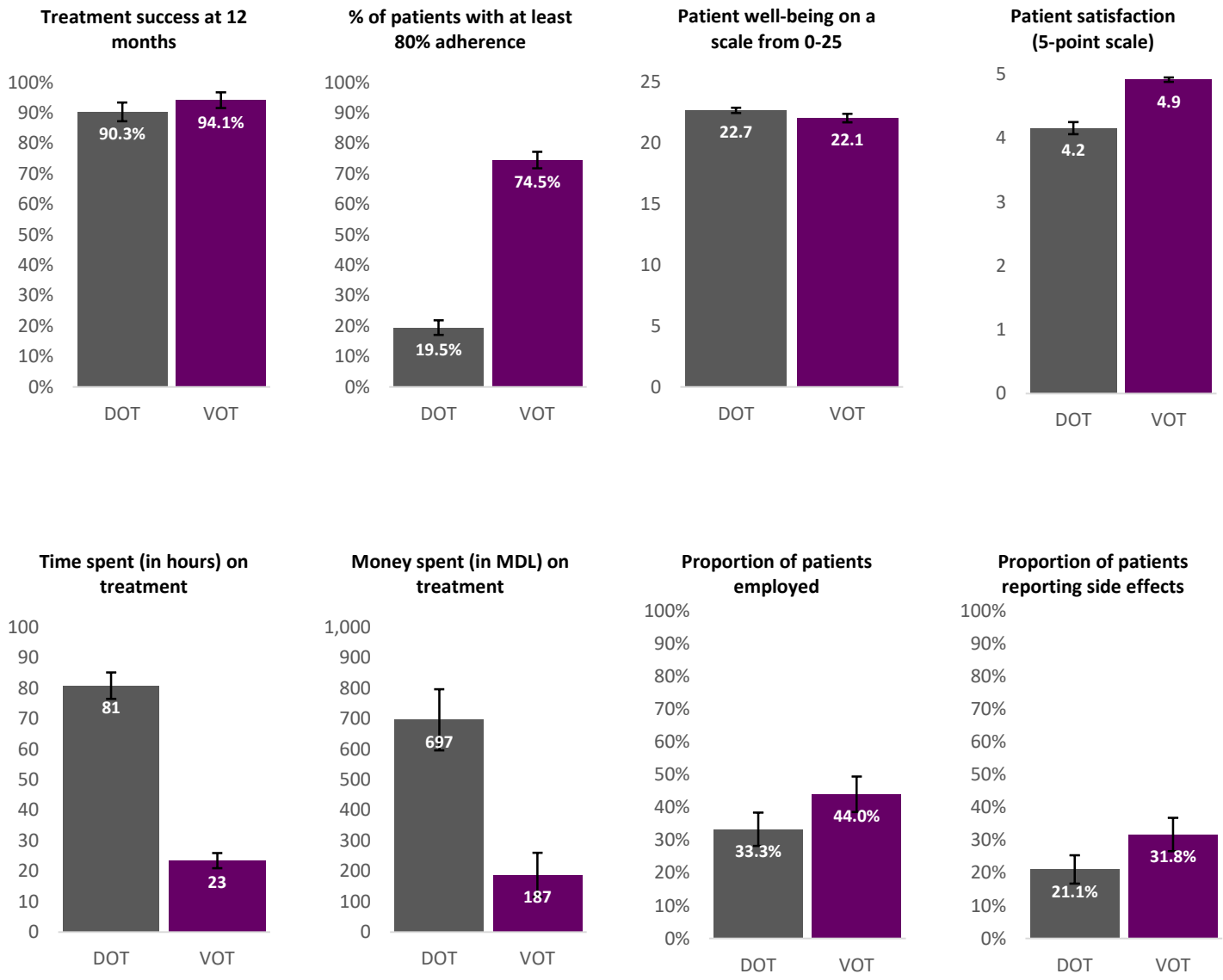


Figure 2: Summary of Secondary Outcomes



Integers are the average of continuous variables; percentages are averages of binary variables.
Error bars are +/- 1 SE

Table S4: Regression of Satisfaction Outcomes

	(1) Satisfaction (binary)	(2) Satisfaction (binary)	(3) Satisfaction (5-point scale)	(4) Satisfaction (5-point scale)
main				
VOT	**16.878****	1.053^{+}	**3.209****	**3.288****
	(17.536)	(0.030)	(0.528)	(0.814)
Age (in years)	1.040^{+}	1.001	0.036**	**0.042***
	(0.021)	(0.001)	(0.012)	(0.018)
Female	1.014	1.013	-0.163	-0.318
	(0.541)	(0.029)	(0.375)	(0.450)
Employed at baseline	1.829	1.046	0.480	0.499
	(1.132)	(0.030)	(0.429)	(0.556)
=1 if satisfied at baseline (Binary)		**2.034****		
		(0.206)		
Drug misuse problem at baseline		1.004	**12.279****	**14.702****
		(0.017)	(1.115)	(1.247)
Alcohol misuse problem at baseline		1.038	**14.788****	**14.207****
		(0.033)	(1.003)	(1.079)
Homeless at baseline		0.936	**-30.987****	**-32.650****
		(0.044)	(1.533)	(1.653)
Satisfaction at baseline (5-point scale)				**3.249****
				(0.596)
Control group mean	0.820	0.820	4.157	4.157
Observations	167	172	172	172

Standard errors in parentheses

Model: Columns 1 and 2: Logistic regression with heteroskedasticity robust standard errors, coefficients show odds ratios. Coefficients are omitted when they predict success perfectly/ are collinear; columns 3 and 4: Ordered logit with heteroskedasticiy robust standard errors.

$^{+}$ $p < 0.10$, * $p < 0.05$, ** $p < 0.01$

Baseline Questionnaire

- Last Name _____ First name(s) _____ UID number _____

- Sex ☐ M ☐ F Polyclinic _____ Are you currently employed? ☐ Y ☐ N

- Access to a desktop computer, tablet or mobile phone that is internet enabled? ☐ Y ☐ N
- Do you have at least 4 months of care remaining? ☐ Y ☐ N
- Problem drug use ☐ Y ☐ N
- Alcohol misuse ☐ Y ☐ N
- Currently homeless ☐ Y ☐ N
- Currently in prison ☐ Y ☐ N
- Injectable drug regime ☐ Y ☐ N

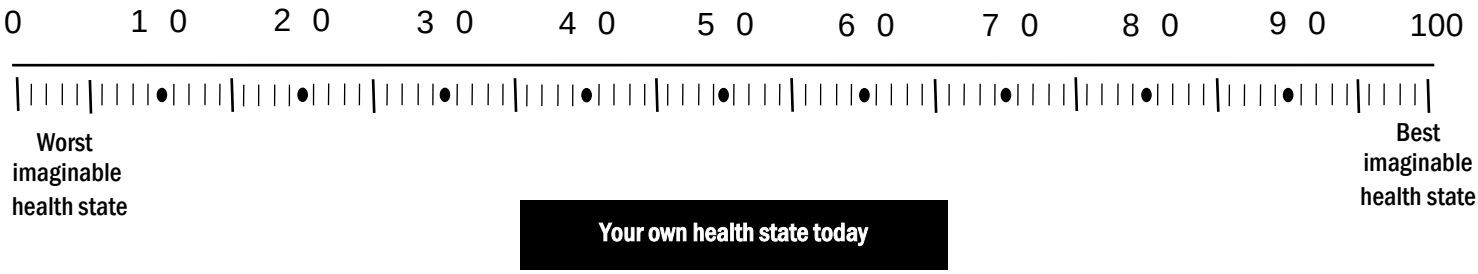
- Please go through the following statements and circle the box that best describes your thoughts and feelings over the last two weeks:

1. I've been feeling optimistic about the future*	None of the time	Rarely	Some of the time	Often	All of the time
2. I've been feeling interested in other people*	None of the time	Rarely	Some of the time	Often	All of the time
3. I've been dealing with problems well*	None of the time	Rarely	Some of the time	Often	All of the time
4. I've been feeling good about myself*	None of the time	Rarely	Some of the time	Often	All of the time
5. I've been feeling close to other people*	None of the time	Rarely	Some of the time	Often	All of the time

- To what extent would you agree with the following statement?

I am satisfied with the treatment that I am currently receiving	Strongly disagree	Somewhat disagree	Neither agree nor disagree	Somewhat agree	Strongly agree

- To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best health state you can imagine is marked 100 and the worst state you can imagine is marked 0. Please indicate on this scale how good or bad your own health is today, in your opinion, by marking with an X on the scale (anywhere from 0 to 100):



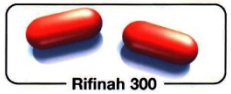
- Which of the following side effects did you experience during the continuation phase of your treatment? (please tick all that apply)

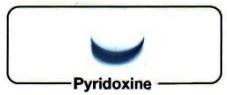
☐ Unusual Tiredness/ Loss of appetite
☐ Fever/Chills/ Headache/ Dizziness
☐ Skin Rash, Severe Itching
☐ Numbness, Tingling in hands or feet
☐ Pain/ Swelling in the face or joints
☐ Eye Problems / blurring
☐ Stomach Pain, Nausea/Vomiting
☐ Yellow Skin or Dark Urine

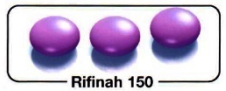
Terapia Virtual Observată (TVO) – Fișa medicamentelor

Numele: _____ Nr. de caz: _____

Medicamentele din faza de continuare:


Rifinah 300


Pyridoxine


Rifinah 150

_____

Vă rugăm să raportați în timpul apelului video dacă aveți sau nu aveți oricare efecte secundare. Specificați numărul și efectul secundar pe care-l suferiți:

1 = Probleme respiratorii – **Dacă da, întrerupeți medicamentul și chemați de urgență medicul.**

2 = Îngălbinirea pielii sau ochilor și urină de culoare foarte închisă **– Dacă da, întrerupeți tratamentul și chemați de urgență medicul.**

3 = Durere în burtă, grețuri și vomă.

4 = Orice probleme de ochi: schimbări de vedere, vedere neclară, orbire, probleme de vedere sau durere în ochi.

5 = Durere sau inflamație în regiunea feței sau articulațiilor.

6 = Amorțeală, durere sau furnicături în mâini sau picioare.

7 = Erupție cutanată, mâncărime severă sau urticarie.

8 = Dureri de cap sau amețeli.

9 = Febră sau frisoane.

10 = oboseală neobișnuită sau lipsa poftei de mâncare.

11 = Niciunul – Nu simt niciun efect secundar

Pregătiți-vă pentru primirea comprimatelor:
plasați comprimatele pe foaie,
paharul cu apă alături,
plasați calculatorul/telefonul în loc bine iluminat

Apel video

- Accesați Programul e-sănătate și apăsați butonul ‘Video Call’
(imagine screen-shot)

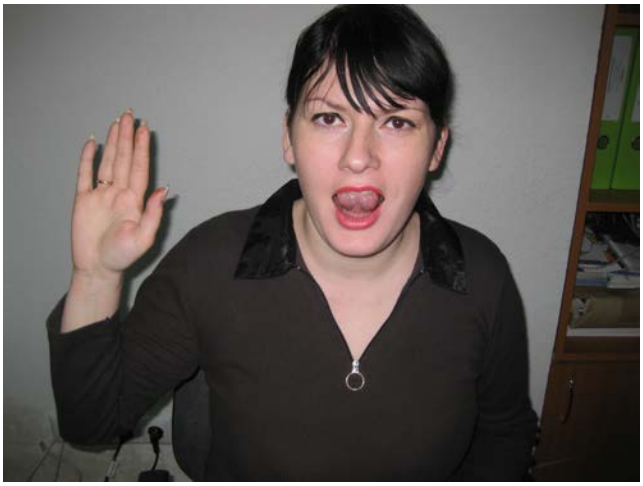
Prezentați-vă - Spuneți numele Dvs. și numărul de comprimate pe care le veți administra
(Salut, sunt [numele]. Iau 4 pastile)

Descrieți setul de pastile :

Arătați primul medicament și spuneți denumirea si numarul de pastile/dimensiunea, forma și culoarea acesteia.

Arătați comprimatele pe limbă și mâinile.

Înghițiți comprimatele și arătați gura deschisă, mișcați limba în sus și în jos



Repetati procedura pentru toate medicamentele!

Bifați simptoamele care le aveți:

	simptoame	da	mesaj
1	Oboseală neobișnuită, pierderea poftei de mincare		Discutați cu medicul despre simptomele Dvs.!
2	Febră, frisoane, dureri de cap, amețeli		Discutați cu medicul despre simptomele Dvs.!
3	Erupții pe piele		Discutați cu medicul despre simptomele Dvs.!
4	Amorțeli, furnicături in maini sau/și picioare		Discutați cu medicul despre simptomele Dvs.!
5	Durere/inflamare a articulațiilor sau feței		Discutați cu medicul despre simptomele Dvs.!
6	Probleme cu vederea		Discutați cu medicul despre simptomele Dvs.!
7	Dureri in abdomen/greață/vomă		Întrerupeți tratamentul și urgent contactați medicul!
8	Ingălbinirea tegumentelor sau urină întunecată		
9	Probleme respiratorii		
10	Mă simt bine, nu am nici		Ne revedem mâine! O

IVth Month - Questionnaire on health and welfare

Suggested revisions by BIT, 23rd January 2017

Part A – For all patients (DOT and VOT)

A.1 General Information:

A.1.1 Date of interview:

A.1.2 Code:

A.1.3 Treatment: ☐ VOT

☐ DOT

A.1.4 Gender: ☐ F

☐ M

A.1.5 Polyclinic:

A.1.6 Are you presently employed? ☐ Yes

☐ No

A.2 Wellbeing & satisfaction

A.2. 1 Read the following statements and circle the box that best describes your thoughts and feelings in the **past two weeks**:

1. I have optimistic visions about my future*	Never	Rarely	Sometimes	Often	Always
2. I am interested in other people	Never	Rarely	Sometimes	Often	Always
3. I get along well with other people *	Never	Rarely	Sometimes	Often	Always
4. I feel good about myself*	Never	Rarely	Sometimes	Often	Always
5. I feel close to other people*	Never	Rarely	Sometimes	Often	Always

A.2.2 To what extent do you agree with the following statement?

I am satisfied with the treatment I received in the continuation phase	I don't agree at all	Somewhat disagree	Neither nor	Somewhat agree	Absolutely agree

A.2.3 *To help our patients state how good or bad their health is, we drew a scale (like a thermometer), where the best condition that you can imagine is 100, and the worst condition is marked 0.*

Please mark on this scale how good or bad your health is today, in your opinion, drawing an X on the scale (from 0 to 100) _____

A.2.4 Which of the following side effects did you experience during the continuation phase of your treatment? (Select all that apply)

	Unusual tiredness / appetite loss		Pain / inflammations in the region of the face or joints
	Fever / shivering / headaches / dizziness		Problems with eyes / blurred vision
	Rash, severe itching		Stomach pain, nausea, vomiting
	Numbness, tingling in hands or feet		Jaundice or dark-colored urine

A.3 Time use and cost

I now want you to think about how much time and money you spend on receiving TB treatment, including on travel to and from the clinic, taking your medication etc.

Transport cost

A.3.1 Please estimate the total transport cost (in lei) for an average trip to the polyclinic. This can be money spent on gas for the car, bus tickets, taxi or any other transport. _____ (Lei).
Note for interviewer: if different modes of transport are used, ask the patient to estimate an average.

Travel time

A.3.2 In minutes how long does it take you, on a normal day, to get to the polyclinic from the place you usually travel from? This could, for example, be either your home or your place of work/ study.
_____ (min)

A.3.3.a [*DOT patients*] How many times did you go to the clinic last week, i.e. in the last 7 days?

_____

A.3.3.b [*VOT patients*] How many times did you go to the clinic last month, i.e. in the last 30 days?

_____

Time spent on treatment

A.3.4 In minutes, how much time do you spend **in the clinic for one normal visit**? Please include the time spent waiting, the time speaking to and being examined by a doctor or a nurse as well as the time it takes to administer the medicine or pick up new medication. _____ min

A.3.5.a *[DOT patients]* In minutes, how much time do you spend **on your TB treatment at home on one day when you do not go to the clinic**, e.g. on weekends or public holidays? _____min

A.3.5.b *[VOT patients]* How much time do you spend, **in one normal day, on taking your TB treatment at home**? Please include the time spent on taking the medication, filming yourself and submitting the video, but exclude any time spent on going to the clinic. _____min

Part B – Only for the VOT patients

Code:

B.1 Device

B.1.1 Over the past four months, what device did you use most often for the VOT messages?

	PC
	Tablet
	Mobile phone
	Other, specify: _____

B.1.2 Over the past four months, which of the following devices did you use to send video messages for TVO (select all that apply)?

	PC
	Tablet
	Mobile phone
	Other, specify: _____

B.1.3 Did you already have a computer, phone or tablet or did you have to borrow a tablet to send the VOT messages?

	I borrowed a tablet
	I used my own device

B.2 Comparison VOT - DOT

B.2.1 What method of adherence monitoring do you prefer?

	VOT (M-Health)
	DOT (polyclynic)

B.2.2 What method of adherence monitoring do you think is best for most patients?

	VOT (M-Health)
	DOT (polyclynic)

B.2.3 What, in your opinion, are the main advantages of VOT compared to DOT?

B.2.4 What, in your opinion, are the main disadvantages of the VOT compared to DOT?

B.2.5 What, in your opinion, are the main advantages of DOT compared to VOT?

B.2.6 What, in your opinion, are the main disadvantages of the DOT compared to VOT?

B.2.7 Do you have any suggestions on how to improve the VOT procedures in the future?

Pregătiți-vă pentru primirea comprimatelor:
plasați comprimatele pe foaie,
paharul cu apă alături,
plasați calculatorul/telefonul în loc bine iluminat

Apel video

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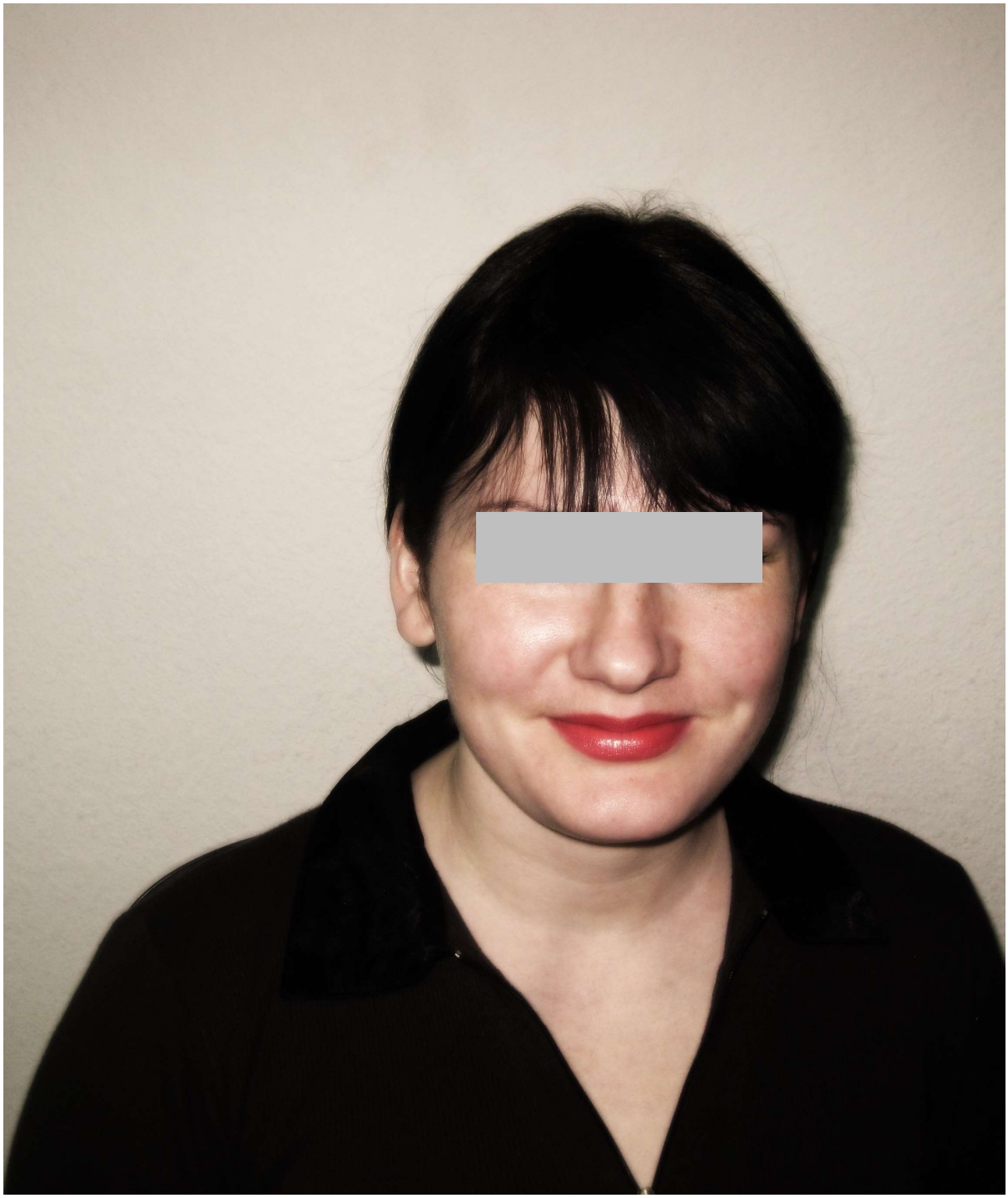

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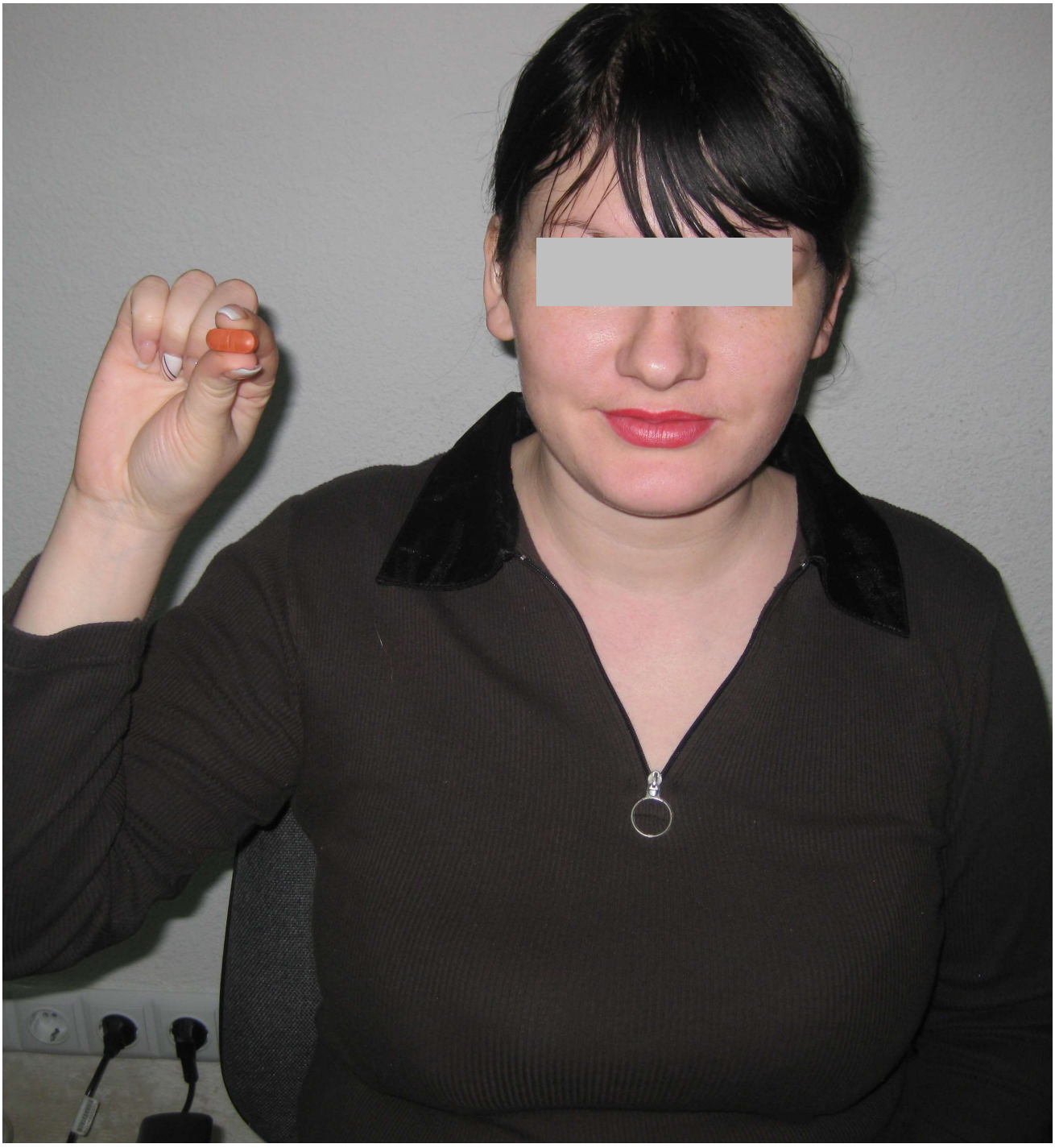
(Salut, sunt [numele]. Iau 4 pastile)



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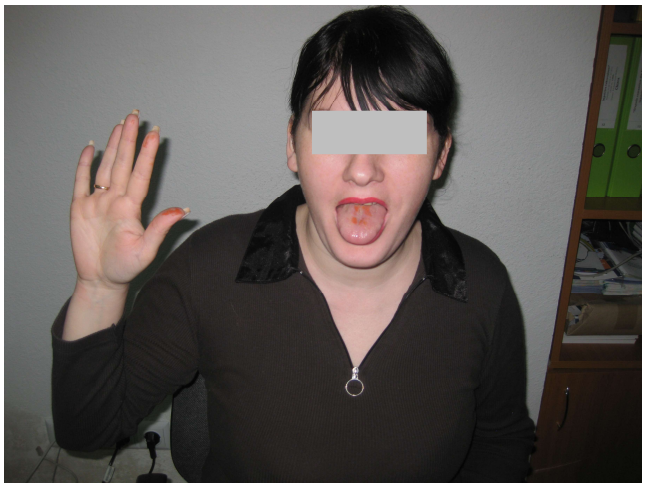
Înghițiți comprimatele și arătați gura deschisă, mișcați limba în sus și în jos



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3	Erupții pe piele		Discutați cu medicul despre simptomele Dvs.!
4	Amorțeli, furnicături in maini sau/și picioare		Discutați cu medicul despre simptomele Dvs.!
5	Durere/inflamare a articulațiilor sau feței		Discutați cu medicul despre simptomele Dvs.!
6	Probleme cu vederea		Discutați cu medicul despre simptomele Dvs.!
7	Dureri in abdomen/greață/vomă		Întrerupeți tratamentul și urgent contactați medicul!
8	Ingălbinirea tegumentelor sau urină întunecată		
9	Probleme respiratorii		
10	Mă simt bine, nu am nici		Ne revedem mâine! O