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Impact of a Digital Health Platform (NimCure) on Adherence Enhancement in Tuberculosis Therapy

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ABSTRACT: The study was a 2-arm individually randomized clinical trial conducted at the Nigeria Institute of Medical Research (NIMR) in Lagos, Nigeria, aimed to improve the overall patient adherence to tuberculosis treatment using Video Observed Therapy (VOT). A total of 100 participants were recruited to this study. Data was collected through the NimCure mobile app and patient records. Results obtained showed a high rate of at least 90% adherence to TB treatment was achieved in both VOT and DOT groups. There was no significant difference in proportions between the two groups, however, the proportion of patients who adhered 100% to TB treatment in the VOT group was statistically significantly greater than that of DOT patients ($t = -2.18$, $p = 0.03$). Rewards points feature on NimCure app significantly increased total submissions among patients ($t = 2.21$, $p = 0.042$). All patients who previously were treated for TB using DOT and relapsed, had successful treatment outcomes with VOT, indicating that VOT presents a viable solution to factors associated with non-adherence. VOT also presents continuous engagement with the patient caregiver. This opens up further research in VOT for TB treatment adherence.

Keywords: Adherence, Direct Observed Therapy, Telemedicine, Tuberculosis, Video Observed Therapy.

Introduction

Tuberculosis (TB) remains one of the leading causes of death worldwide with 1.7 million deaths reported (WHO 2020). Although the number of TB deaths fell by 22% between 2000 and 2016, the increasing rate in human immunodeficiency virus (HIV) infection poses a challenge for TB control especially in low- and middle-income countries (WHO 2016). Despite TB being a major public health threat in Nigeria and a leading cause of death, very little progress has been attained in mitigating the menace of this curable disease (WHO 2017). In global ranking, Nigeria is 4th among 22 high TB burden countries with 4.3% of multidrug resistant and rifampicin resistant (MDR/RR-TB) cases reported (Onyedum *et al.*, 2017). Annually, about 245,000 Nigerians die from TB and 590,000 new cases occur of which 24% are HIV-positive (Michael *et al.*, 2016).

TB treatment requires a multi-drug approach, predisposing patients to adverse drug events especially anti-tuberculosis drug induced liver injury (Jacobs *et al.*, 2015). Effective TB treatment is largely dependent on patients' willingness to comply with prescribed regimen (Michael *et al.*, 2016). As found in the treatment of other chronic

diseases, non-adherence (NA) to treatment is a major problem in the management of TB, it is a prerequisite for treatment failure, easy transmission of TB and MDR-TB (Gomes et al., 2015; Kendall et al., 2018). Reasons for NA are poor initiation, implementation and premature discontinuation of therapy (De, 2013; Liu, et al., 2017).

A recommended strategy to reduce NA is Directly Observed therapy (DOT). With DOT, the patient meets with a healthcare worker every day or several times a week and takes prescribed medications while the healthcare worker watches and monitors response to treatment, throughout the recommended 6 months for TB treatment (WHO 2017). Though DOT has contributed significantly to improvements in TB treatment outcomes in the last two decades (Meltcalfe et al., 2015), its implementation in low- and middle-income countries have some limitations such as high costs, resource-intensiveness and high burden on patients and healthcare workers (Tan et al., 2020). This has led to rampant self-administration by patients (Yellappa et al., 2016). Innovative approaches are needed to achieve the ambitious goals of the 2030 End TB strategy and sustainable development goals.

The effectiveness of DOT is limited by factors such as; (1) It is resource-intensive and can put additional pressure on health systems, particularly in settings with a high TB burden and constrained resources (Parsons et al., 2011; Snidal et al., 2015). (2) It is inconvenient for patients to visit a health clinic daily for treatment supervision, for reasons including travel and waiting times, transportation and maintenance of car fleets, work and school schedules and privacy concerns.

Among alternatives to DOT is digital medication monitoring (DMM) (Falzon et al., 2016; Story et al., 2016) which recently included the use of web-based technology called video-observed therapy (VOT) (Mirsaeidi et al., 2015). VOT is a method of adherence monitoring where patients transmit digital images of their treatment intake to a central location for review; either synchronously or asynchronously. This method could potentially transform adherence support. The use of VOT in some developed countries has been documented to be acceptable, cost effective, and improve patient commitment to treatment (Heorhi et al., 2017). However, there is limited evidence to demonstrate feasibility of digital strategies to support adherence in resource-limited settings (Liu et al., 2017).

Nigeria has one of the fastest growing mobile phone ownerships in the world, with 82 mobile phone subscriptions per 100 people and over 90 million internet subscribers on mobile networks and over 31,000 terabytes monthly consumption (ITU, 2017).

The World Health Organization (WHO) proposed a 90% reduction in TB deaths and an 80% reduction in new cases in the year 2030 (WHO 2020). To achieve this in Nigeria, Vassal and Mustapha, reported a spending of about eighty-one billion Naira yearly to increase detection rates, strengthen primary health care provision and treat many more patients (Vassal and Mustapha 2015). VOT can; minimize public health resources (travel costs, time for staff and patients), reduce potential transmission to caregivers through prolonged contact, and increase patients' privacy. Considering that VOT is feasible and acceptable to patients in some developed countries, it presents an option that can be explored for developing countries like Nigeria with high TB burden. Therefore, a pilot mobile health application tagged "Nigerian Institute of Medical Cure (NimCure)" was developed for this study (Schmidt, 2018).

Materials and Methods

Study Design: The study was conducted at the Centre for Human Virology and Genomics, Centre for Tuberculosis and Clinical Science Department of Nigerian Institute of Medical Research (NIMR). NIMR is a TB and HIV reference centre for Nigeria. The study was a 2-arm individually randomised clinical trial.

A total of 100 participants were recruited to this study. Of the 100, 70 were randomly assigned to the DOT control group and 30 randomised to the VOT treatment group. However, 15 participants with insufficient data were excluded from data analysis. Informed and voluntary consent was sought from both DOT and VOT Patients, with additional consent on collection of video recordings on the platform. A total of 56 DOT and 29 VOT patients completed the trail.

Study objectives: The study aims to improve TB patient treatment adherence in Nigeria with the use of VOT.

Recruitment process: For eligibility,

- A. Confirmed TB patients of not less than 15 years of age, receiving a regimen containing only oral medications,
- B. Completed at least two weeks of DOT
- C. Accurately identify each medication and self-administered by mouth
- D. Have access to private areas that support patient confidentiality in the observation environment.

Exclusion criteria:

- A. Patients with current or prior diagnosis of multidrug resistant (MDR) - TB or a severe mental illness

- B. Patients with disabilities e.g. vision or hearing impaired
- C. Patients who experience adverse reaction(s) to prescribed medication within the first 2 weeks of treatment initiation as revealed by biochemical analysis and clinical features
- D. Patients with low adherence rate on DOT within the first two weeks of DOT
- E. Patients at risk for hepatic complications.
- F. Paediatric patients (<15 years)
- G. Homeless patients (need to establish contact address for proper follow up)

VOT enrollment process: Staff at the DOT Centre were trained to enlighten patients on the trial, its benefits and their commitments as they signed up. The trained staff invited patients seeking TB treatment for study enrollment. Consenting participants were trained on use of NimCure App and asked for information about their demographics, medical history and mobile phone use. Additional information about their diagnosis and treatment regimen were extracted from the participant's medical file. Participants for VOT were assigned a unique number and signed consent on live video therapy and loaner agreement on the care and use of smartphones sponsored by Samsung Mobile. Low-cost smart- phones (android) with 4G connectivity were loaned to participants. Study participants who already owned a smartphone could use their own phone to participate. Data for internet connectivity was provided for all participants' phones. VOT was performed using the NimCure platform (developed by Co-Creation Hub), a synchronous and asynchronous smartphone application. Videos were transmitted over a 3G or 4G mobile network connection unto the smartphone app.

NimCure App use and training: At enrolment, consenting participants were given a 30-minute training session on how to use smartphone and NimCure app. This included a session where participants were given written instructions and they practiced recording and uploading videos unto the NIMCURE smartphone platform. Any participants reporting technical difficulties during the intervention period were provided additional training by study staff. Adherence monitoring using VOT was offered 7 a.m to 7 p.m. Each day, at a time chosen by the study participant, a Short Messaging Service (SMS) message was automatically generated to remind participants to do a video chat or upload a video. If video chat or recording was not received after one hour, a second reminder SMS was sent. If a video session or upload is missed, despite the SMS, study staff called the participant to provide support and remind them to take treatment.

Participant videos were automatically uploaded via the mobile network. Every day, between 7 am and 7pm, the study staff accessed a secure website to monitor and verify the patient's adherence to the TB treatment by reviewing the date and time of the video submission. Participants were asked to report side effects verbally by describing them during the daily video recording. Adherence was recorded by study staff as adequate if participants held up all the required pills, placed the pills in their mouth and swallowed. Video and audio quality were also documented.

At the end of each month, study staff interviewed participants during a scheduled clinic visit. Follow-up was recorded as completed if and when participants returned for a scheduled visit. Aside from the video reviewed, treatment adherence was also determined based on the count of remaining tablets at monthly clinic visit.

Results

The study's primary outcome to be analysed is the proportion of participants completing all doses of self-administered treatment during the study period, according to daily video review and pill count by health workers during the monthly scheduled clinic visits (at least 90% TB treatment adherence) while the secondary outcomes are the proportion of videos uploaded as scheduled, and the proportion of participants discontinuing using VOT.

Patient baseline characteristics

The average age (SD) of all patients was 37.75(11.33). On the other hand, the average age of DOT patients was 37.15 (10.52) while that of VOT patients was 38.79 (12.76). The average weight of DOT patients was 58.74 kg while that of VOT was 62.65 kg. The average height was 1.74 m and 1.72 m for DOT and VOT Patients respectively. We further sought to find out if DOT and VOT patients started treatment the same days after samples were taken and a delay of almost a day was observed in DOT patients (9.33 days for DOT and 8.44 days for VOT patients) (Table 1). When doing the analysis, we excluded HIV-positive patients since those who tested positive for HIV and presented TB symptoms were put on treatment immediately.

Table 1: Patient characteristics

Patient characteristics	DOT		VOT		DOT - VOT Difference	Test statistic	Overall
	Mean	Std Dev	Mean	Std Dev			
Age (in years)	37.16	10.52	38.79	12.76	-1.63	-0.61	37.75
Location in Nigeria (binary)	0.84	0.37	0.64	0.49	0.2	1.88	0.77
Time taken to start treatment (in days)	9.33	15.29	8.44	9.72	0.89	0.32	9.04
Weight (in kg)	58.74	11.48	62.65	11.96	-3.90	-1.40	60.06
Height (in m)	1.74	0.08	1.72	0.09	0.01	0.45	1.74
HIV Prevalence (binary)	0.41	0.5	0.25	0.44	0.16	1.51	0.36
Earlier TB treatment (binary)	0.07	0.26	0.18	0.39	-0.11	-1.32	0.11

Primary outcome: patients' adherence at least 90% TB treatment

One of the main objectives of the trial was to test at least 90% adherence for both DOT and VOT patients. On this, a high rate of at least 90% adherence to TB treatment was achieved. Specifically, 94% (n=49) of DOT patients achieved this, and 100% (n=29) of VOT patients achieved this. A t-test conducted showed that there was no significant difference in 90% adherence between the two patient groups (t=-1.32, p=0.192).

In addition to this, we checked for 100% adherence to TB treatment for both groups. Data showed that 78.85% (n=41) of DOT patients adhered 100% to TB treatment, while 96.55% (n=28) of VOT patients adhered 100% to TB treatment. A t-test conducted showed that this difference in 100% adherence is statistically significant at 95% confidence level (t- -2.18, p= 0.03) (Table 2).

Table 2: Number of times patients missed drugs

No of Times Missed Drugs (Days)	Category			
	DOT		VOT	
0	41	78.85%	28	96.55%
1 to 7	7	13.46%	1	3.45%
8 to 14	1	1.92%	0	0.00%
15 to 21	0	0.00%	0	0.00%
22 to 28	1	1.92%	0	0.00%
More than 28	2	3.85%	0	0.00%
Total	52	100.00%	29	100.00%

Total number of videos uploaded (Total successful submissions)

Rewards points feature was introduced on NIMCURE to motivate patients to use the app. The first round of rewards happened from 1st to 5th of April, 2019. Paired small sampled t-test was used to test whether or not reward points intervention was able to increase total submissions of patients using the platform at significance level $\alpha = 0.05$. There was a significant difference in total submissions before and after introducing reward points on the platform (t = 2.21, p-value=0.042). Therefore, the intervention increased total submissions among patients. The Figure below (Fig 1) shows a video submission rate of over 70% in April 2019, and an increase in the next month, then a slight decline with the lowest (61.5%) being in November 2019. The month of December 2019 saw a sharp increase (90.3%) in submission rate.

Proportion of Successful Submission (%)

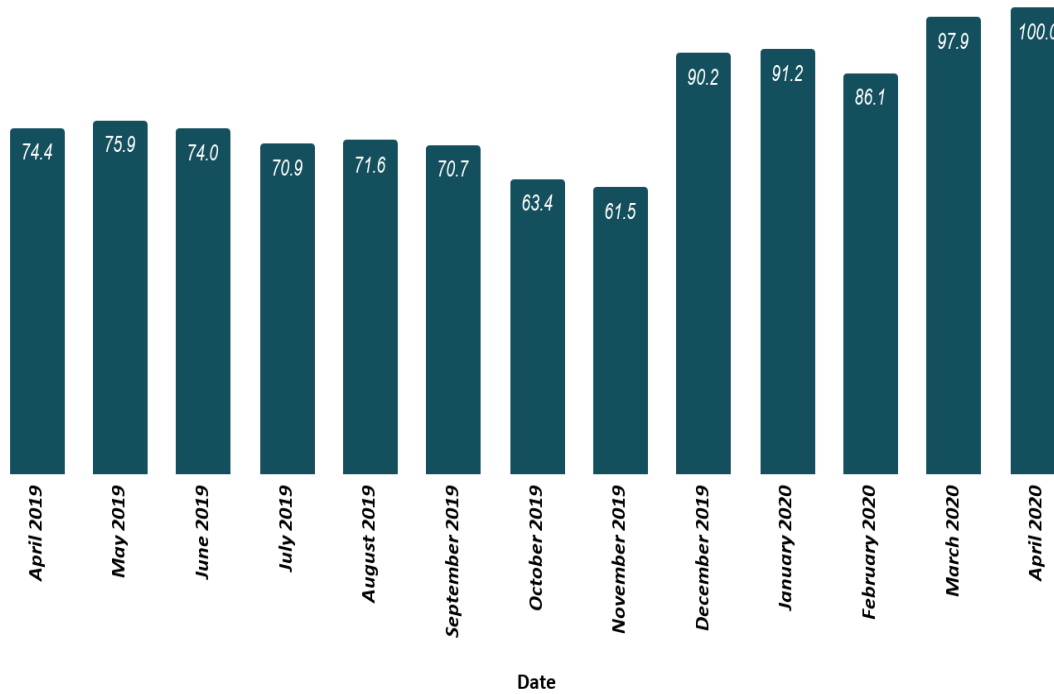


Figure 1: Proportion of successful submissions

Patient entry status

In addition, the study sought to know if the patients in the trial had previously treated for TB and relapsed or not. The majority (92%, n=78) were new patients while 5% (n=4) had relapsed. In addition, a chi-square test conducted to check for association between patient category and entry status revealed that there is no association between the two (chisq=7, df=3, p=0.072) as shown on Table 3.

Table 3: Patient entry status

Entry Status	Category			
	DOT		VOT	
New Patient	53	94.6%	25	86.21%
Previously failed treatment	2	3.6%	1	3.45%
Previously relapsed	1	1.8%	3	10.34%
Total	56	100.0%	29	100.00%

Treatment outcome on DOT and VOT patients

Furthermore, the study checked if there was a change in treatment outcome for both patients. A change in treatment outcome was defined by the question “what was the test result of the patient after their treatment?” This was categorized to three groups, successful (tested negative at the end of treatment), failure (tested positive at the end of the treatment period) and inconclusive (patient either relocated or died). Majority of patients both on DOT and VOT

were successful (91.1% and 86.21% respectively). In addition, a chi-square test conducted to check for association between patient category and treatment outcome showed that there is no association between the two (chisq=2.74, df=3, p=0.254) as shown on Table 4.

Table 4: Patient treatment outcome

Treatment outcome	Category			
	DOT		VOT	
Successful	51	91.1%	25	86.21%
Failed	2	3.6%	0	0.00%
Inconclusive	3	5.4%	4	13.79%
Total	56	100.0%	29	100.00%

Proportion of participants discontinuing or not consenting to use VOT.

Reasons for discontinuing or not consenting to the use of NimCure and their characteristics are shown on Table 5. As a result, 5 of the 9 patients (56%) did not consent to participate in VOT and were moved to DOT. Out of the remaining, 4 patients discontinued, due to death during the course of the study, relocation to another DOT centre, fears concerning their privacy and bad network in their area.

Table 5: Reasons to discontinue or not consent to using VOT

Reason to Discontinue VOT	n	%
Relocation	2	22%
Technical issues	2	22%
Deceased	2	22%
Poor network	1	11%
Started the drug before issue date	1	11%
Family members discouraged him/her	1	11%

Discussion

The results show patients recruited in the two groups (DOT and VOT), had uniform baseline characteristics in this study, albeit the standard deviation of the ages within each group was high (DOT: 10.52 and VOT: 12.76). T and Chi-Square tests used to assess the differences between DOT and VOT patients showed no statistically significant difference between the two study groups in terms of their location, time taken to start treatment (from date of diagnosis), and HIV status. These establish the symmetry across age categories and other clinical characteristics within the DOT and VOT groups, hence, no baseline characteristic significantly skewed the outcome of the analysis. Furthermore, scaling up the sample number in the VOT study group has potential to inform acceptability of this and future VOT platforms, in terms of patient demography, due to the relatively high standard deviations observed in the baseline characteristics (e.g. age).

According to findings from this study, when measuring 90% adherence in patients, the use of the NimCure application as a VOT medium contributed to a 6% increase in success rate than in DOT. Similarly, when measuring 100% adherence, VOT contributed to a 17.7% increase in success rate than in DOT. This suggests that, with the use

of VOT, it is possible to increase that chances of 90% adherence rate in most patients while also increasing the possibility of patients achieving 100% adherence. In concordance with other reports (WHO 2016; Story et al., 2016), the success of these patients' treatment can also be attributed to a number of factors that VOT supports like the convenience of participating in VOT from the comfort of the patients' homes. Patients under VOT also had more interactions with their assigned caregivers which could have created a sense of more accountability on the part of the patients.

Video submission is a vital part of the study, however, because patients needed to upload videos of themselves taking the drugs as at the given time, challenges such as; patients living in areas with poor network connection, and little knowledge of the use of smartphones affected video submission rate. These challenges were addressed through periodic training of participants and follow up from caregivers.

Major reasons for treatment failure include; HIV co-infection, non-adherence or poor adherence to anti-TB drugs as well as drug resistance TB (Fraser and Keshavjee, 2019). A patient is said to have failed treatment when the sputum smear or culture result of the patient after 5 months of drug administration still shows the presence of viable MTB (Harries *et al.*, 2004). This study ascertains the efficacy of VOT especially on patients who had been treated before and failed treatment or relapsed. All participants that initially failed treatment with DOT that enrolled on the VOT arm had successful treatment outcome. This showed that they were able to adhere to their drug regimen with the use of VOT. Participants who were on VOT had less visits to the healthcare facility than participants on DOT, these findings agree with Fraser and Keshavjee that attributed the success of treatment outcome among TB patients that use VOT to reduce burden associated with frequent visits to healthcare facilities during DOT (Fraser and Keshavjee, 2019).

The major aim of this study was to improve treatment outcomes of patients taking anti-TB drugs by ensuring adherence using digital medication monitoring techniques. A successful treatment outcome should be expected if there is strict drug adherence by the patient. Non-adherence would lead to an increase in treatment failure as well as multi-drug resistance in tuberculosis patients (Gebreweld *et al.*, 2018; Dooley *et al.*, 2011). At the end of this study, patients who were recruited on VOT and had completed the regimen, had a 100% (25 out of 25) successful treatment outcome with all patients that completed having a negative result at the 5th month of drug administration, whereas, patients on the DOT arm of the study, who had completed treatment recorded a 96.2% (51 out of 53) successful treatment outcome with 2 patients (3.8%) failing treatment at the end of the study. The significant treatment success margin, recorded in this study portrays a greater chance in the reduction of the spread of the disease using VOT.

The use of VOT in TB monitoring during the course of the trial was accompanied with challenges ranging from poor network service in some rural areas, inability of participants to use the device correctly, unforeseen circumstances such as death of participants and relocation to another state. Some participants showed interest initially in the use of VOT but had to discontinue or decline due to the aforementioned challenges. About 22% (i.e. 2) of participants that enrolled for VOT and began using the Nimcure application relocated and needed to be transferred from the trial facility, 11% (1) of the participants had network challenges in their area of residence, this stalled video submissions, making it difficult to be monitored. Despite the challenges, there were no treatment discontinuation, hence patient treatment was not affected. This is because these categories of patients were reassigned to DOT facilities closer to them.

There was also the issue of privacy, as family members of a particular participant were not comfortable with him sending videos of himself taking drugs, which led to him discontinuing even though necessary precautions were made in ensuring privacy of every participant in this trial. Subbaraman in his article on digital adherence technologies for the management of tuberculosis, cited privacy and security concerns as one of the challenges of Video observed therapy (Subbaraman *et al.*, 2018). Hence, the influence of relatives as caregivers could stall the effective use of VOT, this should be put into consideration in settings planning to deploy VOT on a larger scale.

Conclusion

Non-adherence to the prescribed tuberculosis treatment regimen is a critical issue that contributes to the problem of multidrug-resistant TB and recurrent TB infection. Factors associated with non-adherence such as forgetting to take the medication, lack of money for transportation and the burden of travelling away from businesses or other responsibilities to visit a healthcare facility for Directly Observed Therapy were resolved by the use of VOT. The

inclusion of a reward system helped to motivate the participants to submit their videos on time. A key factor to the success of VOT could also be associated with continuous engagement with the patient and caregiver.

Recommendations

From our findings, VOT through the NimCure smartphone app achieved the 90% adherence objective, we therefore recommend that VOT can be used for remote monitoring and management of Tuberculosis patients. With the current pandemic which has reduced patient visit to the clinic and access to health Personnel, remote monitoring using VOT would better help ensure that patients are observed and monitored nonetheless.

Conflict of Interest

There is no conflict of interest among authors.

Acknowledgement

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Ethical Approval

Ethical approval was obtained from the NIMR institutional review board (IRB 18/025). Only patients that gave their consent were enrolled on the study.

List of Abbreviations

DMM: Digital Medication Monitoring
DOT: Directly Observed Therapy
MTB: *Mycobacterium tuberculosis*
NIMR: Nigerian Institute of Medical Research
VOT: Video Observed Therapy

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