Effectiveness of Video Directly Observed Treatment (DOT Selfie), a Mobile Health Intervention to Increase Treatment Adherence Monitoring and Support for Patients with Tuberculosis in Uganda: A Randomized Controlled Trial

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Abstract

Background: Directly observed therapy (DOT) is the standard for monitoring adherence for tuberculosis (TB) treatment. However, the implementation of DOT is difficult for patients and providers due to a lack of financial and human resources. Mounting evidence suggests that video directly observed therapy (VDOT), an emerging digital adherence technology works but its effectiveness has barely been evaluated in low-income settings where the burden of TB is greatest.

Objective: The study evaluated the effectiveness of Video directly observed treatment for adherence monitoring and support compared to usual care among patients with TB.

Methods: Between July, 2020 and October 2021, we conducted a two-arm parallel group, open-label randomized trial with 1:1 assignment to receive the VDOT intervention (n=72) or usual care DOT (UCDOT) (n=72) for treatment adherence monitoring at public health clinics in Kampala, Uganda. Each group was further stratified to have equal numbers of males and females. Eligible patients were 18-65 years old with a confirmed diagnosis of TB and on daily treatment. The VDOT group received a smartphone with an app while the UCDOT group used the routine practice for monitoring treatment per the Uganda National TB program. We tested the hypothesis that VDOT was more effective for monitoring medication adherence compared to UCDOT. The primary outcome was adherence defined as having >=80% of the expected doses observed during the treatment period of 6 months. Intention-to-treat (ITT) analysis was done, and we performed multivariable logistic regression to estimate the effect of the intervention on adherence monitoring. We present adjusted relative risk ratios and the associated 95% confidence intervals. Secondary outcomes were treatment completion, loss to follow-up, death and reasons for missed videos in the intervention group.

Results: The intention-to-treat analysis included 142 participants. Two participants were excluded due to failure to continue their medication within the first week after enrollment. The median age was 34 years (IQR:26-45). The mean fraction of expected doses observed (FEDO) was significantly higher for the VDOT than the UCDOT group (90% mean FEDO vs 30% mean FEDO, $p < 0.001$). When using a FEDO cut-off of >=80% as optimal adherence, 63 (44.4%) patients achieved the set threshold with a significant difference between VDOT and UCDOT (78.9% vs. 9.9%, p=< 0.001). After adjusting for confounders, VDOT users were significantly more likely to have >=80% of their expected doses observed compared to UCDOT (Adjusted RR. 8.4, 95% CI

4.16- 17.0). The commonest reasons for failure to submit videos of medication intake were an uncharged phone battery, forgetting to record videos during medication intake, and losing a smartphone.

Conclusions: VDOT was more effective for increasing observation of adherence to treatment than UCDOT among patients with TB in Uganda. This evidence supports the promise of digital technologies for improving monitoring and support of treatment adherence in high TB burden settings where human resources are limited. Clinical Trial: The clinical trial was registered with ClinicalTrials.gov (NCT04134689).

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Conclusion: VDOT was more effective for increasing observation of adherence to treatment than UCDOT among patients with TB in Uganda**.** This evidence supports the promise of digital technologies for improving monitoring and support of treatment adherence in high TB burden settings where human resources are limited.

Keywords: tuberculosis; digital adherence technologies; video observed treatment, video directly observed treatment; directly observed therapy, adherence; mHealth, Uganda; Africa.

Background

The End TB Strategy envisions a world free of tuberculosis (TB) with zero deaths, disease, and suffering due to TB by 2035[1]. In 2022, an estimated 10.6 million new cases suffered from TB disease while 1.6 million died worldwide[2]. Although effective treatments for TB disease have existed for over 50 years, non-adherence to medication is a common problem among patients and presents an obstacle to achieving the goals of the End TB Strategy control [1, 3]. Non-adherence reduces cure rates, prolongs infectiousness, and results in poor treatment outcomes such treatment failure, drug resistance, death and relapse[4-7]. The emergence of drug resistant TB and multi-drug resistance (MDR-TB) is partly attributed to patients not taking their medication properly[4]. Globally, there were an estimated 450,000 incident cases of MDR in 2021, up 3.1% from 437,000 in 2020[2]. According to a recent meta-analysis that included 148 studies, the global pooled prevalence of multi-drug resistant TB was 11.6% (95% CI: 9.1–14.5%), this much higher than previous estimates [8].

The World Health Organization (WHO) and the U.S clinical practice guidelines recommend directly observed therapy (DOT) as the standard of care for TB treatment [9, 10]. DOT requires a health care worker to observe a patient in-person while ingesting the TB medications, to monitor adherence and provide support as needed [10]. When implemented properly, in-person DOT can facilitate high levels of medication adherence and cure of TB disease. DOT can also help in early detection of adherence problems, adverse drug reactions, and worsening TB symptoms[11]. Previous estimates show that approximately 50% of patients on long-term treatment for chronic disease often fail to adhere to their prescribed medication regimens both in developed and developing countries[12]. Several barriers hinder the effectiveness of DOT including the inconvenience of daily in-person visits at health facilities, a shortage of health care workers, the high costs of transportation, TB stigma, and long patient waiting times at health facilities [13, 14].

Digital adherence technologies have recently emerged as promising tools to overcome barriers to patient support and treatment monitoring at the health system, patient and structural levels [15-18].Video observed therapy (VDOT) is a novel smartphone-based system that uses an app to record videos of medication intake to facilitate remote monitoring of treatment adherence. VDOT minimizes the need for frequent face-to-face meetings reducing the inconvenience to patients and cost of transportation[19, 20]. Several published observational studies have evaluated the feasibility and acceptability of VDOT, including two from Africa [20-26]. Three randomized clinical trials (RCTs) in the U.S, U.K, and Moldova have evaluated the efficacy of VDOT and shown it to be feasible, acceptable, cost-saving, and convenient to patients [16, 27-29]. A pilot study from Kenya showed video observed therapy to be both technically feasible and acceptable to patients and health professionals[24]. Studies done among patients and health providers in Uganda have shown that VDOT is feasible and acceptable for monitoring and supporting patients in TB treatment [25, 30, 31]. A recent systematic review and meta-analysis showed that VDOT is effective for improving medication adherence and bacteriological resolution compared to in-person DOT care[32]. However, none of the studies in the review were done in Africa because no RCTs comparing VDOT to in-person DOT have been published from Africa. Our study is one of the first RCTs aimed to compare the effectiveness of VDOT and Usual Care DOT for observing and monitoring treatment adherence among patients with TB in Uganda.

Methods

Trial Design

The 'DOT Selfie' study was a parallel group, open-label randomized controlled trial of 144 adult patients with TB at selected treatment clinics in Kampala, Uganda. Participants were randomized to a control group (n=72), that received the usual care DOT (UCDOT) and the intervention group (n=72) that received Video directly observed treatment (VDOT) for adherence monitoring. Participants were enrolled into the RCT from July 13th, 2020 and follow up continued through October 25th 2021. Our published protocol described the details of the design and methods of the randomized control trial [33].

Eligibility Criteria

Eligible participants were adults aged 18 to 65 years with a confirmed diagnosis of drug-susceptible TB in the new or retreatment category who had initiated treatment for no more than one month. Participants provided written informed consent and planned to reside in Kampala for the entire period of 6 months while on treatment to facilitate close study follow-up. Participants were excluded; if they were not able to speak and read either Luganda (local dialect) or English, were too ill to withstand the duration of the study procedures at enrollment, had a self-reported motor, visual, hearing or cognitive disability that would hinder the proper use of a smartphone. We also excluded patients who resided in areas that did not have cellular network coverage or access to electricity to charge the smartphone.

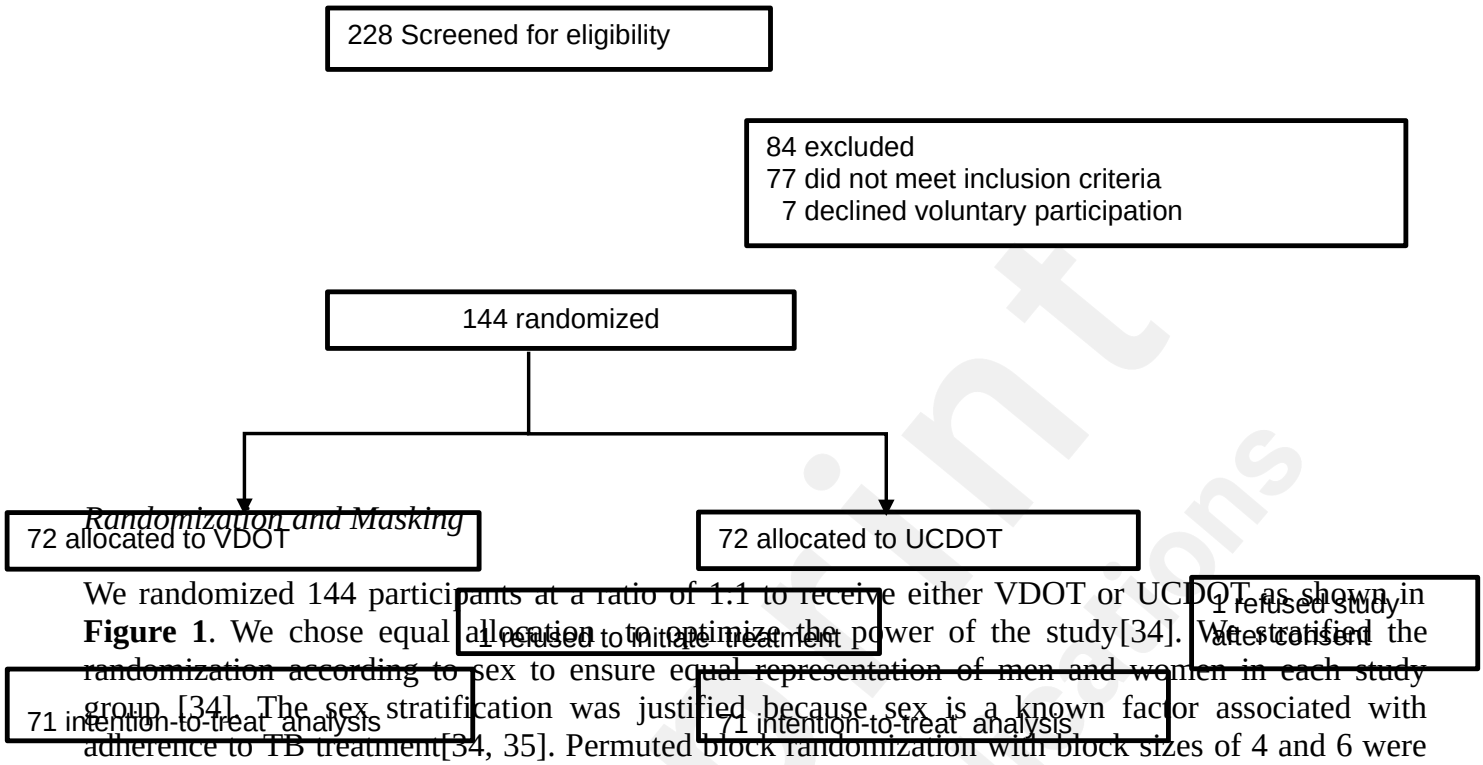
Ethical Considerations

Ethics Approval This study was approved by the institutional review boards at the University of Georgia (ID PROJECT00000571), Makerere University (protocol 756), and the Uganda National Council for Science and Technology. All participants provided written informed consent to participate and audio-record discussions during the exit interviews. Written informed consent was obtained in either English or Luganda language according to patients' preferences. Participants were reimbursed for transportation and their time spent at all scheduled study visits.

Study Setting and Recruitment Procedures

The primary study site was Lubaga TB clinic and secondary recruitment sites were public clinics that provide free TB services in Kampala. All TB clinic sites are located about 10-15 km from Kampala city center and together treat approximately 10,000 TB patients annually. The study team worked closely with clinic nurses who helped to identify potentially eligible patients. Trained research assistants used a screening checklist to assess for study eligibility followed by a brief description of the study. Interested patients provided written informed consent after which they completed a baseline questionnaire. The baseline questionnaire asked about socio-demographics, income, TB diagnosis, initial treatment, experience using regular cellphones and smartphones, social media applications, transportation costs, social support, personal habits, privacy/confidentiality concerns, and perceived stigma related to the TB diagnosis (see supplementary materials S1). All participants received routine health education about TB, including duration of treatment, side effects, and the importance of medication adherence. Participants were then randomized to intervention or control study groups. The study flow is shown in Figure 1.

Figure 1. DOT Selfie Participant Flow Diagram



Randomization and Masking

We randomized 144 participants at a ratio of 1:1 to receive either VDOT or UCDOT as shown in **Figure 1**. We chose equal allocation to optimize the power of the study[34]. We stratified the randomization according to sex to ensure equal representation of men and women in each study group [34]. The sex stratification was justified because sex is a known factor associated with adherence to TB treatment[34, 35]. Permuted block randomization with block sizes of 4 and 6 were generated to ensure a balanced assignment of participants to intervention or control groups and to minimize predictability of study arm assignment. Each block had a specified number of randomly ordered treatment assignments as recommended in methods of clinical trials by Friedman and others [34]. The trial statistician created computer-generated random permuted blocks of variable sizes of 4 and 6 containing equal proportions of control and intervention assignments. Within each block were 4 or 6 sealed, opaque allocation envelopes that were sequentially numbered according to the computer-generated randomization schedule. Study research assistants then received sealed opaque envelopes with individual random assignments. Following informed consent, participants were invited by the study staff to select and open the topmost envelope to reveal their randomization allocation. Due to the nature of the intervention, participants and study staff were not masked to study group assignment. Study investigators were not blinded to allocation information because of the ongoing scientific reviews and clinical decisions about participants' treatment should a need arise to remove them from the intervention. The trial statistician was blinded to the assignment of the study group during the analyses.

Description of the VDOT System

The VDOT is a licensed Health Insurance Portability and Accountability Act (HIPPA) compliant system originally developed by SureAdhere Mobile Technology, an initiative that started at University of California San Diego[36]**.** It consists of three main parts as described previously by Garfein and colleagues[19] and in our published protocol paper[33]**.** The parts include i) the patient-facing part which is the smartphone app used by the patient to record the medication videos ii) The secure cloud-based server which is used to store the uploaded medication videos. iii) the provider-facing part which is the web-based browser accessed through a secured password protected login via computer laptop or tablet used to access the submitted videos for review and daily adherence reports[33]. At the end of each video recording, an automatic, encrypted, time-stamped video was uploaded to the secure cloud server for storage and playback. Once the video submission was

completed, the video was removed from the smartphone such that the patients could not retrieve it. At the health clinic, a trained research staff logged into a secured VDOT system via a tablet or laptop to observe the patients' daily videos and document adherence according to a pre-specified protocol. The study staff tracked missed videos, reported common side effects and follow-up with appropriate support, advice or other actions to patients as prespecified in the study protocol (see details in supplementary materials S2).

Contextual Adaptation of the VDOT System

The VDOT system was adapted to the local Ugandan context in three ways; first, we expanded to English-based SMS text reminders to include motivational message to encourage patients to continue taking their medications and submit videos. Second, we translated the SMS text into Luganda (a local dialect) to facilitate understanding for patients who did not speak English. The following are examples of the text messages reminders and motivational messages we used "It's time to take your pills and send a video". "Taking your pills will help you to get better". Third, an additional text reminder was sent automatically after 8 hours after the standard text reminder that was sent out to participants at 6.00 AM, if a medication video was not received in the VDOT system. After adaptating the VDOT system to the local context, it was dubbed "*DOT Selfie*".

Description of the VDOT System

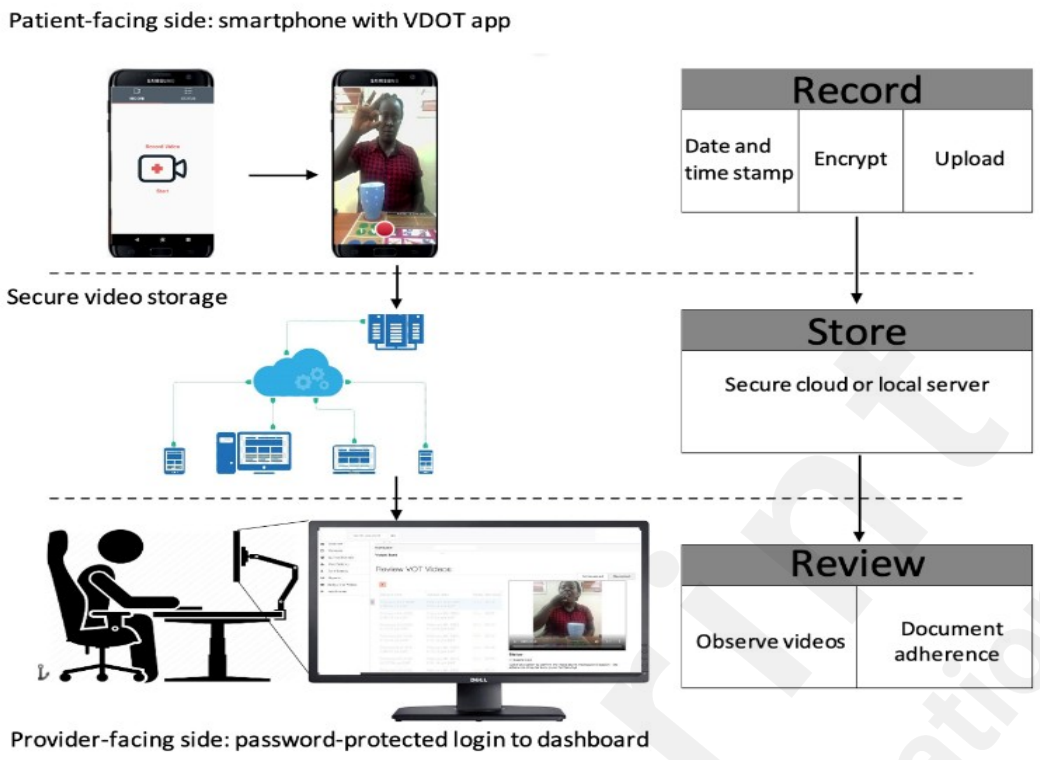


Figure 2. Schematic of asynchronous VDOT system for monitoring tuberculosis treatment (adapted from Sekandi et al[33]

Description of standard procedures

The trial procedures are described in detail in our protocol paper which is published elsewhere[33]. All participants had an initial face-to-face TB education session regardless of the assigned study group. The session provided information on TB medications including dose, timing, and importance of taking daily pills as prescribed and what to do in the event of a missed dose or lost pills. Information on cough hygiene behaviors such as covering their cough to minimize the risk of spreading germs to others was given. Lastly, the education emphasized the importance of reporting any problems related to TB medications such as common medication side effects, adverse events or new symptoms.

Intervention: Asynchronous Video Directly Observed Treatment (VDOT)

We use asynchronous VDOT intervention package which included 1) a loaner smartphone GSM Itel p15 Android model W5005 with a pre-installed VDOT application and a preassigned Sim card with a unique phone number 2) prepaid weekly internet data subscription of 350MBs at the local telecom commercial rates 3) automated daily SMS text reminders to take medications. Participants in the intervention group were enrolled on the VDOT system using a unique login personal identification number (PIN) to set up an account to secure the patient information in compliance with HIPAA [33]. The PIN also prevented access to the VDOT app by non-study participants. The app has a video feature that enables the patients to record themselves while swallowing their daily doses of pills. In addition, patients received weekly incentives equivalent to U.S $0.30 in form of social bundles or airtime minutes conditional on successful submission of videos for seven consecutive days.

On the day of enrollment, participants received detailed training on how to use the VDOT app to record and submit videos of medication intake. They also received an instruction guide with pictorial illustrations (‘pill mat’) showing the step-by-step process of recording the videos and a description of the most common side-effects of the TB medications. The ‘pill mat’ served as a visual aid to facilitate easy reporting of medication side-effects during the video recording session (see details in

Supplementary materials S3). Participants signed agreements to return the study smartphone to the clinic upon completion of their full course of treatment.
At the clinic, a trained study staff logged into the secure VDOT system via a computer or tablet to download, review patients' daily videos, document medication adherence and any self-reported side-effects. The study nurse also tracked missed video recording and undertook follow up actions as pre-defined in the protocol (see details in supplementary materials S2). These included a follow up call to assess actual missed doses, addressing side effects and any other issues as needed. Other secondary methods used were pill counts and tracking prescription refills at the clinic.
Control: Usual Care DOT (UCDOT)

UCDOT was delivered according to routine practice under the Uganda National TB program guidelines update in 2017 [37].The guidelines state that the TB treatment supporter may be a healthcare worker, or a trained workplace or community health worker (CHW) or whoever patients choose to watch them swallowing the tablets. The in-person interaction between the patient and treatment supporter during treatment should happen at least five times a week and observed medication doses documented in the treatment card. Further to the guidelines, DOT services must be organized to suit the patients' circumstances and must be provided as close to their homes as possible, unless patients live close to a clinic and it is convenient for them to take their treatment at the clinic. There is however considerable variation in how DOT is implemented, how contact tracing, TB screening and other services have been integrated into DOT support. According the descriptive narrative by health providers in Kampala [*personal communication*], we provide some insights gained into the typical practice of UCDOT. On the day when TB diagnosis is confirmed TB, patients receive group in-person TB health education at the health clinic. TB medications are prescribed for the first two weeks and the patients return for biweekly refill visits in the intensive phase of treatment (first two months). In the continuation phase, patients return monthly for routine visits for clinical evaluation and prescription refills. The patient and treatment supporter are supposed to agree on a mutual meeting place for treatment observation and support.
Specifically, in Kampala, community linkage facilitators (CLF) are trained TB program workers whose responsibility is to document patients' information on observed adherence, treatment refills and TB screening of household contacts [*personal communication by CLF*]. Adherence is further assessed using patients' self-reports and pharmacy prescription refill during routine clinic visits. The study research staff worked in partnership with the TB clinic nurses or staff, CLFs and treatment supporters to collect information on DOT and adherence from clinic records, patients' treatment cards and using a structured self-reported adherence questionnaire at study follow-up visits. Patients in the UCDOT study group were followed up for missed routine visits according to the National TB program guidelines. These included a follow up phone call if a patient missed a routine visit to refill a prescription and addressing any issues such as side effects as needed. Other secondary methods used were pill counts and checking the patients' treatment card records. We note that there were some unintended modifications of the routine delivery of usual care DOT due to the COVID-19 disruptions.
Follow up of VDOT group for missed videos and study visits

A predefined follow-up protocol was used to contact study participants in case of missed doses or videos (See details in supplementary materials S2). The research staff made two phone call attempts within the first 24 hours of a missed expected video to establish dosing history and the reason for missing videos. If there was no response from the participants within 72 hours, the research team escalated the follow up to a field visit to trace the participant at home or workplace. After 2 weeks of the intensive active follow-up protocol were completed, there was a waiting interval of 2 weeks in case the participant called back or returned to the clinic for a routine visit. If the patient failed to show up for the scheduled clinic visit, the study notified the national TB program staff to get

additional support. According to the standard WHO guidelines, a patient is declared lost to follow-up (LTFU) if he/she did not return to the clinic for their prescription refills for 2 consecutive months [38].

Study Measurements

Outcome Measures

The primary outcome measure was adherence, defined as the fraction (proportion) of expected doses observed (FEDO) over the months of prescribed TB treatment or by the end of the study following randomization. In the UCDOT group, daily direct observation of medication adherence was more difficult to document consistently because of the variable approaches used by the treatment supporters. We mostly used self-reports and refill visits as indirect measures of adherence. Study measurements were done using a questionnaire at baseline and at follow-up months 2, 4, and 6 to ensure close monitoring of all patients in treatment. For internal validity, adherence was also be measured at follow-up visits using a modified 10-item self-reported adherence questionnaire from the Morisky Adherence Scale [39] (see supplementary materials S4).

Secondary Outcomes

Secondary outcomes we selected are considered to be unfavorable outcomes and are also relevant indicators of performance by national TB programs. They include treatment completion, loss-to-follow up, death and treatment failure. The definitions of outcomes were based on the WHO [38] and Uganda National TB program guidelines [37]. Treatment completion was defined as completing all medication doses as prescribed by the TB clinic and confirmed by the clinic records. Loss to follow-up was defined as an interruption of TB treatment for at least 2 consecutive months. Death is considered as any death during treatment regardless of the cause. Treatment failure is defined as TB patient whose sputum smear examination is positive at month 5 or later during TB treatment [38].

Sample Size Estimation

The trial was powered at 80% to detect a 22% difference in the level of medication adherence, as the primary outcome, between the two VDOT (85%) and UCDOT (63%) based on a two-sided significance level of 5%. The levels of adherence for the comparison groups were obtained from previous DOT and VDOT studies done in Kampala, Uganda [25, 40]. To achieve a chi-square test of a difference of 0.22 and odds ratio 0.30, the estimated total sample size was 124. We assumed an attrition rate of 14% based on a randomized controlled trial comparing a usual care and digital adherence intervention in Kenya where the overall loss to follow up rate was 11.7% (9.9% in UCDOT and 1.76% in VDOT)[41]. Another randomized trial using asynchronous VDOT that was done in the U.K had a higher attrition rate of 23% but the study population was very different from our study because it included 58% of homeless subjects [16]. The calculated final sample size was 144 participants with 72 subjects per group. When calculating the power and sample size, we treated the response as binary (0 or 1), corresponding to a cutoff value for non-adherence as fraction of observed doses <80% and adherence if fraction of observed doses >=80% respectively. This binary response variable for adherence was used in the final regression analysis to facilitate comparison with previous clinical trials[16]. Sample size tables were used to estimate precision as described detail elsewhere in our protocol paper[33]. All calculations were performed using the SAS statistical software package version 9.4.

Statistical Analyses

We conducted intention-to-treat (ITT) analysis according to the study group to which the patients were originally randomized. Superiority was determined by a 22% difference in the proportion of patients with the primary outcome (63% *vs* 85%). VDOT treatment observation was classified as completed if ingestion of medication doses were observed by video. UCDOT treatment observation was classified as completed if the patient reported that a designated treatment supporter observed ingestion of prescribed doses.

Univariate analysis was done to describe the baseline characteristics of the study population. Multivariable logistic regression analysis was done to test for significant associations between study groups as the main exposure and the primary binary outcome of adherence (No <80, Yes >=80%). Age and HIV status were selected as potential confounders and adjusted for in all models. Other covariates considered for adjustment during the primary analysis were education level, income, and smartphone ownership at baseline. We did not adjust for sex since the randomization was stratified by this variable. Crude and adjusted Odds Ratios with 95% confidence intervals are presented and statistical significance considered at p-values less than 0.05.

Results

Of 228 patients with confirmed TB who were screened, 144 met the eligibility criteria and were randomized to one of the two study groups. Two participants were excluded from the intention-to-treat-analysis (n-142); one participant who was randomized to VDOT refused to initiate his TB treatment soon after study enrollment and another participant in the UCDOT group declined participation after initiation of treatment. The two participants were included in the baseline analysis but excluded from any further analyses because they did not have the study outcomes of interest. The median age of the participants was 34 years (interquartile range [IQR]: 26-45). There was a significant difference in age between study groups; participants in the UCDOT groups were older. More than one third of participants had attained a low level of education and 37.5% (54/144) were unemployed. The majority (83%,120/144) of participants owned any type of cellphone while 36.8 (53/144) had smartphones. Within the VDOT group, 40.3% (29/72) owned a smartphone. Overall, nearly 32% (46/144) were HIV positive. All other measured baseline characteristics except age were balanced between the study groups (Table 1).

Table 1. Baseline Characteristics of Participants by Study Arm in Kampala, Uganda

N=144

Variables	Total	VDOT Arm	UCDOT Arm	p-value
Sex				
Male	72 (50.0)	36 (50.0)	36 (50.0)	1
Female	72 (50.0)	36 (50.0)	36 (50.0)	
Age in years, median (IQR)	34 (26-45)	29.5 (24- 42)	38 (28- 47)	**0.005**
Age Category				
18 - 24	27 (18.8)	19 (70.4)	8 (29.6)	**0.02**
25 - 34	48 (33.3)	27 (56.2)	21 (43.8)	
35 - 44	30 (20.8)	10 (33.3)	20 (66.7)	
45 - 65	29 (20.1)	16 (41.0)	23 (59.0)	
Highest level of education				
No education or primary	55 (38.2)	27 (37.5)	28 (38.9)	0.117
Secondary	64 (44.4)	28 (38.9)	36 (50.0)	
Tertiary/University	25 (17.4)	17 (23.6)	8 (11.1)	
Marital status				
Currently married	55 (38.2)	23 (31.9)	32 (44.4)	0.333
Previously married	23 (16.0)	13 (18.1)	10 (13.9)	
Never married	66 (45.8)	36 (50.0)	30 (41.7)	
Currently employed				
No	54 (37.5)	29 (40.3)	25 (34.7)	0.606
Yes	90 (62.5)	43 (59.7)	47 (65.3)	
Monthly personal income in USD§, median (IQR)	42.85 (14.29 – 85.71)	42.85 (14.29 – 114.30)	28.57 (11.43 – 85.71)	0.268*
Monthly total household income in USD£, median (IQR)	57.14 (28.57 –142.86)	71.43 (28.57 – 157.14)	57.14 (28.57 – 114.23)	0.559*
Currently owned cellphone				
No	24 (16.7)	14 (9.4)	10 (13.9)	0.502
Yes	120 (83.3)	58 (80.6)	62 (86.1)	

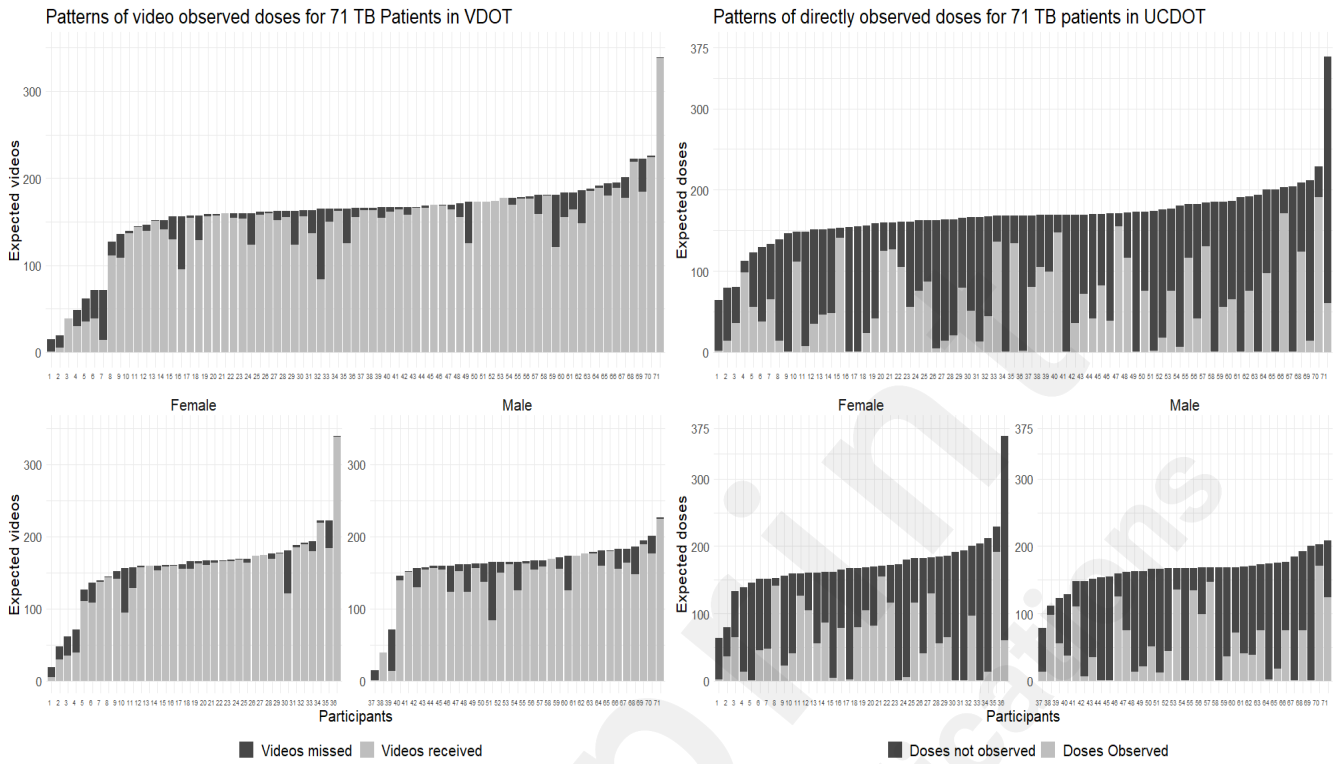
	Owned smartphone				
	No	67 (46.5)	29 (40.3)	38 (52.8)	0.309
	Yes	53 (36.8)	29 (40.3)	24 (33.3)	
	HIV Status				
	Positive	46 (31.9)	24 (33.3)	22 (30.6)	0.554
	Negative	98 (68.1)	48 (66.7)	50 (69.4)	

§1 USD~3,500 UGX (Uganda Shillings), *Kruskal-Wallis test for differences in median

Patterns of treatment observation by VDOT and UCDOT groups and by sex

A visual illustration of the pattern of treatment observation among study participants is shown in Figure 3. For the VDOT group, the light grey bars represent the videos received via the technology system and the dark grey bars show the videos that were not submitted i.e. missed. For the UCDOT group, the light grey bars show the doses that were observed as reported by the patients and the dark grey bars show the unobserved doses. We observe obvious differences in the patterns of observation between the two study groups. However, when the same data is stratified further by sex, there are no obvious differences in patterns of doses observed between men and women within each group.

Figure 3: Patterns of treatment observation among participants in VDOT and UCDOT



Median differences in expected and observed doses by study arm and sex

There was a significant difference in the median number of doses observed by VDOT and UCDOT (Table 2a). However, there were no significant differences in number of doses when comparing male and female participants within the same study arm (Table 2b).

Differences in adherence measured by the fraction of expected doses observed

We evaluated adherence using the fraction of expected doses observed (FEDO) expressed as a percentage as shown in table 2c. The overall median FEDO was 80% (IQR 30,100) but the median adherence for the VDOT arm was 100% (IQR 80,100) and was significantly higher than that of the UCDOT group. When using a cut-off of >=80% for FEDO to categorize optimal adherence and <80% for non-adherence, only 44% of participants achieved an optimal level of their expected doses being observed. VDOT had 79% of participants with an optimum FEDO which was significantly higher that of the UCDOT group. The median FEDO did not significantly differ by sex and age group in each study arm.

Table 2a. Number of Expected and Observed Doses by Study Arm				
	Total	**UCDOT**	**VDOT**	**p-value**
Expected videos/doses, median (IQR)	167 (158, 177)	168 (158, 178)	166 (158, 177)	0.405
Videos/doses observed, median (IQR)	118 (39, 157)	48 (14, 98)	156 (134, 168)	<0.001
Videos/doses not observed, median (IQR)	37 (7, 105)	105 (66, 151)	7 (2, 23)	<0.001

Table 2b. Number of Expected and Observed Doses Within Study Arm Stratified by Sex				
UCDOT arm				
	Total	**Male**	**Female**	**p-value**
Expected doses, median (IQR)	168 (158, 178)	168 (158, 172)	168 (158, 184)	0.490
Doses observed, median (IQR)	48 (14, 98)	41 (14, 86)	56 (12, 99)	0.608
Dose unobserved, median (IQR)	105 (66, 151)	116 (68, 151)	104 (64, 148)	0.963
VDOT arm				
	Total	**Male**	**Female**	**p-value**
Expected videos, median (IQR)	166 (158, 177)	165 (160, 178)	166 (155, 175)	0.569
Video observed doses, median (IQR)	156 (134, 168)	154 (134, 164)	160 (135, 170)	0.373
Videos missed, doses not observed, median (IQR)	7 (2, 23)	10 (3, 26)	4 (2, 14)	0.159

Table 2c. Median Adherence Based on Fraction of Expected Doses Observed (FEDO) by Study Arm				
Variables	**Total**	**VDOT**	**UCDOT**	**p-value**
Adherence, median FEDO (IQR)	80% (30, 100)	100% (80, 100)	30% (10, 60)	<0.001
Adherence, with FEDO as binary outcome [Yes >=80%, No <80%] n (%)				
Yes, n (%)	63 (44.4)	56 (78.9)	7 (9.9)	< 0.001
No, n (%)	79 (55.6)	15 (21.1)	64 (90.1)	
Total	142	71	71	

Factors Associated with Adherence

We performed a multivariable logistic regression analysis to evaluate the factors associated with optimal adherence levels of 80% doses or more observed as measured by the FEDO as shown in table 3. The results from the unadjusted regression models showed that being in the VDOT group and of the Muslim religion were independent factors that were significantly associated with

achieving adherence of 80% or more. We found that participants in the VDOT group were 8.4 times more likely to have 80% or more of their expected doses observed compared to those in UCDOT after adjusting for confounding by age, religion, current cellphone ownership and HIV status. Current phone ownership was significantly associated with reaching the 80% level of adherence based on expected doses observed compared to those who didn't own a cellphone after adjusting for study group and other covariates.

Table 3. Factors Associated with Treatment Adherence Measured by FEDO Among Study participants in Kampala, Uganda

Variables	Unadjusted RR	p-value	Adjusted RR	p-value
Arm				
UCDOT	1.00		1.00	
VDOT	**8 (3.92-16.33)**	**<0.00001**	**8.41 (4.16- 17.00)**	**<0.00001**
Age category (years)				
45 - 65	1.00		1.00	
35 - 44	0.74(0.38-1.45)	0.38	1.02 (0.6-1.74)	0.945
25 - 34	1.18(0.72- 1.93)	0.503	1.06 (0.73-1.54)	0.751
18 - 24	1.46(0.89 -2.41)	0.137	1.03 (0.69-1.52)	0.895
Highest education level				
No education or primary	1.00			
Secondary	0.95 (0.63-1.41)	0.781		
Tertiary/University	0.90(0.52- 1.57)	0.709	-	-
Marital status				
Married	1.00			
Previously married	1.17(0.69- 2)	0.557	-	-
Never married	1.13(0.75- 1.72)	0.556		
Religion				
Catholic	1.00		1.00	
Protestant	1.59 (0.93-2.72)	0.087	1.06 (0.7-1.61)	0.770
Muslim	**1.75(1.04 -2.93)**	**0.034**	1.29 (0.87-1.91)	0.198
Pentecostal/Seventh Day Adventist/Other	1.59 (0.92-2.76)	0.096	1.01 (0.7-1.48)	0.942
Currently owned cellphone				
No	1.00		1.00	
Yes	1.22 (0.7- 2.12)	0.48	**1.62 (1.02-2.57)**	**0.040**

Variables	Unadjusted RR	p-value	Adjusted RR	p-value
HIV status				
HIV negative	1.00		1.00	
HIV positive	0.87 (0.57-1.33)	0.524	0.8 (0.56-1.14)	0.220

Table 4a. Secondary TB Outcomes

Outcome	Total N=142	VDOT N=71	UCDOT N=71
Treatment Completion	128 (90.1%)	67 (94.4%)	61 (85.9%)
Loss-to-Follow Up	9 (6.3%)	2 (2.8%)	7 (9.9%)
Death	5 (3.5%)	2 (2.8%)	3 (4.2%)
Treatment Failure at 5 months	0	0	0

In the intention-to-treat analysis of 142 participants, the secondary TB outcomes evaluated were included treatment completion at 90% for all participants but much higher in VDOT than the UCDOT group. Loss-to-follow up was 6.3% overall but 9% of the UCDOT participants were lost-to-follow up compared to about 3% in VDOT. Overall, there were 5 deaths with nearly an equal number in each study group with the majority (4/5) being HIV-coinfected. The summary is shown in table 4b.

Table 4b. Summary of Deaths

Participants	Study Arm	Sex	Age	HIV status	Treatment doses taken
1	VDOT	Male	29	Positive	56
2	VDOT	Female	28	Positive	84
3	UCDOT	Male	40	Positive	112
4	UCDOT	Female	54	Positive	84
5	UCDOT	Male	62	Negative	128

Reasons for Missed Videos Submissions in the VDOT Group

Based on the standard 6 months regimen of 168 doses and enrollment date, we expected a cumulative total of 11,928 videos. Of those, 92.6% (11,041/11,928) were received from the 71 participants who were included in the intention-to-treat analysis over the study period. For the 887 missed videos, the lack of a charged phone battery was the most common reason reported by the majority of participants accounting for 21% (183/887) of the missed videos. For patient-related issues, 15% (136/887) of missed videos were due to forgetting to record the videos even when the medications were swallowed. More than half of the videos missed were due to a technology related issue. Additional reasons for missed videos are shown in table 5.

Table 5: Reasons for Missed Videos among VDOT Study Participants in Kampala, Uganda

Reasons for missed videos	**Patients reporting, n**	**Videos missed, n**	**Percent of total missed videos**
Technical or technology-related issues			
Phone battery not charged	39	183	20.6%
Phone stolen/lost	6	98	11%
VDOT App errors	23	72	8%
Reported lack of internet connection	22	63	7.1%
Phone malfunction	7	18	2%
Failed to use App, needed retraining	12	16	1.8%
Subtotal			**50%**
Patient-related issues			
Took medications but forgot to record videos	21	136	15%
Traveled to a location that has no electricity	16	74	8%
Too ill to record video but took meds	7	51	6%
Too busy to record videos	13	40	5%
Location not convenient to record	7	24	3%
Ran out of TB medications	16	23	3%
Subtotal			**40%**
Other not classified			
No reason specified	23	89	**10%**
Total	**212**	**887**	**100%**

Discussion

In this study, we aimed to evaluate the effectiveness of VDOT for monitoring adherence to TB treatment compared to the usual care (UCDOT) among patients with drug sensitive disease. We found that VDOT was significantly more effective for observing medication ingestion and monitoring adherence to the expected doses of prescribed medication among patients with TB. This finding of our study is consistent with the conclusions drawn from a recent systematic review and meta-analysis that included studies done in Australia, China, Moldova, U.K and U.S found that monitoring treatment using VDOT was significantly associated with an increased level of adherence and better microbiological outcomes when compared to usual care DOT [32]. Additionally, we found that cellphone ownership was significantly associated with a higher level of observed doses regardless of study group. Although VDOT was effective, there were participants who occasionally failed to submit their videos of medication intake as expected. The commonest reasons included the lack of a charged phone battery, forgetting to record the medication event and loss of the smartphone. This finding is similar to results from our previous pilot study done in Kampala, Uganda [25]. The study was conducted during the COVID-19 pandemic which could have led to an overestimation of the effect of VDOT. However, a study that compared VDOT and usual care DOT before and during COVID-19 found significantly higher adherence to TB treatment when using VDOT during both periods[42]. To our knowledge this study is among the few randomized controlled trials done to evaluate the effectiveness of VDOT in Uganda and Africa. More studies are needed to evaluate the effectiveness of VDOT in the rural African context and other low-resource settings.

There are few published randomized controlled trials that have compared VDOT and in person DOT thus far [16, 28, 29]. Story and colleagues published the first multi-center trial of efficacy of video observed treatment compared to usual care in 2019 [16]. The study was conducted in U.K and involving a larger sample of 226 patients from 22 centers. The sample was also very diverse with 58% of persons with a history of drug and alcohol abuse, homelessness and incarceration. The U.K study reported that on average 70% of patients on VDOT achieved >=80% scheduled observations successfully completed during the first 2 months compared to 31% in usual care DOT. The difference observed in the VDOT arm could be due to the definition of the measurement of primary outcome at 2 months after randomization while our study measured the same outcome at 6 months or until the end of treatment. The Moldova trial by Ravenscroft and colleagues compared patients assigned to VDOT and clinic-based DOT. The study measured the observed medication adherence for every 2-weeks for the entire course of treatment as the primary outcome. The study concluded that VDOT significantly decreased non-adherence compared to the standard DOT and reduced the time and money patients spent during their treatment [28]. Although there were differences in the measurement of the primary outcome, the study's conclusion on effectiveness of VDOT is similar to our study.

The UCDOT group has a low level (30%) of reported observed doses of medication over the 6 months of treatment. This is not surprising because it is very similar to results from the U.K trial despite the differences in the study populations and treatment durations[16]. This finding further reinforces the fact that in-person DOT is difficult to implement particularly in low-resource settings [40, 43]. A Cochrane review of 11 clinical trials concluded that TB cure and treatment completion rates were not improved by DOT[13]. In South Africa, a recent study found that only about 25% received formal DOT support by either home-based or clinic-based DOT [44].

Cellphone ownership was significantly associated with achieving optimal observation of the expected doses of medications regardless of study group. Moreover, we found that nearly 83% of patients owned cellphone while 37% had personal smartphones at baseline. This finding could suggest that having access to a cellphone is an indirect facilitator of adherence support for patient on

treatment. In African settings, smartphone ownership and cellular networks are proliferating presenting a promise for leveraging modern technology to improve health care and service delivery. According to the National Institutes of Health, “there is a need to stimulate research utilizing mHealth tools aimed at the improvement of adherence to treatment, effective patient-provider communication, and self-management of chronic diseases in underserved populations” [45]. There is increased utility and effectiveness of accessible mobile technologies in enhancing the monitoring of patients with chronic diseases which can be attributed to the affordability and reliability of smartphones in both high- and low-income settings [46, 47].

The secondary outcomes including treatment completion, deaths and lost-to-follow up were better in VDOT group than those in the UCDOT group across the board but there were no treatment failures reported. These findings are consistent with the conclusions of a recent systematic review and meta-analysis[32]. The notably higher percentage of TB/HIV con-infected persons among the deaths is consistent with the epidemiologic trends[2]. Large studies are needed to compare these outcomes across the groups to ascertain the true differences.

Reasons for failure to submit videos

Overall, technical or technology-related issues were the most commonly cited for failure to submit videos. The lack of a charged phone battery was the single most common reason for failure to submit videos as sometimes phones turned off during video recording. This finding is similar to results from out pilot study in Kampala [25, 48].To minimize the phone battery issue, patients were trained and encouraged to ensure that phones were always charged nightly or before recording videos. Loss of a smartphone occurred among a few participants but resulted in a substantial number of unsubmitted videos. The study team mitigated the disruption in continuation of data collection by replacing lost phones as soon as they became aware. Missing adherence records were filled using self-reports by patients or clinic records on prescription refills. The self-report method falls short because of a lack of an objective way to validate the doses taken [39].

The main patient-related reasons that mostly prevented the submission of videos included forgetting to record the medication intake, traveling to a location that has no electricity to charge the phone or being too ill to record videos. These findings were similar to those we reported in our first pilot study [25] and in other studies elsewhere [19, 26]. Typically, if patients travel to rural areas in Uganda there is a high likelihood that they would not have access to electricity. When videos were missed because of travel, the research team followed up to gather the missing information using self-reported adherence. A small number of patients stated a lack of a convenient place to record videos similar to our previous study [25]. This is an important concern that could suggest underlying stigma. However, a study done in Turkey that compared the different levels of stigma across patients with TB using in-person versus VDOT concluded that patient who received VDOT reported experiencing less stigma[49]. The role of VDOT in mitigating stigma among patients with TB needs further research in diverse contexts.

Strengths of the study in the context of prior work

First, we note that we evaluated VDOT which is the only digital adherence technology that offers remote visual observation of doses taken that is comparable to the usual care DOT. Other commonly used digital adherence technologies for TB monitoring such 99 DOTS and digital or smart pillboxes (also branded WisePill or EvriMED) only offer indirect signals as proxies to doses of medication intake [18]. Second, we successfully evaluated a culturally adapted VDOT in an RCT in the context of a low income setting. There are cross-cutting limitations for all digital technologies that relate to their sustainability in particularly in low-income settings [18]. Most concerns are related to the limitations of the technology infrastructure, cost and access to smartphones. In our study, we demonstrated that more than one third of the participants owned a person smartphone and these numbers are growing globally. Third, we conducted the study in Kampala, Uganda, where the TB rates are estimated at 250 cases per 100,000 which is much higher than the majority of the settings in which VDOT has been previously evaluated [16, 19, 29]. Fourth, the study facilitated the delivery of a patient-centered approach that was more convenient and less intrusive during the critical period of the COVID-19 pandemic. This additionally catered to the public health mitigation measures to curtail the transmission of COVID-19. Lastly, the RCT results generated in our study provide a basis for systematic evaluation of the implementation process of VDOT. Although there is no gold standard when using digital adherence technologies for monitoring TB treatment, our study adds to the mounting evidence for that supports the digital observation of pill-taking mimics the in-person DOT in usual care.

Study limitations

Our study was conducted during the COVD-19 pandemic therefore some unintended disruptions in the health system could have altered the practical delivery of usual DOT care in Kampala, Uganda. Moreover, the pandemic-related disruptions could have inherently lent some advantage to the intervention group thus resulting in a somewhat more inflated effectiveness of VDOT. However, the effectiveness of the remote VDOT monitoring highlights the need for expanding the use of digital technologies. The unique pandemic period in we conducted our study may limit the generalizability of our findings to patients with TB in a non-pandemic situation. However, a study that compared VDOT and usual care DOT before and during COVID-19 found significantly higher adherence to TB treatment when using VDOT during both periods[42]. Our study did not specifically measure clinical endpoints like sputum conversion at follow up visits. We attempted to extract this information from routine clinic records but the data were incomplete. Our study findings are not generalizable to rural settings since we conducted the study in an urban setting where there is better cellular network, internet coverage and access to electricity to charge phone batteries. The limited technological resources could likely be a barrier to VDOT in rural settings in Uganda.

Implications for future adoption, scale up, sustainability and future research on VDOT

Our study has several implications for broad adoption, scale up and sustainability of VDOT in the future particularly in low-resource settings. Our findings support the need for careful considerations of the known facilitators and barriers of VDOT acceptability as highlighted in the qualitative exit study of patients who used VDOT in Uganda [30]. First, VDOT requires upfront investment in the health system and the local technology infrastructure. A robust system would include the hardware; computers, smartphones, access to electricity and the software; access to the internet, cellular network and the maintenance of the VDOT app. National TB Programs could seek partnerships with private entities like telecommunication companies to leverage their support for vital resources such as internet access. Second, standardized training of health providers to facilitate the proper use the digital technology for the effective and efficient implementation of the system. Third, there is need to integrate the VDOT system into the general Health Management Information

System (HMIS) to ensure interoperability and timely use of the treatment monitoring data. This system could eventually be expanded for monitoring treatment adherence for multiple diseases such as HIV/AIDS, diabetes, hypertension. Fourth, the patients would also need basic training in the use of the VDOT app to ensure ease of use so they can use the system effectively. In our qualitative exit interviews with VDOT users, training in the use of the smartphone app was cited by patients as one the facilitators of ease of use and acceptability for VDOT[30].

Confidentiality, privacy and stigma concerns are overarching issues that must be carefully addressed to alleviate fears of intentional or unintended disclosure of patient disease status. The flexibility of making video recordings at the patient's desired time and place has been greatly enhances privacy[50]. In a VDOT study done the U.S and Mexico, patients agreed that VDOT promotes autonomy and a sense of control over their health[19]. The ethical concerns related to digital technologies could vary widely in relation to collecting, securely storing and accessing videos that contain identifiable information like the patients' faces. The concerns could also have legal and social-cultural contexts to be considered[51]. A recent qualitative study that focused digital health technologies in sub-Sharan Africa concluded that threats to scale-up include the lack of buy-in from both patients and providers, insufficient human resources and local capacity, inadequate governmental support, overly restrictive regulations, and a lack of focus on cybersecurity and data protection [52]. Further research is needed to evaluate the impact of VDOT on patient-centered outcomes such as satisfaction and quality of life, user engagement with the technology and retention to prevent drop out. Other important areas of research include the effect of VDOT on health system workflows and workload, the costs, the cost-effectiveness when compared to the usual care.

Conclusions

VDOT was more effective for increasing observation of adherence to treatment than UCDOT among patients with TB in Uganda**.** This evidence supports the use of digital technologies for improving monitoring and support of treatment adherence in high TB burden settings where human resources are limited. Further research is required to evaluate which subgroups are most likely to benefit from this technology.

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Supplementary Files