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Publication Date

2019-12-01

DOI

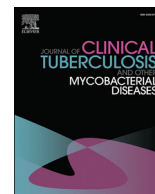
10.1016/j.jctube.2019.100098

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Synchronous and asynchronous video observed therapy (VOT) for tuberculosis treatment adherence monitoring and support

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ARTICLE INFO

Keywords:

Directly observed therapy
Latent tuberculosis infection
Medication adherence monitoring
Mobile health
Patient-centered care
Antimicrobial resistance

ABSTRACT

Directly observed therapy (DOT) for monitoring tuberculosis (TB) treatment is intended to reduce disease transmission, mortality and acquired drug resistance by facilitating treatment adherence and support. Synchronous (S-VOT) and asynchronous (A-VOT) video observed therapy are mHealth solutions for remotely monitoring medication ingestion. This paper synthesizes literature through December 2018 to describe existing VOT approaches, summarize evidence, identify knowledge gaps, evaluate VOT strengths and weaknesses, and examine patient and provider factors influencing VOT feasibility and acceptability. High rates of adherence and patient acceptance were obtained using both VOT methods. VOT reduced travel time for TB program staff and/or patients, improving program efficiency compared to in-person DOT while maintaining high patient satisfaction. The impact of VOT on TB treatment outcomes, such as cure and relapse, require further study with longer follow-up. Individual patient, provider and program factors should be considered in selecting either or both VOT approaches for provision of patient-centered care.

1. Introduction

Worldwide, tuberculosis (TB) is the leading cause of death from an infectious disease, surpassing HIV/AIDS in 2015. Annually, there are over 10 million new TB cases, 600,000 of which are caused by drug-resistant strains of *Mycobacterium tuberculosis*, causing 1.6 million deaths [1]. In the mid-1940s, clinical management of TB was revolutionized by the introduction of antibiotic therapy [2,3]. Because early antibiotics against TB were administered by injection in hospitals, TB treatment, by default, was directly monitored. All-oral anti-TB treatment regimens made ambulatory care possible, especially important after the shuttering of sanatoria [4]. However, poor adherence to self-administered oral medications quickly led to the emergence of drug-resistant strains of TB [5].

It is now well-recognized that without high adherence to TB's long treatment regimens, illness may progress, patients may remain contagious, and mutations may emerge rendering the bacteria resistant to treatment. Drug-resistant TB (DR-TB) requires even longer regimens with more expensive drugs that are less effective and often associated with higher mortality. DR-TB strains can also be transmitted [6,7] resulting in affected drugs being ineffective among new cases. Studies in Hong Kong and Madras highlight the importance of high adherence for

successful treatment outcomes, which prompted development of directly observed treatment (DOT) [8]. As early as 1964, patient factors like poverty and low education were recognized to lower TB treatment adherence [9,10]. Sumartojo also suggested that adherence to therapy can vary within individuals depending on the condition being treated [11]. Thus, individual, social and structural factors influence adherence to treatment, making evident the need for tailored support systems to improve TB treatment outcomes [12–15].

Given the need for strict adherence to TB treatment, the World Health Organization (WHO) recommends DOT as the preferred approach for monitoring TB treatment globally [16]. Patients receiving DOT are observed in-person swallowing their medications. DOT is a key component of the WHO DOT short-course (DOTS) strategy in which patients with drug-susceptible TB receive six to nine months of treatment under direct supervision by a health worker or a designee selected by the health worker and the patient. To increase the likelihood of successful treatment completion and cure under DOTS, TB programs direct observation should be combined with no-cost drugs throughout treatment, a reporting system, improved laboratory analysis, and political commitment [17].

Non-adherence to TB treatment is a complex challenge driven by socioeconomic factors, concomitant disease, and behavioral and

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<https://doi.org/10.1016/j.jctube.2019.100098>

treatment-related factors [18–21]. Non-adherence increases the risk of spreading infection, disease relapse, drug resistance and death [22]. By the end of 2016, 123 WHO member countries had reported cases of extensively drug-resistant TB resistant to first and second line drugs presenting physicians with situations similar to those in the pre-anti-biotic era [1]. This trend is alarming and without effective monitoring and support strategies, acquisition and transmission of DR-TB will continue [23].

DOT has contributed to substantial improvements in TB treatment outcomes. Early studies found that DOT increased treatment completion, decreased relapse, and potentially decreased TB incidence [24–26]. These benefits have also been observed among groups at high risk for non-adherence such as refugees and persons who are homeless or use illegal substances [27,28]. A meta-analysis including only randomized clinical trials found that DOT increased cure rates by 18% and decreased default rates by 46% [29]. Evidence for the effectiveness of DOT has been disputed [22,30], although lower effectiveness may be a consequence of poorly implemented DOT programs, rather than the failure of DOT in principle [31]. For example, clinic-based DOT requires patients to regularly travel to health facilities, resulting in the loss of autonomy, privacy, time and income. Consequently, clinic-based DOT is often inadequately implemented and, even in public sector facilities, at least some medication doses are self-administered. Community-based DOT involves a health worker traveling to the patient's residence or other location to observe them ingesting their medications, which shifts the economic and staffing burden to providers who might be unable to feasibly observe every dose, such as during nights, weekends and holidays [29,32].

DOT proponents [24,33] suggest that social norms or peer pressure experienced by patients during DOT, even if imperfectly implemented, could improve adherence [34]. Those who oppose DOT view it as coercive and removing control of treatment from the patient [35]. Some behaviorists suggest that DOT is a paternalistic approach relying on the efficacy of medications rather than identifying treatment constraints and building patient-provider relationships that support adherence [23]. Others suggest that simplified treatment regimens combined with technology to facilitate patient monitoring and support are needed to improve TB treatment outcomes [36].

Despite its usefulness, several limitations impact DOT implementation. For example, DOT is costly for health systems and inefficiently allocates resources equally across patients even though some patients require less support than others. DOT impacts substantially upon other competing priorities in a patient's life and is sometimes considered patronizing. Thus, even in functioning DOT programs, some TB patients fail to sufficiently adhere to and/or successfully complete their treatment, particularly patients in vulnerable populations [37]. Patient-centered approaches to improve adherence support are needed, preferably that consider patients' daily schedules, travel requirements and out-of-pocket costs for treatment. New treatment support methods are needed that meet the level of assurance provided by DOT, while maintaining patients' sense of agency and decreasing the healthcare costs.

2. Video observed therapy – approaches and evidence

Applying the same principles as DOT, video observed therapy (VOT) is a technological alternative to in-person DOT whereby patients are observed swallowing their medications remotely using live (synchronous) or recorded (asynchronous) video technology via smartphones, tablets or computers [38]. The goal of any new TB treatment support method should be to provide the same or higher quality adherence monitoring as DOT while reducing the cost and burden of delivery for providers and patients. To this end, it is important to understand whether treatment adherence, completion, and occurrence of adverse medication effects differ by monitoring method and, if outcomes are comparable between VOT and DOT, could VOT benefit TB programs by

saving travel costs, staff time and other resources? In this paper, we describe the evidence available through December 2018 on the feasibility, acceptability, efficacy and cost of synchronous and asynchronous VOT, and compare them to DOT where data are available.

2.1. Synchronous video observed therapy

With the advent of videoconferencing technologies for smartphones, tablets and computers, TB programs began experimenting with patient observations by videophone when patients could not meet in person for DOT [39]. Synchronous video observed therapy (S-VOT), as it is sometimes known, involves patients swallowing their medications in front of a computer or smartphone camera while a healthcare worker watches remotely using videoconferencing software and then documents the interaction on the patient's treatment record. S-VOT requires that patients and providers agree upon a videoconference time and ensure that a consistent network connection can be maintained throughout the call. After both parties join the videoconference, the provider confirms the patient's identity, instructs the patient to show and swallow their prescribed medications in view of the camera. Providers may also inquire about potential medication adverse events, promote continued engagement in care and strengthen rapport with patients.

The first published evaluation of S-VOT for TB included six patients from Pierce County, Washington, USA in 1998–2000 [39]. S-VOT was delivered through a touchtone phone and a television that could be used in conjunction with a videoconference device and modem to conduct a two-way videophone link. Patient adherence to therapy was 95% on S-VOT compared to 97.5% on DOT; the average time required for each S-VOT observation was three minutes compared to one hour for DOT; and S-VOT saved the health department \$2870 (all costs in USD) in travel expenses and \$7993 in personnel expenses during the pilot. A subsequent, larger cost analysis in Washington state estimated average yearly savings of \$2448 per patient for S-VOT compared to DOT [40].

Reported adherence rates for patients using S-VOT range from 79.5% to 98% [40–44]. None of these studies involved random assignment to treatment support method (S-VOT vs. DOT); however, three compared patients on S-VOT to patients within their programs who received DOT and found adherence on S-VOT to be comparable or higher [41–43]. For example, in an S-VOT study in New York City, New York, USA, 96% (47/49) of patients on VDOT completed treatment compared to 97% (260/267) of patients on in-person DOT ($P = 0.63$) [41]. The authors noted that S-VOT adherence might have been higher than observed because technical problems prevented some doses from being observed. Of 61 patients who responded to open-ended questions in that study, 59 (97%) reported choosing VDOT over DOT due to its greater convenience, followed by privacy and flexibility [41–43]. A study in Toronto, Canada found that patients on anti-TB treatment were highly satisfied with the flexibility, privacy, and efficiency of monitoring using S-VOT [43]. A pilot study in Illinois, USA found that 100% (11/11) of participants considered S-VOT “an improvement over the traditional DOT and strongly recommended it to other TB patients;” however, the increased patient-provider interaction was seen as an advantage of DOT [45].

S-VOT reduced transportation and personnel costs for treatment support in these programs while maintaining high levels of adherence and treatment completion. S-VOT also allowed each treatment observer to manage twice as many TB patients as community-based DOT while maintaining high patient satisfaction [41]. Supported by evidence from these studies, several United States TB programs have adopted S-VOT as an acceptable option for patients, particularly those who are unwilling or unable to accept DOT [46].

2.2. Asynchronous video observed therapy

The second approach to remote monitoring, referred to as asynchronous video observed therapy (A-VOT), allows patients to video-record their medication ingestion for providers to watch at another time; thus, eliminating the need for ingestion and observation to occur concurrently. For example, DOT workers can observe evening doses the following morning and weekend or holiday doses on the next business day. Since videos recorded on a patient's smartphone using the device's native camera application and sent by email or Multimedia Messaging Service (MMS) fail to meet the standards of United States—Health Insurance Portability and Accountability Act (HIPAA) or European Union—General Data Protection Regulation (GDPR), specialized applications have been developed that can be installed onto a smartphone or tablet computer for recording, encrypting and transferring videos to a secure server for storage and review. The software is typically accompanied by a password-protected website where providers view patient videos and document whether expected doses were taken. Depending on the application, patients may also report medication adverse events by selecting from an in-application list or by mentioning adverse events in their videos. In A-VOT, patients are trained to record themselves swallowing each medication dose in a verifiable manner using the application. A-VOT allows patients to take doses at any hour of the day, although a set time should be established so providers know when to expect videos and patients develop a daily routine.

While available A-DOT applications may differ in functionality, generally when the patient stops the video recorder, the application encrypts the date/time-stamped video, uploads it to a secure server through a cellular or Wi-Fi network, confirms delivery, and deletes the video from the device. If a network connection is not present, recording remains possible because encrypted video files are stored on the device until a connection is established and the application can upload stored videos. Applications that automate this process simplify the operation for patients and ensure fidelity of the videos by preventing editing, deleting or resending videos. Once delivered, TB program staff review the videos through a web browser to observe and document each dose taken, as well as identify accompanying issues such as adverse drug reactions. If patients do not send videos when expected, or if medication ingestion is not clearly presented in the video, the provider is expected to contact the patient as soon as possible to determine the source of the problem and provide support to avoid future missed doses. Some A-VOT applications include text messaging and/or email functions for reminding patients to take their medications and facilitate patient/provider communication, which could improve adherence [47–49]. In addition, the patient's device may be used to access information about TB, thereby improving health literacy.

The first A-VOT pilot study was published in 2010 by Hoffman and colleagues, who assessed the technical feasibility of having patients ($n = 13$) record and send videos of their medication ingestion using mobile phones [50]. They found A-VOT to be viable with 73% of patients reporting that they preferred recording and sending videos to in-person DOT. The providers involved in the study also ranked their satisfaction with the intervention as “very positive.” This proof-of-concept study used unencrypted videos sent by MMS, which would not meet HIPAA or GDPR security requirements. Subsequently, the United States National Institutes of Health funded a project to develop and pilot test a HIPAA-compliant mobile phone application suitable for high- and low-resource TB programs. The study—conducted in San Diego, California, USA and Tijuana, Baja California, Mexico—found high adherence in both cities (93% and 96%, respectively). Most patients reported that they: preferred A-VOT to community-based DOT; would choose A-VOT over DOT if treatment had to be repeated; and would recommend A-VOT to other TB patients [51,52]. Another study from Minsk, Belarus, that included 10 TB patients age 19–50 years, half of whom were female and half of whom had multidrug-resistant TB, found that 97% of expected videos from all patients combined were received and showed

patients taking all their medications [53]. All patients in this study said they would recommend A-VOT to other TB patients, and the staff found A-VOT to be feasible, efficient and cost saving. Based on this study, the national TB program in Belarus adopted A-VOT. According to A. Skrahina (written communication, September 2018), by March 2018, 520 TB patients (51% with DR-TB) were enrolled nationally with 98% of all video sessions being deemed to clearly show medication ingestion. Of the 314 patients with final treatment outcomes to date, 96% were cured or completed treatment.

The largest A-VOT study to date from the United States included 274 patients with TB from three urban and two rural health districts in California [54]. Participants' mean age was 44 (range: 18–87) years, approximately half had less than a high school education, and over two-thirds owned smartphones. The fraction of expected doses observed was higher among A-VOT participants than among historical controls monitored by community-based DOT (93% vs. 66%, $p < 0.001$), which did not differ by urbanicity. Most participants (96%) would recommend A-VOT to others and only 3% preferred DOT to A-VOT. TB program staff reported that VOT was feasible and took less time per patient than DOT. A-VOT also cost 32% less on average than DOT. Similar findings were reported from a cross-over study in Maryland that monitored TB treatment for 28 patients by DOT (mean = 12.2 weeks) followed by A-VOT (mean = 19.2 weeks) [55]. Medication adherence (based on total dose count) while on A-VOT was comparable to that of DOT (94% vs 98%), with a higher observable fraction of expected doses (based on doses taken when expected) during A-VOT than DOT (72% vs 66%, $P = 0.03$). Staff and patients reported increased treatment flexibility, convenience, and patient privacy for A-VOT compared to DOT. This study found that A-VOT cost \$1391 less than DOT for a 6-month treatment course.

Studies of A-VOT from low- and middle-income countries reported similar findings. Among 40 TB patients using A-VOT in Hanoi, Vietnam, most expected videos (median = 88.4%, IQR: 75.8%–93.7%) were received, which was highly correlated with pill counts remaining when participants returned after two months [56]. In addition, 87.5% of participants found A-VOT easy to use and none were opposed to recommending A-VOT for other TB patients. The authors concluded that A-VOT was feasible and acceptable among patients treated in both central- and district-level health systems in Vietnam. A 2016 study among HIV/TB co-infected patients treated for TB in Tijuana compared A-VOT participants ($n = 21$) to historical age- and gender-matched controls at the same clinics monitored by DOT ($n = 42$) [57]. Participants' mean age was 34 (range: 25–56) years, 61% had less than a high school education, and 23% had a history of injection drug use. The investigators found identical adherence (95%) in both groups; however, treatment abandonment was greater in the DOT group (29% vs. 10%; $p < 0.05$). Furthermore, 84% reported that the process was “somewhat/very easy”, and all participants were “somewhat/very satisfied” with A-VOT, preferred A-VOT to DOT, and would recommend A-VOT to other TB patients.

Two randomized controlled trials of A-VOT compared to DOT have been completed in Moldova and the United Kingdom, [58,59] and a third trial is ongoing in New York City [60]. The United Kingdom trial, in which over half the participants had social risk factors for low adherence (i.e., homelessness, substance use, mental illness), found that compared to DOT, participants in the A-VOT arm were 2.5 to 5.5 times more likely to have $\geq 80\%$ adherence to TB treatment [58]. Results of the Moldova trial are pending.

Notably, these trials were implemented in settings with well-functioning DOT programs providing reliable comparisons for VOT. However, DOT implementation varies greatly across TB programs ranging from DOT provided at a clinic requiring that patients visit the clinic for every dose (clinic-based DOT); community health workers making home visits on a daily basis (community-based DOT); others making home visits to inquire about medication-taken but not actually observing ingestion; and household members or other treatment

Table 1
Characteristics of synchronous (S-VOT) and asynchronous (A-VOT) video observed therapy for tuberculosis treatment adherence monitoring and support.

VOT element	A-VOT	S-VOT
<i>Software:</i>		
Free software available	No	Yes
Software requires video encryption and security protocols	Yes	Yes
<i>Hardware:</i>		
Available for iOS and Android devices	Yes	Yes
Requires smartphone, tablet or computer	Yes	Yes
<i>Connectivity:</i>		
Medications may be taken without network connection	Yes	No
Applications can use cellular or WiFi networks	Yes	Yes
Typical video or videoconference length (minutes)	1–2	3–10
VOT device allows access to health information and communication	Yes	Yes
<i>Location and Timing of Medication Ingestion:</i>		
Medication ingestion observable outside of traditional work hours	Yes	No
Time of medication ingestion at patient's discretion	Yes	No
Split doses observable	Yes	Yes ^a
Medication ingestion observable while traveling	Yes	Yes ^b
<i>Patient-Provider Interaction:</i>		
Requires real-time encounter with patients	No	Yes
Patient can communicate with DOT worker during observation	No	Yes
Provides opportunities to build rapport with patient	No ^c	Yes
Captures information about medication adverse events	Yes ^d	Yes
<i>Quality Control:</i>		
Able to re-review observations	Yes	No
Medication ingestion procedures modifiable at the time of ingestion	No	Yes
<i>Stigma and Privacy:</i>		
Medications taken in private setting of patient's choosing	Yes	Yes
Reduces visible exposure to TB care clinics/providers	Yes	Yes

^a Split-doses are only observable when both doses are taken during provider work hours.

^b Network connection and time zone changes potentially a challenge while traveling.

^c Providers may use content of video observations to counsel patients and build rapport during clinic visits or treatment-related phone calls, emails and text messages.

^d Medication adverse events may be entered by patients using in-app checklists or instructed to report them through video recordings; however, provider notification could be delayed if providers do not monitor VOT system regularly.

supporters observing the medication being taken a reporting to the TB program. Thus, future trials, particularly in low-resource settings, must consider the form of DOT that patient monitoring and support applications will be compared to. While more research is needed to evaluate the effectiveness of A-VOT compared to other modes of TB treatment monitoring, as well as the feasibility and acceptability of A-VOT in low-resource settings, the existing evidence consistently suggests that A-VOT is a feasible, acceptable and cost-saving alternative to in-person DOT.

3. Program considerations for S-VOT and A-VOT adoption

Research shows that both S-VOT and A-VOT yield high treatment adherence, high approval from patients and providers, and conserve resources compared to DOT. Here we describe additional features of each form of VOT that should be considered by TB programs in the context of their patient populations and setting to determine which method(s) best suit their needs (Table 1).

3.1. Software

Videoconferencing software (e.g., Skype, Facetime, Google Hangout) that can be used for S-VOT is common and may be free. However, it is important to ensure that the software meets patient-data

security standards set by the country that is planning to implement S-VOT because health departments could be prohibited from using mobile and internet-based applications for S-VOT if security standards are unmet. Newer applications that provide end-to-end encryption are available that may be used in a manner that complies with HIPAA and GDPR but may cost more. In developing countries, privacy and security regulations are evolving. S-VOT does not use recorded videos, like A-VOT; therefore, S-VOT poses less risk of unintentional disclosure of patient information than A-VOT and avoids the cost of storing and streaming videos.

While it is possible for patients to conduct A-VOT by recording videos using their device's native camera software and sending them through email, MMS or other free platforms, these methods are not secure enough to transfer personal health information and put their confidentiality at risk. In addition, this process is vulnerable to video loss or manipulation, and may not provide important metadata such as the date and time when the videos were recorded. Specialized software may be programmed or purchased to securely perform A-VOT, some of which include features that capture medication adherence and other pertinent information, as well as incorporate this information into patients' medical records [61].

3.2. Hardware

Early studies of S-VOT involved hardwired devices and telephone networks. As technologies evolved, wireless devices began replacing hardwired devices for videoconferencing and video recording. S-VOT using mobile devices gives patients greater control of where they take their medications, although observations are typically restricted to traditional business hours when healthcare workers are available. Both S-VOT and A-VOT can run on smartphones and tablets using applications currently available for iOS and Android devices. S-VOT may also be performed using a laptop or desktop computer equipped with a camera and microphone using a variety of free or enterprise Voice-Over-IP software. Smartphone penetration varies by country ranging from 94% of the population using a smartphone at least monthly in the South Korea to 13% in Tanzania in 2017 [62]. Smartphone ownership also varies by gender, age, race, education, income, and area of residence; therefore, TB programs considering VOT should assess the prevalence of smartphone ownership among the patient populations they serve. For example, programs may provide smartphones, require patients to use their own smartphones, or both depending upon resources available. A common concern over lending phones to patients is that they will be lost or stolen; however, evidence from prior studies does not bear this out. For example, a study conducted in United States and Mexico loaned patients smartphones for A-VOT and found that only 13% of the smartphones were lost, stolen or broken [51]. Among 231 patients given phones for A-VOT in Belarus, no phones were lost or traded by the patients (6 phones needed repairs) [53]. Hence, in low income populations, it may be feasible to loan smartphones to patients who do not own one. The ability to keep a smartphone or tablet charged is another consideration for S-VOT and A-VOT. Thus, TB programs considering VOT should anticipate costs for purchasing, upgrading and replacing devices when they are provided by the program.

3.3. Connectivity

Both S-VOT and A-VOT may be performed using cellular or WiFi internet connections. However, S-VOT only works if both patient and provider have a stable, reliable connection. A-VOT allows patients to record medication ingestion without a network connection because stored videos can upload when connectivity is established. Being able to record videos without a network connection is advantageous for patients who travel or live in locations without connectivity. For example, patients may record videos while traveling to areas without a network connection and have those videos upload when they move back into an

area with a connection, thus avoiding unobserved doses. A-VOT is also useful for patients who lack connectivity at their homes but can connect periodically by moving to an area that has cellular coverage or a WiFi hotspot (e.g., internet cafés). As of 2015, two-thirds of the global population had internet access daily, although this number was lower for countries in Africa and south-east Asia [63], which would make S-VOT challenging in these settings. However, cellular and broadband services are continually expanding allowing greater access to mHealth interventions over time.

Another consideration is the cost of cellular data needed to stream or upload videos. The cost and method of paying for data varies by country and service provider, ranging from monthly fees for unlimited usage to pay-as-you-go plans in which patients must ensure they purchase enough data to complete all VOT doses. As an example, unlimited data plans in the United States cost approximately \$60/month, whereas according to J. Sekandi (written communication: September 2018) in Uganda \$1/week will provide enough data for daily A-VOT dosing. The amount of data used for VOT also varies depending on the camera's resolution and software settings. Notably, A-VOT videos average one to two minutes in length and S-VOT videoconferences take approximately three to 10 min per dose [39,41,43].

3.4. Location and timing of medication ingestion

An important advantage of both forms of VOT over DOT is that patients using mobile devices do not have to be physically present with their treatment observers. This is a major advantage over clinic-based DOT because patients do not have to travel to the clinic for every dose. It can also save money and reduce risk to treatment observers by not having to travel to meet patients receiving community-based DOT. Split-dosing is also feasible with VOT because travel is not required. An advantage of A-VOT over S-VOT is that S-VOT must occur in locations with consistent network connectivity, whereas A-VOT videos can be recorded without a network connection and uploaded whenever connectivity is restored. Both forms of VOT may be used by patients while traveling abroad; however, differences in time zones could make the timing of doses difficult for patients.

An important advantage of A-VOT is that it allows patients to take their medications at the time that best suits them, which is not always true for S-VOT and DOT. TB programs using DOT or S-VOT generally do not observe weekend doses, leaving providers to assume that these doses were taken or require additional doses that extend treatment duration. A-VOT allows these doses, as well as doses taken after hours and on holidays, to be observed. Treatment using A-VOT can be completed sooner and published evidence suggesting that treatment is more effective when dosing is daily versus intermittent [64]. Allowing patients to take their medications where and when they choose enhances control over their treatment and could increase adherence by enabling patients to take their medications with meals or at bedtime to avoid experiencing side effects that can adversely impact adherence.

3.5. Patient-provider interaction

Advantages of S-VOT include opportunities to: (1) observe medication ingestion; (2) enquire about medication adverse events; (3) provide patient education; (4) provide patient support; and (5) guide patients in real time if they are not ingesting their medications in an observable manner. Such frequent, direct interaction not only provides evidence of medication adherence, it facilitates adherence through patient perceived subjective norms, educational support, surveillance for adverse events, and alerts providers when counseling may be needed. However, S-VOT restricts patients to taking medications only when providers are available to observe them, which can be disruptive to patients particularly when schedules must be staggered throughout the day to accommodate larger TB program caseloads. TB programs must also budget time for scheduling videoconferences and

rescheduling them when patients miss their appointed times.

In contrast, A-VOT grants patients autonomy to take their medications at the time that best suits their needs. Patients report that this avoids treatment disruption due to adverse events because they can take medications with meals or at bedtime to minimize adverse events. Doses taken outside of business hours (i.e., nights, weekends and holidays) using A-VOT are all observed and counted toward completion. After-hours dosing was found to be an important benefit for observant Muslim patients receiving directly observed preventive therapy for latent TB infection but fasted during the day for Ramadan [65]. However, A-VOT's greater autonomy and reduced burden for patients and providers must be balanced against the reduced patient-provider interaction compared to S-VOT. Since A-VOT only requires patients to meet with their providers during medication refill or clinical follow-up visits, A-VOT has fewer opportunities for building rapport, detecting medication adverse events, and providing patient support compared to S-VOT. Therefore, strategies must be included for patients to report adverse events (e.g., by calling or texting their provider, reporting them in a video, or entering them into the A-VOT application if available), and for providers to contact and offer support to patients who do not send videos and provide effective training to ensure that patients correctly perform each ingestion event. Further research is needed to determine the appropriate balance between patient autonomy and patient-provider interaction.

3.6. Quality control

The ability for TB program managers to perform quality control may be greater with VOT than DOT. For example, with some exceptions, the only evidence of a treatment event under DOT are the observer's notations placed in the patient's adherence record, making it difficult for supervisors to verify whether the medications were truly ingested. In contrast, supervisors can periodically observe S-VOT sessions or compare telecommunication records with DOT records to see if calls were made to the patients. Moreover, A-VOT allows supervisors to re-review stored videos and compare them to patients' adherence records.

The quality of recorded and live video sessions relies on properly training patients not only to use the VOT application, but also how to take their medications in an observable manner. A brief (typically two-week) run-in period of DOT was reported in some studies to evaluate patients for medication adverse events and to establish a dosing habit before initiating VOT [41,44,54,66]. During this period, patients can receive VOT application training and demonstrate mastery before beginning to use the application remotely.

The issue of whether patients who wish to avoid taking their medication could deceive observers by holding the tablet(s) in their cheek or under their tongue and spitting them out once out of the observer's view is a reality for both DOT and VOT. To minimize this risk in both S-VOT and A-VOT, researchers [41,42] and health departments [67,68] established protocols whereby the patient is required to stay on screen at all times, tablets are shown on camera prior to placing them in the patient's mouth one at a time, and the patient must talk or open their mouth to show that all tablets were swallowed.

3.7. Stigma and privacy

Stigma plays an important role in TB control [69]. A multi-country study revealed that stigma varies by area of residence and is higher in India compared to some other Asian and African countries [70]. Studies from Nepal and Zambia found that over half of patients receiving clinic-based DOT experienced stigma. In addition, high-risk patient groups, including patients who relapsed or failed treatment, experience significantly higher stigma compared to other patients. The DOT process contributes to stigma because patients lack privacy during frequent visits from DOT workers or to clinics for TB treatment, which could prevent patients from completing treatment or seeking care for their

illness [71,72]. VOT, particularly among populations that are at higher risk of stigma, could reduce their risk by limiting visible exposure to the healthcare system. While both forms of VOT increase patient privacy, A-VOT lets patients decide when and where they take their medications affording them greater confidentiality.

Since smartphones used for VOT may also be used for other purposes (e.g., gaming, internet browsing and social networking), there may be certain patient populations who could be denied access to such mHealth interventions [73]. Furthermore, capturing the images of female patients in VOT videos may be unacceptable in some cultures. These questions have not been formally evaluated to date, and studies are needed to determine the extent to which this disparity exists and, if so, how it could be mitigated.

4. Conclusions

Mounting evidence indicates that synchronous and asynchronous VOT are feasible, acceptable and achieve adherence for anti-TB treatment that is comparable to or higher than in-person DOT with lower costs. While additional research is needed to determine the effectiveness and best practices for VOT in low-resource, high-TB-burden countries, the findings to date appear similar to those from studies conducted in high-resource settings. VOT achieves the same objective as DOT (i.e., reminds patients to take their medication, provides observable evidence of ingestion and identifies patients who require additional support) while minimizing the individual and structural barriers that make DOT difficult to implement. Delivering care through remote video communication reduces the inconvenience and cost of frequent travel for DOT visits as well as the risk of exposing others to TB while patients are infectious, thereby conserving patient and provider resources. [39,40] While both A-VOT and S-VOT reliably facilitate medication adherence monitoring and support, each method has unique strengths and limitations. S-VOT maintains the real-time communication of DOT that might improve detection of medication adverse events and facilitate rapport-building with patients; however, it requires personnel to schedule observations, relies on consistent network connectivity, and restricts timing of medication doses. A-VOT allows patients to take medications at any time (including weekends and holidays) with or without a network connection but provides fewer opportunities for patient-provider interaction. Conceivably, TB programs might best achieve the goals of patient-centered care and support by offering DOT, A-VOT and S-VOT separately or in combination among other approaches to TB treatment monitoring. Integration of adherence data from all monitoring methods, especially for patients whose monitoring method changes over the course of treatment, will be essential for programs to efficiently track adherence and effectively respond to patient needs when adherence declines. Additionally, TB programs that combine VOT with other adherence monitoring technologies (e.g., 99DOTS, Wisepill, AiCure, Proteus) could maximize adherence by offering a range of patient-centered options.

In 2015, the WHO and the European Respiratory Society determined that VOT addressed the “Integrated, Patient-Centred Care and Prevention” pillar of the End TB Strategy [38]. Given evidence from studies to date, the WHO now endorses VOT as an alternative to DOT wherever the technological capacity is sufficient [74] and has published a handbook providing guidance to TB programs seeking to adopt VOT [75]. Additionally, several state health departments in the United States have incorporated VOT into their routine TB treatment monitoring strategies, as well as provide VOT guidelines [61,66,68,76,77]. Efforts are underway in the United States to make VOT a medical procedure reimbursable by insurers, similar to DOT [78,79]. Beyond active TB, VOT has also been successfully used to treat latent TB infection among exposed contacts [80,81]. While VOT is gaining a foothold globally, more evidence is needed by national TB programs to request support from the Global Fund or other sources for VOT. To better assess the strengths and limitations of VOT, comparative studies are needed that

use existing standard-of-care treatment (typically self-administration of treatment) as the comparator, as well as evaluate the acceptability of VOT in different subpopulations (e.g., women and girls) and in various high-burden and low-resource settings.

It is important to recognize that VOT, like DOT, is a tool for monitoring medication adherence and guiding patient support but does not ensure adherence in the absence of appropriate action by healthcare providers when medications are not taken. Quality control measures necessary for effective VOT implementation include: (1) training patients to show each pill being swallowed in front of the camera so that ingestion is unequivocal; (2) training providers to routinely watch videos and respond promptly whenever a dose is missed or adverse drug reactions are experienced; (3) instituting protocols for supporting patients who do not take every dose as prescribed; and (4) anticipating the possibility that a patient’s current adherence monitoring method might not be working and that switching to another method could improve adherence. VOT is a powerful tool for TB treatment monitoring, and combined with patient support (e.g., encouragement, patient education, management of adverse events and incentives), it provides TB programs new methods to cost-effectively treat patients to completion and cure.

Conflict of interest

Dr. Garfein is a co-founder of SureAdhere Mobile Technology, Inc. – a VOT service provider. No funding or other resources were provided by SureAdhere for the manuscript. Dr. Garfein’s involvement complies with the UC San Diego conflict of interest policies. Dr. Doshi has no financial conflicts of interest related to this publication.

CRedit authorship contribution statement

Richard S. Garfein: Conceptualization, Writing - original draft, Writing - review & editing. **Riddhi P. Doshi:** Writing - original draft, Writing - review & editing.

Acknowledgments

The authors wish to thank Dennis Falzon for his insightful suggestions on this paper. We would also grateful to A. Skrahina, J. Sekandi for her personal communication to the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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